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Mathematical Models for Estimating the Risk of vCJD Transmission

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1 Introduction

Transmissible spongiform encephalopathies (TSE's), also known as prion (proteinaceous infectious particles) diseases, are a group of fatal brain diseases that affect both animals and humans. They are characterized by long incubation periods, spongiform changes, and astrogliosis.

Infective prions propagate by refolding into abnormal structures which cause the conversion of normal protein molecules into the abnormally structured forms. These prions (TSE agents) are resistant to inactivation by conventional decontamination methods. They also resist all routine sterilization procedures commonly used in health care facilities. Because of the unconventional transmissions of these agents, they are of particular concern for public health.

Variant Creutzfeldt Jakob Disease (vCJD) is a human form of Bovine (Transmissible) Spongiform Encephalopathy or mad cow disease. Variant CJD is an infectious disease

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typified by long incubation periods and asymptomatic infections—two factors making epidemiological investigations particularly difficult. Two modes of infection of vCJD have been identified:

- Primary infections: associated with the ingestion of infectious materials (mainly BSE-contaminated beef),
- Secondary infections: associated with receiving blood from an infected blood pool (particularly through transfusions) and with the use of infected surgical instruments.

The number of cases of vCJD is relatively small, but its characteristic incubation period coupled with unconventional transmissibility has presented a challenge for parameter estimation and modeling dynamics. In spite of the fact that only one vCJD case has been detected in Canada (in 2002) it is important to study possible transmission scenarios. Indeed, outbreaks can potentially develop into epidemics, as the outbreak in UK (in the 1990's) has shown.

Since the epidemic course shows geographical differences, every country should assess its specific vCJD risk as a condition for developing a national blood supply strategy. A group was formed for this purpose in Germany in 2001, and its findings are available in [16].

To prevent secondary transmission through blood components, several countries have started to exclude recipients of blood transfusions from being donors. A recent study [7] investigated the effectiveness of this measure using a dynamic age-structured model based on German epidemiological data. An important question for us is whether Canada should ban recipients of blood transfusions from donating blood. On the one hand, this ban could prevent some new cases of the terrible disease vCJD; on the other hand, it would significantly decrease the number of blood units collected by Canadian Blood Services. To help us choose between these alternatives, we would like to predict the number of new vCJD cases that would be prevented if Canada were to enact this ban.

In this report, we use two models to describe the plausible evolutions of vCJD outbreaks in Canada. In the next two sections, these models and their underlying assumptions are thoroughly discussed. In Section 2 we use a classical compartmental model to describe the evolution of the infected population originated from primary infections and secondary infections. We examine possible parameter values and scenarios based on data. The roles of the two key transmission parameters are examined. Section 3 explores a stochastic model that could help predict the consequences of a vCJD-infected individual entering the Canadian blood-donor pool. Both simulation and analytical results are presented. Some brief concluding remarks appear in Section 4.

2 A Deterministic Model

The first basic deterministic time-continuous compartmental models to describe the transmission of communicable disease are contained in a sequence of three papers by Kermack and McKendrick in 1927, 1932 and 1933 [10]. These models have been generalized and a recommended introduction to the topic is provided in the first two chapters in [2].

The deterministic compartmental model can be directly translated into a Markovian stochastic version by reformulating the ordinary differential equations that describe the deterministic dynamics, as the transition probabilities ($+o(dt)$) of the process. In this underlying stochastic model the process has latent (if considering an SEIR model) and infectious periods that are exponentially distributed.

In this section we only explore the deterministic version of the vCJD infectious dynamics considering primary and secondary infections (via blood transfusion) and the sensitivity of outbreak to the change of some parameter values.

The analysis in this section aims to study the general characteristics and rough uncontrolled outbreak scenarios derived from infections by food intake and blood transfusion. The number of infected individuals is obtained in the long term with the purpose of exploring the evolutionary epidemic trends rather than forecasting outbreak outcomes.

2.1 Model. The population is subdivided into susceptible $S(t)$, primary infected (by beef consumption) $I_1(t)$, secondary infected (by blood transfusion) $I_2(t)$, and removed $R(t)$ individuals.

Compartmental models assume that individuals in the entire population mix homogenously, so the rate of interaction between two different subsets of the population is proportional to the product of the number in each subset.

Regarding the vCJD transmissibility in the infectious process, if we have an almost completely susceptible population we suppose that each infected beef cow infects β_1 individuals and that each infected individual annually transmits vCJD to β_2 individuals by blood transfusion.

We also assume that every individual becomes infectious immediately after being infected by either ingesting contaminated beef or receiving infected blood. This, added to the fact that individuals die just a few weeks or months after presenting vCJD symptoms, makes the infectious periods very similar to the illness's latent periods. Here we consider the two kinds of periods as equal.

We include two different incubation periods for primary and secondary cases. In both cases the periods are exponentially distributed but with means $1/\gamma_1$ and $1/\gamma_2$, respectively.

Due to the fact that the evolution of vCJD is long, it is important to introduce the demographical changes that occur in a population. The two demographical variables that we consider in this section are the births and deaths. We respectively denote as π and δ the crude annual birth and death rates in Canada.

Let $N(t)$ be the total population at time t. Since vCJD is a fatal disease, then $N(t) = S(t) + I_1(t) + I_2(t)$. Therefore the interactions of our compartmental model are depicted by Figure 1 and it is formalized by the following differential equations:

$$\frac{dS}{dt} = \pi N - \frac{\beta_1}{N} SC - \frac{\beta_2}{N} S(I_1 + I_2) - \delta S, \tag{2.1}$$

$$\frac{dI_1}{dt} = \frac{\beta_1}{N} SC - \gamma_1 I_1 - \delta I_1, \tag{2.2}$$

$$\frac{dI_2}{dt} = \frac{\beta_2}{N} S(I_1 + I_2) - \gamma_2 I_2 - \delta I_2, \tag{2.3}$$

$$\frac{dR}{dt} = \gamma_1 I_1 + \gamma_2 I_2, \tag{2.4}$$

where C is the number of BSE infected beef cases in Canada in a year. The term $\beta_1 SC/N$ in (2.1) and (2.2) describes the number of susceptible individuals who acquire vCJD by eating BSE infected meat. When $S \sim N$ then this number is equal to $\beta_1 C$ as described above. The expression $\beta_2 S(I_1 + I_2)/N$ in (2.1) and (2.3) describes the number of new infections by blood transfusion from infected individuals (either primary or secondary cases). Then if $S \sim N$ each infective originates β_2 new cases.

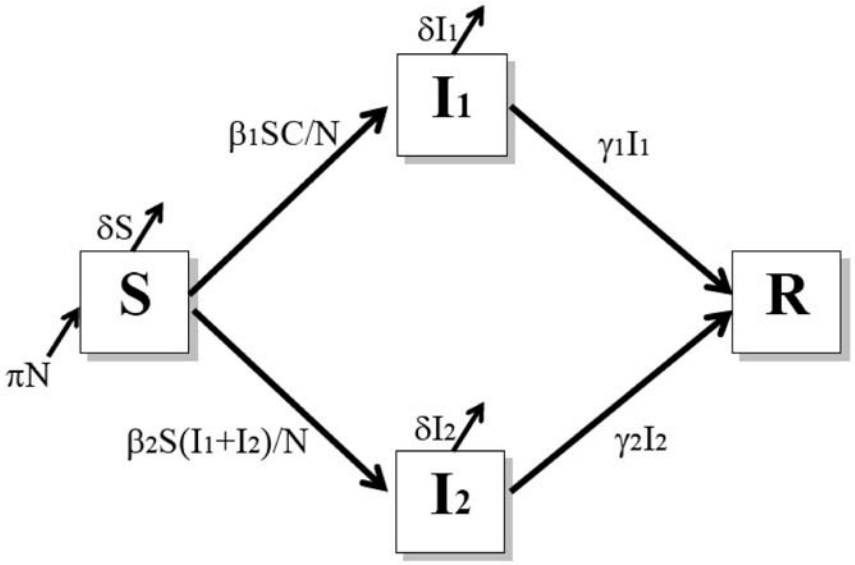


Figure 1 Interactions of the deterministic compartmental model.

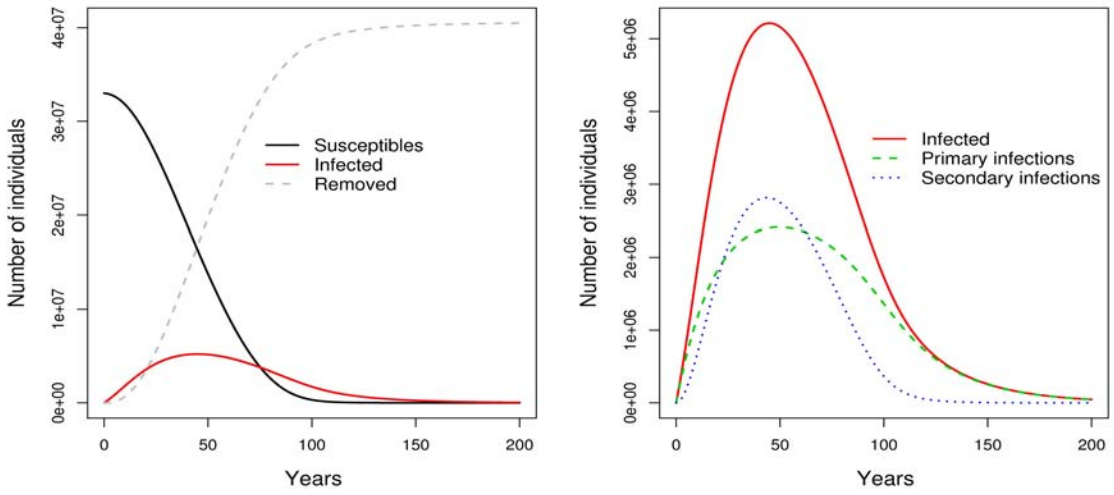
2.2 Parameters. Now we discuss the parameter values used to describe the infectious dynamics. Some infectious scenarios are explored in Section 2.4 by varying some of the parametric values.

Since 1993, one percent of the cattle have been tested in Canada and only 18 have been found to be infected with BSE [4]. On the other hand, according to *Canada Livestock and Products Annual 2007* [17], approximately 3,825,000 heads are slaughtered in Canada every year. If we assume that the 18 infected animals were uniformly found during these 16 years and that beef consumption over this period has been approximately equal to the 2007 levels, then the number of BSE cases during a year is close to $\hat{C} = 3,825,000 \times \alpha = 112.5$, where α is the estimated fraction of infected heads ($\alpha = 2.94 \times 10^{-5}$).

As stated in [15], the annual Canadian beef consumption in recent years has been approximately 23.3 kg per person. We know that a single animal provides between 140 and 200 kg of edible meat. Consequently, we calculate that a single BSE infected bovine can contaminate between 700 (140 kg/200 grams per meal portion) and 6,667 (200 kg/30 grams per meal portion) individuals. If we assume that each bovine provides 170 kg of edible meat and the individual portions are 65 grams (64.7 grams per day = 23.3 kg /360 days), the number of individuals infected by one diseased bovine would be 2,615.

Because the most dangerous parts of the animal are now eliminated from human consumption (those that contain sections of the central nervous system), the probability that an individual acquires vCJD by consuming meat from an infected animal decreases by half. Hence $\hat{\beta}_1 = 1,307$. In the next section we will explore some other values for this parameter.

In order to estimate β_2, we use a case study from Britain where 4 out of a total of 66 individuals who had received blood from a blood pool contaminated by a single infected



(a) (b)

Figure 2 Epidemic curves, (a) evolution of outbreak in Canada, (b) as in (a) except individuals are separated into primary and secondary infections.

donor contracted vCJD after their transfusion. Even though the donor pool size can vary, the number of affected individuals may remain similar due to factors such as dilution of the particles that transmit the disease (see [6]). We consider that the number of infected individuals originated from a single infected person who donates blood is constant and equal to 4.

Now, we also have that the fraction of people that donated blood in Canada in 2007 was 1/60, [3], and from those individuals 335,000 donated once, 90,000 donated twice, 110,500 donated between 3 and 5 times, and 14,500 donated 6 or 7 times during the year. Thus the expected number of times that the same individual gives blood in a year, is approximately 1.91. Hence the estimated new cases an infected individual originates in one year is $\hat{\beta}_2 = 2/60 \times 4 = 0.1333$.

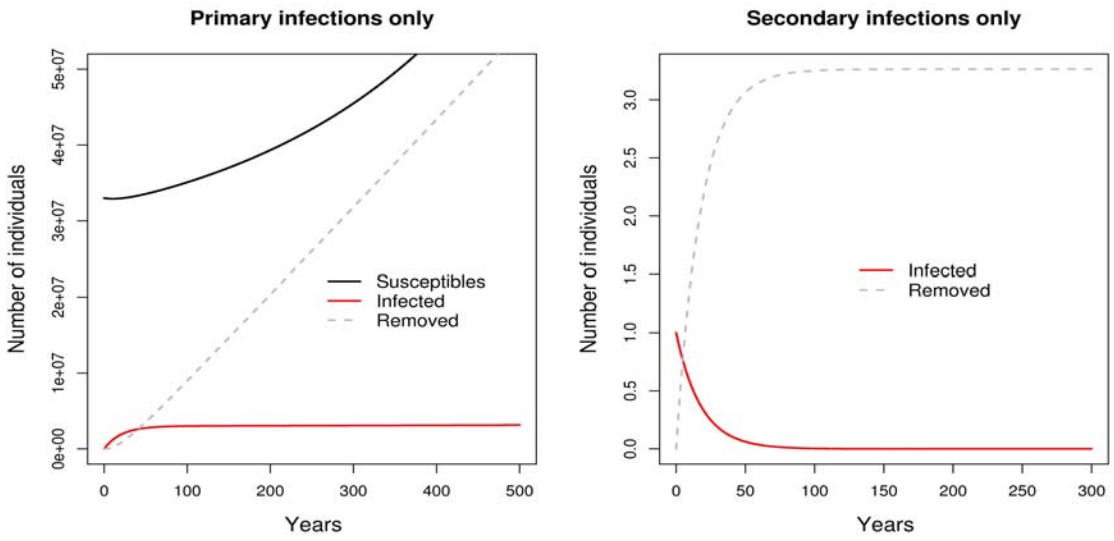
The estimated incubation periods in individuals that acquired vCJD by eating contaminated beef and blood transfusion has been estimated to be between 13 and 40 years and between 5 and 6 years, respectively. Using the midpoints of these intervals we have

$$\hat{\gamma_1} = \frac{1}{26.5} = 0.03773 \qquad \text{and} \qquad \hat{\gamma_2} = \frac{1}{5.5} = 0.181818.$$

From the demographical information in [14] we obtain the crude birth and death rate registered in 2007-2008:

$$\hat{\pi} = \frac{11.1}{1000} = 0.0111 \qquad \text{and} \qquad \hat{\delta} = \frac{7.2}{1000} = 0.0072.$$

2.3 Outbreak Evolution. Assuming that the parameters remain similar every year, the evolution of the outbreak in Canada (population with 33 million people) is as presented in Figure 2 (a). Here we assume that a single case by secondary infection is present at time 0.



(a) (b)

Figure 3 Epidemic curves for the cases of (a) primary and (b) secondary infections.

As shown in Figure 2(a), the epidemic curve reaches its peak at around year 50. While the number of infected individuals remains always less than 5,250,000, by year 200 the number of susceptible individuals decreases to the value of 162. Due to the natural population growth the total number of individuals that die with vCJD symptoms is 40 million.

Figure 2(b) decomposes the total number of infected according to primary and secondary infections. These two curves reach their peaks in the same year. As we will see, this is due to the fact that the incidence of secondary infections follows the incidence of primary infections, and both combined decrease the susceptible population to a level that causes the abrupt decrement in the number of infected cases after year 50.

To understand the interaction of the cases by primary and secondary infections in the outbreak we obtain the outbreak evolution considering that the vCJD can only be acquired by ingesting BSE infected meat (Figure 3(a)), and that infection can only be acquired by blood transfusion (Figure 3(b)).

In the first case we have a rapid increment in the vCJD incidence, and by year 100, 3.01 million people live with vCJD. After this date the increment is steady but slow. By year 500, the number of infected individuals is 3.148 million, and in spite of the fact that the susceptible population increases, a total of 55 million people would have died with vCJD symptoms.

Based on Figure 3(a) we can conclude that the infectious and removal rate (β_1 and γ_1), combined with the fixed birth and death rates would result in the event of vCJD becoming endemic in the population.

In contrast, under the second scenario (Figure 3(b)) we have that the outbreak dies out immediately after starting, affecting only 4 individuals. According to the model, an outbreak originated by secondary transmissions will remain small and this is explained by its basic reproductive number.

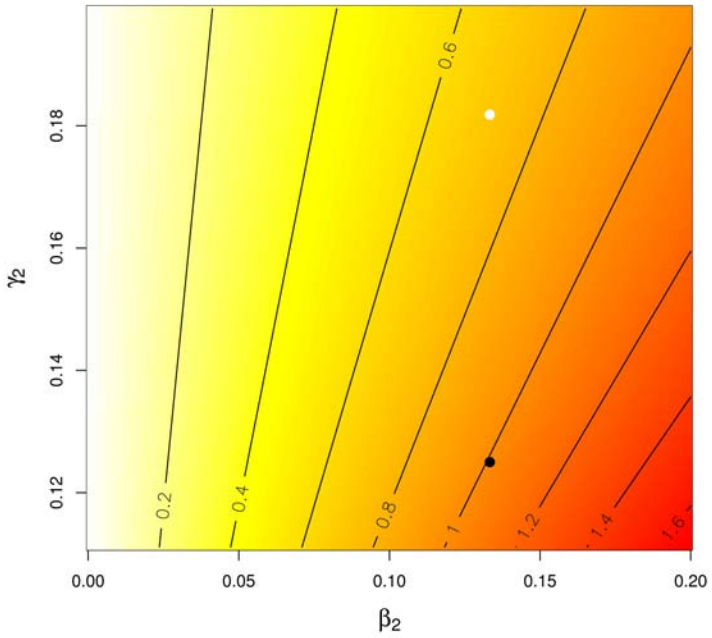


Figure 4 Basic Reproductive Number.

The basic reproductive number ($\mathcal{R}_0$) is defined as the (expected) number of secondary infections produced by an infective individual in a fully susceptible population [1]. This epidemic parameter is used to estimate the size of the population that is infected during an outbreak (final outbreak size). In a deterministic model, if $\mathcal{R}_0 < 1$ an outbreak affects only a reduced number of individuals but an epidemic will always develop if $\mathcal{R}_0 > 1$.

Based on this model, the basic reproductive number for secondary vCJD infections is

$$\mathcal{R}_0 = \frac{\beta_2}{\gamma_2 + \delta}.$$

For the values of $\beta_2 = 0.1333$, $\gamma_2 = 0.1818$ and $\delta = 0.0072$, the basic reproductive number is $0.7054 < 1$ (white dot in Figure 4). Consequently, in the absence of primary infections, all vCJD outbreaks would affect only a handful of individuals.

In order to better understand the sensitivity of this basic reproductive number in terms of β_2 and γ_2, we present the level curves of $\mathcal{R}_0$ in Figure 4. While the parameter β_2 can be modified with criteria that exclude vCJD exposed blood donors, the parameter γ_2 is directly linked to the evolution characteristics of infectious agents in the host. As depicted in Figure 4 the larger the value of β_2 the more sensitive $\mathcal{R}_0$ is to the changes in the incubation period. Considering incubations larger than 6 years, it is notable that for $\beta_2 = 0.1333$ (as before), the epidemic threshold $\mathcal{R}_0 = 1$ is reached for an incubation period of just 8 years ($\gamma_2 = 0.125$, black dot in Figure 4).

In 2002 one vCJD case was detected in Canada and no other case has been identified since then. The discrepancy between the observed and theoretical trends for outbreaks can be due to several reasons such as the effectiveness of the implemented control measures.

Table 1 Parameter values for the different scenarios.

values for β_1		values for β_2	
0.0000	697.0700	0.0000	0.4267
87.1330	784.2000	0.0533	0.4800
174.2700	871.3300	0.1067	0.5333
261.4000	958.4700	0.1600	0.5867
348.5300	1045.6000	0.2133	0.6400
435.6700	1132.7000	0.2667	0.6933
522.8000	1219.9000	0.3200	0.7467
609.9300	1307.0000	0.3733	0.8000

This male (under the age of 50), had multiple stays in the UK during the BSE outbreak and once classified as vCJD suspected, Health Canada immediately advised the hospital to remove from service the medical devices that were in contact with this person, until such time as a diagnosis be confirmed. Once the individual was confirmed with vCJD (through autopsy) the identified individuals who were exposed to the medical devices were advised not to donate blood, organs or tissue.

Another factor that can lead to an overestimation of the transmissibility by food intake is the actual existence of a non negligible latent period in beef cows, during which the animals are infected but not infectious.

2.4 Interaction of primary and secondary infections. With the aim to further study the impact of the interaction between β_1 and β_2 in the outbreaks, we construct a grid where we evaluate the function

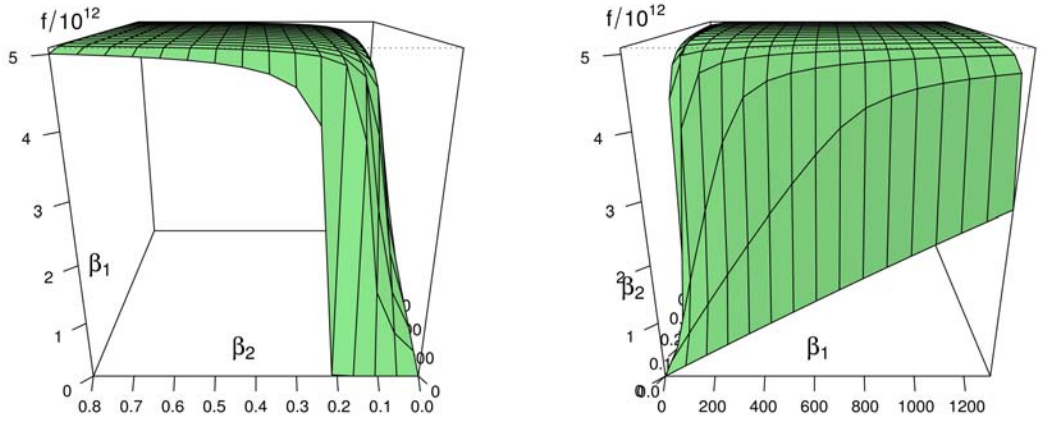
$$f(\beta_1, \beta_2) = \sum_{t=0}^{m} \left(S_{(0,0)}(t) - S_{(\beta_1,\beta_2)}(t) \right),$$

where $S_{(0,0)}(t)$ and $S_{(\beta_1,\beta_2)}(t)$ are the number of susceptible individuals in the population at day $t = \{0, 3.6, 2(3.6), \ldots, n(3.6), \ldots, m = 50001(3.6) \sim 500 \text{ years}\}$, when no transmission can occur ($\beta_1 = \beta_2 = 0$) and when the vCJD outbreak has parameters (β_1, β_2), respectively. This function is a measure of the outbreak severity and when it is evaluated in the grid with parametric values in Table 1, it can be depicted as in Figure 5. Here $f(\cdot, \cdot)$ is divided by 1×10^{12}.

As we can observe in Figure 5, when outbreaks are only due to primary infections, they tend to become epidemics very slowly as β_1 increases (first line in Figure 5(b)); however, combined with secondary infections, even modest increments of β_2 produce large outbreaks even for relatively small β_1.

In contrast, outbreaks due solely to secondary infections tend to be small for values of $\beta_2 < 0.19$. This is in agreement with the threshold value for the basic reproductive number and Figure 4 (when drawing a horizontal line at level of white dot). From Figure 5(a) we see that adding primary infections affects the value of $f(\cdot, \cdot)$ for $\beta_2 < 0.19$ but does not significantly increases the final epidemic size when the outbreaks are already developing into epidemics.

2.5 Discussion and Future Work. The first and largest vCJD outbreak occurred in the UK between 1995 and 2008 (with death prevalence peak during 1998/2000 [11]), but since then the disease incidence is rare. This last fact is to be celebrated, but unfortunately



(a) (b)

Figure 5 Two views of $f(\beta_1, \beta_2)/\left(1 \times 10^{12}\right)$

has led to the problem of not having enough information to fully understand and estimate the human transmission risks and the individual evolution of the illness. From the epidemiological point of view it is important to analyze the dynamics of vCJD to be able to rule in or out certain scenarios and evaluate the impact of control measures.

The first challenge that scientists have to face in order to refine their models is to improve the estimates of the parameters for the different transmission paths. The parameter estimation should also include the estimation for the exposed and infectious periods that animals and humans present when infected by each route.

The model presented here can also become more realistic by considering the specific rates that now are describing the population as one with homogeneous individuals. First, we can introduce the specific birth and death rates by sex and age (or age group, also called cohorts) to model the natural population growth over time. Second, since the probability of receiving/donating blood can significatively vary according to sex and age, it is desirable to incorporate the specific blood exchange for these groups.

The epidemic model in this section can also be generalized by introducing other secondary infections such as those derived from surgical cross contamination (as in [8]) and organ transplants. These two events can be closely related to blood transfusion but they may modify the probability of vCJD transmission.

In laboratory experiments, an epidemiologist may obtain more information about the impact of the pool blood size for the vCJD transmission and based on this new information update the blood transmission parameter that here we have considered fixed.

Since the outbreak size for the transmission via blood transfusion appears to be very sensitive to the incubation periods (Figure 4), the epidemic threshold ($\mathcal{R}_0 = 1$) may also be very sensitive to the asymmetry present in the incubation (and/or latent) period distribution. The authors of [8] estimated that the incubation-latent period for individuals that acquired vCJD via surgery is a random variable with gamma distribution. The model in [8]

is a compartmental model as the one presented here, and the authors introduce the gamma distribution for the incubation period adding as many stages in this period as the estimated gamma distribution.

Due to the fact that the vCJD latent period is long, it is important to incorporate the demographical changes over time. The model introduced here takes into account the crude birth and death rates, but it is important to incorporate as well the migration of susceptible and infected individuals.

The value of the model presented here lies in the ability of drawing general epidemic trend characteristics, but in order to predict the number of infected individuals (or susceptible or removed individuals) at a certain point in time it is not only necessary to obtain the forecasted specific rates (birth, death, migration, transfusion, beef consumption, etc.) but it is also important to incorporate the distribution of latent and incubation periods, and provide a measure of uncertainty to the predicted number (such as confidence intervals).

Finally, the stochastic model obtained after incorporating the illness stage distribution and infectious rates, can also become more realistic by relaxing the assumption that each individual in the same age-sex group is equally likely to be infected during an outbreak. The existence of "superspreaders" (such as individuals that donate blood significantly more times during a year) can importantly modify the outbreak evolution and the impact of control measures [12, 13, 5].

3 A Stochastic Model and Simulation

In this section we present a stochastic model, developed to help us better understand and forecast the dynamics of secondary vCJD infections through blood transfusions. The assumptions and computations that led to the numerical values for the model's parameters are discussed thoroughly in the following sections.

Our model provides a simple probabilistic representation of the blood-donor system, using conditional probabilities. It revolves around the following parameters:

- The probability of an individual donating blood
- The probability of contracting the disease after receiving a transfusion of contaminated blood
- The attrition (or mortality) rate of the infected population

It is possible to estimate the probability of an individual donating blood, from data collected by the Canadian Blood Services. In fact, the data allows us to estimate probabilities of an individual being a first-time and a repeat blood donor. Of particular relevance for our model is the fact that an individual who has donated in the past year has a higher probability of donating than an individual who has not. Past studies also provide clues on the rates of secondary transmission given an exposure to contaminated blood products.

We model the available parameters using conditional probabilities and build an iterative process to study the dynamics of the blood-donor system.

The parameters of our system include the probability of blood donation by an individual (see Table 2), the probability of contracting the disease upon receiving contaminated blood through a blood transfusion $P(c)$, and the attrition (or mortality) rate of an infected individual m. We define the attrition rate to include both the removal of an infected individual from the donor population due to the appearance of vCJD symptoms and the natural mortality. Using these parameters an iterative process was constructed to assess the effects of an infected individual on the Canadian blood-donor population.

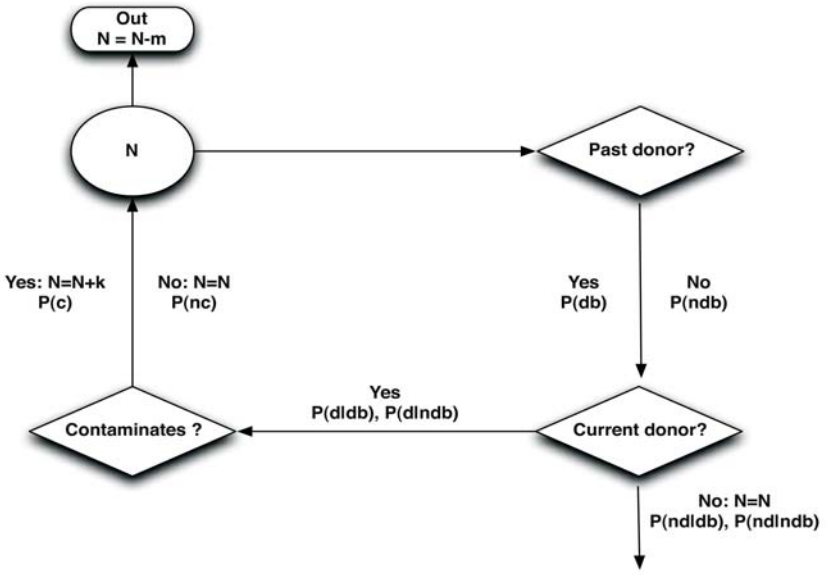


Figure 6 Flowchart of the algorithm with input and output variables given in Table 2.

The algorithm is explained in terms of the input and output parameters in Table 2, and its flowchart is displayed in Fig. 6.

The steps of the algorithm are as follows:

- **Step 0:** Introduce one infected individual into the blood-donor pool and set the number of infected individuals to be $N = 1$.

  As long as $t \leq T$ the following steps are performed in a loop as required to collect M samples of the count N.
- **Step 1:** Assess whether an individual was a past donor:
  - Assign the probability $P(db)$ for the individual of having donated in the past

Table 2 Input and output variables of the algorithm.

Input	
T	Duration of the simulation
$P(d\|db)$	Probability of an individual to donate blood given at least one previous donation
$P(nd\|db)$	Probability of an individual not donating blood given at least one previous donation
$P(d\|ndb)$	Probability of an individual donating blood given no previous donation
$P(nd\|ndb)$	Probability of an individual not donating blood given no previous donation
m	Mortality or attrition rate of infected individuals in the pool of donors
Output	
N	Number of infected individuals, in the pool of potential donors

  - Assign the probability $(1 - P(db))$ for the individual not having donated in the past

- **Step 2:** Determine if an individual donates at the current time

  If the individual has donated in the past:
  - Assign the probability $P(d|db)$ of donating
  - Assign the probability $P(nd|db) = 1 - P(d|db)$ of not donating

  If the individual is not a past donor:
  - Assign the probability $P(d|ndb)$ of donating
  - Assign the probability $P(nd|ndb) = 1 - P(d|ndb)$ of not donating

- **Step 3:** Determine if a donor contaminates one or more others
  - Assign the probability $P(c)$ of contaminating:
    - Compute the number of secondary contaminations C
    - Increment the number of infected individuals by $N = N + k$
  - Assign the probability $1 - P(c)$ of not contaminating:

  No further action

- **Step 4:** Compute the attrition in the pool of infected potential donors

$$N = N - mN$$

3.1 Numerical results and scenario analysis. Using the algorithm presented above, we ran our simulation over a (simulated) duration of 15 years, the approximate time over which individuals remain donors. Simulations were done using a 6-month time-step and iterated 30 times ($T = 30$). Finally, we repeated the whole process 10,000 times ($M = 10,000$).

The results are reported in Table 3.1 and in Figure 7. We see that the expected (mean) number of infected individuals in the pool of potential blood-donors begins with a value of 1 (by construction) and decreases to approximately zero, over the simulation period.

Table 3 Mean number of infected individuals in the potential donor pool and its standard deviation (Stdev.) with time.

Time	Mean	Stdev.	Time	Mean	Stdev.
1	1	0	16	0.1039	0.3051
2	0.8545	0.3526	17	0.0885	0.284
3	0.7373	0.4401	18	0.0763	0.2655
4	0.6354	0.4813	19	0.0664	0.249
5	0.5448	0.498	20	0.0586	0.2349
6	0.4654	0.4988	21	0.0493	0.2165
7	0.3992	0.4898	22	0.0425	0.2017
8	0.3393	0.4735	23	0.0363	0.187
9	0.2897	0.4536	24	0.0312	0.1739
10	0.2465	0.431	25	0.0266	0.1609
11	0.2102	0.4075	26	0.0231	0.1502
12	0.1813	0.3853	27	0.0197	0.139
13	0.1559	0.3628	28	0.0164	0.127
14	0.1311	0.3375	29	0.0139	0.1171
15	0.1191	0.3239	30	0.0161	0.1423
			31	0	0

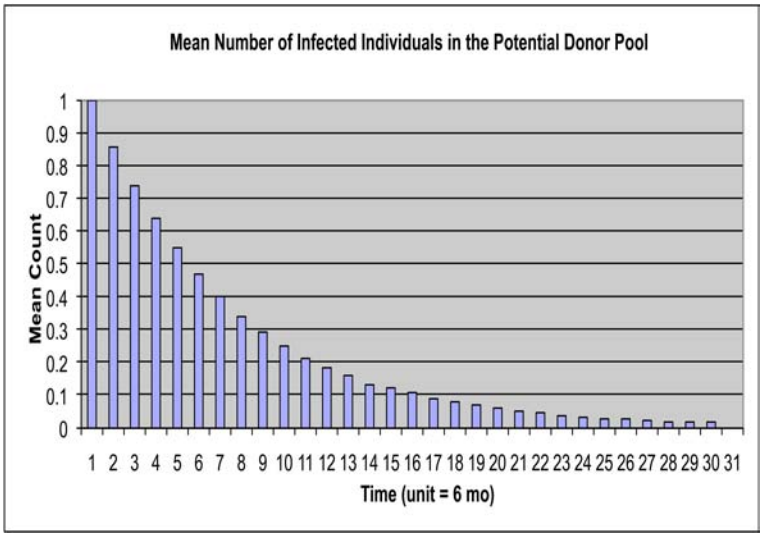


Figure 7 Number of infected individuals in the pool of potential donors

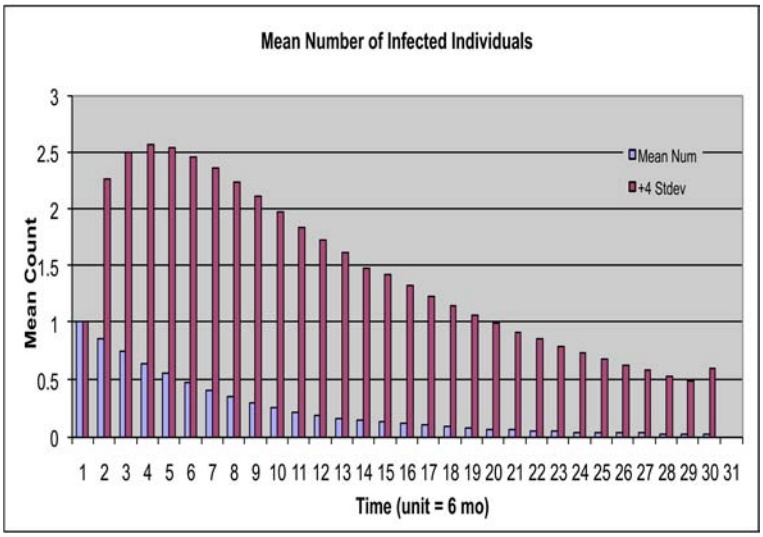


Figure 8 Number of infected individuals and results from the worst-case scenario

To better assess the potential effect of an infected donor entering the Canadian blood-donor pool we examined a "worst-case scenario", using the model presented above. The "worst-case" number of contaminated was defined as the mean number of infected individuals plus four standard deviations. This is a highly unlikely outcome, with a probability of occurring in the order of 10^{-5}, under the assumptions of our model. (Under the normal distribution, the probability of exceeding the mean by at least 4 standard deviations is of the order of 10^{-5}, i.e. 1-F(4) for the normal N(0,1).)

The results are shown in Figure 8. The *worst-case* estimate begins with $N = 1$ (by construction the standard deviation is 0) and attains a peak at approximately 2.5 individuals, after 2 years. The number of infected individuals then decreases over the remaining simulation period, except for a negligible increase in the 30th time-step.

The preliminary results for both the "mean" and "worst-case" scenarios suggest that the effect of an infected individual entering the blood-donor pool would be negligible on the total number of vCJD infections in the overall population. However, future work should focus on estimating the parameters and empirically validating the underlying assumptions of the model. Only then will we be able to rigorously evaluate the risk of vCJD transmissions and draw more complete conclusions.

3.2 Analysis of the Stochastic Model. In this section we present an analysis of the stochastic model described earlier in this section. The analysis will be based on a branching processes formulation.

Consider a single primary vCJD case (a person who acquired vCJD by eating meat infected with BSE). How many secondary cases of vCJD will occur as the result of blood transfusions from this primary case? (We shall count all secondary cases over all times after the primary infection occurs; we do not restrict the count to a single time period.) Some individuals may get vCJD by blood transfusion directly from the primary case; we shall say that such individuals comprise the "first generation" of secondary infections. Individuals in the first generation of secondary infections may donate blood to others, who may acquire vCJD as a result; we shall say that these people comprise the "second generation" of secondary infections. In general, for $k = 1, 2, \ldots$, individuals in the k^{th} generation may donate blood to others, and those people who acquire vCJD by transfusions from people in the k^{th} generation comprise the $(k+1)^{th}$ generation of secondary infections. We wish to study the total number of all of the secondary infections.

To formalize our model, we now define some random variables. Let N_0 denote the number of people who receive blood transfusions from our single primary infected person during his/her lifetime (after he/she becomes infected). Let p be the probability that a single transfusion from an infected person to a second person causes the second individual to become infected. For each $k = 1, 2, \ldots$, let X_k denote the number of secondary infections in the k^{th} generation. Then X_1 has the binomial distribution with parameters N_0 and p; we shall represent this by writing

$$X_1 \;=\; \mathrm{Bin}(N_0, p)\,. \tag{3.1}$$

(Note that this is a generalization of the usual definition of binomial distribution, since N_0 is a random variable instead of a constant. It is more correct to say that the conditional distribution of X_1 given the value of N_0 is binomial with parameters N_0 and p.)

Now consider people who receive transfusions from a given individual with secondary infection. The pattern of blood donation is different from that of our primary case, since people who receive transfusions are not a "typical" group within the population—e.g., they tend to be older and in poorer health. For a single person who has received a transfusion, the random variable N_T shall denote the number of people who receive blood transfusions from this person during his/her lifetime (subsequent to this person receiving the transfusion).

Formally, we can express the random variables X_k ($k > 1$) recursively as follows:

$$X_k \;=\; \mathrm{Bin}\left(\sum_{i=1}^{X_{k-1}} N_T^{(k-1,i)},\, p \right) \tag{3.2}$$

(where $\{N_T^{(j,i)}\}$ are independent, identically distributed copies of N_T; $N_T^{(j,i)}$ represents the number of recipients of transfusions from the i^{th} person in the j^{th} generation of secondary cases). Finally, let Y be the total number of secondary cases that are ultimately due to our initial infected primary individual. Then

$$Y \;=\; X_1 \,+\, X_2 \,+\, X_3 \,+\, \cdots \tag{3.3}$$

It is routine to show that the expected values of the above random variables satisfy

$$E(X_1) \;=\; p\,E(N_0) \tag{3.4}$$

and that

$$E(X_k) \;=\; p\,E(X_{k-1})\,E(N_T) \quad \text{ for } k > 1. \tag{3.5}$$

It follows that

$$E(X_k) \;=\; [p\,E(N_T)]^{k-1}\,E(X_1) \;=\; p^k\,[E(N_T)]^{k-1}\,E(N_0), \quad \text{ for } k \geq 1, \tag{3.6}$$

and that the expected total number of secondary infections (recall (3.3)) is

$$E(Y) \;=\; \sum_{k=1}^{\infty} E(X_k) \;=\; \frac{p\,E(N_0)}{1 \,-\, p\,E(N_T)}\,. \tag{3.7}$$

Public health officials may consider the policy of preventing any recipient of a blood transfusion from themselves donating blood. To assess the possible impact of such a policy, we shall calculate the number of secondary infections that could have been prevented with such policy. The first generation of secondary infections are not preventable in this way, but all subsequent generations of secondary infections are. The total number of infections preventable in this way (per primary infected individual) is $Y - X_1$, and its expected value is

$$E(Y - X_1) \;=\; E\left(\sum_{k=2}^{\infty} X_k \right) \;=\; \sum_{k=2}^{\infty} [p\,E(N_T)]^{k-1} p\,E(N_0) \;=\; \frac{p^2\,E(N_0)\,E(N_T)}{1 \,-\, p\,E(N_T)}\,. \tag{3.8}$$

Now we consider estimates for the values of p, $E(N_0)$, and $E(N_T)$.

For p, we use British data, in which 4 out of 66 known individuals developed vCJD after having received transfusions from a vCJD-infected donor. (The data is not perfect, because some recipients may have developed vCJD after being surveyed, and some may have acquired vCJD by other means.) This gives us the simple point estimate $\hat{p} \;=\; 4/66 \;=\; 0.061$. Even assuming that the data is perfect, we can ask for a 95% confidence bound for p. In other words, for what values of p is it true that $\Pr\{\, \mathrm{Bin}(66, p) \;\leq\; 4\,\} \;\geq\; 0.05$? It turns out that the largest such p is about 0.133. Therefore a 95% confidence bound on p is "$p \leq 0.133$."

For $E(N_0)$, we use the following information from the web pages of Canadian Blood Services (http://www.blood.ca; > Media Room > Resource Center > Quick Facts):

(*i*) about 3.7% of Canadians donate blood at some point in their lives. This says that about 1.2 million Canadians ever donate blood.

(*ii*) There are about 450,000 active donors in Canada (about 1.4% of the population).

(*iii*) About 900,000 units of blood are donated annually in Canada.
(*iv*) A unit of blood can go to up to three recipients.
(*v*) Each active donor gives an average of 2.18 units per year.

We use the above information to obtain a rough estimate of $E(N_0)$ (a better estimate can be obtained by a more careful analysis of available data from Canada Blood Services and Héma-Québec), as follows. Of the 1.2 million Canadians who ever donate blood, some are currently active donors and some are not. If L is the lifetime average number of units given by one donor, then in a given year the average amount given by one donor is $L/80$, where we have used 80 years as the average lifetime of one donor. (Of course, active donors will tend to give more than this, and inactive donors will give nothing, but the average will be $L/80$.) Therefore Canadians give about $1,200,000 \times L/80$ units per year; by (*iii*), this number equals 900,000, so we deduce that $L \approx 60$. In view of item (*iv*) above, we shall assume that each unit goes to an average of two recipients. Therefore the expected number of recipients of transfusions from a single person is

$$E(N_0) = \begin{pmatrix} \text{probability that} \\ \text{the person is} \\ \text{a blood donor} \end{pmatrix} \times \begin{pmatrix} \text{number of} \\ \text{units} \\ \text{per donor} \end{pmatrix} \times \begin{pmatrix} \text{number of} \\ \text{recipients} \\ \text{per unit} \end{pmatrix} \tag{3.9}$$

$$\approx 0.037 \times 60 \times 2$$

$$\approx 4.4. \tag{3.10}$$

Finally, for $E(N_T)$, we modify our calculations as follows.

- 53% of transfusion recipients die within 5 years of receiving the transfusion. It seems reasonable to assume that a negligible number of these 53% donate blood after receiving the transfusion (due to age and/or poor health). So among transfusion recipients, we expect that the fraction of future donors is at most 47% of the global proportion of 3.7%, which comes to 1.7%.
- For someone who acquires secondary vCJD by transfusion, the average incubation time (i.e. the time until symptoms appear) is 3 years. We assume that such a person would not donate blood after vCJD symptoms appear. Active blood donors among this group (which is precisely the group that concerns us when it comes to passing along the infection) would give an average of 2.18 units per year (by item (*v*) above) for an average of three years, for a total of about 6.5 units.

Therefore, the analogous calculation to (3.9) is

$$E(N_T) \approx 0.017 \times 6.5 \times 2 \approx 0.22\,.$$

We can now insert the above estimates into (3.7) to give the number of infected secondary cases from one person:

$$E(Y) = \frac{0.061 \times 4.4}{1 - 0.061 \times 0.22} = 0.27, \quad \text{using } p = 0.061, \tag{3.11}$$

$$E(Y) = \frac{0.133 \times 4.4}{1 - 0.133 \times 0.22} = 0.60, \quad \text{using } p = 0.133. \tag{3.12}$$

Finally, from (3.8) we compute the expected number of cases that would be prevented if all recipients of blood transfusions could be prevented from themselves donating blood:

$$E(Y - X_1) = \frac{(0.061)^2 \times 4.4 \times 0.22}{1 - 0.061 \times 0.22} = 0.0037, \quad \text{using } p = 0.061, \tag{3.13}$$

$$E(Y - X_1) = \frac{(0.133)^2 \times 4.4 \times 0.22}{1 - 0.133 \times 0.22} = 0.018, \quad \text{using } p = 0.133. \tag{3.14}$$

These estimates are much smaller than those in (3.11) and (3.12).

3.3 Conclusions and Future Work. In this section, we created a probabilistic model of the blood-donor system. We then simulated the effect of an infected individual on the entire Canadian blood-donor pool, which we found to be quite small. Analytic results supported this conclusion.

Our preliminary simulation results suggest that an infected individual entering the blood-donor pool would only have negligible effects. As shown in Table 3.1, the expected number of infected individuals in our population never exceeds one. Even in our worst-case scenario, the total number of infected potential donors never exceeds 2.5 (see Figure 8).

The calculations of (3.11)–(3.14) show that each primary infected individual has a significant chance of infecting others by blood transfusion, but the chances are much smaller that a secondary infected individual will infect others. Because only transmissions from secondary individuals could be avoided under a policy that would ban recipients of blood transfusions from donating blood, only a minimal number of cases would be prevented. Indeed, given the small number of primary cases in Canada and the precautions now in place, such a policy may only prevent a few transmissions per century. The concern with implementing such a policy is that it would have a significant impact on the number of eligible donors, which in turn could have serious ramifications for people in need of blood donations.

We must emphasize that although our findings from the stochastic model may seem reassuring, even in the worst-case scenario, they are far from rigorous. Given the very strong assumptions that were required to build our model and the lack of data available to estimate model parameters, it is not possible to draw any definitive conclusions based on our numerical results.

4 Concluding Remarks

We have presented two different simple models for vCJD transmission by blood transfusion. Both models indicate that transfusions alone are unlikely to cause more than a few infections, unless the number of primary cases increases.

To improve our models, future work should pursue data collection, empirical estimation of the model parameters, and examination of the underlying assumptions of our frameworks.

Further improvements could also include examining susceptibility to vCJD infection by age group and iatrogenic infections introduced through surgical instruments. Regarding the latter, it may be worthwhile to conduct experiments to quantify the transmission of prions from an infected surgical instrument after repeated sterilization procedures.

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