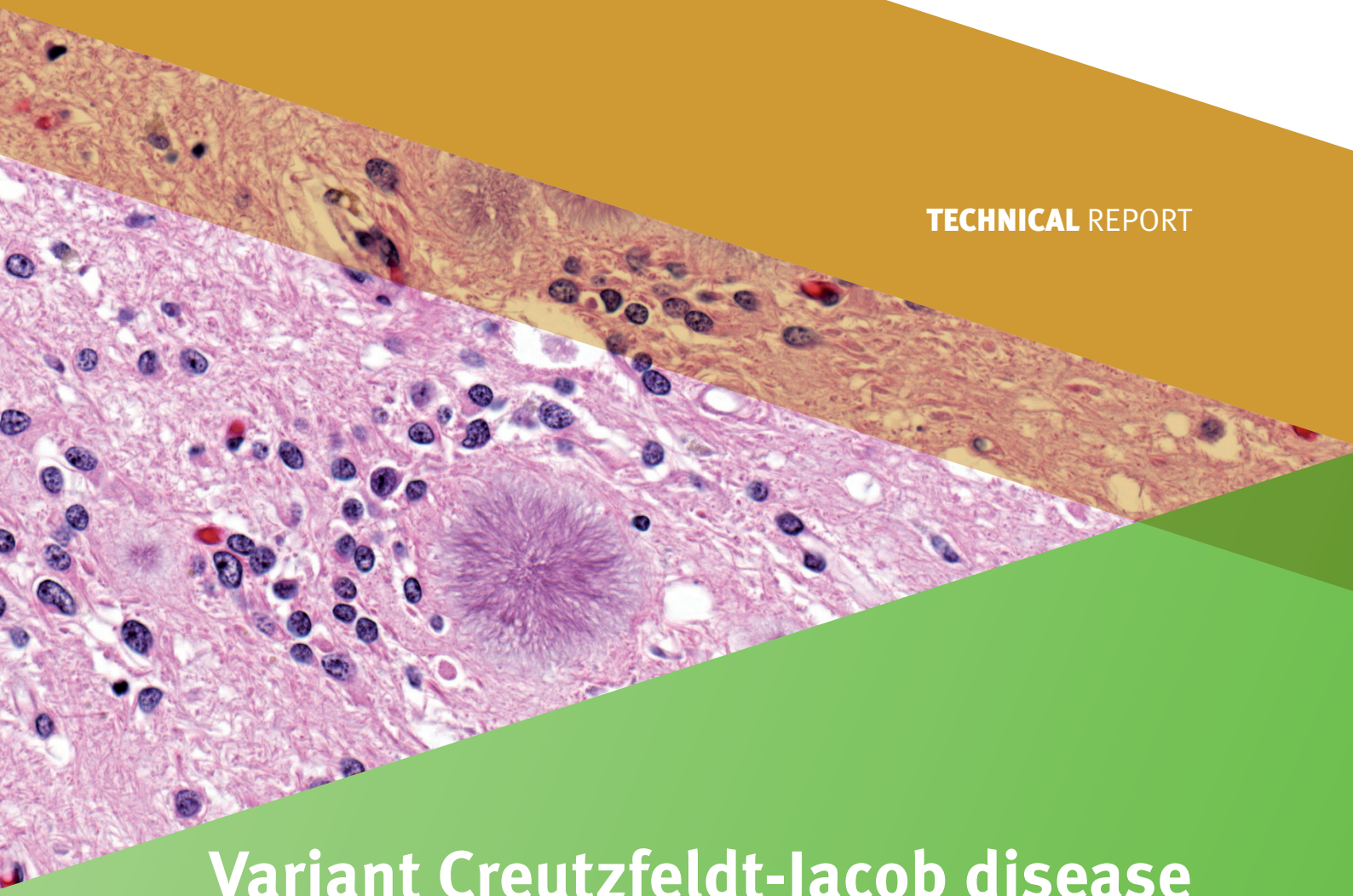

TECHNICAL REPORT

Variant Creutzfeldt-Jacob disease in donors of blood and plasma having temporarily resided in or visited the United Kingdom

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Variant Creutzfeldt-Jacob disease in donors of blood and plasma having temporarily resided in or visited the United Kingdom

This report of the European Centre for Disease Prevention and Control (ECDC) was coordinated by Francois-Xavier Lamy.

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Abbreviations

BSE	Bovine spongiform encephalopathy
CI	Confidence interval
CJD	Creutzfeldt-Jakob disease
EC	European Commission
EU/EEA	European Union and European Economic Area
US FDA	United States Food and Drug Administration
NCJDRSU	National CJD Research & Surveillance Unit (UK)
PDMP	Plasma-derived medicinal products
PRNP	Prion protein
PRP^{C}	Cellular prion protein
PRP^{Sc}	Proteinaceous infectious particles
SoHO	Substances of human origin
TGA	Therapeutic Goods Administration (Australia)
TMER	Transfusion Medicine Epidemiological Review
TSE	Transmissible spongiform encephalopathy
UK	United Kingdom
US	United States
vCJD	Variant Creutzfeldt-Jakob disease

Executive summary

Variant Creutzfeldt-Jakob disease (vCJD) is a rare neurodegenerative zoonotic disease, classified as a prion disease or transmissible spongiform encephalopathy, characterised by progressive neurodegeneration ultimately leading to the death of the host. As there is a risk of secondary infection through transfusion, some countries have imposed deferrals for blood donors considered to have had a risk of exposure due to prior residency in the United Kingdom (UK).

In 2022, both the United States (US) Food and Drug Administration (FDA) and the Australian Therapeutic Goods Administration (TGA) removed the restrictions on blood donors who had previously spent time in the UK. In the light of these decisions, ECDC has been requested to consider whether the current deferral in the EU for prospective donors of blood and plasma after prior temporary residency or visit to the UK is still relevant and justified by scientific evidence, or could be removed.

Since the risk assessment published by ECDC on the risk of vCJD disease transmission via blood and plasma-derived medicinal products (PDMP) manufactured from donations obtained in the UK (August 2021), no new cases of transfusion-transmitted vCJD or cases associated with dietary exposure have been reported in the European Union and European Economic Area (EU/EEA), or in the rest of the world. As such, the overall risk assessment for vCJD transmission through blood remains unchanged: in the absence of a reliable diagnostic blood test, the risk of vCJD infection transmission through blood components remains uncertain. The decisions taken by the US and Australian regulators were based on the results of mathematical models. The modelling estimated the increased risk of transfusion-transmitted vCJD after the removal of restrictions as very low or negligible, with no or a very low increase in the projected number of vCJD cases. This risk was considered acceptable by the US and Australian regulators, supporting the decision to remove the restrictions. Although they are robust to sensitivity analyses, the number of projected cases of transmission resulting from these models are strongly influenced by the assumptions on the prevalence of carriers of infectious vCJD agent in the UK, and this is an estimate for which there remains much uncertainty. In order to determine whether current restrictions for prospective donors of blood and plasma due to temporary residency or having visited the UK are still justified, EU/EEA countries could consider assessing the impact of these restrictions on the local increased risk of transmission of vCJD through blood by using similar mathematical models. This risk could then be balanced against the blood and plasma supply needs in the country, and the expected benefit from removing the restriction. In the future, ECDC intends to support countries with decision-making through the newly-created SoHO-network which will also be a platform for EU/EEA country exchange on national risk assessments, risk models, and decision-making on the deferral of donors due to the risk of vCJD transmission.

1. Background

Context

In 2021, following the decision taken by the UK in February 2021 to lift its ban on the use of UK-sourced plasma to produce immunoglobulin products (originally implemented in 1999), the European Commission (EC) asked ECDC to provide evidence-based advice on the impact of collecting substances of human origin (SoHO) from donors who had lived in the UK during the outbreak of variant Creutzfeldt-Jakob disease (vCJD), taking into account any relevant risk reduction during processing or manufacturing.

In August 2021, ECDC published a risk assessment of vCJD disease transmission via blood and plasma-derived medicinal products (PDMP) manufactured from donations obtained in the UK [1]. This assessment concluded that the risk of vCJD infection transmission through blood components and PDMPs from UK-sourced blood and plasma was unknown, but appeared to be very low. The options for response included the recommendation that EU/EEA Member States should assess their own endogenous risk and, given the relative differences between these risks and those of using PDMPs produced from UK-sourced plasma, balance the assessed threat against supply needs. As no new cases of transfusion-transmitted vCJD or cases associated with dietary exposure have been reported since the previous risk assessment, the conclusions drawn at the time remain valid.

In 2022, both the US FDA [2] and the Australian TGA [3] removed existing restrictions on blood and plasma donors who had previously been temporary residents of or visitors to the UK to defer. The FDA decision was supported by prior risk assessments, as well as the risk assessments published by the UK's Advisory Committee on the Safety of Blood, Tissues and Organs (SaBTO) and the Medicines and Healthcare products Regulatory Agency (MHRA). The Australian regulator's decision was taken in response to the findings of the risk assessment conducted by the Australian Red Cross Lifeblood [4]. The decisions from both regulators were guided by ethical considerations and the need to increase the supply of blood and blood products.

In the light of these developments, the EC asked ECDC to consider whether the current deferral of prospective blood and plasma donors in the EU who had temporarily resided in the UK was still relevant and justified by scientific evidence or whether it could be removed.

Pathogen and disease characteristics

Variant Creutzfeldt-Jakob disease is a rare neurodegenerative zoonotic disease, classified as a prion disease or transmissible spongiform encephalopathy (TSE). There is strong evidence that primary cases of vCJD resulted from eating meat products contaminated with prions causing bovine spongiform encephalopathy (BSE) in cattle [5]. The pathophysiological mechanism of TSE is not fully understood, but it is believed that proteinaceous infectious particles (PrP^{Sc}) convert 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. This structural transition is accompanied by profound changes that make the protein highly insoluble and resistant to proteinase digestion. The subsequent aggregation and accumulation of PrP^{Sc} in neurological tissues induces the classic spongiform change (vacuolation of grey matter), microglial activation and neuronal loss. This leads to progressive neurodegeneration and astrogliosis over time which ultimately leads to the death of the host. No vaccine or specific disease treatment is available. While the structural changes of PrP^{C} are occurring, 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 [6].

The incubation period for vCJD is difficult to establish since the timing of causative dietary exposure in affected individuals is unknown. The estimated incubation period (defined as the time from infection to death as confirmation is post-mortem) for primary transmission infection is around 10 years, approximately reflecting the interval from the peak BSE exposure in 1989 and 1990 to the peak of vCJD deaths in 2000 [7]. In general, it is estimated that the incubation period may extend over a whole lifetime as an asymptomatic, latent infection, depending on the genotype at codon 129 [8]. A polymorphism at codon 129 in the *PRNP* gene is associated with the clinical features of human prion diseases, with nearly all vCJD cases having tested homozygous for the methionine (129MM) genotype [9]. This suggests that individuals with such a genotype are substantially more susceptible to vCJD than individuals with heterozygosis (MV) or valine-valine (VV) homozygosis.

The definitive diagnosis of vCJD is only available post-mortem, based on neuropathological findings in material obtained from a cerebral biopsy or brain examination at autopsy showing the presence of florid plaques in large numbers, and marked accumulation of protease-resistant prion proteins with an increased glycoform ratio. While a new diagnostic test - cerebrospinal fluid real-time quaking-induced conversion (CSF RT-QuIC) - has been developed for sporadic CJD (the test is negative for vCJD), no approved diagnostic or screening test is available for the detection of vCJD prion protein in blood, body fluids or tissues. A more detailed presentation of laboratory tests under investigation is available in ECDC's risk assessment of vCJD disease transmission via blood and plasma-derived medicinal products (PDMP) manufactured from donations obtained in the UK, published in 2021 [1].

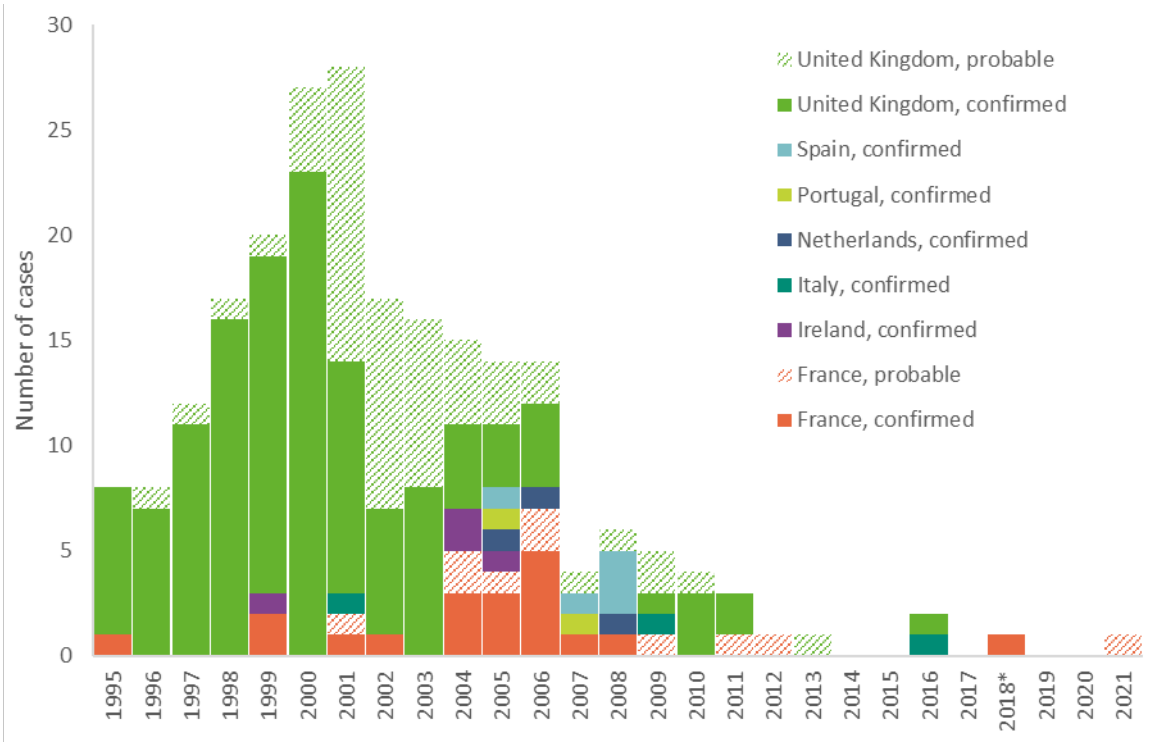
Disease epidemiology

Surveillance activities for Creutzfeldt-Jakob disease (CJD) were strengthened significantly in the late 1990s, following the identification of vCJD and response to concerns about a possible epidemic of vCJD in humans exposed to BSE. In the EU/EEA, the European Creutzfeldt-Jakob Disease Surveillance Network (EuroCJD) was set up in 1993 to establish a surveillance system and perform research. In 2000, the surveillance of vCJD became mandatory in the EU/EEA (including the UK, at the time) and all vCJD cases, including historical ones, have been reported to ECDC since 2012. The vCJD cases are classified according to the EU/EEA case definition for CJD [10-12].

Since 1995 and as of 31 August 2022, 224 vCJD cases (159 confirmed and 65 probable cases) have been reported to ECDC 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 46 cases in total, with France reporting the majority of these (29 cases).

Of the 178 vCJD cases in the UK, 161 were genetically tested. Only one 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). The last known UK case of vCJD was reported in 2016, with a clinical onset in 2014. To date, no vCJD cases have been identified in the UK among individuals born after 1989 [13]. The latest non-UK cases were reported in France in 2021 and 2019 (onset of disease in 2018) (Figure 1), and both were associated with possible occupational (i.e. a laboratory accident) rather than dietary exposure. The 2019 case was reported to be homozygous (MM) at codon 129 [14].

Figure 1. Number of confirmed and probable vCJD cases reported to ECDC, by year and country, in the EU/EEA and the UK, 1995 to 31 August 2022



**This case had a disease onset in 2018 and died in 2019. The case was associated with potential occupational exposure in a laboratory [14].*

All cases had died as of 31 August 2022.

Data collected by the UK National CJD Research & Surveillance Unit (NCJDRSU) show that vCJD mortality in the UK peaked in 2000 and has been decreasing ever since. Estimates based on knowledge in the early stages of the vCJD crisis predicted a relatively high level of infection among the UK population. These estimates were subsequently adjusted downwards in the light of declining case numbers as most of the early predictions were no longer considered tenable and needed to be lowered, even though there were still uncertainties concerning the possibility of a secondary peak after 2010 [7,15-17].

Transfusion transmission

In Europe, vCJD cases with a history of blood donation have been identified in France, Ireland, Italy, Spain and the UK. The Transfusion Medicine Epidemiological Review (TMER), established in 1996 to investigate the link between vCJD and blood transfusion in the UK, identified 24 vCJD cases in the UK population with blood donation history. Blood components from 18 vCJD cases were distributed to hospitals and in total, 67 blood components from these donations were transfused to 67 recipients [18]. Among these recipients, there were three probable transfusion-transmitted vCJD cases between 1996 and 1999 [19-21]. In addition, one probable case of vCJD was detected in 2004 in a transfusion recipient who showed post-mortem evidence of PrPSc deposition in the spleen, although the cause of death was unrelated to vCJD [22]. All four cases received transfusion of non-leukoreduced red blood cells. A further presumed transmission case in a haemophilia patient, receiving factor VIII concentrates prepared from plasma pools known to include donations from a vCJD-infected donor, was identified in 2009 [23].

In the EU, the safety and quality of blood and blood components is regulated in part by Directive 2004/33/EC on technical requirements for blood and blood components [24]. This Directive requires permanent deferral of individuals with a family history placing them at risk of developing a TSE, persons who have received a corneal or dura mater graft, or those who have been treated in the past with medicines made from human pituitary glands. The Directive also states that further precautionary measures may be recommended for vCJD although it does not provide any specific measures.

In its guide to the preparation, use and quality assurance of blood components ('Blood Guide') the European Directorate for the Quality of Medicines & HealthCare (EDQM, Council of Europe) recommends that for vCJD countries assess their own risk and balance this against sufficiency of supply [25].

Among EU Member States that reported this information (n=22), the majority (n=19) indicate that a deferral of prospective blood and plasma donors having visited or resided in the UK is currently in force. Approximately two-thirds (n=12) of these Member States defer donors who have spent a cumulative period of six months or more in the UK between 1980 and 1996, while the remainder (n=7) defer donors with a cumulative period of 12 months or more during this timeframe. The majority of countries (n=10) implemented these deferrals in 2000–2001 while in other countries the deferrals were implemented in 2004–2005 or later.

Estimating the prevalence of PrP^{sc}

The current projections of the likely number of cases in the UK are based on the evidence from clinical cases and retrospective studies of appendix samples. Two immunochemistry screening studies of appendectomy samples estimated the prevalence of PrP^{Sc} in the UK population exposed to meat from animals with BSE. The first study identified PrP^{Sc} in three of 12 674 samples examined from surgical patients between 1995 and 1999 [26], giving an estimated prevalence of 237 per million population (95% confidence interval [CI]: 49–692 per million population). The second study screened appendix samples obtained between 2000 and 2012 [27] and detected 16 PrP^{Sc}-positive samples from 32 441 samples examined, giving an estimated prevalence of 493 per million population (95% CI: 269–1596 per million population).

In contrast to these studies based on appendix specimens, a study analysing 63 007 tonsillar specimens obtained between 2004 and 2008 in the UK did not detect PrP^{Sc} in any specimen [28]. The extent to which tonsillar tissue accumulates PrP^{Sc} is unknown and since it may only be affected late in the disease process, it may not be the tissue of choice for such a study. Following these conflicting results, the UK Advisory Committee on Dangerous Pathogens TSE Subgroup advised that an additional study should be carried out on tissues from a population unexposed to BSE.

The Appendix III study was performed on 29 516 appendix samples that were surgically removed between 1962 and 1979 (i.e. pre-BSE-exposure period) from patients born between 1891 and 1965, as well as on appendices removed between 2000 and 2014 from patients born in 1996 or later (i.e. post-BSE-exposure period) [29]. Seven appendix samples were positive for PrP^{Sc}, two of which were removed during the pre-BSE-exposure period and five during the post-BSE-exposure period. Two interpretations were proposed to explain this result. The first was that there is a low background prevalence of PrP^{Sc} in human lymphoid tissues that may not progress to vCJD, and this background prevalence is unrelated to the extent of dietary exposure to BSE. A second interpretation was that human exposure to BSE began earlier than thought (late 1970s) and continued until the end of the 1990s, although at a much lower rate than during the peak of the BSE epidemic [30].

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. The confirmation of the first UK patient heterozygous for the PRNP codon 129 (129MV), with a disease onset in 2014 [31], introduced the possibility that a higher proportion of individuals (i.e. not only 129MM individuals) exposed to PrP^{Sc} are potential carriers, possibly with a lower susceptibility of clinical disease and/or longer incubation periods. Newer models considering possible infections in 129MV and 129VV individuals estimated substantially longer incubation periods for 129MV (mean 34 years, 95% credible interval: 19–73 years) and 129VV individuals (mean 52 years, 95% credible interval: 26–77

years) than for 129MM individuals [7]. Consequently, recognising significant uncertainty at the 'tail' end of the epidemic, Garske and Ghani predicted approximately five vCJD cases per year after 2011, up to a peak of around 10 cases per year between 2020 and 2035 (95% credibility interval: 1–65 cases) [7]. Available surveillance data in the UK report one case in 2013 and one case in 2016 [32].

Although the policies implemented to control the BSE epidemic in cattle have contributed to the decline of vCJD cases, the prevalence of individuals carrying infectious prions in their peripheral organs and fluids remains uncertain. The limited extent of historical dietary exposure to BSE prion and the low number of clinical vCJD cases in countries other than the UK strongly supports the view that the prevalence of infectious prion carriers in the EU/EEA is much lower than that estimated in the UK population through the appendix studies, as per previous estimates by France [33], Ireland [34] and the Netherlands [35].

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 [29]. However, 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 [36].

2. Modelling of the risk of transfusion-transmitted vCJD

In the absence of a reliable blood screening test for PRP^{Sc}, many countries attempted to minimise the potential risk from vCJD by implementing geographical deferrals, based on risk areas defined by the presence of BSE and notified cases of vCJD. These deferrals also considered the duration of exposure to BSE and several countries deferred donors with six months or more cumulative residency in the UK (with the US also including Ireland and France) between 1980 and 1996.

United States

In 2014, the US FDA published a model developed to estimate the residual risk of vCJD transmission from transfusions in the US [37]. The primary approach of this model was to:

- Estimate the prevalence of asymptomatic carriers of infectious vCJD agent in the UK.
  A high-prevalence scenario was based on the second appendix study [27], with an estimate of 493 (95% CI, 282–801) asymptomatic vCJD infections per million people. A low-prevalence scenario was based on the models from Garske and Ghani [7], with an estimate of 1.7 (95% CI, 0.2–3.7) asymptomatic vCJD infections per million people.
- Estimate the prevalence of carriers of infectious vCJD agent in US donors and the rates of units containing PRP^{Sc}.
  The vCJD risk was modelled for groups of donors having a history of residency in the UK, France, other countries in Europe, and on US military bases in Europe. The number of US donors with PRP^{Sc} in the blood at the time of donation was then estimated based on the probability that a US donor was infected with vCJD and the probability that an infected donor had the vCJD agent in the blood at time of donation. These probabilities rely on the following assumptions:
  - blood is likely to be infectious during the last 75% of the incubation period;
  - mean incubation period for primary vCJD is 15 years for individuals with MM genotype at codon 129 and 35 years for individuals with non-MM genotype;
  - donor screening based on donor history identifies 85% to 99% at-risk donors.

  The number of vCJD-containing blood units was modelled from the estimated number of contaminated US donors and the probability of being infected by the vCJD agent at the time of donation. The rate of contaminated blood units was calculated by dividing the estimated number of blood units containing the vCJD agent by the total number of blood units collected.
- Predict the risk of transmission of vCJD through transfusion in the US.
  The probability of a recipient receiving a transfusion containing PRP^{Sc} was estimated based on the mean number of units administered per transfusion and the prevalence of units containing the infectious vCJD agent calculated in the previous step.

Finally, the projected total number of transfusion-transmitted vCJD infections was modelled based on the annual number of transfusions in the US, the probability of receiving a vCJD unit through a transfusion and the risk that an infected unit may transmit vCJD to a recipient, expressed as an infectious dose per unit.

This model predicted a mean probability of receiving any infected unit of one in 134 million transfusions for the low UK prevalence assumption, and one in 480 000 for the high UK prevalence assumption, resulting in 0–6 infections in 2011 depending on the choice for the UK prevalence, and a cumulative mean number of clinical cases of 0 (low prevalence) and nine (high prevalence) between 1980 and 2011. The number of cases observed during this time period in the US was considered concordant with the results based on the low prevalence estimate. A sensitivity analysis to determine which model inputs had the greatest impact on the final results (importance analysis) identified the prevalence of carriers of infectious vCJD agent in the UK as the input with the greatest impact on the risk estimate.

A subsequent risk-ranking model [38] estimating the country-specific, relative risk of possible exposure to vCJD concluded that the UK, Ireland and France accounted for most of the potential risk of exposure to vCJD. These results led to the revision of US FDA recommendations to limit deferral based on residency in the UK, Ireland, and France (as opposed to all European countries with possible BSE exposure).

In May 2022, the US FDA finally recommended removing deferral for individuals who had spent time in the UK, Ireland, or France between 1980 and 2001 [2]. This decision was guided by the prior risk assessments led by FDA, as well as by the review and evaluation of the SaBTO [39] and MHRA [40] risk assessment models on plasma and platelets, and immunoglobulins, respectively. These risk assessment models and their assumptions are discussed in the risk assessment published by ECDC [1]. Results from these models indicated that removing the ban on UK-sourced plasma would have a very limited impact on the risk of vCJD infections through plasma and platelets, and immunoglobulins manufactured through plasma. Results from these models projected an additional 1–15 cases attributable to plasma transfusions over the next 50 years [39] and 1–24 cases over the next 33 years for

immunoglobulins sourced from plasma [40]. These risks were found to be acceptable and led to the decision to lift the ban on UK-sourced plasma for producing immunoglobulin products. With these results considered to be valid estimates of risk, the US FDA concluded that they supported the removal of the deferral for individuals having spent time in the UK. Since the assessment also covered the risk of transfusion-transmitted vCJD in recipients of plasma and platelets, the US FDA also removed the recommendation for indefinite deferral of individuals having received a blood transfusion in the UK.

By extrapolation, given the smaller number of reported vCJD cases in France and Ireland, the FDA concluded that the risk of vCJD transmission by blood and blood components in France and Ireland would be even lower than in the UK. This led to the removal of the deferral recommendation for individuals with prior residency, or history of transfusion, in France and Ireland as well as the UK.

Australia

In July 2022, the Australian regulator Therapeutic Goods Administration removed geographical deferrals for blood donors having a cumulative length of residency in the UK of six months or more between 1980 and 1996. This decision was based on the risk assessment from the Australian Red Cross Lifeblood [4]. The assessment built on the methodology published by the US FDA [37] described above, which was adapted to Australia. The following steps and assumptions were followed:

- Estimating the prevalence of asymptomatic carriers of infectious vCJD agent in the Australian population. Based on a similar approach to the one proposed by the US FDA, the model relied on a UK prevalence estimate of 1.7 asymptomatic vCJD infections per million people [7] and an estimation of the age-specific prevalence of undiagnosed asymptomatic carriers of infectious vCJD agent by genotype in the UK, itself based on specific assumptions about incubation time by genotype. The prevalence of asymptomatic carriers of the vCJD agent by genotype, age and duration in Australia was then simulated from the number of citizens with the UK as country of birth (by year of arrival) and the number of travellers returning from the UK by duration of stay and year of return to Australia[1].
- Estimating the number of asymptomatic infectious blood donors in Australia.
  The number of asymptomatic infectious donors was estimated from the prevalence of carriers of the vCJD agent in the Australian population, the age distribution of blood donors in Australia, and simulated vCJD incubation periods by genotype. It was then adjusted by the proportion of time for which the blood is infectious.
- Estimating the risk for transfusion-transmitted vCJD.
  Three different measures of risk were considered: 1) the risk of vCJD contamination per unit of blood; 2) the risk of transfusion-transmitted infection based on the simulated probabilities of infectious dose per unit transfused; 3) the risk of clinical (symptomatic) vCJD based on the simulated probabilities of recipient survival beyond the genotype-specific incubation period.

This model predicted a mean of 0.015 asymptomatic infectious donors in 2020, or one donation every 65 years. The mean risk of transmission was estimated at one in 389 million units and the risk of a clinical case occurring was estimated as one in 1.45 billion units. These results were associated with an estimated total of 14 016 donors that would have met the UK deferral criteria in 2020, corresponding to 3.5% of the 395 625 donors of fresh blood components that year.

Contrary to the US model, no 'high-prevalence' assumption, using estimates from the appendix studies, was considered in the primary analysis. According to the authors, the 'low-prevalence' assumption, based on the model from Garske and Ghani [7], already probably overestimated the risk of clinical vCJD prevalence as it predicted around five cases per year between 2011 and 2020, whereas there has been less than one case per year on average in the UK during that period and only a single case since 2014. The importance analysis (the sensitivity analysis determining which model inputs have the most impact on the results) conducted for this model indicated that the infectious dose per transfused unit and the prevalence of carriers of infectious vCJD agent in the UK had the most impact on the risk of vCJD transmission through blood in Australia. Sensitivity analyses conducted with the 'high-prevalence' assumption (i.e. a prevalence of 493 asymptomatic infections per million people) led to a risk of one transmission per 1.4 million units and the risk of a clinical case occurring as one in 5.24 million units. The cumulative mean number of clinical cases derived from this model was zero for the low prevalence estimate and eight for the high prevalence estimate between 1980 and 2020. As for the US, the number of cases observed during this period is concordant with the low prevalence estimate.

Based on these results it was concluded that removing the geographical deferral for UK residency would lead to a miniscule additional risk of vCJD transmission by transfusion in Australia. Based on this model and its conclusions, the Australian regulator approved the removal of this deferral in July 2022 [3].

[1] Numbers made available by the Australian Bureau of Statistics.

3. Discussion

Since the risk assessment published by ECDC in August 2021 on the risk of vCJD disease transmission via blood and PDMP manufactured from donations obtained in the UK, no new cases of vCJD associated with dietary exposure or transfusion of blood or blood components have been reported in EU/EEA or in the rest of the world. The overall risk of vCJD transmission through blood remains unchanged [1]. A literature search covering the period between 2021 and August 2022 did not identify any relevant new information likely to have a significant impact on this risk. The risk assessment concluded that, in the absence of a reliable diagnostic blood test, the risk for vCJD infection transmission through blood components remains uncertain and EU/EEA countries should consider assessing their endogenous risks and balancing the assessed threat against the supply need in their country. In the absence of any new evidence, the conclusions drawn at the time remain valid.

The recent decisions by the US FDA and the Australian regulator to remove donor deferrals for residency in the UK during the BSE epidemic (1980–1996) relied on country-specific risk assessments published by the US FDA [37], SaBTO [39] and MHRA [40] in the UK and the Australian Red Cross Lifeblood [4]. These risk assessments modelled the risk of vCJD transmission through blood and blood components as well as immunoglobulins for each of the countries considered and relied on several country-specific assumptions and data. All of these models concluded that there was a very low risk of vCJD disease transmission via blood and PDMP after removal of the geographical deferrals due to prior residency in the UK during the BSE epidemic.

The Australian risk model describes a 3.5% proportion of donors meeting UK deferral criteria [4], and it could be considered that countries with a similar, or lower, proportion of donors meeting these criteria would see a similar or lower risk of transmission of vCJD through transfusion. However, such an approach should take into account the similarity of the country-specific population data used to inform the model, in particular the genetic susceptibility to infection (i.e. the distribution of codon 129 genotypes); the age profile of the donor population and the age profile of the donors meeting the UK deferral criteria, and the life tables of the population (age-specific survival).

Sensitivity analyses for these risk models indicated that the choice of the assumption on the prevalence of carriers of the vCJD agent was the input parameter with the highest impact on the risk estimates. The estimates of PRP^{Sc} prevalence in the UK used in these models range from 1.7 per million people (low-prevalence estimate) to 493 per million people (high-prevalence estimate). The higher estimate is based on the second appendix study which detected 16 positive samples among 32 441 samples examined [27]. Depending on the choice of a low- or high-prevalence estimate for carriers of the vCJD agent in the UK, the risk of vCJD infection was found to increase significantly: from one in 134 million to one in 480 000 transfusions in the US model for 2011 and from one in 389 million to one in 1.4 million in the Australian model for 2020. It is important to highlight that these models rely on an assumption of infectivity per unit transfused based on animal studies [41] and do not account, in the primary analyses, for the impact of leucodepletion, which would probably decrease the risk further as sensitivity analyses accounting for leucodepletion suggest a three to five-fold reduction of the transmission risk [4,40].

The predicted number of cases of vCJD from models based on the high prevalence estimate from the appendix studies has been inconsistent with the actual observed number of transfusion-transmitted cases in the past decade, and authors of the US model concluded the low-prevalence assumption provided more "reasonably accurate predictions for clinical cases" [37]. The latest models used in the UK relied on the prevalence assumptions from the appendix studies but required model calibration to ensure plausible estimates consistent with observed cases [39] as there have been no cases of transfusion-transmitted vCJD in the UK since the implementation of universal leucodepletion, despite approximately 50 million transfusions of blood components in the UK during this period [4].

The low-prevalence assumption is based on the model developed by Garske and Ghani [7] in 2010 which aimed to account for a subclinical carrier state, as suggested by the discrepancy between the estimated prevalence in the appendix studies and the actual, much lower, number of cases observed. Twelve years later, at the time of the publication of the Australian model, this prevalence estimate was considered to overestimate the risk as only two cases were reported in the UK between 2013 and 2022 [32]. While the current trend of a small and decreasing number of cases in the EU is a likely scenario, the possibility of a secondary outbreak cannot be completely dismissed as previous models have estimated a peak of cases occurring during the period 2020–2035 [7] caused by a longer incubation period from infection to death among 129MV individuals and 129VV individuals. Based on the number of cases observed to date, this secondary peak does not represent the most likely scenario, but in the absence of robust evidence, it cannot be conclusively ruled out and the occurrence of a transfusion-transmitted case of vCJD in the EU in the future would have significant public health impact. In light of this fact, surveillance of vCJD in the EU through the EuroCJD in the near future remains important in order to reassess the likelihood of these different scenarios.

4. Conclusions and potential implications

The recent decisions taken by the US FDA and the Australian TGA to remove existing restrictions on blood donors who had spent time in the UK has prompted the EC to ask ECDC to consider whether the current deferral for prospective donors of blood and plasma in the EU due to temporary UK residence is still relevant and justified by scientific evidence or could be removed. The mathematical models reviewed by the US and Australian regulators estimate the increase in the risk of transfusion-transmitted vCJD after removing the restrictions as very low or negligible, with a null or very low increase in the projected number of cases. This risk was considered acceptable in terms of the expected benefits for the US and Australian regulators. While robust to sensitivity analyses, the number of projected cases of transmission resulting from these models is strongly impacted by the assumptions on the UK prevalence of carriers of infectious vCJD agent - an estimate for which there remains much uncertainty. To determine whether current restrictions for prospective donors of blood and plasma due to temporary residency in or visits to the UK are still justified, countries may consider assessing the proportion of blood donors deferred and, with this proportion, they can approach the increase in transmission risk by comparing with the results of the Australian model. Where this option is not feasible, EU/EEA countries may consider assessing the proportion of blood donors deferred due to prior temporary UK residency. They could also approach the increase in transmission risk by comparing the results of the 2022 Australian Red Cross Lifeblood risk model with the premise that a similar, or lower proportion of donors meeting this criterion could correspond to a similar or lower risk of transmission. Country decision-making on whether, and how to adapt and apply existing mathematical models should consider the country-specific differences in populations (e.g. in terms of demography, genetic susceptibility to infection, and the country-specific life tables for people with UK residency over time). Moving forward, ECDC intends to support countries with decision-making through the newly-created SoHO-network. This network will also be a platform for EU/EEA country exchange on national risk assessments, risk models and decision-making on the deferral of donors due to the risk of vCJD transmission.

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