Update on TT vCJD investigations in UK

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NHS Blood and Transplant Colindale
Definite or probable vCJD cases (UK n=177)

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age at death:</td>
<td>30 (range 14-75)</td>
</tr>
<tr>
<td>Median age at death:</td>
<td>28</td>
</tr>
<tr>
<td>Mean age at onset:</td>
<td>29 (range 12-74)</td>
</tr>
<tr>
<td>Median age at onset:</td>
<td>26</td>
</tr>
<tr>
<td>Median duration of illness:</td>
<td>14 months (range 6-114)</td>
</tr>
</tbody>
</table>

101 males: 75 females

160 cases tested: all MM at codon129 of the PrP gene
UK vCJD Cases

- 122 neuropathologically confirmed
- 55 no post mortem
Number of onsets per annum of vCJD in the UK

- 1994: 8
- 1995: 10
- 1996: 11
- 1997: 14
- 1998: 17
- 1999: 29
- 2000: 24
- 2001: 17
- 2002: 14
- 2003: 5
- 2004: 9
- 2005: 6
- 2006: 3
- 2007: 2
- 2008: 3
- 2009: 3
- 2010: 1
- 2011: 1
- 2012: 1
- 2013: 1
- 2014: 1

### Number of vCJD cases by 10-year age group

<table>
<thead>
<tr>
<th>Age at death</th>
<th>Number of vCJD cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-19</td>
<td>22</td>
</tr>
<tr>
<td>20-29</td>
<td>78</td>
</tr>
<tr>
<td>30-39</td>
<td>52</td>
</tr>
<tr>
<td>40-49</td>
<td>9</td>
</tr>
<tr>
<td>50-59</td>
<td>11</td>
</tr>
<tr>
<td>60-69</td>
<td>3</td>
</tr>
<tr>
<td>70+</td>
<td>2</td>
</tr>
<tr>
<td>TOTAL</td>
<td>177</td>
</tr>
</tbody>
</table>
Follow up of donations from individuals with CJD
(Transfusion Medicine Epidemiology Review)

Dr Patricia Hewitt
Dr Charlotte Llewelyn
Professor R Will
Jan McKenzie

NHS Blood and Transplant, UK
National CJD Research and Surveillance Unit
Study outline

• TMER (Transfusion Medicine Epidemiology Review) links databases of UK Blood Services and NCJDRSU

• cases of CJD are actively investigated for history of blood donation/transfusion

• blood donations are traced through to names of recipient/donors: lookback and traceback

• passive surveillance of those identified: death certificates examined
TMER forward arm: lookback

BSE               vCJD infection                   incubation (10-20 years)            death

(after M.Busch)
Age distribution for red cell recipients
National Study (24 hospitals) (n=10080)

(Williamson, Murphy, Llewellyn et al, ‘03)
vCJD – BLOOD DONORS

total number of vCJD cases in the UK 177
number who were eligible to donate (ie aged ≥ 17) 167
number reported by relatives to have been blood donors 32
number of cases where donor records have been traced 24*
number of cases from whom components were actually issued 18
number of recipients identified from 18 cases where recipient and component information is available 67***

* donor records were traced on four cases where the relatives had reported the case not to be a donor; one of these had donated while the other 3 were registered as donors but never donated
*** some other recipients not identified
TMER forward arm: lookback recipient outcome

• 34/67 recipients < 5 years survival since transfusion

• 14/67 recipients currently alive

• all living recipients have survived > 10 years
Decesed recipients with < 5 year survival (n = 34)

- cause of death known; none suggest prion disease
- none had post-mortem/ tissue examination
Deceased recipients with
> 5 years survival (n = 19)

19 deceased
> 5 years

- 3 clinical vCJD at 6.5 to 8 years
- 1 abnormal prion protein at 5 years
- 4 negative tissue examination
- 11 no further information
Recipients (n=67) of labile blood components donated by donors who developed vCJD

DEAD (n=53) (Interval from transfusion to death)  ALIVE (n=14) (Interval from transfusion to end 2014)

- Dead - untested
- Dead - tested positive for PrP deposition
- Dead - tested negative for PrP deposition
- Alive - untested
- Alive - tested for PrP deposition

a an individual with presumed pre- or sub-clinical vCJD infection (Case 2)
b vCJD case (Case 1)
c vCJD case (Case 3)
d vCJD case (Case 4)
Living recipients
Recipients of blood from donors who later developed vCJD

Number of years lived following exposure for recipients currently alive, n=14

<table>
<thead>
<tr>
<th>Number of years since exposure</th>
<th>Current age group of living patients</th>
<th>Total alive by years since exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-9</td>
<td>0-9</td>
<td>10-19</td>
</tr>
<tr>
<td>0-4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>5-9</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>10-14</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>15-19</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>≥20</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
TMER reverse arm: traceback

BSE

vCJD infection

incubation (10-20 years)

death

(after M. Busch)
### Blood Transfusion in vCJD cases: traceback

<table>
<thead>
<tr>
<th>Total number of vCJD cases in the UK</th>
<th>177¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of vCJD cases reported to have received a blood transfusion</td>
<td>15²</td>
</tr>
<tr>
<td>▪ Number not transfused:</td>
<td>1</td>
</tr>
<tr>
<td>Number of donors identified who gave blood to 10 vCJD cases</td>
<td>193</td>
</tr>
<tr>
<td>Number of donors already listed on the NCJDSU register as vCJD cases</td>
<td>2³</td>
</tr>
</tbody>
</table>

¹ Note: recipient with pre-clinical infection (Case 2) is not included in this slide as this patient did not have a diagnosis of vCJD.

² An additional case received a transfusion after onset of symptoms of vCJD and therefore is not included in the table.

³ two donors diagnosed with vCJD, one with one red cell recipient (Case 1 transfused in 1996), the other with two red cell recipients (Cases 3 and 4, both transfused in 1997).
vCJD CASES WHO RECEIVED BLOOD TRANSFUSION(S) IN THE PAST

<table>
<thead>
<tr>
<th>Recipient</th>
<th>Transfusion</th>
<th>Number of donor exposures</th>
<th>Interval from transfusion to onset of illness</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>38</td>
<td>4 years, 9 months</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>65</td>
<td>4 years, 6 months</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>2</td>
<td>15 years, 11 months</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>3</td>
<td>6 years, 3 months</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>4</td>
<td>5 years, 4 months</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>5</td>
<td>8 months&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>5 (Case 1)</td>
<td>1</td>
<td>5&lt;sup&gt;2&lt;/sup&gt;</td>
<td>6 years, 6 months</td>
</tr>
<tr>
<td>6 (Case 3)</td>
<td>1</td>
<td>56&lt;sup&gt;2&lt;/sup&gt;</td>
<td>7 years, 10 months</td>
</tr>
<tr>
<td>7</td>
<td>1</td>
<td>2</td>
<td>13 years, 11 months</td>
</tr>
<tr>
<td>8</td>
<td>1</td>
<td>4</td>
<td>16 years, 9 months</td>
</tr>
<tr>
<td>9 (Case 4)</td>
<td>1</td>
<td>21&lt;sup&gt;2&lt;/sup&gt;</td>
<td>8 years, 4 months</td>
</tr>
<tr>
<td>9 (Case 4)</td>
<td>2</td>
<td>2</td>
<td>7 years, 8 months</td>
</tr>
<tr>
<td>10</td>
<td>1</td>
<td>2</td>
<td>5 years, 11 months</td>
</tr>
</tbody>
</table>

<sup>1</sup>timing of clinical illness excludes blood transfusion as the source of infection in one case.

<sup>2</sup>one donor developed vCJD.
vCJD in transfusion recipients

- 10 cases with history of blood transfusion (209 donors)
  - 1 case transfused 8 months before onset (5 donors)
  - 3 cases linked to 2 known infected donors
  - 6 cases: could be transfusion-associated (120 donors)
BSE → vCJD infection → incubation (10-20 years) → death

(TMER reverse arm: case 1)

(after M. Busch)
TMER Reverse arm: cases 3 and 4

BSE

vCJD infection

incubation (10-20 years)

death

(after M Busch)
DONOR TO CASES 3 AND 4 AND OTHER DONATIONS MADE

- **Red cells**
  - Died - vCJD

- **Fresh Frozen Plasma**
  - Died same day as transfusion - cancer

- **Whole blood**
  - Died - cancer

- **Red cells**
  - Died - CVA

- **Fresh Frozen Plasma**
  - Died – heart disease

- **Red cells**
  - Died - MI/renal failure/IHD/diabetes

- **Fresh Frozen Plasma**
  - Alive

**Year and Quarter**

- 1997-1
- 1997-2
- 1997-3
- 1997-4
- 1998-1
- 1998-2
- 1998-3
- 1998-4
- 1999-1
- 1999-2
- 1999-3
- 1999-4
- 2000-1
- 2000-2
- 2000-3
- 2000-4
- 2001-1
- 2001-2
- 2001-3
- 2001-4
- 2002-1
- 2002-2
- 2002-3
- 2002-4
- 2003-1
- 2003-2
- 2003-3
- 2003-4
- 2004-1
- 2004-2
- 2004-3
- 2004-4
- 2005-1
- 2005-2
- 2005-3
- 2005-4
- 2006-1
- 2006-2
- 2006-3
- 2006-4
- 2007-1
TMER reverse arm

• 209 donor exposures, 193 identified donors traced of whom 2, already known to have developed vCJD, donated to 3 recipients

• remaining donors to recipients 5, 6, and 9, with already identified infected donor: no further action

• remaining donors in cases with no identified infected donor: notified “at risk of vCJD for public health purposes” and continue under passive surveillance
## vCJD Cases Who Received Blood Transfusion(s) in the Past

<table>
<thead>
<tr>
<th>Recipient</th>
<th>Transfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>5 (Case 1)</td>
<td>1</td>
</tr>
<tr>
<td>6 (Case 3)</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>9 (Case 4)</td>
<td>1</td>
</tr>
<tr>
<td>9 (Case 4)</td>
<td>2</td>
</tr>
<tr>
<td>10</td>
<td>1</td>
</tr>
</tbody>
</table>

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<td>4 years, 9 months</td>
</tr>
<tr>
<td>65</td>
<td>4 years, 6 months</td>
</tr>
<tr>
<td>2&quot;</td>
<td>15 years, 11 months</td>
</tr>
<tr>
<td>3</td>
<td>6 years, 3 months</td>
</tr>
<tr>
<td>4</td>
<td>5 years, 4 months</td>
</tr>
<tr>
<td>5</td>
<td>8 months&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>52</td>
<td>6 years, 6 months</td>
</tr>
<tr>
<td>56&lt;sup&gt;2&lt;/sup&gt;</td>
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<td>2&quot;</td>
<td>13 years, 11 months</td>
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<tr>
<td>21&lt;sup&gt;2&lt;/sup&gt;</td>
<td>8 years, 4 months</td>
</tr>
<tr>
<td>2</td>
<td>7 years, 8 months</td>
</tr>
<tr>
<td>2</td>
<td>5 years, 11 months</td>
</tr>
</tbody>
</table>

<sup>**</sup> donors not traced

<sup>1</sup> timing of clinical illness excludes blood transfusion as the source of infection in one case.

<sup>2</sup> one donor developed vCJD.
Patients at increased risk traced to a variant Creutzfeldt-Jakob disease (vCJD) case through blood donations.
Data source: Transfusion Medicine Epidemiology Review (TMER) study.

- Total UK vCJD Cases 177
- 18 vCJD cases donated blood to recipients
- 67 recipients of blood donated by vCJD cases
- 10 vCJD cases received blood transfusions
- 34 people received blood from donors who donated to vCJD cases
- 112 blood donors donated to 5 vCJD cases
Enhanced surveillance of people at increased risk of Creutzfeldt-Jakob Disease
Biannual Report, February 2015

Summary of groups identified as at increased risk of CJD on which data are collected (Data correct as at 31st December 2014):

<table>
<thead>
<tr>
<th>‘At risk’ Group</th>
<th>Identified as ‘at risk’</th>
<th>Number notified as being ‘at risk’</th>
<th>Cases</th>
<th>Asymptomatic infections</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>All</td>
<td>Alive</td>
<td></td>
</tr>
<tr>
<td>Recipients of blood from donors who later developed vCJD</td>
<td>67</td>
<td>27</td>
<td>14</td>
<td>3</td>
</tr>
<tr>
<td>Blood donors to individuals who later developed vCJD</td>
<td>112</td>
<td>108</td>
<td>104</td>
<td>0</td>
</tr>
<tr>
<td>Other recipients of blood components from these donors (reverse risk recipients)</td>
<td>34</td>
<td>32</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Plasma product recipients (non-bleeding disorders) who received UK sourced plasma products 1980-2001</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Certain surgical contacts of patients diagnosed with CJD</td>
<td>196</td>
<td>163</td>
<td>139</td>
<td>0</td>
</tr>
<tr>
<td>Highly transfused recipients</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>
Follow-up surveillance is conducted by the CJD team at Public Health England, based on data provided by the TMER

**P-447**

Ten years on–follow up of cohorts with an increased risk of variant CJD through donating or receiving blood

Poster prepared by Katy Sinka and Marta Checchi of the CJD team at PHE
Variant CJD and Blood Transfusion: are there additional cases?

LRR Davidson, CA Llewelyn, JM Mackenzie, PE Hewitt, RG Will: Vox Sanguinis 2014 107 220-225
National CJD Research and Surveillance Unit and NHS Blood and Transplant

- 15 vCJD cases who received a blood transfusion
  - No donor record in 4 cases
  - 10 vCJD cases
    - No transfusion in one case
      - 3 vCJD cases previously identified by TMER as transfusion transmitted
      - one case transfused at symptom onset
        - 6 vCJD cases who received a blood transfusion but not linked to a donor with vCJD
          - 112 donors identified, 105 under continuing surveillance
Donor survival from transfusion in index case (n=112)

Variant CJD and Blood Transfusion: are there additional cases?
LRR Davidson, CA Llewelyn, JM Mackenzie, PE Hewitt, RG Will
<table>
<thead>
<tr>
<th>Year of Death</th>
<th>Interval from transfusion in index case to death in donor</th>
<th>Cause of death in donor</th>
</tr>
</thead>
</table>
| 1994          | 1 year                                                 | Injury to abdominal aorta causing haemorrhage  
Verdict: Death by Misadventure |
| 2001          | 8 years                                                | Hypertensive heart disease  
(Coroner’s post mortem without inquest) |
| 2006          | 13 years, 4 months                                     | Pulmonary embolism/Deep vein thrombosis/ischaemic heart disease  
(Coroner’s post mortem without inquest) |
| 2008          | 15 years, 2 months                                     | Bronchopneumonia/disseminated sigmoid colon carcinoma, pulmonary embolism |
| 2012          | 18 years, 8 months                                     | Complications of heart valve surgery |

Variant CJD and Blood Transfusion: are there additional cases?
LRR Davidson, CA Llewelyn, JM Mackenzie, PE Hewitt, RG Will
Age at onset in variant CJD cases

- Mean age at onset in primary vCJD cases 28.4 years

- Mean age at onset in 3 transfusion transmitted cases 57.6 year

- Mean age at onset in 6 recipients unlinked to an affected donor 35.5 years
Conclusion: In conclusion, it is possible that one or more of the vCJD cases that received a blood transfusion derived from an individual not known to have vCJD were infected by the blood transfusion. However, the evidence for this is weak, and the absence of a past history of transfusion in most cases of vCJD excludes a large number of unrecognised transfusion-transmitted cases.

LRR Davidson et al, 2014 107 220-225
Older patients with clinical vCJD are more likely to have been transfused, and the mean age will be higher than the whole cohort. Based on the age-adjusted transfusion prevalence, the mean age of cases that might have received an unlinked prior transfusion is 33.4 years. This compares with the observed figure given by Davidson et al. of 35.5 years.
TMER summary

- TMER has used standard blood transfusion lookback and traceback procedures
- and linked blood service and NCJDRSU records
- to investigate any linkage between donors and recipients with vCJD
TMER conclusions

- 4 cases of prion transmission by transfusion (3 fatal) have been identified from lookback on transfusions in 1996 – 1999

- no further cases of transfusion-transmissions have been identified through traceback from infected recipients

- continued surveillance will be necessary for many years
Acknowledgements

Jan MacKenzie
Prof Bob Will
Charlotte Llewelyn

Staff in all four UK blood services and in hospital blood transfusion laboratories

The TMER is funded by the Department of Health
HEV and interventions: UK perspective

Patricia Hewitt NHS Blood and Transplant

ISBT TTID Working Party June 2015
NHSBT Hepatitis E study 2012-13

• screened 225,000 blood donations over a 12 month period

• 79 (1 in 2850) donations HEV RNA positive

• overall transmission rate 42%

• all recipients eventually cleared infection
SaBTO HEV sub-group

• UK-wide, with representation from all 4 UK blood services

• examining options, operational and financial considerations
HEV and blood donations: options

• no screening

• universal screening

• screening for selected recipients (cf HCMV)
Donor management?

• follow-up testing before return to donation, if so, when?
  2013: 5/37 had low level detectable viraemia at 4 weeks after pick-up

• return to donation after set period, if so, when?

• special considerations for “valuable” component (platelet) donors?
Donor management: workload

- within NHSBT, extrapolating from previous data, universal HEV screening would yield 386 confirmed positive donations in first year, assuming 2012/13 incidence levels

- this is greater than for all other infections combined: 2014: approx 177 in total
Outcome?

- report to extraordinary meeting of SaBTO in July 2015
- SaBTO make recommendations to Ministers