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Is there the potential for an epidemic of variant Creutzfeldt–Jakob disease via blood transfusion in the UK?

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The discovery of three individuals suspected to have contracted variant Creutzfeldt–Jakob disease (vCJD) through blood transfusions has heightened concerns that a secondary epidemic via human-to-human transmission could occur in the UK. The Department of Health responded immediately to this threat by banning those who had received blood transfusions since 1980 from donating blood. In this paper, we conduct a sensitivity analysis to explore the potential size of a blood-borne vCJD epidemic and investigate the effectiveness of public health interventions. A mathematical model was developed together with an expression for the basic reproduction number (R_0). The sensitivity of model predictions to unknown parameters determining the transmission of vCJD via infected blood was assessed under pessimistic modelling assumptions. We found that the size of the epidemic (up until 2080) was bounded above by 900 cases, with self-sustaining epidemics ($R_0>1$) also possible; but the scenarios under which such epidemics could arise were found to be biologically implausible. Under optimistic assumptions, public health interventions reduced the upper bound to 250 and further still when only biologically plausible scenarios were considered. Our results support the belief that scenarios leading to large or self-sustaining epidemics are possible but unlikely, and that public health interventions were effective.

Keywords: basic reproduction number; blood transfusion; Creutzfeldt–Jakob disease; epidemiology; mathematical model

1. INTRODUCTION

The primary epidemic of variant Creutzfeldt–Jakob disease (vCJD) is believed to have been caused by the consumption of beef infected by bovine spongiform encephalopathy (BSE; Bruce *et al.* 1997; Hill *et al.* 1997; Scott *et al.* 1999). As of January 2007, there have been 158 deaths attributed to vCJD in the UK, but the annual incidence of clinical vCJD has continued to decline since peaking in 2000, with only five deaths recorded in 2006 (NCJDSU 2007). While the tailing off of the epidemic is reassuring from a public health perspective, recent results suggest it is too early to assert that the epidemic is dying out. A study of 13 000 tonsil and appendix samples was conducted to assess the extent of vCJD infection in the UK population (Hilton *et al.* 2004). The prevalence of infection was estimated to be far higher than previously thought, and poses the question as to why there have been only hundreds rather than thousands of clinical cases. One explanation is that a large proportion of those infected entered a 'carrier state' in which they may be infectious to others, but will not go on to develop clinical symptoms during their lifetime (Hill & Collinge 2003). The subclinical vCJD infection hypothesis is supported by data from experiments involving animal prion diseases (Asante *et al.* 2002) and by statistical modelling of the vCJD epidemic (Clarke & Ghani 2005).

Compelling evidence of human-to-human transmission of vCJD by blood transfusion first emerged in autumn 2003 when a patient who died of vCJD was found to have received blood from a blood donor who himself went on to die of vCJD (Llewelyn *et al.* 2004). Subsequently, a second such case was identified (HPA 2006) and a third recipient of blood from a vCJD case was found to show signs of vCJD infection after *post-mortem* (Peden *et al.* 2004). Together with the unexpectedly high vCJD prevalence discussed above, these discoveries have led to fears that a large-scale self-sustaining epidemic of vCJD could arise via blood transfusion with serious implications for public health (Farrugia *et al.* 2005; Dolan 2006; Hilton 2006; Ironside 2006).

In this paper, we explore the potential for a secondary, blood-borne epidemic of vCJD by performing a sensitivity analysis based on a mathematical

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transmission model. We use this analysis to gain insight into how the scale of the epidemic may vary according to different assumptions about its epidemiology. We assume that the two clinical cases described above certainly contracted vCJD via blood transfusion and thus ignore any uncertainty about their actual infection routes. The sensitivity analysis is based on a deterministic compartmental model for transmission through the human population by infected individuals donating blood which is subsequently used in blood transfusions. Some model parameters index population demographics and the UK blood supply, for which robust estimates based on data from the Census and the National Blood Service (NBS) are used. The remaining parameters index the epidemiological characteristics of vCJD for which the estimates are less robust. For the primary epidemic via bovine-to-human transmission, we use estimates based on a previous model of the primary epidemic which allows a carrier state; for parameters of the blood-borne transmission process where much is uncertain, we vary these parameters over their domain to quantify the variation in epidemic predictions and produce bounds on the extent of the epidemic. It should be understood that it is impossible to produce fully robust predictions of the secondary epidemic at the current time, and we do not claim to do so. Instead, we aim to describe the dynamics of the epidemic and explore its order of magnitude in worse-case scenarios *given current knowledge*.

This paper is arranged as follows. In §2, we introduce the data on which estimates of the human mortality and the UK blood supply are based. In §3, we introduce a mathematical model, present an expression for the basic reproduction number under this model, extend the model to allow for interventions and describe the design of the sensitivity analysis. The results of the sensitivity analysis are presented in §4 and discussed in §5.

2. DATA SOURCES

Information about the population size in each birth cohort and survivorship within these cohorts from all causes were taken from UK Census data. The vast majority of blood is used for red cell transfusions and all three individuals suspected of contracting vCJD via blood transfusion received red blood cells (Hewitt *et al.* 2006). Hence, we restrict our analyses to this transmission route.

Data on the rates and types of red cell transfusions were obtained from a prospective observational study over 28 days carried out in the North of England (Wells *et al.* 2002). Over this period, the use of 9848 units of red blood cells was recorded, of which approximately 41% was used in surgery, 52% in general medicine (including anaemia, haematology and gastrointestinal bleeds) and 6% in obstetrics and gynaecology. Data on the survivorship of patients receiving blood transfusions were obtained from a related study in which 2899 patients at a single centre transfused in June 1994 were followed for 5 years (Wallis *et al.* 2004). A total of 10 760 red blood cell units were used for transfusions over this period. The age distribution of those receiving transfusions is similar to that obtained in the earlier study (Wells *et al.* 2002). After 5 years of follow-up, 47% of the transfusion recipients remained alive.

Blood donation data were obtained from the NBS, which covers all donations in England and North Wales (Det Norske Veritas 2003). These figures show that, in 1996/1997, there were 1.9 million donors who donated 2.2 million units of usable blood. More recent figures from 2004/2005 showed there were fewer donors (1.6 million), but each donor donated more blood (2.1 million units of usable blood). However, these later figures were obtained following the introduction of leucodepletion and changes in the definitions of those allowed to donate blood. Hence, we use the earlier figures to enable consideration of epidemic predictions prior to interventions (which include leucodepletion). Blood donors are normally between 18 and 65 years of age. Donors are allowed to donate blood up to 3 times per year, but on average do so 1.2 times per year.

Age is potentially a critical factor determining vCJD spread via blood transfusion and must be included in the mathematical model. Epidemiological analysis of the primary epidemic found vCJD to depend strongly on age, with a significant excess of vCJD cases in young individuals. In addition, rates of blood donation and transfusion depend on age. Figure 1*a* shows the age-dependent donation rate for 1997 obtained from figures provided by the NBS (Det Norske Veritas 2003). Across all age groups, an average of 4300 units of blood were donated per 100 000 population per year, with 70% of donations received from those under 50 years of age. In contrast, transfusion-associated procedures are primarily undertaken in the elderly, with 66% undertaken in those aged 60 years and above (figure 1*b*; Wells *et al.* 2002). Finally, we must also allow for age-dependent excess mortality due to survival following surgical procedures incorporating transfusion, because infected patients may die before passing on the disease or developing clinical disease (figure 1*d*; Wallis *et al.* 2004).

3. A MATHEMATICAL MODEL

3.1. Basic model structure

The deterministic compartmental model for the transmission of vCJD infection in the UK has three components: (i) the primary epidemic through bovine-to-human transmission (i.e. through consumption of BSE-infected food material) which produces the initial background infection level for human-to-human transmission, (ii) the donation of blood which is packaged into blood units and stored for subsequent use in blood transfusions, and (iii) transmission through transfusions of infected blood into a susceptible host and their subsequent infection.

The first component described above determines bovine-to-human transmission in the initial primary epidemic and is modelled as an age- and time-dependent hazard of infection in which individuals are assumed to enter a carrier state (or not) with a fixed probability after infection. The parameters of this model are taken to equal updated maximum-likelihood estimates from a survival model for the primary epidemic (Clarke & Ghani 2005) fitted to data from clinical cases taken up until the end of

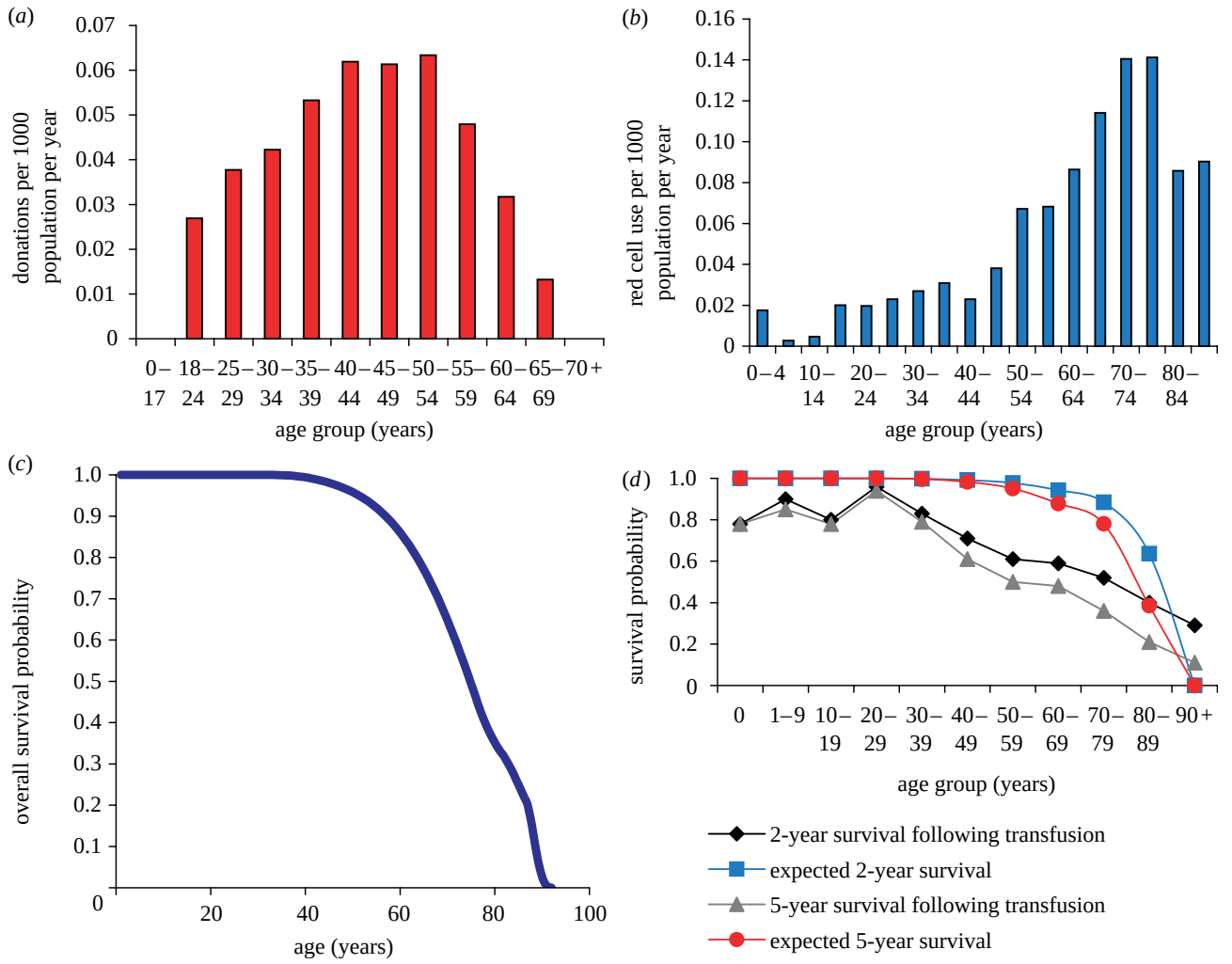

Figure 1. Data on blood supply and UK mortality rates. (*a*) Whole blood donation rates by age obtained from national figures provided by the NBS in 1997. (*b*) Red cell transfusion rates by age group obtained from a 28-day prospective observational study in the North of England (Wells *et al.* 2002). The destination of 9848 units (97% of expected blood use) was recorded. (*c*) The overall survival probability for the UK obtained from 1993 census data (Ghani *et al.* 1998). (*d*) 2- and 5-year survival probabilities by age group for patients receiving red cell transfusions from the prospective observational study in the North of England (Wallis *et al.* 2004). Corresponding estimates of the 2- and 5-year post surgery survival probabilities used in the mathematical model are also shown.

2005. Components (ii) and (iii) are two interrelated models describing blood-borne transmission of vCJD. UK blood stocks are treated as a pool of blood from which a fixed number of units are taken for procedures requiring blood transfusions; the rate at which blood is used and donated, estimated from the NBS data, ensures realistic storage times for donated blood units. For the secondary epidemic, we follow recent research and assume all genotypes are susceptible to infected blood (Bishop *et al.* 2006). The same research further suggests that infected blood may induce subclinical infection with an unknown carrier state probability, and so we also allow for this in the model.

3.2. Model specification

The model is specified in continuous epidemic time indexed by t, with the assumption that $t=0$ corresponds to the origin of the BSE epidemic on 1 January 1980. Birth cohorts are defined according to the calendar year in which individuals were born and are indexed by c. We make the weak assumption (i.e. one having little effect on the results) that all individuals in a birth cohort were born at the start of that calendar year. Denote the time at which people in birth cohort c were born by t_c, which take integer values corresponding to calendar years. For example, $t_{1980}=0$ for those born in 1980 and $t_{1970}=-10$ for those born in 1970. The age of those in birth cohort c at time $t>0$ can thus be defined $a_{ct}=\lfloor t-t_c \rfloor$, where $\lfloor z \rfloor$ is the largest integer less than or equal to z.

Now let $X_c(t)$ denote the number of susceptible individuals in birth cohort c at epidemic time t. For cohorts in which individuals were born prior to 1980, $X_c(0)$ is equal to the cohort size at the start of 1980. For cohorts in which individuals were born after 1980, $X_c(t_c)$ is equal to the number born during that year. Further, let $Y_{c,f}(t)$ and $Z_{c,f}(t)$ represent the number of primary- and blood-route-infected individuals in birth cohort c, respectively, where $Y_{c,f}(0)=Z_{c,f}(0)=0$ for all c and f.

Subscript f denotes infection status, where $f=0$ denotes subclinical infection and those with preclinical infection move successively through F stages of incubation indexed by $f=1, \ldots, F$, with death occurring

immediately following stage F (i.e. we ignore the lag between clinical diagnosis and death). Note that the incubation period is divided into multiple stages to ensure that they follow a Gamma distribution under the model; the stages do not have any intrinsic biological interpretation. Finally for the human population, the cumulative numbers of deaths at time t from the primary and blood infection routes are denoted by $D_1(t)$ and $D_2(t)$, respectively.

The rate at which the size of each compartment changes in birth cohort c at time t is governed by the following set of differential equations:

$$\begin{aligned} X_c'(t) &= -X_c(t)(\hat{\eta}_c(t)+\lambda_c(t)+\delta_c(t)) \\ Y_{c,f}'(t) &= \begin{cases} X_c(t)\hat{\omega}_1\hat{\eta}_c(t) - Y_{c,0}(t)\delta_c(t) & \text{if } f=0, \\ X_c(t)(1-\hat{\omega}_1)\hat{\eta}_c(t) - Y_{c,1}(t)(\delta_c(t)+\hat{\gamma}) & \text{if } f=1, \\ Y_{c,(f-1)}(t)\hat{\gamma} - Y_{c,f}(t)(\delta_c(t)+\hat{\gamma}) & \text{if } f>1, \end{cases} \\ Z_{c,f}'(t) &= \begin{cases} X_c(t)\omega_2\lambda_c(t) - Z_{c,0}(t)\delta_c^*(t) & \text{if } f=0, \\ X_c(t)(1-\omega_2)\lambda_c(t) - Z_{c,1}(t)(\delta_c^*(t)+\xi) & \text{if } f=1, \\ Z_{c,(f-1)}(t)\xi - Z_{c,f}(t)(\delta_c^*(t)+\xi) & \text{if } f>1, \end{cases} \end{aligned} \tag{3.1}$$

where $X_c'(t), Y_{c,f}'(t), Z_{c,f}'(t)$are the derivatives of $X_c(t)$, $Y_{c,f}(t)$ and $Z_{c,f}(t)$, respectively, with respect to t; $\hat{\eta}_c(t)$is the best estimate of the rate of primary infection; $\lambda_c(t)$ is the rate at which transfusion-acquired infections occur; $\delta_c(t)$ is the death rate from non-vCJD-related causes; $\delta_c^*(t)$ is the death rate among the transfusion recipient population; $\hat{\gamma}$ is the best estimate of the rate at which individuals leave primary incubation stage $f>0$; $\hat{\omega}_1$ is the best estimate of the proportion of primary infections that are subclinical; ξ is the rate at which individuals leave transfusion-acquired incubation stage $f>0$; and ω_2 is the proportion of subclinical transfusion-acquired infections.

Cumulative deaths from the primary and secondary infection routes increase at rates

$$D_1'(t) = Y_{+,F}(t)\hat{\gamma} \text{ and } D_2'(t) = Z_{+,F}(t)\xi, \tag{3.2}$$

where $D_1'(t), D_2'(t)$ denote the derivatives with respect to t and a '+' subscript denotes summation over all levels of the obscured index.

For the blood population, let $U(t)$ and $C(t)$ denote the number of uncontaminated and contaminated blood units at t, where $V(t)=U(t)+C(t)$ is the blood population size and $U(0)=V(0)$, $C(0)=0$. We then make the further weak assumption that the population size is fixed over time, $V(t)=V$. Using this notation, the force of infection via the blood transfusion route above is given by the mean-field equation

$$\lambda_c(t) = W_c(t)\tau(t)\psi(a_{ct})\left(1-(1-\beta_2 C(t)/V)^{b(a_{ct})}\right), \tag{3.3}$$

where a_{ct} is the age of those in birth cohort c at time t (defined above); $\tau(t)$ is the rate of procedures requiring transfusions; $\psi(a_{ct})$ is the proportion of these procedures carried out on those age a_{ct}; β_2 is the transmission probability for blood-route infection; and $b(a_{ct})$ is the average number of blood units user per transfusion on patients age a_{ct}. Finally, the weight $W_c(t)=N(t)/N_c(t)$ converts a per-age group rate into a per-birth cohort rate (required because each age group generally includes multiple birth cohorts).

Using a similar notation, the corresponding model for infection of the blood population at time t is given by

$$\begin{aligned} U'(t) &= \sum\nolimits_c X_c(t)\rho(a_{ct}) \\ &\quad - \sum\nolimits_c N_c(t)\phi(t,a_{ct})\,U(t)/V, \\ C'(t) &= \sum\nolimits_c (N_c(t)-X_c(t))\rho(a_{ct}) \\ &\quad - \sum\nolimits_c N_c(t)\phi(t,a_{ct})\,C(t)/V, \end{aligned} \tag{3.4}$$

where $N_c(t)=X_c(t)+Y_{c,+}(t)+Z_{c,+}(t)$ is the size of the surviving population in birth cohort c at time t; $\rho(a_{ct})$ is the rate at which people age a donate blood units (blood units per person per year); and $\phi(t,\ a_{ct})$ is the rate at which blood units are used in red cell transfusions among those age a_{ct} at time t. This last quantity is given by

$$\phi(t,\ a_{ct}) = W_c(t)\tau(t)\psi(a_{ct})b(a_{ct}). \tag{3.5}$$

3.3. Parameter values

Values for $\tau(t)$, $\psi(a)$, $b(a)$ and $\rho(a)$ were obtained from the data sources described in §2. The estimates of $\hat{\eta}_c(t)$ and $\hat{\omega}_1=0.1$ were obtained by fitting a previously developed survival model (Ghani *et al.* 2000; Clarke & Ghani 2005) to (i) the time- and age-stratified counts of vCJD deaths updated at the end of 2005 and excluding the two clinical cases assumed to be blood infected and (ii) the results from the survey of 12 674 tonsil and appendix tissues (Hilton *et al.* 2004), assuming that the diagnostic tests are sensitive only in the final 50% of the incubation period.

The death rate in the general population due to causes other than vCJD is calculated using estimates of population survivorship made by the Government Actuary's Department. Denote the survivorship until calendar year u for those age a by $S(u,\ a)$. Ignoring temporal variation in the population survivorship by setting $S(u,\ a)=S(a)$ and assuming a constant death rate within each age group, standard results give

$$\delta_c(t) = \begin{cases} -\log S(a_{ct}|a_{ct}-1) & \text{if } a_{ct}=1,\ldots,91, \\ -\log S(0) & \text{if } a_{ct}=0, \end{cases}$$

where $S(a|a-1)=S(a)/S(a-1)$ is the conditional survivorship function for interval $(a-1,\ a]$. Owing to low survivorship beyond age 91 years, we assume that everyone dies instantaneously on their 92nd birthday. The death rate among the transfusion recipient population is set to be $\delta_c^*(t)=\mathrm{e}^{\xi}\delta_c(t)$, where $\mathrm{e}^{\xi}=\exp(\xi)$ is the relative hazard such that $S^*(a+1)=S(a+1)^{\exp(\xi)}$. The value $\zeta=1.25$ was chosen to approximate Kaplan–Meier estimates of age-stratified survivorship (Wallis *et al.* 2004).

3.4. Self-sustaining epidemics and the basic reproduction number

In addition to the total size of the epidemic (as measured by the total number of people infected), it is of interest to establish whether the epidemic could be self-sustaining. The basic reproduction number (R_0) is

used to quantify this idea. It is defined as the expected number of infections caused by introducing one vCJD-infected individual into an otherwise susceptible population at the start of the epidemic. It has the property, in an infinite population, $R_0 > 1$ indicates that a self-sustaining epidemic is certain. More practically, in very large but finite closed populations, it indicates that a self-sustaining epidemic occurs with probability close to 1.

If we assume the ultimate size of the epidemic can only be small compared with the total population size, an analytical expression for R_0 can be derived using the method proposed by Diekmann *et al.* (1990). For the model described above, it can be shown that

$$R_0 = \sqrt{\beta_2 \sum_a \frac{N_a}{N} \sum_{u=0}^{91-a} \rho(a+u) S(a+u|a) \left\{ (1-\omega_2) \mathrm{e}^{-u\xi} \sum_{r=0}^{F-1} \frac{\xi^r}{r!} k_r(u,a) + \omega_2 m(u,a) \right\}}, \tag{3.6}$$

where

$$k_r(u,a) = \begin{cases} \dfrac{(u+1)^r \mathrm{e}^{-\xi} S(a+u+1|a+u) - u^r - r k_{r-1}(u,a)}{-\xi + \log S(a+u+1|a+u)} & \text{if } r = 0, \ldots, F-1, \\ 0 & \text{if } r = -1, \end{cases}$$

$$m(u,a) = \begin{cases} \dfrac{S(a+u+1|a+u)-1}{\log S(a+u+1|a+u)} & \text{if } S(u+a+1|a+u) < 1, \\ 1 & \text{otherwise,} \end{cases}$$

and N_a/N is the proportion aged a in 1980. The derivation of this expression is similar to that set out for a closely related model by Garske *et al.* (2006).

3.5. Interventions

In 1997/1998, the UK Department of Health responded to the theoretical risk of vCJD being spread by blood transfusion by requiring that all donated blood underwent leucodepletion to remove potentially infectious leucocytes. Subsequently, early in 2004 following discovery of the first two suspected blood-related vCJD infections, the Department of Health additionally excluded all those who were known to have had blood transfusions since 1980 from donating blood.

We investigate the potential effect of these two interventions by extending the mathematical model above to simulate their impact (the implementation is described in appendix A). Leucodepletion has been found to reduce infectious dose by 40% (Gregori *et al.* 2004). However, the effect this has on transmission coefficient β_2 depends on the relationship between dose and transmission, and on the threshold below which transmission cannot occur, both of which are unknown. Thus, we consider the two extremes: an 'optimistic' scenario in which leucodepletion is 60% effective, and a 'pessimistic' scenario in which it is 0% effective. For the donation ban, we consider an optimistic scenario of a 90% effective ban and a pessimistic 0% effective ban.

3.6. Sensitivity analysis

As described above, the parameters determining the UK population demographics and its blood supply were fixed at the estimates obtained using the data on survival, blood donation and transfusion. Epidemic scenarios are generated by varying the three remaining parameters: the transmission probability of disease, given the contact with infected blood (range 0–1); the proportion of transfusion-acquired infections entering a carrier state (range 0–1); and the ratio between the mean incubation periods of preclinical transfusion- and bovine-to-human-acquired vCJD (range 0–5). Note that the latter parameter corresponds to an absolute measure of length because the mean primary incubation period distribution is fixed.

Scenarios are generated at random using Latin Hypercube Sampling, i.e. drawing triples at random from the domain of the three parameters (Stein 1987). A batch of 10 000 scenarios was analysed to explore the scale and dynamics of the secondary epidemic. Scenarios were included only if they were consistent at the 95% level with the two clinical cases observed by the end of 2005. For simplicity, the scenarios were not constrained to match the third non-case found in 2004 because neither its infection time nor whether it is a pre- or subclinical infection is known. Latin hypercube sampling cannot be exhaustive, but further batches of 10 000 were analysed (results not shown) to ensure the original batch was representative of the parameter space.

4. RESULTS

4.1. Potential for self-sustaining epidemics

The results presented are taken from a single representative batch of 10 000 scenarios. In total, 7702 scenarios were accepted as consistent with the two clinical cases observed. In the scenario analysis, we first consider the potential size of the epidemic in the hypothetical situation that the Department of Health did not introduce leucodepletion or ban donations from former donors. The basic reproductive number (R_0) ranged between less than 0.001 and 1.35. The wide range incorporates both epidemic extinction and self-sustaining epidemics, and the range itself quantifies

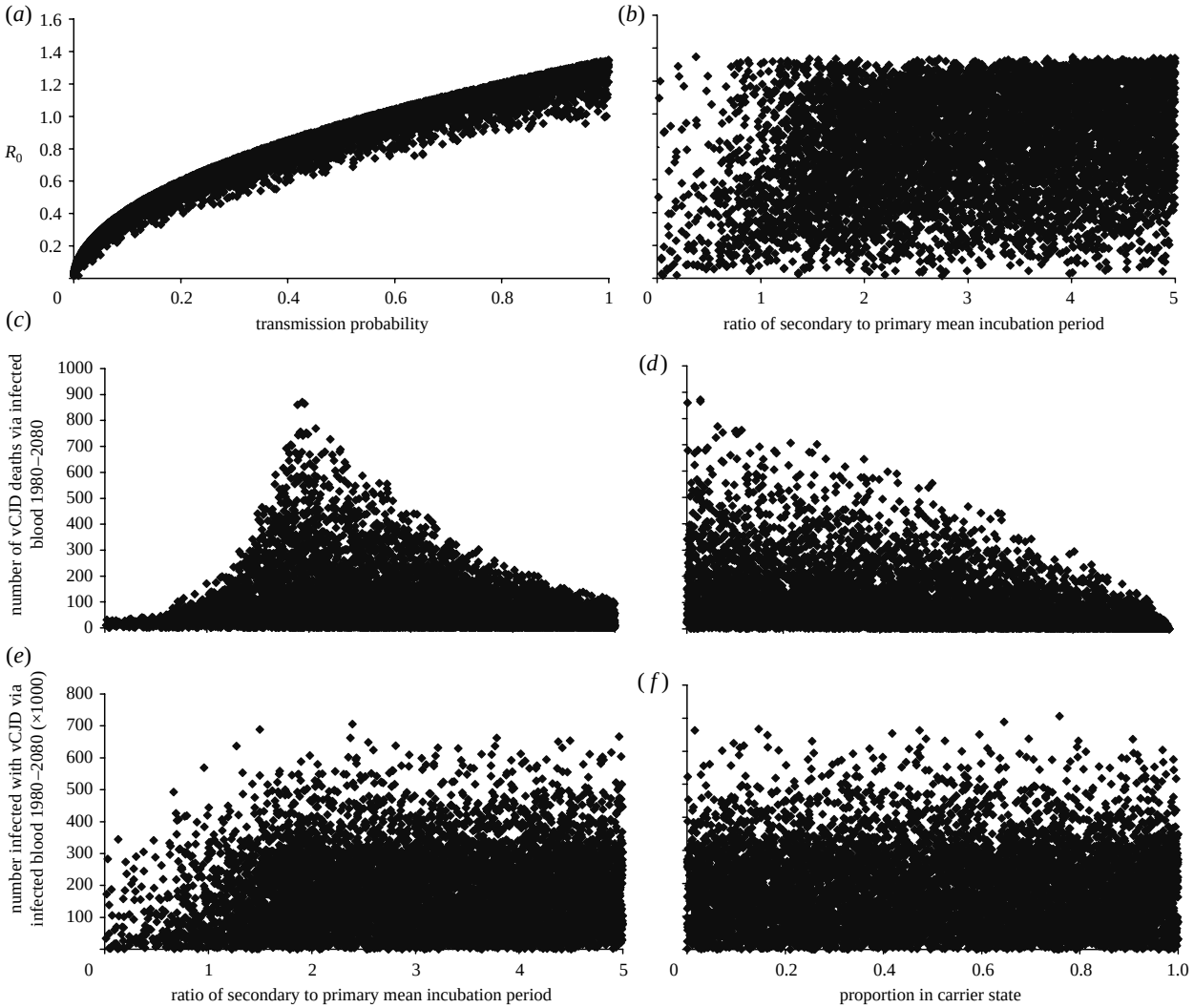

Figure 2. Sensitivity analysis. The relationship between R_0, epidemiological parameters and future infections and clinical cases without interventions. (*a*) R_0 and the transmission probability from blood. (*b*) R_0 and the ratio of the mean incubation period in those infected via blood transfusion to the mean incubation period in those infected via consumption of BSE-infected beef. (*c*) The total number of clinical cases by 2080 and the ratio of the mean incubation periods for those infected via blood transfusion and those infected via consumption of BSE-infected beef clinical cases by 2080. (*d*) The total number of clinical cases by 2080 and the probability of entering a carrier state after infection via blood transfusion. (*e*) The total number of people infected via blood transfusion by 2080 and the mean incubation period ratio. (*f*) The total number of infections by 2080 and the carrier state probability for blood-borne infections.

uncertainty about the transmissibility of vCJD via infected blood. If there was complete uncertainty, then we would have expected the upper bound for R_0 to be much higher. In the event, the worse-case scenario is limited by the rates and age distributions of those donating blood and receiving transfusions. Self-sustaining epidemics with $R_0 > 1$ occur when the transmission probability is high (clearly shown in figure 2*a*) and when the mean incubation period for transfusion-acquired (human-to-human) infection is longer than for primary (bovine-to-human) infections: the scatter of $R_0 > 1$ scenarios is sparse in the region of figure 2*b* where the ratio is less than 1. The latter scenario is biologically plausible because within-species transmission usually results in shorter incubation periods than between-species transmission (Kimberlin & Walker 1978; Bruce *et al.* 1994; Bruce 1996). Hence, it is unlikely that this route of transmission will give rise to a self-sustaining epidemic.

4.2. Potential scale of the epidemic

Continuing with the hypothetical 'no intervention' situation, we now consider the size of the blood-borne vCJD epidemic up until 2080. The first row of table 1 contains the range of transfusion-acquired clinical case numbers. The worst-case scenario without any intervention results in an expectation of 871 deaths by 2080. The first factor limiting the epidemic is the constraint that scenarios should be consistent with the two observed cases infected by blood transfusions by 2006, which automatically excludes the most extreme scenarios.

We can explore the dynamics of the epidemic further to establish the remaining factors limiting epidemic potential. The relationship between the mean secondary incubation period and the total number of vCJD cases/deaths by 2080 is shown in figure 2*c*. Short secondary incubation periods correspond to small

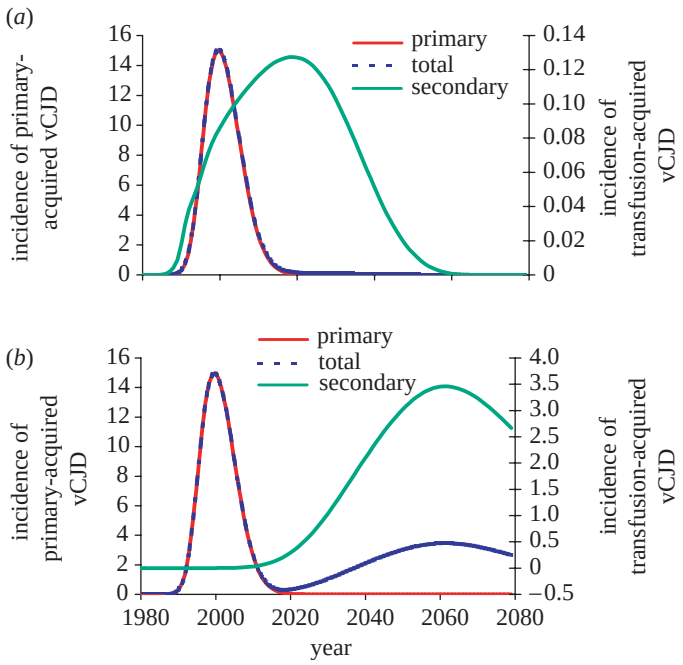

Figure 3. A sample epidemic. Two scenario epidemics. (*a*) An epidemic with low $R_0=0.03$ showing that the vast majority of vCJD clinical cases arise via primary infection. (*b*) An epidemic with high $R_0=1.3$ showing a multi-modal distribution of vCJD cases with the first peak occurring in 2000 from primary transmission and a second, much lower, peak in 2060 from transfusion-acquired infection. In both the scenarios, it is assumed that 10% of those infected via blood transfusion go on to develop clinical disease and that no interventions have taken place.

Table 1. Upper bounds from sensitivity analysis. Range from scenario analysis of the expected number of deaths from vCJD contracted via blood transfusion. The intervention scenarios incorporate the ban on blood donations from those who have previously received blood and the introduction of leucodepletion in 1997 (effective leucodepletion reduces the transmission probability by 40%, while ineffective leucodepletion has no effect on the transmission probability). The ban on blood donations from those who have previously received a blood transfusion from 2004 onwards is assumed to be 90% effective). '0' indicates a small positive value less than 0.001.

	clinical cases			
	2005–2010	2005–2015	2005–2020	1980–2080
no intervention	0–19	0–52	0–104	0–871
effective leucodepletion only	0–17	0–40	0–67	0–294
ban only	0–19	0–45	0–100	0–569
both leucodepletion and ban	0–17	0–40	0—67	0–257

epidemics as one might expect. However, increasing secondary mean incubation periods correspond to decreasing epidemic sizes because age and non-vCJD post-transfusion mortality limits the number of future donations. Another factor limiting the epidemic size is the carrier state probability. Figure 2*d* shows the relationship between the probability of entering a carrier state and the total vCJD deaths. If the probability of entering a carrier state is close to one, the size of the epidemic is limited because most of those infected enter a carrier state and thus cannot die of vCJD. In contrast, if this probability is small then the majority of infections develop into clinical cases, with worst-case scenarios resulting if additionally the mean secondary incubation period is roughly twice that for primary infections.

If the epidemic size is expressed in terms of numbers infected rather than clinical cases then a slightly different picture emerges. From figure 2*e*, it can be seen that longer secondary incubation periods do not correspond to small epidemics, but that the worst case epidemic for longer mean incubation periods plateaus. In figure 2*f*, the distribution of epidemic sizes is independent of the value assumed for the probability of entering a carrier state, and so there is a weaker relationship between the number of people infected and clinical case numbers for scenarios in which the probability of entering a carrier state is close to 1. The level of the plateau comes partly from the rates and age distribution of blood use in the UK.

Now consider the effect of interventions. If leucodepletion was the sole intervention and reduced the transmission coefficient by 40%, from table 1 it can be seen that the worst-case scenario is reduced by 66% to 294 deaths. The subsequent introduction of the ban on donations from transfusion recipients causes a more modest reduction in the worst-case scenario from 294 to 257 deaths (assuming the ban is 90% effective). If the ban was introduced without leucodepletion then the worst-case scenario would lead to 569 deaths, a reduction of 35% from that without interventions.

For more biologically plausible scenarios in which the mean incubation period for transfusion-acquired cases is similar or shorter than that for primary cases, the maximum number of future cases is substantially smaller (46 compared to 171). Similarly, in scenarios where a large proportion of those infected enter a carrier state (>85%) the upper bound is 53 compared

with 202 without interventions. The basic reproduction number has the same upper bound ($R_0=1.35$) in all scenarios and biologically plausible scenarios because high basic reproductive numbers tend to occur in scenarios in which there is a high probability of entering a carrier state. In all scenarios, a large proportion (30–60%) of clinical cases are expected to occur in those aged over 60 years (not shown), and the current prevalence of transfusion-acquired infection is expected to be low (16–27 infections per million population).

It is useful to know whether the pattern of the epidemic over the coming years can provide any clues as to the extent of transfusion-acquired infection. Figure 3 shows the evolution of the primary- and transfusion-acquired epidemics for two simulated scenarios in the absence of any interventions. In the first (figure 3*a*), R_0 is very low with few transfusion-acquired clinical cases over time and a continued decline in primary cases from 2005 to 2010. In the second scenario (figure 3*b*), $R_0>1$ and the clinical case distribution peaks in 20 years time, with a long tail stretching over decades. These results suggest that it would be difficult to identify the degree of transfusion-acquired infection on the basis of the cases alone in the coming years. Caution is also required in drawing firm conclusions from a second peak, given the other remaining uncertainties in the epidemiology of vCJD, in particular, the possibility of wider genetic susceptibility.

5. DISCUSSION

We have produced upper bounds for the size of the vCJD epidemic via blood transfusion, given current understanding of the disease and making many pessimistic assumptions about the disease epidemiology. An upper bound of the order of hundreds rather than millions of deaths clearly demonstrates that the data we have are informative about the scale of the epidemic. Our results demonstrate that there is unlikely to be a self-sustaining secondary epidemic of vCJD due to blood transfusions. This is particularly apparent when considering only biologically plausible scenarios. We also found that the early introduction of leucodepletion and the subsequent ban on donors donating were timely and effective interventions, leading to substantial reductions in the upper bound for the ultimate size of the secondary epidemic.

The major limiting factor for the secondary epidemic appears to be the rate at which blood is donated and used in transfusions, which is low enough to limit the potential for onward transmission. In addition, it appears that the age of donors (below 60 years) and the age of transfusion recipients (above 60 years) also limits the potential for a self-sustaining epidemic: after one generation of infections (from young to old), the chance of onward infection (from old to young) is reduced. The basic reproductive number for transmission via this route is further reduced owing to the reduction in life expectancy of those infected via blood transfusions owing to competing morbidities.

It is important to acknowledge that our results must be interpreted carefully. The problem of predicting the secondary vCJD epidemic is one in which uncertainty is attached to most of the key parameters. Thus, it is not possible to provide fully robust predictions with the usual statistical rigour. What we do provide, under plausible assumptions regarding the transmission route, genotype, incubation period and carrier state for vCJD, together with assumptions about the effectiveness of current interventions, is a bound for the order of magnitude of the epidemic in the worst case.

The advantage of our sensitivity analysis approach is that all the sources of uncertainty are clearly set out and their combined effect on predictions quantified. However, there are sources of uncertainty we have not considered. While there are additional risks from blood components other than red blood cells (e.g. the past use of UK-derived pooled blood products such as the clotting factors received by haemophiliacs; Dolan 2006), the vast majority of blood use is for red cell transfusion. The important influence of absolute rates of blood use/donation in secondary epidemic dynamics would suggest that such additional risks could only be expected to modestly increase our upper bounds if included in our analysis. Additionally, we have not considered here that a secondary epidemic could arise via other routes of human-to-human transmission, in particular through contaminated surgical instruments. This risk has been considered elsewhere (Garske *et al.* 2006), but to fully assess the risk from human-to-human routes, further work will be required to combine these models because the overlap between human-to-human routes is substantial (approx. 40% of blood transfusions occur during surgery; Wells *et al.* 2002).

The ultimate aim of modelling work should be to provide robust estimates of the secondary vCJD epidemic via human-to-human transmission. The model results presented here demonstrate that one of the major uncertainties limiting assessment of the potential scale of this epidemic is the lack of data on the prevalence of preclinical and subclinical vCJD infection in the population. A large study is currently underway to better assess the prevalence of asymptomatic infection via detection of abnormal prion protein in tonsil tissues removed during routine operations. Recent findings may eventually shed further light on the relationship between genotype, susceptibility, incubation period and the carrier state (Ironside *et al.* 2006). As more cases emerge, further work will be undertaken to estimate the parameters of the mathematical model from case data and new data on infection prevalence. Using Bayesian statistical techniques, uncertainties such as those about the infection route for each case can be incorporated, and these robust estimates will be important in refining the sensitivity analysis presented here to predict the future scale of this major public health concern.

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APPENDIX A

A.1. Leucodepletion

As described in §3.3, the optimistic scenario is taken to be a 60% effective ban, corresponding to a 40% reduction in the transmission coefficient. Let $t^{\mathrm{L}}=16$ be the time at which leucodepletion was first introduced, and substitute all occurrences of β_2 in the model above by $\beta_2(t)=(0.6)^{i_{\mathrm{L}}}(t)\beta_2$, where $i_{\mathrm{L}}(t)=1$ if $t\geq t^{\mathrm{L}}$ or 0 otherwise.

A.2. Ban on blood donations

The ban excludes those who received blood at any time since 1980 from donating blood after 2004, i.e. $t\geq 24$. We assume (optimistically) this ban is 90% effective. We do not explicitly exclude those who receive blood but are not themselves infected because we assume any shortfall are offset by eligible donors from the susceptible population; nor do we explicitly exclude those transfusion recipients who were infected by the primary route because the number of such people is small. Let $t^{\mathrm{B}}=24$ be the time at which the ban on blood donations from transfusion recipients was introduced, then equation (3.4) can be rewritten as

$$U'(t)=\sum\nolimits_c X_c(t)\rho(a_{ct})P(a_{ct})^{i_{\mathrm{B}}(t)} - \sum\nolimits_c N_c(t)\phi(t,a_{ct})U(t)/V,$$

$$C'(t)=\sum\nolimits_{c,f}\left(Y_{c,f}(t)P(a_{ct})^{i_{\mathrm{B}}(t)}+(1-i_{\mathrm{B}}(t)Z_{c,f}(t)\right)\rho(a_{ct}) - \sum\nolimits_c N_c(t)\phi(t,a_{ct})C(t)/V,$$

where $P(a_{ct})$ is the proportion of those age a_{ct}, who have not received any blood since 1980, and $i_{\mathrm{B}}(t)=0.9$ if $t\geq t^{\mathrm{B}}$ or 0 otherwise. In practice, we assume that $P(a)\approx 1$ and so $Y_{c,f}(t)P(a_{ct})\approx Y_{c,f}(t)$ and $X_c(t)P(a_{ct})\approx X_c(t)$. The exclusion from March 2004 onwards of those who have received blood transfusions after 1980 from donating blood will mean the effective reproduction number (i.e. the basic reproduction number immediately following intervention) is close to 0.

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