

Institution: The University of Edinburgh
Unit of Assessment: 4
Title of case study: H: Identification of transmission risk of variant Creutzfeldt-Jakob disease (vCJD) via blood and blood products defines critical changes to health policy
<p>1. Summary of the impact (indicative maximum 100 words)</p> <p>Impact: Changed public health policy by quantifying the level of asymptomatic vCJD infection in the population and the mechanism of its transmission, and by identifying cases of human–human transmission of vCJD via blood products.</p> <p>Significance: UoE work informed the public and policy-makers of the risk of vCJD transmission, which resulted in policy changes and the implementation of precautions to prevent vCJD transmission and to limit the chance of a self-sustaining blood- or tissue-contamination-related secondary epidemic.</p> <p>Beneficiaries: Patients, the NHS and healthcare delivery organisations, government, policy-makers.</p> <p>Attribution: The work was carried out at UoE in the National Creutzfeldt-Jakob Disease Research and Surveillance Unit (NCJDRSU) and the Roslin Institute UoE (Roslin) with UK collaborators.</p> <p>Reach: International, particularly UK and North America.</p>
<p>2. Underpinning research (indicative maximum 500 words)</p> <p>UoE Professors James Ironside (Professor of Clinical Neuropathology, UoE, 1994–present), Robert Will (Professor of Clinical Neurology, UoE, 2006–present), Richard Knight (Professor of Clinical Neurology, UoE, 1996–present) and Jean Manson (Professor of Neurodegenerative Disease, UoE, 1989–present) and Dr Mark Head (Reader, UoE, 1998–present) undertook ground-breaking research that demonstrated vCJD prion protein in tonsil and appendix from asymptomatic individuals. Furthermore, they unequivocally demonstrated human-to-human transmission. This work was crucial in defining the transmission in humans of vCJD, a transmissible spongiform encephalopathy (TSE) related to Bovine Spongiform Encephalopathy (BSE), quantitating the risk of human-to-human transmission and thus allowing the establishment of protocols to prevent a secondary vCJD epidemic.</p> <p>In the UK, the prevalence in the general population of vCJD, the human form of BSE, is the highest in the world: of the approximately 200 cases identified worldwide to July 2010, 173 were in the UK. Following the identification of vCJD, concerns were raised about the potential significance of a secondary human-to-human transmission epidemic, particularly via blood and blood products. UoE scientists based in the NCJDRSU (Ironside, Will, Knight and Head) and Roslin (Manson), using complementary models and, crucially, human studies, addressed these issues. They determined the general population level of asymptomatic vCJD infection and detected and characterised actual instances of human-to-human transmission, whilst establishing in mammalian models the efficiency of blood as a route of transmission of infectivity, and the role of specific blood components and tissues [3.1–3.6].</p> <p>Specifically, the NCJDRSU researchers set up a tissue-based prevalence study of vCJD infection via the analysis of lymphoreticular tissue for the vCJD-related prion protein in anonymised routine surgical tonsil and appendix specimens. This study, led by Ironside, identified vCJD-positive samples and both confirmed the presence of asymptomatic infection in the general population and allowed an estimate of its prevalence [3.1].</p> <p>A major danger to humans is the transmission of vCJD by blood and blood products. To address</p>

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this concern, the NCJDRSU researchers identified vCJD cases through surveillance, by obtaining direct individual information about blood and blood products exposure and blood donation. Four studies were undertaken: the Transfusion Medicine Epidemiology Review [3.2, 3.3]; the Department of Health (DoH) Haemophilia Study [3.4]; the DoH Paediatric Immunodeficiency Syndrome Study; and a study to address whether the prion protein PrP^{Sc} represented vCJD infectivity in the periphery of an asymptomatic individual.

In parallel, Manson and colleagues at Roslin demonstrated that all individuals are susceptible to vCJD, and that the genotype of the human prion protein gene may influence whether disease appears in a clinical or asymptomatic form [3.5]. Furthermore, they established that there was little evidence for vCJD strain modification following human-to-human transmission of vCJD by blood transfusion. Following evidence of blood transfusion as a route of transmission, Manson ascertained that all blood components and leucoreduced blood have the ability to transmit BSE and vCJD [3.6].

3. References to the research (indicative maximum of six references)

- 3.1 Hilton D, Ghani A, Conyers L...Ironsides J. Prevalence of lymphoreticular prion protein accumulation in UK tissue samples. *J. Pathol.* 2004;203:733-9. DOI: 10.1002/path.1580.
- 3.2 Llewelyn C, Hewitt P, Knight R...Will R. Possible transmission of variant Creutzfeldt-Jakob disease by blood transfusion. *Lancet.* 2004;363:417-21. DOI: 10.1016/S0140-6736(04)16811-1.
- 3.3 Hewitt P, Llewelyn C, Mackenzie J, Will R. Creutzfeldt-Jakob disease and blood transfusion: results of the UK Transfusion Medicine Epidemiology Review study. *Vox Sang.* 2006;91:221-30. DOI: 10.1111/j.1423-0410.2006.00833.x.
- 3.4 Peden A, McCardle L, Head M,...Ironsides J. Variant CJD infection in the spleen of a neurologically asymptomatic UK adult patient with haemophilia. *Haemophilia.* 2010;16:296-304. DOI: 10.1111/j.1365-2516.2009.02181.x.
- 3.5 Bishop MT...Head M, Ironsides J, Will R, Manson J. Predicting susceptibility and incubation time of human-to-human transmission of vCJD. *Lancet Neurol.* 2006;5:393-8. DOI: 10.1016/S1474-4422(06)70413-6.
- 3.6 McCutcheon S, Alejo Bianco A, Houston E...Manson JC. All clinically-relevant blood components transmit prion disease following a single blood transfusion: A sheep model of vCJD. *PLoS One.* 2011;6:e23169. DOI:10.1371/journal.pone.0023169.

4. Details of the impact (indicative maximum 750 words)

UoE researchers have identified asymptomatic carriage of vCJD-related prion protein and cases of secondary human-to-human transmission of vCJD infection via blood and blood products. Through tractable models, they have established the absolute and relative risk of transmission via blood products in a manner that informed and had significant impact on public health policy worldwide, particularly in the UK, Europe and North America.

Pathways to impact and public engagement

Edinburgh researchers have advised policy-makers on the risk and risk management of TSEs, and more specifically CJD and vCJD [5.1]. Professors Manson, Ironsides, Will and Knight and Dr Head are all members of national and international advisory committees and risk assessment policy groups: these include the Advisory Committee on Dangerous Pathogens (ACDP) [5.2], the Advisory Committee on the Safety of Blood, Tissues and Organs (SaBTO), the UK Blood Services Prion Working Group (PWG) and the Spongiform Encephalopathy Advisory Committee (SEAC). These groups discussed issues and provided reports directly to the DoH on a range of issues and activities associated with potential transmission risks of TSEs, including blood and blood product transfusion, surgical technique and tissue handling, and cleaning of reusable instruments and equipment (for example, endoscopes) [5.3].

Just a few of many examples of meetings at which UoE research was discussed are: at the ACDP-

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TSE Risk Assessment and Risk Management Group (November 2009, February 2010, July 2010 and November 2011); at the PWG (December 2011 and November 2012); and at SEAC (November 2009 and February 2010). The ACDP Annual Report 2010 refers to reviews of major surgical procedures, disposal of surgical instruments and reviews of the World Health Organization (WHO) guidelines. The ACDP Annual Report 2012 refers to a discussion of the risk assessment associated with the Roslin (Manson) activities on scrapie and BSE [5.4]. In addition to their individual contributions to policy groups, NCJDRSU staff regularly provide data to the DoH in relation to parliamentary questions.

International examples of UoE involvement with policy-making bodies include the participation of Will in meetings of the European Medicines Agency (2011) and the US Food and Drug Administration (FDA) Transmissible Spongiform Encephalopathies Advisory Committee (2009, 2010, 2011, 2013). Both Will and Manson have served as expert advisors to the European Food Safety Authority committees.

Impact on public policy

The participation of UoE researchers in national and international policy-making bodies demonstrates the clear impact that their work and expertise has had, and continues to have, on public policy in respect to TSEs and in particular vCJD. UoE's contribution and value to policy in the UK is highly valued by the DoH [5.5]. UoE's identification of blood-related secondary transmission of vCJD led to a number of precautionary health policy changes, such as withdrawal and recall of blood and associated products obtained from donors who develop vCJD, importation of plasma for UK plasma fractionation, and leucodepletion of all blood components. These precautions almost certainly prevented further vCJD transmissions and critically limited the possibility of a self-sustaining blood-related secondary epidemic [5.6]. All these policies are continually reviewed and remain in place, and are dependent on the ongoing provision of data by the NCJDRSU.

Specific examples include the participation of Ironside and Will on the CJD Incidents Panel (CJDIP), set up to advise hospitals, trusts and public health teams across the UK about management of incidents involving all forms of CJD, and reporting to the ACDP TSE Risk Management Subgroup. The CJDIP culminated in the establishment of new 2013 guidelines covering all aspects of CJD management, from reporting new cases and infection control to public health advice and control of CJD risk and spread for both public and health workers. In the 2013 risk assessment of vCJD and transfusion of blood products produced by the Health Protection Analytical Team at the DoH, approximately 20% of the references are from UoE researchers [5.7]. In a further example, in the updated (2012) ACDP TSE Risk Management Subgroup guidance document "Transmissible spongiform encephalopathy agents: safe working and the prevention of infection" 8 out of the 17 references cited are from UoE researchers [5.6].

Impact on international policy

In 2010, WHO updated its earlier (2006) "Guidelines of Tissue Infectivity Distribution in Transmissible Spongiform Encephalopathies". It is clear that UoE researchers had major impact on the updated guidelines. Of the invited expert scientific presentations (Annex 2 of WHO document) UoE researchers contributed significant numbers in many relevant disciplines, for example: Ironside and Will in "epidemiology" (2 out of 5); and Professor Marc Turner (Professor of Cellular Therapy, UoE 1997–2011; Director of the Scottish National Blood Transfusion Service) in both 'evaluation of TSE blood transmission risk' and 'evaluation of TSE removal procedures'. Further, of the total Annex 2 references, almost 20% are accredited to UoE researchers, including 8 out of 17 in the "epidemiology" section. In the Annex 1 "Tables on Tissue Infectivity Distribution in Transmissible Spongiform Encephalopathies"; of 22 references in the "Human TSE" section, 8 constitute UoE-based research [5.8].

The WHO guidelines in turn are referenced in European Commission (EC) guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary products. The most recent (2011) position statement from the European Medicines Agency Committee for Medicinal Products for Human Use on CJD and plasma- and urine-derived

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medicinal products refers frequently to UoE researchers and studies (e.g., the Transfusion Medicine Epidemiological Review) [5.9].

The United States Food and Drug Administration (FDA) and other international bodies have instituted similar policies. UoE impact in North America is demonstrated by the production in May 2010 by the FDA of preventive measures to reduce the possible risk of transmission of CJD and vCJD by blood and blood products, updating earlier guidance in place since 2002. The new guidance, in which the UoE team is frequently referenced, incorporated donor deferral recommendations for donors who have received a transfusion of blood or blood products in France, provided updated scientific information on CJD and vCJD and revised labelling recommendations for transfusion products [5.10].

5. Sources to corroborate the impact (indicative maximum of 10 references)

- 5.1 TSE Guidance from the ACDP (Advisory Committee on Dangerous Pathogens). <http://www.dh.gov.uk/ab/ACDP/TSEguidance/index.htm>
- 5.2 Advisory Committee on Dangerous Pathogens. <https://www.gov.uk/government/policy-advisory-groups/advisory-committee-on-dangerous-pathogens>.
- 5.3 CJD Incidents Panel. Management of possible exposure to CJD through medical procedures. Framework Document. August 2005 amended January, April & May 2011. http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1296688508456
- 5.4 Advisory Committee on Dangerous Pathogens (2013) meetings reports <http://www.hse.gov.uk/aboutus/meetings/committees/acdp/>.
- 5.5 Letter from Lead of CJD Policy, Department of Health, London. *[Available on request. Corroborates importance of UoE research to DoH.]*
- 5.6 Minimise transmission risk of CJD and VCJD in healthcare settings (2013) <https://www.gov.uk/government/publications/guidance-from-the-acdp-tse-risk-management-subgroup-formerly-tse-working-group>.
- 5.7 vCJD and transfusion of blood components: an updated risk assessment. Peter Bennet and Maren Daraktchiiev. Health Protection and Analytical Team, Department of Health. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/186959/risk_assessment_Feb_2013.pdf
- 5.8 WHO Guidelines on Tissue Infectivity Distribution in Transmissible Spongiform Encephalopathies. <http://www.who.int/bloodproducts/TSEPUBLISHEDREPORT.pdf>
- 5.9 CHMP position statement on Creutzfeldt-Jakob disease and plasma-derived and urine-derived medicinal products, June 2011 EMA. http://www.ema.europa.eu/docs/en_GB/document_library/Position_statement/2011/06/WC500108071.pdf
- 5.10 Guidance for Industry. Revised Preventative Measures to reduce the possible risk of transmission of Creutzfeld-Jacob Disease (CJD) and variant Creutzfeld-Jacob disease (vCJD) by blood and blood products <http://www.fda.gov/downloads/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/ucm213415.pdf>