Guidance Agenda: Guidance Documents CBER is Planning to Publish During Calendar Year 2022

(January 2022)

This is the list of guidance topics CBER is considering for development during Calendar Year 2022. The list includes topics that currently have no guidance associated with them, topics where updated guidance may be helpful, and topics for which CBER has already issued Level 1 draft guidances that may be finalized following review of public comments. We currently intend to develop guidance documents on these topics; however, the Center is neither bound by this list of topics, nor required to issue every guidance document on this list. We are not precluded from developing guidance documents on topics not on this list.

For further information regarding specific topics or guidances, please contact the Office of Communication, Outreach and Development, Center for Biologics Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 71, Rm. 3128, Silver Spring, MD 20993-0002, 1-800-835-4709 or 240-402-8010, ocod@fda.hhs.gov.

Guidance Documents CBER is Planning to Issue in 2022:

CATEGORY – Blood and Blood Components:

- Blood Pressure and Pulse Donor Eligibility Requirements; Compliance Policy; Draft Guidance for Industry
- Alternative Procedures for Cold-Stored Platelets Intended for Transfusion; Draft Guidance for Industry
- Collection of Platelets by Automated Methods; Guidance for Industry[1]
- Investigational COVID-19 Convalescent Plasma; Guidance for Industry (Updated January 2022)
- Compliance Policy Regarding Blood and Blood Component Donation Suitability, Donor Eligibility and Source Plasma Quarantine Hold Requirements; Draft Guidance for Industry
- An Acceptable Circular of Information for the Use of Human Blood and Blood Components: Guidance for Industry

[1] We intend to issue a Level 2 guidance to revise existing recommendations to address statistical sampling plans for process validation.

CATEGORY – Tissues and Advanced Therapies:

- Human Gene Therapy for Neurodegenerative Diseases; Guidance for Industry
- Considerations for the Development of Human Gene Therapy Products Incorporating Genome Editing; Draft Guidance for Industry
- Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell Therapies; Draft Guidance for Industry
- Regulation of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) - Small Entity Compliance Guide; Guidance for Industry
- Voluntary Consensus Standards Recognition Program for Regenerative Medicine Therapies; Draft Guidance for Industry and Staff
- Recommendations for Determining Eligibility of Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps); Draft Guidance for Industry

CATEGORY – Vaccines:

- Emergency Use Authorization for Vaccines to Prevent COVID-19; Draft Guidance for Industry and Staff

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Guidance Documents CBER is Planning to Issue in 2023:

CATEGORY – Blood and Blood Components:

- Collection of Platelets by Automated Methods; Draft Guidance for Industry
- Recommendations for Evaluating Donor Eligibility Using Individual Risk-Based Questions to Reduce the Risk of Human Immunodeficiency Virus Transmission by Blood and Blood Products; Draft Guidance for Industry (Issued January 2023)
- Alternative Procedures for the Manufacture of Cold-Stored Platelets Intended for the Treatment of Active Bleeding when Conventional Platelets Are Not Available or Their Use Is Not Practical; Draft Guidance for Industry
- Compliance Policy Regarding Blood and Blood Component Donation Suitability, Donor Eligibility and Source Plasma Quarantine Hold Requirements; Guidance for Industry
- Blood Pressure and Pulse Donor Eligibility Requirements; Compliance Policy; Guidance for Industry
- Recommendations for Testing Blood Donations for Hepatitis B Surface Antigen; Draft Guidance for Industry

CATEGORY – Tissues and Advanced Therapies:

- Voluntary Consensus Standards Recognition Program for Regenerative Medicine Therapies; Guidance for Industry and Staff

- Considerations for the Use of Human- and Animal- Derived Materials and Components in the Manufacture of Cell and Gene Therapy and Tissue-Engineered Medical Products; Draft Guidance for Industry

- Safety Testing of Human Allogeneic Cells Expanded for Use in Cell-Based Medical Products; Draft Guidance for Industry

- Recommendations for Determining Eligibility of Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps); Draft Guidance for Industry

- Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products; Draft Guidance for Industry

- a ban on human consumption of slaughtered cattle more than 30 months old;
- prohibition of mechanically recovered meat;
- a ban on mammalian-derived feed for ruminants;
- use of certain rendering processes; and
- additional herd control and surveillance (Ref. 20).

The timing and degree to which the European countries have implemented such controls has varied (Refs. 20, 23). The current prevalence of BSE in each country is uncertain because active surveillance of the epidemic has not been completely implemented (Refs. 5, 6, 20, 23).

BSE has been detected in many, but not all, European countries, and the increase or decrease of BSE in many countries is not predictable (Refs. 5, 23). Food chain control measures (and their enforcement) vary, and cannot be assured for all time periods in question. Because of these uncertainties, and the evolving BSE epidemic, donor deferrals on a country-by-country basis are not practical at this time. FDA, therefore, has developed a uniform recommendation for donor deferral based on exposure in Europe outside of the U.K. The highest prevalence of BSE that has been observed in a European country with a strong surveillance program (Switzerland) is approximately 1.5% of the BSE prevalence that was observed for the United Kingdom between 1980 and 1996. Also, residents in France consumed an estimated 5% British beef during the epidemic period, and other Europeans probably ate less. Therefore, the current estimated maximum risk of BSE exposure in Europe is approximately 1.5-5% of that in the United Kingdom. Assuming a "worst-case" relative risk of 5% per day of exposure, a deferral of donors resident in Europe for 5 years (60 months) is equivalent to the currently recommended deferral for donors with a history of three months of cumulative travel or residence in the U.K. This is the basis for our recommendation to exclude HCT/Ps from donors with a history of 5 or more years of residence or travel in Europe outside of the U.K. from 1980 to the present.

Article

Is there a real risk of transmitting variant Creutzfeldt–Jakob disease by donor sperm insemination?

David Mortimer gained his PhD from Edinburgh University in 1977 and received post-doctoral training in Edinburgh, Paris and Birmingham before joining the faculty of the University of Calgary in 1983 and was Scientific Director of the Infertility Programme. In 1991 he moved to Sydney IVF. He held positions at Sydney University and the Royal Prince Alfred Hospital, also working on the WHO's Manual for the Standardized Investigation, Diagnosis and Management of the Infertile Male. He moved back to Canada in 2000 and established an international consulting company. Major consultancy projects since 1986 have included andrology labs, sperm banks and IVF units, and advice on accreditation, total quality management and risk management.

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Abstract

Although >99% of cases of Creutzfeldt–Jakob disease (CJD) are caused by spontaneous or inherited mutations in the prion protein, 'variant' CJD (vCJD) arose from dietary exposure to meat products infected with the bovine spongiform encephalopathy prion. While European and Canadian sperm donor candidates are rejected for significant CJD risk factors, American sperm donors are managed like blood donors (excluding all men who spent ≥3 months in the UK during 1980–1996 or ≥5 years in Europe since 1980), even though no evidence exists for sexual transmission of prion disease. This study surveyed international experts on either prions/prion disease or donor sperm/cryobanking as to the risk of vCJD transmission via semen/donor spermatozoa (45/104 replied). Consensus expert opinion was that the risk of transmission was <1:10,000,000, even for UK men, hence ultra-conservative risk avoidance would have minimal impact on public safety. Defining 'high vCJD risk' should be based on knowledge rather than fear, and due caution founded upon quantifying real risks rather than avoiding theoretical risks. Women seeking treatment using donor spermatozoa should be allowed to judge the negligible risk of vCJD infection in comparison with acceptable everyday risks, and given the choice of accepting spermatozoa from donors screened according to European-style criteria.

Keywords: *Creutzfeldt-Jakob disease, donor insemination, donor spermatozoa, prions, risk management, screening*

Introduction

Transmissible spongiform encephalopathies (TSE), which include scrapie in sheep, BSE (bovine spongiform encephalopathy) in cattle, and Kuru and Creutzfeldt–Jakob disease (CJD) in humans, are infectious neurodegenerative diseases that are uniformly fatal (see Cashman, 1997; Belay, 1999; Brown *et al.*, 2001; Aguzzi *et al.*, 2004; Collins *et al.*, 2004; Collinge, 2005; European Commission, 2005; Johnson, 2005; Hilton, 2006; Watts *et al.*, 2006). It was the 'mad cow' crisis in the United Kingdom (UK), followed by the 'epidemic' of a 'new variant' of CJD (now called variant CJD or vCJD), that brought TSE to the attention of the public. vCJD is a highly dreaded disease: it is invariably fatal and with currently no screening test (although a very recent paper has reported a possible technology for this: Saá *et al.*, 2006), no diagnostic test, and no treatment available. In summary, TSE affecting humans can be classified as follows.

Sporadic CJD (sCJD) accounts for ~85% of all CJD cases and has a mean age at onset of about 60 years. Although some cases of sCJD survive more than 2 years, 90% die within 12 months of the disease manifesting (median 5 months). There is no evidence of any difference in the incidence of sCJD, which occurs at a prevalence of 1–2 per million (Watts *et al.*, 2006) in all countries worldwide where surveillance has been carried out. sCJD presents with a marked clinical and molecular heterogeneity (Schoch *et al.*, 2006).

Familial CJD (fCJD) is one of three genetically determined TSE (the others being Gerstmann–Sträussler–Scheinker syndrome and fatal familial insomnia), all of which are transmitted by autosomal dominant inheritance. In general, fCJD has an earlier age of onset and longer clinical course than sCJD, and it accounts for ~10–14% of total CJD cases.

Iatrogenic CJD (iCJD) is rare, with 267 cases having been reported worldwide up to 2000 (Brown *et al.*, 2000). Transmission of iCJD has occurred with corneal transplants, dura mater grafts, injections of hormones extracted from human pituitary glands, and from the use of contaminated neurosurgical instruments.

Variant CJD (vCJD) emerged in the UK in 1994 and has a distinctively different course and pathology from sCJD: younger age at onset (mean of 26 years), a prominence of psychiatric and sensory symptoms, and a long disease course. The prevalence of vCJD may be as high as 3% of CJD cases in the UK, but is <1% elsewhere. It is generally accepted that vCJD was caused by dietary exposure to BSE-infected foodstuffs during the 1980s and 1990s (see Bradley and Wilesmith, 1993; Collins *et al.*, 2004; Ward *et al.*, 2005), although fortunately a significant species barrier limited transmission (e.g. Bishop *et al.*, 2006).

Kuru is a geographically limited endemic in the Fore linguistic group in the eastern highlands of Papua New Guinea, where its prevalence has steadily declined since the cessation of cannibalism in the mid/late 1950s (see Collinge *et al.*, 2006 for a recent review).

In its Thirteenth Annual Report, the UK National CJD Surveillance Unit (National CJD Surveillance Unit, 2005) recorded 153 cases of definite or probable vCJD identified in the UK since 1990 when surveillance began, with 148 deaths reported up to 31 December 2004. The most recent data (see www.cjd.ed.ac.uk) now include 1136 deaths from definitive and probable CJD, with vCJD accounting for 155 deaths (out of a total of 161 cases of vCJD). Congruent with the link to BSE, the number of new cases being reported in the UK fell to five in 2005 compared with 28 in 2000 (the height of the BSE crisis), when a large number of individuals were exposed to BSE infected material. Only 11 cases of vCJD have been reported in France, and only nine in the rest of the world, hence vCJD is regarded as a primarily UK disease (Ladogana *et al.*, 2005). Globally, the death rate from all types of CJD is about one person per million of population per year, hence the general vCJD death rate is about one per 100 million people per year.

The future number of cases in the UK population remains of concern, with estimates of subclinical disease varying around an average of 273 cases (95% confidence intervals 49–692) per million of population (Hilton *et al.*, 2004). However, a more recent report suggested no clinical evidence of 'hidden' vCJD in UK children (Verity *et al.*, 2006). According to RG Will (presentation at the PrioNet 2006 conference held in Vancouver, BC, Canada, June 2006), nine children were conceived or born during clinical illness of vCJD in their mothers; all are still alive with no clinical evidence of disease (although the oldest child is still only 9 years old). Although there is likely to be a number of asymptomatic 'carriers' of disease within the UK and hence a potential for iatrogenic spread of vCJD (Hilton, 2006), the risk of human–human transmission of vCJD must be very low because there are very few cases despite very large amounts of exposure. Also, the risk of fCJD transmission from an unaware affected male has been estimated at $\geq 10^{-6}$ (Collins *et al.*, 2004). Only two cases of vCJD transmission by blood products have been reported (Llewelyn *et al.*, 2004; Peden *et al.*, 2004, 2005; Farrugia *et al.*, 2005), and there is epidemiological evidence that classical sCJD is not transmitted by blood transfusion (Ludlam and Turner, 2005). In the absence of serological or biological screening tests for abnormal prions, the UK Department of Heath has developed a series of measures to reduce secondary transmission of vCJD, including barring blood donations from individuals suspected of having sCJD or with a family history of prion disease. These measures also include using only using imported plasma from BSE-free countries for recipients of clotting factor concentrate, and universal leukodepletion for fresh blood transfusions. While urine can be a vector for horizontal prion transmission in scrapie-infected mice, and chronic inflammation of the excretory organs might increase prion spread (Seeger *et al.*, 2005), there is no evidence that vCJD (or sCJD) has been acquired through receiving urinary gonadotrophins (Ward *et al.*, 2004). The 2004 Conference on the Bio-Safety of Urinary Derived Medicinal Products stated that no CJD infectivity in human urine has been demonstrated, and no definite cases of transmission via urine have been reported (Balen and Lumholtz, 2005). They concluded that human urinary-derived gonadotrophins appear to be safe (see also European Commission, 2005), an opinion that is widely shared among reproductive medicine specialists, although certain pharmaceutical companies who manufacture recombinant gonadotrophins still promote the notion of their increased biosafety from the perspective of both virus and prion contamination (e.g. Casper, 2005; Ludwig and Keck, 2005; Out, 2005). Finally, although there is a theoretical risk of transmitting prion disease via dental treatment, provided optimal standards of infection control and decontamination procedures for all infectious agents are maintained, the risk is considered to be very low (Department of Health, 2005; Azarpazhooh and Leake, 2006).

Interestingly, there is a wide divergence in how different jurisdictions have considered the risk of CJD transmission by sperm donors. In the UK the Human Fertilization and Embryology Authority Code of Practice (2003) refers to the screening guidelines of the British Andrology Society (1999) for semen donors, which themselves make no mention of TSE, prion diseases or vCJD. However, in France, Décret no. 96–993 du 12 Novembre 1996 relatif aux règles de sécurité sanitaire applicables au recueil et à l'utilisation de gamètes humains provenant de dons en vue de la mise en oeuvre d'une assistance médicale à la procréation (translation: 'Decree 96–993 of 12 November 1996 concerning rules for health safety relevant to the recovery and use of human donor gametes for the purpose of assisted conception') specifies that donor candidates who represent a potential risk of transmitting CJD or other subacute spongiform encephalopathies must be excluded. In particular, this relates to individuals with family members who have recently died of such diseases, or individuals who report having received human-derived products that might have been contaminated, or who have undergone invasive neurosurgical procedures (Dominique Le Lannou, personal communication). In Canada, pertinent sperm donor exclusion criteria are similar: (i) diagnosis with CJD or first degree family member with a history of CJD; (ii) receipt of human pituitary-derived growth

hormone or dura mater; and (iii) spongiform encephalopathy or prion disease (Health Canada, 2000).

In the near future, recruitment, selection and screening of all donors within the European Union will be based on Directive 2006/17/EC (European Union, 2006), which clearly separates donors of reproductive material from other cells and tissues. In the latter case, risk criteria for the transmission of prion diseases include: (i) people diagnosed with CJD or vCJD, or having a family history of non-iatrogenic CJD; (ii) people with a history of rapid progressive dementia or degenerative neurological disease, including those of unknown origin; and (iii) recipients of hormones derived from the human pituitary gland and recipients of grafts of cornea, sclera and dura mater, and persons that have undergone undocumented neurosurgery (where dura mater may have been used). This clause also notes that for vCJD, further precautionary measures may be recommended. However, the annex governing donors of reproductive cells makes no specific mention of prion diseases.

In contrast, in the United States of America (USA) the Federal Food and Drug Administration (FDA) has adopted the same exclusion criteria for sperm donors as for blood donors: men are precluded from donating spermatozoa if they have spent either more than 3 months in the UK during the period 1980–1996, or more than 5 years (cumulatively) in any European country(ies) since 1980 (Food and Drug Administration, 2004). In this unique approach, donor spermatozoa are considered no differently to all other human cells, tissues, and cellular and tissue-based products ('HCT/Ps'). One surprising aspect of this concern is that if semen from British men represents such a risk for transmission of vCJD, then why does the Centres for Disease Control and Prevention 'vCJD – Risk for Travelers' (Centres for Disease Control and Prevention, 2005a) not include a warning to American travellers to the UK of the risk of vCJD infection if they were to be inseminated by such individuals? According to the CDC frequently asked questions page (Centres for Disease Control and Prevention, 2005b) 'the current risk for infection with the BSE agent among travellers to Europe is extremely small, if it exists at all', and they state that the current risk of acquiring vCJD from eating beef and beef products in the UK 'appears to be extremely small, perhaps about 1 case per 10 billion servings' (Centres for Disease Control and Prevention, 2005a).

TSE are caused by an atypical infectious agent called a 'prion' (Prusiner, 1982; Cashman, 1997) which is a host-encoded protein that becomes misfolded. The normal cellular isoform of the prion protein (PrP^{C}) is a cell surface sialoglycoprotein that is expressed preferentially in the central nervous system (CNS) and at lower levels in a number of other non-neural tissues. While PrP^{C} is predominantly an α-helical molecule, the misfolded, infectious isoform, PrP^{Sc} (terminology based on the original description of this misfolding in scrapie) has a predominantly β-sheet content. The PrP^{Sc} isoform readily aggregates, and larger aggregate 'particles' have a greater converting activity, recruiting more Pr^{PC} to re-fold into PrP^{Sc} (Silvera *et al.*, 2005). Although sCJD incubates almost exclusively in tissues of the CNS, vCJD seems to incubate more peripherally. Interestingly, the processes of seeded aggregation of misfolded host proteins involved in prion propagation are of far wider significance in understanding more common neurodegenerative diseases, e.g. misfolding of a Cu–Zn superoxide dismutase in motor neurons causes ALS (amyotrophic lateral sclerosis) in mice (Nordlund and Oliveberg, 2006).

Although the pathogenesis of vCJD in humans is not fully understood, available data suggest that oral exposure to BSE is rapidly followed by accumulation of PrP^{Sc} in gut-associated lymphoid tissue and then throughout the reticulo-lymphatic system; spread to the CNS might not occur for several years (Hilton *et al.*, 2004). Given the million-fold difference in infectivity between CNS tissues and muscle/other extraneural tissues, important measures in minimizing TSE transmission include butchering the carcasses to prevent any spattering of brain or spinal cord onto the meat, eliminating mechanical meat recovery in which neural tissues are included, and regulation of 'health supplements' that may contain CNS tissues (Johnson, 2005).

A polymorphism at codon 129 of the prion protein gene PRNP influences host susceptibility to CJD: over 80% of patients with sCJD are homozygous at this locus compared with 49% of healthy controls (Ironside *et al.*, 2006). Although all tested cases of vCJD have occurred in methionine homozygotes, Bishop *et al.* (2006), using modelling studies with transgenic mice, concluded that all individuals irrespective of their codon-129 genotype could be susceptible to secondary transmission of vCJD through routes such as blood transfusion. The long incubation period after growth hormone injections presumably reflects the peripheral route of inoculation in contrast to intracerebral placement of contaminated dura mater; in both situations, homozygosity at codon 129 seems to increase susceptibility to iatrogenic disease (Collins *et al.*, 2004).

Genetic transmission in humans has been documented only with fCJD, and genetic transmission of TSE in animals has not been observed (Johnson, 2005). BSE is not transmitted horizontally through cattle populations, unlike scrapie in sheep and CWD (cervid wasting disease in North America). Studies in mice have shown no vertical transmission of disease to offspring born to vCJD-infected females, or to normal females mated with inoculated males (Taguchi *et al.*, 1993). There are no reports that semen is infectious for TSE in cattle, sheep or goats (R Bradley, personal communication). Furthermore, semen and male reproductive organs have shown no detectable infectivity following inoculation of susceptible mice (see World Health Organization, 2003), although only limited experimental studies have been undertaken to date. An extensive study on bovine embryos (Wrathall *et al.*, 2002) concluded that embryos are unlikely to carry BSE infectivity, and hence the risk of vertical TSE transmission is negligible – evidence that was accepted by the European Community's Scientific Steering Committee's 2002 amendment of its 1999 report on the possible vertical transmission of BSE (European Commission, 1999, 2002). Moreover, bovine semen and embryos are traded freely, even from countries with BSE (Office International des Épizooties, 2005), confirming the general acceptance of a negligible risk of vertical BSE transmission.

The C-terminus of PrP includes the glycosylphosphatidylinositol (GPI) membrane anchor, a region of the molecule that likely plays a role in the pathogenesis of prion disease (Chesebro *et al.*, 2005), and while isoforms of PrP devoid of this region would still be active as PrP^{C}, they would be incapable of participating in the conversion process to PrP^{Sc}. That only a C-terminally

truncated PrP^{c} isoform was associated with spermatozoa from the ram testis, cauda epididymidis and semen, and with cytoplasmic droplets (Ecroyd *et al.*, 2004) is therefore a very important finding. A C-terminal truncated PrP isoform has also been demonstrated in mature human spermatozoa (Shaked *et al.*, 1999). Taguchi *et al.* (1993) reported that male mice infected with prions lost their fertility before clinical signs of disease became noticeable. Knockout mice lacking the *Prnp* gene showed male sterility, perhaps due to an inability of the spermatozoa to perform the acrosome reaction (Paisley *et al.*, 2004). The Prnp protein may have important antioxidant functions necessary for sperm integrity and male fertility, with reduced availability of PrP^{c} (due to its conversion to PrP^{sc}) apparently causing subfertility in prion-infected males via mechanisms involving oxidative stress or damage to spermatozoa and/or the sperm genome (reviews by Agarwal *et al.*, 2006; Aitken and Baker, 2006).

All the above findings are consistent with the general notion that prion diseases are not transmitted sexually, and it seems possible that men with prion disease would become subfertile (which would reduce the likelihood of their being accepted as sperm donors). So just how much of a real public health risk does vCJD in sperm donors represent? Given the current figures from National CJD Surveillance Unit (see above) that there are just six vCJD cases still alive in the UK with about five new diagnoses of vCJD per year (half of whom are women and cannot be sperm donors). Therefore, among the approximately 18.4 million men aged between 18 and 40 (i.e. potential sperm donor candidates) (Government Actuary's Department, 2003), the likelihood of a vCJD positive man even being accepted as a sperm donor is remarkably small. Similar data are not available for other European countries, but the relative risk of vCJD for France has been estimated by the FDA as 0.05 × UK, and for Europe in general as 0.015 × UK levels (Anderson, 2005). Beyond that, there remains the lack of any scientific evidence that any TSE is actually transmitted via semen or spermatozoa. Consequently, it seemed appropriate that a risk assessment of the likelihood of vCJD being transmitted by a sperm donor should be attempted.

Materials and methods

A questionnaire was prepared that included seven questions aimed at elucidating people's knowledge and perceptions of the risks or likelihood of vCJD being transmitted via donor spermatozoa. The questionnaire was then sent via e-mail to as many internationally recognized experts on either prions and prion disease (group A) or on donor spermatozoa and/or sperm cryobanking (group B) as the authors could identify. These experts were identified based upon their publication record in peer-review journals and/or known expertise in the aforementioned specialist areas established via the authors' professional networks, as well as their knowledge of English in order to avoid misunderstanding of questions. However, several individuals were not sent the questionnaire due to reasons such as their expecting consultancy fees for completion of the survey, or people whose participation was precluded due to their working for a government agency. The questionnaire was therefore sent to 64 people in group A and 44 in group B. A further five recipients were not in the original mailing but added in response to either suggestions from other recipients or where the questionnaire was passed on by the original recipient (three in group A and two in group B). It is considered that the populations surveyed represent the great majority of individuals working in the pertinent fields who might be expected to provide scientifically dependable responses. All original recipients who had not responded by 3 weeks after the original mailing were sent a single reminder by e-mail, and data analysis was undertaken in the fifth week (mid-July 2006). Questionnaire recipients were informed that any question left blank would be taken as a 'don't know' response.

Question 1: Are you aware of any case of transmission of vCJD via human insemination (either coitus or artificial insemination)? If 'yes', how many cases?

Question 2: If a man has preclinical vCJD, could you estimate the likelihood of him infecting his partner in a co-habiting sexually active couple? (Obviously men with clinical vCJD would have been excluded, or would not be used as sperm donors.) Respondents were asked to choose one option on a logarithmic risk scale: 'very high' (>1:10,000); 'high' (1:10,000–1:100,000); 'moderate' (1:100,000–1:1,000,000); 'low' (1:1,000,000– 1:10,000,000); 'very low' (<1:10,000,000); and 'trivial' or 'incalculably small'. This scale is two orders of magnitude lower than the commonly used Calman Scale (Calman, 1996), but the generally very low prevalence of vCJD in the human population, even in the UK, was felt to warrant this.

Question 3: In an attempt to estimate relative risk, how would you rate the following previous activities of a UK sperm donor in relation to his representing a risk of vCJD infection? Respondents were asked to enter a value between 0 and 100 for each list item, where his having been a 'recipient of dura mater transplant' was rated at 100. The previous activities listed were:

(a) Neurosurgery not involving dura mater transplantation,
(b) Eating brains during the period 1980–1995,
(c) Eating T-bone steaks during the period 1980–1995,
(d) Eating T-bone steaks after 2000,
(e) Eating trimmed steak during the period 1980–1995,
(f) Eating trimmed steak after 2000,
(g) Being a vegetarian.

Question 4: How much do you consider that leukodepletion of semen would decrease the risk of vCJD transmission via semen? Respondents were asked to choose either 'little or no decrease', 'the same as for blood (by perhaps 40%)', or 'more than for blood (i.e. by more than 50%)'.

Question 5: In trying to estimate the relative risk of a man transmitting vCJD to a woman, and in particular the perceived importance of white blood cells (WBC) in the inseminate, the questionnaire asked how respondents would rate the following activities: (i) unprotected sexual intercourse (i.e. not using condoms); (ii) artificial insemination with whole semen (but $\geq 10^6$ WBC/ml); and (iii) artificial insemination with washed spermatozoa (no WBC). Respondents were asked to rate each activity for three geographic areas (UK, other European countries, and the USA), using the same list of terms as in question 2. This question was designed to consider the different biomass that a woman would receive, ranging from multiple whole ejaculates in (i), to a part of an ejaculate, typically a maximum of 0.5 ml of whole semen,

per insemination in (ii), and spermatozoa alone, without any contaminating other cellular elements in (iii). The quantities of leukocytes (WBC) were based on the screening criteria for normality of donor semen ($<10^6$/ml as per World Health Organization, 1999), and the exclusion of WBC during density gradient preparation of the spermatozoa (Mortimer, 2000).

Question 6: Which of the following options in regard to sperm donors should be adopted in order to achieve a reasonable level of public safety for patients undergoing infertility treatment (i.e. the risk for vCJD would likely be considered acceptable by properly informed patients in comparison with other common risks)? Respondents were asked to choose as many of the following options as they wished:
(a) Exclude all men who spent >3 months (total) in the UK during the period 1980–1995
(b) Exclude all men who spent >5 years (total) in Europe, but not in the UK, since 1980
(c) Exclude only men who are at high risk for vCJD
(d) Exclude only men who are at moderate risk for vCJD
(e) Exclude only men who are at low risk for vCJD
(f) Exclude only men who are at minimal risk for vCJD
(g) Exclude no-one. An example of a person at high risk was a dura mater recipient, or someone who had ever eaten brains; at moderate risk was someone who had had other neurosurgery or had eaten T-bone steaks or burgers during the period 1980–1995. Similarly, an example of a person at low risk was someone who ate only fully trimmed beef steaks during the period 1980–1995, and vegetarians were suggested as persons at minimal risk.

Question 7: Is there evidence of any value of using PRNP codon 129 genotyping to establish relative risk in either recipients of donor spermatozoa or sperm donors?

Statistical analysis

Data were tabulated using spreadsheets (Excel 2003; Microsoft Corporation, Redmond, WA, USA). Frequency data between groups were analysed using chi-squared tests (MedCalc v7.4, MedCalc Software, Mariakerke, Belgium). Figures were prepared using Corel Draw v12 (Corel Corporation, Ottawa, ON, Canada).

Results

Of the 108 individuals to whom the questionnaire was sent (allowing for the five that were passed on), four e-mail addresses were invalid (all from group A, prion experts), hence it is considered that only 104 questionnaires were issued for the survey: 60 to group A and 44 to group B (donor sperm/cryobanking experts). Responses were received from 45 individuals, 18 from group A and 27 from group B, an overall response rate of 42.3%. While the numbers of respondents might seem low to some, they do represent the available population of experts willing to contribute opinions to the study that the authors were able to identify and approach. Moreover, a response rate of over 40% is quite respectable for a voluntary survey. Given the overall similarity of their responses (see below), it is believed that they do represent valid sampling of the populations. Due to the non-quantitative nature of the data collected, statistical power calculations could not be undertaken.

A total of eight people (three from group A and five from group B) declared that they were unable to respond to the questionnaire because they felt their knowledge was too limited for them to give meaningful answers. This was considered, given the nature of the field of prions and prion diseases, to be a valid response, hence 17.8% of survey respondents were deemed to have been 'unable to respond'.

Question 1: All 45 respondents who completed the questionnaire were unaware of any case of transmission of vCJD via human insemination.

Question 2: Four of the group B respondents did not provide answers to this question, and were excluded from this analysis. The frequency distributions of the responses to question 2 from groups A and B are shown in **Figure 1**. While group B tended to feel that there was a higher level of risk than group A, the distribution of answers between the two groups was not significantly different.

Question 3: The responses to question 3 concerning the perceived risk of vCJD infectivity of a UK sperm donor based on his previous activities are tabulated for groups A and B separately, as well as combined, in **Table 1**. Having had neurosurgery that did not involve dura mater transplantation was seen as having an inherent, but very wide ranging risk. Moreover, there was a wide spread of opinion between the respondents for all the more risky behaviours, but there was clear evidence for the perceived risk decreasing from having eaten brains in the 'danger years', through having eaten T-bone steaks and trimmed steak during the 'danger years', to a much lower risk from having eaten steak since 2000 (with T-bone steaks still being seen as slightly more risky). Having been a vegetarian was perceived as affording a much lower risk of infectivity that for non-vegetarians.

Question 4: This question sought to ascertain whether washing spermatozoa for intrauterine insemination (IUI), which would be a highly effective means of leukodepletion, would reduce the risk of vCJD infectivity. Three respondents in group A, and two in group B were unable to provide an answer to this question, and the responses from groups A and B are shown in **Figure 2**. Some of the group B respondents did feel that sperm washing would reduce vCJD infectivity, perhaps because of their greater knowledge of sperm preparation technology; however, the distribution of answers between the two groups was not significantly different. A Fisher's exact test was also performed comparing minimal versus some/more decrease between the two groups and gave a *P*-value of 1.0, hence although 59% of respondents believed that sperm washing would be beneficial, opinion was statistically equally divided in both groups between no or some beneficial effect of sperm washing.

Question 5: This question sought to estimate the relative risk of a man transmitting vCJD to a woman by different insemination modalities. In group A, one respondent declined to estimate the risk for men in either the UK or other European countries, but all estimated the risk for men in the USA; among group B respondents the number declining to provide estimates were five for the UK, three for the rest of Europe and five for the USA. There was no apparent relationship between a respondent's geographic location and declining to estimate risk.

Comparison of the responses provided by the two groups to this

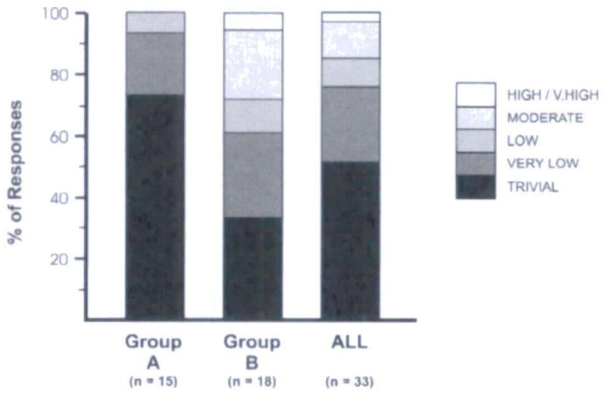

Figure 1. Frequency distributions of the responses from prion experts (groups A) and donor sperm/cryobanking experts (group B) to question 2, estimating the likelihood of a man who has pre-clinical variant Creutzfeldt–Jakob disease infecting his partner in a co-habiting sexually active couple. Logarithmic risk scale: 'very high' (>1:10,000); 'high' (1:10,000–1:100,000); 'moderate' (1:100,000–1:1,000,000); 'low'(1:1,000,000–1:10,000,000); 'very low' (<1:10,000,000); and 'trivial' or 'incalculably small'.

Table 1. Responses to question 3 concerning the previous activities of a UK sperm donor in relation to his representing a risk of variant Creutzfeldt–Jakob disease infectivity from prion experts (groups A) and donor sperm/cryobanking experts (group B), as well as for all respondents combined. Values are mean/mode (median; range).

Previous activities	*Group A*	*Group B*	*ALL*
Recipient of a dura mater transplant	Defined as 100		
Neurosurgery not involving dura mater transplantation	26/50 (6; 0–90)	33/10 (10; 0–100)	30/10 (10; 0–100
Eating brains during the period 1980–1995	42/10 (50; 1–100	51/80 (50; 1–100	48/80 (50; 1–100)
Eating T-bone steaks during the period 1980–1995	13/50 (5; 10^{-5}–50	23/1 (10; 0–70	20/1 (10; 0–70
Eating T-bone steaks after 2000	4/1 (1; 0–20	9/0 (1; 0–60)	7/0 (1; 0–60)
Eating trimmed steak during the period 1980–1995	6/10 (2; 0–30)	15/1 (5: 0–70)	12/1 (5; 0–70)
Eating trimmed steak after 2000	1/1 (1; 0–5)	5/0 (1; 0–40)	4/0 (1; 0–40)
Being a vegetarian	$<10^{-9}/10^{-9}$ (10^{-9}; 0–2)	0.2/0 (0; 0–1)	0.1/0 (0; 0–2)

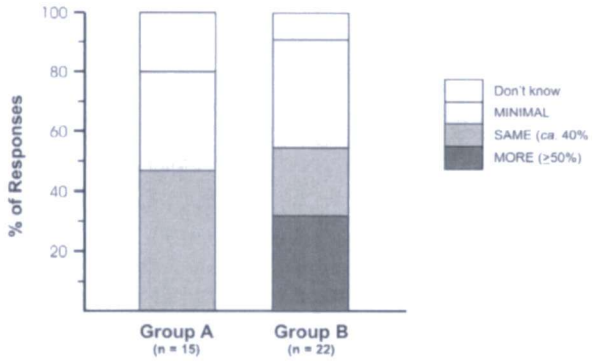

Figure 2. Frequency distributions of the responses from prion experts (groups A) and donor sperm/cryobanking experts (group B) to question 4, considering how much leukodepletion of semen would decrease the risk of variant Creutzfeldt–Jakob disease transmission via semen.

question revealed no significant differences in the distributions of responses, and responses from the two groups were therefore combined within each question for each geographic region (see **Figure 3**).

While there was little perceived difference in risk between insemination via unprotected sexual intercourse or artificial insemination (AI) with whole semen, AI using washed spermatozoa (no WBC) was considered slightly safer for each geographic region. The perceived risk of a man infecting his spouse decreased slightly from men in the UK, through men in other European countries, to men in the USA. Responses to this question clearly illustrated that both groups of experts considered the overall risk of infection to be extremely low: 60% of all rated responses stated 'trivial' and a further 31% stated 'very low', i.e. over 91% of all responses perceived a risk of less than 1:10,000,000. Moreover, there was a clear trend from 85% in the UK, through 91% in the rest of Europe to 98% in the USA.

Question 6: This question sought to elucidate which measures the expert groups considered should be adopted in order to achieve a reasonable level of safety from sperm donor-derived vCJD infection for patients undergoing infertility treatment. Two group A respondents, and one from group B, declined to respond to this question, but comparison of the responses provided by the two groups revealed no significant differences in the distributions of responses (see **Table 2**).

Interestingly, four of the prion expert group (group A), and one person from group B (the donor sperm/cryobanking experts), considered that no sperm donor candidates needed to be excluded, although there was a clear majority opinion that men at 'high risk' for vCJD should be excluded. In this regard it should be noted that, according to the questionnaire, a high risk person was someone who was a dura mater recipient, or someone who had ever eaten brains. Having had other neurosurgery or eaten T-bone steaks or burgers during the period 1980–1995 was considered to be only a moderate risk.

Question 7: Perhaps surprisingly there was no significant differences in the responses provided by the two groups of experts to either part of this question, which sought to discover whether the experts believed there was evidence of any value of using PRNP codon 129 genotyping to establish relative risk in either recipients of donor spermatozoa or sperm donors, although 38% of respondents declined to provide an opinion. The actual responses provided are shown in **Table 3**, and clearly reveal that no such value can be ascertained for either recipients of donor spermatozoa or sperm donors.

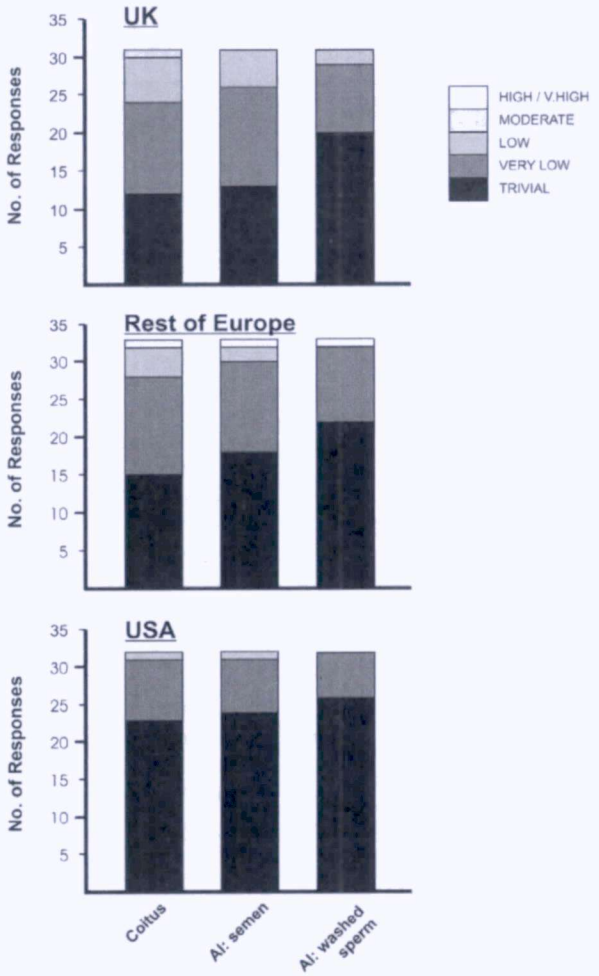

Figure 3. Frequency distributions of the responses from prion experts (group A) and donor sperm/cryobanking experts (group B) to question 5, trying to estimate the relative risk of a man transmitting variant Creutzfeldt–Jakob disease to a woman via different reproductive activities. AI = artificial insemination.

Table 2. Responses to question 6 concerning which measures the expert groups considered should be adopted in order to achieve a reasonable level of safety from sperm donor-derived variant Creutzfeldt–Jakob disease (vCJD) infection for patients undergoing infertility treatment (i.e. the risk for vCJD would likely be considered acceptable by properly informed patients in comparison to other common risks). Group A = prion experts; Group B = donor sperm/cryobanking experts.

Categories of donor candidates to be excluded	*Group A*[a]	*Group B*[a]
Exclude all men who spent ≥3 months (total) in the UK during the period 1980–1995	4	5
Exclude all men who spent ≥5 years (total) in Europe, but not in the UK, since 1980	0	2
Exclude only men who are at high risk for vCJD	5	13
Exclude no-one	4	1
No response	2	1

[a]Not everyone responded to all questions: there were some areas where people felt themselves unable to respond leading to slightly lower numbers than mentioned in text for some responses.

Table 3. Responses to question 7 concerning whether the expert groups believed there was evidence of any value of using PRNP codon 129 genotyping to establish relative risk in either recipients of donor spermatozoa or sperm donors. Group A = prion experts; group B = donor sperm/cryobanking experts.

Perceived value of PRNP codon 129 genotyping	*Recipients of donor spermatozoa*[a]		*Sperm donors*[a]	
	Group A	*Group B*	*Group A*	*Group B*
Unable to respond	5	9	5	9
No	9	5	7	5
Perhaps	1	7	3	8
Yes	0	1	0	0

[a]Not everyone responded to all questions: there were some areas where people felt themselves unable to respond leading to slightly lower numbers than mentioned in text for some responses.

Discussion

The survey revealed that the risk of a man transmitting vCJD to his spouse was estimated as being <1:10,000,000 in 85% of the expert responses received for men in the UK, 91% for men in the rest of Europe, and 98% for men in the USA. Combining this with the absence of evidence for any form of CJD being transmitted via human insemination (either coitus or artificial insemination), and the extensive scientific background knowledge of prions and prion diseases summarized in the Introduction, the stance taken by public health regulatory authorities in the UK and Europe appear to be perfectly adequate to manage such a level of risk, with that of the US FDA being clearly discordant with expert opinion. To understand how such a discrepant situation could have come about, it is necessary to consider how risk is perceived by individuals, by society, and by government regulators.

Risk can be defined as the likelihood that a substance, action or situation will create harm under a particular set of conditions. It is therefore a combination of two factors: the likelihood that an adverse event will occur, and the consequences of that adverse event. There are two fundamental ways by which individuals understand and assess risks for acceptability, the 'experiential' system, and the rational or 'analytical' approach. The experiential system is intuitive, and largely subconscious, being based upon perceptions and associations that integrate experiences and emotions: this 'risk as a feeling' typically results in a layperson applying a simple binary classification of a particular risk as being either good or bad, allowing them to either accept or reject it. However, the analytical approach attempts to quantify, using statistical probabilities, the likelihood and severity of a given risk, and is the approach that policy makers, health care administrators and insurers rely upon for decision making. In the analytical approach numerical estimates are more useful than qualitative results, but when a risk likelihood is extremely low, reliable, accurate data can be impossible to obtain. Animal models can be used to investigate many health risks, but extrapolation to the human species is by no means a simple process. Such disease models are valuable in terms of research into fundamental physiological processes or molecular mechanisms, but model systems with clear cross-species equivalence are difficult to establish.

It is widely accepted that many individuals have a very poor understanding of risk. Most daily activities carry some level

of risk, but these risks are not considered numerically, they are typically borne voluntarily or perceived to be acceptable. The best way to communicate low probability risks, or new risks, to the general population is by relating them to already known risks encountered in people's daily activities, risks with which individuals have experience. Descriptive verbal scales of risk (e.g. 'low', 'moderate' or 'high') allow individuals to assign different levels of risk on a personal basis. However, societal norms for risk acceptability, which are usually expressed in probabilistic terms, are integral to guidelines established by public health authorities, and public interpretation of such norms in generally understandable terms requires the development of reference scales (Hammitt, 1990). One such scale is that defined by Calman (1996), which anchored particular probabilities to verbal descriptors, dividing risk into six main categories ranked, on a logarithmic scale, from 'high' (<1:100) to 'negligible' (<1:1,000,000). For example, in establishing guidelines for drinking water quality maximum acceptable concentrations are often based on an essentially negligible lifetime risk level of 1:100,000 to 1:1,000,000 – or 'minimal/acceptable' to 'negligible/insignificant' on Calman's verbal scale. Premature death is often used as the criterion for severity to construct 'risk ladders' that provide a range of probabilities of mortality for readily understood events such as lightning strikes (e.g. Wilson and Crouch, 1987).

Individual and collective perceptions of risk that are based on cultural and social circumstances can be amplified by the media, resulting in heightened concern about certain risks, the 'mad cow' epidemic/crisis being a good example of this. In addition, when the outcome from a risk or hazardous event is substantially delayed in time, assessing the level of risk might not be seen as 'real' (i.e. the outcome is dissociated from the risk). Establishing a causative link and estimating the overall duration level of exposure might also be problematic. Cigarette smoking is a good example of a risk that has delayed mortality over a prolonged period of exposure, and is ignored by many people.

Whereas medicine is the art and science of caring for the health of individual people, public health has been defined as the science and art of promoting health, preventing disease, prolonging life and improving the quality of life through the organized efforts of society. Risk assessment by government officials (as well as by industry) has steadily increased as a priority during the last few decades, attempting to develop more effective ways to meet the public's demands for improved health and a safer environment. Population health risk management is therefore a process that involves identifying and analysing options for addressing health risks, developing and implementing strategies for managing those risks, monitoring and evaluating the effectiveness of the strategies, and, most importantly, communicating information both about the risk and about the decision-making process to the public. At the different levels, i.e. individual, population and governmental, what is an 'acceptable' risk depends mainly on a quasi-mathematical concept of the benefits outweighing the risks. In some cases, however, a risk might be 'tolerable', i.e. it will never be accepted, but will be tolerated for a particular activity or for a specified time period on the basis of its benefits. Accepted risk differs from tolerable risk in that people accept it voluntarily, e.g. tobacco smoking. Obviously, these concepts of acceptable and perceived risk are tightly linked, and the classification of new risks requires incorporating new information in to a pre-existing mental framework (i.e. education). Therefore, the best policy guidelines for acceptable risk arise when government regulators, who primarily use the analytical mode of risk analysis, also incorporate aspects of the experiential mode in order to determine levels of acceptable risk that incorporate both real and perceived risks from the perspective of those who are 'at risk'.

When risks are unavoidable but controllable, then consensus can be used to establish an acceptable level of exposure. The acceptance of risk consensus will involve a process of negotiation and perhaps also trade-offs between all stakeholders. In this way, regulatory consensus and legislation to manage many common risks, such as speed limits and acceptable levels of contaminants in drinking water and food, is achieved. The situation is confounded further when the adverse event has not actually occurred (i.e. the risk is only theoretical), it being statistically extremely difficult to prove a zero prevalence.

Public tolerance is lowest for risks that are both unknown and dreaded, such as nuclear reactor accidents and genetically engineered foods. Certainly vCJD or 'mad cow' disease fell into the 'highly dreaded' category, yet in France dread was balanced by a preference for beef (Setbon *et al.*, 2005), and the end of the BSE crisis in the UK soon led to a return to a more-or-less normal pattern of beef consumption in France. This illustrates how the determinant of perceived risk is a major component of risk management and communication, i.e. public education. **Table 4** shows a list of some commonly accepted risks in everyday life, collected from a wide variety of Internet sources, with comparative figures for the UK and USA. The risk of becoming infected by vCJD, even in the UK, appears to be no greater than such risks as dying in an airliner crash, or being killed by lightning; it is far less likely than dying in an automobile accident or being murdered, and extremely small when compared with other health risks such as dying from influenza or as the result of a medical error. From **Table 4**, it might also be concluded that, in spite of vCJD, it is in many ways safer to live in the UK than in the USA.

In terms of a woman who decides to try and have a child, a risk of 1:20,000 of dying in labour is rarely given any consideration, nor are the many specific genetic disorders that could arise in her offspring (and for which genetic screening in spermatozoa and egg donors has not been suggested by any regulatory authority). Therefore, it might be expected that, if a woman is properly informed of the consensus 'trivial' (<1:10,000,000) risk of acquiring vCJD via donor spermatozoa, she would accept that risk in favour of accessing the donor spermatozoa. This attitude will become even stronger as the availability of donor spermatozoa decreases, which is itself a growing problem in many countries (e.g. Paul *et al.*, 2006).

Disease prevention is the fundamental tenet of public health regulation, but to be effective it requires reliable, applicable information about risk, and responsible public health measures must balance risks and benefits: good decisions are ethical and reflect cultural preference (hence they can be different in different countries). Communication and transparency with society and individuals builds trust, although some countries apply a more 'paternalistic' approach than others. In many 'western countries' it is becoming ever more apparent that the public is more discerning about judging risks, and the public is

Table 4. A selection of commonly accepted risks of death. Data were derived from a wide variety of Internet sources, but primarily government agencies (where risks were calculated by the authors the original numbers are shown in parentheses); risks have been rounded to the nearest thousand. Population figures for the UK and USA are 60 and 298 million respectively. NDF = no data found.

Risk of death	*UK*	*USA*	*Calman scale*
An airliner crash	1:3,900,000 (121/year in 477 million flights)		Negligible
By lightning	1:20,000,000	1:3,300,000	Negligible
Under general anaesthetic	1:200,000	NDF	Minimal
During childbirth (obstetrical complications)	1:20,000	NDF	Very low
Murder	1:70,000 (850/year)	1:19,000 (15,500/year)	Very low
As a result of medical error	1:29,000 (2081/year)	1:7000 (44,000/year)	Very low (UK) Low (USA)
Automobile or road accident	1:19,000 (3221/year)	1:7000 (~42,000/year)	Very low (UK) Low (USA)
Influenza	1:17,000 (est. 3000–4000/year)	1:15,000 (est. 20,000/year)	Very low

increasingly prepared to accept a more transparent answer that admits areas of uncertainty than they are to accept a paternalistic 'trust us, we know what's best for you' attitude. Consequently, even though there is a fundamental deep conservatism in public health regulators, 'modern' public decision processes for determining regulatory acceptability or tolerability of risks should include consideration of public opinion and public perceptions of the risk, making it a 'shared responsibility' decision.

Consequently, highly conservative health risk regulation, especially in situations where there is no evidence of a real risk, and/or where the accepted risk presents no (or only a theoretical) secondary risk to others, could undermine the regulator's public credibility. To be credible, a risk must be more than a theoretical extrapolation. While vCJD remains a dreaded disease, attempting to prevent the theoretical risk of vCJD transmission by sperm donors is highly unlikely to have any significant impact upon public health. Although arguments can always be made for the ultra-conservative perspective, there is now a broad base of knowledge that indicates a negligible risk of vCJD transmission by donor spermatozoa, including:

(i) No evidence for the transmission of sCJD, by far the most common form of CJD, between spouses.

(ii) No evidence for the sexual transmission of any TSE in any species, not even BSE by known infected bulls.

(iii) No transmission of fCJD between spouses, and no disease in offspring unless they were mutation carriers themselves. Indeed, one prion disease expert respondent to our survey stated 'Therefore I think that is no risk whatsoever in prion'.

(iv) The peak of vCJD is now well past (see Collins *et al.*, 2004), and the prevalence of vCJD infection in the recruitment population for UK sperm donors (which is, *de facto*, the highest prevalence worldwide) is only of the order of 1:1,000,000, which is generally accepted in public health terms to be negligible. Europe is seen as having only ×0.015 the risk of the UK, although France is estimated at ×0.05 (figures from the FDA: Anderson, 2005). On this basis, the prevalence of vCJD infection in donor spermatozoa from the CECOS organization in France or the large sperm banks in Denmark could be estimated at 1:20,000,000 and 1:67,000,000 respectively.

(v) The PrP molecule in spermatozoa seems to be missing its C-terminus, reducing its ability to convert to the PrPSc isoform.

(vi) Equivalent screening criteria to those employed in the UK for blood donors would eliminate essentially all individuals who were at risk of other forms of CJD (see **Table 5**). This specific suggestion was made by another prion disease expert who responded to the survey and, indeed, these criteria could be applied internationally.

(vii) Men with vCJD could show subfertility prior to showing clinical symptoms of the disease, and hence be less likely to be recruited as sperm donors. Indeed, since this infertility seems to be based on sperm dysfunction (Taguchi *et al.*, 1993; Shaked *et al.*, 1999; Paisley *et al.*, 2004), sperm function testing could be incorporated into donor selection criteria, which would not only further reduce the potential risk, but would improve the quality of donor spermatozoa as well.

(viii) The biomass inseminated during donor sperm treatment is only a fraction of an ejaculate per treatment cycle, compared with numerous entire ejaculates in a normal sexual relationship.

(ix) Fertility clinics could also use only washed spermatozoa, prepared using rigorously controlled density gradient methods, for donor insemination in 'high risk' donors as a further precautionary measure (an opinion expressed by nearly 40% of survey respondents) since that would be equivalent to the leukodepletion processing employed for donated blood, except that a properly performed density gradient sperm washing procedure should eliminate leukocytes entirely. Given the general absence of any transmission of infection by semen or sperm, this processing would make donor inseminates safer than transfusions of leukodepleted blood plasma. Intrauterine

Table 5. Categorization of patient by risk, according to the Joint Working Group of the UK Advisory Committee on Dangerous Pathogens/Spongiform Encephalopathy Advisory Committee (from Azarpazhooh and Leake, 2006; and Department of Health, 2005).

Patient group	*Risk criteria*
Symptomatic patients	Patients who fulfil the diagnostic criteria for definite, probable or possible CJD or vCJD Patients with neurological disease of unknown cause who do not fit the criteria for possible CJD or vCJD, but in whom the diagnosis of CJD is being considered
Asymptomatic patients at risk for familial forms of CJD linked to genetic mutations	Individuals who have or have had two or more blood relatives affected by CJD or another prion disease or a relative known to have a genetic mutation indicative of familial CJD. Individuals who have been shown by specific genetic testing to be at significant risk of CJD or another prion disease
Asymptomatic patients potentially at risk because of iatrogenic exposure	Recipients of hormone derived from human pituitary glands, e.g. growth hormone, gonadotrophin Individuals who have received a graft of dura mater (people who underwent neurosurgical procedures or operations for a tumour or cyst of the spine before August 1992 may have received a graft of dura mater and should be treated as being at risk, unless there is evidence that dura mater was not used) Patients who have been identified as potentially at risk because of exposure to instruments used on, or receipt of blood, plasma derivatives, organs or tissues donated by, a patient who went on to develop CJD or vCJD

vCJD = variant Creutzfeldt–Jakob disease.

insemination (which is how such sperm preparations would be used) of a small fraction of a millilitre of sperm suspension is also a less 'risky' route for transfer of infection that an intravenous transfusion of volumes that are 5–6 orders of magnitude greater.

Finally, it should be remembered that even excluding possibly vCJD-infected men will not alter the prevalence of other forms of CJD in the USA, forms which, together, account for 100 times as many cases of CJD as vCJD. The overwhelming opinion expressed by the survey respondents (all recognized experts in their fields) was that the risk of vCJD transmission by donor spermatozoa, especially in the USA, is trivial. Consequently the FDA's ruling to exclude anyone who has spent more than 3 months in the UK in the'danger years', or more than 5 years in Europe since 1980, is out-of-step with all other public health regulatory authorities, and could be seen as more pandering to a culture of fear rather than achieving any measurable increase in public safety for those individuals who will be affected by it. The FDA's own relative risk estimates for France and Europe (Anderson, 2005) would certainly not appear to support the latter exclusion criterion, where the risk would be expected to be below 1:67,000,000. No-one would argue against reasonable steps being taken to exclude men with a high risk of vCJD from the sperm donor population: but the key here is the definition of 'high' risk. Risk must be based on knowledge rather than fear, and due caution must be founded upon attempts to quantify real risks rather than avoiding theoretical risks. In this regard the categorization of risk from the UK Advisory Committee on Dangerous Pathogens/Spongiform Encephalopathy Advisory Committee (see **Table 5**) seems to be well-suited to this purpose. A properly informed public, and, more importantly, those individuals who are actually affected by the risk, can evaluate the situation regarding vCJD transmission by donor spermatozoa relative to the other risks in everyday life. Seen from this perspective, a strong case could be made for the FDA allowing donor spermatozoa to be evaluated independently of other HCT/Ps.

In conclusion, infertile women seeking treatment using donor spermatozoa should be properly informed of what is clearly a negligible risk of contracting vCJD, allowed to judge the acceptability of that risk in comparison to everyday risks (such as being killed by lightning, which is about the same, or being killed in an automobile accident, which is 500–1000 times greater), and given the choice of accepting spermatozoa from donors who have been screened according to European-style criteria. While this will become moot once a screening test for human PrP^{Sc} in blood becomes available and donors could be screened for all forms of CJD, such a routine test is, in all likelihood, several years away. In the meantime, the use of washed sperm preparations that are free of leukocytes could provide a further measure of perceived security.

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Disclaimer: David Mortimer has undertaken consulting work since 1986, and has been a full-time freelance consultant since October 1999. He has performed work for numerous companies and organizations in the reproductive biomedicine field, but no commercial or financial interest has influenced the statements made in this article. Chris Barratt performs consulting work on an interim basis for a number of companies and individuals. He is a member of the Human Fertilisation and Embryology Authority and a member of the Scientific Advisory Board of Genosis Ltd. No commercial or financial interests have influenced the statements made in this article.

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Variant Creutzfeldt-Jakob Disease: The Challenge of Preventing a Rare but Potentially Devastating Exposure

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Abstract

Although rare, patients with variant Creutzfeldt-Jakob Disease (vCJD) in their differential diagnosis of progressive dementia and movement disorder could continue to present to hospitals for care. However, U.S.-based infection control guidelines do not fully address the possibility of vCJD. After near-misses involving increasing numbers of patients with clinical findings and epidemiologic risks compatible with vCJD, or exposures to chronic wasting disease, we sought to improve recognition and prevention of iatrogenic spread of these prion-related diseases.

Introduction

Transmissible spongiform encephalopathies (TSEs) are progressively fatal neurodegenerative diseases caused by infectious, misshapen prion proteins (PrP^{Sc}). In humans, they include variant and classic (or sporadic) Creutzfeldt-Jakob Disease (vCJD/sCJD), the latter being far more common in the U.S. Animal forms of prion disease include bovine spongiform encephalopathy (BSE) and chronic wasting disease in cervids and some rodents.

TSEs present substantial diagnostic, infection control, and patient notification challenges detailed in the discussion section below. Because prions resist usual standard disinfection and sterilization protocols, iatrogenic exposures can occur via contaminated instruments or equipment. Iatrogenic TSE can also be transmitted by percutaneous exposure to certain types of tissue (mostly neural for sCJD), while vCJD can also be transmitted by exposure to infected lymphoid tissue and possibly blood transfusions. This is why people from regions where BSE was prevalent are still precluded from donating blood.[1-3]

However, U.S.-based cleaning and disinfection and control guidelines and updates do not address the possibility of vCJD.[4, 5] One of the reasons it is not included in general procedures is that it is a rare occurrence and a special consideration. vCJD involves separate procedures. that are not applied across all reprocessing procedures, and different types of tissue that are potentially infectious (not only neural).

Those guidelines do, however, recommend heightened awareness and policy modification as events dictate.[4, 5] Additionally, experts have noted persistent risk of TSEs other than sCJD in unsuspected geographic locations and a need for heightened suspicion and surveillance.[6, 7] Furthermore, surveys of lymphoid tissue where PrP^{sc} is found in cases of vCJD,

suggest the prevalence of asymptomatic disease can be as high as 1 in 2,000 in persons born between 1941 and 1985.[8]

Two Illustrative Incidents

Two incidents typified the challenges we faced in caring for these and similar patients and provided the impetus for this approach. The first incident involved a patient who presented with memory problems, apathy and depression leading to job loss. These symptoms were followed by confusion, impaired gait, occasional jerking movements and eventually dementia. The patient lived in England and France from 1985 to 1993 and ate canned dog food occasionally. The patient also required urgent pelvic and abdominal surgery immediately after admission. MRI showed restricted diffusion in the frontal, parietal, and occipital cortexes. 14-3-3, and Tau protein were negative. Since immune mediated encephalitis was also a leading consideration on the list of possible diagnoses, the patient underwent plasma exchange. 13 days later, the RTQuIC result became available and was positive. Contact tracing revealed that in the meantime, three other patients had undergone pheresis on the same machine. The Red Cross was contacted and recommended decommissioning the machine until further notice. The dilemma of patient notification was debated by the ethics, risk management, infection control team and the hospital leaders (Table 1).

The second incident involved a middle-aged patient who presented with psychiatric symptoms and cognitive decline. The patient, who was an avid hunter and consumed venison and squirrel brains, also developed impaired gait. An MRI showed bilateral pulvinar signs. The EEG did not reveal periodic sharp waves, but showed nonspecific abnormalities including intermittent rhythmic delta activity. The patient required several diagnostic and therapeutic procedures including endoscopies and endotracheal intubation that entailed exposure to

lymphoid tissue. Approximately 2 weeks after admission, 14-3-3, Tau protein, and RTQuIC results became available and were positive, creating a dilemma for reprocessing critical and semi-critical equipment. After several months in the hospital, the patient was discharged to a long-term care facility, and died more than 11 months after symptom onset. vCJD could not be definitively excluded until autopsy results became available several months later and revealed sCJD.

Against this backdrop, we sought to enhance our efforts to detect and prevent iatrogenic spread of TSE, including vCJD. We also aimed to increase awareness among all providers, prevent over-reaction or unnecessarily discarding expensive equipment, while simultaneously not missing an opportunity to prevent avoidable exposures.

Methods

Rochester Regional Health System consists of 8 hospitals and 9 urgent care centers in St Lawrence County, and the 9 counties comprising the Finger Lakes region of NY. The system serves diverse populations including refugee communities and permanent or temporarily relocated citizens or expatriates from many countries. In 2018, requests for CSF analysis for suspected TSE increased 20% compared to the preceding four years.

The two-part intervention consisted of an educational campaign nearly identical to the one successfully used for device-related infections and described previously.[9] The second component entailed and an extensive revision of our existing CJD policy, incorporating guidelines from the UK Department of Health and Social Care Advisory Committee and the World Health Organization regarding vCJD.[10, 11] Briefly, the educational campaign included one-on-one engagements between infection preventionists (IPs), the hospital epidemiologist, the neurologist champion and frontline nurses and providers. Modes of delivery included individual

face-to-face meetings, team huddles, committee meetings, group lectures and grand rounds. Relevant guidelines were posted on hospital websites and intranet.

One goal of the policy revision was early notification of all teams involved in the care including physicians, nursing staff including laboratory and sterile processing. Another goal was a simplified classification scheme of potentially infected tissue. Tissues were divided into three categories depending on their risk of infectivity: high, low, and no detectable infectivity (Table 2). Only single use or disposable instruments are recommended for suspected cases who undergo surgery or invasive procedures involving contact with other than "no-risk" tissues. Non-disposable instruments or durable medical equipment that contact other than no risk tissues should be quarantined for possible decommissioning with appropriate labeling. All instruments are considered potentially contaminated when used on patients with conditions not clearly diagnosed before the procedure, and those instruments are either reprocessed according to prion guidelines or quarantined until the diagnosis is confirmed.

Results

During the 2-year follow up period, there were no similar incidents or other near misses. In response to queries from other IPs and epidemiologists, the policy was shared with hospitals outside of the network. Feedback was uniformly positive.

Discussion

TSEs present diagnostic, infection control and patient notification challenges. Most clinicians are unfamiliar with TSEs due to the rarity of those diseases. vCJD and CJD can be hard to distinguish clinically. No gold standard laboratory test exists for differentiating types of TSEs. The turn-around-time for RT-QiC can be up to 14 days or longer. In some cases, definitive

diagnosis requires brain biopsy or only becomes available after autopsy. Last, the National Prion Center typically only releases autopsy results to public health departments, furthering diagnostic delay.

This approach could be criticized for not being warranted or justifiable due to the fact vCJD is extraordinarily uncommon. Even though sCJD is far more common than vCJD in the U.S., patients with suspected vCJD have been increasingly encountered in our health system. The suspicion was based on epidemiologic exposures and symptoms or signs consistent with vCJD. For example, having lived in the United Kingdom or France for several years or decades, or occupational exposure as taxidermists or abattoirs, or regular consumption of animal brains or cervid meat products. Furthermore, available data indicate that the incidence of CJD in cervids is increasing, and the potential exists for transmission to humans and subsequent human disease, and the species barrier is not static.[7] These occurrences are unlikely to be unique to our healthcare system. To that end, we make our policy to those interested. It is available from the corresponding author upon request.

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176 **Table 1: Diagnostic, Infection Control, and Notification Challenges Associated with**

177 **Transmissible Spongiform Encephalopathies**

Diagnostic Challenge
Most clinicians are unfamiliar with TSEs due to the rarity of those diseases.
vCJD and CJD can be hard to distinguish clinically.
No gold standard laboratory test exists for differentiating types of TSEs.
Turn-around-time for RT-QiC can be up to 14 days or longer.
In some cases, definitive diagnosis requires brain biopsy or only becomes available after autopsy.
The National Prion Center typically only releases autopsy results to public health departments, furthering delay.
Infection Control Challenges
Prions resist usual disinfection and sterilization methods.
US-based disinfection and sterilization guidelines do not address possibility of vCJD contaminated equipment.
Notification Challenges or Considerations
Should potentially exposed patients be informed given the below considerations?
i. Potential negative impact of informing patients about a fatal, untreatable brain disease.
ii. No effective screening test is available for TSE.
iii. No post exposure prophylaxis is available.
iv. Contaminated instruments often become mixed during re-processing making identification and linkage to specific patients nearly impossible.
v. Autoclaving is generally superior to chemical reprocessing for prions.
vi. If equipment was re-processed more than twice, prions would be less likely to survive.

178 **Table 2: Infectivity of Specific Types of Tissue**

	Classic/ Sporadic CJD	**Variant CJD**
High Infectivity Tissue **NO Reprocessing Allowed***	Brain (including dura mater) Spinal cord Posterior eye Pituitary tissue	Brain (including dura mater) Spinal cord, spinal ganglia Posterior eye Pituitary tissue Trigeminal ganglia
Low Infectivity Tissue **NO Reprocessing Allowed***	Cerebrospinal fluid (CSF) Liver Lymph node Kidney Lung (Bronchoscope) Spleen Placenta Olfactory epithelium	Adrenal gland Blood Tonsils (Laryngoscope) Cerebrospinal fluid (CSF) Intestine (Endoscope) Bone marrow Liver Lymph node Kidney Lung (Bronchoscope) Spleen Skeletal muscle Placenta Olfactory epithelium Peripheral Nerves Rectum (Endoscope)
Tissue with no detectable infectivity **OK to Reprocess***	Peripheral nerve Intestine Bone marrow Whole blood, leukocytes, serum, plasma Thyroid gland Adrenal gland Heart Skeletal muscle Adipose tissue Gingiva Prostate and testis Tears, sweat, saliva, and sputum Urine, and feces Semen, vaginal secretions, Milk	Thyroid gland Heart Adipose tissue Gingiva Prostate and testis Tears, sweat, saliva, and sputum Urine, and feces Semen, vaginal secretions, Breast milk

179

*Applies to surgical instruments and certain invasive equipment such as endoscopes and laryngoscope blades

vison)and cynomolgus macaques (*Macaca fascicularis*) are also susceptible to oral inoculation. Common marmosets (*Callithrix jacchus*) and squirrel monkeys (*Saimiri sciureus*) have been infected by intracerebral inoculation; however, their natural susceptibility to BSE is unknown, as this method bypasses normal species barriers to prions. Pigs could be infected by simultaneous intracranial, intravenous and intraperitoneal routes or by intracerebral inoculation alone, but short-term feeding trials did not cause disease. One study reported that sea bream (*Sparus aurata)* seemed to be susceptible to oral inoculation.

L-BSE can infect sheep and cynomolgus macaques by intracerebral inoculation, but there are currently no reports of their susceptibility by ingestion. However, L-BSE has been transmitted to lemurs by the oral route, with the development of neurological signs. Mice have been infected with L-BSE and H-BSE by intracerebral inoculation.

Zoonotic potential

Humans occasionally develop variant Creutzfeldt-Jakob disease after eating prion-containing tissues from an infected animal. To date, all known cases have been caused by the classical BSE prion. Whether H-BSE and L-BSE can cause disease in people is still uncertain. Some studies in laboratory models, but not others, have suggested that humans may be susceptible to L-type BSE.

Geographic Distribution

Cases of classical BSE have been reported in indigenous cattle in some European countries, Canada, Israel and Japan. Some of these countries may have eradicated this disease, as it has not been reported in some time. Classical BSE was documented only in imported cattle in some nations, including the U.S., the Falkland Islands and Oman. Other countries, such as Iceland, Australia and New Zealand, seem to have remained completely free of classical BSE. The presence or absence of this disease cannot be determined in countries without adequate surveillance programs.

Atypical BSE prions have been reported in Europe, the U.S., Canada, Japan and Brazil, as the result of surveillance programs for BSE. They are also likely to exist in other countries.

Transmission

BSE is usually transmitted when an animal or human ingests tissues containing the BSE prion. Young animals may be particularly susceptible: some studies suggest that most cattle become infected with BSE during the first six months of life. Sheep are, likewise, most susceptible to experimental (oral) inoculation during the first few months of life, especially during the first few weeks. In cattle, the prions are thought to replicate initially in the Peyer's patches of the ileum, then are transported via the peripheral nerves to the central nervous system (CNS). Prions have been found in the brain of cattle as soon as 16-24 months after infection.

The highest prion concentrations occur in the CNS (both the brain and spinal cord) and in the ileum. However, very sensitive detection methods have also found this agent in lymphoid tissues associated with the jejunum and colon, various nerve ganglia, peripheral nerves and adrenal glands, and in the optic nerve and retina. The accumulation of BSE in peripheral nerves, nerve ganglia and adrenal gland seems to coincide with or follow prion accumulation in the CNS. However, one group detected BSE in the jejunum as soon as 4 months after oral inoculation. There have been rare reports of BSE prions or infectivity in other locations, such as the tonsils; bone marrow; mesenteric lymph nodes; the esophagus, abomasum and rumen of one animal (possibly in nerve endings); sensory receptors (muscle spindles) of muscles but not myofibrils; one muscle sample (probably associated with the endings of the sciatic nerve); the tongue and nasal mucosa of cattle in the terminal stages of the disease; and even in concentrated saliva. These studies have generally used very sensitive techniques, found very small quantities of prions, and reported that these tissues contain prions only in animals with clinical signs. In cattle, BSE prions do not seem to occur in the spleen or lymphatic tissues other than those associated with the gastrointestinal tract. Most studies have also not detected BSE in muscles. While one group reported evidence of its presence in a few plasma samples from cattle, others have not detected these prions in bovine blood. Epidemiological evidence and transmission studies suggest that BSE is not transmitted in milk, semen or embryos.

There is no evidence that BSE is transmitted horizontally between cattle; however, there is an unexplained increase in the risk of BSE among the offspring of infected animals. In one study, calves seemed to be more likely to develop BSE when the dam was in the later stages of infection (i.e., nearer to the onset of clinical signs). These observations have led to speculation that vertical transmission might be possible in cattle. If this occurs, it seems to be rare, and the route is unknown.

In experimentally infected sheep, BSE prions are more widely disseminated in the body than in cattle. They are readily found in many lymphoid tissues including the spleen, lymph nodes and gut-associated lymphoid tissue (GALT), as well as in the CNS. Blood-borne transmission has been demonstrated in this species. A number of ewes (18%) also transmitted BSE to their lambs in an experimental flock. The lambs were more likely to become infected if the dam was in the later stages of the disease. Prions were not found in the placenta, except in one stillborn lamb, and the live lambs were thought to have been infected shortly after birth. One lamb born to an BSE-negative sheep became infected; however, such horizontal transmission appears to be rare. In this experimental flock, a low transmission rate suggested that sheep would not maintain BSE long-term.

Prions in the environment are not thought to be significant in the epidemiology of BSE. Nevertheless, there have been concerns about their possible longevity in sources such as buried carcasses. In one study, infectivity was reported to persist for at least 265 days in sewage or phosphate buffered saline, under laboratory conditions. BSE prions detected by immunoblotting disappeared sooner than

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Risk assessment of variant Creutzfeldt-Jakob disease in corneal transplantation

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ABSTRACT

Purpose: While corneal transplantation is known to have a potential risk of transmission of variant Creutzfeldt-Jacob Disease (vCJD), the magnitude of this risk has not been quantified.
Observations: A case report is presented of a 73 year-old man with a penetrating keratoplasty graft from corneal tissue that was recalled after transplantation due to risk of vCJD because it was later discovered that the donor had traveled to the United Kingdom (UK). Probabilities of vCJD transmission were extrapolated using Creutzfeldt-Jacob Disease (CJD) mortality (incidence) rate, all-cause death rate, and rate of recovery for intended transplantation.
Conclusions: An overestimate of the risk of transplanting a cornea infected with vCJD in 2018 was 1 in 940,000. The true risk of vCJD transmission would be even lower due to an incomplete infectivity rate. We conclude that the risk of transmission of latent vCJD by corneal transplantation from a donor who traveled to the UK from 1980 to 1996 is exceedingly low.

1. Introduction

Prion disease occurs when the cellular prion protein (PrP^{c}), a cell surface receptor protein, undergoes conformational change to scrapie prion protein (PrP^{sc}). The misfolded PrP^{sc} form aggregates in neural tissue and can propagate causing devastating neurologic damage known as transmission spongiform encephalopathy. The transmission spongiform encephalopathies are most commonly sporadic (sCJD), but 10% of cases are familial (fCJD), and variant disease (vCJD) is rare.[1] vCJD refers to prion disease acquired by consumption of beef from cattle infected with bovine spongiform encephalopathy (BSE), a neurodegenerative disease of cattle that emerged in the late 1980s in the UK. This outbreak led the European Union to ban the export of British beef worldwide from 1996 to 2006, but people residing in the UK may have consumed infected beef before this time when the causal relationship between BSE and vCJD was not understood.[2]

According to the medical standards of the Eye Bank Association of America (EBAA), persons who spent three months or more cumulatively in the United Kingdom from 1980 to 1996 are ineligible to donate eye tissue due to the risk of transmission of variant Creutzfeldt-Jakob Disease (vCJD). This risk exists because vCJD can have a latency period (average of 11–12 years) between the time of infection and the time of presenting symptoms. Last updated in 2014, the Donor Risk Assessment Interview (DRAI) also has addenda to exclude tissue from donors with history of travel to regions with endemic Ebola and Zika virus transmission. The aforementioned exclusion criteria regarding travel to the UK between 1980 and 1996 is the only uniform travel screening criteria on the DRAI still in effect from prior to 2014.[3] Only about 1.2–1.6% of the approximately 32,000 corneas in 2018 intended for transplant but not released were rejected due to travel history, and postoperative recalls due to travel history audits are rare.[4]

2. Case report

A 73 year-old male with blurry vision in his left eye and no significant past medical history had phacoemulsification cataract surgery. The cataract surgery was complicated by posterior capsule rupture with retained lens fragments. He underwent multiple additional surgeries including pars plana vitrectomy and epiretinal membrane peel. The post-operative course was further complicated by cystoid macular

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Average vCJD death rate for a 52 year-old female averaged from May 1995-December 2018 according to the UK's National CJD Research & Surveillance Unit[8]	Time frame for disease development per template from Matheswaran et al.[5]	Number of people aged 51-60 in the U.S.	Estimate of latent cases of vCJD when death rate is used to approximate incidence
0.15 deaths/million/year	x 11 years	x 46 million	= **76 latent cases**

Calculated estimate of latent vCJD cases (from donors aged 51-60)	Approximate all-cause death rate in the U.S. in 2018 (for ages 51-60)	Maximum number of donated corneas per donor	Estimated number of donated corneas infected with vCJD in 2018
76 latent cases	x 663/100,000	x 2 corneas/case	= **1 donor cornea**

Estimated number of donated corneas infected with vCJD in 2018	Approximate number of corneal transplants performed in the U.S. in 2018[4]	Probability that a given cornea (from donor aged 50-60) will be used for transplant (1 in 18.9)[4]	Calculated overestimate of the risk of transplanting a cornea infected with vCJD in 2018
1 donor cornea	÷ 50,000 transplants	x 0.0529	= **1/940,000**

Fig. 1. Overestimated Risk of vCJD Transmission via Corneal Transplantation in 2018. Calculations to find the risk of vCJD transmission by transplant with a cornea from a 52 year-old female donor with history of time spent in the UK.

edema and corneal edema secondary to pseudophakic bullous keratopathy. He subsequently underwent successful penetrating keratoplasty for his left eye. Three months after the surgery, the eye bank recalled the corneal tissue transplanted in this patient due to eligibility concerns for the donor tissue.

Eligibility screening for corneal donation is performed, in part, through the DRAI questionnaire. This donor's family reported on the DRAI that the donor had visited Scotland for an unknown period of time. A quality-control audit performed subsequent to release of tissue and subsequent to use for transplantation revealed that the donor had lived in Scotland for more than two years during the 1990s. The key question in this case was: What is the risk of this patient developing vCJD due to this corneal transplant tissue?

3. Discussion

Martheswaran et al. described a method of approximating the number of corneas from donors with latent CJD recovered for intended transplant in a given year.[5] First they divided the United States (U.S.) population into cohorts by decades of age. Then CJD mortality data (an approximate of incidence) for a given cohort was multiplied by 10 years to approximate the prevalence within that cohort. The prevalence estimate was then multiplied by the all-cause death rate for that age cohort to approximate the number of deceased donors with latent CJD, and that value was doubled (two corneas per donor) to arrive at the number of infected corneas. Finally, that figure was multiplied by a factor specific to each age group representing the probability that a given cornea would be recovered for intended transplant from that age group. Using this methodology, they predicted that there were 3.8 corneas expected to be infected with latent CJD recovered for intended transplant in 2018 for all age groups combined. When these same calculations were aggregated across all age groups and across all years from 1979 to 2018, they estimated that 47 CJD-infected corneas have entered the donor pool. Only five actual documented cases were believed to cause infection in the recipient, suggesting that the infectivity rate may be as low as 10.6%.

We performed a similar calculation (Fig. 1) for the risk of vCJD transmission by transplant with a cornea from a 52 year-old female donor with history of time spent in the UK as in the case presented in this report. According to the National CJD Research & Surveillance Unit in the UK, the average vCJD death rate for a 52 year-old female has been 0.15 deaths/million/year averaged from May 1995-December 2, 018.[6] This incidence would overestimate the risk for U.S. donors because this figure includes a population that resides in the UK (rather than visitation from the U.S.) and present incidence of vCJD is considerably less than it was in the late 1990s and early 2000s. We used this figure to overestimate the number of corneas from donors with latent vCJD that have been recovered for intended transplant in a given year. These calculations suggest that an overestimate of the risk of transplanting a cornea infected with vCJD in 2018 was 1 in 940,000. The true risk of vCJD transmission would be even lower due to the incomplete infectivity rate. Note that these calculations are limited by the use of some population averages (e.g. death rates, number of corneal transplants performed) which can change with time and the use of average disease latency which may have significant variability across individuals.

After literature review and analysis as discussed above, the patient was counseled that his probability of contracting vCJD from corneal transplantation was exceedingly low. The decision was made not to explant the corneal graft from this patient. Besides the risk of infection transmission, other variables that we considered included the age of the patient (at age 73, the patient was not concerned about a low risk of a disease with a 10+ year latency), ocular comorbidities that might complicate additional ocular surgery (he had multiple prior ocular surgeries), and the timing of recall following the transplant surgery (his corneal transplant was healing well at 3 months post-surgery when the recall occurred). Because of this exceedingly low probability of transmission of vCJD and because there are no effective treatments for CJD aside from supportive care, the burdens of additional testing for the

patient far outweigh any benefits that early diagnosis would provide. These burdens include time and discomfort of testing to the patient, financial costs to the healthcare system, and psychological stresses associated with the testing. However, providers for this patient should have CJD within their differential diagnosis if the patient develops signs/symptoms of CJD in the future, such as altered mental status or hyperreflexia. While definitive diagnosis can only be made with brain biopsy, supplemental testing that may aid in the diagnosis of suspected CJD includes electroencephalogram, lumbar puncture, and magnetic resonance imaging of the brain. As of the publication of this report, the patient has not experienced any neurologic sequelae to raise suspicion for acquired vCJD. Our analysis is limited to a theoretical calculation of risk based on empirical population-based data. Unfortunately (or thankfully), there are no confirmed cases of vCJD transmission via corneal transplantation for evaluation of outcomes analysis.

PrP^{sc} has not been directly detected by biochemical or immunohistochemical means in corneal tissue and penetrating keratoplasty performed in guinea pigs and non-human primates with CJD have not been shown to result in transmission of the disease.[7] However, there have been two confirmed cases of CJD transmission resulting in death in humans through corneal transplantation with diagnosis of CJD confirmed by autopsy in both the patient and the donor.[5] There have been eight other cases worldwide in which CJD transmission through corneal transplant has been suspected, with an average incubation period of 8–12 months. There have been no reported cases of CJD transmission through corneal transplantation since 2006 and none of the ten cases mentioned prior were suspected to involve vCJD.

Rates of vCJD in the UK and around the world have been declining since about 2000. There have been approximately 180 confirmed cases of vCJD in the UK and an additional 50 cases in the rest of the world. The last known death from vCJD was in the UK in 2016, although a researcher in France died from vCJD in 2019 after accidently inoculating herself with contaminated tissue.[8,9] Only four cases of vCJD have ever been identified in the U.S. and only two of those individuals had prior travel to the UK. The other two cases were believed to originate in the Middle East, or possibly Russia.[10] There have been more recent confirmed outbreaks of BSE in Wales (2013) and in Scotland (2018). While BSE outbreaks are monitored closely due to their potential to evolve into outbreaks of vCJD, there have been no records of associated human infection in these cases.

4. Conclusions

The risk of transmission of latent vCJD by corneal transplantation from a donor who traveled to the UK from 1980 to 1996 is exceedingly low. While this tissue recall placed a burden on the patient and physicians to understand the risk involved, the data summarized here may guide others encountering or studying this problem.

Patient consent

Written informed consent for publication was obtained from the patient described in this case report.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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vCJD Cases Worldwide

	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
Canada								1	0	0	0	0	0	0	0	0	1
France		1	0	0	0	1	1	3	0	2	6	6	3	0	2	0	0
Ireland					1	0	0	0	0	0	2	1					
Italy									1	0	0	0	0	0	0	0	1
Japan										1							
Netherlands											1	1	0	1			
Portugal													1	0	1		
Saudi Arabia																1	
Spain											1	0	1	2	1		
Taiwan																1	
UK	3	10	10	18	15	28	20	17	18	9	5	5	5	2	3	3	5
USA										1		2					

vCJD Cases Worldwide

2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2019	2020	2021	2022	2023	2024	Alive	Total
0	0	1																2
2	0	0	0	1	1	0	0	0	0	1	1							28
																		4
0	0	1	0	0	0	0	1											3
																		1
																		3
1																		2
	1																	1
1																		5
	1																	1
3	3	5	0	1	0	0	1											178
					1													4

Recommendations to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease and Variant Creutzfeldt-Jakob Disease by Blood and Blood Components

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Guidance for Industry

This guidance is for immediate implementation.

FDA is issuing this guidance for immediate implementation in accordance with 21 CFR 10.115(g)(4)(i). Submit one set of either electronic or written comments on this guidance at any time. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. You should identify all comments with docket number FDA-2016-D-1342.

Additional copies of this guidance are available from the Office of Communication, Outreach and Development (OCOD), 10903 New Hampshire Ave., Bldg. 71, Rm. 3128, Silver Spring, MD 20993-0002, or by calling 1-800-835-4709 or 240-402-8010, or email ocod@fda.hhs.gov, or from the Internet at https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances.

For questions on the content of this guidance, contact OCOD at the phone numbers or email address listed above.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
April 2020
Updated August 2020

Contains Nonbinding Recommendations

Recommendations to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease and Variant Creutzfeldt-Jakob Disease by Blood and Blood Components

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Guidance for Industry

Note: Changes have been made to update the guidance of the same title dated April 2020, including:

- Revised the terminology used to describe familial prion diseases.
- Revised the Background in section II. and Discussion in section III. to update information on the National Hormone and Pituitary Program in the United States.
- Clarified the recommendation to permanently defer individuals who have received cadaveric pituitary human growth hormone in section IV. and the Appendix.

Contains Nonbinding Recommendations

Table of Contents

Contains Nonbinding Recommendations

Recommendations to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease and Variant Creutzfeldt-Jakob Disease by Blood and Blood Components

Guidance for Industry

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

We, FDA, are issuing this guidance document to provide you, blood establishments that collect blood and blood components, with revised recommendations intended to reduce the possible risk of transmission of Creutzfeldt-Jakob disease (CJD) and variant Creutzfeldt-Jakob disease (vCJD) by blood and blood components. The recommendations in this guidance apply to the collection of Whole Blood and blood components intended for transfusion or for use in further manufacturing, including Source Plasma. We are revising or removing our prior recommendations to screen blood donors for: 1) geographic risk of possible exposure to bovine spongiform encephalopathy, including time spent on United States (U.S.) military bases in Europe; 2) receipt of a blood transfusion in certain vCJD risk countries; 3) risk factors for iatrogenic CJD (i.e., a history of taking cadaveric pituitary human growth hormone (hGH)); 4) having blood relatives with CJD; and 5) a history of injecting bovine insulin. These changes are summarized in the Appendix of this guidance.

This guidance updates the guidance of the same title dated April 2020. The April 2020 guidance finalized the draft guidance of the same title, dated January 2020, and superseded the document entitled "Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease and Variant Creutzfeldt-Jakob Disease by Blood and Blood Products, Guidance for Industry" dated May 2010 and updated January 2016 (2016 guidance).

In general, FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA's guidances means that something is suggested or recommended, but not required.

APPENDIX

Table 1: Comparison of Recommendations in 2016 Guidance and 2020 Guidance

2016 Guidance		**2020 Guidance**	
Section	**Recommendations**	**Section**	**Recommendations**
IV.A.1.	Defer permanently donors who have been diagnosed with vCJD or any other form of CJD.	IV.A.2.a.	Defer permanently a donor who has been diagnosed with vCJD, CJD or any other transmissible spongiform encephalopathy **or who has a blood relative diagnosed with familial prion disease (e.g., fCJD, GSS, or FFI).** Note: We do not recommend questioning donors for vCJD, CJD, or any other TSE or for blood relatives with familial prion disease (e.g., fCJD, GSS, or FFI) because of the inability to identify asymptomatic individuals harboring TSEs, the rarity of the conditions, and the available evidence from lookback studies that have not identified a case among recipients of blood from infected donors. However, individuals that volunteer such information should be permanently deferred.
IV.A.2.	Defer permanently donors if they have received: • A dura mater transplant.	IV.A.2.b.	Revised to clarify the source of tissue that is a cause for deferral: • Defer permanently a donor who has received a **human cadaveric (allogeneic)** dura mater transplant.

2016 Guidance		2020 Guidance	
Section	**Recommendations**	**Section**	**Recommendations**
	• an injection of human cadaveric pituitary-derived growth hormone (hGH).	**N/A**	**Defer permanently a donor who received cadaveric pituitary hGH.** Note: The prevalence of individuals who might have been exposed to cadaveric pituitary hGH is very low among blood donors, and the transmission risk of CJD by blood components remains theoretical. Consequently, we recommend that establishments may remove hGH from their medication deferral lists used in donor screening educational materials. However, individuals that volunteer such information should be permanently deferred.
	Defer indefinitely donors with one or more blood relatives diagnosed with CJD.	**N/A**	**Revised (see IV.A.2.a.).**
IV.A.3.	Defer indefinitely donors who have spent 3 months or more in U.K. from 1980-1996.	IV.A.2.c.	No change
IV.A.4.	Defer indefinitely donors who have spent 5 years or more cumulatively in France from 1980 – present.	IV.A.2.d.	Defer indefinitely a donor who has spent 5 or more years cumulatively in France **or Ireland** from the beginning of 1980 **to the end of 2001.** Note that this assessment does not include time spent in the U.K., which is assessed separately in IV.A.1.b. This assessment also does not apply to French overseas departments (e.g. Martinique, French Guiana, Guadeloupe, Mayotte, and Réunion).

2016 Guidance		2020 Guidance	
Section	**Recommendations**	**Section**	**Recommendations**
IV.A.5.	Defer indefinitely former or current U.S. military personnel, civilian military personnel, and their dependents, for residence on: • U.S. military bases in Northern Europe (Germany, U.K., Belgium, and the Netherlands) for 6 months or more from 1980 through 1990, or • U.S. military bases elsewhere in Europe (Greece, Turkey, Spain, Portugal, and Italy) for 6 months or more from 1980 through 1996.	**N/A**	**Deleted**
IV.A.6.	Defer indefinitely donors with a history of transfusion in the U.K. or France from 1980 – present.	IV.A.2. e.	Defer indefinitely a donor with a history of transfusion in U.K. (i.e., England, Northern Ireland, Scotland, the Isle of Man, the Channel Islands, Gibraltar, or the Falkland Islands), France, **or Ireland** from the beginning of 1980 to present.
IV.A.7.	Defer indefinitely donors who have injected bovine insulin since 1980, unless you can confirm that the product was not manufactured after 1980 from U.K. cattle.	**N/A**	**Deleted**
IV.A.8.	Defer indefinitely donors who have spent 5 years or more in Europe from 1980 - present.	**N/A**	**Deleted**

Prevention

Creutzfeldt-Jakob disease

Although Creutzfeldt-Jakob disease (CJD) is very rare, the condition can be difficult to prevent.

This is because most cases occur spontaneously for an unknown reason (sporadic CJD) and some are caused by an inherited genetic fault (familial CJD).

Sterilisation methods used to help prevent bacteria and viruses spreading also aren't completely effective against the infectious protein (prion) that causes CJD.

But tightened guidelines on the reuse of surgical equipment mean that cases of CJD spread through medical treatment (iatrogenic CJD) are now very rare.

There are also measures in place to prevent variant CJD spreading through the food chain and the supply of blood used for blood transfusions (Link: www.nhs.uk/conditions/blood-transfusion/).

Protecting the food chain

Since the link between bovine spongiform encephalopathy (BSE, or "mad cow" disease) and variant CJD was confirmed, strict controls have been in place to stop BSE entering the human food chain.

These controls include:

- a ban on feeding meat-and-bone mix to farm animals
- the removal and destruction of all parts of an animal's carcass that could be infected with BSE
- a ban on mechanically recovered meat (meat residue left on the carcass that's pressure-blasted off the bones)
- testing on all cattle more than 30 months old (experience has shown that infection in cattle under 30 months of age is rare, and even cattle that are infected haven't yet developed dangerous levels of infection)

Blood transfusions

In the UK, there have been 5 cases where variant CJD has been transmitted by blood transfusion.

In each case, the person received a blood transfusion from a donor who later developed variant CJD.

3 of the 5 recipients went on to develop variant CJD, while the other 2 recipients died before developing variant CJD but were found to be infected following a post-mortem examination.

It's not certain whether the blood transfusion was the cause of the infection, as those involved could have contracted variant CJD through dietary sources.

Nevertheless, steps were taken to minimise the risk of the blood supply becoming contaminated.

These steps include:

- not allowing people potentially at risk from CJD to donate blood, tissue or organs (including eggs and sperm for fertility treatments)
- not accepting donations from people who have received a blood transfusion in the UK since 1980
- removing white blood cells, which may carry the greatest risk of transmitting CJD, from all blood used for transfusions

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