RISK ASSESSMENT

The risk of variant Creutzfeldt-Jakob disease transmission via blood and plasma-derived medicinal products manufactured from donations obtained in the United Kingdom

3 August 2021

Summary

Risk assessed

In February 2021, the United Kingdom (UK) lifted its ban on the use of UK-sourced plasma to produce immunoglobulin products. The UK assessed the variant Creutzfeldt-Jakob disease (vCJD) risk for immunoglobulin products manufactured from UK plasma as very low and acceptable in the context of overall vCJD risk in the general population, taking into consideration a risk-benefit analysis. The presence of transmissible proteinaceous infectious particles – called prions (PrP^{Sc}) –have been linked to vCJD among asymptomatic blood and plasma donors. Therefore, the European Centre for Disease Prevention and Control (ECDC) assessed the risk to the European Union and European Economic Area (EU/EEA) of the presence and the possible transmission of PrP^{Sc} by blood and plasma-derived medicinal products (PDMPs) manufactured from donations obtained in the UK.

The prevalence of vCJD-related PrP^{Sc} in the UK blood donor population is likely to broadly mirror the prevalence of PrP^{Sc} in the UK population as a whole. Evidence from retrospective cohort studies using peripheral lymphoid tissue suggests that the underlying prevalence of people that may be in the vCJD carrier state is in the order of 0.05%, although there remains much uncertainty around this estimate. The contrast between the estimated prevalence of vCJD-related PrP^{Sc} and the reported number of clinical vCJD cases seen to date strongly suggests that those in whom PrP^{Sc} is detected through an antemortem lymphoid tissue survey may never develop any symptoms of prion disease. Further uncertainty exists regarding the extent to which individuals who may be carrying PrP^{Sc} as latent or subclinical vCJD infection are capable of transmitting the infection to others, including through donation of blood and blood products.

The vCJD infection risk from the donations and final products is decreased by the safety measures implemented to reduce the risk of donation by exposed donors and during whole blood processing or plasma fractionation. However, the absence of a reliable diagnostic blood test makes it difficult to assess the residual risk for transmission of vCJD infection through blood components and PDMPs obtained from UK-sourced blood and plasma donations with any degree of confidence.

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Options for response

In order to determine whether the use of immunoglobulins and other PDMPs produced from UK plasma would pose an increased threat, EU/EEA countries may consider assessing their endogenous risks, evaluating product-specific data packages (including the prion-reduction capacities of applied fractionation procedures), and balancing the assessed threat with the supply need for PDMPs and source plasma in their country. Until such data are available, EU/EEA countries may consider, as a precautionary measure, preventing the use of immunoglobulins and other PDMPs derived from UK plasma, as well as the fractionation of UK plasma in EU/EEA facilities.

Event background

Since 1996, when the causal association between vCJD and bovine spongiform encephalopathy (BSE) was established [1,2], the public health risk of contracting vCJD through blood or blood products from silently infected donors has remained a major concern. To reduce the risk of transmitting vCJD through blood and PDMPs, several countries – including the UK – implemented a series of precautionary measures. Among these, the UK government implemented a ban on the use of domestic human plasma for the preparation of all PDMPs in 1999 [3,4]. After this measure was taken, the plasma needed for the production of PDMPs by fractionation was imported to the UK [5] and UK plasma was not used for fractionation in any EU/EEA country.

The growing need for treatment with immunoglobulin products [6], the supply constraints caused by the need to import plasma for fractionation and the global decline in blood collections – worsened by the COVID-19 pandemic – have raised concerns about the future availability of immunoglobulins in the UK. Therefore, in 2020, the UK Medicines and Healthcare products Regulatory Agency (MHRA) reviewed the evidence on the safety of UK blood plasma for manufacturing immunoglobulins. The evidence was scrutinised in consultation with stakeholders and the risk was assessed by mathematical modelling. After reviewing the evidence in October 2020, the UK Commission on Human Medicines (CHM) concluded that the risk of vCJD cases arising from the use of UK plasma for the manufacture of immunoglobulin medicinal products would be negligible and advised that UK-sourced plasma is 'acceptably safe for the manufacture of immunoglobulin medicinal products' provided that relevant risk-mitigation measures (e.g. the use of leukoreduction, deferral of high-risk donors, traceability between donor and recipient, and requirements for manufacturers to obtain licencing approval for each immunoglobulin product) were in place [7]. On 25 February 2021, the UK government lifted its ban on the use of UK plasma for the manufacturing of immunoglobin products [8].

Lifting the ban could raise safety concerns among EU/EEA plasma supply stakeholders, health authorities and industry. Therefore, the European Commission has asked ECDC to provide robust, evidence-based advice on the risks that the use of plasma and blood from UK donors poses to the safety of manufactured human immunoglobulin products, taking into account any risk-reduction measures that could be applied during donation, processing or manufacturing. As the source plasma is relevant to both agencies' mandates, ECDC has been working closely with the European Medicines Agency (EMA) on developing this advice.

Disease background

Variant Creutzfeldt-Jakob disease (vCJD) is a relatively new and rare neurodegenerative zoonotic disease, classified as a prion disease or transmissible spongiform encephalopathy (TSE). Human forms of TSEs include sporadic, familial and acquired (iatrogenic and variant) Creutzfeldt-Jakob disease (CJD); Kuru; familial Gerstmann–Sträussler–Scheinker syndrome (GSS); and sporadic and familial fatal insomnia (FFI). vCJD was first identified in March 1996 in the UK, when 10 cases of a new disease with neurological symptoms were reported [9]. Soon thereafter, it was associated with BSE, referred to as 'mad cow' disease. There is strong evidence that primary cases of vCJD resulted from eating meat products contaminated with prions causing BSE [9,10]. The clinical, epidemiological, neuropathological and experimental data all point to vCJD being caused by the same strain of prions as BSE, which are different from those seen in sporadic CJD (sCJD) [10].

BSE was first recognised in the UK in 1986 [12], after which the syndrome spread worldwide. The annual number of BSE cows in the UK peaked in 1992, but has declined significantly, with only two classical BSE cows reported since 2014: one in 2015 and one in 2018 [13,14]. In addition to the UK population's most likely widespread dietary exposure to BSE-contaminated, animal-derived material [14-16], population exposure also occurred in more than 20 other countries that imported British beef and cattle or contaminated ruminant-derived, rendered meat-and-bone meal, particularly in France [18]. One study showed a positive correlation between quantities of live bovines imported from the UK and numbers of vCJD human cases during BSE outbreaks in other countries between 1980 and 1990 [19]. As a result of strict control measures in the UK and worldwide, the incidence of BSE is now negligible [14]. Occasional cases of BSE are reported infrequently, but due to control measures, none of these animals entered the food chain.

Pathogen characteristics

The pathophysiological mechanism of TSE is not fully understood, but it is believed that PrP^{Sc} converts normal cellular prion protein (PrP^{C}) into a new PrP^{Sc} by refolding a portion of its α-helical and coil structure into β-sheets [20]. This structural transition is accompanied by profound changes in the physico-chemical properties of PrP^{Sc} that make the protein highly insoluble and resistant to proteinase digestion. The subsequent multimerisation, aggregation and accumulation of PrP^{Sc} in neurological tissues induce the classic spongiform change (vacuolation of grey matter), microglial activation and neuronal loss, leading to progressive neurodegeneration and astrogliosis over time. This extensive neurodegeneration ultimately leads to the death of the host [21].

During the structural changes of PrP^{C}, the amino acid sequence of the proteins remains unchanged, which is one of the reasons why it is difficult to identify PrP^{Sc} with conventional molecular biology techniques. Different prion diseases are caused by different forms of PrP^{Sc}, known as prion strains [22]. The diversity of PrP^{Sc} strains depends on multiple factors, including the glycoform ratio and the polymorphisms at amino acid codon 129 in the prion protein (*PRNP*) gene [23,24]. The vCJD strain has been classified as type 2B, consisting of predominantly diglycosylated proteins [2]. Prions are stable and resistant to commonly used disinfectants (e.g. formaldehyde, glutaraldehyde, ethanol, iodine). Immersion in undiluted bleach (60 000 ppm or mg/L of available chlorine) for one hour is only partially effective. While the normal cellular PrP^{C} shows intermediate stability and is prone to degradation, PrP^{Sc} is resistant to ultraviolet light and ionising radiation, ultrasonication, nucleases, boiling and heat. For disinfection, high concentrations of NaOH (1-2 N) and prolonged autoclaving (one to five hours) at high temperatures (120-135°C) are recommended. Treatment with 2% sodium hypochlorite (20 000 ppm) for 60 minutes at room temperature can be considered as a fully effective treatment for prion infectivity inactivation, as shown by in vitro results and infectivity studies in transgenic mice [25]. The World Health Organization (WHO) and the United States (US) Centers for Disease Control and Prevention (CDC) have developed specific CJD infection control guidelines that can be a valuable guide for cleaning and reprocessing methods used in healthcare facilities [26,27].

Disease characteristics

The incubation period for vCJD is difficult to establish given the unknown timing of causative dietary exposure in affected individuals and is likely to be dependent on a number of pathogen and host factors that remain poorly described. The estimated mean incubation period (defined as the time from infection to death) for primary transmission infection approximately reflects the interval from the peak BSE exposure in 1989 and 1990 to the peak vCJD deaths in 2000 [27-29]. A French study on vCJD cases estimated the incubation period to be around 13 years (95% confidence interval (CI): 9.7-17.9 years) [31]. In general, it is estimated that the mean incubation period is likely to be at least 5 to 10 years after dietary exposure and may extend over a whole lifetime as an asymptomatic, latent infection [32].

There is individual variation in susceptibility to infection, with possible factors including age and the *PRNP* genotype. A polymorphism at codon 129 in the *PRNP* gene is associated with the clinical features of human prion diseases [32-35]. The majority of vCJD cases tested were homozygous for methionine (129MM) genotype [37], suggesting that individuals with such genotype are susceptible to vCJD. In populations of European descent, ca 40% of individuals have the 129MM genotype, ca 50% of individuals are heterozygous for methionine and valine genotype (129MV) and ca 10% are homozygous for the valine (129VV) genotype. Compared to sCJD, which tends to affect middle-aged to elderly individuals, vCJD predominantly affects younger individuals [29]. Among all confirmed vCJD cases (n = 159) in the EU/EEA, as reported to The European Surveillance System (TESSy) from 1995 to 2021, the age at disease onset ranged from 12 to 74 years, with a median age of 28 years old [38].

Patients with vCJD have prominent psychiatric (most often depression, anxiety and withdrawal) or sensory symptoms, followed by delayed onset of neurological abnormalities, including ataxia, within weeks or months, then dementia and myoclonus late in the illness. Among these 159 confirmed vCJD cases, the duration of illness has ranged from 6 to 105 months, with a median of 13 months; however, in 89.2% of cases, the illness lasted for up to 24 months [38]. No vaccine or specific disease treatment is available.

Diagnosis

The definitive diagnosis of vCJD depends on neuropathological findings in material obtained by a cerebral biopsy or brain examination at autopsy that show the presence of florid plaques in large numbers and marked accumulation of protease-resistant prion proteins with an increased glycoform ratio. Clinical diagnosis is based on the typical clinical features, electrophysiological investigation, magnetic resonance imaging (MRI) and biological assays on animal models (Table 1). There is a continuing need for validated, non-invasive, antemortem tests to help in the identification of patients with a higher risk of developing vCJD. Such tests could potentially be applied to screening of blood and plasma donors or quality control in the production of biological therapeutics such as PDMPs.

Table 1. Main characteristics of sporadic CJD and variant CJD

Characteristics	Sporadic CJD	Variant CJD
Median age at death	68 years	28 years
Median duration of illness	4 to 5 months	13 to 14 months
Clinical signs and symptoms	Dementia, early neurological signs	Prominent psychiatric/behavioural symptoms, painful dysesthesia, delayed neurological signs
Periodic sharp waves on electroencephalogram	Often present	Often absent
Pulvinar sign on MRI	Not reported	Present in >75% of cases
Presence of florid plaques on neuropathology	Rare or absent	Present in large numbers
Immunochemical analysis of brain tissue	Variable accumulation	Marked accumulation of protease-resistant prion protein
Presence of agent in lymphoid tissue	Not readily detected	Readily detected
Increased glycoform ratio on immunoblot analysis of protease-resistant prion protein	Not reported	Marked accumulation of protease-resistant prion protein

Source: Adapted from [39].

At the time of this assessment, no approved diagnostic or screening test for the detection of prion protein in blood, body fluids or tissues is available. The laboratory tests under investigation [40,41] include the Direct Detection Assay (DDA coupled with the Standard Steel Binding Assay (SSBA)) [41,42], real-time quaking-induced conversion (RT-QuIC) [44] and protein misfolding cyclic amplification assay (PMCA) [44-46]. The PMCA assay detects small quantities of PrP^{Sc} particles using iterative cycles of sonication and incubation in the presence of excess amounts of PrP^{C} substrate. In preclinical plasma samples, the PMCA assay detected PrP^{Sc} with 100% sensitivity and 99% analytical specificity immediately after experimental infection in animals and one to three years before clinical signs in humans [39,45].

The impact of vCJD testing on blood and plasma donation is not known. Preliminary surveys suggest that testing for vCJD could have a major impact on the availability of healthy donors, who may be reluctant to be tested for a lethal disease that lacks effective interventions [47,48]. Regardless, screening blood donors for the presence of the vCJD agent would be an important measure to improve public health and the safety of blood transfusion and PDMPs.

Disease transmission

The majority of vCJD cases were primary transmissions associated with dietary exposure to BSE agents in beef. Secondary transmission through exposure to blood transfusion or PDMPs contaminated with PrP^{Sc} has also been documented. In addition, at least one case of vCJD outside the UK (in France) has been associated with potential laboratory occupational exposure [50]. The iatrogenic transmission of CJD from patients with sporadic or familial forms of CJD has been reported, particularly in recipients of human pituitary-derived growth hormone [51], human dura mater grafts [51,52] and cornea transplants [53-55], or through contaminated instruments (e.g. during neurosurgery) or brain depth electrodes (e.g. during electroencephalography) [57,58]. However, no evidence of vCJD iatrogenic transmission by any form of surgery, dentistry, endoscopy, childbirth or transplantation of organs, cells or tissues (excluding blood and blood components) has been identified. However, the iatrogenic transmission of vCJD through prion-contaminated medical devices and instruments seems plausible.

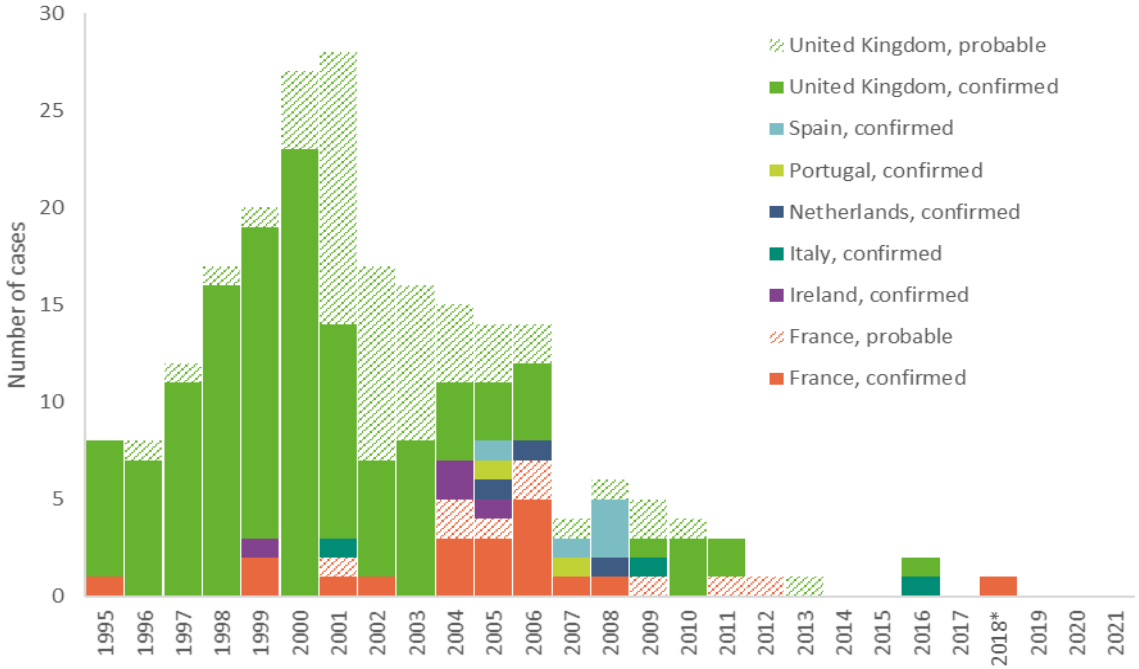
Disease epidemiology

Surveillance activities for CJD were strengthened significantly in the late 1990s following the identification of vCJD and response to concerns about a possible epidemic of vCJD among human populations exposed to BSE. In the EU/EEA, the European Creutzfeldt-Jakob Disease Surveillance Network (EuroCJD) was established in 1993 to establish a surveillance system and perform research. Following the establishment of ECDC, and after evaluation of the network's activities, the coordination of surveillance and research in EU/EEA countries [59] was outsourced to the University of Edinburgh from 2008 to 2021 (contract ended in April 2021). The surveillance of vCJD became mandatory in the EU/EEA in 2000 (including the UK, at the time) [60] and all vCJD cases, including historical ones, have been reported in TESSy since 2012. The vCJD cases are classified according to the EU/EEA case definition for CJD [61].

Since 1995 and as at 30 July 2021, 223 vCJD cases (159 confirmed and 64 probable cases) have been reported to TESSy from seven EU/EEA countries, with the highest number of cases (178 cases) reported from the UK (Figure 1). Within the

EU/EEA, six countries have reported 45 cases in total, with France reporting the majority of these (28 cases) (Table 2) [62]. Among the 223 confirmed and probable cases, the age at disease onset ranged from 12 to 74 years old, with a median age of 37 years old. Of these cases, 120 (53.8%) were male (Table 3). There were no differences by sex across age groups. The duration of illness was <2 years in 87.0% of cases, with a median of 14 months.

Figure 1. Number of confirmed and probable vCJD cases reported to TESSy, by year and country, in the EU/EEA and the UK, 1995 to 30 July 2021



**This case had disease onset in 2018 and died in 2019. The case has been associated with potential occupational exposure in a laboratory [50].*

Table 2. Number of confirmed and probable vCJD cases reported to TESSy in the EU/EEA and the UK, 1995 to 30 July 2021

Country	Confirmed	Probable	Total
France	19	9	**28**
Ireland	4	0	**4**
Italy	3	0	**3**
Netherlands	3	0	**3**
Portugal	2	0	**2**
Spain	5	0	**5**
United Kingdom	123	55	**178**
Total	**159**	**64**	**223**

Table 3. Number of confirmed and probable vCJD cases reported to TESSy, by age group and sex, in the EU/EEA and the UK, 1995 to 30 July 2021

Age group (years)	Male	Female	Total
10–19	20	19	**39**
20–29	50	39	**89**
30–39	31	22	**53**
40–49	9	11	**20**
50–59	6	11	**17**
≥60	4	1	**5**
Total	**120**	**103**	**223**

In the UK, the National CJD Research & Surveillance Unit (NCJDRSU) is responsible for monitoring the characteristics of all forms of CJD, identifying trends in incidence rates, studying risk factors for disease development and contributing to improving the quality of care for those with CJD. NCJDRSU notifies UK Blood Services of all probable or definite vCJD cases. Upon receiving such a notification, blood services records are then checked to see if any donations were made by the vCJD case and, if so, all involved blood components are traced through hospital records. Information on named recipients and donors is provided back to the NCJRDS to establish if any matches exist between recipients or donors and the vCJD case. Recipients of blood components donated by vCJD cases are also flagged at the UK Office of National Statistics (ONS) to establish the date and cause of death [37][63].

According to the '28th Annual report 2019 on Creutzfeldt-Jakob disease in the UK' [37], out of the 178 vCJD cases reported in the UK, 75 (42%) were female and 103 (58%) were male. The median age at disease onset was 26.5 years old and the median age at death was 28 years old. The youngest case was aged 12 years at disease onset, while the oldest case was aged 74 years at disease onset. Between 1990 and 2019, the median duration of illness from the onset of first symptoms to death was 14 months (range: 6-114 months). The last known UK case of vCJD was reported in 2016. From those 178 vCJD cases in the UK, 161 were genetically tested. Only 1 case of confirmed vCJD was methionine/valine (MV) heterozygous at codon 129 of the *PRNP* gene, while the remaining 160 definite or probable vCJD cases were methionine homozygous (MM). To date, no case of vCJD has been identified in the UK among individuals born after 1989 [37].

Disease prevention

Primary vCJD transmission via dietary exposure in humans in the EU/EEA is prevented by a series of control measures implemented in a food safety system designed to prevent the entry of BSE-contaminated meat and tissues into the food chain. These strategies for preventing the introduction of BSE and managing occurrences of BSE [64,65] resulted in a decrease in the number of classical BSE cows in the EU/EEA, with the latest case reported in 2018 in a cow born after the revised feed ban in the UK [14,66].

Measures to prevent secondary transmission of vCJD by transfusion, transplantation and the therapeutic use of PDMPs aim to permanently defer donors at risk of exposure to BSE or vCJD and to reduce potential infectivity in donated blood or plasma and PDMPs. If the transfusion risk is assessed as high, countries can temporarily discontinue the use of some blood components and PDMPs produced from domestic blood or plasma, import source plasma or PDMPs, or switch to the use of recombinant products when available.

Donor selection

The vCJD selection criteria for blood, tissue and cell donors are defined in EU directives [67,68] within the general exclusion criteria for all types of CJD. According to these criteria, individuals are permanently deferred from donation if they are at risk for CJD transmission. Individuals considered to be at risk for CJD include:

- people diagnosed with CJD or vCJD, or that have a family history of non-iatrogenic CJD;
- people with a history of rapid progressive dementia or a degenerative neurological disease, including those of unknown origin;
- recipients of hormones derived from the human pituitary gland (such as growth hormones), as well as cornea sclera and dura mater grafts, and people who have undergone undocumented neurosurgery (where dura mater may have been used).

The risk of endogenous vCJD varies between countries depending on the size of the endogenous BSE epizootic [69], whether cattle and bovine materials are imported from risk areas and enter the national food chain [19], and whether there is a difference in the genetic susceptibility to vCJD (M/V polymorphism at codon 129) between populations [70]. UK citizens born before 1996 (or, more conservatively, before 2001) should be considered at higher risk of transmitting vCJD through blood donation than EU citizens. Therefore, precautionary measures may be considered and are suggested by the European Directorate for the Quality of Medicines (EDQM) guidelines [71]. Many countries outside the UK defer donors who have lived in the UK for a minimum defined period between 1980 and 1996 [72]; EMA recommends a minimum of one year (cumulative) of UK residence for the permanent deferral of potential donors of plasma for fractionation [73]. In some instances, deferrals also apply to donors who have lived in or visited other countries with reported cases, such as France [73]. Deferral of donors who have received a blood transfusion in the UK since 1980 has also been instituted. In its revised recommendations, intended to reduce the possible risk of transmission of CJD and vCJD by blood and blood components, the US Federal Drug Administration recommends a permanent deferral of blood donors with a history of blood transfusion in the UK, France and Ireland from 1980 to the present [74].

Donor screening

There is no validated laboratory screening test available for the detection of PrP^{Sc} in blood, bodily fluids or tissues at the time of this assessment. Although some candidate tests have shown acceptable sensitivity and specificity, tests are very difficult to validate and adapt for high-throughput systems. There are also ethical issues, including the need to notify donors of positive results when the risk of developing clinical disease remains uncertain [75]. Therefore, donors may be unwilling to donate under such a screening policy.

Leukoreduction

Leukoreduction as a risk-reduction measure for vCJD was informed by data from sheep transfusion experiments and bioassays performed with transgenic mice and macaques. The highest levels of infectivity were associated with the buffy coats that are rich with leukocytes [75-77]. The results of a sheep model study of the distribution of BSE infectivity in sheep's blood indicate that all blood components are capable of transmitting BSE infection, but with varying efficiency. The highest transmission rates were found in recipients of whole blood (50%) and buffy coats (42%), while the lowest transmission rate (19%) was in recipients of plasma, platelets and red blood cells [79]. The probability of BSE transmission in this sheep study correlated with the donor *PRNP* codon 141 genotype. The highest transmissibility was by blood from leucine homozygous sheep at codon 141 [79]. BSE transmission rates were 14%, 5% and 9% in recipients of leukoreduced red blood cells, platelets and plasma, respectively, compared to 30%, 32% and 19% in recipients of the equivalent non-leukoreduced components [79]. All subsets of leukocytes may transmit the infection to various not fully determined extents [79,80]. Data obtained in a scrapie sheep model indicate that a few thousand leukocytes are sufficient to transmit the disease [80]. These and other studies showed that the leukoreduction of blood components might substantially reduce, but does not eliminate, the risk of transfusion-transmitted vCJD in the animal model. The experimental transfusion of vCJD-infected blood in mice and macaques showed the transmission of atypical prion disease in non-human primates that was not prevented by the leukoreduction of infected blood [82]. Nevertheless, no human cases of vCJD transmission through leukoreduced blood components have been reported.

Leukoreduction involves the removal of leukocytes by filtration from blood components. The practice of preventing some adverse effects of transfusion using leukoreduced red blood cells and platelets began in the 1970s when highly effective blood filters became available [83]. Since 1998, several countries have implemented universal leukoreduction of red blood cells, plasma and platelets to mitigate public health risks from secondary transmission of vCJD that arose following vCJD cases associated with transfusion of non-leukoreduced red blood cells, as described in Table 4. It has been shown that leukoreduction is not detrimental to the quality of the final blood components in terms of the generation of microvesicles or the release of prion proteins [84]. Data from 2016 show that 11 EU/EEA Member States have implemented mandatory or voluntary universal leukoreduction [85]. However, the Scientific Committee on Medicinal Products and Medical Devices (SCMPMD) did not find compelling evidence for introducing leukoreduction as a precaution against vCJD transmission through PDMPs [83,86]. Leukoreduction offers other benefits besides the potential reduction of vCJD transmission, including a reduced risk of transmission of cell-based viruses such as cytomegalovirus and human T-cell lymphotropic virus, and reduced rates of alloimmunisation, immunomodulatory effects and transfusion-mediated graft versus host disease [86-88]. Therefore, universal leukoreduction of blood components might remain in practice, irrespective of the limited ability to reduce the risk of prion transmission.

Prion removal during plasma fractionation

In addition to strict donor selection, prion removal steps in the process of plasma fractionation serve as a measure to reduce the possible risk of prion transmission through PDMPs. Manufacturing steps – in particular, ethanol fractionation, depth filtration, nanofiltration and chromatography – can remove prions by partitioning and size-exclusion/trapping mechanisms [94]. In addition, a vCJD-specific affinity ligand filter for removal of prions from

blood components and plasma has been developed and showed promising initial results in reducing the risk of transfusion-transmitted vCJD. However, independent studies failed to demonstrate a clear effect of the prion affinity filters [94,95].

The Committee for Medicinal Products for Human Use (CHMP) guidelines from 2004 require manufacturers to critically evaluate their manufacturing processes for the capacity to remove the CJD agent [97]. Data provided by manufacturers indicate that manufacturing processes for PDMPs would reduce vCJD infection if it was present in human plasma [97-99]. The capacity of manufacturing steps to eliminate or reduce infectious material that could be present in the plasma pool used as the starting material for the preparation of PDMPs has been established in spiking studies that use animal material. However, data show that prion removal capacity may vary according to the spiking preparation (dispersion and TSE agent strains), particularly for steps based on retention mechanisms [101]. These data raise questions about the relevance of some experimental approaches used to determine prion removal capacity in plasma production steps. Therefore, EMA recommends using various forms of spike preparations in order to obtain insight into their influence on prion reduction at the specific investigated step, as compared to what has been published in the literature [73].

Risk-reduction measures in the UK

The UK Department of Health and UK Blood Services have implemented several vCJD risk-reduction measures for blood, blood products and blood components. These include:

- Since December 1997, all blood components, blood products or tissues obtained from any individual who later developed clinical vCJD were withdrawn and recalled to prevent their use.
- Since October 1999, white blood cells (which are thought to contain most of the infectious agent that causes vCJD) have been reduced in all blood components used for transfusion, by leukoreduction.
- As of 2004, all individuals who have received a transfusion of blood components (anywhere in the world) since January 1980 have been excluded from donating blood.
- Since 1999, plasma for the manufacture of fractionated plasma products, such as clotting factors and immunoglobulins, has been obtained from sources outside the UK.
- Since 1998, synthetic (recombinant) clotting factor for the treatment of haemophilia has been provided to those under 16 years of age and, since 2005, this measure has been extended to all patients for whom it is clinically appropriate.
- Since 2004, plasma for transfusion to those born on or after 1 January 1996 has been obtained from outside the UK.
- Since 2005, platelets have been collected from a single donor by apheresis for transfusion to children under 16; in 2013, this was extended to include all individuals born on or after 1 January 1996.
- From 2009 to 2013, a minimum of 80% of platelets were collected from single donors by apheresis, for transfusion to all recipients. This measure was reassessed and rescinded in 2013.

Based on an evaluation of the risk of vCJD transmission undertaken in 2019, the UK's Advisory Committee on the Safety of Blood, Tissues and Organs (SaBTO) recommended that the provision of imported plasma and apheresis platelets for individuals born on or after 1 January 1996 or with thrombotic thrombocytopenic purpura should be withdrawn, but that other risk-reduction measures for vCJD should remain in place [102].

In 2020, the UK lifted its ban on the use of UK plasma to manufacture plasma-derived immunoglobulin products that was introduced in 1999 to mitigate the risk of vCJD transmission. Following external consultation and mathematical modelling, the MHRA concluded that the use of plasma from UK donors for the manufacture of human immunoglobulin products would expose the target patient population in the UK to no or minimal additional risk of vCJD.

ECDC risk assessment for the EU/EEA

This assessment is based on information available to ECDC at the time of publication and, unless otherwise stated, the assessment of risk refers to the risk that existed at the time of writing.

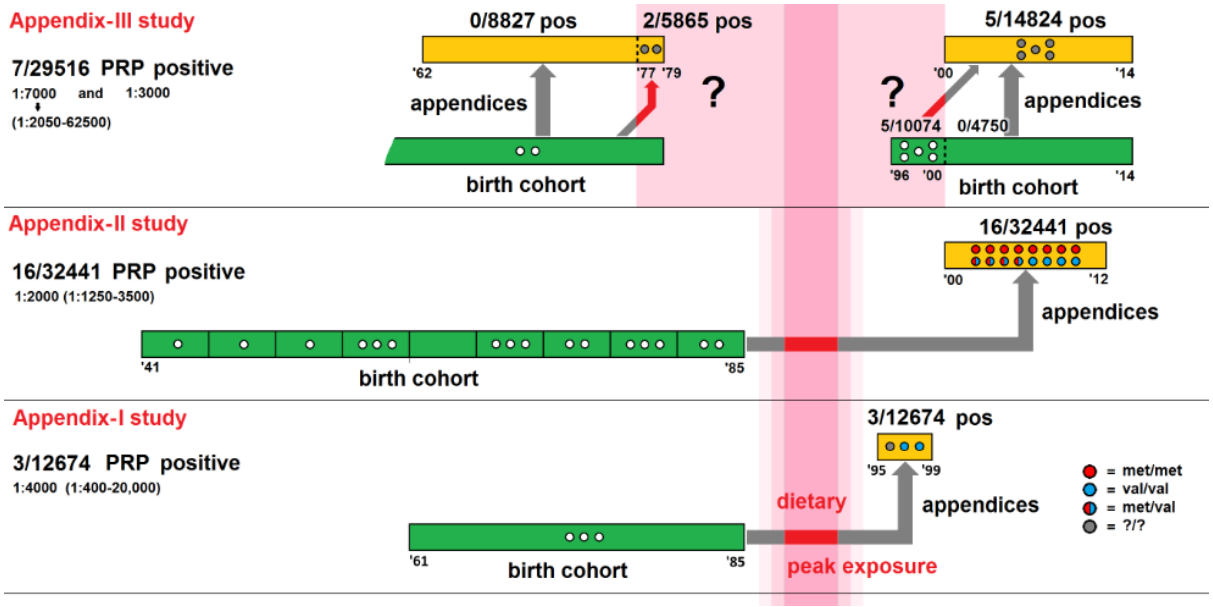
Risk assessment questions

What is the current rate of carriage of vCJD-related PrP^{Sc} in the lymphoreticular systems of healthy individuals in the UK?

Data collected by the UK NCJDRSU show that vCJD mortality in the UK peaked in 2000 and has been decreasing ever since. Among all 178 vCJD cases identified in the UK, the last case was reported in 2016 [37]. The UK has the highest vCJD case rate and risk contribution (86.3%) in the world, as estimated from country-specific vCJD case rates [103].

Estimates based on knowledge in the early stages of the vCJD crisis predicted a relatively high level of infection among the UK population. However, the occurrence of clinical cases over time has shown that most of the predictions are generally no longer tenable [104]. The current projections of the likely number of cases in the UK are based on the evidence of clinical cases and retrospective studies of appendix samples (Figure 2). The two immunochemistry screening studies of appendectomy samples (Appendix I and II retrospective cohort studies) estimated the prevalence of PrP^{Sc} in the UK population exposed to BSE. The first study found PrP^{Sc} in 3 out of 12 674 examined samples from surgical patients between 1995 and 1999. These data gave a prevalence of 237 per million population (95% CI: 49-692 per million population) or 1 per 4 000 population in people born between 1961 and 1985, which comprises most vCJD cases. The second study screened appendix samples obtained between 2000 and 2012. Sixteen PrP^{Sc}-positive samples were detected among 32 441 examined samples from surgical patients born between 1941 and 1985. The estimated prevalence was 493 per million population (95% CI: 269-1596 per million population), or 1 in 2 000 [105]. In contrast to these two appendix studies, a cohort study analysing 63 007 tonsillar specimens obtained between 2004 and 2008 in the UK did not find PrP^{Sc} in any specimen, including the 32 661 samples obtained from individuals born before 1996 [106]. The extent to which tonsillar tissue accumulates PrP^{Sc} is unknown, although tonsillar tissue positivity has a 100% diagnostic accuracy in clinical cases of vCJD [107]. Therefore, the absence of infection in such a large sample size may offer some reassurance about the extent to which the UK population carries the vCJD-related PrP^{Sc}. It should be noted, however, that many participants in the tonsillar study were young, so they may not have acquired extensive PrP^{Sc} accumulation [107].

Figure 2. Schematic presentation of the cohorts and findings of the Appendix I-III studies



Source: [108]

The Appendix III study was performed on 29 516 appendix samples that were surgically removed between 1962 and 1979 from patients born between 1891 and 1965, as well as those born after 1996 who had been operated on between 2000 and 2014. Seven appendix samples were positive for PrP^{Sc}, of which two were removed during the pre-BSE-exposure period (1977 to 1979) and five were removed during the post-BSE-exposure period (2000 to 2014). The presence of PrP^{Sc} accumulation in two patients who were not considered to have had exposure to BSE, as their appendices were removed before 1980, suggests that there is either a low background prevalence of PrP^{Sc} in human lymphoid tissue that might not represent subclinical vCJD and would be unlikely to progress to vCJD, or that the BSE epidemic took place over a longer period than previously thought [109].

All clinical vCJD cases that occurred before 2014 were MM at codon 129 of the *PRNP* gene (129MM), suggesting that the population at risk was restricted to 129MM individuals, estimated to be 42% of the UK population. The confirmation of the first UK patient heterozygous for the *PRNP* codon 129 (129MV) with disease onset in 2014 introduced the possibility that a higher proportion (89%, comprised of 42% 129MM and 47% 129MV) of the UK population exposed to BSE are potential carriers. In addition, the second of the four transfusion recipients listed in Table 4 and the patient with haemophilia referred to later – both of whom had evidence of PrP^{Sc} – were heterozygous at this locus. Also, two of the three patients positive for PrP^{Sc} accumulation in the retrospective study of tonsil and appendix samples were homozygous for valine [110]. These observations suggest that other genotypes may also be susceptible to infection with vCJD agents, possibly with a lower frequency of clinical disease and/or longer incubation periods (as has been seen in some cases of Kuru and peripherally transmitted iatrogenic CJD). The contrast between the estimated prevalence of PrP^{Sc} and the reported number of clinical vCJD cases seen to date strongly suggests that those in whom PrP^{Sc} is detected through an antemortem lymphoid tissue survey may never develop any symptoms of prion disease [109]. The absence of symptoms does not preclude the presence of PrP^{Sc} in the blood. Experimental animal models indicated the early presence of PrP^{Sc} in blood and lymphoid tissues after peripheral or intracerebral prion inoculation. Most transgenic mice inoculated with human PrP^{Sc} become positive quite early in the lymphoid tissue, but do not develop the disease [111].

Although the policies implemented to control the BSE epidemic have contributed to the decline of vCJD cases, the prevalence of individuals carrying infectious prions in their peripheral organs and fluids is uncertain. However, the limited extent of historical dietary exposure to BSE and the low number of clinical vCJD cases in countries other than the UK strongly support the view that the prevalence of vCJD carriers in the EU/EEA is much lower than what is estimated in the UK population.

According to the Appendix I and II studies, the prevalence of vCJD-related PrP^{Sc} in the UK population is estimated to be between 1 per 2 000 population and 1 per 4 000 population. As described previously, due to several uncertainties, it is not possible to accurately estimate the extent of the current carriage of the vCJD agent in the lymphoreticular systems of healthy individuals in the UK.

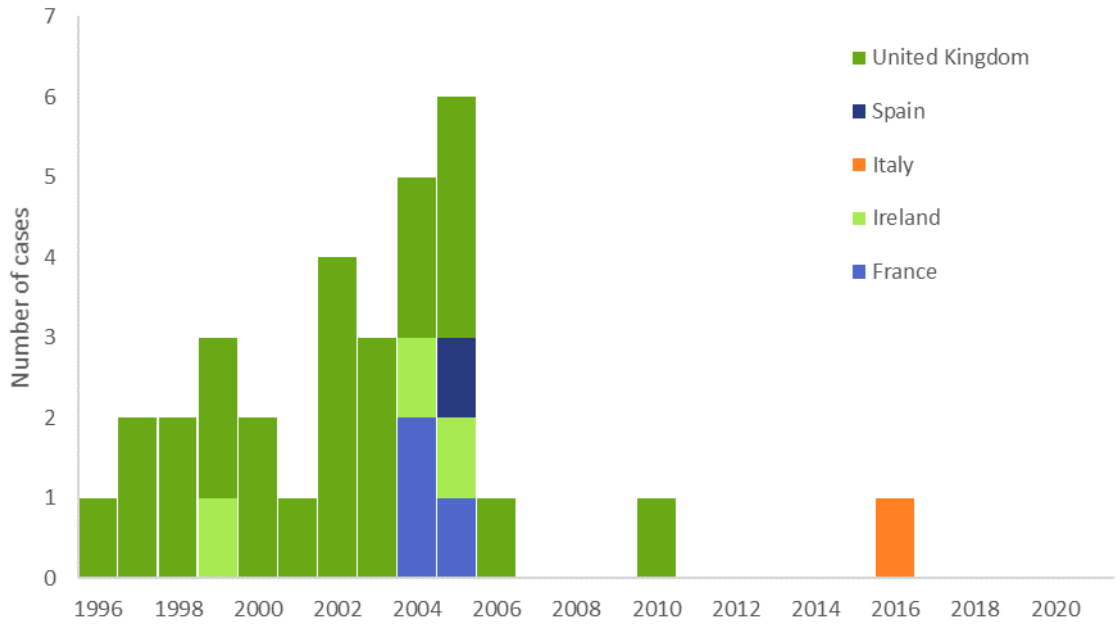
What is the likelihood of the vCJD-related PrP^{Sc} being present in donor blood and entering the blood and plasma supply in the UK?

At the outset of the vCJD outbreak in the UK, concerns about the potential risk of transfusion-transmitted vCJD were based on reports of other forms of CJD being transmitted by transplantation, and the possibility of prions entering the bloodstream during spread from the gut to the central nervous system after ingestion of contaminated food or through recirculation of lymphocytes from secondary lymphoid tissue [111,112]. Studies in rodent models demonstrated low levels of prion infectivity in blood, the majority of which appeared to be associated with leukocytes [113-116]. From 2000 onward, studies in sheep showed that prion infection could be efficiently transmitted to other sheep following transfusion of whole blood taken from infected sheep during the symptom-free phase [78,117-119].

Infectivity of human blood cells and plasma from both vCJD and sCJD patients has been demonstrated by inoculation of transgenic mice overexpressing either bovine or human prion protein genes [121]. Douet et al. reported the presence of PrP^{Sc} infectivity in the plasma of one person with vCJD disease and in the plasma of two out of four people whose tests were positive for sCJD [121]. Prions were also detected by PMCA throughout the preclinical phase in the blood of all macaques infected via intracerebral injection with brain homogenates from a confirmed vCJD patient [40] and in patients with clinical vCJD [121]. In another study, PMCA revealed the carriage of prions 1.3 and 2.6 years before clinical onset in two blood donors who later developed vCJD [46].

In Europe, vCJD cases with a history of blood donation have been identified in France, Ireland, Italy, Spain and the UK (Figure 3). Among 223 confirmed and probable vCJD cases reported to TESSy since 1995, 32 have donated blood, most of whom (n = 24; 75.0%) are from the UK. Blood donors' ages have ranged from 17 to 59 years old, with a median of 31 years old. Two UK cases have been both a donor and a blood transfusion recipient. The first case had disease onset in 1999 and the second case in 2005. The most recent blood donor in the UK with vCJD died in 2010 (disease onset at 59 years old, in 2007).

Figure 3. Number of blood donors (n = 32) among confirmed and probable vCJD cases (n = 223) reported to TESSy, by year of statistics, in the EU/EEA and the UK, 1996 to 30 July 2021



The Transfusion Medicine Epidemiological Review (TMER) was established in 1996 to investigate the link between vCJD and blood transfusion in the UK [123]. Of 24 vCJD cases in the UK population with blood donation history, blood components from 18 vCJD cases have been distributed to hospitals. In total, 67 blood components from these donations were transfused to 67 recipients [63]. Among these recipients, there were three presumed transfusion-transmitted vCJD cases between 1996 and 1999 [89,91,92]. In addition, one probable case of vCJD was detected in a transfusion recipient who showed post-mortem evidence of PrPSc deposition in the spleen, though the cause of death was unrelated to vCJD [91]. All four cases received transfusion of non-leukoreduced red blood cells (Table 4). Although dietary exposure could not be completely excluded in three of these vCJD cases, transfusion of infectious blood was established as the source of infection beyond a reasonable doubt. No cases of vCJD transmission via fresh frozen plasma or platelets have been reported. A further presumed transmission of prions was described in February 2009. A haemophilia patient had received factor VIII concentrates prepared from plasma pools known to include donations from a vCJD-infected donor. The patient died of other causes, but evidence of prion accumulation in the spleen was found post-mortem [124]. These cases showed that vCJD could be transmitted by blood transfusion and prompted a re-evaluation of vCJD infection risks associated with all blood products. In France, three patients that developed signs of vCJD in 2004 and 2005 were blood donors. A total of 42 recipients of blood components donated by these donors were identified, with 17 recipients still alive in 2006 [125]. The most recent vCJD case with blood donation history was reported in Italy in 2016 (Figure 3).

Table 4. Cases of transfusion-transmitted vCJD in the UK

Case	Transmission link	Year of report	Blood component (year of transfusion)	Blood donor		Transfusion recipient		
				vCJD onset after donation	Year of donor death	Age at time of transfusion	vCJD onset after transfusion	*PRNP* gene codon 129
1 [90]	Presumed	2003	Red blood cells, non-leukoreduced (1996)	40 mo	2000	62 y	6.5 y	MM
2 [91]	Probable	2004	Red blood cells, non-leukoreduced (1999)	18 mo	2001	Unknown	5 y*	MV
3 [92]	Presumed	2006	Red blood cells, non-leukoreduced (1998)	21 mo	Unknown	23 y	7.8 y	MM
4 [93]	Presumed	2007	Red blood cells, non-leukoreduced (1999)	17 mo	Unknown	Unknown	8.5 y	MM

M: methionine; mo: month; V: valine; y: year.
** Case never developed clinical vCJD and died from unrelated causes. Post-mortem evidence of PrP^{Sc} deposition in the spleen was found five years after transfusion.*

In the UK, the blood and plasma donor population represents a group of adults aged 17 years and older (though more detailed health checks are performed on donors over the age of 65 years) who donated >1.7 million units of whole blood in 2019 [126]. In 2020, 2 074 517 blood components (red blood cells, platelets, and clinical plasma and cryoprecipitate) have been issued to hospitals in the UK [127]. The active blood donor population represents only a fraction of the UK population, which comprises >65 million people.

Cumulative evidence from the retrospective cohort studies (Appendix I and Appendix II studies) suggests that up to 1 in every 2 000 people living in the UK may have PrP^{Sc} in their peripheral organs. However, the prevalence of prion accumulation in the pre-1980 and post-1996 cohorts described by the Appendix III study raises questions around the specificity of appendiceal prion accumulation as a marker of vCJD infection. No studies have been performed in other countries that have less or no exposure to BSE. In addition, these prevalence estimates have large confidence intervals and thus may not reflect the true incidence of PrP^{Sc} carriers. The ability of individuals in a vCJD carrier state to transmit prions via blood presumably depends on several factors, including the time from infection, infectious dose, route of exposure and host genetic factors. Therefore, it remains unknown to what extent a vCJD carrier can infect others, but the potential risk of secondary transmission cannot be excluded.

The prevalence of carriage of the vCJD-associated PrP^{Sc} in the UK blood donor population is likely to broadly mirror the prevalence of carriage of this PrP^{Sc} in the UK population as a whole. Thus, potentially infected individuals with subclinical or latent infection may donate blood or plasma while asymptomatic. It is uncertain whether and when

such donations may contain vCJD infectivity, as well as whether and when they may have the potential to transmit the disease by transfusion or other iatrogenic routes.

Nevertheless, a number of precautionary measures have been implemented to attempt to manage the risk of vCJD presence in donor blood entering the blood and plasma supply in the UK. Universal leukoreduction of blood has been implemented and PDMPs have been produced from plasma donated outside the UK since 1999. In addition, potential donors at risk of secondary exposure to vCJD through transfusion after 1980 have been deferred from donation in the UK since 2004. The effectiveness of the implemented measures is difficult to assess, although there is evidence of transfusion-transmitted vCJD cases between 1996 and 1999, prior to the introduction of these measures. Around 50 million blood components have been transfused in the UK since the introduction of universal leukoreduction, with no evidence of any transfusion-transmitted vCJD. The absence of transfusion-related vCJD cases following the implementation of measures may be significant, albeit against a background of declining vCJD clinical case numbers in the general UK population, in which underlying levels of infection or carriage of PrP^{Sc} remains unknown. Animal models showed that leukoreduction of blood components and manufacturing processes in plasma fractionation have the capacity to reduce potential vCJD infectivity of blood and plasma products. However, in the absence of a robust diagnostic test that could be applied to screen for the presence of vCJD agents in donated blood and plasma, there is no way to verify that donated blood is not infectious. Hence, precautionary risk-reduction measures will remain a key component in the prevention of secondary vCJD associated with blood and plasma products.

What is the risk that blood components and medicinal products manufactured from UK plasma can transmit vCJD?

In 2019, the UK Department of Health and Social Care (DHSC) published the latest risk assessment for the transmission of vCJD by blood components [128]. To estimate the number of transfusion-transmitted clinical cases and infections of vCJD, an analytical probabilistic model combining population data for both blood donors and recipients with probability distributions describing various aspects of the disease was used. To account for the scientific uncertainties about vCJD, the model combined a scenario-based approach with Monte Carlo simulations.

The model makes several precautionary assumptions, including that:

- there is a subclinical carrier state present in the UK population, which facilitates infection transmission via blood (i.e. the more precautionary interpretation of the Appendix III study is correct);
- the number of blood components issued is the same as the number used and each of these units is transfused to a separate recipient, maximising the number of recipients exposed to any risk;
- all recipients are completely susceptible to infection and these infections are equally likely to develop into clinical cases regardless of genotype;
- the risk in MV heterozygotes and VV homozygotes is the same, even though VV is believed to be lower risk;
- when calibrating, there is a high level of under-ascertainment of clinical cases, while also not limiting the number of cases in individuals older than 75 years old.

Input parameters include the prevalence of infected individuals in the donor population in the UK, as determined in the Appendix I–III studies; the onset of vCJD infectivity in infected donors; the infectivity of blood components from infectious donors; the level of susceptibility and duration of incubation following secondary transmission; and the donor and recipient populations in the UK.

Using the mathematical modelling-based estimates, the plausible number of vCJD cases estimated from the 90 million blood components administered in the UK over the next 50 years would be between zero and approximately 62 cases (for plasma: 0-31 vCJD cases from 4 million transfusions over the next 50 years; for platelets: 0-84 vCJD cases from 19 million transfusions over the next 60 years). The independent experts from the Advisory Committee on Dangerous Pathogens' Transmissible Spongiform Encephalopathy (ACDP TSE) subgroup reviewed the model and supported that its outputs provide both a highly precautionary estimate of the number of future cases and infections and also the only practicable way of assessing the benefit of further interventions until more empirical evidence becomes available.

The SaBTO working group used predictions from the risk assessment to establish if the risk-reduction measures of fresh frozen plasma importation and provision of apheresis platelets are still appropriate. The modelling showed that the additional risk of death from transfusion-acquired vCJD would, on average, be 1 in every 5.2 million units of UK-sourced plasma transfused and 3.1 million units of pooled rather than apheresis platelets transfused.

The blood transfusion risk mathematical model was modified and applied to estimate the risk of vCJD infection and clinical cases for 17 normal immunoglobulins and six hyperimmune immunoglobulins. Long-term immunoglobulin treatments with highly precautionary dosing and patient exposure assumptions have been considered. For normal immunoglobulin products prepared from non-leukoreduced plasma, the estimated risk of infection was from 0.0007 to 324 per million single maximum doses and the risk of clinical cases ranged from 0.00005 to 24 per million single maximum doses. For hyperimmune immunoglobulins, the risk of infection ranged from 0.0000045 to 0.0009 and the risk of clinical infection ranged from 0.0000003 to 0.00007 per million single maximum doses. The impact of

leukoreduction of plasma decreased the risk of infection by a factor of ca 5 and the risk of a clinical case by a factor of ca 3.5, which would be negligible for low-risk products but more significant for the highest risk products.

The UK estimated that the risk of vCJD transmission through blood and blood components, including plasma for fractionation, donated by UK donors is very low. Therefore, UK-sourced plasma has been assessed as 'acceptably safe for the manufacture of immunoglobulin medicinal products' given the risk of vCJD in the general population and provided that relevant risk-mitigation measures are adhered to and manufacturers are newly licensed for the production of each immunoglobulin product [7].

The current endogenous risk of vCJD in the EU/EEA is unknown, but it appears to be very small and probably lower than in the UK, according to previous estimates by France [129], Ireland [130] and the Netherlands [131]. When making decisions regarding the use of PDMPs manufactured from UK-sourced plasma, EU/EEA Member States will need to assess their own endogenous and PDMP-associated vCJD risks and then consider the likely relative differences between these risks and those of using PDMPs produced from UK-sourced plasma.

Modern plasma fractionation includes production steps for the sequential and complete isolation of crude fractions of coagulation factors, albumins and immunoglobulins, which are then purified into individual therapeutic products. As the UK has only lifted the ban on the use of domestic plasma for the production of immunoglobulins, several questions and concerns related to the allocation of unprocessed crude plasma fractions and the disinfection and safety of production lines may arise. As decontamination of prion-contaminated stainless steel surfaces is difficult, UK-sourced plasma fractionation could contaminate processing facilities' equipment and subsequently cross-contaminate PDMPs produced using plasma donated outside the UK, which could then be distributed in the EU/EEA.

Conclusion

The UK assessed the vCJD risk for immunoglobulin preparations produced from UK plasma as very low and acceptable in the context of overall vCJD risk in the general population, taking into consideration a risk-benefit analysis. The prevalence of vCJD-related PrP^{Sc} in the UK blood donor population is likely to broadly mirror the prevalence of vCJD-related PrP^{Sc} in the UK population as a whole. Evidence from retrospective cohort studies using peripheral lymphoid tissue suggests that the underlying prevalence of people that may be carrying vCJD-related PrP^{Sc} may be in the order of 0.05%, although there remains much uncertainty around this estimate. The contrast between the estimated prevalence of vCJD-related PrP^{Sc} and the reported number of clinical vCJD cases seen to date strongly suggests that those in whom PrP^{Sc} is detected through an antemortem lymphoid tissue survey may never develop any symptoms of prion disease. Further uncertainty exists regarding the extent to which individuals who may be carrying PrP^{Sc} as latent or subclinical vCJD infection are capable of transmitting the infection to others, including through donation of blood and blood products. The vCJD infection risk from donations and final products is decreased by the safety measures implemented to reduce the risk of donation by exposed donors and during whole blood processing or plasma fractionation. However, the absence of a reliable diagnostic blood test makes it difficult to assess the level of risk for vCJD infection transmission through blood components and PDMPs from UK-sourced blood and plasma donations with any degree of confidence.

Options for response

In order to determine whether the potential use of immunoglobulins and other PDMPs produced from UK plasma would pose an increased threat, EU/EEA countries may consider assessing their endogenous risks, evaluating product-specific data packages (including prion-reduction capacities of applied fractionation procedures) and balancing the assessed threat with the supply need for PDMPs and source plasma in their country. Until such data are available, EU/EEA countries may consider, as a precautionary measure, preventing the use of immunoglobulins and other PDMPs manufactured from UK plasma, as well as fractionation of UK plasma in EU/EEA facilities.

A validated, highly sensitive and specific test for the detection of PrP^{Sc} in blood and bodily fluids would be of high value for validation of PrP^{Sc} inactivation or removal methods. The potential use of such a test for blood and plasma donation screening requires further research and development. Given uncertainties regarding the extent of vCJD infectivity in the populations, continuous surveillance and vigilance should remain a priority in EU/EEA countries and worldwide.

Limitations

This assessment is undertaken based on facts known to ECDC at the time of publication. There is considerable uncertainty about the extent of vCJD in the UK and EU/EEA populations, the transmissibility of vCJD through blood and plasma, and the residual risk of vCJD in blood components and plasma-derived medicines. In light of these limitations, more evidence of endogenous risks in EU/EEA countries is needed to adequately assess the levels and acceptability of these risks.

Source and date of request

Request from the European Commission, 14 April 2021.

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European Directorate for the Quality of Medicines & HealthCare (EDQM) expert: Richard Forde

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All experts have submitted declarations of interest, and a review of these declarations did not reveal any conflict of interest.

Disclaimer

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This report was written with the coordination and assistance of an Internal Response Team at the European Centre for Disease Prevention and Control. All data published in this risk assessment are correct to the best of our knowledge at the time of publication. Maps and figures published do not represent a statement on the part of ECDC or its partners on the legal or border status of the countries and territories shown.

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