Transmissible Spongiform Encephalopathies Advisory Committee
24th Meeting, March 14, 2013

Topic

Preliminary results from FDA's quantitative risk assessment of the vCJD risks potentially associated with the transfusion of red blood cells in the U.S.

Issue

FDA seeks advice from the Committee on the inputs, model structure and interpretation of its draft Risk Assessment for the risk of vCJD from red blood cells in the US.

Summary

Variant Creutzfeldt-Jakob disease (vCJD) is a fatal human neurodegenerative disease with a long asymptomatic incubation period. Dietary exposure to beef products from cattle infected with bovine spongiform encephalopathy (BSE) is the likely cause of human vCJD. Individuals with symptomatic vCJD infection have abnormal prion protein present in brain and lymphoid tissue. Infectivity is also present in blood. A total of three symptomatic vCJD infections and one asymptomatic infection transmitted by red blood cell (RBC) transfusion, as well as one case of asymptomatic infection linked to use of plasma-derived Factor VIII, have been reported in the United Kingdom (U.K.) (Llewelyn et al., 2004; Peden et al., 2010; Peden et al., 2004; HPA, 2006; HPA, 2007).

Since some U.S. blood donors may have been exposed to the BSE agent during travel or residence in the U.K. or certain other countries, these individuals may have unknowingly been infected with vCJD. In order to reduce the risk of transfusion-transmitted vCJD (TTvCJD), FDA has recommended deferral of certain blood donors with a history of travel to or residence in the U.K. and other countries in Europe (FDA, 2010a). However, some risk to transfusion recipients remains because of the limitations of deferral policies.

FDA conducted a risk assessment to estimate the probability of vCJD infection and clinical disease acquired through RBC transfusion in the U.S. In developing its risk assessment model, FDA used two different values for the assumed prevalence of vCJD in the U.K. A high prevalence input was derived from data on abnormal prion protein reactivity detected in anonymous tonsil and appendix samples from the U.K., and a low prevalence input was based on modeling of vCJD in the U.K. Results obtained with the FDA model used for risk assessment are highly dependent on this particular prevalence input. The predicted risk with transfusion of one RBC unit using the high prevalence input is 1 infected unit in 480,000 units transfused (2.5 to 97.5 percentile: 1 in 4.3 million to 1 in 110,574) and using the low prevalence input is 1 in 134 million (2.5 to 97.5 percentile: 0 to 1 in 8.7 million).

Based upon a comparison of the respective model outputs using the high and the low UK prevalence estimates against the current epidemiology of symptomatic vCJD infection (number of reported vCJD cases in the US, and TTvCJD cases in the UK and France), and taking into consideration current scientific uncertainty regarding the significance of the U.K. appendix data,

FDA believes that the model output based on the low UK prevalence assumption is more likely than that based on the high UK prevalence assumption to represent the risk of TTvCJD in the U.S.

FDA seeks the advice of the committee on whether or not the data inputs, model structure, assumptions, and results are reasonable, and whether they agree with FDA's interim interpretation that the risk of TTvCJD in the U.S. is likely to be very small.

Background

Dietary exposure to beef products from BSE-infected cattle is the likely cause of primary vCJD (Bruce et al., 1997; Hill et al., 1997). vCJD is a fatal human neurodegenerative disease with a long asymptomatic incubation time. Individuals with symptomatic vCJD infection have abnormally folded prion protein (PrPTSE) present in brain and lymphoid tissue. Infectivity is also present in blood, given that several cases of TTvCJD have been observed in the U.K. Therefore, a blood donor, unknowingly infected with vCJD and healthy at the time of donation, could potentially donate infectious blood. As of December 2012, a total of 227 vCJD cases have been recognized worldwide, of which 176 cases were reported from the U.K. and 27 cases from France (two French vCJD cases are currently alive). The risk that donors of RBC in the U.S. may acquire vCJD infection through consumption of U.S. beef is thought to be negligible, because BSE has been detected in so few U.S. cattle. In particular, there have been only four reported U.S. cases of BSE: three in U.S.-born cattle and one in a cow imported from Canada (CDC, 2012; USDA, 2013). In addition, none of the three cases of vCJD recognized in individuals in the U.S. appears likely to have resulted from U.S. exposure: two cases occurred in long-time U.K. residents and a third occurred in a recent immigrant from Saudi Arabia. However, some U.S. blood donors might have been exposed to the BSE agent during travel or residence in the U.K. and other countries with increased BSE risk.

In 1999, consistent with advice from the Transmissible Spongiform Encephalopathies Advisory Committee (TSEAC), FDA recommended precautionary deferral of blood and plasma donors who had traveled or lived for six months or longer in the U.K. during the period from the presumed start of the BSE outbreak in 1980 until the end of 1996, when the U.K. had fully implemented a full range of measures to protect animal feed and human food from contamination with the BSE agent (TSEAC, 1999). In 2002, FDA recommended enhancing the vCJD geographical donor deferral policy by reducing the time that an otherwise suitable blood donor might have spent in the U.K. from six to three months (FDA, 2002). FDA also recommended deferring donors who had spent five or more years cumulatively in France or other countries in Europe listed by the USDA as either having had BSE or having had a significant risk of BSE, and donors with a history of blood transfusion in the U.K. after 1979. In 2010, FDA issued a revised guidance document to include deferral of blood donors transfused in France since 1980 (FDA, 2010a).

No cases of TTvCJD have been identified in the U.S. However, some risk to the recipients of blood and blood products may exist. From 2003 to 2010, FDA conducted risk assessments for potential risk of vCJD transmitted via U.S.-licensed plasma-derived products, factor VIII

(pdFVIII) to patients with severe hemophilia A or von Willebrand disease (type-3 vWD) and via U.K.-manufactured factor XI to a small group of U.S. patients who participated in an investigational drug study. The risk assessment and their revisions were presented at TSEAC meetings in 2006, 2009 and 2010. Based on the results of these risk assessments, FDA concluded that "the risk of vCJD transmitted via plasma-derived products is highly uncertain, but likely to be extremely small" (FDA, 2006a; FDA, 2006b; FDA, 2010b). The considerations for the assessment of vCJD risk for plasma-derived products vary somewhat from those for RBCs. During manufacturing, plasma from thousands of donors is pooled for processing, and a unit of plasma from a single infected donor has the potential to contaminate a large batch of product that may be transfused into hundreds of patients. However, plasma fractionation and other purification steps significantly reduce risk by removing most of the infectious vCJD agent from the final purified product. By contrast, the risk from an RBC unit is different because it is not processed and is collected from a single donor and most often administered to a single recipient. Thus, the TTvCJD risk for an RBC unit is likely to be higher for a single recipient than that for a person treated with a plasma derivative.

Cases of TTvCJD have been documented in the U.K. during the past ten years. A total of three symptomatic vCJD infections (HPA, 2006; HPA, 2007; Llewelyn et al. 2004) and one asymptomatic infection transmitted by RBC transfusion (Peden et al., 2004), as well as one case of asymptomatic infection linked to use of plasma-derived Factor VIII, have been reported (Peden et al., 2010). In addition to these epidemiologic data, there are also informative data on the number of individuals potentially exposed to vCJD derived from the immunohistochemical examination of thousands of archived surgical specimens. In particular, studies have examined lymphoid tissues, including tonsil and appendix, since they are known to have detectable abnormal prion protein (PrP^{TSE}) in symptomatic individuals dying with vCJD. An initial study including 12,674 evaluable appendectomy and tonsillectomy specimens from the U.K. found accumulations of the abnormal prion protein in three appendectomy specimens, providing an estimate of 237 vCJD infections per million population (95% CI 49-692 per million persons) (Hilton et al., 2004). A further study in 63,007 anonymous tonsil specimens from the U.K. found no abnormal prion protein when screened by a relatively insensitive immunoassay (Clewley et al., 2009), but reevaluation of a subset of the same tonsil specimens with a more sensitive immunohistochemical technique yielded an inconclusive positive result (de Marco et al., 2010). A second appendix survey using immunohistochemistry detected abnormal PrP in 16 of 32,441 U.K. samples, leading to a final mean estimate of 493 possible latent vCJD infections per million persons (95% CI: 282-801 per million persons) in the U.K. (HPA, 2012).

The significance of the findings from the tonsil and appendix studies is not fully known. The appendectomy findings may have identified a group of individuals who will eventually develop symptomatic vCJD after a time to onset dependent, at least in part, on the *PRNP* codon-129 genotype. Almost all individuals symptomatic with vCJD to date have been methionine-homozygous (MM) at *PRNP* codon 129. However, one individual of the MV genotype was diagnosed with vCJD, though tissue never became available to confirm the diagnosis by testing for PrP^{TSE} (Kaski et al., 2009). It is believed that at least some infected non-MM genotypes will eventually develop vCJD later. Since the appendix survey potentially reflects the highest prevalence of latent infection in the U.K. population demonstrated to date, data from this study was used in the model presented subsequently as the "high-prevalence" estimate.

Because the data from the appendix survey were de-identified, it is difficult to learn whether any individuals with abnormal prion protein detected in the appendix later developed symptomatic disease; preliminary current analysis suggested that none have so far (HPA, 2012). To date, efforts to transmit vCJD agent from the reactive appendices to experimental animals have not been informative. In addition, considering the apparent discordant results of the tonsil and appendix surveys, and given the epidemiology of overt cases of vCJD in the U.K. to date, it is possible that the finding of PrP^{TSE} in appendices represents cross-reactivity with another protein, rather than detecting the misfolded PrP generally associated with the infectious TSE agent in tissue. Finally, even if appendiceal involvement truly indicates vCJD infection, the time that must elapse for infectivity to appear and circulate in blood is unknown. In short, it remains unknown whether the findings of the U.K. appendix survey reliably indicate the true prevalence of latent vCJD infections in the U.K. population, and if so, how many persons with latent vCJD infection will ultimately develop overt disease, or whether the blood of some latently infected persons contains the transmissible agent. U.K. authorities have offered precautionary responses to each of those questions (HPA, 2012).

FDA Risk Assessment for Transmission of vCJD via RBC Transfusion

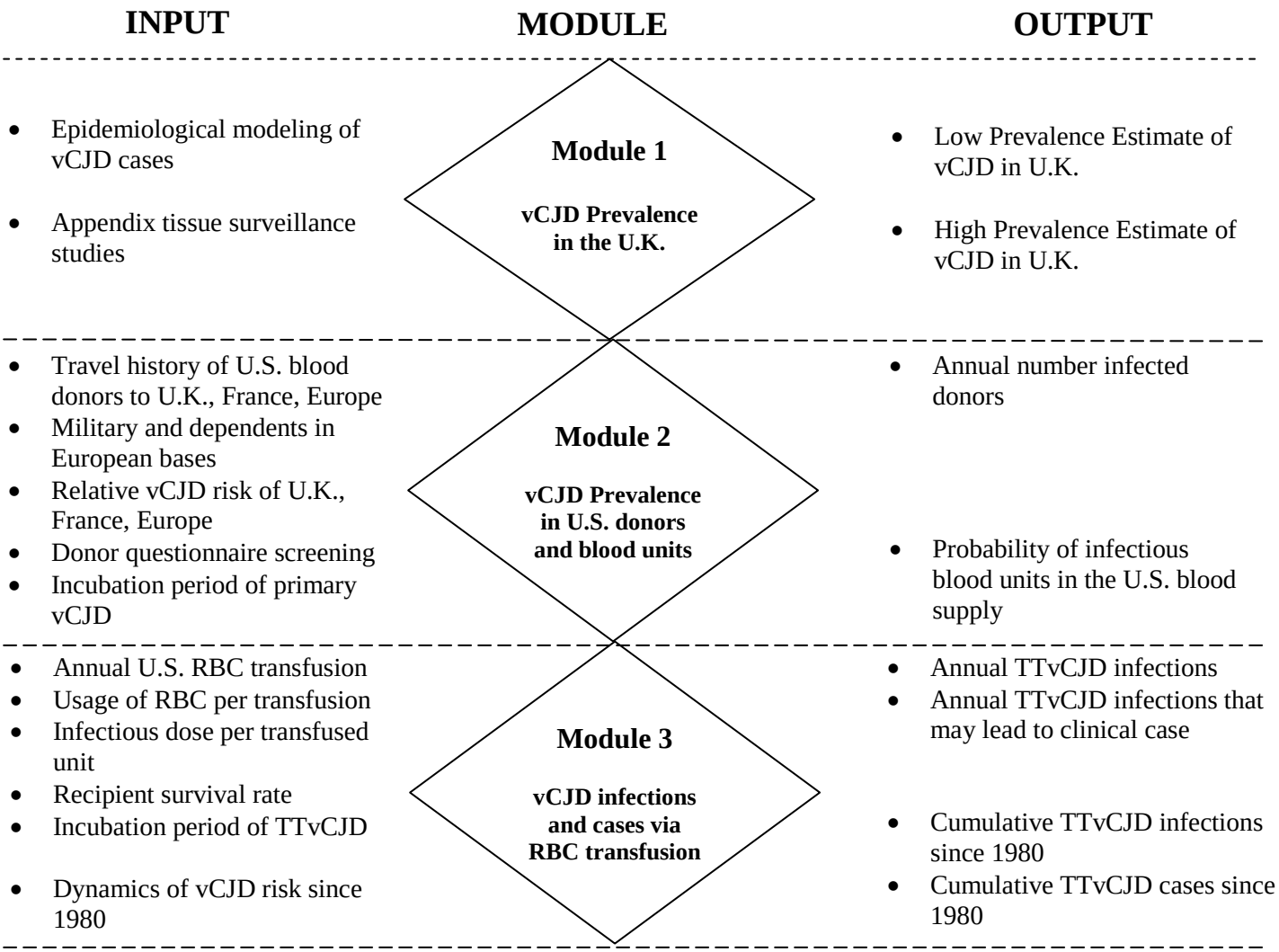
FDA conducted a risk assessment to explore the potential risk of vCJD transmission through RBC transfusion. The RBC risk assessment model estimated the annual risk of TTvCJD infections for the year 2011 and the number of infections that may progress to clinical cases in the future. The risk assessment model also estimated cumulative numbers of infections and clinical cases for the years 1980 through 2011 resulting from RBC transfusion. To better understand whether the model used generated reasonable estimates of vCJD infections and cases, FDA compared the results from the model to the number of observed vCJD cases in the U.S. and the observed TTvCJD cases in the U.K. and France.

I. Overview of the FDA Risk Assessment Model

The FDA developed a computer-based simulation model consisting of three modules (Figure 1). The U.K. vCJD prevalence is estimated in Module 1; U.K. prevalence provides the foundation of the model used to generate other critical prevalence estimates. The estimated prevalence is applied in Module 2 to generate estimates of vCJD prevalence for France, for other countries in Europe and for U.S. military personnel posted to bases in Europe. vCJD risk is then estimated for U.S. blood donors who have traveled to these countries since 1980. The risk for a U.S. blood donor is calculated as a proportion composed of travel time spent in the destination country (where the donor may have been exposed to the BSE agent) versus risk for a permanent resident who is assumed to have lived in the destination country for all 16 years of the whole risk period (at which point the resident's risk is equivalent to the country's vCJD prevalence). FDA assumed the risk period in the U.K. began in 1980, when the epidemic of BSE is thought to have started in the U.K., and to end in 1996 when strict risk control measurements were rigorously implemented in the U.K. The use of 16 years as the exposure interval for other countries in Europe represents a simplified approximation, reflecting the belief that the predominant portion of the risk in these countries had been reduced since 1996 because of the ban on U.K. beef exports and the reduced

risk from U.K. beef itself. This proportion is then multiplied by the vCJD prevalence for the country or region to obtain the vCJD prevalence for the U.S. donor. Accordingly, the model incorporates estimates of vCJD prevalence for the destination country; donor travel data such as destination, year and duration; and the efficiency of U.S. donor deferral policies in removing infected donors to generate the probability of vCJD infection of a U.S. blood donor(s). In Module 3, one model output estimates the number of possible TTvCJD infections among U.S. RBC transfusion recipients for the year 2011 based on the total annual number of blood donations and transfusions, amount of blood used per transfusion and the quantity of infectious agent per unit of blood; a second output provides estimates the number of TTvCJD infections that may progress to clinical cases (accounting for the incubation period of the disease and post-transfusion survival of the RBC recipients). Finally, the number of infections for the year 2011 is extrapolated for the number of infections for the individual year between 1980 and 2011 and then summed to generate a cumulative estimate of the number of TTvCJD infections and cases.

Figure 1. Exposure Assessment Model Diagram



Most model inputs (assumptions) are statistical distributions representing the variability and uncertainty associated with the input variables. These are shown in Table A-1 of the Appendix. Many of the input distributions or values used in this risk assessment are the same as those used in the previous FDA pdFVIII Risk Assessment (FDA, 2010b). However, some inputs have been updated based on new scientific research data and information (Table 1). Monte Carlo simulation was applied to integrate variability and uncertainty of all model inputs by randomly selecting a single input value from a statistical distribution of each input variable, applying the appropriate mathematical functions to generate a result for each iteration or run of the model. The model was run tens of thousands of times and the results/output was assembled in a final aggregate distribution. The outputs of the distributions are described using the mean and the 2.5th and 97.5th percentiles.

Table 1. Summary Update of Input Assumptions for Current FDA RBC Risk Assessment (2013) from Previous FDA FVIII-vCJD Risk Assessment (2010)

Input Name	**Current FDA RBC Risk Assessment (2013)**	**Previous FDA FVIII Risk Assessment (2010)**	**Justification**
U.K. vCJD Low Prevalence Estimate	1.7 per million* (0.2-3.7 per million)	~4.5 per million	Current Low Prevalence Estimate used in the FDA RBC Risk Assessment (2013) used updated epidemiological model by Garske and Ghani (Garske and Ghani, 2010). Previous FDA FVIII Risk Assessment model (2010) Low Prevalence Estimate was generated using epidemiological model by Clarke and Ghani (Clarke and Ghani, 2005).
U.K. vCJD High Prevalence Estimate	493 per million* (282 - 801 per million)	267 per million * (55 - 779 per million)	Current High Prevalence Estimate used in the FDA RBC Risk Assessment (2013) was updated to include new results from surveys with a much larger number of appendices (HPA, 2012b). Previous High Prevalence Estimate for the FVIII Risk Assessment model (2010) was generated based on the first appendix study (Hilton et al., 2004).
Relative risk for France	10% (of UK)	5% (of UK)	Current relative risk for France in the FDA RBC Risk Assessment (2013) was updated to reflect the increased rate of cases in France relative to the UK. Accordingly, we increased the Relative Risk of France to 10% in this Red Cell Risk Assessment. Previous FDA FVIII risk assessment (FDA, 2010b) we assumed the Relative Risk for France is 5% of the UK risk.
Risk for France	1980 - 2001	1980 - current	Current risk for France in the FDA RBC Risk Assessment (2013) was updated to account for additional BSE and human food safety control measures implemented in France since 2001 (Afssa, 2007). Accordingly, we reduced the number of years in the risk window period for France to include the years 1980 through 2001. Previous FDA FVIII Risk Assessment (FDA, 2010b) assumed a risk period for France ranging from 1980 to present.
Incubation period for primary vCJD in MM	Lognorm distribution: Mean=15 years,	Gamma distribution: Mean=15 years,	Current incubation period for primary vCJD in MM persons in the FDA RBC Risk Assessment (2013) was updated and the 5th percentile value was changed based on CDC's assumption that the minimum incubation

	Median=12 years 5th =9 years, 95th =35 years	Median=12 years 5th=5 years, 95th=35 years	period for vCJD in MM is 9 years. No Gamma distribution fit the required mean, medium, 5th and 95th, therefore, the Gamma distribution was replaced by Lognorm distribution.
Incubation period for primary vCJD in non-MM	Lognorm distribution: Mean=35 years, Median=32 years 5th =23 years, 95th =55 years	Gamma distribution: Mean=35 years, Median=32 years 5th=25 years, 95th=55 years	Current incubation period for primary vCJD in non-MM persons in the FDA RBC Risk Assessment (2013) was updated and the 5th percentile value of 23 years was calculated by summing 9 years (5th for MM) plus 14 years (the time delay on the appearance of the first MV case from that of the first MM case). No Gamma distribution fit the required mean, medium, 5th and 95th, therefore, the Gamma distribution was replaced by Lognorm distribution.
Infection dose in blood of infected donors	**ID per transfused unit** **(**1 transfused unit=500 ml**)** Triangular distribution (min, most likely, max) of 0.56, 0.75, 0.96	**ID_{50} per ml blood** Lognorm distribution Min=0.1 5th perc =2 median=12 95th perc =30 Max=1000	We recently reported a statistical analysis of published data from sheep transfusion experiments and U.K. Transfusion Medicine Epidemiology Review suggesting that the infection dose in infected blood is likely to be lower than previously assumed (Gregori et al., 2011). In our FVIII risk assessment we assumed a higher probable dose of infectious agent in blood of humans incubating vCJD based on published rodent studies.
Donor age	10-year age shifting to reflect aging of the donor populations	Age reported in a U.S. blood donor travel survey conducted in the year 2000	Donor travel data used in FDA model was collected approximately 10 years ago. In Red Cell Risk Assessment donor age was shifted by 10 years to reflect current donor age in 2011. In previous FVIII Risk assessment model we used donor age reported in the donor travel survey.

*mean value with 95% confidence interval in parentheses

Module 1- vCJD Prevalence in the U.K.

This module estimated vCJD prevalence in the U.K., which in turn was used as the basis for estimating vCJD prevalences in France and other countries in Europe. These prevalence values were then used to estimate the risk of vCJD infection in U.S. blood donors who traveled to the U.K., France and other countries in Europe as a proportion based on the time spent in the country versus a permanent resident who lived for the entire 16 years of the simplified risks period (using risk period for the U.K. 1980-1996 as reference). Because of the considerable uncertainties associated with estimating vCJD prevalence, we derived two estimates of U.K. vCJD prevalence using two different data sources. The FDA computer model calculated risk outcomes stratified by these two prevalence estimates. The discrepancy between these two prevalence estimates contributed the greatest amount of uncertainty to the final risk estimates – more uncertainty than for any other parameters used in the model.

<u>Low Prevalence Estimate:</u>
Epidemiological modeling by a U.K. research group (Garske and Ghani, 2010) predicted 100 (95% CI: 11-220) primary cases remaining after 2010. Since 1996 the U.K. has implemented a full range of measures to protect animal feed and human food from contamination with the BSE infectious agent. Accordingly, FDA assumed no primary vCJD infections were acquired in the U.K. after 1996, and all predicted cases after 2010 were incubating in 2011. Given a total U.K. population of about 60 million, the estimated number of future vCJD cases was translated to a

mean prevalence of approximately 1.7 asymptomatic vCJD infections per million U.K. population (95% CI: 0.2-3.7 infections per million) in year 2011.

High Prevalence Estimate:
This estimate is based on the detection of accumulated abnormal prion protein (PrP^{TSE}) in tissues of the lymphoreticular system. After an initial finding of three PrP^{TSE} positive appendices out of 12,674 stored tonsil and appendix tissues from U.K. patients in 2004 (Hilton et al., 2004), a subsequent study tested 32,441 archived appendix specimens and found 16 positive specimens (HPA, 2012). The prevalence with a mean estimate of 493 infections per million persons (95% CI: 282-801 per million persons) calculated based on the second study was recently endorsed by the U.K. Advisory Committee on Dangerous Pathogens TSE Risk Assessment Subgroup (ACDP 2012).

Module 2- vCJD Prevalence in U.S. Blood Donors and Blood Units

This module estimates the annual number of U.S. blood donors who were at risk of vCJD infection because of travel to the U.K., France and other countries of Europe, who may have been exposed to the BSE agent, infected with vCJD and carried vCJD infectious agent in their blood at the time of donation. The outcome of the module provides the probability of an infectious blood unit entering the U.S. blood supply for transfusion.

First, the module calculated the annual number of U.S. blood donors who were at risk of vCJD infection due to travel to or residence in the U.K., France and other countries of Europe using data from a blood donor travel survey (TSEAC, 2000). The survey was conducted by American Red Cross (ARC) in the year 2000, collecting information on blood donors and their history of travel to the U.K., France and other countries of Europe during a risk period between 1980 and 1996 (TSEAC, 2000). FDA modeled risk for four groups of U.S. donors: (1) donors who traveled to or lived in the U.K. during the years 1980-1996, (2) donors who traveled to or lived in France during the years 1980-2001, (3) donors who traveled to or lived in other countries in Europe since 1980, and (4) donors deployed to a U.S. military base in Europe during the years 1980-1996.

Second, the module calculated the risk of vCJD infection of U.S. donors based on their age, destination, year and duration of travel. The module integrated estimates of UK vCJD prevalence (from Module 1) and the relative risk for France, other countries in Europe, and U.S. military personnel posted to bases in Europe (relative risk for UK, France, other countries in Europe and military bases are 1, 0.1, 0.015 and 0.35, respectively) to derive the vCJD prevalence for the different at-risk countries. Relative risk of specific at-risk countries was determined based on factors such as the number of reported vCJD cases in humans, the amount of beef imported from the U.K., the number of domestically acquired case of BSE in cattle, and other factors (TSEAC, 1999). The model allocated risk to each individual year in the 16-year risk period (1980- 1996) for the U.K. by assuming that the risk of exposure in a specific year was in proportion to the number of BSE cases reported in that year. The model further assumed that the risk of exposure was in proportion to the duration of stay in the at-risk countries, and that donors who had

cumulative stays of 5 years or longer in an at-risk country during the years between 1980 to 1996 had the same risk as a full-time residents of that country.

Third, the module calculated the total number of infected donors, the number of donors whose blood contained infectious vCJD agent at the time of donation and the probability that a blood unit might have contained the infectious agent in 2011. The FDA model assumed vCJD agent most likely first appears in the blood of infected persons during the last 75% of the incubation period (that is, after 25% of the incubation period has elapsed). The infectivity might first appear, at the earliest, during the last 90% of the incubation period (that is, after 10% of the incubation period has elapsed) and at the latest after 50% of the incubation period has passed. Therefore, only a portion of infected donors may actually have infectious agent in their blood at the time of donation. The model also incorporated the risk reduction effect of FDA's recommended donor deferral policies. The FDA model assumed the efficiency of the donor questionnaire to identify at-risk donors (and remove them from the donor pool) to range from 85% to 99%. The vCJD donors who actually donate were either not deferred by current FDA recommendation because of limitations in the screening such as short-term travel that falls below FDA guidelines or failure to recall travel, among other explanations.

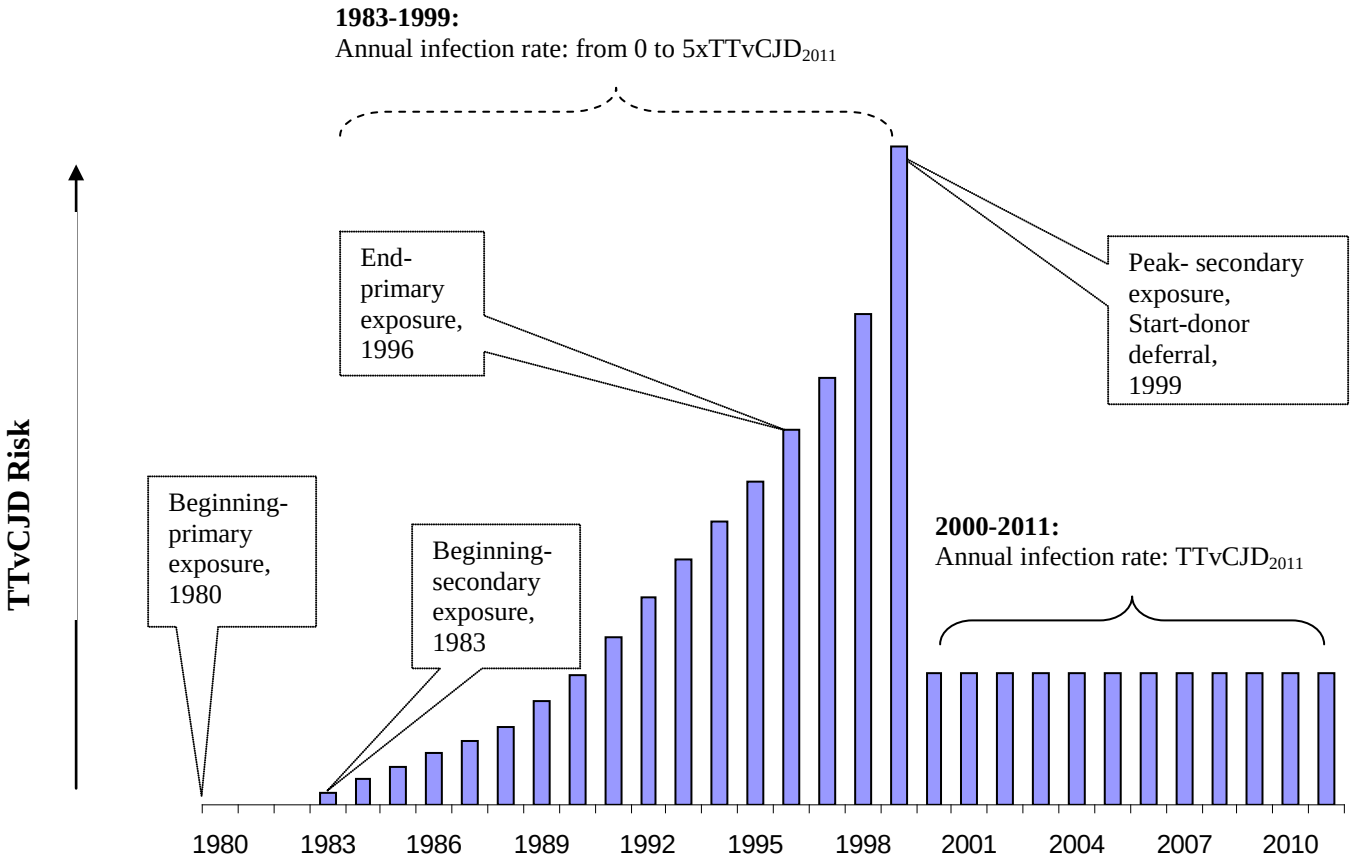
Module 3- vCJD Infections and Cases in the U.S. via Blood Transfusion

Incorporating data and information on U.S. blood donation and transfusion (Anderson et al., 2007; HHS, 2009), this module calculated the probability a U.S. RBC recipient would receive a RBC unit containing an infectious dose based upon the estimated vCJD prevalence in the U.S. blood supply (calculated in Module 2). As explained in a published analysis of data from the U.K. Transfusion Medicine Epidemiological Review (TMER, 2013), FDA assumed that a unit of infectious RBC would likely contain a mean of 0.75 infectious doses (ID) with a range of between 0.56 and 0.96 ID (Gregori et al., 2011). The module calculated the annual number of TTvCJD infections acquired in the year 2011 and further calculated the number of these infections that may progress to clinical cases after adjustment for post-transfusion survival. Extrapolating from the incubation time for the development of vCJD following consumption of BSE-contaminated beef, FDA assumed the incubation period for TTvCJD in persons of the MM genotype as a mean of 10 years with a range of 6-20 years, the incubation period for TTvCJD in persons of the non-MM genotype being a mean of 20 years with a range of 16-30 years. Infection was assumed to progress to an overt clinical case of vCJD only when patient's survival exceeds the incubation period.

The module also calculates the cumulative number of TTvCJD infections acquired since 1980 and the cumulative number of TTvCJD clinical cases that should have been observed (Figure 2). FDA assumed there was a three-year delay in the appearance of infectious agent in the blood of an infected person from the time of infection (since it is assumed that infectious agent does not appear in blood until 25% of the 12-year median incubation period has elapsed). TTvCJD risk emerged in the U.S. in year 1983 (three-year delay from beginning of risk of BSE exposure in 1980), peaked in 1999 (three-year delay from 1996, the end of risk period for food-borne vCJD in the U.K.), was reduced by approximately five-fold (as indicated by model result) after 1999 because of implementation of current donor deferral policy (80% risk-reduction provided by donor deferral), and then remained unchanged after 2000. The total cumulative number of

clinically overt TTvCJD cases expected to have been observed during the years 1980 through 2011 was calculated (taking into account the incubation period of TTvCJD and post-transfusion survival rate).

Figure 2 Graphic Representation of Calculations Used to Estimate Cumulative Risk for TTvCJD in the U.S. During the Years 1980 Through 2011



II. Model Outputs for U.S. Risk of TTvCJD

The FDA RBC risk assessment estimates the potential number of vCJD infections acquired through RBC transfusions in the U.S. during the year 2011, and the number of those infections that progress to clinical cases. The risk assessment also estimates the total number of cumulative vCJD infections predicted to occur between 1980 and 2011 and the number of clinical cases predicted to occur by 2011. The mean, 2.5th and 97.5th percentile values shown in Table 2 briefly summarize of the aggregate output distributions generated by the model.

Table 2. Model Results Showing the Mean vCJD Infection Risk per RBC Transfusion, the Mean TTvCJD Risk for the Year 2011 and the Total Mean Cumulative Risk for the Years 1980 Through 2011 in the U.S. (2.5th-97.5th percentiles shown in parentheses).

		Annual risk (2011)		Cumulative risk 1980-2011	
	Risk per RBC transfusion	**Infections**	**Clinical cases**	**Infections**	**Clinical cases**
Low prevalence (1.7 infections per million)	1 in 134 million (0 to 1 in 8.7 million)	0 (0-0)*	0 (0-0)*	0.8 (0-0)*	0 (0-0)*
High prevalence (493 infections per million)	1 in 480,000 (1 in 4.3 million to 1 in 111,000)	6 (0-27)	1 (0-5)	210 (0-942)	9 (0-47)

*The (2.5th-97.5th) values of (0,0) indicate that the predicted risk is zero or nearly zero. Specifically, for at least 97.5% of the model runs there are zero infections or clinical cases predicted.

Using the low vCJD prevalence assumption, the model estimated that the chance of receiving an infected unit in a transfusion is a mean of 1 in 134 million. The estimate with the high vCJD prevalence assumption resulted in a mean of 1 in 480,000. The model also estimated an annual risk of zero TTvCJD infections for the year 2011 with the low prevalence scenario and six TTvCJD infections with the high prevalence scenario. The TTvCJD infections acquired in 2011 would lead to 0 and 1 clinical case for low and high prevalence estimates, respectively. The model also estimated a mean of approximately one cumulative infection and zero clinical cases when the low prevalence estimate was used, and a mean of 210 infections and 9 possible clinical cases when the high prevalence estimate was used.

III. Model Validation: Model Predictions versus Observed cases

1. Primary vCJD cases in the U.S.

To better understand whether the model used generated reasonable estimates of vCJD infections and cases, we compared the results from the model to the number of observed vCJD cases in the U.S. For this model validation, we extrapolated model results for the number of vCJD cases predicted for the U.S. blood donors and adjusted the number to reflect the larger general U.S. population. We then predicted the total cumulative primary vCJD cases in the U.S. population since 1980 to compare with number of cases actually observed. Three vCJD cases have been reported in the U.S. since 1980. Based on their history of residence, CDC attributed all three cases to infection acquired outside the U.S. (CDC, 2010). The model predicted cumulatively a mean of one case of vCJD in the U.S. since 1980 when the low prevalence estimate was used and 256 cases when the high prevalence estimate (Table 3) was used. The model predictions derived

using the low prevalence estimate was generally consistent with the three vCJD cases actually reported in the U.S. to date; using the high prevalence estimate, the model predicted many more overt clinical cases than have actually been observed.

Table 3. Observed and model-Predicted Mean Numbers of vCJD Cases in the U.S. (2.5th-97.5th percentiles shown in parentheses)

Observed cases*	**Model Prediction (cases)**	
	Low Prevalence Estimate (1.7 infections per million)	**High Prevalence Estimate** (493 infections per million)
3	1 (0-8)	256 (0-528)

*****Note that CDC attributed all three cases to infection acquired outside of the U.S.

2. TTvCJD Cases in the U.K. and France

We further used the model to predict the numbers of cumulative TTvCJD cases in the U.K. and France for the years spanning 1980 through 2011 and compared the model predictions with observed numbers of TTvCJD cases reported in these two countries. Three clinical vCJD cases associated with blood transfusion have been identified in the U.K., and zero cases have been reported in France. For the years 1980 through 2011 the model predicted means of one and 289 cumulative TTvCJD cases for the U.K.; and zero and 33 cases for France using the low and high prevalence estimates, respectively (Table 4). Using the low U.K. prevalence estimate, the FDA model predicts numbers of cases of TTvCJD in the U.K. and France that are generally consistent with reported numbers of cases; the high U.K. prevalence estimate causes the model to overestimate greatly the number of clinical cases of overt vCJD attributed to transfusion to date.

Table 4. Observed and model-Predicted Mean Numbers of TTvCJD Cases in the U.K. and France (2.5th-97.5th percentiles shown in parentheses)

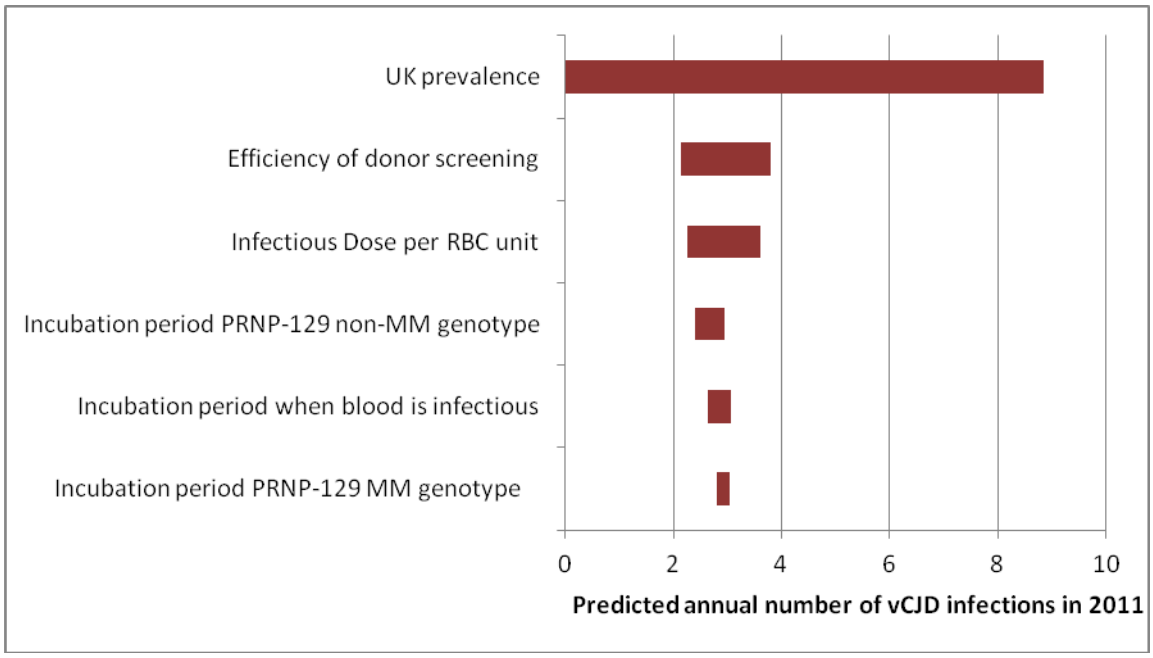
	Observed cases	**Model Predictions (cases)**	
		Low Prevalence Estimate (1.7 infections per million)	**High Prevalence Estimate** (493 infections per million)
U.K.	3	1 (0-7)	289 (3-925)
France	0	0.2 (0-0)*	33 (0-0)*

*The (2.5th-97.5th) values of (0,0) indicate that the predicted risk is zero or nearly zero. Specifically, for at least 97.5% of the model runs there are zero infections or clinical cases predicted

IV. Importance/sensitivity Analysis

An importance analysis was conducted to determine which inputs in the FDA RBC risk assessment model would have the largest impact on the model estimates of risk. The output variable selected for the importance analysis was the annual number of infections in the U.S. during the year 2011. Six input variables selected were the following: the U.K. vCJD Prevalence, Efficiency of Donor Screening, Infectious Dose (ID) in a unit of RBCs, Incubation Period Primary vCJD PRNP-129 MM genotype, Incubation Period when Blood is Infectious, and Incubation Period Primary vCJD PRNP-129 non-MM genotype. The statistical distributions of these model inputs were generated using assumptions based on limited data and information for human vCJD, published findings for other TSEs or other animal models; accordingly, they are less certain than the other model inputs. The importance analysis was conducted using Monte Carlo simulation sequentially varying each of the inputs from a low value to a high value while randomly selecting values of other inputs from statistical distributions. The low and high values of the inputs were the 2.5th and 97.5th percentile of input distributions used in FDA RBC risk assessment (see Table A-1 in the appendix). The variation between the results obtained for the low and high values were aggregated by input variable and plotted as a tornado chart (Figure 3). The results of the importance analysis indicated that the model input for the U.K. vCJD prevalence estimate had the greatest impact on the model estimation of the annual number of vCJD infections in the U.S. in year 2011. The risk driver of next greatest impact is the efficiency of donor screening.

Figure 3. Importance Analysis: Impact of Input Variables on the Model Outputs for the Annual Number of Infections in U.S. Donors in 2011



V. Uncertainties and Data Gaps

The largest uncertainty in this RBC risk assessment is associated with the estimates of U.K. vCJD prevalence. There is a large discrepancy between the low and high prevalence estimates used in the model, and both prevalence estimates have their limitations. The low prevalence estimate was calculated based on estimates of the future number of vCJD cases in the U.K. as predicted by an epidemiological model (Garske and Ghani, 2010) under many simplifying assumptions. Although these simplifying assumptions are a necessary part of vCJD case estimation efforts, they contribute considerable uncertainty to the final number of cases estimated by the model. Since the low prevalence estimate was derived based on modeling of vCJD cases, it is perhaps not surprising that it more accurately "predicted" the number of overt clinical cases observed. The high prevalence estimate, calculated using data from the appendix tissue surveillance study (HPA, 2012), also has its limitations. Among others, one major limitation is that neither the sensitivity nor specificity of the immunohistochemical tissue testing method used to identify persons who might be infected with the vCJD agent has been well established. In order to reduce the uncertainties for the very different U.K. vCJD prevalence estimates used in our model, more studies are needed to understand variations in infection and eventual progression of infections to cause overt vCJD. Many questions remain unanswered. These include the features associated with susceptibility of the human population and subpopulations to vCJD infection and disease, duration of the incubation period, and the dependency of susceptibility and incubation period on the age and genotype of persons exposed to the agent. This information is critical to reconcile prevalence estimates from the epidemiological model and tissue studies and for determining which of the two prevalence estimates more accurately reflect TTvCJD risk and should be used in risk assessment to support risk management decisions.

VI. Discussion

At first glance, the FDA risk assessment and the recently revised analysis by the UK Department of Health's Health Protection Analytical Team (HPA, 2013) might seem to have yielded quite different estimates for the future likelihood of transfusion-transmitted vCJD in the UK and US. The apparent differences largely result from different approaches we took to deal with the apparent inconsistency between (1) a high prevalence of latent vCJD infections in the UK implied by results of the PrP^{TSE} appendix survey, and (2) the actual number of clinically overt cases of foodborne cases of vCJD observed to date in the UK, France and the US and the absence of TTvCJD cases reported from France. It is clear to both FDA and UK authorities that the population of potentially vCJD-infected persons detected by the UK appendix survey (none of whom have been diagnosed with vCJD to date) must differ significantly from the population of 173 cases of overt vCJD (all of whom have died by the end of 2011). UK authorities responded by "calibrating" their risk assessments to accept the results of the appendix survey as possibly reflecting the true prevalence of latent vCJD infection but proposing several scenarios involving new assumptions (e.g. a small percentage of short incubation periods among infected

persons with the MM phenotype at PrP codon 129; or variable susceptibility to disease) that might explain the limited numbers of cases actually observed—an understandable precautionary approach, considering that the UK must confront a worst-case scenario in which many blood recipients may have already been exposed to the vCJD agent and others might be exposed in future transfusions. FDA's approach to resolution of the same inconsistency consisted in provisionally concluding that the possible worst-case prevalence (based on the UK appendix survey) is less likely than the substantially lower prevalence (based on clinical modeling of the UK epidemic), because the lower prevalence remains more consistent with cases observed to date. FDA nonetheless considers it prudent to keep an open mind about the true prevalence of latent vCJD infections in the UK and therefore potentially in the US. Biological explanations for this discrepancy, while credible, are speculative at this time. Also, we await a future determination of the specificity of the immunohistochemical test for PrP^{TSE} used in the UK appendix survey (a major technical limitation of which has been a lack of control appendix samples from a low-risk population). FDA also intends to run the model using assumptions modified as suggested by the UK scenarios.

Conclusions

For U.S. blood donors, the FDA model assumes that the major source of vCJD risk is dietary exposure during travel or residence in the U.K., France, or other countries in Europe since 1980. Donor deferral criteria, in place since 1999, are believed to have removed approximately 80% of the risk from donations by vCJD-infected persons. However, some infected donors are probably not deferred and might donate an RBC unit that could potentially transmit vCJD to a recipient. The FDA risk assessment model provides only an approximate estimate of the vCJD risk to individual transfusion recipients and the recipient population as a whole. Analysis of the risk assessment model indicates that the largest amount of inherent uncertainty comes from the estimate of U.K. vCJD prevalence. Based upon a comparison of the results of the high and low prevalence risk estimates with the current epidemiology of symptomatic vCJD infection, and taking into consideration current scientific uncertainty regarding the significance of the U.K. appendix data, FDA believes that the low prevalence risk model is more likely than the high risk model to be predictive of the risk of TTvCJD in the U.S. This supports the interpretation that the risk of vCJD from red blood cells in the U.S. is likely to be very small. However, given the current state of TSE science, estimates of the probability of vCJD infection or illness arising from exposure to the vCJD agent are still highly uncertain. This risk assessment nonetheless provides a platform for discussion of the research needed to improve model-based estimates of risk, evaluation of risk control measures, as well as risk communication that appropriately conveys the probabilities of the risks and the associated uncertainties.

Questions for the Committee

1. Does the Committee agree that the FDA Risk Assessment Model is structured appropriately?

   Please comment on any specific modifications to the model structure that FDA should consider.

2. Does the Committee agree with the inputs and assumptions used in the FDA Risk Assessment Model?
   Please consider any specific inputs or assumptions that FDA should consider.

3. Does the Committee agree that the validation exercises (predictions of primary vCJD case in the U.S. and TTvCJD cases in the U.K. and France) support FDA's conclusion that outputs of the FDA risk model based upon the low prevalence estimate of vCJD in the U.K. is likely to be more reliable than those based on the appendix survey?

4. Does the Committee agree with FDA's interpretation that the risk of TTvCJD in the U.S., while highly uncertain, is likely to be very small, based upon the results of the Risk Assessment Model in the context of other available evidence?

APPENDIX

Table A-1. Major input distributions used in exposure assessment model.

Variable name and description	Type of distribution or estimate used	Value and range	Reference
Prevalence estimates of vCJD in the UK 1. Low vCJD Case Prevalence (**$Pv_{vCJD\text{-}UK:}$**) 2 High vCJD Infection Prevalence (**$Pv_{vCJD\text{-}UK:(20\text{-}30yrs)}$**)	 Triangular distribution Triangular distribution	 Mean= 1.7 cases/million, 95% CI=0.2-3.7 cases/million Mean= 493 cases/million, 95%CI=282-801 cases/million	 (Garske and Ghani, 2010) (Hilton, 2004; HPA, 2012)
RR_{UK}: Relative vCJD exposure risk in the UK	Point estimate	1	(Williams, 2004)
RR_{FR}: Relative vCJD exposure risk in the France	Point estimate	0.10	(Williams, 2004)
RR_{EU}: Relative vCJD exposure risk in the other countries in Europe	Point estimate	0.015	(Williams, 2004)
RR_{DOD}: Relative vCJD exposure risk in the US military bases in Europe	Point estimate	0.35	(Williams, 2004)
$N_{DR\text{-}US}$: Annual number of blood donations in the US	Normal distribution	Mean=17 million SD = 189,000	(HHS, 2009)
$P_{DR\text{-}USa}$: Percentage of donors per US donor age group	Age specific percentage		(Forshee and Walderhaug, 2009)
$N_{DN\text{-}DY\text{-}USa}$: Average number of donations per US blood donor per year	Age specific rate	Min=1, Mean=1.4, max=1.5	(HHS, 2009)
IP_{MM}: vCJD Incubation time for primary case with the MM genotype	Lognorm distribution	Median=12 years, 90%CI=9-35 years Mean=15 years	(Collinge et al., 2006; Garske and Ghani, 2010; Ghani et al., 2003)
$IP_{MV,}$ IP_{VV}: vCJD Incubation time for primary case with the MV and VV genotype	Lognorm distribution	Median=32 years 90%CI=23-55 years Mean=35 years	(Collinge et al., 2006)
IP_{infbl}: Percentage of late incubation period start having infectious agent present in blood	Triangular distribution	Min=50%, Most likely=75%, Max=90%	(Houston et al., 2008)
$Perc_{MM}$: Percentage of UK population who are MM genotype	Point estimate	40%	(Alperovitch et al., 1999)
$Perc_{MV}$: Percentage of UK population who are MV genotype	Point estimate	50%	(Alperovitch et al., 1999)
$Perc_{VV}$: Percentage of UK population who are VV genotype	Point estimate	10%	(Alperovitch et al., 1999)
R_{SC}: Efficiency of US donor screening	Uniform	Min=85%, Max=99%	(TSEAC, 2005)
$N_{TF\text{-}US}$: Annual number of blood transfusions in the US (million)	Normal distribution	Mean=3.8 million, 95%CI= 3.5-4.0	(Anderson et al., 2007; HHS, 2009)
$N_{U\text{-}TF\text{-}US}$: Number of blood units per transfusion in the US	Empirical discrete distribution	95%CI=3.8-4.0	(Anderson et al., 2007)
ID: Infectious doses in RBC unit	Triangular distribution	Min=0.56, Mean=0.75, Max=0.96	(Gregori et al., 2011)
IS_{MM}: vCJD Incubation time for secondary transfusion-transmitted case with the MM genotype	Triangular distribution	Min=6 years, mean=10 years and Max=20 years	(Bennett P and Daraktchiev M, 2011)
$IS_{MV,}$ IS_{VV}: vCJD Incubation time for secondary transfusion-transmitted case with the MV and VV genotype	Triangular distribution	Min=16 years, mean=20 years and Max=30 years	(Bennett P and Daraktchiev M, 2011)
S_{uv}: Post-transfusion survival rate	Function of number years after transfusion ($Year_{post\text{-}transfusion}$)	0.61 - 0.028 x $Year_{post\text{-}transfusion}$	Regression model derived from UK data (Bennett P and Daraktchiev M, 2011)

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