First evidence of intracranial & peroral transmission of Chronic Wasting Disease (CWD) into Cynomolgus macaques: a work in progress

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Chronic Wasting Disease (CWD)

- Prion disease of cervids (deer – WTD, BTD, MD, RD, RD; elk, & moose). Farmed & free-ranging animals
- CWD prions widely distributed in infected animal (including blood, muscles)
- CWD prions shedding in saliva, feces & urine
- Direct spread by animal-to-animal contact; indirect by contamination of soil & water (salt licks, plants)
- Found in 3 Canadian provinces, 24 US states, Norway, Finland & South Korea. Continuous spread
- 40% elk in Estes Park/Colorado. 40% WTD in hot spots in Wisconsin. 30% mature male MD in hot spots in Alberta. Alberta CWD prevalence increases dramatically & spreads westwards (2005-2016 n= 592; 2017 n=327)
- Long & clinically silent incubation period (elk > 34 months, deer ~ 25 months)
- Invariably fatal, no treatment, no vaccine

Zoonotic potential?
CWD Transmission into non-human Primates

• Project
  • Transmissibility - to investigate zoonotic potential of CWD (1/5 goals)
  • Clinical endpoint (in extremis)
  • Project start 2009

• Experimental Design
  • 21 macaques, different routes of challenge (n=18). 3 mock controls
  • Intracranial – proof of concept
  • Per oral – risk via consumption
  • Skin scarification – risk via field dressing
  • Intravenous – risk via blood transfusion
Animals & challenge material

• Animals:
  Cynomolgus macaques, female, 4 years, Mauritian origin (Noveprim/Spain)
  Wild-type PrP, 129 MM homozygous

• CWD of 2 Canadian & 4 US origin:
  WTD (farmed & hunted): 2 distinct CWD isolates
  WTD (experimental) challenged with elk, MD & WTD
  Elk (experimental): CWD2; $1.0 \times 10^{7.0 - 7.2}$ i.c. ID50/g brain
  tg mice
  MD (hunted)
  Blood from Non-clinical donor macaques challenged with CWD
  MD, elk & WTD; $1.0 \times 10^6$ to $2.0 \times 10^9$ i.c ID50/g brain tg mice
PrP\textsuperscript{CWD} presence in WTD skeletal muscles (Pet-Blot)

CWD  ➔  Macaques ?
# Animal data

<table>
<thead>
<tr>
<th>Animal #</th>
<th>AU153</th>
<th>AU389</th>
<th>AU519</th>
<th>AU520</th>
<th>AU408</th>
<th>AU469</th>
<th>AU467</th>
<th>AU501</th>
<th>AU385</th>
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<td>4.5</td>
<td>5.2</td>
<td>6.3</td>
<td>6.5</td>
<td>6.9</td>
<td>5.8</td>
<td>5.4</td>
<td>6.2</td>
<td>7.4</td>
</tr>
<tr>
<td>Route</td>
<td>i.c. sw</td>
<td>i.c. sw</td>
<td>i.c. sw</td>
<td>i.c. sw</td>
<td>i.c. sw</td>
<td>oral</td>
<td>oral</td>
<td>oral</td>
<td>oral</td>
<td></td>
</tr>
<tr>
<td>Inocul.</td>
<td>WTD</td>
<td>Elk</td>
<td>WTD</td>
<td>ELK</td>
<td>WTD</td>
<td>WTD</td>
<td>WTD</td>
<td>WTD</td>
<td>WTD</td>
<td>WTD</td>
</tr>
<tr>
<td>Clinical present.</td>
<td>-</td>
<td>anxiety ataxia tremor wasting</td>
<td>-</td>
<td>wasting</td>
<td>-</td>
<td>apathy wasting</td>
<td>wasting</td>
<td>anxiety ataxia tremor wasting</td>
<td>apathy ataxia tremor wasting</td>
<td>ileus</td>
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<tr>
<td>Clinpath</td>
<td>-</td>
<td>Glucose</td>
<td>-</td>
<td>Glucose</td>
<td>Glucose</td>
<td>-</td>
<td>-</td>
<td>Glucose</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>
**Histopath & PrP IHC**

**Spinal Cord**

**Midbrain**
**IHC cont’**

GFAP

Neg. cont, 6H4
Spinal cord involvement: progression over time

i.c./s.w., 4.5 years p.c.  
p.o. 7.4 years p.c.

Western Blot (PrP27-30 in spinal cord from CWD-Challenged Macaques)

MW 385 389 A4
L4 L4 Cer.

Lanes*
MW: Low Molecular Weight Marker
AU385 L4 [7.5 x 10^{-4} gram equivalents / lane]
AU389 L4 [7.5 x 10^{-4} gram equivalents / lane]
A4 Cer: Cerebrum BSE macaque [1.0 x 10^{-5} gram equivalents / lane]

Blot 2017-08-18 - Exp 9 - 02h - 01.JPG
Blot: 2017-08-18
Film exposure time: 2 h
Antibody: 3F4
PK digest.: 75 µg/ml
PNGase F digest.: No

(M. Beekes/RKI)
RT-QuIC: lumbar spinal cord

(fluorescence curve)

Spinal Cord (Lumbar) w. Macaque rPrPc

***Mean Fluorescence

CWD Challenged Macaques

- Au385
- Au389
- Au408
- Au501
- Au519

RFU (ThT 450/480)

0 10 20 30 40 50 60 70 80 90 100

TSE+ Controls

TSE- Controls

(Cortex)

Elk#168

(Au242)

DPZ#16825

DPZ#16828

Elk#181

(Au385)

Au389

Au408

Au501

Au519

MaqA4 BSE+

MaqA4 BSE+

Lum.SpCd

(John Gray/Czub lab)
CWD → Macaques!

Histopathology, CWD prion deposition (IHC) & amyloid seeding
CWDmac $\rightarrow$ tg mice ?
**TgELK challenge**  
*(AU519 CWD WTD, i.c./sw, 5.3 years)*

20 µl 10% medulla homogenate i.c. in tgElk brain; 150 dpi

Exp. time 10 sec  
control: MD  CWD in TgElk; 10% brain; 50 µg/ml PK

Schaetzl & Gilch, UCVM/UofC
Histopathology tgElk

corpus callosum, parietal cortex, inner mol layer, cerebell. peduncle
IHC TgElk - Olfactory Bulb

Animal #1, 12F10 (+PK), x20

Animal #2, 12F10, x40

Animal #3, R145, x40

Animal #5, F99, x20

Animal #6, 12F10, x20
“Negative” IHC Controls

TgElk mouse #6, ob, 3F4, x200

Tg650 mouse A, F99, ob, x400
CWDmac $\rightarrow$ tg mice !

infectious
CWD Macaque Transmission: a work in progress (October 2018)

- 11/21 animals to assess; 4/11 with neurological signs
- 6/11 animals with wasting (5/11 animals with diabetes) (co-factor ? Disease indicator ?)

**So far:**
- CWD challenge of macaques is possible
- Sub-clinical not full-blown CWD disease (yet ?)
- “Atypical” spinal cord & midbrain involvement by-passing obex
- CWDmac transmissible: clinical tgElk; subclinical TgHu mice. Connecting structures not nuclei involved

**Ongoing:**
- More macaques /mice to be tested; bank vole challenges; second passage 2 tg lines
- Assays repeated in partner labs (PMCA, PET-BLOT, IHC, RT-QuiC, IHC)
- Post mortems of remaining animals in 2019 (in absence of clinical disease)

• Precautionary approach applies!
Spread & Distribution of C-type BSE  
(Ch. Hoffmann et al, 2011)

- 1) Peyer’s patches
- 2) Sympathetic Ganglion Chain
- 3) Obex
- 4) Vagal nerve
- 5) Spinal cord
Acknowledgments:

- **CFIA TSE Laboratory:**
  - Drs. S. Czub & R. Katoch: pathologists
  - K. Colwell, Y. Fang, T. Pickles, K. Santiago Mateo: histology group

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- Drs. J. Langenberg & M. Samuel (Wisconsin)
- Dr. T. Leighton (Canadian Cooperative Wildlife Health Center/SK & PrioNet Tissue Bank)
- Dr. J. Richt (Kansas State University)
Epidemiology: no evidence?
in vitro assays: no/(yes) (PMCA, RT-QuIC)
tg mouse models: no (1 exception?)
non-human primates: no/yes

3 pubs RML say no in macaques
I am sure they are right

Chronic wasting disease Agents in Nonhuman Primates

CZUBS/UCVM/CFIA
Prions – Past, Present, Policy and What May Lie Ahead
Faculty Disclosures

The following faculty have no relevant financial relationships to disclose:

– Whitney Steele PhD, MPH
– Stefanie Czub DVM, PhD

The following faculty have a relevant financial relationship:

– Robert Will
  Ferring Pharma:
  Consultant
Learning Objectives

• Differentiate between the TSEs discussed
• Trace the evolution of the vCJD issue from recognition to blood safety response
• Contrast the policy implications related to vCJD and CJD deferrals based on the known research
• Identify the ways in which the prion disease CWD in deer is a relevant public health threat
• Hypothesize about the future threat TSEs might be to the blood supply
4 cases of apparent vCJD transfusion transmission
  - Risk mitigation strategies in place
0 recorded cases of sCJD transfusion transmission
Studies suggest transfusion transmission of sCJD, if possible, is very rare
Concern over sCJD transfusion transmission and subsequent vCJD outbreaks
Continued surveillance is necessary
What are the current implications of CJD?

- Variant CJD has been shown to be transfusion transmissible
  - Four cases of transfusion transmission

- FDA Final Rule:
  “[…] CJD and vCJD are relevant transfusion- transmitted infections because of the risks they present. Screening tests are not yet available for CJD and vCJD. It is current practice for establishments to perform screening by means of a medical history interview […] Consistent with these current practices, we have included CJD and vCJD in the definition of a relevant transfusion- transmitted infection […].”
Donor History Questionnaire

- From 1980 through 1996,
  - Did you spend time that adds up to 3 months or more in the United Kingdom?
  - Were you a member of the U.S. military, a civilian military employee, or a dependent of a member of the U.S. military?
- From 1980 to the present, did you
  - Spend time that adds up to 5 years or more in Europe?
  - Receive a blood transfusion in the United Kingdom or France?
- Have you ever received a dura mater (or brain covering) graft or xenotransplantation product?
- **Bovine Insulin / Human Pituitary Derived Growth Hormone**
- Have any of your relatives had Creutzfeldt-Jakob disease?
Results from Risk Assessment Model with 3 Leukoreduction (LR) Options

Current LR in the U.S. estimated between 71.3% and 95% of units

<table>
<thead>
<tr>
<th>Policy Option*</th>
<th>Donor deferral only</th>
<th>Donor deferral plus 71.3% RBC LR</th>
<th>Donor deferral plus 95% RBC LR</th>
<th>Donor deferral plus universal RBC LR</th>
<th>Annual number of donors potentially reentered</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Option 1</strong></td>
<td>79.0%</td>
<td>87.1%</td>
<td>89.8%</td>
<td>90.4%</td>
<td>-</td>
</tr>
<tr>
<td><strong>Option 2</strong></td>
<td>78.0%</td>
<td>86.5%</td>
<td>89.3%</td>
<td>89.9%</td>
<td>~100,000</td>
</tr>
</tbody>
</table>


FDA risk assessment model predicted that proposed modifications to the current deferral policy would maintain the current level of risk while allowing a modest number of donors currently deferred to be reentered and substantially simplify donor questionnaire.
FDA: Draft Guidance for Industry

- Amendment to older guidance “Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease and Variant Creutzfeldt-Jakob Disease by Blood and Blood Products”

- Issued for public comment 22 Dec. 2017
- Comments closed 90 days later
- FDA has reviewed comments and is preparing responses
<table>
<thead>
<tr>
<th>Current deferrals</th>
<th>Proposed deferrals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donors who spent cumulatively $\geq 3$ months in the U.K. from 1980 to 1996</td>
<td>Unchanged</td>
</tr>
<tr>
<td>Donors who spent cumulatively $\geq 5$ years in France or other countries in Europe from 1980 to present</td>
<td>Donors who spent cumulatively $\geq 5$ years in France or Ireland from 1980 to 2001</td>
</tr>
<tr>
<td>Donors with a history of blood transfusion in the U.K. and France from 1980 to the present</td>
<td>Donors with a history of blood transfusion in the U.K., France, or Ireland from 1980 to the present</td>
</tr>
<tr>
<td>Donors based on time and duration of exposure at military bases in Europe during periods in which commissaries and mess halls were supplied with beef products from the U.K.</td>
<td>Unchanged</td>
</tr>
</tbody>
</table>
Main points from Draft Guidance

- Individuals who resided in any European countries (other than U.K., Ireland and France) for any period of time will no longer be deferred from donating blood in the U.S.

- The risk period for donating blood if the donor resided in Ireland or France is no longer open-ended (1980 to present) but it ends in 2001 (1980-2001)
Donor History Questionnaire

- From 1980 through 1996,
  - Did you spend time that adds up to 3 months or more in the United Kingdom?
  - Were you a member of the U.S. military, a civilian military employee, or a dependent of a member of the U.S. military?

- From 1980 to the present, did you
  - Spend time that adds up to 5 years or more in Europe?
  - Receive a blood transfusion in the United Kingdom or France?

- Have you ever received a dura mater (or brain covering) graft or xenotransplantation product?
  - *Bovine Insulin / Human Pituitary Derived Growth Hormone*

- Have any of your relatives had Creutzfeldt-Jakob disease?
Next steps?

- FDA will address questions and comments from the public and clarify recommendations

- Additional changes to guidance considered?

- Release of the final guidance expected in 2018?
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Prions – Past, Present, Policy and What May Lie Ahead
Learning Objectives

- Differentiate between the transmissible spongiform encephalopathies (TSEs) discussed
- Trace the evolution of the vCJD issue from recognition to blood safety response
- Contrast the policy implications related to vCJD to CJD deferrals based on the known research
- Identify the ways in which the prion disease chronic wasting disease (CWD) in deer is a relevant public health threat
- Hypothesize about the future threat TSEs might be to the blood supply
Transmissible Spongiform Encephalopathies (TSEs) / Prion Diseases

- Feline Spongiform Encephalopathy
- Chronic Wasting Disease
- Bovine Spongiform Encephalopathy (mad cow disease)
- Kuru (Human)
- Scrapie
- Variant Creutzfeldt Jakob Disease (Human)
- Sporadic Creutzfeldt Jakob Disease (Human)

*Slide courtesy of L. Gregori*
Prions: What is a prion disease?

- These neurological diseases affect mammals and are uniformly fatal with no curative treatments available.
- The agent of disease (the prion) can be transmitted.
- What is a prion specifically?
  - Protein and infectious
  - -ion (infectious, e.g. virion)
  - No nucleic acid (e.g. DNA, RNA)
  - Non-degradable by typical sterilization
Creutzfeldt-Jakob disease (CJD), other than variant CJD (vCJD)

- 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

- Rapidly progressive - median duration of 4-5 months

- Cases are:
  - > 85% Sporadic
  - 5-15% Genetic/Familial
  - Less than 1% iatrogenic/acquired
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 – sporadic 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
Creutzfeldt–Jakob disease and blood transfusion: updated results of the UK Transfusion Medicine Epidemiology Review Study


1 National CJD Research & Surveillance Unit, Western General Hospital, Edinburgh, UK
2 NHS Blood and Transplant, Cambridge Centre, Cambridge, UK
3 NHS Blood and Transplant, Colindale Centre, Cambridge, UK

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 – CJD 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 – CJD

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

AABB Boston, 16th October 2018

RG Will
University of Edinburgh, UK
A new variant of Creutzfeldt-Jakob disease in the UK


Summary
Background Epidemiological surveillance of Creutzfeldt-Jakob disease (CJD) was reinstated in the UK in 1990 to identify any changes in the occurrence of this disease after the epidemic of bovine spongiform encephalopathy (BSE) in cattle.

Methods Case ascertainment of CJD was mostly by direct referral from neurologists and neuropathologists. Death certificates on which CJD was mentioned were also obtained. Clinical details were obtained for all referred cases, and information on potential risk factors for CJD was obtained by a standard questionnaire administered to patients' relatives. Neuropathological examination was carried out on approximately 70% of suspect cases. Epidemiological studies of CJD using similar methodology to the UK study have been carried out in France, Germany, Italy, and the Netherlands between 1993 and 1995.

Introduction
Because of the epidemic of bovine spongiform encephalopathy (BSE) in cattle, surveillance of Creutzfeldt-Jakob disease (CJD) in the UK was reinstated in May, 1990. The purpose of the surveillance is to identify changes in the pattern of CJD which might indicate an association with BSE. We report ten cases of CJD in the UK with clinical onset of disease in 1994 and 1995. These cases all have neuropathological changes which, to our knowledge, have not been previously reported. They are also unusual in that they occurred in relatively young people, and the clinical course was not typical of cases of sporadic CJD in the UK.

Methods
Since May, 1990, cases of CJD have been identified to the CJD Surveillance Unit, usually by direct referral from professional groups, which include neurologists and neuropathologists. All
MRI scan and brain immunocytochemistry in variant CJD
Transmission of TSEs to mice

Mean incubation period ± SEM (days)
vCJD CASES BY YEAR AND COUNTRY
1994-2017 (n=230)
Furthermore, the threshold dose estimate of approximately $12 \text{ bID}_{50}$ with an equivalent weight of $1.2\text{g}$ of a BSE infected bovine brain also appears reasonable, which may alternatively be interpreted as the species barrier between bovine and human.
Codon 129 genotype in vCJD

- 160/161 tested cases in UK: MM
- 1/161 tested cases in UK: MV
- 52/52 cases outside UK: MM
- Normal UK population: MM 44% MV 45% VV 11%
Median and posterior distributions of projected time series

Cases:
A: Total number
B: Transfusion associated
C: Unidentifiable transfusion associated

Genotypes:
D: MM
E: MV
F: VV
Probable pattern of tissue infectivity in variant CJD, based on scrapie models
Tissue Infectivity in CJD

**sCJD centrifugal spread**

- HIGH
  - Brain
  - Spinal cord
  - Cranial nerves & ganglia
  - Posterior eye
  - Pituitary gland

- MEDIUM
  - Spinal ganglia
  - Olfactory epithelium

**vCJD peripheral pathogenesis**

- HIGH
  - Brain
  - Spinal cord
  - Cranial nerves & ganglia
  - Posterior eye
  - Pituitary gland

- MEDIUM
  - Spinal ganglia
  - Olfactory epithelium
  - Tonsil
  - Appendix
  - Spleen
  - Thymus
  - Adrenal gland
  - Lymph nodes and gut associated lymphoid tissue
Transfusion Medicine Epidemiology Review

- NHS Blood and Transplant
- Scottish National Blood Transfusion Service
- Welsh Blood Service
- Northern Ireland Blood Transfusion Service
- National CJD Research & Surveillance Unit
## vCJD - Blood Donors

<table>
<thead>
<tr>
<th>Year Death</th>
<th>Total vCJD cases</th>
<th>Total eligible to donate</th>
<th>Number reported to be blood donors</th>
<th>Number registered with UK Blood Services¹</th>
<th>Number with donations²</th>
</tr>
</thead>
<tbody>
<tr>
<td>1995-1999</td>
<td>56</td>
<td>54</td>
<td>11</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>2000-2004</td>
<td>92</td>
<td>84</td>
<td>17</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>2005-2009</td>
<td>20</td>
<td>20</td>
<td>3</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>2010-2014</td>
<td>9</td>
<td>9</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2015-2018</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>178</strong></td>
<td><strong>168</strong></td>
<td><strong>32</strong></td>
<td><strong>24</strong></td>
<td><strong>18</strong></td>
</tr>
</tbody>
</table>

¹Donor 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.

²Donors found on UKBTS system for whom components were actually issued (eg some donors were registered but did not donate.)
VARIANT CJD BLOOD DONORS
BY YEAR OF ONSET

*one case from Ireland with onset in 2004 was a blood donor while resident in the UK – recipients not identified
Possible transmission of variant Creutzfeldt-Jakob disease by blood transfusion

C A Llewelyn, P E Hewitt, R S G Knight, K Amar, S Cousens, J Mackenzie, R G Will

Summary

Background Variant Creutzfeldt-Jakob disease (vCJD) is a novel human prion disease caused by infection with the agent of bovine spongiform encephalopathy (BSE). Epidemiological evidence does not suggest that sporadic CJD is transmitted from person to person via blood transfusion, but this evidence may not apply to vCJD. We aimed to identify whether vCJD is transmissible through blood transfusion.

Introduction

Human prion diseases include sporadic Creutzfeldt-Jakob disease (CJD), which is of unknown cause; hereditary forms associated with mutations of the prion protein gene; variant CJD (vCJD), which has been causally linked to the bovine spongiform encephalopathy (BSE) agent; and iatrogenic cases transmitted via human pituitary hormones, human dura mater grafts, corneal grafts, and neurosurgical devices. All instances of iatrogenic transmission of CJD to date have been due to cross-
Interval from recipient transfusion to disease onset in donor (top bar) and interval from transfusion to disease onset in recipient (bottom bar)
SURVIVAL PERIOD:
TRANSFUSION TO DEATH
(n=53)
FOR RECIPIENTS OF vCJD
COMPONENTS ACCORDING TO
INTERVAL BETWEEN DONATION AND
ONSET OF CLINICAL SYMPTOMS IN
THE DONOR
SURVIVAL OF LIVE RECIPIENTS (n=14) OF COMPONENTS FROM vCJD DONORS ACCORDING TO INTERVAL BETWEEN DONATION AND ONSET OF CLINICAL SYMPTOMS IN DONOR (AS AT SEPTEMBER 2018)
<table>
<thead>
<tr>
<th>Age</th>
<th>Codon 129</th>
<th>Component</th>
<th>Time since transfusion to 30 September 2018</th>
<th>Donation to onset in donor</th>
</tr>
</thead>
<tbody>
<tr>
<td>80</td>
<td>MV</td>
<td>RBC</td>
<td>25+ years</td>
<td>3.85 years</td>
</tr>
<tr>
<td>62</td>
<td>MV</td>
<td>RBC</td>
<td>23+ years</td>
<td>1.25 years</td>
</tr>
<tr>
<td>46</td>
<td>MM</td>
<td>Cyro-depleted plasma</td>
<td>23+ years</td>
<td>7 months</td>
</tr>
<tr>
<td>87</td>
<td>MV</td>
<td>RBC</td>
<td>22+ years</td>
<td>5.83 years</td>
</tr>
<tr>
<td>55</td>
<td>MV</td>
<td>RBC</td>
<td>19+ years</td>
<td>5 months¹</td>
</tr>
<tr>
<td>77</td>
<td>MM</td>
<td>RBC (LD)</td>
<td>18+ years</td>
<td>3.65 years</td>
</tr>
<tr>
<td>45</td>
<td>MV</td>
<td>RBC (LD)</td>
<td>17+ years</td>
<td>9 months</td>
</tr>
<tr>
<td>70</td>
<td>MM</td>
<td>RBC (LD)</td>
<td>16+ years</td>
<td>1.6 years</td>
</tr>
<tr>
<td>51</td>
<td>MM</td>
<td>RBC (LD)</td>
<td>15+ years</td>
<td>7 months</td>
</tr>
</tbody>
</table>

¹same donor as 2 of the transfusion transmission cases (tonsil biopsy negative – June 2008)
RECIPENTS OF LABILE BLOOD COMPONENTS DONATED BY vCJD CASES (n=67)

DEAD, n=53  
(interval from transfusion to death)

ALIVE, n=14  
(interval from transfusion to Sep 2018)

- Dead – untested
- Dead – tested positive for PrP deposition at PM
- Dead – tested negative for PrP deposition at PM
- Alive - untested
No Major Change in vCJD Agent Strain after Secondary Transmission via Blood Transfusion

Matthew T. Bishop, Diane L. Ritchie, Robert G. Will, James W. Ironside, Mark W. Head, Val Thomson, Moira Bruce, Jean C. Manson

Citation: 2008 PLoS ONE 3(8): e2878. doi:10.1371/journal.pone.0002878
Detection of prions in blood from patients with variant Creutzfeldt-Jakob disease

Luis Concha-Marambio,1,2 Sandra Pritzkow,1 Fabio Moda,1,3 Fabrizio Tagliavini,3 James W. Ironside,6 Paul E. Schulz,1 Claudio Soto1,2*

Table 1. Blood samples and PrPSc detection by PMCA.

<table>
<thead>
<tr>
<th>Clinical diagnosis</th>
<th>Total patients</th>
<th>PrPSc detected in blood</th>
</tr>
</thead>
<tbody>
<tr>
<td>vCJD</td>
<td>14</td>
<td>14/14</td>
</tr>
<tr>
<td>sCJD*</td>
<td>16</td>
<td>0/16</td>
</tr>
<tr>
<td>Other neurodegenerative diseases†</td>
<td>62</td>
<td>0/62</td>
</tr>
<tr>
<td>Other neurological diseases‡</td>
<td>26</td>
<td>0/26</td>
</tr>
<tr>
<td>Healthy controls</td>
<td>49</td>
<td>0/49</td>
</tr>
</tbody>
</table>

*Of these 16 sCJD samples analyzed, 6 were whole blood, 5 were plasma, and 5 were white blood cells from distinct sCJD patients. †Include samples from patients with Alzheimer's disease, Parkinson's disease, Lewy body dementia, and frontotemporal dementia. ‡Include samples from patients with vascular dementia, seizures, epilepsy, psychiatric diseases, traumatic brain injury, mild cognitive impairment, demyelinating disease, and encephalitis.
Detection of prions in the plasma of presymptomatic and symptomatic patients with variant Creutzfeldt-Jakob disease

Daisy Bougard,1* Jean-Philippe Brandel,2,3,4 Maxime Bélondrade,1 Vincent Béringue,5 Christiane Segarra,1 Hervé Fleury,6 Jean-Louis Laplanche,6,7 Charly Mayran,1 Simon Nicot,1 Alison Green,8 Arlette Welaratne,9 David Narbey,9 Chantal Fournier-Wirth,1 Richard Knight,8 Robert Will,8 Pierre Tiberghien,9,10 Stéphane Haïk,2,3,4 Joliette Coste1,9,8

Prevalent abnormal prion protein in human appendixes after bovine spongiform encephalopathy epizootic: large scale survey

- 16/32,441 samples positive
- 493 per million (95%CI: 282-801)
- 1 in 2,000
- Codon 129: MM 8, MV 4, VV 4
## Summary of issues by UK Blood Services 1999-2009 (SHOT, 2010)

<table>
<thead>
<tr>
<th>Year</th>
<th>Red Blood Cells</th>
<th>Platelets</th>
<th>FFP</th>
<th>Cryoprecipitate</th>
<th>Totals</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999–2000</td>
<td>2,737,572</td>
<td>249,622</td>
<td>365,547</td>
<td>94,114</td>
<td>3,446,855</td>
</tr>
<tr>
<td>2001–2002</td>
<td>2,679,925</td>
<td>251,451</td>
<td>385,236</td>
<td>88,253</td>
<td>3,404,865</td>
</tr>
<tr>
<td>2002–2003</td>
<td>2,678,098</td>
<td>251,741</td>
<td>377,381</td>
<td>92,768</td>
<td>3,399,988</td>
</tr>
<tr>
<td>2004–2005</td>
<td>2,428,934</td>
<td>258,528</td>
<td>313,019</td>
<td>102,719</td>
<td>3,103,200</td>
</tr>
<tr>
<td>2005–2006</td>
<td>2,316,152</td>
<td>259,654</td>
<td>320,852</td>
<td>106,139</td>
<td>3,002,797</td>
</tr>
<tr>
<td>2006–2007</td>
<td>2,235,638</td>
<td>255,474</td>
<td>306,444</td>
<td>116,672</td>
<td>2,914,228</td>
</tr>
<tr>
<td>2008–2009</td>
<td>2,209,153</td>
<td>266,312</td>
<td>306,740</td>
<td>121,555</td>
<td>2,903,760</td>
</tr>
</tbody>
</table>
Current studies

Further Survey of Archived Appendix Specimens
Public Health England & partners

3 year study

• Samples prior to the BSE outbreak (pre-1980)
• Samples after further measures put in place to protect the human food chain (post-1996)
The Appendix-III survey examined by immunohistochemistry (IHC) appendices removed at operation and collected from 44 hospitals throughout England. Abnormal prion accumulation was detected within the follicular dendritic cells of seven appendices out of 29,516 suitable samples examined.
Summary results of the third national survey of abnormal prion prevalence in archived appendix specimens

Appendix 3  Appendix 2  Appendix 3


16+  2+  16+  5+
The other five positive samples were found in the 14,824 appendices from subjects born in 1996 or later and removed at operation in 2000 through 2014: all five were in the sub-group of 10,074 born in 1996 through 2000.

[i.e. aged 4-18 years]
UK CASES OF vCJD BY YEAR OF BIRTH
AND NON-UK CASES BORN AFTER 1989

YEAR OF BIRTH

NUMBER

UK MM

UK MV

non-UK MM

SBO ban UK
Staff at the NCJDRSU

- Jan Mackenzie
- Terri Lindsay
- James Ironside
- Richard Knight
- Suvankar Pal
- Alison Green
- Anna Molesworth
- Mark Head
- Matthew Bishop
- Graeme Mackenzie
- Gavin Langlands

Transfusion Medicine Epidemiology Review

- Patricia Hewitt
- Charlotte Llewelyn
- National Blood Services
- Health and Social Care Information Centre

Clinicians throughout the UK

Patients and their families

The Roslin Institute

- Jean Manson
- Abigail Diack

Public Health England

- Katy Sinka