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ON vCJD TRANSMISSION THROUGH BLOOD COMPONENTS: RECONCILING MODELLED RISKS WITH CASE EVIDENCE

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Summary

EOR has modelled the possible secondary transmission of vCJD via blood and blood components. This paper attempts to test the plausibility of infectivity estimates (provided by consultants DNV) used so far to generate baseline scenarios for blood-borne infection. It argues that the resulting scenarios do appear to "over-predict" the possible number of infections via blood components to the end of 2002, though the many unknowns surrounding vCJD may prevent a definitive test.

Methodology

We explore two separate ways of checking the feasibility of scenarios, using data on:

- the histories of 129 clinical vCJD cases to date (few of whom have any record of being transfused)
- 33 incidents in which patients have received vCJD-implicated transfusions (none of whom have so far shown any symptoms of the disease).

Data on known clinical cases

Given DNV inputs on infectivity, the transmission model developed by EOR implies that many of the clinical cases seen to date would have been infected by blood components – an implausible result given the rarity of any transfusion history. The scale of this over-prediction depends on other assumptions: it is least pronounced for longer secondary incubation periods and shorter primary incubation periods. In most scenarios, a very large reduction in infectivity would be needed to reconcile model predictions with the case data. We also explore an alternative modification: that of a delay in the *onset* of infectivity in blood following primary infection. This appears a more promising way of reconciling the model with the data.

Recipients of implicated blood.

Data on the known "vCJD incidents" involving blood reinforces the point that if blood is as infective as suggested, very large intravenous doses must be followed by long incubation periods. This is evidenced by the symptom-free survival of individuals transfused with blood from donors who were found to be incubating the disease.

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1. INTRODUCTION

1.1 Analyses produced by EOR (EOR, 2001a; 2002a) have considered how many secondary vCJD infections might be caused by blood-borne routes, as a proportion of the primary outbreak. Though the main aim has been to examine the potential impact of specific options – e.g. the possible exclusion of blood component recipients from the donor pool – the analysis has more general implications. In particular, it suggests that the proportionate impact of blood-borne transmission could be large. In many scenarios, infections transmitted by blood components alone (leaving aside any risks posed by pooled plasma derivatives) would eventually exceed the number of primary infections.

1.2 EOR's previous work raised the question of how realistic such scenarios could be, given what is known about the vCJD cases recorded to date, and the Committee on the Microbiological Safety of Blood and Tissues (MSBT) requested further investigation of this point. A preliminary draft paper was produced in the first half of 2002, based on data on vCJD cases and recipients of implicated blood available to the end of 2001. The present paper updates that analysis. It uses data available to the end of 2002, and also makes use of a recent NBS pilot survey to more adequately model the expected survival of blood component recipients.

1.3 Though considering a wide range of scenarios, our models have taken some estimates for the potential infectivity of blood components provided by risk consultants DNV Ltd and used these as a baseline. Both EOR and DNV have emphasised the large uncertainties around any such estimates. Indeed DNV stress that their estimates are conditional on blood from donors incubating vCJD being infective. (There is no direct evidence at present for any infectivity in human blood, and DNV do not attempt to address this question.)

1.4 Given this uncertainty, and the lack of evidence for any blood-borne transmission to date, the question arises as to whether the DNV infectivity estimates are overly-pessimistic. This paper addresses this question. It considers whether the resulting scenarios for blood-borne transfusion are credible given current evidence on:

- The number of vCJD cases to date with a known history of blood transfusion
- Individuals who are known to have received blood components sourced from donors subsequently found to have vCJD, none of whom has so far shown any symptoms of the disease.

1.5 The longest section of the paper (Section 2) considers the former evidence, Section 3 the latter. In principle, both provide ways of starting to "calibrate" the transmission model and the inputs to it. However it is rather difficult to put clear-cut limits on feasibility, as each scenario for secondary transmission necessarily rests on a complex "bundle" of interrelated inputs and assumptions. (This applies particularly to infectivity levels, and the mean and distribution of secondary incubation periods.) Nevertheless Section 4 draws together some provisional conclusions for further discussion.

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2. EVIDENCE FROM vCJD CASES TO DATE

2.1 Methodology

2.1.1 The model developed by EOR is described more fully in the papers already cited. Given estimates for the infectivity of different blood products and data on their usage, it tracks the process of secondary (person-to-person) transmission against scenarios for the size and timing of the primary vCJD outbreak. It uses System Dynamics to generate alternative scenarios through time, taking account of the frequency of blood donations and the age distributions of both donors and recipients. We also make allowance for the poor survival rate of some recipients (many of whom are seriously ill or injured, and unlikely to survive long enough to develop vCJD symptoms).

2.1.2 While the existing analysis considers a wide range of scenarios, a starting-point is provided by the infectivity estimates prepared by DNV, based in turn on their reading of the published research literature. These are discussed further below. Despite the uncertainties around these estimates, their use makes one output of the transmission model strikingly robust. That is, anyone receiving a transfusion of *blood components* (whole blood, platelets, plasma, or red blood cells) from an infective donor would have received a very large dose prior to the introduction of leucodepletion in 1999 - potentially some hundreds of ID_{50}s.

2.1.3 Given the other assumptions underlying the transmission model, such recipients would have been infected with vCJD for certain. Furthermore, they might be likely to have comparatively short incubation periods before showing symptoms. The robustness of this finding within the model makes it attractive as a way of "calibrating" the transmission model.[1] Specifically, we can produce scenarios for the *proportion* of clinical vCJD cases to date that would have been caused by receipt of blood components. These can then be compared with the proportion of cases with any history of transfusion. The latter should provide an upper limit for the proportion of blood-borne infections, since those with a transfusion history *might* have been infected that way, while those never transfused must have been infected by another route.

2.1.4 Apart from the infectivity of blood components, the model's outputs will depend strongly on both primary and secondary incubation periods. Amongst clinical cases appearing so far, the predicted proportion of secondary infections will be greater

[1] Another approach toward calibrating the transmission model would be to apply it to the transmission of Sporadic CJD, given that incidence data are available for a much longer historical period. This form of calibration was carried out for the EOR model for vCJD transmission via surgical instruments [EOR, 2001 b]. In that case, however, surgery involving the CNS might be expected to encounter infectivity of a similar order for both diseases. For blood, the epidemiological evidence tells against sCJD being transmitted by transfusion, but there seems to be no reason to suppose that infectivity in sCJD would be as great as for vCJD, especially in view of the greater involvement of peripheral tissue in vCJD. One would thus expect the vCJD transmission model to "over-predict" cases of iatrogenic disease if applied to sCJD.

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- for shorter mean secondary incubation periods, and
- for longer primary incubation periods.

We have therefore considered a range of values for each of these.

2.1.5 A further consideration is the survival of those receiving blood components. This is a key concern here because someone infected with vCJD but dying of other causes before showing its symptoms will by definition never show up as a vCJD "case". So one explanation for a lack of observed blood-borne infections is simply that most of those infected would have died within the incubation period of the disease. The longer the mean secondary incubation period is, the more plausible this argument becomes. We therefore factor in, as adequately as possible, what is known about long-term survival after transfusion.

2.2 Data on clinical cases

2.2.1 CJDSU have kindly provided data, in confidence, on the transfusion histories of all 129 definite or probable cases of vCJD recorded to mid-December 2002. This shows that only 8 patients had a *reported* history of blood transfusion. Of these, three were transfused prior to 1980 (plus one in the late 1980s). Given the assumed timing of primary vCJD infections relative to the BSE outbreak, there are thus at least three cases in which the transfusion occurred too early to have been a possible source of vCJD infection.

2.2.2 If the reported case-histories are accurate, then, they suggest that *at most* 5 of cases could have been caused by receipt of blood components. It should be stressed that this is a maximum figure: it would remain perfectly possible for all 5 to have been infected by diet or some other route. Even allowing for the possibility of some under-reporting of transfusion, as discussed below, it seems fair to conclude that only a rather small proportion of the cases seen so far are possible candidates for blood-borne infection.

2.3 DNV Estimates of infectivity

2.3.1 DNV's work is based on critical reviews of the research literature. It represents a considered interpretation of that evidence, acknowledging the difficulty of reconciling estimates derived from different animal models and using different experimental procedures.

2.3.2 DNV's initial review (1999) proposed that whole blood should be regarded as having infectivity of the order of 1 intravenous ID_{50} per ml, present throughout the incubation period of the disease – i.e. between infection and onset of symptoms. A second study currently in draft (DNV, 2003) - suggests that this be increased by a factor of 2 (due to a reduction in the assumed differential between the efficiency of intracerebral and intravenous routes of infection).

2.3.3 DNV also consider the breakdown of this infectivity between the major components of blood - Red Cells, platelets and plasma. They also allow for the possible effects of product processing, in particular the filtering out of white cells (leucodepletion). This was considered to have a 100-fold effect on residual infectivity: however the impact of leucodepletion on plasma has been

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called into question. At the time of writing, DNV's suggestions on potential infectivity of blood components can be summarised in Table 1 below. These estimate the infectivity in each component within a unit of donated blood, similar volumes generally being contained in therapeutic units of each component (with the exception of platelets, as noted).

Table 1: Breakdown of Infectivity in blood components, as suggested by DNV, per donated unit of whole blood

Blood Product	**Infective dose** (i/v ID50)
Whole blood	900
Plasma Plasma (leucodepleted)	480 up to 480
Red cells Red cells (leucodepleted)	219 2
Platelets (leucodepleted)	2*

** Where units are produced by pooling 4 donations, this dose is per infected donation. Additional infectivity may also be carried by the plasma in which platelets are suspended.*

2.3.4 Even after leucodepletion, it can be seen that receipt of any unit would result in a dose of at least 2 ID_{50} - though only just, in the case of Red Cells. Used in conjunction with a simple linear dose-response model, these estimates imply that receiving an infected therapeutic unit of any component would result in certain infection. In addition, leucodepletion of plasma would need to reduce infectivity by a factor of over 200 to have any impact on the probability of infection, so this particular uncertainty has no bearing on the analysis offered here. It may also be noted that a very large proportion of transfusions (of the order of 80%) are of Red Cells, so the large majority of expected blood-borne vCJD transmissions would occur via this route.

2.3.5 Moreover the present analysis is concerned only with recipients already showing clinical vCJD symptoms. Had these patients been infected by blood products, this would very probably have been prior to the introduction of leucodepletion in 1999. For present purposes, therefore, we are concerned with the historical infection risks from non-leucodepleted products. In this scenario, such products would have carried some hundreds of ID_{50} per unit.

2.3.6 Within the logic of the model, receipt of an infected unit of any blood component would be more than enough to cause definite infection. For non-leucodepleted components, this result is insensitive to large changes to assumed infectivity. Any decrease becomes significant only if of the order of at least 100-fold.

2.3.7 The analysis also takes account of the additional risks arising from pooling of platelets. At present, about 40% of platelet units are derived from a single donor (using apheresis). The rest are manufactured from buffy coats from four separate donors. As argued elsewhere [EOR2002b], in high-infectivity scenarios this increases the risk of transmission by a factor of four. This is because a unit transfused would contain enough infectivity to transmit the

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disease for certain if any one of the four donors were infective. The model runs shown below contain an adjustment for this, on the basis of a constant 60% of platelets having been derived from pooled donations. (This will slightly underestimate the expected number of transmissions if apheresis has been less used historically than at present.) The adjustment does not have a large impact on the expected number of transmissions, as platelets comprise a small proportion of the total number of units transfused.

2.4 Survival of Recipients

2.4.1 As already noted, survival after transfusion is a key factor affecting the number of secondary infections that would show up as clinical vCJD cases. In previous versions of this analysis, this issue was modelled rather crudely by dividing recipients into those suffering from "acute" and "chronic" recipients, and then discounting a proportion of the former thought to die soon after transfusion. Here, however, a more satisfactory approach is adopted, based on new evidence on the longer-term survival of UK recipients of blood components.

2.4.2 This evidence has come from a study carried out by NBS in collaboration with Freeman Hospital, Newcastle upon Tyne. This as-yet unpublished study tracked the fate of patients transfused during a chosen month (June 1994) within the former Northern Region Health Authority. Though also intended as a pilot study for a larger national project, this is a substantial study in its own right, having tracked almost 3,000 patients in receipt of over 14,000 units of blood components.)

2.4.3 This study provides plentiful data on survival at periods up to 5 years, broken down by component usage and by age. It also provides estimated survival rates for longer periods based on actuarial tables – noting that by 5 years after transfusion, survival appears to be essentially "normal for age".

2.5 Model runs with "DNV" Infectivity Inputs

2.5.1 Given the need to consider different scenarios, the transmission model has been re-run with a wide range of inputs for both primary and secondary incubation periods.

- Mean primary incubation periods of 10.3, 19 and 30 years are used. These correspond to illustrative scenarios from the large range generated in modelling of the primary outbreak by Ghani *et al* [1998], and also used in the EOR Risk Assessment for surgical transmission.
- Mean secondary incubation periods considered are of 3, 6, 9,12 and 15 years. [**DN**: current tables use just 3,9 and 15 – keep it simple, or fill in the gaps?] The range 3 – 12 years is used in the existing EOR Risk Assessments for blood-borne transmission, and also for surgery (endorsed in that context by SEAC). DNV assume a median of 15 years, and a 15-year mean is therefore included for completeness. However it should be noted that DNV's assumption is applied to blood-borne transmission in general, including both pooled plasma derivatives (where doses might be very small) and blood components

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transfused unpooled and in large volumes. The use of such a long incubation period in conjunction with such large assumed doses may be questionable: this is discussed at various points below.

- It is generally accepted that (at least for substantial doses) secondary incubation periods are liable to be shorter than primary, given the lack of any species barrier and a less peripheral route of transmission. In choosing combinations of the two periods, we therefore focus on those scenarios.

2.5.2 These model runs are used to estimate the expected percentage contribution of blood-borne infection *amongst vCJD cases that would have presented by the end of 2002*. This percentage is independent of the absolute size of the outbreak. Its calculation involves two main steps for each model run, as follows:

- For an assumed (arbitrary) number of primary infections and inputs for primary and secondary incubation periods, we estimate how many primary cases and secondary (blood-borne) cases would have occurred so far – *if all those infected by either route had survived long enough to develop symptoms*. In other words, we make no allowance for the fact that some might have died of other causes first.
- These estimates are then *adjusted to allow for survival rates*. Strictly speaking, the question here is of the differential in survival "to symptoms" for those infected by primary and secondary routes. For simplicity, however, we ignore the chance of those infected in the *primary* outbreak having already died of other causes. This seems a fair approximation, if most infections occurred around 1990, and given that most cases seen so far have been relatively young. For the secondary infections, we apply survival percentages suggested by the NBS study.

2.5.3 To illustrate the second step, suppose we are considering a scenario with a mean secondary incubation period of **n** years. From the NBS data, suppose that in the absence of vCJD, 40% of units transfused would go into patients surviving at least **n** years. Then the theoretical number of clinical cases calculated in the previous step would simply be multiplied by 0.4.

2.5.4 Specifically, for the mean secondary incubation periods of 3, 6 and 15 years considered here, we apply "survival proportions" of 50%, 35% and 30% respectively. The first two figures are based on the NBS survey results, the last on an extrapolated estimate in the same study. All are adjusted downward to reflect the point that survival calculated "per unit transfused" is somewhat lower than that "per recipient" –those receiving more units typically being more severely ill. Because the chance of vCJD infection is proportionate to the number of units received, the per-unit survival rate is most relevant here.

2.5.5 Applied to scenarios with different primary and secondary incubation periods, these steps provide estimates for the expected number of primary and secondary cases that should have appeared to date, discounting infection of those that would have died of other causes first. From these, one can simply calculate the proportion of all cases that "should" have been due to secondary infection.

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2.5.6 Results are shown in Table 2 below. The shaded cells represent scenarios in which the mean secondary incubation period would be longer than the primary: these are regarded as implausible, as already noted. The percentages shown should be seen as rough estimates for each scenario rather than deterministic (or statistically-valid) predictions, especially since individual incubation periods will vary about the given. (Caveats to this exercise are discussed further below).

Table 2: Implied % of clinical vCJD cases appearing by end 2002 due to blood-borne infection: Scenarios using DNV infectivity inputs

		Mean primary incubation period (yrs)		
		10.3	**19**	**30**
Mean secondary incubation period (yrs)	**3**	31	63	87
	9	12	32	65
	15	4	12	36

2.6 Discussion

2.6.1 In general, these percentages are implausibly high when compared with the 5 of 129 known cases (i.e. 4%) with a relevant transfusion history. Most are of the wrong order of magnitude, except where short primary incubation periods are coupled with long secondary incubation periods. The point can be starkly illustrated by applying the percentages shown to the total number of cases. That is, we estimate how many of the 129 should – according to the transmission model – have been infected via blood components. For example, if 31% of cases appearing so far were due to blood-borne transmission (as in the first cell of Table 2), then these would comprise 40 of the 129 cases.

Table 3: Predicted numbers of cases due to blood-borne infection, out of 129 total to end 2002. Scenarios using DNV infectivity inputs

		Mean primary incubation period (yrs)		
		10.3	**19**	**30**
Mean secondary incubation period (yrs)	**3**	40	81	112
	9	15	41	84
	15	5	15	46

2.6.2 At first sight then, use of the model with DNV inputs does appear to overestimate the possible impact of blood-borne infection. One possible explanation is that these estimates of infectivity are too high – the initial

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concern of this paper. However other potential explanations warrant consideration. These include the following:

(a) *Errors within the transmission model.* Error can never be completely excluded, but the internal logic of the System Dynamics model has been audited (in two successive versions) by external consultants and judged fit for purpose.

(b) *Reporting error in the data.* As CJDSU themselves point out, there might be some under-reporting of transfusion history, especially given reliance on relatives' knowledge and recall of events. However it is difficult to envisage reporting error being sufficient by itself to make many of the scenarios above plausible.

(c) *Inaccuracies in other model inputs.* The scenarios generated by the transmission model depend on other inputs, notably on donor and recipient age profiles, and recipient survival rates. Ages of donors and recipients are well documented. Definitive data on recipient survival are not yet available, but it would be very surprising if the results of the NBS study were grossly unrepresentative. To explain the non-appearance of secondary cases, patient survival would need to be very much worse than supposed here. In fact the NBS survival figures already give poorer survival rates than earlier international studies (e.g. Vamvarkis & Taswell, 1993).[2]

(d) *Distribution of incubation periods around the mean.* The existing model uses Erlang (Gamma)-5 distributions of incubation periods around the mean, for both primary and secondary infections. One alternative that has already been used in generating scenarios for the primary outbreak (e.g. Ghani *et al*, op cit) is to incorporate a "cut-off" in the distribution – that is a minimum duration below which no incubation period can fall, even with a very small probability. This will decrease the number of infections that would show up as early clinical cases. Applying such a model to the development of *secondary* infection could help account for a lack of clinical cases to date.

(e) Related to the previous point, it should be admitted that our method for discounting "non-survivors" remains somewhat crude. If "x%" of recipients survive for a period equal to the mean secondary incubation period, it does not strictly follow that the same "x%" of those infected will survive to develop symptoms: the distribution of incubation periods around the mean might be significantly skewed.

2.6.3 These possibilities are not mutually exclusive, and some combination of factors might apply. The last two, in particular, mean that it would be futile to test scenarios against case data with much precision. The best we can do is to check for gross inconsistencies. With this in mind, a pragmatic judgement would be to regard as "seriously problematic" only those scenarios in which more than 10% of vCJD cases seen to date would have been blood-borne – rather than insisting on a maximum of 4%.

[2] This in turn may be explained by changing patterns of usage. Being based on transfusions that took place in 1994, the NBS study applies squarely to the period most relevant to our analysis.

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2.6.4 Even adopting this looser criterion, the figures shown in Tables 2 and 3 remain seriously problematic. The following section considers the effect of changing the infectivity inputs to the model, in terms either of level or of duration.

2.7 Varying infectivity levels

2.7.1 As noted, the scenarios produced by the model are quite insensitive to changes in infectivity levels. Starting from almost any of the values given in Table 1, very large reductions would be needed to bring the dose per unit of infected product below 2 ID_{50}s. The only exceptions refer to leucodepleted products introduced in 1999, which are anyway irrelevant to the present calculations. (Given the assumptions in the transmission model, any blood-borne infections that had already led to a clinical vCJD case would almost certainly have occurred prior to the introduction of these products.)

2.7.2 To explore this argument more quantitatively, changes can be made either to the assumed infectivity of specific components, or more globally to the infectivity of blood as a whole. Sensitivity analysis in DNV's study takes the second approach, and suggests that from their baseline values:

- If infectivity were reduced across the board by a factor of 100, the predicted number of infections (prior to 1999) would remain essentially the same.
- A reduction by a factor of 1,000 would reduce the expected number of infections by a factor of about 5.

2.7.3 While DNV do not specify how the latter calculation was carried out, similar results are obtained using the EOR model. Again, a 100-fold reduction has no predicted impact, while model runs based on a 1000-fold reduction are as in Table 4 below:

Table 4: Implied % of clinical vCJD cases due to blood-borne infection: Scenarios with inputs 1/1,000th of DNV values

		Mean primary incubation period (yrs)		
		10.3	**19**	**30**
Mean secondary incubation period (yrs)	**3**	5	15	41
	9	2	5	17
	15	0	2	6

2.7.4 As compared with Table 2, these reductions are of the same order (5-fold) as implied by DNV's own sensitivity analysis (in scenarios with the15-year mean secondary incubation period they consider). This large reduction in the assumed infectivity of blood is sufficient to make some of the modelled scenarios compatible with observation, though by no means all. In reality, the effect of reduced dosage on the number of clinical cases to date may be

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somewhat greater than suggested here, if smaller doses are associated with longer incubation periods.

2.8 Varying the onset of infectivity

2.8.1 The existing analysis is based on the full infectivity levels being present throughout the incubation period. A significant delay in onset of infectivity would affect the timing, as well as the numbers, of blood-borne infections. Because earlier infections would be removed, there would be a disproportionate reduction in secondary clinical cases seen so far. This may represent a promising line of enquiry, not previously considered in quantitative terms.

2.8.2 Clearly, a number of models are possible for a growth in infectivity during the incubation period. Infectivity might grow steadily, or increase suddenly at one particular point. For present purposes, we consider the simplest possible model, in which infectivity in blood simply appears part-way through the incubation period. (A similar model is used in EOR's surgical risk assessment with regard to the onset of infectivity in CNS and posterior eye.) The aim here is to explore the implications of a simple delay in onset of infectivity.

2.8.3 As the transmission model divides the incubation period into 5 segments, we consider in turn the effect of infectivity in blood only appearing after the first 20%, 40%, 60% or 80% of the incubation period. As before, various combinations of mean primary and secondary incubation periods are considered. Model outputs for these are set out in Table 5 below, in the same format as Table 2.

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Table 5: Implied % of clinical vCJD cases due to blood-borne infection

(a) Blood infective (at "DNV" level) after 20% of primary incubation period

		Mean primary incubation period (yrs)		
		10.3	**19**	**30**
Mean secondary incubation period (yrs)	**3**	29	50	76
	9	8	18	40
	15	2	5	15

(b) as above, with blood infective after 40% of primary incubation period

		Mean primary incubation period (yrs)		
		10.3	**19**	**30**
Mean secondary incubation period (yrs)	**3**	18	34	56
	9	5	8	17
	15	1	2	4

(c) as above, with blood infective after 60% of primary incubation period

		Mean primary incubation period (yrs)		
		10.3	**19**	**30**
Mean secondary incubation period (yrs)	**3**	11	18	28
	9	2	3	5
	15	1	1	1

(d) as above, with blood infective after 80% of primary incubation period

		Mean primary incubation period (yrs)		
		10.3	**19**	**30**
Mean secondary incubation period (yrs)	**3**	5	6	8
	9	1	1	1
	15	0	0	0

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Further commentary

2.8.4 Clearly, these changes have a marked impact when compared with Table 2. Even a delay leaving most of the incubation period infective - e.g. as in Table 5(b) - removes much of the previous gross disparity between the model and the available evidence. While the "predicted" contribution of blood-borne infection is still high compared with the CJDSU case data, some percentages are of the right order. With some allowance for possible under-reporting of blood transfusion history (and perhaps also a cut-off in the incubation period distribution), several of these scenarios might be considered feasible. However those with short secondary incubation periods still appear problematic.

2.8.5 With a 60% delay in infectivity as in Table 5(c), the majority of percentages are in single figures. In the final table – admittedly a radical departure from the original assumptions – all scenarios are compatible with the CJDSU case data, and there are some in which no blood-borne cases at all would have appeared so far.

2.8.6 Introducing a delay in the onset of infectivity is speculative – though we understand that some work-in-progress with animal models would lend it some plausibility. For comparison, in the study of blood-borne TSE transmission in sheep by Hunter *et al* (2002), all four transmissions of natural scrapie were from donor animals more than half-way through their incubation period (57%, 69%, 77% and 100%). The two reported transmissions of BSE were from donor animals 50% and an estimated 45% through their incubation periods.

2.8.7 **We have however shown that the transmission model is much more sensitive to changes in the timing of infectivity in blood than to its level.** Delay in the onset of infectivity represents one hypothesis that would account for a lack of blood-borne infections amongst the clinical vCJD cases to date.

Potential policy implications

2.8.8 If delayed onset of infectivity is a hypothesis worthy of consideration, it is also appropriate to discuss the potential implications of such scenarios for risk management. The important point here is that while a delay in infectivity can have a very great effect on the cases to be expected so far, its effect on *future* transmission risks may be small.

2.8.9 Delays in infectivity having a marked effect on the number of blood-borne cases expected up to the end of 2002 can lead to much less dramatic reductions in future infections. In other words, the lack of observed cases so far does not necessarily invalidate the need for precaution when considering future infection risks.

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3. EVIDENCE FROM TRANSFUSION INCIDENTS

3.1 Known incidents

3.1.1 We now consider what can be deduced from recorded "incidents" in which individuals have received blood components subsequently traced to a donor who went on to develop vCJD. To date, none of these recipients has developed symptoms of the disease. Though the numbers involved are small, this in principle places some constraints on feasible scenarios for its transmission. Table 6 shows all known incidents in order of transfusion date. The incidents involve 33 recipients in total, and blood donated from 10 donors.

Table 6: Data on transfusions from donors known to have developed vCJD

	DONOR	TRANSFUSION			RECIPIENT		
	Onset	Date	Interval before donor onset	Product	Fate		Symptom-free survival
1	Nov-97	23-Dec-81	15.9 yrs	Red cells	d	22-Mar-96	14.3 yrs
2	May-96	06-Sep-84	11.6 yrs	Whole Blood	A		18.3 yrs
3	Aug-94	29-Sep-89	4.9 yrs	Red cells	d	28-Dec-89	3 months
4	Aug-94	06-Feb-90	4.5 yrs	Red cells	d	22-Feb-91	1.1 yrs
5	May-98	07-Sep-90	7.7 yrs	Red cells	d	12-Sep-90	5 days
6	Nov-96	16-Jan-93	3.8 yrs	Red cells	A		10.0 yrs
7	Mar-96	13-Jan-95	1.2 yrs	Red cells SAGM	A		8.0 yrs
8	Mar-96	17-Aug-95	0.6 yrs	Red cells	d	21-Nov-95	3 months
9	Nov-1996	21-Sep-95	1.7 yrs	Red cells BCD	d	26-Sep-95	5 days
10	Mar-1996	29-Sep-95	0.5 yrs	Cryo-depleted plasma	A		7.3 yrs
11	Mar-96	31-Jan-96	0.2 yrs	Cryoprecipitate	d	02-Feb-96	3 days
12	Jul-99	18-Mar-96	3.3 yrs	Red cells	A		6.75 yrs
13	Nov-96	08-May-96	0.5 yrs	Red cells BCD	d	11-Jan-01	4.5 yrs
14	Jul-99	23-Dec-96	2.8 yrs	Red cells	d	21-May-97	5 months
15	May-99	13-Sep-97	1.7 yrs	Red cells	A		5.3 yrs
16	May-99	23-Dec-97	1.4 yrs	Red cells	A		5.0 yrs
17	May-99	02-Jan-98	1.3 yrs	FFP	d	02-Jan-98	0 days
18	May-99	24-Apr-98	1.1 yrs	Red cells	A		4.7 yrs
19	May-99	29-Apr-98	1.1 yrs	FFP	d	30-Apr-99	1.0 yrs
20	May-99	28-Aug-98	0.75 yrs	Whole Blood	d	26-Mar-99	7 months
21	May-99	30-Dec-98	0.4 yrs	Red cells	A		4.0 yrs
22	May-99	08-Jul-99	(- 0.1 yrs)	FFP	A		3.5 yrs
23	March-01	24-Oct-99	1.4 yrs	Red cells (L'depleted)	d	10-Jan-00	2.5 months
24	Oct-01	01-Feb-00	1.7 yrs	Red Cells (L'depleted)	A		2.9 yrs
25	March-01	25-Feb-00	1.1 yrs	Red cells (L'depleted)	d	18-Aug-00	7 months
26	March-01	11-June-00	0.8 yrs	Red cells (L'depleted)	d	27-Oct-00	4.5 months
27	Oct-01	08-Jul-00	1.25 yrs	Red Cells (L'depleted)	d	28-Oct-00	3.5 months
28	March-01	21-Oct-00	0.4 yrs	Red cells (L'depleted)	A		2.2 yrs
29	Oct-01	21-Jan-01	0.75 yrs	Red Cells (L'depleted)	A		1.9 yrs
30	March-01	15-Feb-01	0.1 yrs	Red cells (L'depleted)	d	30-Mar-01	1.5 months
31	March-01	8-June-01	(- 0.25 yrs)	Red cells (L'depleted)	A		1.5 yr
32	March-01	21-Sept-01	(- 0.5 yrs)	FFP	d	30-Sept-01	7 days
33	Oct-01	20-Mar-02	0.4 yrs	Red Cells (L'depleted)	A		0.8 yrs

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3.1.2 In the above table, shaded cells indicate recipients dying shortly after transfusion. Individual donors can be distinguished by dates of disease onset: for example incidents 15-23 all involved blood from one donor, whose vCJD symptoms began in March 2001) The "fate" column records whether recipients are alive or dead (latest data being as of 19 December 2002, and all those listed as still alive are presumed still to be so now. [**DN**: have any more of died since?]

3.1.3 In each case, we have calculated:

- For the donor, how long after the transfusion onset of symptoms occurred. Note that the donation will have occurred some time before the transfusion - perhaps significantly so if the product is one that can be stored, e.g. FFP. (In incidents 22, 31 and 32, the transfusion apparently took place *after* the donor's onset of symptoms). So this column represents the minimum period between donation and onset.
- For the recipient, the elapsed period from the transfusion to the time of death or, if the patient is still alive, to the present. Given that no recipient has shown symptoms of vCJD this period of symptom-free survival places a lower bound on the incubation period, if that patient had been infected by the transfusion.

3.2 Discussion

3.2.1 As already noted, outputs of the transmission model rest on a complex set of inputs. Whether any of these recipients would have developed the disease by now depends on many factors. These include not only the level of infection (if any) in the blood product, but also:

- its (presumably variable) duration prior to onset of symptoms in the donor,
- the mean secondary incubation period for recipients, and
- the distribution of individual incubation periods around that mean - including the existence or otherwise of a minimum "cut-off" period.

3.2.2 Given this complexity, and the small number of data, elaborate statistical testing may not be feasible. However some conclusions can be suggested on a more common-sense basis.

3.2.3 Firstly, there are some incidents that essentially provide no information. Most of these concern recipients who died shortly after the transfusion episode – in several cases within a matter of days. In 16 incidents (shown shaded on Table 6) the recipient died of other causes within about a year of transfusion (well below the shortest mean incubation period considered in the model). For simplicity, all these are excluded from further discussion.

3.2.4 It is also difficult to draw any conclusions from the first incident listed, as the donor might well have contracted the disease after donating – given that the transfusion was in 1981, well before most primary infections should have occurred. In addition, donation was almost 16 years prior to the onset of symptoms, so even if the donor had already been infected, donation would

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have been during the early stage in the incubation period. The same argument applies – though less conclusively - to the second incident (donation in 1984, and over 11 years prior to onset of symptoms). In both cases, the non-appearance of symptoms in the recipient can be fairly easily explained.

3.2.5 We therefore concentrate attention on the remaining 15 incidents, for which the relevant data are summarised in Table 7 below. These are of interest for present purposes in that:

(a) the transfusion took place not very long before (in two cases actually after) the onset of the donor's symptoms, and

(b) recipients survived an appreciable length of time.

Table 7: Data on transfusions from 15 selected incidents

	DONOR	TRANSFUSION			RECIPIENT		
	Onset	Date	Interval before donor onset	Product	Fate		Symptom-free survival
6	Nov-96	16-Jan-93	3.8 yrs	Red cells	A		10.0 yrs
7	Mar-96	13-Jan-95	1.2 yrs	Red cells SAGM	A		8.0 yrs
10	Mar-1996	29-Sep-95	0.5 yrs	Cryo-depleted plasma	A		7.3 yrs
12	Jul-99	18-Mar-96	3.3 yrs	Red cells	A		6.75 yrs
13	Nov-96	08-May-96	0.5 yrs	Red cells BCD	d	11-Jan-01	4.5 yrs
15	May-99	13-Sep-97	1.7 yrs	Red cells	A		5.3 yrs
16	May-99	23-Dec-97	1.4 yrs	Red cells	A		5.0 yrs
18	May-99	24-Apr-98	1.1 yrs	Red cells	A		4.7 yrs
21	May-99	30-Dec-98	0.4 yrs	Red cells	A		4.0 yrs
22	May-99	08-Jul-99	(- 0.1 yrs)	FFP	A		3.5 yrs
24	Oct-01	01-Feb-00	1.7 yrs	Red Cells (L'depleted)	A		2.9 yrs
28	March-01	21-Oct-00	0.4 yrs	Red cells (L'depleted)	A		2.2 yrs
29	Oct-01	21-Jan-01	0.75 yrs	Red Cells (L'depleted)	A		1.9 yrs
31	March-01	8-June-01	(- 0.25 yrs)	Red cells (L'depleted)	A		1.5 yr
33	Oct-01	20-Mar-02	0.4 yrs	Red Cells (L'depleted)	A		0.8 yrs

3.2.6 These recipients survived – or are surviving - with no symptoms of vCJD for a median period of 4.5 years. However it should be stressed that the final column above is strictly a lower bound on incubation period – there is no implication that disease would have (or will) develop after that time. For this reason neither the median nor the mean survival period is of overriding interest. Rather, the point is that *no individual recipient* has developed vCJD symptoms within the timescales given.

3.2.7 Several of the earlier incidents, in particular, cast some doubt on the plausibility of high-infectivity scenarios. All those up to No 22 occurred prior to the introduction of leucodepletion, and most were followed by periods of symptom-free survival lasting several years.

3.2.8 Mathematically, all incidents would be consistent with DNV's suggested median incubation period of 15 years. At the other extreme, scenarios involving a mean as short as 3 years appear infeasible against these data. For

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intermediate figures – say 6 years – the situation is less than clear-cut. For example the symptom-free survival of 10 years after incident No.6 would represent an outlier. Such an outlier could be more easily accounted for if incubation periods varied a good deal about the mean. But a high variability would in turn make it more surprising that *none* of the individual incubation periods have been short enough for symptoms to have shown up.

3.2.9 These arguments are not entirely conclusive, given that many factors could have affected this rather small data set. (For example, incidents 4, 6 and 12 occurred well before onset of donor symptoms, so might be accounted for by late onset of infectivity as discussed in the previous section. Buffy Coat Depletion might have reduced the infectivity of the Red Cells in incident 13, and so on.) Nevertheless the non-appearance of symptoms in recipients to date requires secondary incubation periods to be quite long even after receipt of a large intravenous dose. Unless this is accepted as being biologically plausible, these data tell against scenarios with high infectivity.

3.2.10 It should be possible to draw some stronger conclusions in the future, if recipients continue to survive without symptoms. However continued survival will add only slowly to the set of useful information. On this point, little can be concluded from any incidents until long after they occur.

4. CONCLUDING COMMENTS

4.1 Starting with "DNV" inputs on infectivity, we have used EOR's vCJD transmission model to investigate whether scenarios based on these inputs "over-predict" the impact of blood-borne vCJD infection. This has done so by reference to two sets of real data:

- on how many of the known vCJD cases to date have any history of having undergone blood transfusion.
- on known transfusion "incidents" in which patients received blood components from donors who developed vCJD.

4.2 The first comparison suggests that:

- Given the DNV inputs, the transmission model does "over-predict" the number of known cases that could have been due to blood-borne infection.
- This disparity appears across a wide range of assumptions on primary and secondary incubation periods. However its scale is dependent on these assumptions. Within the ranges considered, inconsistencies with the case data are smallest if the secondary incubation period is long, especially if the primary incubation period is also short.
- Any reduction in assumed infectivity levels would have to be very large in order to have a substantial effect on model outputs. For example, a 1,000-fold reduction would make some (though by no means all) scenarios roughly compatible with the data.
- Another line of enquiry is to consider whether the onset of infectivity in blood components after primary infection might occur some way

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into the incubation period. Making such an assumption greatly reduces disparity with the case data. However such a modification to the model might be considered rather ad hoc: its biological plausibility remains to be examined.

- It is also of interest that a delay in infectivity might have little effect on the number of *future* blood-borne infections. So under this hypothesis, the lack of observed blood-borne cases to date does not necessarily reduce the need for precaution against future risks.

4.3 The second comparison – i.e. that with known transfusion incidents - also suggests that if blood components are infective, secondary incubation periods must be quite long. DNV themselves use a median of 15 years, which would be compatible with this data. However, theirs is a general figure applied to any blood-borne transmission, regardless of the potential infective dose. The incidents considered here involve large volumes of the relevant product. If blood components carry the infectivity suggested by DNV, each transfusion would have carried a high dose – especially for incidents prior to 1999, involving non-leucodepleted products. It seems questionable whether such high doses would be followed by such long secondary incubation periods.

4.4 Overall, the relatively small number of vCJD cases to date means that the available data are sparse. In addition, there are many variables intervening between receipt of some infective dose and the onset of symptoms. This makes it difficult to rule out hypothesised infectivity levels definitively. Nevertheless, the evidence does suggest that the DNV inputs on infectivity produce implausibly pessimistic scenarios, especially if applied throughout the primary incubation period. Finally we stress again that DNV's estimates are intended as conditional figures that would apply *if* human blood were to carry vCJD infection. It remains possible that it does not do so.

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