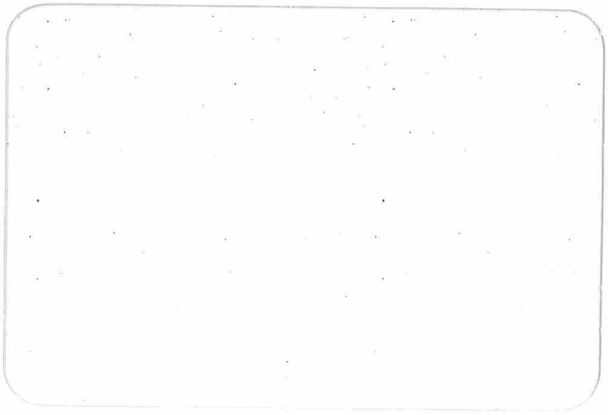

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Assessment of the Risk of Exposure to vCJD Infectivity in Blood and Blood Products

DRAFT FINAL REPORT

For the

Spongiform Encephalopathy Advisory Committee

and the

Department of Health

CONFIDENTIAL

Approved by: GRO-C

Philip J Comer
Director of Client Services

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Assessment of the Risk of Exposure to vCJD Infectivity in Blood and Blood Products

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Management Summary

This report is the result of a study that was initiated following a recommendation by the Spongiform Encephalopathy Advisory Committee (SEAC) that Government should consider a precautionary policy of extending the use of leucodepleted blood as far as is practicable and that risk assessments be carried out to inform decisions on any measures that may be necessary to protect recipients of blood and blood products from the transmissible agent of new variant Creuztfeldt Jacob Disease (vCJD). The implementation of precautionary measures recognises the potential for blood transfusion to act as a vehicle for further dissemination of the transmissible agent. The objectives of this study were defined as: to assess the magnitude of the risk that could result from the infective agent for vCJD being present in blood, to identify those groups of patients most at risk and to consider the effectiveness of possible measures to reduce the risks.

Whilst the available evidence for infectivity in blood is reviewed, and it is concluded that blood from people with vCJD may contain infectivity that could be transmitted through blood transfusions, this has not been proved conclusively, and *it is not the purpose of this assessment to provide an answer to this question*. The study is based on *the assumption* that infectivity is present in blood.

The study has considered the way in which blood is collected and processed, how the various blood components (red cells, fresh frozen plasma and platelets) are used for patient treatments, and the exposure of patients to plasma derivatives such as Factor VIII, Immunoglobulin (IgG) and albumin. The level of infectivity in whole blood, the blood components and the plasma derivatives has been estimated as a reference case, and the range of possible values identified. The exposure of a defined set of representative patient groups to vCJD infectivity has then been assessed to estimate the number of new infections and the number of vCJD cases that could result. The results have been presented in terms of the numbers of infections or cases per infected donation.

At each stage assumptions have to be made about the factors that characterise the infectivity and the way in which the disease develops. There is considerable uncertainty about many of these factors, and hence considerable uncertainty in the predicted results.

A sensitivity assessment has been carried out to identify the sensitivity of the results to variations in the main assumptions and the effectiveness of a number of risk reducing measures evaluated.

Conclusions:

1. It is not possible to make any firm predictions about the level of risk from any vCJD infectivity that may be present in the blood of people incubating the disease. With our current level of knowledge, it is not possible to draw any firm conclusion as to whether or not infectivity can be transmitted through blood transfusions or plasma derivatives and the number of people who may have been infected with vCJD is simply not known. For these reasons it has not been possible to estimate the absolute level of risk and the results have been presented in terms of the risks per infected donation.

2. The evidence for infectivity in blood is based on experiments with animal models that have shown that blood from an animal artificially infected with a TSE (transmissible spongiform encephalopathy) can be infective when inoculated intracerebrally into the same species. There has been a single report of a TSE being successfully transmitted by

blood transfusion in an animal model, but this result has not been verified or published. All other such experiments with animal models have failed.

3. Infectivity appears to be linked to white blood cells, but it may also occur in other components. Some experiments have shown significant levels of infectivity in plasma and this is not consistent with the hypothesis that infectivity is proportional to white cell content.

4. If it is assumed that blood from a person infected with vCJD can carry infectivity, and the level of infectivity is as suggested by the animal models, then the infectivity level in a full unit of red blood cells, platelets or plasma may be sufficient to cause infection. Patients receiving any of these products from an infected donation would therefore be at risk of infection. This conclusion seems to be valid across a wide range of assumptions regarding the infectivity of blood components.

5. The infectivity levels in certain plasma derivatives could be such that recipients of these products, if derived from a plasma pool containing a significant proportion of infected donations, would have a risk of infection. This result is highly uncertain, and varies significantly with the assumptions made about the level of infectivity and its distribution across plasma fractions.

6. The levels of infectivity in blood components and plasma fractions have been estimated based on experiments in an animal model. The applicability of these data to vCJD infectivity in human blood is not known, but they are the best data available. Estimates of infectivity in plasma derivatives have been based on these results together with an assumption that the infectivity in the product is proportional to its protein content and that there is no reduction in infectivity from further processing steps, such as fractionation, filtration and chromatography. This is considered to be very pessimistic, so that the estimated infectivities in plasma derivatives are likely to be over estimated.

7. Using these infectivity estimates, an infected donation is estimated to result in up to 2.6 new infections of which 0.8 are predicted to live long enough to develop vCJD. About half these new infections and cases are predicted to be due to blood transfusions and half due to plasma derivatives.

8. The sensitivity assessment has shown that the number of vCJD cases per infected donation resulting from blood components (red cells, FFP and platelets) is relatively robust across a wide range of tested parameters. For example, if the infectivity in blood were 100 times lower than the reference case it would have a negligible effect; if the infectivity is 1000 times lower the number of cases reduces by a factor of 10.

9. On the other hand, the number of vCJD cases resulting from plasma derivatives has been shown to be highly uncertain. An increase in infectivity by a factor of 10 would increase the number of cases by the same amount, whilst a reduction by a factor of 10 virtually eliminates the risk from plasma derivatives. Many other changes in assumptions would also virtually eliminate the risk from plasma derivatives; e.g. plasma infectivity based on white cell content; plasma derivative infectivity based on clearance factors, etc.

10. The effectiveness of a number of possible measures to reduce the risk of infection with vCJD from blood products has been assessed. No measures have been identified that can eliminate all the risk, but several provide significant risk reductions. In particular:

- **Leucodepletion**. Leucodepletion appears to have significant benefit in reducing risk of vCJD infection through blood transfusion, although the degree of benefit is extremely uncertain. Since there are some scenarios where leucodepletion has significant benefit, and considerable uncertainty about those scenarios where it does not have benefit, it would be prudent to adopt leucodepletion as a risk reduction measure.

- **Elimination of UK Plasma Products**. Eliminating UK plasma products will clearly eliminate any risk there may have been from infectivity in these products, assuming there is no vCJD in the source country. However, the degree of benefit is highly sensitive to several uncertain assumptions. The uncertainty here is not in how effective the measure would be, but the magnitude of the risk from vCJD in plasma products that it is mitigating. Since there are some scenarios where the risk is significant, the UK plasma product ban could be considered prudent in the absence of better information.

11. The other risk reduction measures considered were:

- *Reduction in use of blood components:* If blood usage could be reduced without increasing risk to patients, it would be moderately effective in helping to reduce the exposure to any infectivity in blood.
- *Preventing blood transfusion recipients donating blood:* Preventing recipients of blood transfusions from donating blood could result in a moderate reduction in the additional cases of vCJD due to infectivity in blood. This should be balanced against the need to avoid adverse impacts on the overall blood supply.
- *Maximising use of whole blood:* Using whole blood rather than components derived from separate donors may be preferable for some patients, but the overall benefit appears small and uncertain.
- *Autologous transfusions:* Maximising autologous transfusions could make a small reduction in the risk of vCJD due to infectivity in blood.
- *Use of imported pooled plasma:* If the prevalence of vCJD among the donor population were negligible, the risk from fresh frozen plasma (FFP) would be eliminated. However, if vCJD did exist among the donor population, pooling plasma would have an adverse impact unless the infectivity in plasma was at least 200 times less than estimated here.
- *Use of high purity Factor VIII:* Although a selective ban on intermediate purity Factor VIII could achieve a significant risk reduction, the uncertainties are too great to have confidence in the validity of this estimate.
- *Prophylaxis treatment against vCJD:* There is reasonable evidence to suggest that polysulphonated polyglycosides such as pentosan polysulphate can reduce the susceptibility to infection from TSEs in animal models, and its effectiveness as a prophylactic against vCJD is worth investigating further.

Acknowledgements

The preparation of this report has required the collection and review of a large amount of information; we are grateful to all those that helped both in providing information and in making sure that we have interpreted it correctly. The following individuals have been consulted during the course of the study;

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Dr Terry Snape	Technical Director, Bio Products Laboratory
Tony Wilson	Chief Executive, Haemophiliac Society

In addition to those listed above the Draft Report was sent out by the Department of Health for peer review by a panel of experts. This Final Report has taken account of the comments from these reviewers.

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1. INTRODUCTION

At their meeting on the 24th October 1997 the Spongiform Encephalopathy Advisory Committee (SEAC) reviewed the safety of blood and blood products, and provided advice to Government on these matters. The Committee advised that recent research has suggested that the pathogenesis of new variant Creuztfeldt Jacob Disease (vCJD) differs from that of classical Creuztfeldt Jacob Disease (CJD) and that vCJD may have more involvement of lymphoreticular tissues possible involving circulating lymphocytes. SEAC recommended that the Government should consider a precautionary policy of extending the use of leucodepleted blood and blood products as far as is practicable. SEAC also recommended that risk assessments, making assumptions of various possible incidences of vCJD, be carried out to inform decisions on any measures which may be necessary to protect recipients.

In response to this request, the Department of Health organised a meeting on the 25th November 1997 for a panel of experts to discuss the basis for a risk assessment of the possible infectivity of vCJD in blood and blood products. Following that meeting, the Department of Health contracted Det Norske Veritas (DNV) to carry out a risk assessment study. This report is an Interim Report of the work completed so far.

DNV were asked to undertake this study as experts in risk assessment who had already undertaken a number of risk assessment studies of BSE for both the Environment Agency and for MAFF.

1.1 Objectives

The objectives of the risk assessment were stated to be:

- To assess which components of blood and blood products are risk factors to human health by analysing the processes involved in blood transfusion and the preparation and use of blood products.
- To identify those groups of patients which are at high risk from blood and blood products.
- To consider the benefits and disbenefits of introducing a range of measures aimed at reducing the risks identified above.

2. OVERALL APPROACH

The overall approach to this risk assessment is based on that used in previous studies for the Spongiform Encephalopathy Advisory Committee, such as 'Assessment of Risk from Possible BSE Infectivity in Dorsal Root Ganglia'. A central assumption to this approach is that variant CJD is caused by consumption of the infective agent of BSE present in food derived from cattle incubating BSE, and that the risk to people of being infected by vCJD can be assessed by estimating the amount of BSE infectivity consumed.

In trying to assess the risk of being infected by vCJD due to blood and blood products the key question is whether the infective agent is present in blood. Whilst the evidence for infectivity in blood is reviewed (see Appendix II) ***it is not the purpose of this assessment to provide an answer to this question***. In fact the study is based on the assumption that infectivity is present in blood.

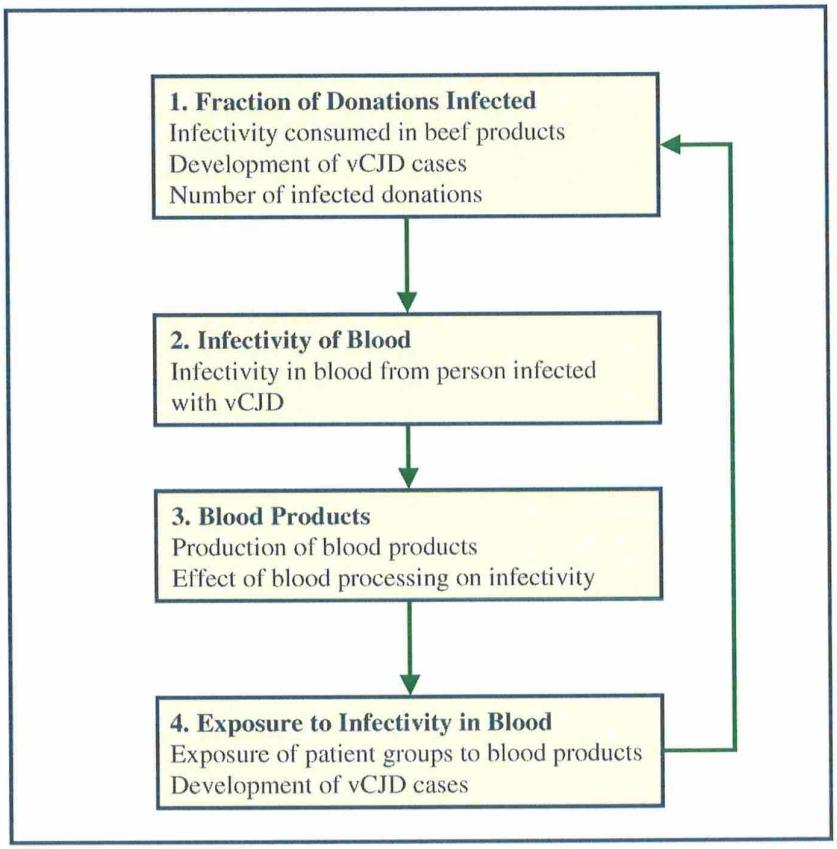
With this in mind, the objectives of the study could be re-stated as:
On the assumption that the infective agent for vCJD is present in blood, to assess the extent of the potential exposure to vCJD infectivity, identify those groups of patients at most risk and consider the effectiveness of possible measures to reduce the risks. That is what this study attempts to do.

It is important to recognise that this study is not a scientific review of all the evidence concerning the potential for vCJD to be transmitted by blood. That is not our expertise. It is a risk assessment study that is intended to provide some practical insights into the possible risks from an uncertain hazard. The study has tried to assess the state of knowledge, draw assumptions based on the best scientific evidence that is available, and then to assess the range of implications from those assumptions. In this way a risk assessment can inform a decision making process, but it can never provide all the answers or consider the full range of issues that have to be weighed up in making a decision. The results of the study should not be seen as absolute estimates; they are predictions based on a set of assumptions. The value of the study lies as much in setting out those assumptions and highlighting the limitations of the data as with the quantitative results presented.

Form of Results. The main results of this assessment are presented in terms of the number of vCJD cases due to blood per infected donation. This removes the need to estimate the absolute numbers of cases.

The main steps required to estimate the exposure to infectivity in blood are summarised in Figure 1. To complete the analysis a sensitivity assessment to a range of the uncertainties in the assumptions is carried out, and an assessment of the effect of possible measures to reduce the risk. The main features of each of these steps are described below.

Figure 2.1 Overview of Risk Model



2.1 Fraction of Donations Infected

In order to estimate the potential exposure to vCJD infectivity in blood it is necessary to have an estimate of the number of people who may be incubating the disease and donating blood. At the present time there is not enough data or knowledge about the causes of the disease to provide any definitive estimate. Estimates that have been made (e.g. Cousens et al, 1997) give a wide range of predictions. Again, it is not the purpose of this assessment to attempt to provide an estimate of the potential size of the vCJD epidemic in the UK. However, it is not enough simply to take a range of possible values for the ultimate size of the epidemic as the time history is also important.

In order to provide an input into this study, some previous work undertaken for SEAC to estimate the potential exposure to BSE infectivity from food has been developed further to provide an estimate of the numbers of people incubating vCJD over time and hence the fraction of donations that may be infected. This is described in Chapter 3. It should be emphasised here that the resulting estimates are very dependent on the assumptions made, and it is only possible to put a range on the values. The sensitivity of the results of this study to this range will be investigated.

2.2 Infectivity in Blood

The next stage of the study is to consider in detail how blood is collected, processed and used. This is described in detail in Appendix I, and some of the key points summarised in Chapter 4. As already stated, this assessment is based on the premise that the infective agent for vCJD may be present in the blood of a person incubating the disease. The evidence for this is presented in Appendix II. This Appendix also presents the evidence for the choice of the amount of infectivity that may be present. This is an area for which there is considerable uncertainty.

2.3 Blood Processing and Plasma Derivatives

The various ways in which blood is separated into its main components and the plasma processed to produce plasma derivatives are summarised in Appendix I. The purpose of this is to reflect our understanding of the steps and processes involved. Many of the steps involved in producing plasma derivatives, e.g. Factor VIII, Albumin etc, such as ultra-filtration and chromatography, are likely to be effective in removing infectivity. However, it is hard to demonstrate this, as there is very little data on the effect that blood processing may have on any infectivity present. The production process also involves significant dilution. The model of infectivity in plasma derivatives takes account of the pool size from which products are made, and thus the expected number of infected donations included, and the fraction of material present in the final product. Any possible effect from the various purification steps is not included.

2.4 Exposure to Infectivity in Blood

The final stage of the analysis is to assess the exposure of the population to infectivity in blood by considering the amount of blood transfused and the treatment of patients with blood products. This needs to consider the relative vulnerability of different patient groups depending on treatment regimes. The potential for patients treated with infected blood to develop vCJD will then depend on the dose received, the incubation period of the disease and also on their life expectancy. The final step would then be to close the loop and consider the new infections caused by blood affecting the donor population.

2.5 Sensitivity Assessment

There is considerable uncertainty about many of the values on which this study has been based, and in many cases it is not possible to select most likely values, for example for the level of infectivity in blood. A sensitivity assessment has been carried out to explore the variation in the results, in terms on the number of additional cases of vCJD per infected donation, for ranges of values of all the key assumptions. The main assumptions are summarised in Appendix IV.

2.6 Risk Reduction Measures

Various possible measures have been suggested to reduce the risk of infection with vCJD from blood products. Some measures are already being implemented following recent announcements and others are still under consideration. The effects of these measures on the risk levels are investigated using the measure of the number of new vCJD cases per infected donation.

3. INFECTION FROM FOOD

3.1 Introduction

A study was carried out by DNV in November 1997 to assess the potential exposure of the UK population to BSE infectivity in food. This was proposed by in part to put the results of the assessment of the risk from dorsal root ganglia into context. An interim report "Assessment of BSE Infectivity in Food for Human Consumption" was presented to SEAC and discussed by them. It was recognised that many of the inputs into this study were uncertain and needed to be improved before the results could be used with any confidence, and it was planned that the study would be reviewed and modified as appropriate.

Some of the work needed to develop the Assessment of BSE Infectivity in Food study has been carried out in order to provide an input into this assessment. The fundamental approach is the same as that reported in the Interim Report, and the main developments included are reported here. Further work to develop the previous assessment is still ongoing, including work from other research programmes.

The basic approach was:

1. To review and evaluate all the potential pathways by which people could be exposed to BSE infectivity in the food chain. This included both consumption of potentially infected tissues and contamination in the abattoir.

2. To consider the infectivity density in the various bovine tissues. This included assuming a low level of infectivity (at 1% of the limit of detection) in meat.

3. To estimate the numbers of animals with a significant level of infectivity that may have been slaughtered for food. In the Interim Report this was based on the numbers of mature cattle slaughtered as opposed to prime beef before the introduction of the over thirty month scheme (OTMS), and subsequently on the numbers of BSE cases in animals less than 38 months. This latter was based on the findings from the pathogenesis experiment that there was infectivity present 3 months before clinical symptoms but not 9 months before.

4. To combine the above to estimate the total numbers of infective units consumed. In doing this factors to take account of differences in consumption over time and the implementation of the Specified Bovine Material (SBM) regulations were included.

3.2 Updated Assessment

In updating the assessment the first two stages described above have remained effectively the same. There still remains a need to review many of the assumptions used in assessing consumption of different tissues, but these are not expected to have a major effect on the results. The main changes that have been implemented are in improving the modelling of the BSE epidemic and the estimates of the numbers of highly infected animals slaughtered.

3.2.1 The BSE Epidemic in Cattle and Consumption of Infectivity

The starting point for this assessment is an estimate of the numbers of animals infected with BSE each year. This has been based on the results of the back calculation model reported by Ferguson et al (1997). A simple model combining the average life expectancy of cattle with an incubation period of BSE is then used to predict the number of cases, the number of infected animals eaten and the numbers with advanced infections eaten. The incubation period is modelled as a log normal distribution with a mean of 5 years and a variance of 1.6 (Anderson, 1996). An advanced infection has been defined as one 75% or more through the incubation period.

The results of the model are illustrated in Figure 3.1. This shows the input data, as the total number of new infections per year, and then the three sets of results; total infected animals eaten, animals with advanced infection eaten and the number of BSE cases. The model predicts a total of 190,000 cases of BSE, 730,000 asymptomatic infected cattle slaughtered for food of which 43,500 were advanced infections.

The estimates of the numbers of animals slaughtered for food with advanced infection are then combined with the estimates of the amounts of different bovine tissues eaten to give an estimate of the overall consumption of BSE infectivity by the UK population.

3.2.2 Epidemic of vCJD due to Food

The next stage in the model is to take the estimates of infectivity consumed and to use these to predict the numbers of vCJD cases that could result. This requires assuming a dose response relationship and an incubation period for vCJD. Information on the choice of incubation period is described in Appendix II.5. Much of the data on incubation periods for TSEs involves infection within a species. For example, iatrogenic CJD involves infection with a human-passaged agent. This may be appropriate for vCJD from blood transfusion, but could be too short for vCJD obtained direct from BSE in food. When crossing a species barrier, the mean incubation period is expected to increase and could be doubled, and the spread would also be likely to increase. The model also includes a mortality rate to take account of the chance that anyone being infected will live long enough to develop the clinical disease. In order to provide a match with the known cases of vCJD the value of the species barrier is adjusted so that the cumulative number of cases up to 1997 is equal to 23.

Varying the mean value of the incubation period from 5 years to 40 years results in a range of values for the total number of cases from 40 to 120,000 with an equivalent variation in species barrier from 90,000 to 17. The range of values for the species barrier required to match the epidemic to 23 cases up to 1997 lies within the range of values proposed by SEAC for all incubation periods other than 5 years. However a species barrier of 90,000 is also plausible. The results are highly dependent on the assumptions made, and there is no basis for selecting one combination of incubation period distribution and species barrier as the most likely.

For this study we are interested in the fraction of blood donations that could be infected. This depends on the total number of people infected at any time, as it is assumed that blood could be equally infective throughout the incubation period. A plot showing the range of values for the fraction of blood donations infected as a function of incubation period is shown as Figure 3.2.

Figure 3.1 BSE Cases Predicted from Estimated Infections

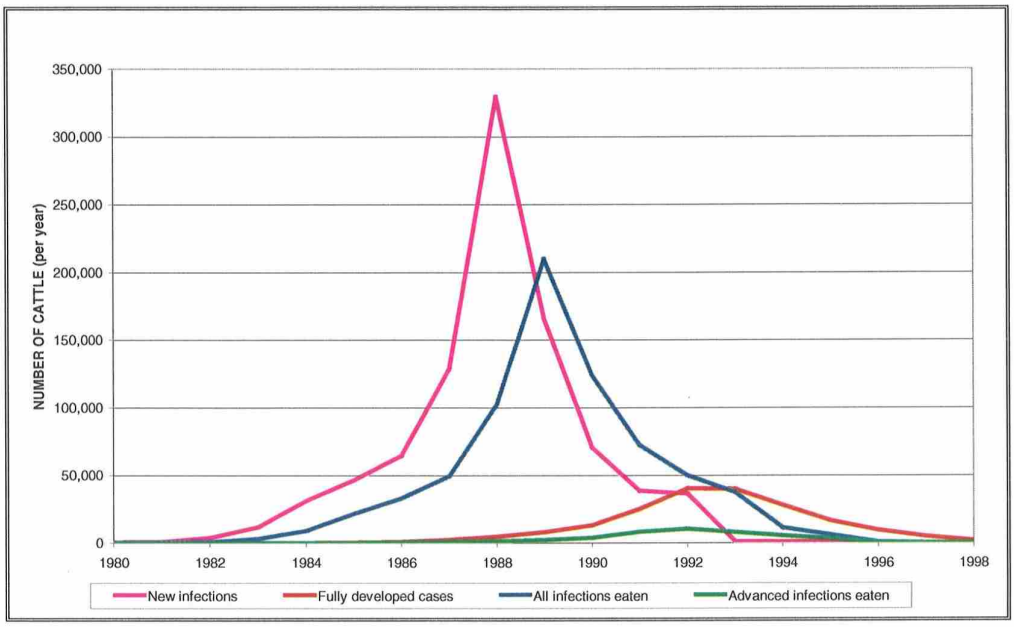
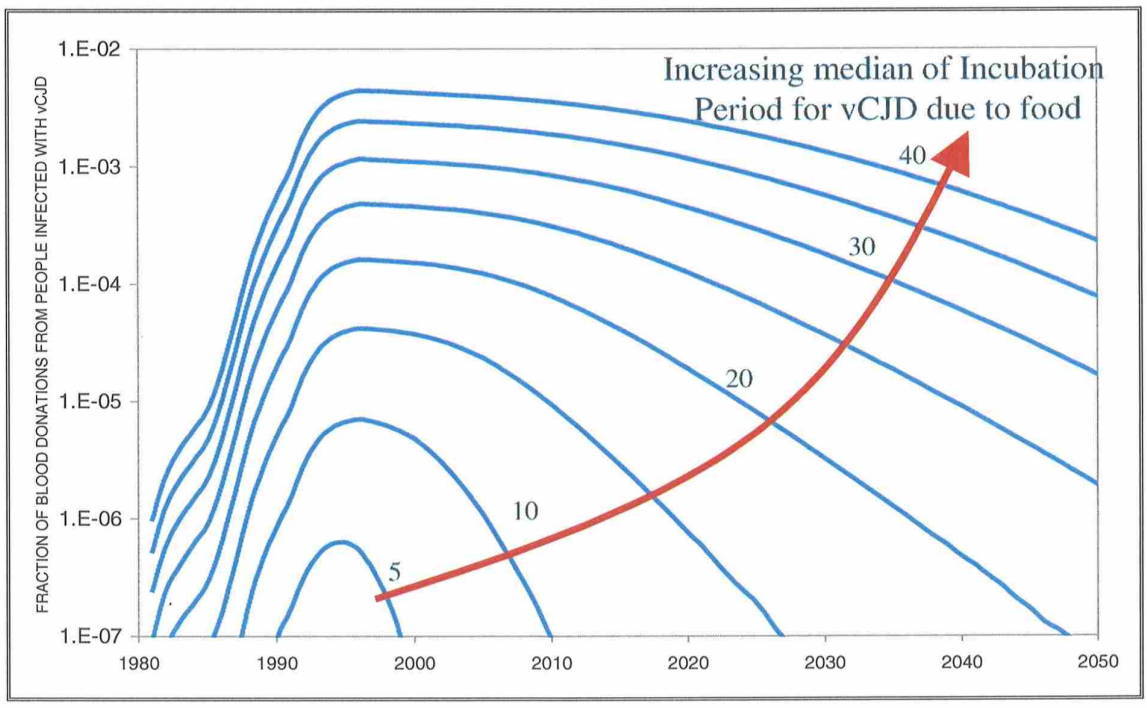


Figure 3.2 Fraction of Donations from People Incubating vCJD



4. RISK FROM vCJD DUE TO BLOOD

A model has been developed to track infectivity from people who are infected with vCJD donating blood and to assess the exposure of the population to this infectivity, both from blood transfusions and from plasma derivatives. The main output from this model will be the number of cases due to blood and plasma derivatives per infected donation. This gives a measure of the relative risk due to blood.

4.1 Blood Donations and Blood Processing

Appendix I - "Extraction and Use of Human Blood Products" presents the information and assumptions that have been used in this study to represent the various processes involved in the collection, processing and use of human blood.

In the area of England and North Wales covered by the National Blood Service (NBS) during 1996/97, 1,907,000 donors donated 2,215,000 units of usable blood. A conventional whole-blood donation consists of 450 ±45 ml of blood. The average rate of blood donation, based on 2,215,000 donations among the England & Wales population of 51.8 million for 1995, is estimated as 0.043 donations per person year.

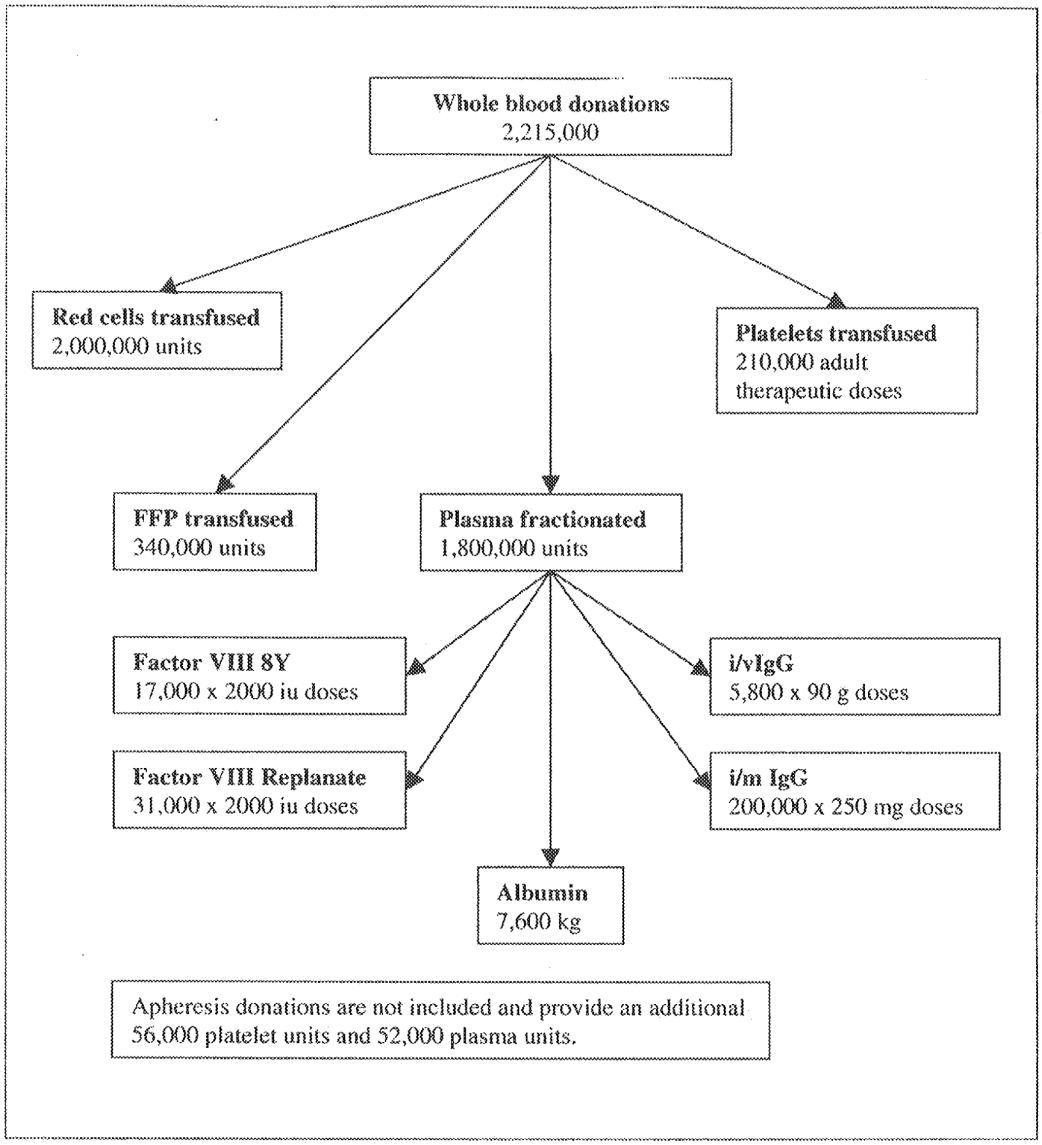
Primary processing of donated whole blood involves segregation by centrifugation into either two components (red cells + buffy coat and plasma) or three (red cells, plasma and buffy coat). The buffy coat consists of white cells and platelets. Modern medicine rarely requires whole blood transfusions and most transfusions involve one of several forms of red cells. One unit of red cells is produced from one whole blood donation. Platelets are produced from the pooled buffy coat from four whole blood donations. Until May 1998 about 80% of the collected plasma would have been sent to the Bio Products Laboratory (BPL), part of the National Blood Service, for processing into plasma fractions. The remaining plasma would be used as fresh frozen plasma (FFP) with one unit of FFP being produced from one donation.

In May 1998, BPL discontinued fractionation of UK fresh frozen plasma, in response to advice by the UK Committee on the Safety of Medicines, and now fractionates imported plasma. The data used in this report are based on 1997/98, the last full year of manufacture from UK plasma.

At BPL the plasma is processed in batches of about 6400 kg, containing plasma from approximately 22,000 donations. The first stage of processing plasma into blood products is cryoprecipitation followed by ethanol fractionation. This is followed by a series of stages depending on the product, involving precipitation, centrifugation, filtration, virus inactivation, formulation and heat treatment. The main plasma derivatives produced are: Factor VIII, a blood clotting agent used in the treatment of Haemophilia A and produced in two forms 8Y and Replenate; Factor IX, a blood clotting agent used in the treatment of Haemophilia B; Albumin, which may be transfused directly into patients and is used as an additive in formulating other medical products; and both intravenous (i/v) and intramuscular (i/m) immunoglobulin, IgG.

The main flows of these blood products in England and Wales is shown in Figure 4.1.

Figure 4.1 Products from Blood Donations in England & Wales



4.2 Infectivity in Blood

Appendix II provides an overview of the available evidence for the presence of infectivity from TSEs in blood, and estimates for the level of that infectivity. All the evidence for infectivity from TSEs in blood is based on animal models. A review of epidemiological evidence concludes that there is no evidence that sporadic CJD has ever been transmitted by blood transfusion. Although such transmissions may have occurred, the numbers would have to have been very small to escape detection. However, it is not certain that this also applies to vCJD.

A number of studies have failed to show any infectivity in the blood from sporadic CJD patients when inoculated intracerebrally into monkeys, chimpanzees and guinea pigs. However, there have been 4 experiments in which infectivity was detected by intracerebral inoculation in the recipient animal (mouse, hamster or guinea pig). These results are surprising because it would be expected that it would be easier to infect primates with human CJD than rodents. There has also been criticism of these experiments in the literature (Brown, 1995). Other experiments using TSE models in laboratory animals have detected infectivity in blood when inoculated intracerebrally. No published reports of transmission following intravenous inoculation have been identified.

A number of experiments to estimate the level of infectivity in blood have been reviewed. These are all based on animal models and intracerebral injection and give estimates of infectivity in blood ranging from 4 to 300 i/c ID_{50}/ml. Since these experiments all used species and disease strains that have been selected to achieve transmission, it is likely that they would provide an over-estimate of the infectivity of vCJD in humans. Therefore, it is proposed that a value of 10 i/c ID_{50}/ml is used as the basis for this study, being at the lower end of the range.

In order to estimate the infectivity for intravenous inoculation, it is assumed that the i/v route is 10 times less efficient than the i/c route. Combined with the estimate of i/c infectivity above, this gives 1 i/v ID_{50}/ml blood, with a range of approximately 0 to 30 i/v ID_{50}/ml.

4.3 The Level of Infectivity in Blood Components

The only known investigations of the distribution of infectivity in different blood components are those of Brown et al (1998). They carried out two sets of experiments. The high input "spiking" experiment involved spiking hamster adapted scrapie infectivity into human blood, which was then separated by centrifugation into the three main components, red cells, white cells/platelets and plasma, and the plasma was then subjected to Cohn fractionation, as used by the American Red Cross. Titrations in each component were then determined, which showed that the majority of the infectivity went into the red cell component but that there was still significant infectivity in the plasma. However, only 32% of the infectivity in the whole blood was recovered in the three components.

In the second "endogenous" infectivity experiment, clinically ill mice that had earlier been inoculated intracerebrally with a mouse adapted strain of human TSE were bled and the resulting 45 ml of pooled blood separated as before. Because of the need to dilute the specimens only a small fraction of each specimen was inoculated. Specimens from buffy coat, plasma, cryoprecipitate and Cohn fractions I+II+III transmitted disease to a few animals, but no transmissions occurred from whole blood, red cells or Cohn fractions IV and V. The absence of transmission from whole blood and red cells does not imply no infectivity. With the fractions inoculated, an infectivity of 10 IU/ml in whole blood would have been expected to have resulted in less than 1 infection in the panel of 11 mice used.

A third set of experiments in which blood from symptomatic hamsters inoculated with hamster adapted scrapie was inoculated intravenously and intracerebrally into other hamsters has been reported by Rohwer in evidence to the FDA, and in presentations to conferences and expert meetings.

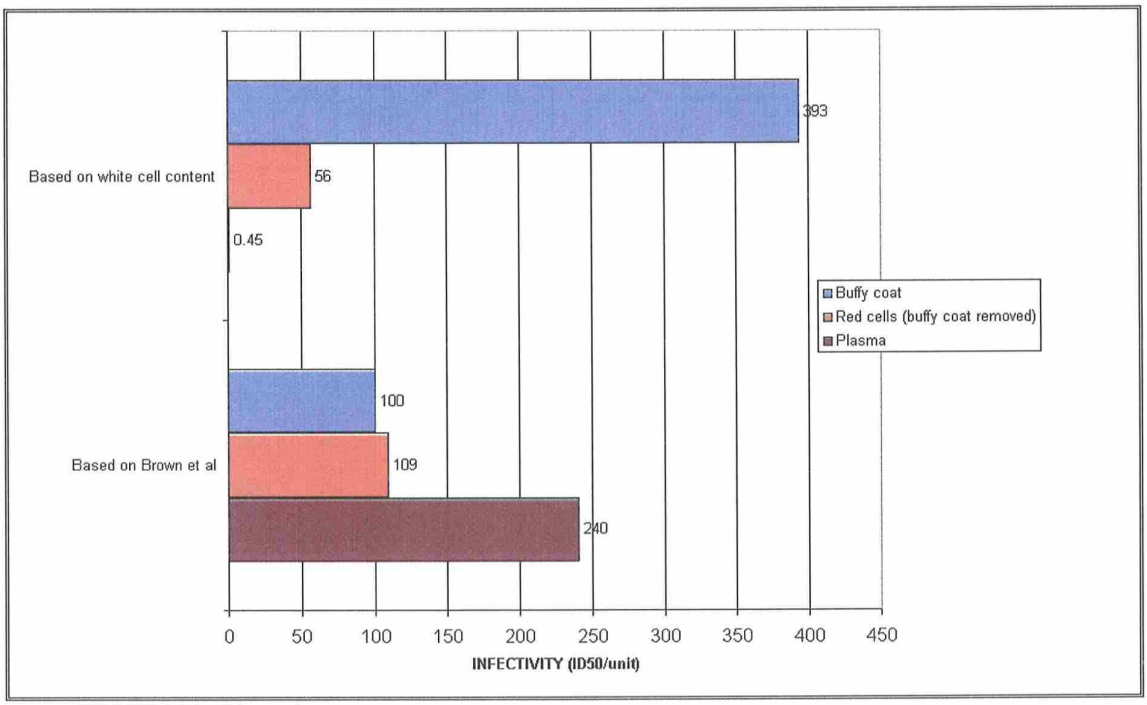
The results from these experiments can be interpreted in a number of ways as shown in Appendix II, Section II.3.6.4. The favoured approach is to use the estimate of infectivity in whole blood as above (1 i/v ID_{50}/ml) and to combine this with the relative infectivity in plasma and buffy coat found in the endogenous experiment. This enables the infectivity in red cells to be estimated by difference.

An alternative approach, based on the recent work implicating B lymphocytes in the development of experimental scrapie, would be to assume that the level of infectivity would be proportional to the number of B cells present. There is no data on the numbers of B cells in each blood product, so these are assumed to be in proportion to the number of white cells.

Results from the two approaches are compared in Figure 4.2, which shows the infectivity per unit in red cells, plasma and buffy coat. This shows that if infectivity were related to white cell content then most of the infectivity would be in the buffy coat, a small fraction in the red cell units and very little (0.5 ID_{50}/unit) in plasma. In contrast, the Brown et al experiments indicated that about half the infectivity in whole blood was in the plasma, with the remainder being spilt equally between red cells and buffy coat.

The estimates based on the interpretation of the Brown et al data described above are used as the reference case for this risk assessment. The infectivity based on white cell content, and ranges of values for the infectivity in whole blood will be used in the sensitivity assessment.

Figure 4.2 Comparison of Estimates of Infectivity in Blood Components



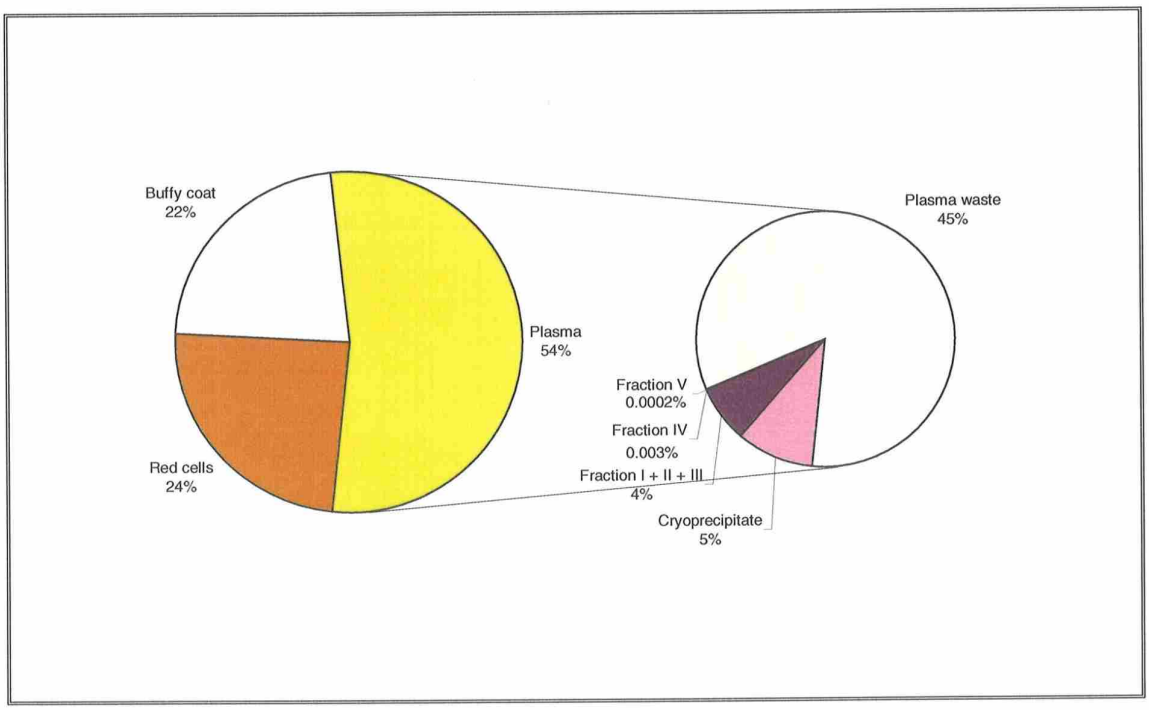
4.4 The Effect of Plasma Fractionation and Blood Product Production on Infectivity

Production of the various plasma derivatives involves cryoprecipitation of the frozen plasma followed by various stages of fractionation, precipitation, centrifugation, filtration, virus inactivation, formulation and heat treatment. Several of these steps are intended to achieve a major reduction in viruses, and it is possible that they could also have a significant effect on infectivity. On the other hand, TSE infectivity has been shown to be highly resistant to conventional inactivation methods. In plasma derivative production many of the steps involve physical removal of fractions, and it is these that are expected to reduce TSE infectivity. A number of these processing steps in series, each with some affect in removing infectivity, could result in very substantial reductions. For example Albumin has 8 or 9 steps each of which could reduce infectivity.

The infectivity in the plasma fractions has been assessed as described in Appendix II.3.7. This is based on the Brown et al endogenous experiment as described above for cryoprecipitate and Fraction I, II & III, and on the relative infectivity found in Fractions IV & V in the spiking experiment. The overall proportion of infectivity in the various fractions is shown in Figure 4.3.

Figure 4.3 Breakdown of Infectivity in Blood Components and Plasma Fractions

(based on Brown et al)



Two possible approaches to estimating the infectivity in the various plasma derivatives have been considered:

- Infectivity concentrations based on values in the Brown et al experiments for the cryoprecipitate or other appropriate fraction, combined with the protein contents in the

plasma derivatives. This in effect assumes that infectivity splits between the finished product and the waste material in proportion to the protein contents of the two, which is believed to be a reasonable approach, neither pessimistic nor optimistic. It also assumes **no further reduction in infectivity** from further filtration or purification steps after the fractionation, and this is considered to be very pessimistic.

- Infectivity based on the value for plasma in the Brown et al experiments combined with TSE clearance factors estimated by Foster (1998) based on Scottish National Blood Transfusion Service (SNBTS) production methods. Clearance factors are the reduction in infectivity achieved in any process step. This assumes that the processing steps produce additive effects in reducing infectivity, and is considered optimistic. In this approach, the reduction in product volume is included in the clearance factor, which refers to total infectivity, not infectivity concentration.

The results from applying these two approaches to several key plasma derivatives are shown in Figure 4.4 for derivatives made entirely with infected blood. The results are expressed in the form of infectivity for typical dose units given to patients. Although they are not strictly comparable, this form of presentation shows the very low infectivity estimated for most derivatives, even assuming that they are produced entirely from infected blood.

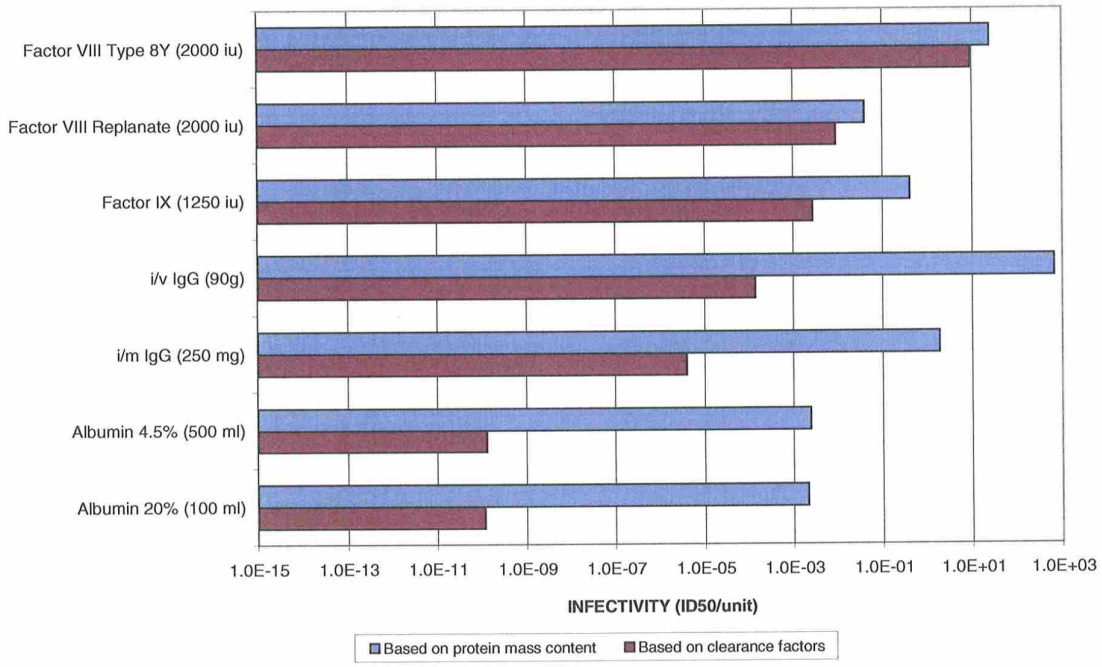
There are large differences between the two approaches for many of the products, and this indicates the very large degree of uncertainty in this part of the analysis. In the absence of a better model of the effects of plasma processing on infectivity, it is appropriate to use the more pessimistic approach for this risk assessment. In each case, the approach based on protein content is the most pessimistic.

The approach based on clearance factors gives the lowest values for derivatives with the most processing steps, like albumin. Although it is reasonable to assume that the process steps will have some effect in removing infectivity, it is probably not correct to assume that they are additive, and the resulting overall values are very low and considered to be overly optimistic.

The approach based on protein content gives higher values for products involving larger amounts per dose, combined with relatively high infectivity in the starting fraction, such as i/v IgG. Although likely to be pessimistic, in that it takes no account of clearance of infectivity by filtration or other process steps, it is used as a cautious best estimate in the study. It may be excessively pessimistic for some products, such as i/v IgG, in which there are many process steps between the intermediate fraction used as the basis for the infectivity concentration and the final product.

From Figure 4.4 it can be seen that there are two products with relatively high predicted infectivities. These are i/v IgG, which is estimated to have 660 ID_{50} units per dose if made entirely from infected donations, and Type 8Y Factor VIII with 24 ID_{50} units per dose. For a dose of i/v IgG to contain more than 1 ID_{50} unit the fraction of donations infected would need to be greater than 1.5×10^{-3}; i.e. 33 infected donations in a pool of 22,000. However, as noted above, this is thought to be excessively pessimistic. For Type 8Y Factor VIII the fraction of donations infected would need to be greater than 0.04 for a dose to contain more than 1 ID_{50} i.e. 880 infected donations in a pool of 22,000. This would be an extremely high level of infected donations and is outside the range predicted in Figure 3.2. It is thought to be very unlikely.

Figure 4.4 Comparison of Estimates of Infectivity in Plasma Derivatives Made Entirely from Infected Blood



4.5 Summary of Assumptions on CJD Infectivity in Blood

The following conclusions are drawn about CJD infectivity in blood:

- Blood from humans with symptomatic CJD may contain infectivity at a relatively low level. Experiments on animals indicate that it is sometimes capable of causing infection when inoculated intracerebrally into rodents. It is possible that these experiments are all flawed, but at present it is prudent to assume that blood from a person with symptomatic CJD could be infective for other humans.

- Experiments in several animals models have shown that blood from an animal infected with a TSE can be infective when inoculated intracerebrally into the same species.

- There has been a single report of a TSE being successfully transmitted by blood transfusion in an animal model, but this result has not been verified or published. All other such experiments with animal models have failed. No human cases are known, although a few cases could have occurred without being detected.

- Blood from vCJD cases may be infective at a higher level than blood from sporadic CJD cases, although this has not been demonstrated. This would make infection through blood transfusions more likely for vCJD.

- Evidence about the infectivity of blood from asymptomatic infections is unclear. At present, it is prudent to assume that infectivity is present throughout the incubation period.

The following assumptions are made for quantitative modelling of the infectivity of vCJD in blood:

1. Infectivity of blood from vCJD cases is assumed to be 1 human i/v ID_{50}/ml human blood (based on tests on mice with CJD). The range (based on other animal experiments) could be 0.1 to 30 human i/v ID_{50}/ml human blood.

2. Infectivity is assumed to be constant throughout the incubation period. It is also possible that it is higher at first but progressively declines through the incubation period, or alternatively that it is low at first but rises through the incubation period.

3. The incubation period for vCJD derived from blood is assumed to have a median of 15 years and a 90% range of 5 to 30 years (based on cases of CJD due to human growth hormone).

4. Infectivity in blood components is assumed to vary from the value for whole blood according to the ratios determined from the endogenous low dose experiment using blood from mice inoculated with a mouse adapted human TSE.

5. The infectivity in plasma derivatives is assumed to have the same infectivity per gram of protein as in the plasma fraction from which they are made. For a sensitivity test, the total infectivity is assumed to be reduced according to clearance factors established for each of the process steps.

6. The dose-response function for vCJD infectivity is assumed to be linear with no threshold. A dose of 1 ID_{50} is assumed to give a 50% chance of infection, and smaller doses give proportionately smaller chances of infection. A dose of 2 ID_{50} or more is assumed to give certain infection. For a sensitivity test, any dose below 0.01 ID_{50} could be assumed to have negligible chance of causing infection.

4.6 Numbers of Patients & Patient Groups

Data on the numbers of units transfused are given in Appendix I.6. The estimates of blood components transfused in England & Wales are summarised in Table 4.1.

Table 4.1 Summary of Transfused Components

COMPONENT	UNITS TRANSFUSED (per year)	UNITS TRANSFUSED (per patient)	PATIENTS TRANSFUSED (per year)
Red cells/ whole blood	2,000,000	5	400,000
Platelets *	210,000	3	70,000
Plasma (FFP)	340,000	3	114,000

* adult therapeutic doses

The age distribution of patients and their survival probability are important factors in estimating the number of cases of vCJD that could result given infection. Information on the

age distribution of transfusion patients and their expected survival probabilities following a blood transfusion is given in Appendix I.6.10. For the present study, it is assumed that overall 50% of transfusion patients die within 1 year from the condition requiring the transfusion, and that patients who survive this period have largely unaffected natural life expectancy. The post-operative survival probabilities assumed for other patient groups are given in Table 4.2.

In order to estimate the risks from infectivity in blood it is necessary to consider how the blood products are used to treat patients. Some patients may be treated with several different blood products. The treatment of individual patients varies widely, and no data has been identified that categorises the treatments systematically. It would not be appropriate for this risk assessment to try and consider all possible treatment regimes and so a **representative set** of patient groups has been developed to represent the range of treatment regimes. The patient groups proposed are inevitably simplified and arbitrary. The numbers of patients in each group have been adjusted to match the total amounts of blood products estimated to be transfused each year so they should provide a reasonable basis for the risk assessment.

Details of these patient groups are given in Appendix I, Section I.7. Summary information on the selected patient groups and their exposure to the major blood components is given in Table 4.2. The table also shows the assumptions made on life expectancy or survival probability for each group. There is a lack of data on these values and they are simply estimates. However, the study results will not be very sensitive to variations in individual values.

Table 4.2 Exposure of Representative Patient Groups to Blood Components

PATIENT GROUP		PATIENTS (per year)	NEXT YEAR	BLOOD PRODUCT	DOSE (units/year)	LIFE EXPECTANCY (years) or SURVIVAL PROBABILITY
	Example condition					
A	Acute blood loss (inc surgery)	72,000	New	Red cells	2	90% survival
B	Acute blood loss with complications	80,000	New	Red cells Plasma	5 2	50% survival
C	Massive blood transfusion	8,000	New	Red cells Platelets Plasma	15 3 5	20% survival
D	Chronic acquired anaemia	144,000	Ongoing	Red cells	3	15
E	Bone marrow failure	60,000	Ongoing	Red cells Platelets	10 3	5
F	Anaemia/coagulopathy	24,000	Ongoing	Red cells Plasma	10 5	5
G	Congenital anaemia	12,000	Ongoing	Red cells	5	25
H	Anaemia of prematurity	6,000	New	Red cells	1	50% survival
I	HDN babies	920	New	Red cells	1	95% survival

These figures indicate a total of approximately 170,000 new patients per year, and 240,000 patients receiving on-going treatment. It is assumed that patients receiving on-going treatment will not be able to donate blood in the future. Of the new patients, some will be eligible to donate blood, although a proportion of those that survive the episode are likely to be excluded on the basis of underlying disease and/or age (see section 4.8).

A simplified summary of the estimated exposure of UK patients to plasma derivatives made from UK plasma at BPL, prior to the changes announced in 1998, is given in Table 4.3. Exposures of UK patients to foreign-sourced plasma derivatives are not included. Immunoglobulins are assumed all to be issued as 250 mg doses, giving a total of 583 kg issued per year.

For simplicity, most plasma derivative patients are assumed to have normal remaining life expectancy (40 years) and negligible risk of death from treatment. Exceptions are albumin patients, who are assumed to have 50% chance of survival, and i/v IgG patients, who are assumed to have 50% chance of surviving the episode and 15 years remaining life expectancy. Improved data for all these assumptions would be desirable as they are very uncertain.

Table 4.3 Exposure of Representative Patient Groups to UK Plasma Derivatives

REPRESENTATIVE PATIENT GROUP		PRODUCT	UK ISSUES (per year)	PATIENTS (per year)	TYPICAL DOSE	DOSE RATE (dose/year)
J	Haemophilia A	Factor VIII	100 m iu	1800	2000 iu	27
K	Haemophilia B	Factor IX	16 m iu	250	1250 iu	52
L	Shock	Albumin 4.5%	120,000 l	59,000	1 litre	2
M	Intensive care	Albumin 20%	11,000 l	27,500	100 ml	4
N	ITP + PIA	i/v IgG	526,000 g	1450	90 g	4
O	HAV prophylaxis	NIgG (i/m)	27,500 g	90,000	250 mg	1.2
P	HDN prophylaxis	Anti D IgG	33,000 g	88,000	250 mg	1.5
Q	Tetanus prophylaxis	Tetanus IgG	2,000 g	8,000	250 mg	1
R	HBV prophylaxis	Hepatitis B IgG	750 g	3000	250 mg	1
S	Var zoster prophylaxis	Var zoster IgG	1,350 g	1800	250 mg	3
	Sepsis	Anti Thrombin	1.2 m iu	34	7000 iu	5
	Warfarin overdose	Factor VII	0.75 m iu	30	4000 iu	6
	Factor XI deficiency	Factor XI	0.13 m iu	40	1000 iu	3
	Factor XIII deficiency	Factor XIII	0.32 m iu	6	4000 iu	12
	Rabies prophylaxis	Rabies IgG	130 g	178	250 mg	3

4.7 Risk of Infection by Patient Group

The risk of infection for each of the patient groups is estimated as a function of the fraction of donations infected. This is done by combining the estimates of the infectivity per dose with the numbers of doses received by each patient group, and taking account of the probability of surviving the episode and the life expectancy of patients in the different groups. The calculation flow is summarised in Figure 4.5, and a worked example for one patient group is shown in Figure 4.6.

Figure 4.5 Risk Calculation Flowchart

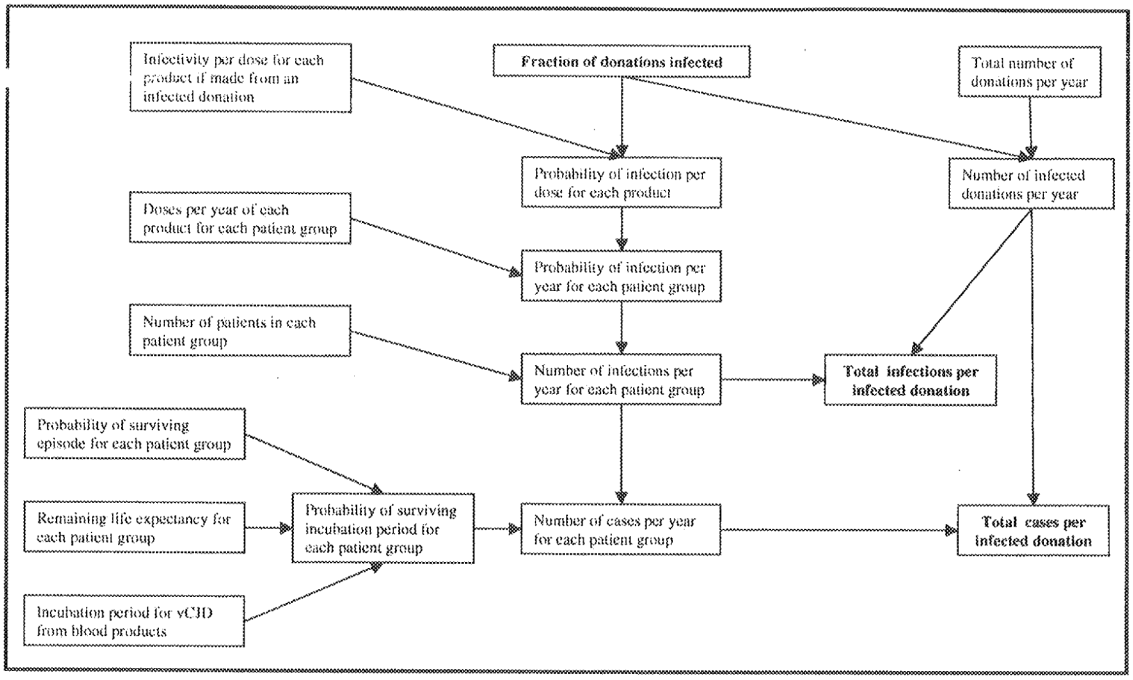
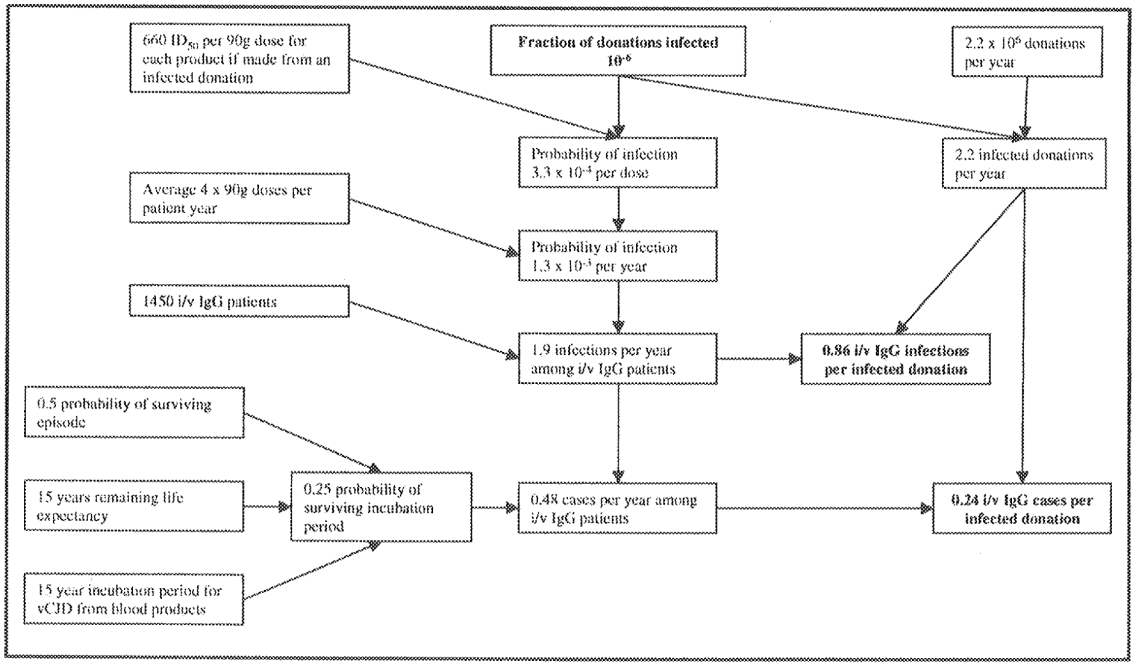


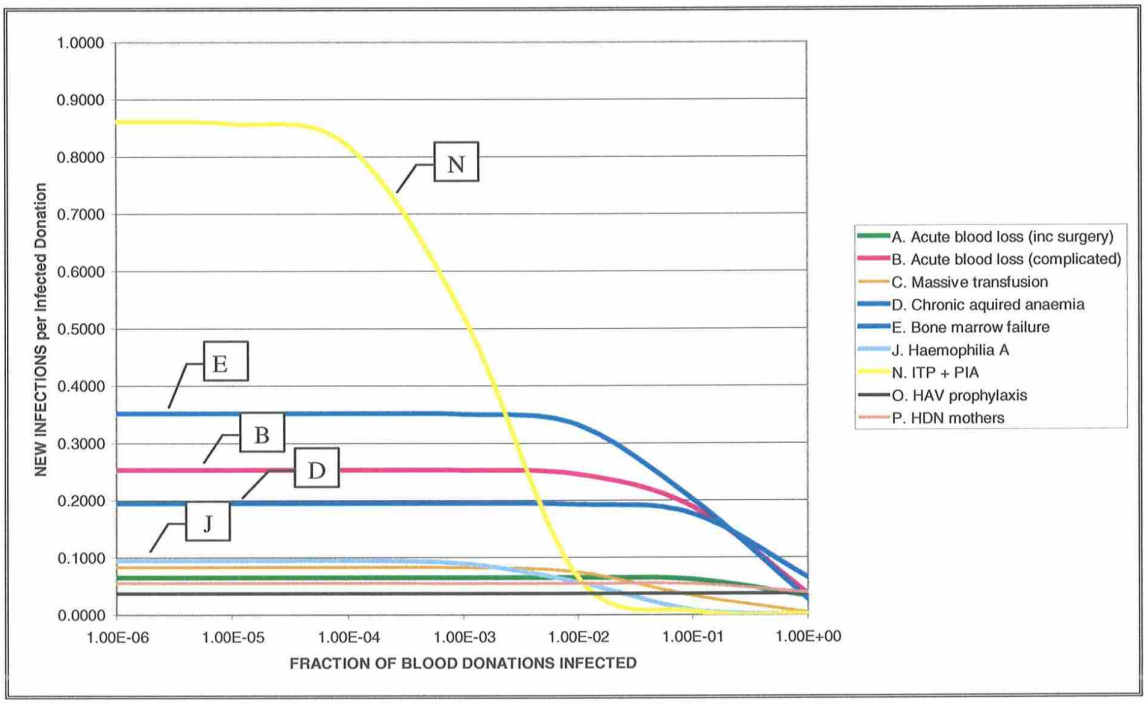
Figure 4.6 Example Calculation for i/v IgG Patients



The worked example in Figure 4.6 shows the calculation for Group N (patients receiving i/v IgG). This shows that if the fraction of doses infected was 1×10^{-6} (1 in a million), then the probability of infection from one 90g dose would be 3×10^{-4}, or 1×10^{-3} per year from an average of four doses, all assuming that there is no dose threshold. This would result in 2 infections per year among the 1450 Group N patients. If it is assumed that this group of patients have a 50% chance of surviving the episode and then a remaining life expectancy of 15 years they would have a 25% chance of surviving an incubation period of 15 years, resulting in 0.5 cases of vCJD per year. The results can then be presented per infected donation by dividing by the number of infected donations (2.2) and giving 0.86 infections per infected donation and 0.24 vCJD cases per infected donation.

This calculation is repeated for all the patient groups and for a range of values for the fraction of blood donations infected from 10^{-6} to 1. The results for selected patient groups are given in Figure 4.7. The value of 0.86 infections per infected donation for Group N calculated above can be seen as the top line at low fractions infected. As the fraction of donations infected increases above 1×10^{-4}, the number of infections per infected donation for Group N drops rapidly. This is because the patient group is fairly small (1450) and has become saturated; i.e. all patients have been infected. This can be seen in Figure 4.8, which shows the risk of infection for the first year of exposure. This approaches 1 for Group N as the fraction of infected donations exceeds 10^{-3}.

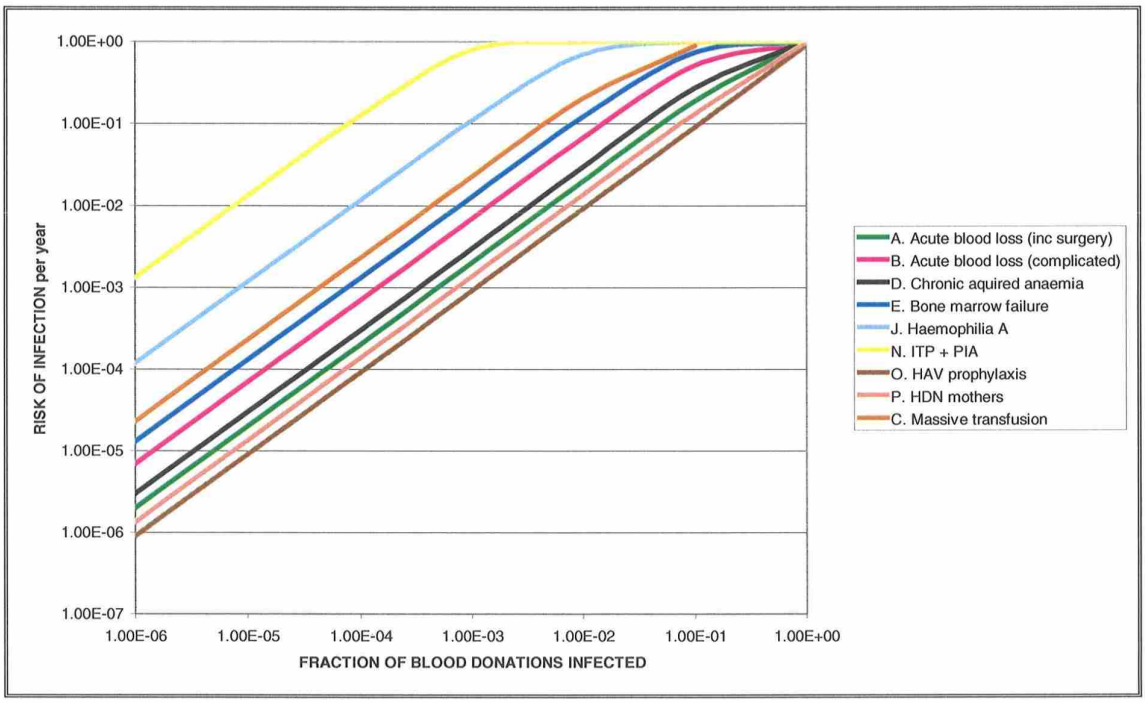
Figure 4.7 New Infections per Infected Donation by Patient Groups in First Year after Exposure



Other patient groups show a similar but less dramatic pattern. Thus for Group B patients the number of infections per infected donation remains constant at about 0.25 until the fraction of donations infected exceeds 1 x 10^{-2}, and then falls to 0.04. For most groups the numbers of infections per infected donation remain constant up to 10^{-2} blood donations infected.

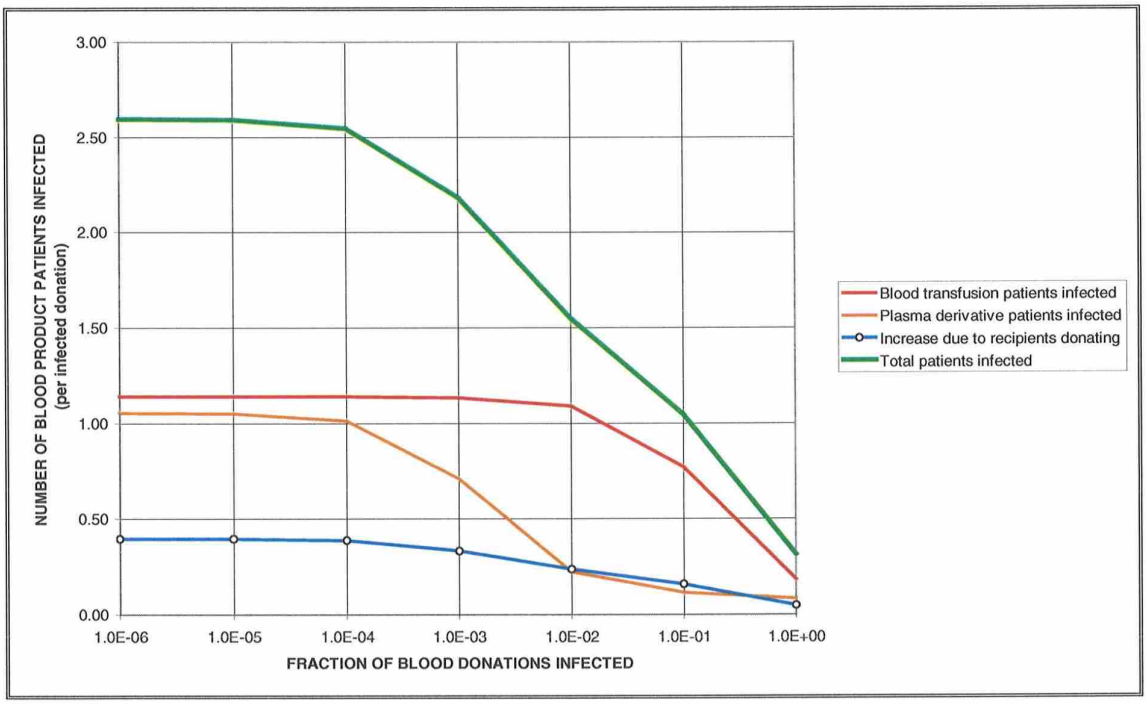
For Group J, Haemophilia A patients, the number of infections per infected donation starts at 0.1 for low fractions of donations infected, and then falls as the fraction of donations infected exceeds 10^{-3}. As the fraction of donations increases the number of new infections approaches the total number of Haemophilia A patients, with the risk of infection approaching unity at 10^{-2} donations infected.

Figure 4.8 Risk of Infection by Patient Group in First Year after Exposure



The overall results for blood transfusion patients and plasma derivative patients are summarised in Figure 4.9. This shows the total number of new infections per infected donations for the two groups, as well as the additional contribution that would result from blood transfusion recipients donating blood. From this plot it can be seen that if the fraction of donations infected is less than 10^{-4}, then there will be about 2.6 new infections per infected donation, with about equal contributions from blood transfusion patients and plasma derivative patients. At higher fractions of blood infected there will be relatively more blood transfusion patients infected than plasma derivative patients. This is because the numbers of blood transfusion patients infected can go on increasing, whilst the Group N patients, which dominate the plasma derivative group, rapidly reach the total number of patients in the group.

Figure 4.9 New Infections per Infected Donation in First Year after Exposure



4.8 Additional Infections due to Recipients Donating

Some recipients of both blood components and plasma derivatives are able to donate blood at a later stage, and this forms a feedback mechanism that may eventually increase the number of people infected. It is assumed that 50% of new acute patients are able to donate once recovered, allowing for those that do not survive the episode or who are barred from donating for other reasons, whilst patients receiving on-going blood treatment are unable to donate at a later stage (see Tables I.7.1 and I.7.2). At a prevalence of 10^{-6}, each infected donation results in 2.2 new infections, of which 0.3 are predicted to survive the episode and be fit to donate at a later stage. If it is assumed that these people are as likely to donate as average among the population, with 0.043 donations per person per year (Appendix I.3.1), then each infected donation would lead to a further 0.013 infected donations per year. Although the average incubation period is taken as 15 years, the time between recovering from the episode requiring transfusion and falling sick with vCJD would be less, and an average period of 12 years is assumed. Thus each infected donation would lead to a further 0.15 infected donations. Since each of these leads to further infected donations in turn, the overall total is $0.15 + 0.15^2 + 0.15^3 + \ldots = 0.18$. Hence this feedback is estimated to amount to an 18% increase in overall infections for the base case.

4.9 Numbers of vCJD Cases by Patient Group

The incidence of predicted vCJD cases from blood components and plasma products per infected donation are shown in Figure 4.10 and the individual risk of vCJD cases occurring for selected patient groups in Figure 4.11. From Figure 4.10 it can be seen that a total of

about 0.75 new vCJD cases are predicted per infected donation, with about equal contributions from transfusion cases and plasma derivatives, while the prevalence is below about 10^{-4}. At higher prevalence the number of cases will increase, but the proportionate rise is less.

As shown in Figure 3.2, no scenarios are expected to result in a prevalence higher than 10^{-2}, and many scenarios do not exceed a prevalence of 10^{-4}.

In Figure 4.11 it can be seen that there are two patient groups that have an individual risk of getting vCJD that is significantly greater than all the others. These are Group N (patients receiving i/v IgG), and Group J (Haemophilia A patients). The risk of *infection* becomes 1 for Group N at a prevalence in excess of 10^{-3} and for Group J at a prevalence in excess of 10^{-2} (see Figure 4.8). The risk of vCJD cases then depends on the assumed survival probabilities. Together these two patient groups comprise 80% of the vCJD cases resulting from plasma derivatives.

The high risk contributions for i/v IgG, and intermediate purity Factor VIII (Type 8Y) reflect the relatively high infectivity per dose for these products as shown in Figure 4.4. It should be recalled that the infectivity estimate is based on the infectivity in the plasma fractions found in Brown & Rohwer's experiments combined with the protein content in the final product (see section 4.4). This assumes that subsequent processing steps have no further effect on the infectivity. This could be very pessimistic, especially for a product like i/v IgG which has several additional steps that would be likely to reduce infectivity.

Figure 4.10 Incidence of vCJD Cases due to Blood Products

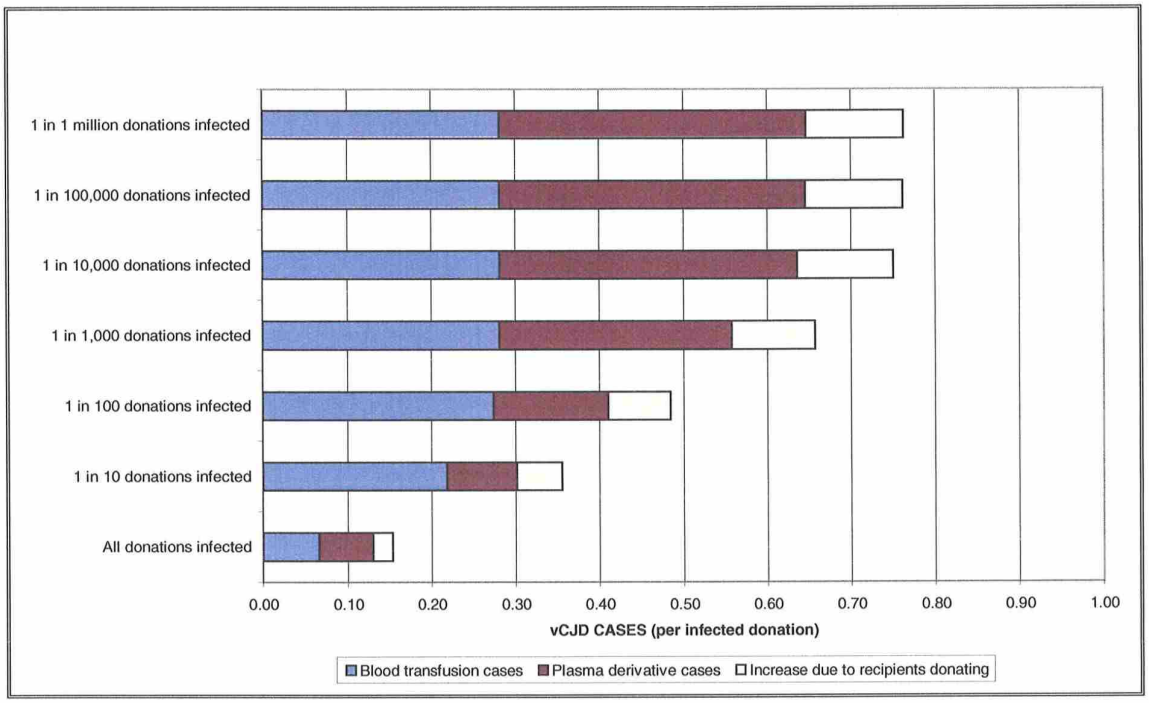
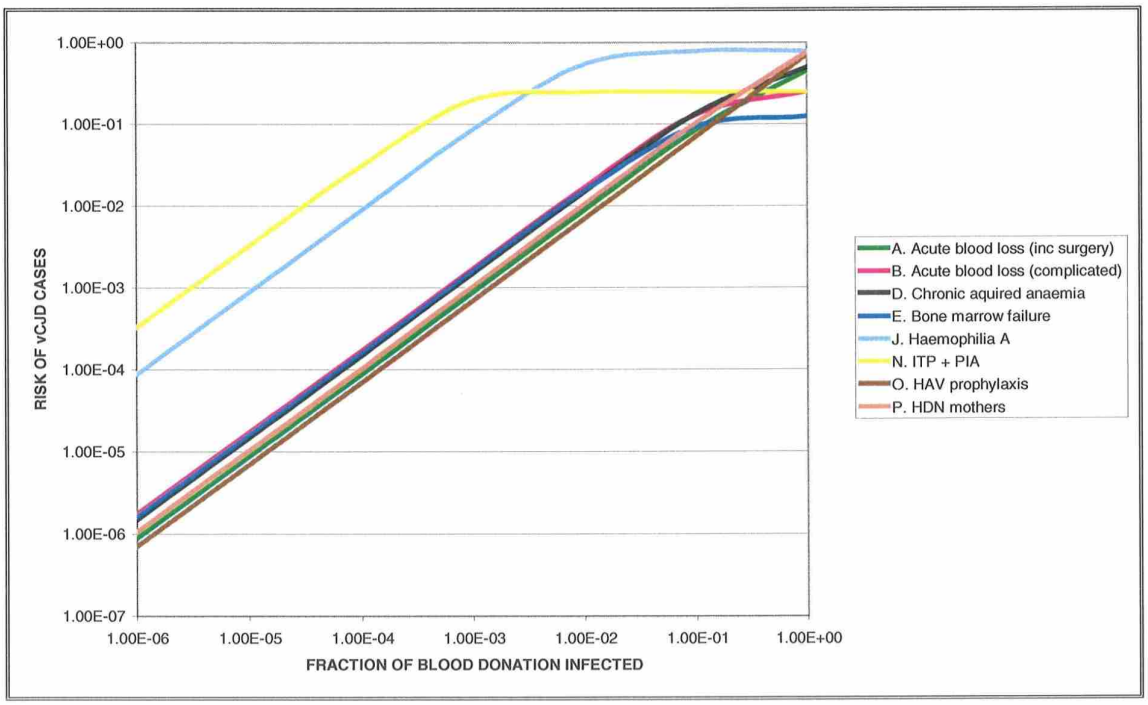


Figure 4.11 Risk of vCJD Cases by Patient Group



5. SENSITIVITY ASSESSMENT

5.1 Sensitivity to Assumptions about Food Exposure

For sensitivity tests in this report, the chosen measure of risk is the number of additional vCJD cases per infected donation. This is a relative measure of the risk increase due to blood, and attempts to be independent of the actual level of risk. Clearly, the first test that is required is to show its sensitivity to the prevalence of the disease (i.e. the actual number of infected donations).

The sensitivity of the number of cases per infected donation to the fraction of donations that are infected has already been shown as Figure 4.10. As expected, this shows very little effect while the prevalence is below 10^{-4}, corresponding to roughly 5,000 people infected and 200 infected donations per year. Greater numbers of infections produce more cases in total, but the rise is less than proportionate, resulting in smaller numbers of cases per infected donation. In simple terms, the limited number of patients in each category begin to receive more than one infective dose per year, so that additional infected donations produce no more cases in these categories.

Hence, the chosen form of presentation is independent of the number of people infected, provided this number is low. If the number of people infected is above about 5,000, the presented ratios will tend to over-estimate the risks, and hence may over-estimate the effects of risk reduction measures.

5.2 Sensitivity to assumptions about blood infectivity

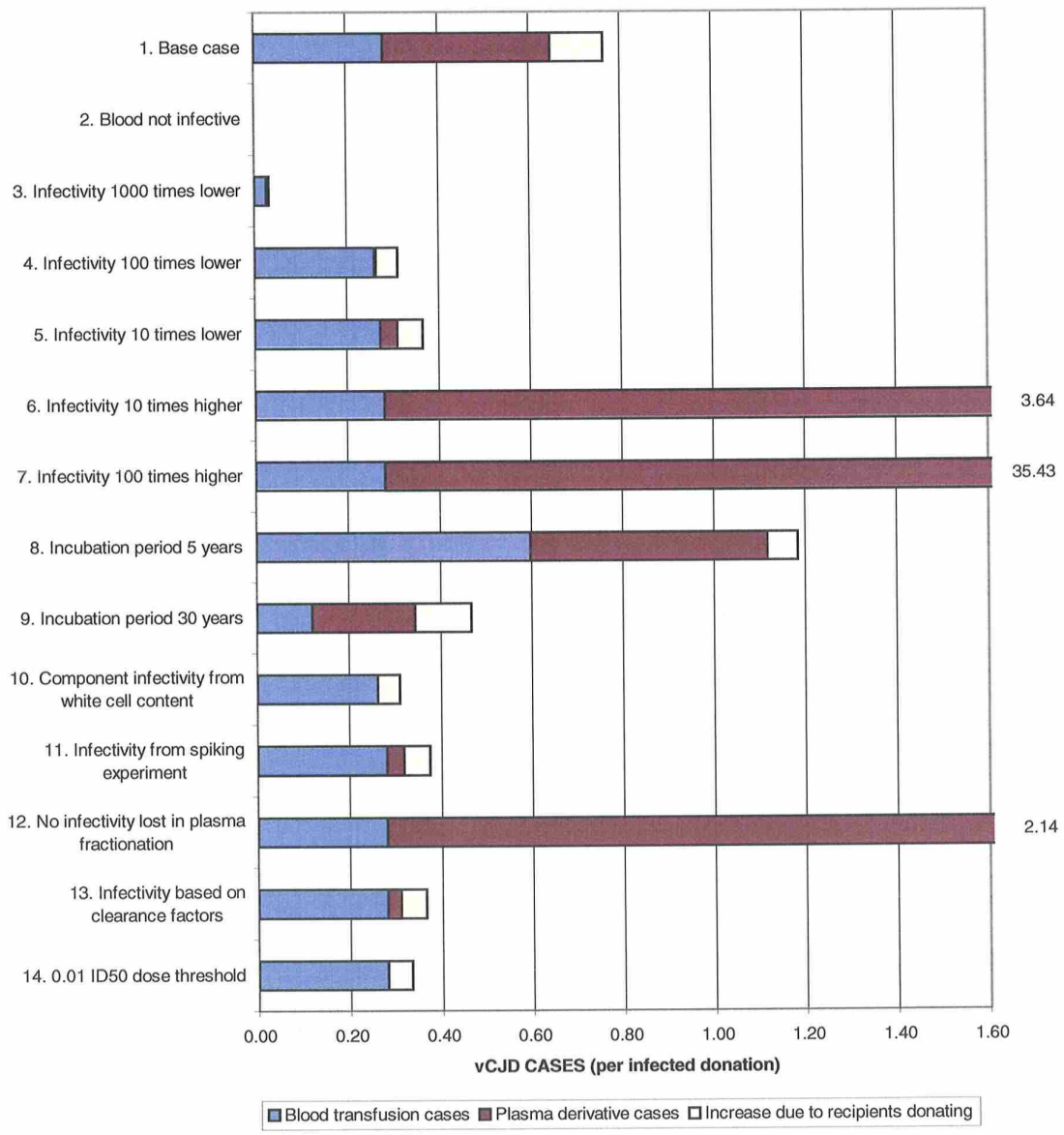
Figure 5.1 shows the sensitivity of the risk result (the number of cases per infected donation) to the key assumptions about blood infectivity listed in Appendix IV. They are compared to a "Base Case" or reference case. This reference case assumes that blood from a person infected with vCJD contains infectivity at 1 i/v ID_{50}/ml, and the distribution between the blood components and plasma fractions is based on the endogenous experiment of Brown et al as described in Sections 4.3 & 4.4.

The effects can be summarised as follows:

1. If human blood is not infective, then clearly all risk results in this report become zero. The assumption that blood is infective is therefore fundamental to this study.

2. Infectivity of blood in various animal experiments shows a range from 100 times lower or higher than used in the base case. As shown by bars 4 to 7 in Figure 5.1, the risk from blood components is virtually unaffected within this range. This is because the estimated infectivity in an average red cell unit is nearly 200 ID_{50}, and hence an infected unit would still deliver an infective dose even if the infectivity were 100 times lower. The risk from plasma derivatives varies roughly in proportion to the level of infectivity. This is because the infectivity per dose is always less than 1 ID_{50}. Hence, within this range, the assumed infectivity in blood is only important for the risk from plasma derivatives.

Figure 5.1 Effect of Assumptions About Blood Infectivity on Number of Cases per Infected Donation



3. The intravenous route could be up to 100 times less efficient than assumed in the base case. The effects of this are as for the general level of infectivity above. If the combined effects of lower i/v efficiency and lower overall infectivity were considered, this might produce an overall i/v infectivity 1000 times lower than assumed. The risk from blood components would then be significantly reduced as shown by bar 3 in Figure 5.1. Variations in infectivity through the incubation period could mean that the average level of infectivity was 10 times higher or lower than assumed. The effects of this are as for the general level of infectivity above.

4. The incubation period for vCJD derived from blood might be as low as 5 or as high as 30 years. Longer incubation periods increase the potential for recycled infectivity as transfusion recipients donate blood, and this would make a small increase in the number of new infections. However, as shown by bars 8 & 9 in Figure 5.1, the effect on the number of vCJD *cases* is outweighed by the fact that longer incubation periods would make blood recipients more likely to die from other causes before developing any vCJD symptoms. Hence longer incubation periods would lead to fewer vCJD cases.

5. If only the 37% of people who are homozygous for methionine at Codon 129 were vulnerable to infection, the number of infections and cases would be reduced by 63% for all blood products.

6. If the split of infectivity between the blood components were based on the white cell content as shown in Figure 4.2, the risk from plasma derivatives would be virtually eliminated (bar 10, Figure 5.1). Although this approach would give much lower infectivity in red cells, the contribution from the buffy coat in many units would offset this and hence there would be little effect on the risk for blood component patients. If the split of infectivity were based on the spiking experiment of Brown et al (Appendix II.3.6.4), this would also greatly reduce the risk from plasma derivatives (Figure 5.1, bar 11).

7. If the split of infectivity between the plasma fractions were based on the endogenous experiment excluding lost infectivity, this would greatly increase the risk from plasma derivatives (Figure 5.1, bar 12). The assumption that the experiments are correct in showing lost infectivity in fractionation is very significant for the risk from plasma derivatives.

8. If the infectivity in plasma derivatives were based on clearance factors, the risk from plasma derivatives would be significantly reduced (Figure 5.1, bar 13). Hence, the choice of the approach based on protein contents is clearly very significant for the risk from plasma derivatives.

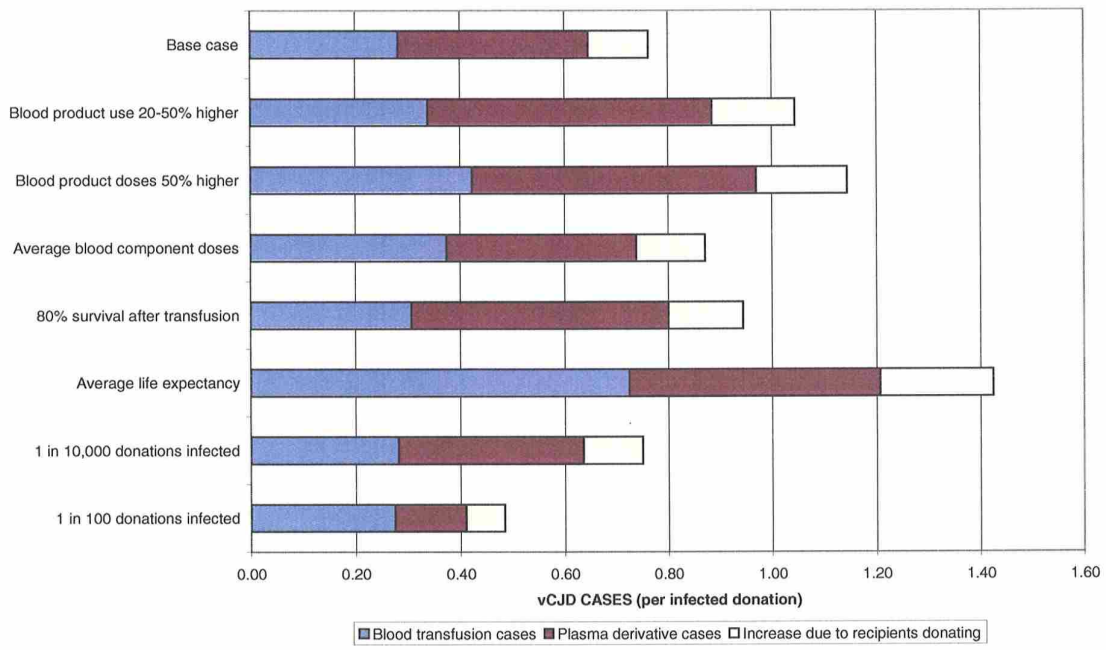
9. Uncertainties in the protein contents of plasma fractions and plasma derivatives are assumed to be 20% higher or lower, and would have the same effect on the risks. These are negligible compared to other uncertainties.

10. If the dose-response function for vCJD infectivity were given a threshold of 0.01 ID_{50}, the risk from plasma derivatives would be virtually eliminated (Figure 5.1, bar 14), but the risk from blood transfusions would not be affected. Hence, the choice of a linear dose-response function is very significant for the risk from plasma derivatives.

5.3 Sensitivity to Assumptions about Patient Exposure

Figure 5.2 shows the sensitivity of the risk result (the number of cases per infected donation) to the key assumptions about patient exposure listed in Appendix IV.3. The same reference case is used.

Figure 5.2 Effect of Assumptions About Patient Exposure on Number of Cases per Infected Donation



The effects can be summarised as follows:

1. If the total numbers of blood components (red cells, FFP and platelets) transfused were 20% higher or lower, the blood component risk would change by the same amount.

2. If the average numbers of blood component units per patient transfusion were 50% higher or lower, the blood component risk would change by the same amount.

3. If it were assumed that all patients receive average numbers of blood component units per year, thus eliminating the assumptions about patient groups, the total risk would increase by 14%. This relatively small change suggests that the assumptions about patient groups are not important to the overall risk.

4. If the total numbers of plasma derivative doses used were 50% higher or lower, the plasma derivative risk would change by the same amount.

5. If the average numbers of plasma derivative doses per patient year were 50% higher or lower, the plasma derivative risk would change by the same amount.

6. If the average survival probability following transfusion was taken as 80% instead of 50%, the total number of cases would increase by 24%, but the number of infections would be unaffected.

7. If the life expectancy of blood product patients were taken as 40 years, thus eliminating the assumptions about life expectancy for patient groups, the total number of cases would increase by 87%, but the number of infections would be unaffected.

These sensitivity tests indicate that the uncertainties about patient groups are much less significant than those about blood infectivity, and that their main effect is on the probability of developing vCJD following infection.

5.4 Conclusions

The following conclusions are drawn from the above sensitivity tests.

1. The number of new infections per infected donation resulting from blood components (red cells, FFP and platelets) is relatively robust and is unaffected to within about a factor of 2 by most tested parameters. The key assumption that has a greater effect than this is the overall level of infectivity. If the infectivity were 1000 times lower than estimated, the number of infections would be 10 times lower than estimated. However, reductions of only 100-fold would have negligible effect. If only 37% of people were genetically susceptible to infection, the number of infections would be 2.7 times lower than estimated.

2. The number of vCJD cases per infected donation resulting from blood components is slightly less robust. It is significantly affected by the overall level of infectivity, as above. It is also affected by the incubation period - if this was less than 5 years, the number of cases would be 2.1 times higher than estimated. It is also affected by the life expectancy of transfusion patients - if this was as high as average for the population, the number of cases would be 2.6 times higher than estimated.

3. The number of new infections per infected donation resulting from plasma derivatives is highly uncertain. Some changes in assumptions would increase it by a factor of 10 or more - increases in the overall level of infectivity by the same amount, or assuming no infectivity was lost in plasma fractionation. Many other changes in assumptions would virtually eliminate the risk from plasma derivatives - reductions in the overall level of infectivity by a factor of 10 or more; plasma infectivity based on white cell content; plasma derivative infectivity based on clearance factors; use of a threshold dose of 0.01 ID_{50}.

4. The number of vCJD cases per infected donation resulting from plasma derivatives is even more uncertain than the number of infections. It is significantly affected by the factors identified in (1), (2) and (3) above

The parameters that are most uncertain, and hence most deserving of further research, are as follows:

- Whether or not blood is infective, and the actual level of infectivity via the i/v route. Here, the key issue is whether it is more than 1000 times less infective than indicated by Brown et al. Infectivity at such low levels would be very difficult to detect, but this is one of the key uncertainties that may lead to lower risks than estimated here.

- The partitioning of infectivity between the blood components. Here, the key issue is whether the infectivity follows the white cell content or whether there is infectivity in plasma as indicated by the experiments of Brown et al.

- The partitioning of infectivity between the plasma fractions, and the level that remains in plasma derivatives. Here, the two available approaches give widely different results.

- The incubation period of the vCJD infection in humans.

- The life expectancy of patients following blood transfusion.

- The overall prevalence of vCJD among the human population. This parameter is relatively unimportant for the relative risk measures adopted here, but would be much more important for the absolute risk levels.

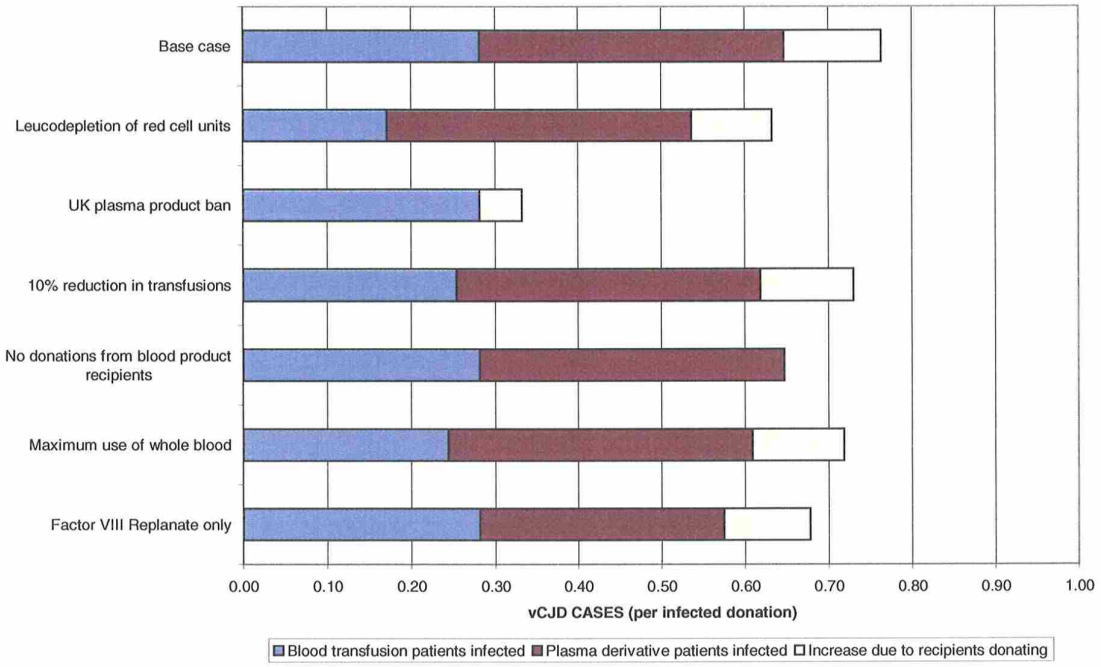
6. MEASURES TO REDUCE RISK OF INFECTION FROM BLOOD

6.1 General Approach

Various possible measures have been suggested to reduce the risk of infection with vCJD from blood products. Some measures (elimination of UK plasma products and leucodepletion of red cell units) are being implemented following recent announcements. Others are still under consideration. In this section, their effects on the risk levels are investigated using the measure of the number of new vCJD cases per infected donation.

Figure 6.1 compares the overall effects of all measures investigated. They are discussed in turn below.

Figure 6.1 Effects of Risk Reduction Measures on vCJD Cases



6.2 Leucodepletion

6.2.1 Definition

Recent work that has implicated B lymphocytes in the development of experimental scrapie, has suggested that infectivity may be contained in these cells. This has led to the suggestion that leucodepletion, the removal of white cells from the blood by simple filtration, could reduce the risk of infection.

6.2.2 Effect on Risks

As summarised in Appendix II, Section II.4.2, leucodepletion is believed to reduce the white cells by a factor of 10,000 compared to whole blood or red cell concentrate. This is based on

the number of intact cells and does not take account of cell fragments. An optimistic estimate would be that it had the same effect on the infectivity.

There are no experiments to show the effect of leucodepletion on infectivity, and other experiments on B lymphocytes have not confirmed their importance. The experiments by Brown et al show considerable infectivity in plasma, which is not consistent with the hypothesis that infectivity is proportional to white cell content.

Therefore it is appropriate to assume that leucodepletion reduces infectivity substantially, but by less than the reduction in the white cell content. The infectivity in leucodepleted red cells is therefore assumed to be 100 times lower than in red cells with buffy coat removed. Combined with the infectivity breakdown from Brown et al, this gives infectivity 400 times lower than in whole blood. A factor of 10,000 will be used as a sensitivity test.

Based on the infectivity breakdown from Brown et al, the infectivity of a red cell unit is 210 ID_{50}, or 110 ID_{50} with buffy coat removed. The infectivity of a leucodepleted red cell unit is therefore estimated as 1 ID_{50}. This gives a 50% probability of infection for recipients, compared to 100% at present. However, allowing for infections from platelet and FFP units, assumed not to change under this scenario, the reduction in infections of blood component patients is estimated as 36%. Allowing for unchanged infections of plasma derivative patients, the overall reduction in the number of vCJD cases is estimated to be 17% (see Figure 6.1).

6.2.3 Sensitivity Tests

The estimated benefit is very sensitive to the effect of leucodepletion on the infectivity, and also to the overall level of infectivity in red cell units.

If the level of infectivity in blood is less than that assumed or the effect of leucodepletion is greater, the estimated benefit of leucodepletion would increase significantly. If leucodepletion reduced the infectivity by a factor of 10,000 compared to whole blood it would virtually eliminate red cells as a cause of infection, with the overall reduction in vCJD cases reaching 37%, as compared with 17% given above. This percentage benefit would increase if the contribution of plasma derivatives reduced as well, as it does in several sensitivity tests.

Conversely, if the effect of leucodepletion was less than assumed, or if the overall level of infectivity was higher, leucodepletion would have negligible benefit.

6.2.4 Non-Risk Factors

Leucodepletion has some therapeutic benefits, as reflected by the minority of red cell units that are already being leucodepleted. Some countries only use leucodepleted blood for this reason, and others are planning to do so. It is clearly practical and within current technology. Its main dis-benefit is cost, but this is understood not to be an over-riding constraint.

6.2.5 Conclusion

Leucodepletion appears to have significant benefit in reducing risk of vCJD infection through blood. However, the degree of benefit is extremely uncertain, due to a lack of experimental investigation and uncertainty in the level of infectivity in blood. Since there are some

scenarios where leucodepletion has significant benefit, and considerable uncertainty about those scenarios where it does not have benefit, it would be prudent to adopt leucodepletion as a risk reduction measure.

6.3 Elimination of UK Plasma Products

6.3.1 Definition

In May 1998, following a review by the Committee for Safety of Medicines, the Secretary of State for Health decided that, since the theoretical risk that vCJD could be transmitted by blood products cannot be discounted, UK plasma should no longer be used for the manufacture of pooled plasma derivatives. In May 1998, BPL discontinued fractionation of UK fresh frozen plasma, and now fractionates plasma imported from the USA, from which products will become available during 1999.

The analysis in this report refers to 1997/98, the last full year of manufacture from UK plasma. The following section addresses the benefits of the changes already implemented.

6.3.2 Effect on Risks

It is very difficult to make any assessment of the risk that there may be people infected with vCJD in the country from which the plasma would be sourced. For the present study, it is assumed that the replacement plasma does not contain any vCJD infectivity; in other words that the prevalence of vCJD in the source country is negligible. This then eliminates the risk from plasma products.

The results given in Section 4 show that plasma products are estimated to account for 41% of patients infected and 49% of new vCJD cases due to blood. Eliminating the risk from plasma products would therefore reduce the total by this amount.

6.3.3 Sensitivity Tests

The sensitivity tests in Section 5 show that the estimated risk from plasma products is highly uncertain. The risk may be much higher than estimated, or may be entirely negligible. The benefit of eliminating UK plasma products is similarly very uncertain.

6.3.4 Non-Risk Factors

The use of foreign sourced plasma introduces a risk of importing some other, possibly unknown, infective agent, which is difficult to quantify. However, suppliers of plasma will need to demonstrate that they have equivalent safety checks and quality controls as would have been the case with UK sourced plasma. This measure may also have an impact on the availability of some of these products, both in the UK and elsewhere.

6.3.5 Conclusion

Eliminating UK plasma products will clearly eliminate any risk there may have been from infectivity in these products, assuming there is no vCJD in the source country. However, the degree of benefit is highly sensitive to several uncertain assumptions. The uncertainty here is not how effective the measure would be, but the magnitude of the risk from vCJD in plasma

products that it is mitigating. Since there are some scenarios where the risk is significant, the UK plasma product ban could be considered prudent in the absence of better information.

6.4 Reduction in Use of Blood Components

6.4.1 Definition

With over half of the risk from vCJD in blood coming from transfusions of red cells, and to a lesser extent platelets and plasma, any reduction in the use of blood will result in a reduction in the numbers of new cases. Clearly blood is normally only given because of need. However there are variations in the usage of blood between different hospitals, and this suggests that critical consideration of the need for blood, or the amount to be transfused, could lead to a reduction in usage. A reduction in the unnecessary use of blood would bring a range of other benefits, and it is understood that an initiative on this has been started by the Chief Medical Officer.

6.4.2 Effect on Risks

As an illustration, a reduction in usage of blood components by 10% is estimated to lead to 10% reduction in infections from blood components, and a 4% reduction in overall new vCJD cases due to blood. This will only bring a benefit if the reduction in use is very carefully targeted at unnecessary usage. In general, the benefit to a patient in need of a transfusion will far outweigh any risks from vCJD infectivity in the blood.

Assuming that blood is only given because of need, a reduction in usage of blood components would be expected to lead to an increase in risk from the condition requiring the transfusion. Surprisingly, no data is available on this. Since the overall probability of death following blood transfusion is estimated as 50%, even a small change in this would outweigh the extra risks from vCJD infection, even if the prevalence of infection in the blood supply were very high.

6.4.3 Conclusion

The risk of vCJD infection from blood transfusion needs to set against the benefit that the patient would derive from the transfusion. In the absence of data on the latter, this balance is impossible to quantify at present. Nevertheless, since blood transfusion appears to involve a risk of vCJD infection, it would be sensible to minimise blood transfusions wherever possible. If blood usage could be reduced without increasing risk to patients, it would be moderately effective in helping to reduce the exposure to any infectivity in blood.

6.5 Prevention of Transfusion Recipients Giving Blood

6.5.1 Definition

If recipients of blood transfusions are the people most at risk from vCJD infectivity in blood, then preventing them giving blood could remove the possibility of a feed back loop that could result in further infections.

6.5.2 Effect on Risks

It has been estimated that about 6% of blood donors have received a transfusion in their life. However, this figure is very uncertain, and it is possible that transfusion recipients may account for up to 20% of blood donations.

The contribution to risk from people infected by blood transfusion subsequently donating blood and infecting other people has been very crudely estimated to provide an 18% addition to the overall risk levels. Therefore, if transfusion recipients were prevented from donating blood, the risks would be reduced by this amount.

6.5.3 Sensitivity Test

The above estimate is based on a simple distinction between patient groups who are treated on a one-off basis and those who have chronic conditions and would therefore be unfit to donate blood in later life. It also assumes that the former group of transfusion recipients, on average, give the same number of donations per year after transfusion as the population average. This may be an under-estimate, in which case the additional risk from transfusion recipients would be higher than estimated.

6.5.4 Non-Risk Factors

Because transfusion recipients are often committed donors, preventing them from donating blood could have an adverse impact on the blood supply. It is possible that this would result in greater risk due to scarcity of blood than the risk reduced by this means.

6.5.5 Conclusion

Preventing recipients of blood transfusions from donating blood could result in a moderate reduction in the additional cases of vCJD due to infectivity in blood. This should be balanced against the need to avoid adverse impacts on the overall blood supply.

6.6 Maximising Use of Whole Blood

6.6.1 Definition

Severely ill patients are often treated with red cell, platelet and FFP units derived from different donors. One possible change would be to make more use of whole blood derived from single donors.

6.6.2 Effect on Risks

The maximum benefit of this has been estimated by assuming that all patients requiring two or more different components are given whole blood from single donors. This is estimated to reduce the number of infections from blood components by 20%, and the total vCJD cases from blood by 5%. The relatively modest effect on the number of cases arises because the greatest benefit is obtained for more severely ill patients, who are less likely to survive to develop the disease.

6.6.3 Sensitivity Test

If the infectivity of blood in general was lower, but the proportion due to plasma remained high, it is possible that the use of whole blood could increase the risk rather than reduce it in a few scenarios.

6.6.4 Non-Risk Factors

Therapeutic issues in this measure have not yet been investigated.

6.6.5 Conclusion

Using whole blood rather than components derived from separate donors may be preferable for some patients, but the overall benefit appears small and uncertain.

6.7 Autologous Transfusions

6.7.1 Definition

Autologous transfusions involve collecting blood from patients in advance of a planned operation and returning it to them during or after the operation. Up to 4 pre-deposit autologous transfusions can be collected at weekly intervals pre-operatively. There may be some scope for increasing the use of this procedure as a way of reducing the risk of infection through blood transfusions.

Autologous transfusion is not widely used in the UK. In the NBS it accounts for only 0.05% of blood donations. In countries where this approach has been actively promoted, autologous transfusion accounts for approximately 5% of red cell usage. For this study, it is assumed that autologous transfusions could eventually reach this level in the NBS.

6.7.2 Effect on Risks

The effect of 5% autologous transfusions on risks of vCJD infection would be roughly half of that estimated above for a 10% reduction in blood components. This would be a 5% reduction in infections from blood components, and a 2% reduction in overall new vCJD cases due to blood

6.7.3 Non-Risk Factors

Autologous transfusion may reduce the risk of incompatibility and infection from some agents, but its relatively unusual nature introduces other risks of procedural errors and bacterial contamination. Bacterial contamination may be just as common as with donor blood, since its main source is from the skin puncture at the time of collection.

6.7.4 Conclusion

Maximising autologous transfusions could make a small reduction in the risk of vCJD due to infectivity in blood.

6.8 Use of Pooled Plasma

6.8.1 Definition

A source of virally activated plasma is now available, produced from German volunteer donors using 600-donor pools. This could be used by NBS instead of UK plasma for clinical applications of FFP. For the present study, it is assumed that UK FFP could be entirely replaced by this source.

6.8.2 Effect on Risks

As for the UK plasma product ban, quantifying the effects of this requires an assumption about the prevalence of vCJD among the donor population in the source country. If this were negligible, the risk from FFP would be eliminated. Then there would be a 12% reduction in infections from blood components, and a 4% reduction in overall new vCJD cases due to blood

However, if the prevalence of vCJD among the German donor population were the same as in the UK, pooling the plasma among 600 donors would cause a significant *increase* in the risks of infection through blood transfusion, unless the prevalence was already higher than 1 in 600.

Based on the infectivity breakdown from Brown et al, the infectivity of a plasma unit is 240 ID_{50}. If 1 out of the 600 units in the pool were infected, this would be sufficient to cause 120 infections, compared to the 1 that would result if the units were kept separate. This is estimated to cause a factor of 16 increase in infections from blood components. Allowing for the relatively low survival probability for FFP recipients, it is estimated to cause a factor of 6 increase in overall new vCJD cases due to blood.

6.8.3 Sensitivity Test

The estimated effects are clearly very sensitive to the assumed prevalence of vCJD infection among the donor population. They are also sensitive to the contribution of plasma to total infectivity derived from the experiments by Brown et al. If the infectivity breakdown based on white cells were used, the contribution of plasma to risk would be negligible, and this measure would have virtually no effect.

6.8.4 Conclusion

Despite the large uncertainties, two conclusions can be drawn from this case. First, replacing UK blood donations with otherwise equivalent products drawn from sources with lower prevalence of vCJD infection is clearly beneficial, although demonstrating the levels of vCJD prevalence in a population would be extremely difficult at present. Second, pooling plasma products would have a seriously adverse impact unless the infectivity in plasma was at least 200 times lower than estimated here.

6.9 Conversion to High Purity Factor VIII

6.9.1 Definition

Factor VIII is predicted to be a significant contributor to risk from plasma derivatives, and much of the risk comes from the intermediate purity product that includes a significant proportion of the protein present in the cryoprecipitate whereas the high purity form produced by monoclonal antibody affinity chromatography, is predicted to have much lower risks. Therefore, converting production entirely to the high purity form would be a possible measure.

6.9.2 Effect on Risks

This measure is estimated to achieve a 10% reduction in infections from plasma derivatives. Because of the relatively high survival probability for haemophiliacs, it would also achieve a 10% reduction in overall new vCJD cases due to blood.

6.9.3 Sensitivity Test

This measure is very sensitive to the several factors that influence the overall risk of plasma products. If infectivity were based on white cell content, it would have no significant effect. The relatively low infectivity of the high purity form derives from the experimental evidence for low infectivity in Fraction V, used to manufacture the ablumin excipient, together with the estimate of plasma product infectivity based on the protein content from each plasma fraction, assuming no preferential concentration in the Factor VIII. If this approach was invalid, the difference between the high and intermediate purity products might be reduced.

6.9.4 Non-Risk Factors

Given that UK plasma products have already been banned in totality, it would be difficult to secure public acceptance for reducing this to a selective ban.

6.9.5 Conclusion

Although a selective ban on intermediate purity Factor VIII products can achieve a significant risk reduction, the uncertainties are too great to have confidence in the validity of this estimate. It is also no longer relevant following the ban on the use of UK sourced plasma.

6.10 Prophylaxis Treatment against vCJD

6.10.1 Definition

Of the various chemicals that have been tested for their affect on TSE disease or prion formation, particular attention has been given recently to the polysulphonated polyglycosides (PGs), which include dextran sulphate 500 and pentosan polysulphate. It has been suggested (e.g. Dealler, 1998) that PGs could be used to reduce the risk of infection following exposure to potentially contaminated blood. In vitro studies (Caughey et al, 1993 & 1994) have indicated that PGs interact with PrP at an heparan binding site on the molecule and inhibit the production of PrP^{Sc}. This suggests that PGs could be effective with a range of TSEs. There have been a number of in vivo studies with a limited selection of strains of mice and strains of scrapie (e.g. Ehlers & Diringer, 1984; Farquhar & Dickinson, 1986; Kimberlin & Walker,

1986; Diringer & Ehlers, 1991). These studies have shown that in general treatment with a PG prior to or after inoculation with scrapie results in a reduced susceptibility to infection, in terms of both an increase in the incubation period and an increased survival probability, especially at low doses of infectivity. They indicate an apparent loss of infectivity of 1 to 2 logs in the animal models, although there is considerable variation in the effects.

With no specific proposal for a prophylactic treatment, this risk reduction measure has been included as an hypothetical example to illustrate the potential benefit and to compare with other measures, such as leucodepletion. For this purpose, it has been assumed that recipients of blood components would be treated over a period following a transfusion. With the slow development of TSEs, it has been suggested that treatment with PGs may still be effective some time after exposure to the infective agent (Dealler, personal communication), at least before the infectivity has spread to the central nervous system, but this needs to be verified experimentally. Thus it is possible that patients could be given the prophylactic treatment after they had recovered from whatever had required the blood transfusion.

6.10.2 Effect on Risks

At present PGs have only been tested in a limited range of animal models, and so it is not possible to be certain how effective prophylactic treatment with a PG, such as pentosan polysulphate, would be against any vCJD infectivity that may be present in blood. Evidence from animal studies suggests that it could reduce the infectivity by 2 logs, and it is possible that at low levels of infectivity, such as may be present in blood, the PG could prevent the conversion of PrP^{c} into PrP^{Sc} and so prevent the disease developing. The effect on the risk of infection will depend on both the level of infectivity present in the blood and on the effectiveness of the treatment. If infectivity is reduced by 2 logs, then its effectiveness will be similar to that predicted for leucodepletion. If infectivity is reduced by more than this, and the level of infectivity in blood is no more than assumed for the base case in this report, then this treatment would significantly reduce the risk of infection for those treated. A combination of leucodepletion and prophylactic treatment could provide a high level of protection against all likely levels of infectivity in blood.

6.10.3 Non Risk Factors

As noted above, there is no proof available that PGs would be effective against vCJD, and the necessary experiments would take some years to yield results. The use of a drug, the effectiveness of which it is hard to prove, in order to mitigate a theoretical risk will raise some difficult questions, even if the drug has a low toxicity.

6.10.4 Conclusion

There is reasonable evidence to suggest that PGs can affect the build up of PrP^{Sc}, and so reduce the effective infectivity of a TSE. However, its effectiveness has only been tested in a limited range of animal models. If it was found to be effective with vCJD, and the toxicity effects were acceptable, this could prove to be a worthwhile risk reducing measure and would be worth investigating further. The toxicity of the drug and any known side effects, including its anti-coagulant properties, would need to evaluated carefully, and balanced against the expected benefits, recognising that this usage could involve a large number of people.

7. CONCLUSIONS

1. It is not possible to make any firm predictions about the level of risk from any vCJD infectivity that may be present in the blood of people incubating the disease. With our current level of knowledge, it is not possible to draw any firm conclusion as to whether or not infectivity can be transmitted through blood transfusions or plasma derivatives and the number of people who may have been infected with vCJD is simply not known. For these reasons it has not been possible to estimate the absolute level of risk and the results have been presented in terms of the risks per infected donation.

2. The evidence for infectivity in blood is based on experiments with animal models that have shown that blood from an animal artificially infected with a TSE (transmissible spongiform encephalopathy) can be infective when inoculated intracerebrally into the same species. There has been a single report of a TSE being successfully transmitted by blood transfusion in an animal model, but this result has not been verified or published. All other such experiments with animal models have failed.

3. Infectivity appears to be linked to white blood cells, but it may also occur in other components. Some experiments have shown significant levels of infectivity in plasma and this is not consistent with the hypothesis that infectivity is proportional to white cell content.

4. If it is assumed that blood from a person infected with vCJD can carry infectivity, and the level of infectivity is as suggested by the animal models, then the infectivity level in a full unit of red blood cells, platelets or plasma may be sufficient to cause infection. Patients receiving any of these products from an infected donation would therefore be at risk of infection. This conclusion seems to be valid across a wide range of assumptions regarding the infectivity of blood components.

5. The infectivity levels in certain plasma derivatives could be such that recipients of these products, if derived from a plasma pool containing a significant proportion of infected donations, would have a risk of infection. This result is highly uncertain, and varies significantly with the assumptions made about the level of infectivity and its distribution across plasma fractions.

6. The levels of infectivity in blood components and plasma fractions have been estimated based on experiments in an animal model. The applicability of these data to vCJD infectivity in human blood is not known, but they are the best data available. Estimates of infectivity in plasma derivatives have been based on these results together with an assumption that the infectivity in the product is proportional to its protein content and that there is no reduction in infectivity from further processing steps, such as fractionation, filtration and chromatography. This is considered to be very pessimistic, so that the estimated infectivities in plasma derivatives are likely to be over estimated.

7. Using these infectivity estimates, an infected donation is estimated to result in up to 2.6 new infections of which 0.8 are predicted to live long enough to develop vCJD. About half these new infections and cases are predicted to be due to blood transfusions and half due to plasma derivatives.

8. The sensitivity assessment has shown that the number of vCJD cases per infected donation resulting from blood components (red cells, FFP and platelets) is relatively robust across a wide range of tested parameters. For example, if the infectivity in blood were 100 times lower than the reference case it would have a negligible effect; if the infectivity is 1000 times lower the number of cases reduces by a factor of 10.

9. On the other hand, the number of vCJD cases resulting from plasma derivatives has been shown to be highly uncertain. An increase in infectivity by a factor of 10 would increase the number of cases by the same amount, whilst a reduction by a factor of 10 virtually eliminates the risk from plasma derivatives. Many other changes in assumptions would also virtually eliminate the risk from plasma derivatives; e.g. plasma infectivity based on white cell content; plasma derivative infectivity based on clearance factors, etc.

10. The effectiveness of a number of possible measures to reduce the risk of infection with vCJD from blood products has been assessed. No measures have been identified that can eliminate all the risk, but several provide significant risk reductions. In particular:

    - **Leucodepletion**. Leucodepletion appears to have significant benefit in reducing risk of vCJD infection through blood transfusion, although the degree of benefit is extremely uncertain. Since there are some scenarios where leucodepletion has significant benefit, and considerable uncertainty about those scenarios where it does not have benefit, it would be prudent to adopt leucodepletion as a risk reduction measure.

    - **Elimination of UK Plasma Products**. Eliminating UK plasma products will clearly eliminate any risk there may have been from infectivity in these products, assuming there is no vCJD in the source country. However, the degree of benefit is highly sensitive to several uncertain assumptions. The uncertainty here is not in how effective the measure would be, but the magnitude of the risk from vCJD in plasma products that it is mitigating. Since there are some scenarios where the risk is significant, the UK plasma product ban could be considered prudent in the absence of better information.

11. The other risk reduction measures considered were:

    - *Reduction in use of blood components:* If blood usage could be reduced without increasing risk to patients, it would be moderately effective in helping to reduce the exposure to any infectivity in blood.
    - *Preventing blood transfusion recipients donating blood:* Preventing recipients of blood transfusions from donating blood could result in a moderate reduction in the additional cases of vCJD due to infectivity in blood. This should be balanced against the need to avoid adverse impacts on the overall blood supply.
    - *Maximising use of whole blood:* Using whole blood rather than components derived from separate donors may be preferable for some patients, but the overall benefit appears small and uncertain.
    - *Autologous transfusions:* Maximising autologous transfusions could make a small reduction in the risk of vCJD due to infectivity in blood.
    - *Use of pooled plasma:* If the prevalence of vCJD among the donor population were negligible, the risk from fresh frozen plasma (FFP) would be eliminated. However, if

vCJD did exist among the donor population, pooling plasma would have an adverse impact unless the infectivity in plasma was at least 200 times less than estimated here.

- *Use of high purity Factor VIII:* Although a selective ban on intermediate purity Factor VIII could achieve a significant risk reduction, the uncertainties are too great to have confidence in the validity of this estimate.
- *Prophylaxis treatment against vCJD:* There is reasonable evidence to suggest that polysulphonated polyglycosides such as pentosan polysulphate can reduce the susceptibility to infection from TSEs in animal models, and its effectiveness as a prophylactic against vCJD is worth investigating further.

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