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Ten-year follow-up of two cohorts with an increased risk of variant CJD: donors to individuals who later developed variant CJD and other recipients of these at-risk donors

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Background Transmission of variant Creutzfeldt–Jakob disease (vCJD) through blood transfusion is implicated in three deaths and one asymptomatic infection. Based on this evidence, individuals assessed to be at increased risk of vCJD through donating blood transfused to individuals who later developed vCJD, or through being other recipients of such donors, are followed up to further understand the risks of vCJD transmission through blood.

Objectives To provide a ten-year follow-up of these at-risk cohorts.

Methods Blood donors to patients who later died from vCJD were identified by the Transfusion Medicine Epidemiological Review (TMER) study. A reverse risk probability assessment quantified the risk of blood transfusion or exposure through diet as the source of vCJD in the recipients. Donors to these recipients, and these donors' other recipients, with a probability risk above 1%, are classified as at increased risk of vCJD for public health purposes. These cohorts are monitored for any vCJD occurrences.

Results A total of 112 donors and 33 other recipients of their donated blood have been classified as at increased risk. After 2397 and 492 vCJD-free years of follow–up, respectively, no deaths in either at-risk cohort were of vCJD-related causes.

Conclusions The at-risk cohorts have survived disease-free far longer than the estimated incubation time for dietary-acquired vCJD (donors) and transfusion-acquired disease (other recipients). However, due to our still limited understanding of, and a lack of a reliable test for, asymptomatic vCJD infection, public health follow-up is necessary for continued monitoring of at-risk cohorts.

Key words: blood safety, epidemiology, prions, transfusion – transmissible infections.

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Introduction

Creutzfeldt–Jakob disease (CJD) is a human form of transmissible spongiform encephalopathy (TSE), or prion disease, and was first described in 1920 as what is now known as sporadic CJD (sCJD) [1]. A new form of the disease, termed variant CJD (vCJD), was recognized in 1996 and is accepted as being linked to dietary exposure to

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bovine spongiform encephalopathy (BSE)-infected cattle [2]. To date, 177 cases of clinical vCJD have been recorded in the UK, with a peak in the epidemic curve of 28 deaths occurring in the year 2000 [3]. All but three of the 177 cases are attributed to dietary exposure.

Transmission of variant CJD through blood transfusion is implicated in the deaths of the remaining three people who developed clinical vCJD and in the finding of abnormal prion deposition at post-mortem in one asymptomatic individual [4–6]. Each of these four individuals received transfusion of non-leucodepleted red cells from apparently healthy donors who later developed vCJD. Prevalence of asymptomatic vCJD infection in the population remains an area of ongoing research, though estimates from surveys of abnormal prion protein presence in archived human appendix samples are approximately 1:2000 [7].

Transmissibility of TSE via blood has been tested and confirmed in various animal models, including vCJD in mice and cynomolgus monkeys [8–10]. Experimental data from these animal models have indicated that infectivity may appear in blood not only during clinical illness but also throughout the incubation period of vCJD, suggesting that asymptomatic individuals could donate potentially infectious blood [1, 8]. Additionally, the observed three cases of vCJD transmission by blood transfusion were linked to donors who showed no clinical signs of disease, further corroborating the animal model findings.

The prospect of a widespread, hidden threat of secondary spread of vCJD through transfusion led to the adoption of a number of precautions to minimize this risk (Table 1). These measures included identification of individuals assessed to be at increased risk of vCJD because of their transfusion or donation history (Fig. 1).

In addition to direct recipients of blood from donors who later developed vCJD, referred to above and described in detail elsewhere [5, 11], two further groups of donors and recipients were identified using reverse risk assessment as being at risk of onward transmission of vCJD (Fig. 1).

These individuals are followed up to further understand the risks of vCJD transmission through blood. This study provides a ten-year follow-up of these two at-risk cohorts.

Methods

Donors and recipients at increased risk were identified by the Transfusion Medicine Epidemiological Review (TMER) study, a collaboration between the National CJD Research and Surveillance Unit (NCJDRSU) and the UK Blood Services (UKBS), which assessed the donation and transfusion history of individuals diagnosed with vCJD [11–13]. In total, 10 vCJD cases with a history of blood transfusion were identified. Three index recipients had already been linked to donors known to have later developed vCJD. A further four recipients had some or all of their donors identified, and none of these donors had developed vCJD. Of the remaining three recipients, one was transfused 8 months before disease onset and is excluded from the study, and for two others, donors could not be identified. The two cohorts identified as being at increased risk and described in this study were therefore 1) donors to an individual who later developed vCJD, where none of the donors had developed vCJD, and 2) other recipients of blood from these donors. All donors and their other recipients comprising these cohorts thus have a direct or indirect link to one of four index patients who developed clinical vCJD and had a history of blood transfusion from donors who remained clinically well.

The reverse risk assessment was carried out in 2005. It considered the relative risks from the possible exposures to vCJD in a transfused index patient, namely dietary exposure or transmission from an infected but asymptomatic donor [14], where none of the donors subsequently developed clinical vCJD. The relative likelihood depends on the probability of blood-borne transmission from an infected donor. The analysis considered a wide range of possibilities, but the final policy risk assessment used the most precautionary approach, in which transmission from an infected donation was taken to be certain. In the absence of any further information, there is then an equal chance of the index patient having acquired vCJD from each individual donor, or from dietary exposure. If there are n donors to an index case, the chance of each individual being the source of infection is thus $1/(n+1)$. As there are between two and 103 donors to each such index patient, the probability-based risk ranges from ~1% to 33% per individual donor (Fig. 2). The second stage of the assessment considers the risk to these donors' other recipients. Irrespective of the number of other

Importation of plasma for fractionated blood products	1998
Leucodepletion of all blood components	1999
Importation of fresh frozen plasma for all patients born on/after 1 January 1996	2002
Exclusion of blood donors who have received a blood transfusion in the UK since 1980	2004

Table 1 vCJD risk reduction measures introduced in the UK

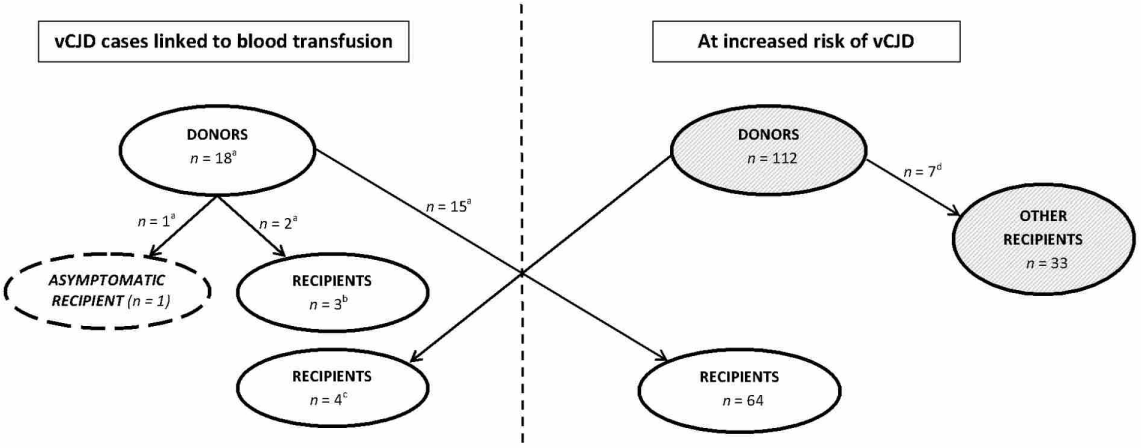

Fig. 1 At risk cohorts in a wider context. The figure outlines the two at-risk cohorts covered by this review (vCJD at-risk donors and their other recipients, marked in the figure by shaded ovals) in a wider context of blood transfusion-associated vCJD index cases and at increased risk individuals. [a]Of these 18 donors, 2 were linked to a vCJD index case recipient, 1 was linked to a recipient with preclinical vCJD infection, and 15 were linked to recipients who did not develop vCJD (died from other causes/remain alive). [b]These 3 recipients were presumed to have been infected through blood transfusion (linked to a vCJD index case donor). [c]These 4 recipients have an equal probability of having been infected through diet or blood transfusion (not linked to a vCJD index case donor, but traced and found to have received a blood donation). [d]7 of these 112 at-risk donors were traced and found to have donated blood to 33 other recipients.

recipients each donor is associated with, and again assuming a transmission probability of 1, each other recipient would have the same risk as the donor from whom they received a blood transfusion [15]. In earlier vCJD risk assessments, individuals assessed to be above a 1% at-risk threshold using precautionary assumptions had been identified and notified for public health reasons, and the same approach was used in this context with one modification. For the cluster with 103 donors, the implied risk to each was slightly below 1% even in the worst case, but their proximity to the threshold led to the pragmatic decision to include them. The much larger number of other recipients ($n > 1000$) from these donors were not, however, included, on the basis that their calculated risk diminishes much more rapidly once one moves away from the worst case scenario of certain transmission [15].

At-risk cohorts are monitored for CJD by Public Health England (PHE) and Health Protection Scotland (HPS) using a combination of records flagging, post-mortem medical notes review (MNR) and, where possible, a post-mortem examination of brain tissue to detect signs of asymptomatic disease. MNR is carried out by the NCJDRSU and findings are routinely shared with PHE. Causes of death were obtained by a combination of records flagging and MNR. Years of follow-up for the two cohorts were calculated from date of donation to vCJD index case recipients (donors) or from date of transfusion from donors (other recipients) until 31 December 2015 or date of death.

This surveillance was established under PHE's cover under section 251 of the National Health Service Act 2006 and Statutory Instrument 2002 No. 1438, the Health Service (Control of Patient Information) Regulations 2002, to process personal identifiable information (PII) for surveillance purposes. Research Ethical Committee and Research Governance approval are therefore not required.

Results

For four vCJD index patients, transfused in 1993 (two), 1994 and 2002 from donors who had not subsequently developed vCJD, 112 donors and 33 other recipients of their donated blood were identified as being at increased risk of vCJD (Fig. 2). Two of these donors did not donate blood to any other recipients. One donor who resides outside of the UK was excluded from the analyses as this individual was not followed up over time. Years of follow-up, age of survivors and numbers and causes of death are summarized in Tables 2 and 3 for donors and other recipients, respectively, and by networks linked to specific index patients. Median age of survivors for donors and their other recipients was 59 and 60, respectively. In total, the donors and their other recipients have had 2397 and 492 vCJD-free years of follow-up, respectively. For donors, the median (range) number of years of follow-up since index case donation was 22 (0·7–23). For their other recipients, the median (range) number of years of follow-up was 14 (7–28). Amongst the donor group,

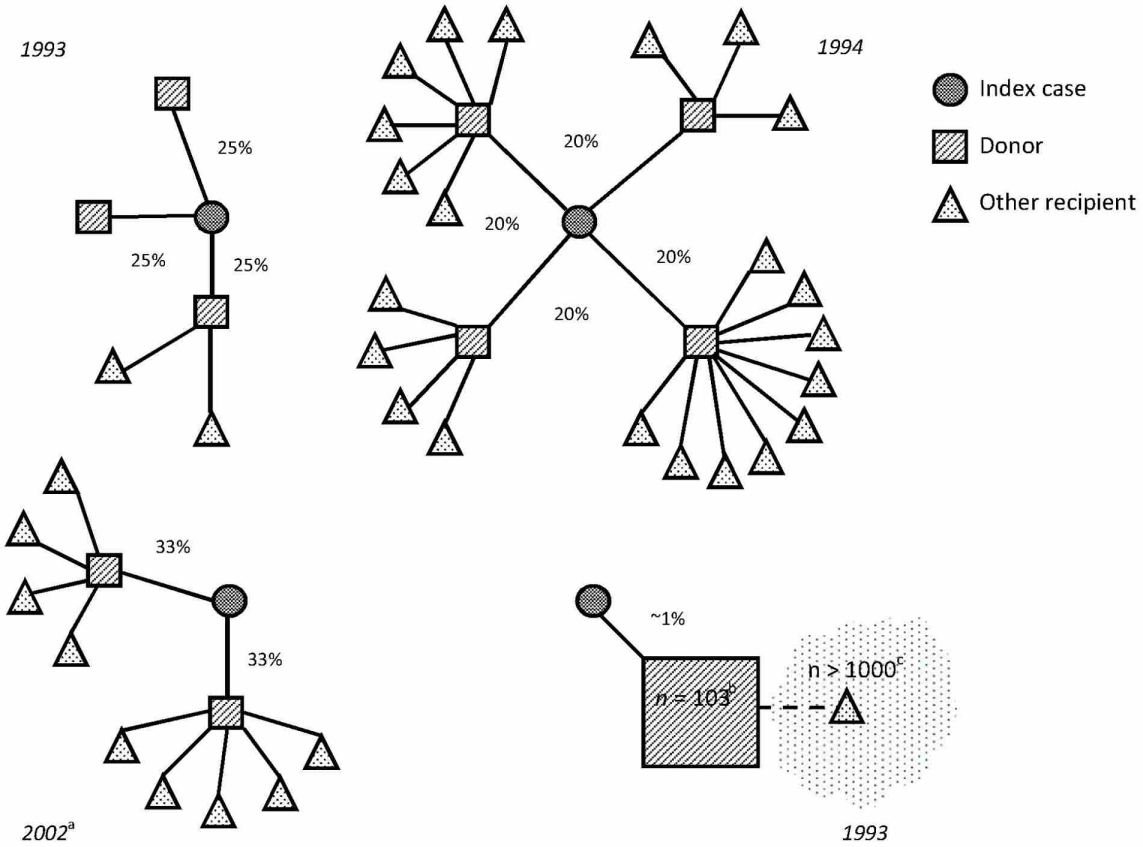

Fig. 2 Index cases, donors, other recipients and their associated risk. [a]Leucodepletion introduced in 1999. Based on the assumptions that (a) all individuals have an equal, small probability of infection via diet and (b) transmission via an infected blood transfusion is certain, 'expected' numbers of vCJD-infected individuals were calculated for each cluster as follows, reading the clusters in the diagram clockwise from top left, results expressed to the nearest whole number: *Donors:* $(3 \times 0{\cdot}25) + (4 \times 0{\cdot}20) + 1^{b} + (2 \times 0{\cdot}33) = 3$. *Other recipients:* $(2 \times 0{\cdot}25) + (22 \times 0{\cdot}20) + (9 \times 0{\cdot}33) = 8$. Based on our probability assumptions, it follows that: [b]1 of the 103 donors would almost certainly have been the source of infection, hence contributing 1 individual to the total. [c]As a consequence, some of the other recipients within this cluster would also have been infected. However, these recipients were not classed as at risk and have not been followed up and are thus excluded in the calculations for this study.

for survivors, specifically the median year of follow-up was again 22 years, with 14 years being the minimum. Survivors in the other recipients' cohort were characterized by a median of 18 years of follow-up, with 7 being the minimum. Of these donors and their other recipients, respectively, 7 (6·3%) and 16 (48·5%) have died. None were diagnosed with or died from vCJD in either at-risk cohort and the causes of death in both cohorts were cardiovascular, infection, cancer or neurological. Only two individuals, one from each of these two at-risk cohorts, had a neurological condition (non-CJD related dementia) listed as either a primary or a secondary cause of death. The seven donors who died survived an average of 15 years from their date of donation until death, with all except one surviving at least five years since donation. Similarly, the 16 deceased other recipients survived an average of 12 years from transfusion until death. All survived at least five years since transfusion.

Discussion

Structured follow-up of at-risk donors and other recipients identified in the TMER study for disease outcomes has been in place for ten years. With the relevant transfusion events chiefly occurring some years earlier, a longer average vCJD-free period of 22 years and 14 years has elapsed for the donors and their other recipients, respectively. This compares with the estimated average incubation period of 10–15 years for dietary-acquired vCJD [16] and the observed range of 6- to 8·5-year incubation time for the documented transfusion transmitted episodes [13].

Table 2 Years of follow-up since donation to vCJD index case recipient

	Years of donor follow up since transfusion to vCJD-case recipient						
	All		Survivors only				
	To date or to date of death	Median (range)	To date	Median (range)	Number who have died (%)	Causes of death (summary)	Median age of survivors (range)
111[a] donors to 4 recipients	2397	22 (0·7–23)	2299	22 (14–23)	7 (6·3%)	Cardiovascular (5) neurological (1) cancer(1)	59 (35–85)
102[a] donors to recipient 269	2215	22 (0·7–23)	2117	22 (22–22)	7	Cardiovascular (5) neurological (1) cancer(1)	60 (41–85)
3 donors to recipient 328	68	23 (23–23)	68	23 (23–23)	0	N/A	53 (44–56)
4 donors to recipient 330	86	22 (22–22)	86	22 (22–22)	0	N/A	60 (48–62)
2 donors to recipient 592	28	14 (14–14)	28	14 (14–14)	0	N/A	47 (35–58)

[a]Excludes 1 donor who resides outside the UK and has therefore not been followed up.

Table 3 Years of follow-up for other recipients of transfusions from vCJD index case-linked donor

	Years of recipient follow-up since their own transfusion						
	All		Survivors only				
	To date or to date of death	Median (range)[a]	To date	Median (range)[a]	Number who have died (%)	Causes of death (summary)	Median age of survivors (range)
All 33 recipients from 7 donors	492	14 (7–28)	295	18 (7–28)	16 (48·5%)	Cardiovascular (11) infection (2) cancer (2) unknown (1)	60 (13–92)
2 recipients from donor 399	29	15 (7–22)	22	22	1	Cardiovascular (1)	78
9 recipients from donor 417	135	16 (8–19)	67	17 (14–19)	5	Cardiovascular (4) cancer(1)	47 (13–77)
3 recipients from donor 418	48	11 (10–26)	26	26	2	Cardiovascular (2)	66
4 recipients from donor 419	87	22 (15–28)	72	25 (19–28)	1	Cardiovascular (1)	75 (41–83)
6 recipients from donor 420	94	15 (10–21)	39	20 (18–21)	4	Infection (2) cardiovascular (1) cancer(1)	49 (37–60)
5 recipients from donor 508	54	10 (7–14)	30	8 (7–14)	2	Cardiovascular (1) unknown (1)	44 (41–79)
4 recipients from donor 509	46	13 (7–14)	40	13 (12–14)	1	Cardiovascular (1)	67 (23–92)

[a]Large range seen in years of follow-up reflects the long time span of donation for some donors, leading to considerably longer vCJD-free years of follow-up.

The question of why we have not seen any cases of vCJD in these two at-risk cohorts inevitably arises and a number of possible scenarios may provide a rationale for the lack of disease observed in both the donors and their other recipients.

The first explanation is that vCJD in the index blood recipient was dietary acquired, and the donor was not the source of the infection. In this case, the donors and their other recipients would not be at any increased risk over and above that of the general population. This option has more credence in the donor–recipient cluster where the transfusion event occurred after the introduction of leucodepletion as a vCJD risk reduction measure in 1999 [17]. In the remaining three clusters on the other hand, the transfusion events predate the introduction of leucodepletion.

A second possible explanation is that infected individuals have remained asymptomatic or presymptomatic due to having a more resilient genotype. Specifically, all patients with clinical presentation of vCJD to date have been classified with a homozygous genotype for methionine at polymorphic codon 129 of the prion protein gene, PRNP, where either methionine or valine can be encoded [18]. In the general UK population, the prevalence of the PRNP codon 129 genotypes is 40% methionine homozygous, 10% valine homozygous and 50% heterozygous [19]. As infection with vCJD through dietary exposure is taken to be rare, we assume that the chances of more than one individual in each donor–recipient cluster having been infected by that route are negligible. Within each of these independent clusters, we also assume that each individual has the same prior probability of carrying infection. It follows that the worst case scenario, using a simple method and making the same precautious assumptions as in the original risk assessment, assumes that one donor per donor–recipient cluster was certainly infected and selects the donor who also donated to the largest number of other recipients. In this worst case scenario of transmission being certain, the 'expected' number of infections amongst all these 112 donors is 3 (albeit subject to considerable chance variation). On the same assumption, one would also expect around 8 consequential infections amongst the 33 other recipients followed up (i.e. excluding the large number linked to the 103 donors in that cluster). The relevant calculations are set out below Fig. 2. With a 40% prevalence of the methionine homozygous genotype in the UK population, a rough approximation of 4, one donor and 3 other recipients, might be expected to be of the methionine homozygous genotype. Despite the possibility that this actual number could be even smaller, it is unlikely to be zero, but as individuals at risk are not routinely genotyped, this cannot be definitively concluded. It remains that most of this cohort will have the presumed more resilient genotypes, with the potential for asymptomatic carriage.

Even presuming infection amongst individuals with more susceptible genotypes, those affected may have died of other causes before developing clinical vCJD disease. Incubation periods for peripheral inoculation and oral exposures to TSEs have been seen to have a wide range, from 4 to 40 years [16]. Conclusive data on the absence of vCJD exposure and infection in the at-risk donors and other recipients are limited by the lack of available post-mortem examinations. Asymptomatic deposition of prion protein has been found at post-mortem in other at-risk cohorts on two prior occasions, in the previously mentioned TMER blood recipient, and in an individual treated with UK-sourced pooled factor concentrates [20, 21]. Amongst the at-risk donors and other recipients that have died, however, average survival time for both cohorts was longer than documented incubation times of vCJD blood transmission, with all but one surviving at least 5 years from transfusion until death [13, 16].

The at-risk individuals identified in the donor and other recipients' cohorts are potentially at a much reduced risk compared to other at-risk cohorts for whom the risk has been calculated following receipt of an identifiable implicated blood or plasma product with an associated infectious dose. The at-risk donors and other recipients' risk assessment used probability to calculate the relative likelihood of an index patient with vCJD being infected by transfusion or diet. Whilst further information about some component elements of this risk assessment is now available to us from animal models exploring the infectivity of blood and the transmissibility of infection, nothing has emerged as of yet that would significantly alter the original precautionary interpretation [22, 23]. However, more subjectively, the relative chance of transmission through blood in these cases must be considered smaller as the time since transfusion increases, and the donors remain free from signs of disease.

This is the first time that these two cohorts have been described in detail. Although it had been forecast that further donors and other recipients might be identified as additional patients with vCJD with a history of blood transfusion were diagnosed, this has not materialized. Ongoing TMER study results confirm that no new cases of transfusion-associated vCJD have emerged since 2007 [11]. As long as there continues to be an absence of new vCJD diagnoses, the numbers of individuals included in this cohort, as currently defined, will not increase. Instead, numbers will diminish as further individuals die of other causes, or if any changes were to be made to the risk assessment based on the emergence of new evidence regarding iatrogenic risk or asymptomatic prevalence of

Table 4 Advice given to individuals at increased risk of CJD

- Do not donate blood (no one who is at increased risk of CJD, or who has received blood donated in the United Kingdom since 1980, should donate blood)
- Do not donate organs or tissues, including bone marrow, sperm, eggs or breast milk
- In the case of any medical, dental or surgical procedures, clinicians should be advised beforehand to make special arrangements for the surgical instruments used
- Family should be told about increased risk status

vCJD, suggesting that the degree of risk attributable to these individuals is substantially lower.

Not unexpectedly, the median age of surviving other recipients is slightly greater than that of the donors, reflecting the generally older age of transfusion recipients. The cohort does, however, include individuals of a much younger age, which dictates a need to maintain very long-term follow-up of these other recipients. These and all individuals at increased risk of vCJD are asked to follow specific advice to prevent onward transmission (Table 4).

Conclusions

Many years have passed without detecting any clinical cases of vCJD in these at-risk donors and their other recipients. Each of these cohorts has survived disease-free far longer than the estimated incubation time for dietary-acquired CJD (donors) and transfusion-acquired disease (other recipients) based on cases seen to date. However, since our understanding of the nature and prevalence of asymptomatic vCJD infection remains poor, and there is as yet no means to reliably detect such infection, the absence of disease on its own may not be sufficient to completely rule out the risk in these individuals.

Author contributions

MC undertook the analysis of the data. RGW completed post-mortem review of deceased patients. MC and KS wrote the first draft of the manuscript. All authors contributed to drafting the manuscript, and all approved the final version.

Conflict of interest

The authors declared that they have no conflict of interests.

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