

# ISBT TTID Working Group

## TSE subgroup

Recent developments regarding Creutzfeldt-Jakob disease and blood safety

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# Updates - Overview

- Transfusion transmissibility of sporadic CJD
  - No evidence for Transfusion Transmitted sporadic CJD using look-back studies Checchi et al. 2016; Urwin et al., 2016; Ritchie et al., 2016 (blood transmitted GSS); Crowder et al., 2017
- Sporadic CJD in 2 Plasma recipients
- Confirmed vCJD clinical case with MV (129) prion protein genotype
- vCJD blood screening tests in development
- Comments
- Future Work/Collaboration

## BRIEF REPORT

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### **Creutzfeldt-Jakob disease lookback study: 21 years of surveillance for transfusion transmission risk**

*Lauren A. Crowder,<sup>1</sup> Lawrence B. Schonberger,<sup>2</sup> Roger Y. Dodd,<sup>3</sup> and Whitney R. Steele<sup>1</sup>*

**RESULTS:** To date, 65 CJD donors have been enrolled along with 826 of their blood recipients. These recipients have contributed 3934 person-years of follow-up and no transfusion-transmitted cases of CJD have been recognized.

**CONCLUSION:** From this study, as well as other epidemiologic studies, there is no evidence of CJD transfusion transmission; this risk remains theoretical.

# ARC lookback – classic CJD

- 826 recipients from 65 donors enrolled
- Of the 826, 645 (78%) are deceased and 154 (18.6%) were still alive
- Recipients, including those lost to follow-up, account for 3933.9 person-years of follow-up.
- 105 are both long survivors (5+ years survival) and proximal recipients (blood drawn 5 years of less before donor Dx of CJD)
- All Neuro causes of death checked and none were CJD
- No case of CJD was found in any recipient

## ORIGINAL PAPER

# Creutzfeldt–Jakob disease and blood transfusion: updated results of the UK Transfusion Medicine Epidemiology Review Study

P. J. M. Urwin,<sup>1</sup> J. M. Mackenzie,<sup>1</sup> C. A. Llewelyn,<sup>2</sup> R. G. Will<sup>1,a</sup> & P. E. Hewitt<sup>3,a</sup>

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## Vox Sanguinis

**Background and Objectives** This paper reports the results to 31 May 2015 of an ongoing UK study to look for additional cases of variant Creutzfeldt–Jakob disease (vCJD) transmission by blood transfusion, and to seek evidence whether other subtypes of Creutzfeldt–Jakob disease (CJD) may be transmissible via blood components.

# TMER study in UK – sCJD results only

- 29 sCJD donors identified with transfusion to 211 recipients
- Of the 211, 143 (67.8%) are deceased and 44 (21%) are still alive
- The 44 still living recipients have all survived more than 9 years since transfusion; 22 received donations from CJD donors less than 5 years before symptoms
- 5 Neuro causes of death but none of them were CJD
- No case of CJD was found in any recipient

# Combined data – classic CJD

	ARC - CDC	TMER
Follow-up data through	31 December 2014	31 May 2015
Number of sCJD Blood Donors	63	29
Number of sCJD recipients	817 (638 deceased / 152 alive /27 LTF)	211 (143 deceased/44 alive /24 LTF)
Number of fCJD Blood Donor	1	4
Number of fCJD recipients	1 (1 alive)	15 (8 deceased /4 alive /3 LTF )
Number of iCJD Blood Donors	1	
Number of iCJD Blood Recipients	8 (7 deceased / 1 alive)	
Total Person Years Follow-up	3933.9	1194 (sCJD only)

## Sporadic Creutzfeldt-Jakob Disease in 2 Plasma Product Recipients in the United Kingdom

Patrick Urwin, Kumar Thanigaikumar, James W. Ironside, Anna Molesworth, Richard S Knight, Patricia E. Hewitt, Charlotte Llewelyn, Jan Mackenzie, Robert G. Will

Sporadic Creutzfeldt-Jakob disease (sCJD) has not been previously reported in patients with clotting disorders treated with fractionated plasma products. We report 2 cases of sCJD identified in the United Kingdom in patients with a history of extended treatment for clotting disorders; 1 patient had hemophilia B and the other von Willebrand disease. Both patients had been informed previously that they were at increased risk for variant CJD because of past treatment with fractionated plasma products sourced in the United Kingdom.

*Emerging infectious diseases*, June 2017  
doi: 10.3201/eid2306.161884

*Slide modified from R.G. Will, with permission*



<u>Case 1</u>	<u>Case 2</u>
Von <b>Willebrand's</b> Disease	Haemophilia B
Rx: Since aged 9	Rx Since early 40s
Blood transfusions	6 units FFP
Platelet transfusions	Factor IX (UK sourced and recombinant)
Factor VIII (UK sourced and recombinant)	
Notified to be at risk of vCJD	Notified to be at risk of vCJD
No history of iatrogenic exposure	No history of iatrogenic exposure
No family history of dementia/CJD	Vascular dementia

*Table from R.G. Will, with permission*

“The balance of evidence indicates that, if sCJD is transmitted by blood transfusion it must be a rare event, if it happens at all, and Transfusion transmission is probably not the explanation for the 2 cases we describe.” - Urwin et al. 2017

# Comments/Conclusions - CJD

- These 2 long-term on-going lookback studies continue to show no evidence of CJD transfusion transmission in blood recipients
  - Unlike vCJD, the risk of transmission of classic CJD by cellular products remains theoretical
  - Prions have been detected in patient blood; Animal models show infectivity of blood
  - In addition, case-control and autopsy studies have not revealed any evidence of CJD TTI in humans
- The 2 cases of sporadic CJD in the UK plasma product recipients are concerning but may represent chance events
  - But they were not linked to identified donors.
  - These cases highlight the need for continued surveillance

# Variant Creutzfeldt–Jakob Disease in a Patient with Heterozygosity at *PRNP* Codon 129

Male, aged 36 years

No significant past medical or family history

2015: apathy, depression, altered behaviour and difficulty managing at work for the preceding year

Developed ataxia, myoclonus and progressive cognitive impairment

Died 2016

Duration of illness: 20 months

MRI: high signal in caudate and putamen

Codon 129 genotype: MV

Post mortem: variant CJD

160/161 tested cases in UK : MM

1/161 tested cases in UK : MV

52/52 cases outside UK: MM

Letter to the Editor:

NEJM 376;3

January 19, 2017

Normal UK population: MM 44% MV 45% VV 11%

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# vCJD blood test: latest developments

- Protein Misfolding Cyclic Amplification (PMCA) in vitro test for PrP<sup>TSE</sup> or PrP<sup>sc</sup>
- Suitable for detection of analyte in blood
- Two new studies were published in 2016:
  - Modification of PMCA method
  - Highly laborious
  - Research tests
  - Small number of samples tested
  - Unknown clinical specificity

PRION DISEASES

## Detection of prions in blood from patients with variant Creutzfeldt-Jakob disease

Luis Concha-Marambio,<sup>1,2</sup> Sandra Pritzkow,<sup>1</sup> Fabio Moda,<sup>1,3</sup> Fabrizio Tagliavini,<sup>3</sup>  
James W. Ironside,<sup>4</sup> Paul E. Schulz,<sup>1</sup> Claudio Soto<sup>1,2\*</sup>

Concha-Marambio *et al.*, *Sci. Transl. Med.* **8**, 370ra183 (2016) 21 December 2016 include sporadic  
d by interspecies

- 250  $\mu$ L Whole Blood (WB) centrifuged to remove interfering substances and concentrate PrP<sup>TSE</sup>
- PMCA for 6 days
- Detected 14/14 vCJD WB and no reactive with sCJD (0/16), other disease (0/88) and controls (0/49)
- All vCJD samples from clinical patients
- Not a blind study
- Estimated [PrP<sup>TSE</sup>] =  $5 \times 10^{-13}$  g/mL blood

## PRION DISEASES

## Detection of prions in the plasma of presymptomatic and symptomatic patients with variant Creutzfeldt-Jakob disease

Daisy Bougard,<sup>1\*</sup> Jean-Philippe Brandel,<sup>2,3,4</sup> Maxime Bélondrade,<sup>1</sup> Vincent Béringue,<sup>5</sup> Christiane Segarra,<sup>1</sup> Hervé Fleury,<sup>6</sup> Jean-Louis Laplanche,<sup>4,7</sup> Charly Mayran,<sup>1</sup> Simon Nicot,<sup>1</sup> Alison Green,<sup>8</sup> Arlette Welaratne,<sup>3</sup> David Narbey,<sup>9</sup> Chantal Fournier-Wirth,<sup>1</sup> Richard Knight,<sup>8</sup> Robert Will,<sup>8</sup> Pierre Tiberghien,<sup>9,10</sup> Stéphane Haïk,<sup>2,3,4</sup> Joliette Coste<sup>1,9\*</sup>

<sup>1</sup> Bougard *et al.*, *Sci. Transl. Med.* **8**, 370ra182 (2016) 21 December 2016 <sup>2</sup> in the consumption of meat <sup>3</sup> :hy. Evidence supporting the

- 450 mL plasma + plasminogen capture of PrP<sup>TSE</sup>
- PMCA for ~ 7 days with vCJD clinical plasma
- Detected 18/18 vCJD, 1/67 sCJD, 0/134 other diseases. Blind test
- Detected 2/2 presymptomatic vCJD plasma. Not a blind test
  - One case was PrP<sup>TSE</sup> positive 31 months before onset
  - One case was PrP<sup>TSE</sup> positive 16 months before onset

# Comments/conclusions - vCJD

- BSE and vCJD epidemics are in decline by surveillance
- Do the appendix studies (I – III – presented by L. Gregori at Dubai WP) and the MV genotype case indicate that there could be an resurgence of the disease in the future?
- PMCA gives encouraging results for a blood screening test; performs well and reproducibly
- While PMCA is a promising blood-based assay, in the present configuration seems unsuitable to screening the entire blood supply
- PMCA tests might be developed for diagnostic purposes

# Future activities of the TSE group

- Because of the small size of the TSE subgroup and overlap of members with other subgroups what will be the focus/work of the subgroup?
- Proposed collaboration with SRAP group
  - Comparison of deferral strategies for sCJD and vCJD in different countries
    - Quantifying on-going impact of the deferrals in numbers
    - Possible evolution / relaxation of vCJD strategies in non-endemic countries now that the vCJD epidemic is in decline – could donors be regained?



# TSE and SRAP Collaboration

Afternoon Break-out Session

# Transmissible Spongiform Encephalopathies (TSEs)



Feline Spongiform Encephalopathy



Chronic Wasting Disease



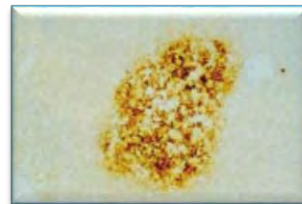
Bovine Spongiform Encephalopathy (mad cow disease)



Kuru (Human)



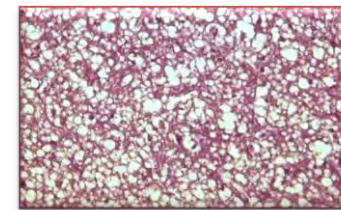
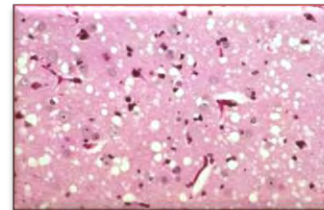
Variant Creutzfeldt Jakob Disease (Human)



Scrapie



Sporadic Creutzfeldt Jakob Disease (Human)



# Variant Creutzfeldt-Jakob disease (vCJD)

- Linked to dietary exposure to bovine spongiform encephalopathy (BSE)
- vCJD and BSE are in decline
- Transmissible by blood transfusion and plasma products
  - In the UK, there has been 4 cases of variant CJD, 3 clinical and 1 subclinical, linked to transfusion of blood from asymptomatic donors who later died of variant CJD.
- No blood screening test: donor deferral policies

# VARIANT CREUTZFELDT-JAKOB DISEASE: CURRENT DATA (MAY 2017)

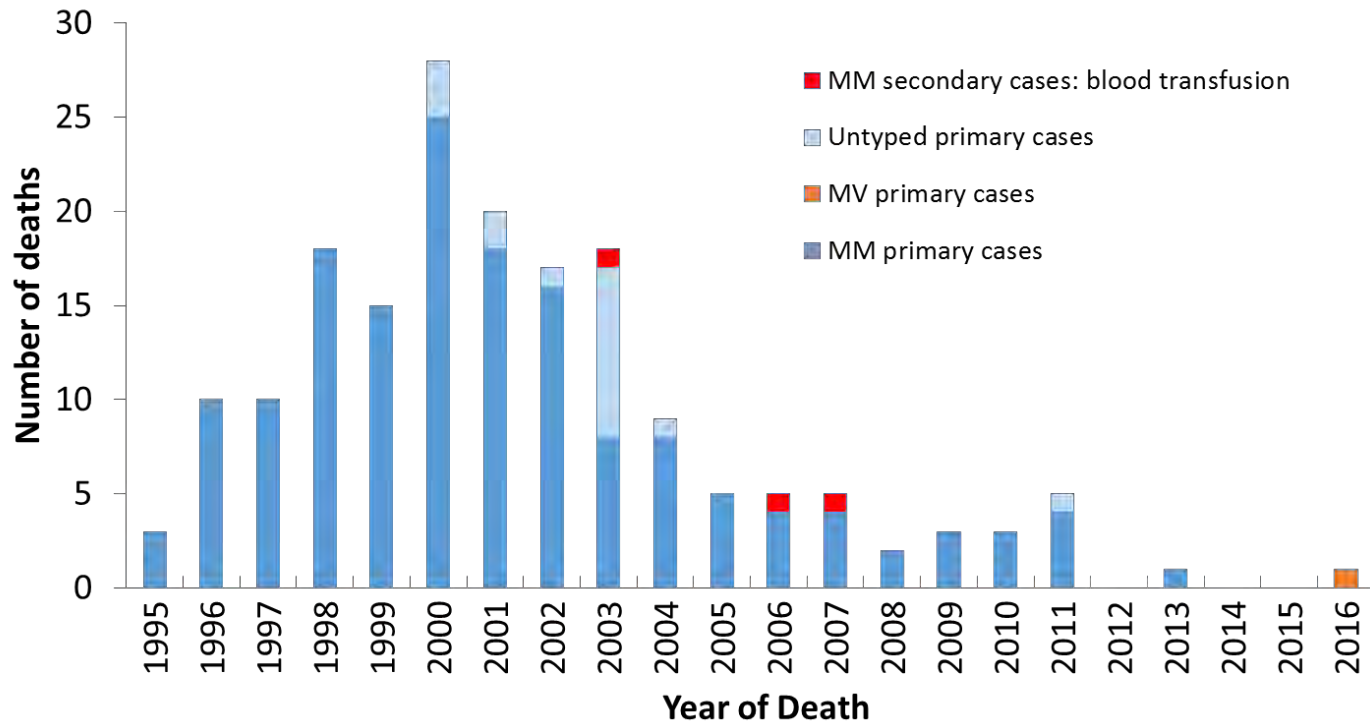
COUNTRY	TOTAL NUMBER OF PRIMARY CASES (NUMBER ALIVE)	TOTAL NUMBER OF SECONDARY CASES: BLOOD TRANSFUSION (NUMBER ALIVE)	RESIDENCE IN UK > 6 MONTHS DURING PERIOD 1980-1996
UK	175 (0)	3 (0)	178 <sup>1</sup>
France	27 (0)	-	1
Republic of Ireland	4 (0)	-	2
Italy	3 (0)	-	0
USA	4 <sup>2</sup> (0)	-	2
Canada	2 (0)	-	1
Saudi Arabia	1 (0)	-	0
Japan	1 <sup>3</sup> (0)	-	0
Netherlands	3 (0)	-	0
Portugal	2 (0)	-	0
Spain	5 (0)	-	0
Taiwan	1 (0)	-	1

<sup>1</sup>case 178 from the UK was heterozygous at codon 129 of the *PRNP* gene

<sup>2</sup>the 3<sup>rd</sup> US patient with vCJD was born and raised in Saudi Arabia and has lived permanently in the USA since late 2005. According to the US case-report, the patient was most likely infected as a child when living in Saudi Arabia. In the 4<sup>th</sup> US patient, the history indicated that exposure to infection most likely occurred prior to moving to the USA.

<sup>3</sup>the case from Japan had resided in the UK for 24 days in the period 1980-1996.

# vCJD cases in the UK



- Two secondary transmissions in MV recipients that were pre-clinical (or subclinical) at time of death
- Primary transmissions in MV and VV genotypes (from appendix surveys)
- All genotypes are susceptible to vCJD infection

# Classic CJD

- Classic Creutzfeldt-Jakob disease (CJD) is a neurodegenerative disease caused by prions.
- The disease is rapidly progressive with a median duration of 4-5 months.
- In all cases it is fatal with no curative treatments available.
- Classic CJD cases are :
  - > 85% Sporadic
  - 5-15% Genetic/Familial
  - Less than 1% Iatrogenic

# Epidemiology of Classic CJD

- Overall the rate of CJD is around one case per million persons but that rate is strongly age dependent
  - In the US there are about 400 deaths per year
  - Incidence in 65-69 year olds is almost 6 cases per million
  - Median age at death – 68 years

# Proposed Methods

- Model malaria comparison study
- Current deferral policies – vCJD and CJD
  - US caveat: call major blood centers to ask about reentry process for classic CJD family members with testing; applicable other countries?
- Current deferral impact – numbers of individuals deferred most recent year, 2 years of data?
- Any proposed changes to criteria being considered?



# US vCJD Deferral Criteria

- have lived in, or traveled to, the United Kingdom for 3 months or longer from 1980-1996
- have been a member of the military, a civilian employee of the military or a dependent of a military member and spent 6 months or longer in Belgium, the Netherlands or Germany from 1980-1990
- have been a member of the military, a civilian employee of the military or a dependent of a military member and spent 6 months or longer in Spain, Portugal, Turkey, Italy or Greece from 1980-1996
- have lived in or spent time totaling 5 years or more in Europe from 1980-present
- received a blood transfusion in the United Kingdom or France from 1980-present

# US CJD Deferral Criteria

- have ever received a dura mater graft or xenotransplantation product
- have any relatives had Creutzfeldt-Jakob disease

*While there is a reentry allowance for those donors whose family member is shown to not have had familial CJD, through genetic sequencing, we believe few, if any, blood centers have a reentry protocol for this.*

# Proposed modifications to donor deferral policies for vCJD in the US (1)

- Low risk for TTvCJD
- No available blood donor screening test
- ~72% of RBC/WB units leukocyte-depleted
- Donor deferral is the major safeguard to mitigate TTvCJD risk from transfusable blood components
- Donor deferral based on risk from travel/residence in certain countries during certain years

# Proposed modifications to donor deferral policies for vCJD in the US (2)

- US FDA proposed modification to deferral policies to the TSE Advisory Committee in a meeting in 2015:
- Current indefinite deferral for travel/residence:
  - UK  $\geq 3$  months from 1980-1996
  - All other EU countries  $\geq 5$  years from 1980-present
- Proposed indefinite deferral for travel/residence:
  - UK  $\geq 3$  months from 1980-1996
  - France and Ireland  $\geq 5$  years from 1980-2001
  - No other geographic deferral recommended
- Proposed option with current level of LR would maintain a risk reduction similar to current situation