Institution: University of Edinburgh

Unit of Assessment: 4

Title of case study: J: Change in UK blood donation policy around plasma and platelets following accurate definition of vCJD transmission risks leads to simpler logistics and cost savings

Period when the underpinning research was undertaken: 2000 – 2018

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Colin Smith	Personal Chair Neuropathology	2001 – present
Richard Knight	Personal Chair Clinical Neurology	1996 – present
Alison Green	Reader in Biochemistry	2000 – present
Anna Molesworth	Senior Epidemiologist	2010 – 2020
Marcelo Barria Matus	Post-Doctoral Research Fellow	2010 – present
Robert Will	Emeritus Chair of Clinical Neurology	1990 – 2019

Period when the claimed impact occurred: 2019 – 2020

Is this case study continued from a case study submitted in 2014? N. This is distinct from 2 REF2014 case studies from the same research group, which were on transmission risk of vCJD via blood (REF2014/4/H) and diagnostic criteria for human prion disease (REF214/4/G).

1. Summary of the impact

Underpinning Research: Researchers at Edinburgh Neuroscience's National Creutzfeldt-Jakob Disease Research and Surveillance Unit developed and validated sensitive and specific tools to diagnose sporadic and variant Creutzfeldt-Jakob Disease. These have enhanced robust clinical surveillance, which has demonstrated negligible transmission risks associated with clinical use of plasma and platelets: no cases of vCJD were observed from either plasma or platelet transfusion by February 2019, although the UK Department of Health had predicted 86 cases from plasma and 92-132 from platelets.

Significance and Reach of Impact: In September 2019, UK ministers withdrew an age-related restriction on use of UK-sourced plasma and pooled platelets, and the Irish Blood Transfusion Service reversed its former ban on donations from individuals who resided in the UK prior to 1996. As a result, plasma and pooled platelets from UK donors can now be used for all patients in the UK regardless of their date of birth. The consequent reduced reliance on imported plasma and simpler logistics in haematological units result in estimated cost-savings of approximately GBP814,000,000 to the NHS over a 50-year period.

2. Underpinning research

The Challenge: Creutzfeldt-Jakob Disease can be transmitted through blood

Human prion diseases are a group of rare fatal neurodegenerative diseases. Of these, the sporadic form of Creutzfeldt-Jakob disease (sCJD) is the most common variant (although still rare; 1 – 2 cases per million population per year). sCJD can arise spontaneously and no predisposing factor has been identified. In 1996, Edinburgh Neuroscience researchers identified a novel form of CJD, variant CJD (vCJD); an acquired zoonotic disorder, initially caused by consumption of meat from cows with bovine spongiform encephalopathy (BSE; "mad cow disease").

Although the risk of contracting vCJD through food was virtually eradicated by 1996 through stringent food safety controls, Edinburgh Neuroscience research has demonstrated that there is a secondary route of transmission: vCJD could be transmitted between humans via transfusion of blood or blood products (reported in REF2014/4/H).

This discovery led to the UK Department of Health and Social Care and the UK blood services implementing a host of risk reduction measures to minimise the risk of vCJD transmission through blood, based on estimates of incidence at the time. The most recent measures, pertinent to this case study, were for patients born after 1995, who would not have been exposed to BSE in the food chain. Under the measures, these patients would only receive:

- plasma imported from countries where the vCJD risk is lower (introduced in 2004)
- platelets from a single donor ('apheresis platelets') rather than platelets pooled from multiple donors (introduced in 2014).

Diagnostic tools and surveillance maintain an accurate record of vCJD in the UK

Since Edinburgh Neuroscience research had highlighted the possibility of vCJD transmission of vCJD between humans via blood tranfusion, it is an important public health priority to identify cases of vCJD, and distinguish these from sCJD, as only the former is transmissible between humans through blood and thus requires specific interventions [reported in REF2014; updates in 3.1. 3.2]. The Edinburgh National Creutzfeldt-Jakob Disease Research and Surveillance Unit (NCJDRSU) plays a key role in this goal in two ways: 1) Developing sensitive and specific diagnostic tools to enable a definitive diagnosis of CJD; and 2) Ongoing robust clinical surveillance of all cases of CJD in the UK.

Diagnostic tools allow reliable distinction between sCJD and vCJD

A definitive diagnosis of CJD requires neuropathological examination, usually at autopsy. However, a diagnosis during life is critical for surveillance studies and determining risk of transmission. To this end, Edinburgh Neuroscience researchers have, together with international partners, developed clinical diagnostic criteria including magnetic resonance imaging of the brain and laboratory tests of blood and cerebrospinal fluid (CSF) that have allowed greater clinical certainty during life. In particular, the detection of very small amounts of disease-related protein by protein amplification techniques (real-time quaking-induced conversion, RT-QuiC, and protein misfolding cycling amplification, PMCA) has aided confirmatory diagnosis. In sCJD, RT-QuiC of CSF has a sensitivity of 89.6%, a specificity of 100% and an efficiency of 98.5% [3.3; 3.4]. The equivalent figures for the previously used CSF test (14-3-3) were: 72%, 94.3% and 91.3%. In vCJD, PMCA has a sensitivity of 93% and a specificity of 100% [3.5]. Since RT-QuiC is positive in most cases of sCJD and negative in all cases of vCJD, and PMCA is the opposite, it is now possible to more reliably distinguish between sporadic and variant forms during life. This is important both for public health actions around individual cases.

Ongoing clinical surveillance maintains an accurate record of vCJD cases in the UK

NCJDRSU has in place comprehensive mechanisms to ascertain cases of variant and sporadic CJD in the UK. All suspected cases of prion disease are referred to NCJDRSU by the attending clinician, after which a research registrar from NCJDRSU visits the patient and ascertains the diagnosis based on criteria including the above described diagnostic tools. Through this ongoing surveillance, NCJDRSU maintains an accurate and up-to-date record of the current incidence of vCJD in the UK. Overall, this surveillance has revealed that in the UK, there have been 178 definite and probable cases of vCJD since it was identified in 1995 (in one of the cases, the distinction between variant and sporadic CJD would have been impossible to make without Edinburgh Neuroscience's RT-QuiC and PMCA tools because the clinical presentation was inconclusive [3.6]).

Importantly, the surveillance has found substantially fewer than expected cases of vCJD from contaminated blood: based on NCJDRSU surveillance data, the UK Department of Health risk assessment in 2013 had expected 86 future clinical cases from fresh frozen plasma, 2 of them before the end of 2017 [5.1], but none were observed by February 2019 [5.2]. Similarly, 92-132 cases were expected from platelets, 2 of them before the end of 2017 [5.1], but again none were observed by February 2019 [5.2]. Overall, there have been only 3 cases of blood-related vCJD since surveillance began in 1995 and none diagnosed since 2006 [5.1]. The conclusion was therefore that there was no observable transmission risk of vCJD from blood transfusions of plasma and platelets.

3. References to the research

[3.1] Urwin PJM, Mackenzie JM, Llewelyn CA, Will RG, Hewitt PE. Creutzfeldt-Jakob disease and blood transfusion: updated results of the UK Transfusion Medicine Epidemiology Review Study. *Vox Sanguinis* 2016; 110: 310-316. doi: 10.1111/vox.12371

[3.2] Urwin P, Thanigaikumar K, Ironside JW, Molesworth A, Knight RS, Hewitt PE, Llewelyn C, Mackenzie J, Will RG. Sporadic CJD in 2 plasma product recipients, United Kingdom. *Emerg Infect Dis* 2017; 23:893-897. doi:10.3201/eid2306.161884.

[3.3] Peden AH, McGuire LY, Appleford NEJ, Mallinson G, Wilham JM, Orrú CD, Caughey B, Ironside JW, Knight RS, Will RG, Green AJE, Head MW. Sensitive and specific detection of sporadic Creutzfeldt–Jakob disease brain prion protein using real-time quaking-induced conversion. *J Gen Virol*. 2012; 93: 438–449. doi: 10.1099/vir.0.033365-0.

[3.4] McGuire LI, Poleggi A, Poggiolini I, […], Green AJE.: Cerebrospinal fluid real-time quaking-induced conversion is a robust and reliable test for sporadic Creutzfeldt-Jakob Disease: An international study. *Ann Neurol*. 2016; 80(1):160–5. doi: 10.1002/ana.24679

[3.5] Barria MA, Lee A, Green AJE, Knight RJ, Head MW. Rapid amplification of prions from variant Creutzfeldt–Jakob disease cerebrospinal fluid. *J Pathol Clin Res*. 2018; 4(2): 86–92. doi: 10.1002/cjp2.90

[3.6] Bougard D, Bélondrade M, Mayran C, Bruyère-Ostells L, Lehmann S, Fournier-Wirth C, Knight RS, Will RG, Green AJE. Diagnosis of Methionine/Valine Variant Creutzfeldt-Jakob Disease by Protein Misfolding Cyclic Amplification. *Emerg Infect Dis*. 2018; 24: 1364–1366. doi: 10.3201/eid2407.172105.

Key grants:
The Unit Core Grants that have been renewed several times within the REF period: e.g. Department of Health and Social Care (PR-ST-0614-0008) GBP1,800,000

4. Details of the impact

Pathways to impact

Since 2010, members of Edinburgh's NCJDRSU have been invited to present their research and surveillance data to review panels at the Advisory Committees for the Safety of Blood, Tissue and Organs (SaBTO) and Dangerous Pathogens Transmissible Spongiform Encephalopathy (ACDP TSE) subgroups; independent committees hosted by The Department of Health and Social Care. In addition, Public Health England twice a year analyses and reports the incidence of vCJD to the health ministers of the 4 UK nations based on real-time data from NCJDRSU [5.3]. In 2014, the UK Government described the national surveillance by NCJDRSU and Public Health England as "*the cornerstone of its policy to monitor and control the spread of vCJD*" [5.4].

Impact on UK legislation

In March 2019, SaBTO recommended that the current risk reduction measures on importation of plasma and provision of apheresis platelets for individuals born post-1995 be withdrawn [5.5], and this recommendation was accepted by Government ministers in September 2019 [5.6].

SaBTO's recommendation came following a regular review of its recommendations. As part of this, a working group was set up in 2017 to establish whether the measures of importing plasma and using apheresis platelets for patients born after 1995 should be maintained or withdrawn [5.5]. The Chair confirmed that: "*This working group used the research and surveillance data from University of Edinburgh's National Creutzfeldt-Jakob Disease Research and Surveillance Unit (NCJDRSU) as the sole source to estimate the current incidence of vCJD in the UK."* [5.7].

During this review, NCJDRSU surveillance findings of no cases of blood-related vCJD since 2006 led the existing predictive model to be recalibrated to reflect the actual observations [5.7]. The recalibrated risk assessment estimated that stopping importation of plasma from abroad may lead

to 1 additional death from vCJD for every 5,200,000 units of UK plasma given (approximately 45 years' worth of transfusions). This analysis convinced SaBTO that the risk of vCJD transmission through blood transfusion was too low to justify the practical and financial difficulties incurred by the risk reduction measures [5.5]. Their recommendation to withdraw the measures was accepted by the UK Government on the 9th of September 2019 [5.6].

Impact on clinical practice

The measures to reduce risk of vCJD transmission meant that until September 2019, the UK imported *all* the plasma needed for patients born after 1995, and could only provide apharesis platelets for this group. Withdrawing these requirements resolved the key operational challenges that had been associated with implementing them: Firstly, by 2013, patients born after 1995 were beginning to exit paediatric care and enter adult care, meaning that hospitals were obliged to maintain two separate stocks of plasma, and both apharesis and pooled platelets, in the same setting. Secondly, hospital stakeholders report that it was often challenging to ensure a sufficient supply of imported plasma that meets UK quality standards [5.5].

As part of the review, to better understand the operational challenges faced by hospitals and patients as a result of the precautions, SaBTO sought feedback from 34 key stakeholders, including Great Ormond Street Hospital, Haemophilia UK, Sickle Cell Society and the Royal College of Paediatrics and Child Health. SaBTO summarised the feedback as follows: "*There are practical difficulties for hospital departments having to maintain dual stocks of imported and UK plasma and of pooled and apheresis platelets to treat each patient group. This increases complexity, risk, cost and wastage of valuable resources. Hospital stakeholders were keen to emphasise the potential benefits to patients of lifting the current restrictions, which can lead to delays in the provision of care and the use of less suitable or effective plasma components*." [5.5].

Based on this feedback, SaBTO concluded that allowing the use of UK-sourced plasma and pooled platelets on all patients would enable more equal provision of blood and blood products across the country, while streamlining hospital procedures and reducing operational complexities [5.5]. Now that the restriction has been lifted, these benefits are being felt across the UK.

Impact on economy

The withdrawal of the precaution requiring imported plasma significantly reduces the reliance on plasma imports, resulting in major cost-savings. Prior to the withdrawal, importing plasma had become increasingly costly and precarious: in 2017, 110,000 units of imported plasma were issued in the UK under the old policy, with the year-on-year increase in plasma demand estimated at approximately 4% per annum between 2020 and 2030 [5.5]. Safe plasma supplies are a limited resource with high demand worldwide. Furthermore, the political and logistical complications around Brexit were likely to make the continuous supply of plasma from overseas even more uncertain.

SaBTO calculated that the overall savings achieved by the withdrawal of the precautions requiring imported plasma and apharesis platelets would reach GBP814,000,000 over a 50-year period. To arrive at this estimation, they calculated the costs (the blood components purchased) and patient impact (premature deaths due to vCJD), measured in Quality Adjusted Life Years (QALYs) and estimated that maintaining the practice of importing plasma for individuals born after 1995 would have cost GBP30,000,000 more per QALY than using UK-sourced plasma. Similarly, maintaining a supply of apheresis platelets for these individuals would cost an additional GBP7,000,000 per QALY compared to using pooled platelets. Overall, SaBTO concluded that by 2020, the additional cost of plasma importation alone was approximately GBP5,000,000 per annum, and with increasing costs and patient numbers, this would have been expected to incur a total additional cost of GBP814,000,000 over a 50-year period from the report [5.5].

Impact on Irish Blood Transfusion Service policy

In 1999, the Irish Blood Transfusion Service (IBTS) had introduced a policy that prevented individuals who had lived in the UK between 1980 and 1996 from donating blood. On the 29th of April 2019, the IBTS Medical Advisory Committee held a special policy review meeting to review

this policy. Knight was invited to this meeting to present surveillance data from NCJDRSU. As a result of the evidence, IBTS decided to reverse this policy from 7th October 2019 [5.8]. The press release announcing this decision refers to NCJDRSU data finding only 4 cases of blood-related vCJD in the UK, and the IBTS Medical and Scientific Director acknowledged the input of the NCJDRSU was *"immense"* and that the decision to reverse the policy was heavily based on the detailed surveillance data provided by NCJDRSU [5.9].

This decision means that the IBTS can now recall the 10,000 regular donors they had lost when the deferral was introduced, leading to increased stocks of blood [5.10].

5. Sources to corroborate the impact

[5.1] Department of Health and Social Care Risk assessment of vCJD transmission by blood, February 2013, by the Health Protection Analytical Team. This risk assessment was based on NCJDRSU surveillance data, as evidenced by this section on page 5: "*Clearly, it is important to establish how many clinical cases of vCJD might already have been caused by transfusion. Evidence on this comes primarily from the Transfusion Medicine Epidemiology Review (TMER) study, undertaken jointly by the National CJD Research and Surveillance Unit (NCJDSU) and the UK Blood Services which investigates both donors and recipients found to have vCJD*."

[5.2] NCJDRSU Annual Report 2019

[5.3] Examples of biannual reports by PHE, from February 2014 and February 2019

[5.4] UK Parliament publication 24th July 2014 "After the Storm? UK blood safety and the risk of variant Creutzfeldt-Jakob Disease - Science and Technology Committee"

[5.5] SaBTO working group report March 2019

[5.6] Ministerial announcement Commons September 2019 (p. 557)

[5.7] Testimonial from Chair of SaBTO working group

[5.8] IBTS press release, 9th September 2019 (available at: https://web.archive.org/web/20210121174109/https://www.giveblood.ie/Media/Newsroom/Press_Releases/2019/)

[5.9] Email from Irish Blood Service, October 2019

[5.10] Article in Irish Examiner 10th September 2019