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

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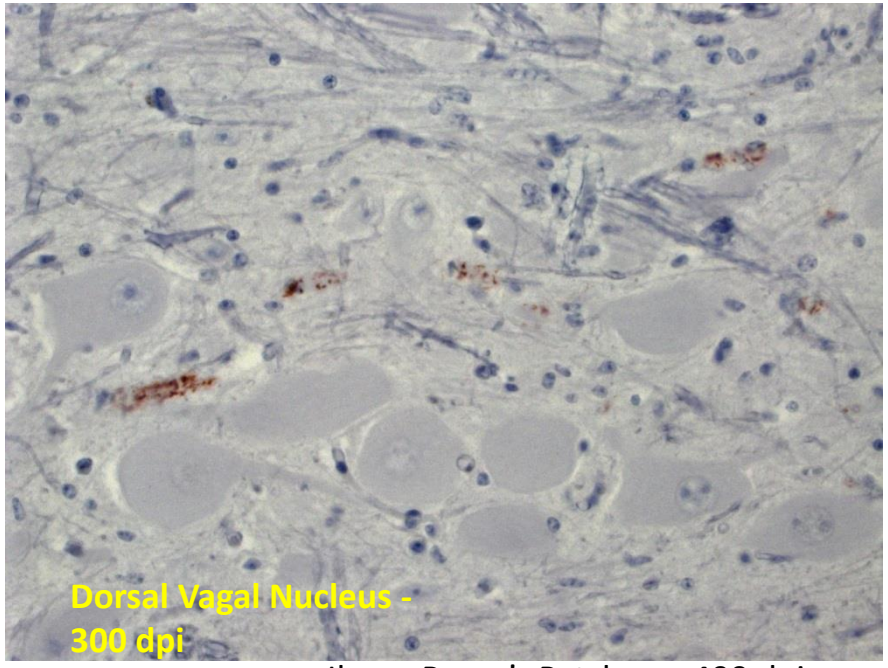
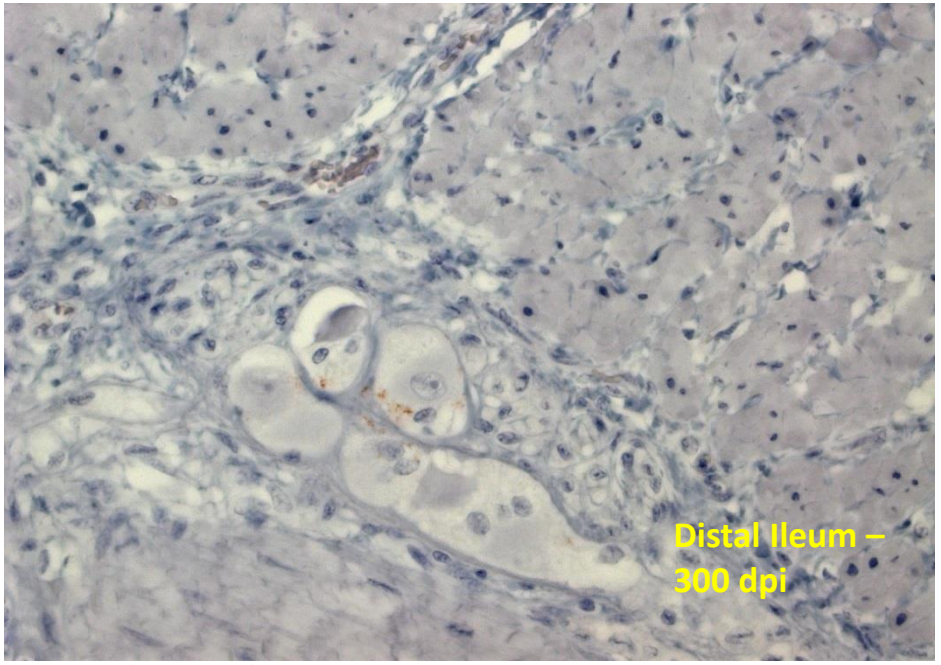
Chronic Wasting Disease (CWD)

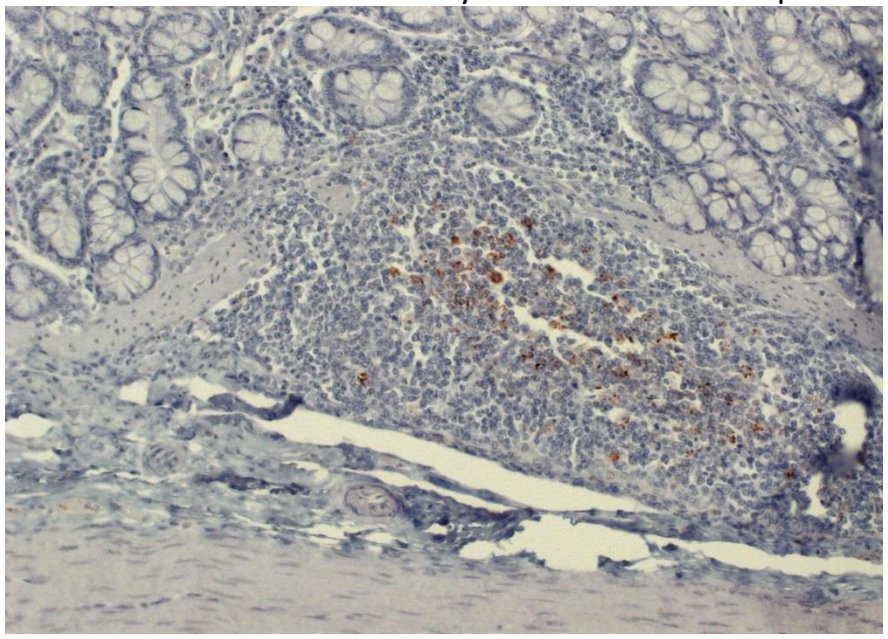
- Prion disease of cervids (deer – WTD, BTD, MD, RD, RD; elk, & moose). Farmed & free-ranging animals
- CWD prions widely distributed in infected animal (including blood, muscles)
- CWD prions shedding in saliva, feces & urine
- Direct spread by animal-to-animal contact; indirect by contamination of 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?*

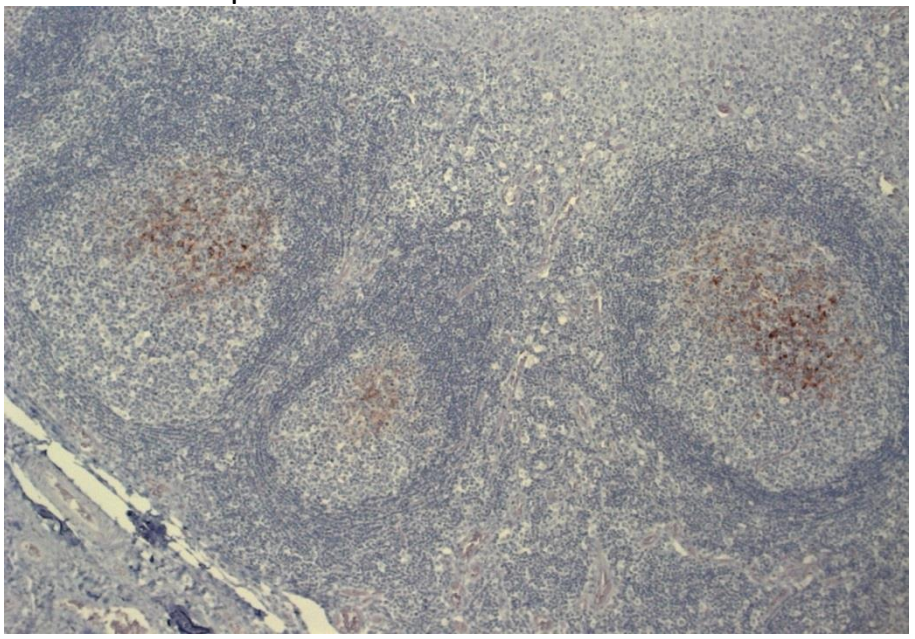




Ileum Peyer's Patches - 400 dpi



Tonsil – 400 dpi



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

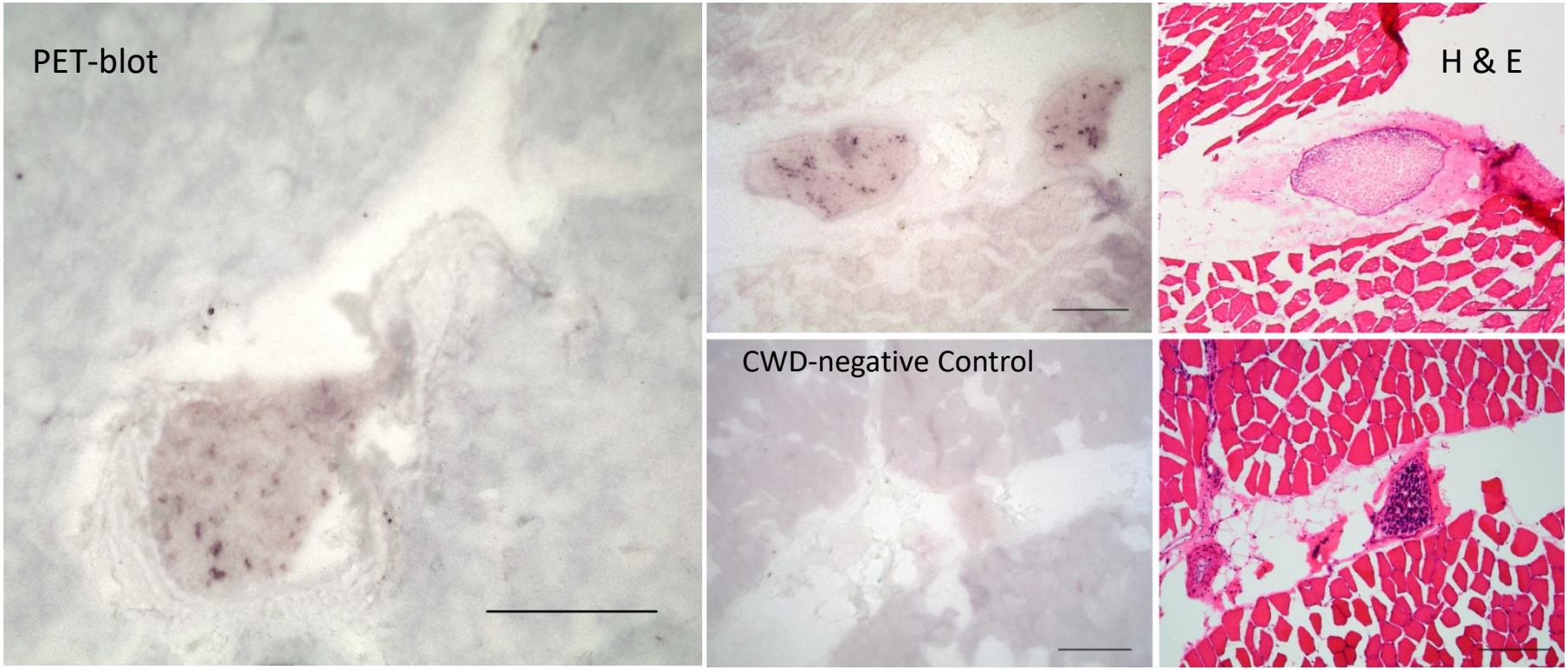
  WTD (experimental) challenged with elk, MD & WTD

  Elk (experimental): CWD2; 1.0 $x10^{7.0 - 7.2}$ i.c. ID50/g brain tg mice

  MD (hunted)

  Blood from Non-clinical donor macaques challenged with CWD MD, elk & WTD; 1.0 x 10^{6} to 2.0 x 10^{9} i.c ID50/g brain tg mice

PrP^{CWD} presence in WTD skeletal muscles (Pet-Blot)



mAB: P4, bar = 250 µm

Daus ML et all, PLoS One 2011

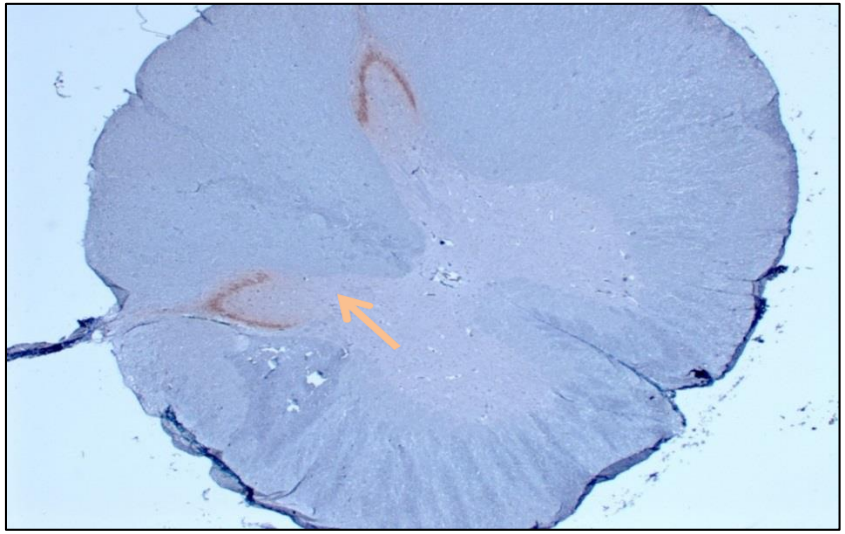
CWD ➡ ***Macaques ?***

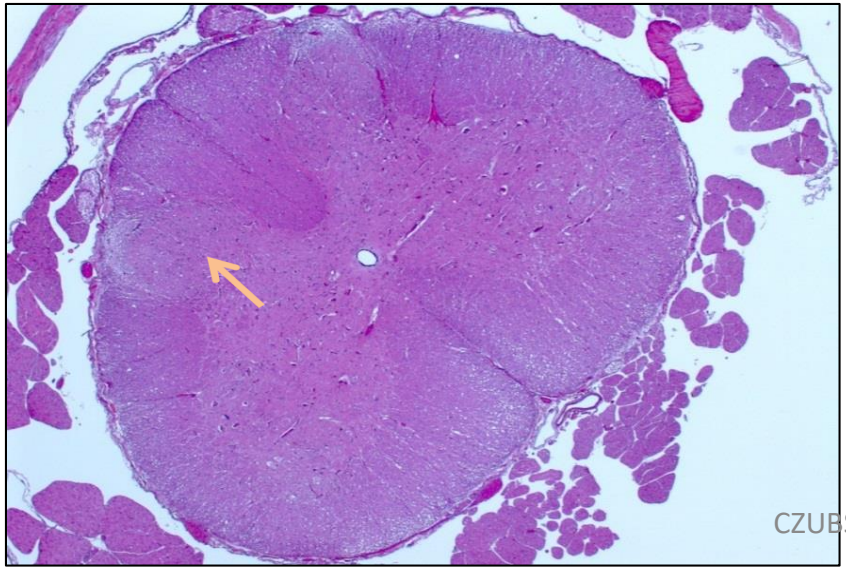
Animal data

Animal #	AU153	AU389	AU519	AU520	AU408	AU469	AU467	AU501	AU385	AU316
Years p.c.	2.8	4.5	5.2	6.3	6.5	6.9	5.8	5.4	6.2	7.4
Route	i.c. sw	i.c. sw	i.c. sw	i.c. sw	i.c.	i.c.	oral	oral	oral	oral
Inocul.	WTD	Elk	WTD	ELK	WTD	WTD	WTD brain	WTD,MD muscle	WTD, MD muscle	WTD,MD muscle
Clinical present.	-	anxiety ataxia tremor wasting	-	wasting	-	apathy wasting	wasting	anxiety ataxia tremor wasting	apathy ataxia tremor wasting	ileus
Clinpath	-	Glucose	-	Glucose	Glucose	Glucose	-	-	Glucose	-
	pm	Euthan. CWD ?	pm	Euthan.	Died (CSF)	Euthan. CWD?	Died (asphy)	Euthan. CWD	Euthan. CWD?	Euthan.

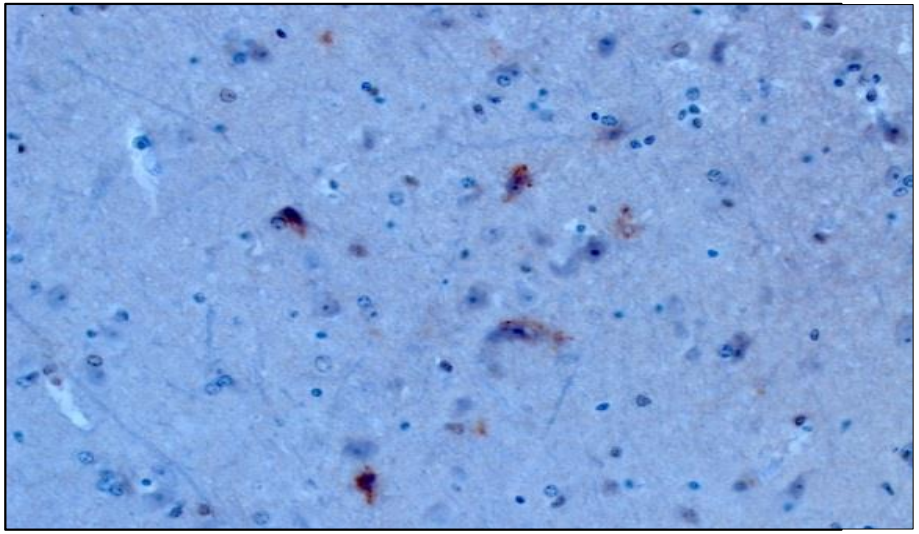
Histopath & PrP IHC

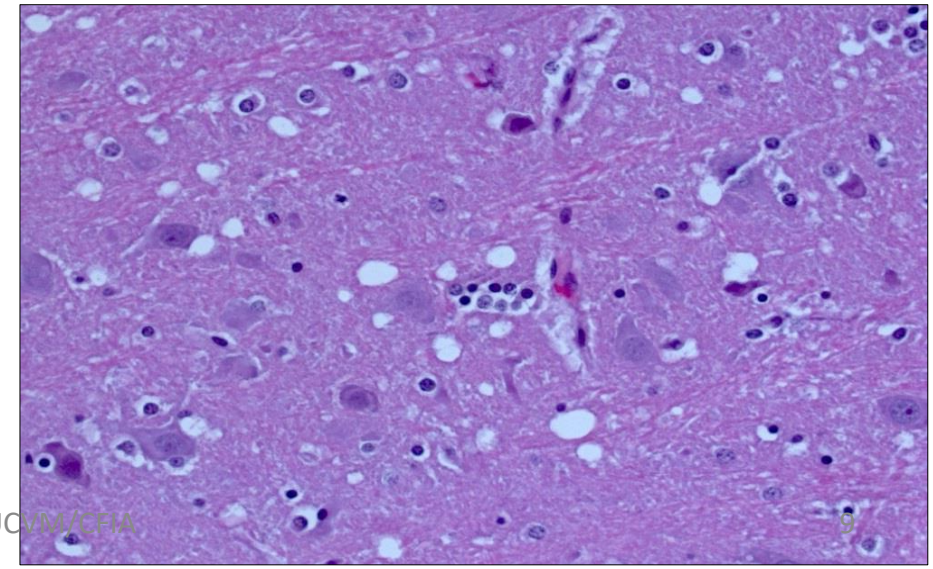
Spinal Cord



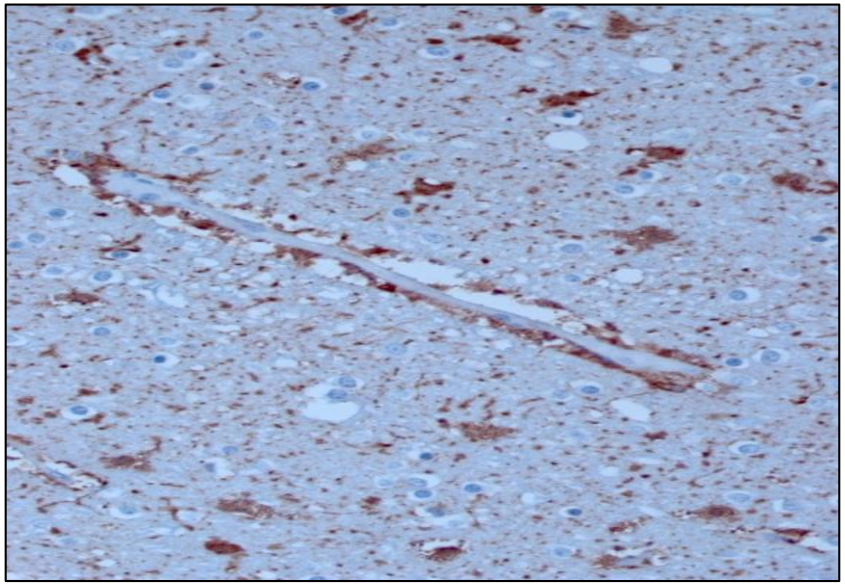


Midbrain



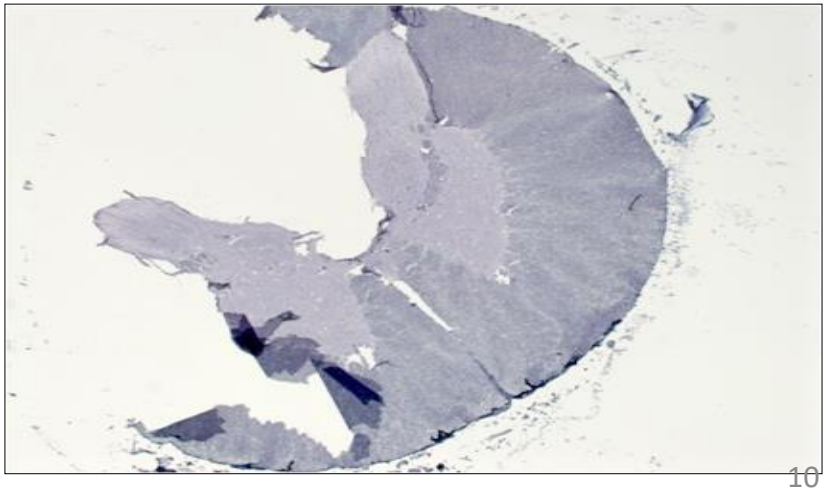


IHC cont'



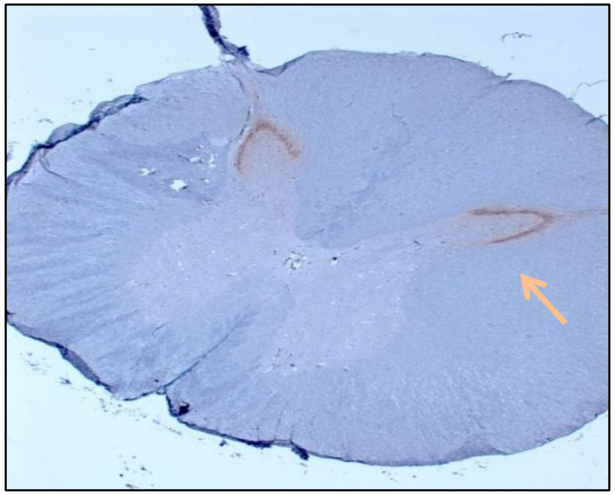
GFAP

Neg. cont, 6H4

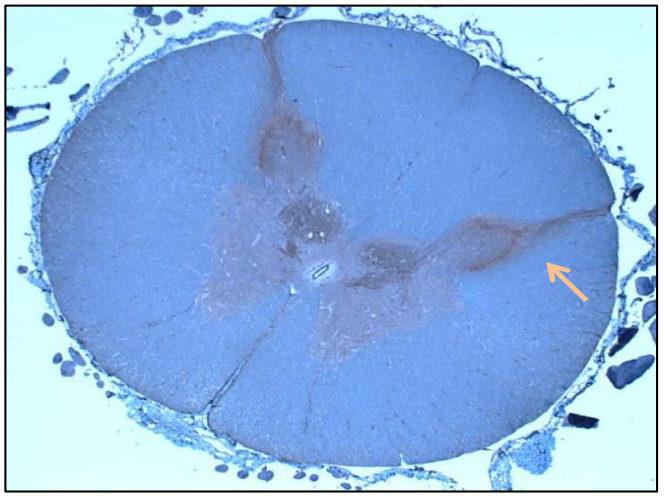


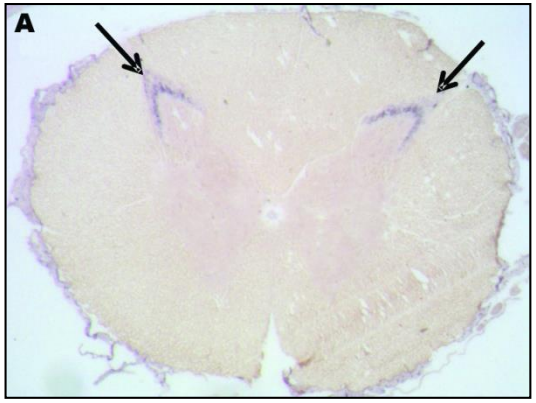
Spinal cord involvement: progression over time

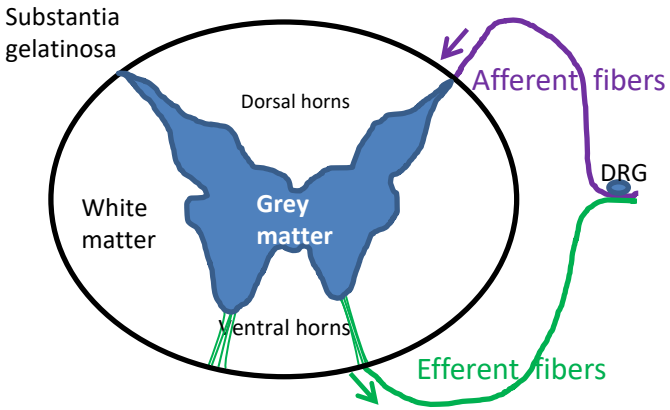
i.c./s.w., 4.5 years p.c.

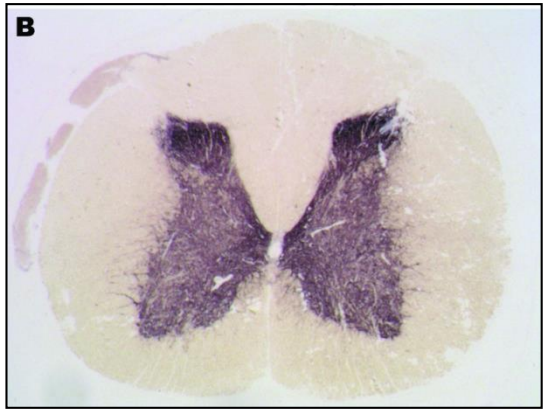


p.o. 7.4 years p.c.



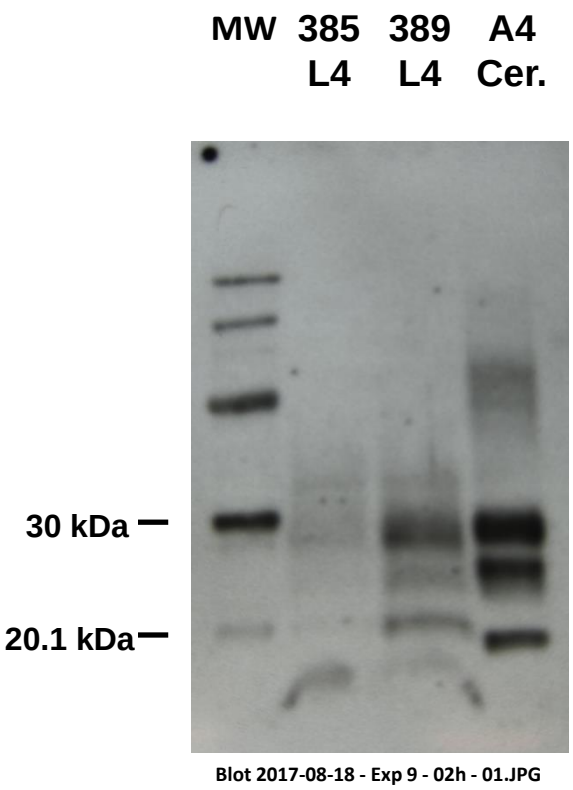






Holznagel E, Yutzy B, Schulz-Schaeffer et al. Emerg Infect Dis. 2013 May; 19(5): 712–720

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



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

Lanes*

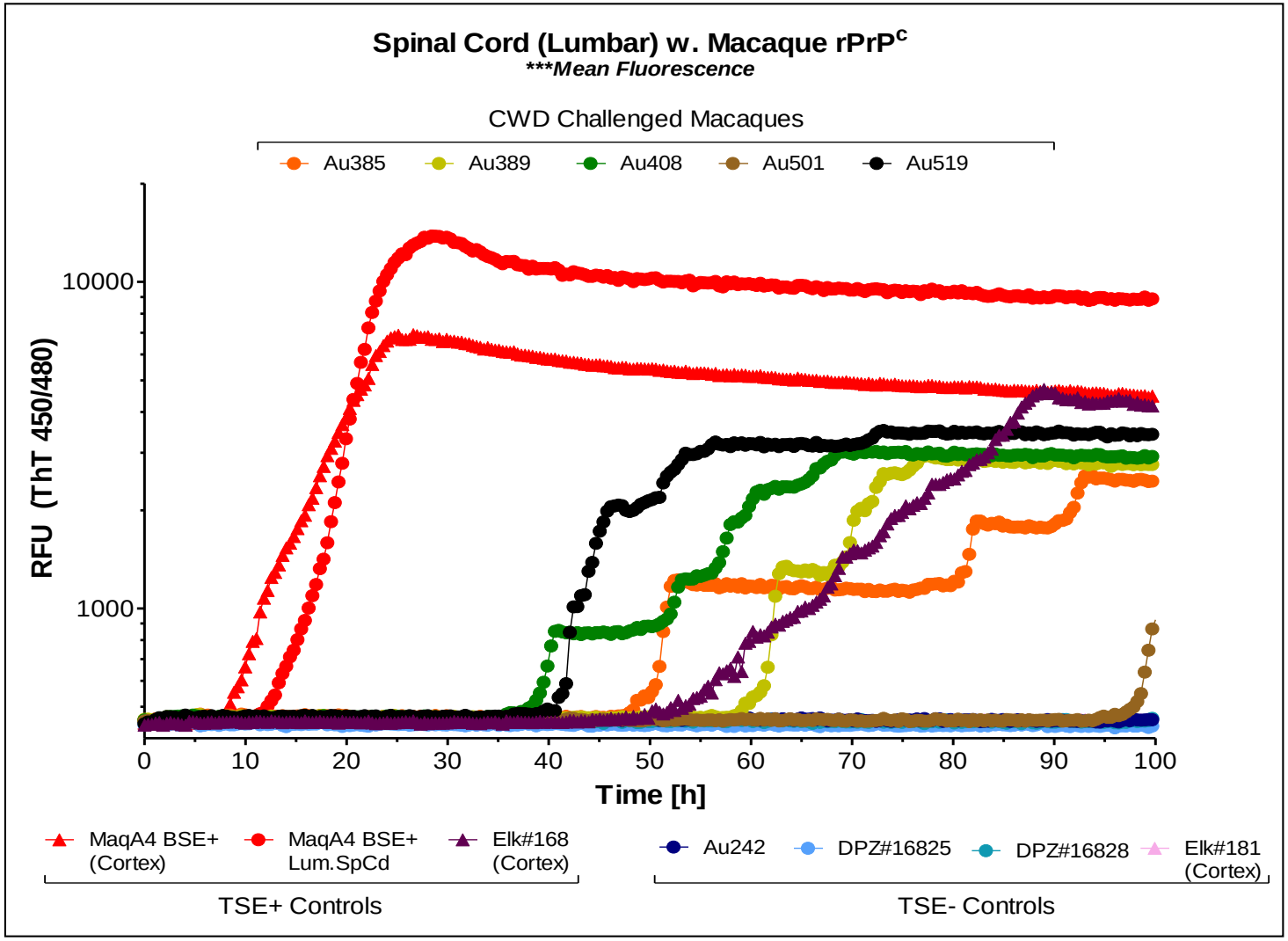
MW: Low Molecular Weight Marker

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]

(M. Beekes/RKI)

RT-QuIC: lumbar spinal cord

(fluorescence curve)



(John Gray/Czub lab)

CWD ⟹ ***Macaques !***

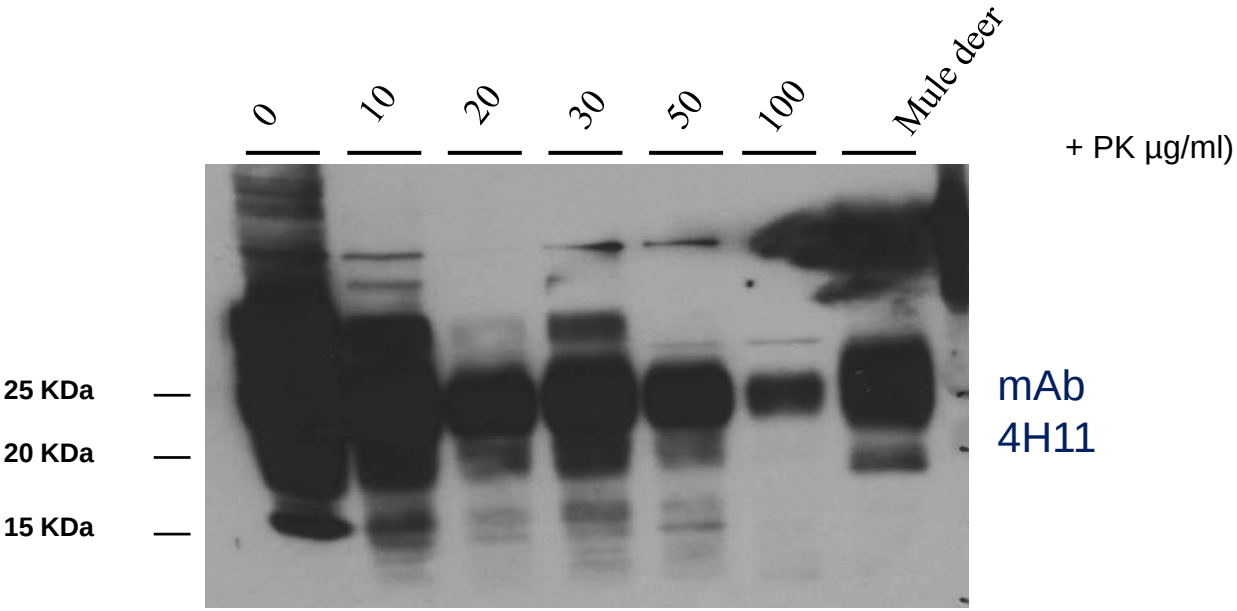
Histopathology, CWD prion deposition (IHC) & amyloid seeding

CWDmac ⟹ ***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

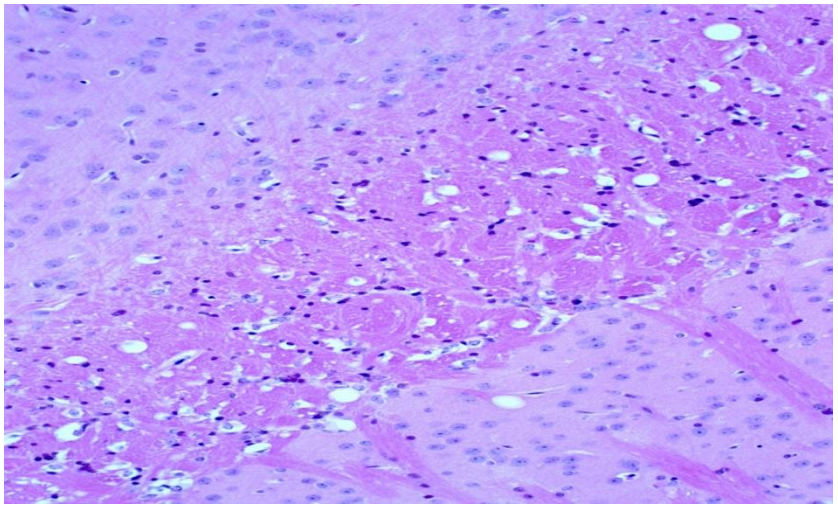


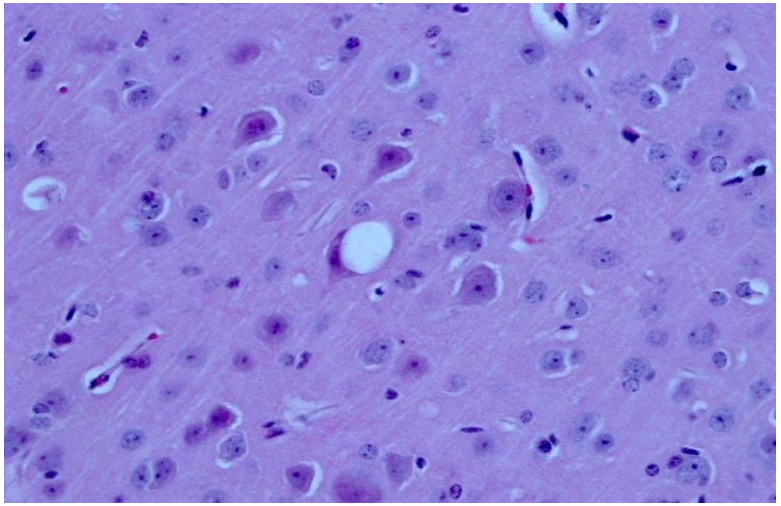
Exp. time 10 sec

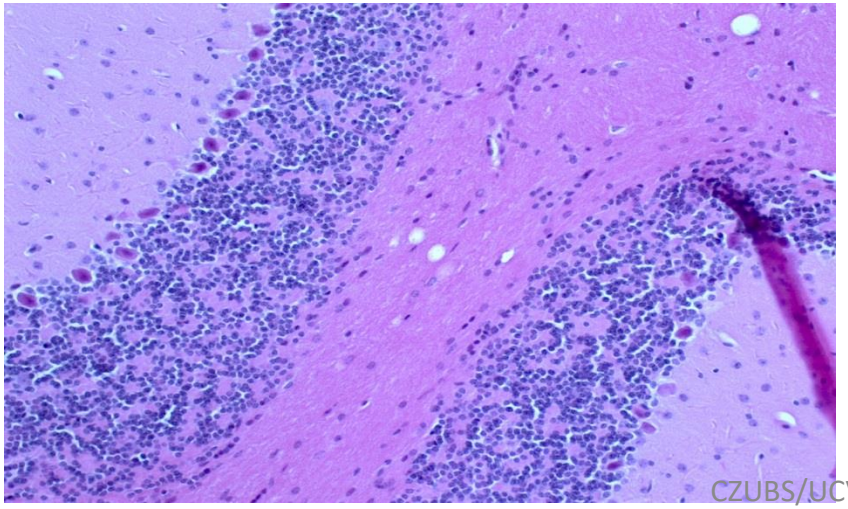
control: MD CWD in TgElk; 10% brain; 50 µg/ml PK

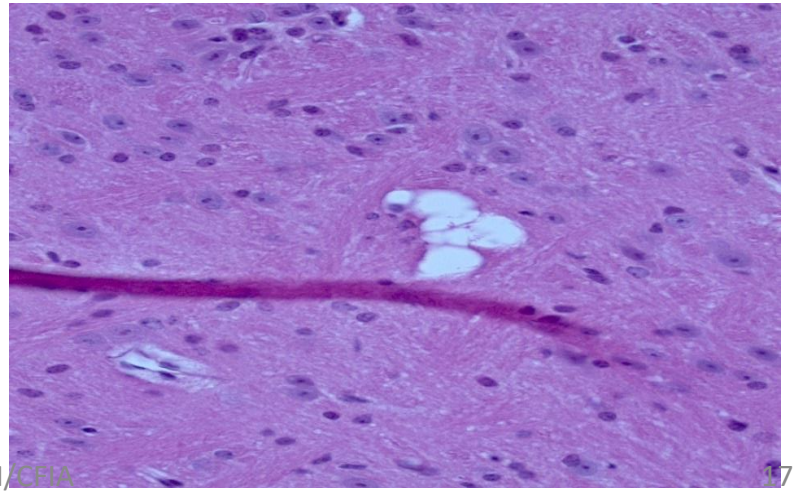
Histopathology tgElk

corpus callosum, parietal cortex, inner mol layer, cerebell. peduncle



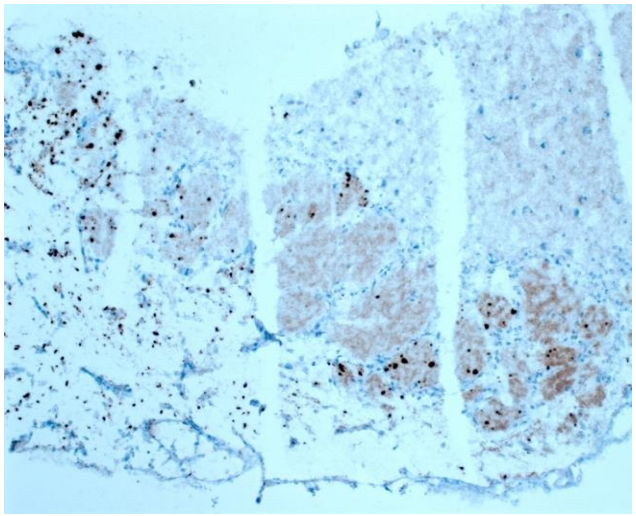




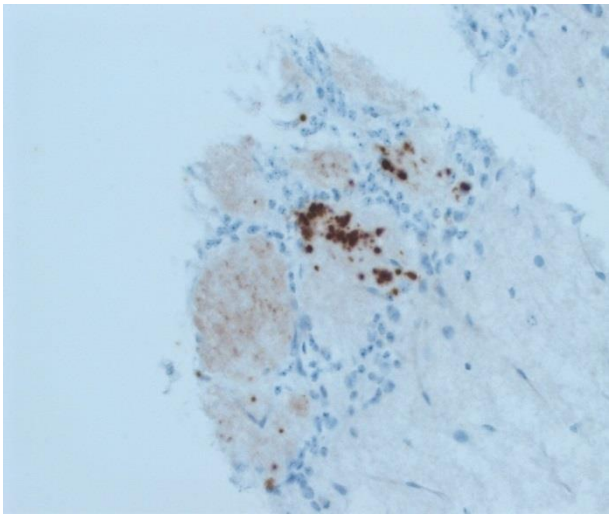


IHC TgElk - Olfactory Bulb

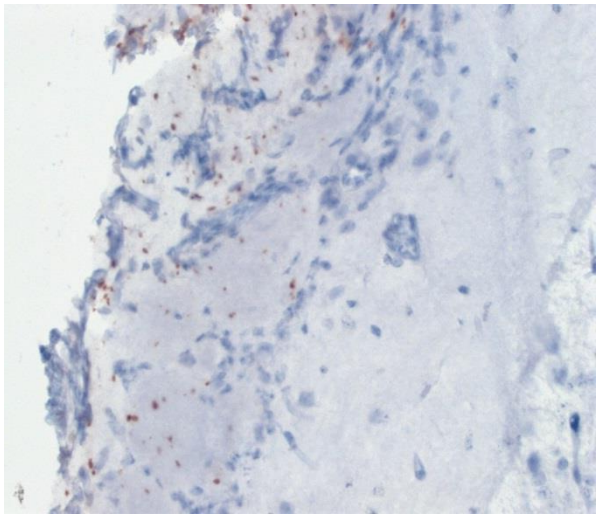
Animal #1, 12F10 (+PK), x20



Animal #2, 12F10, x40

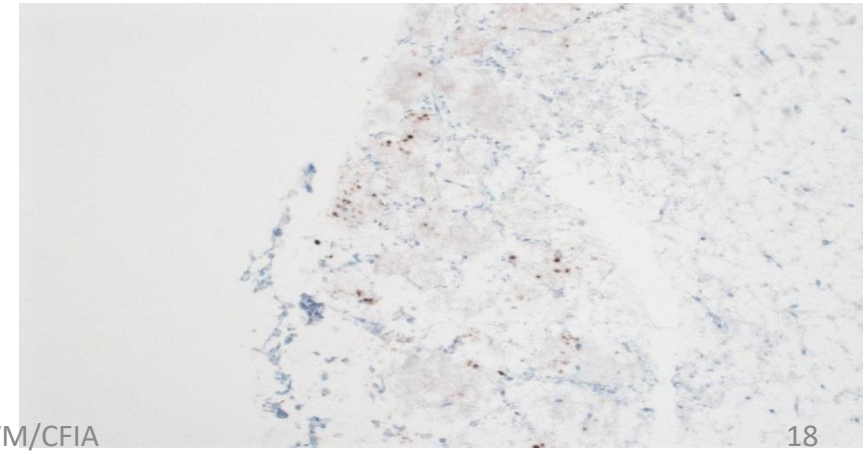


Animal #3, R145, x40



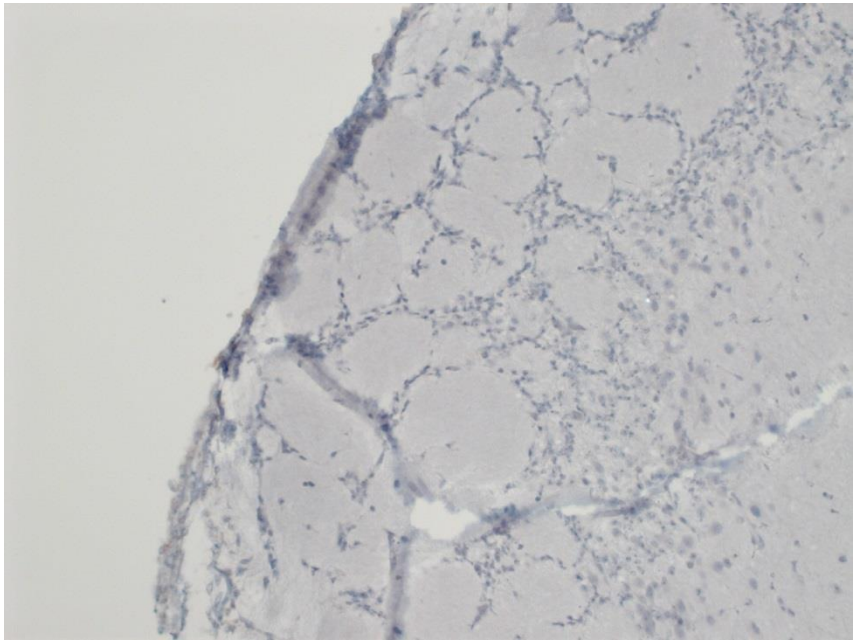
Animal #5, F99, x20

Animal#6, 12F10, x20

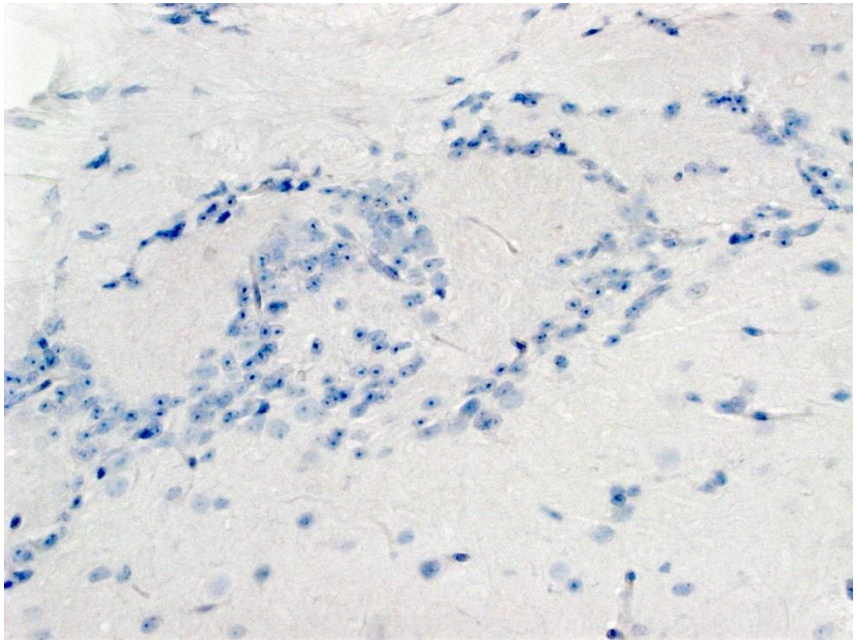


“Negative” IHC Controls

TgElk mouse #6, ob, 3F4, x200



Tg650 mouse A, F99, ob, x400



CWDmac ➡ ***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 :

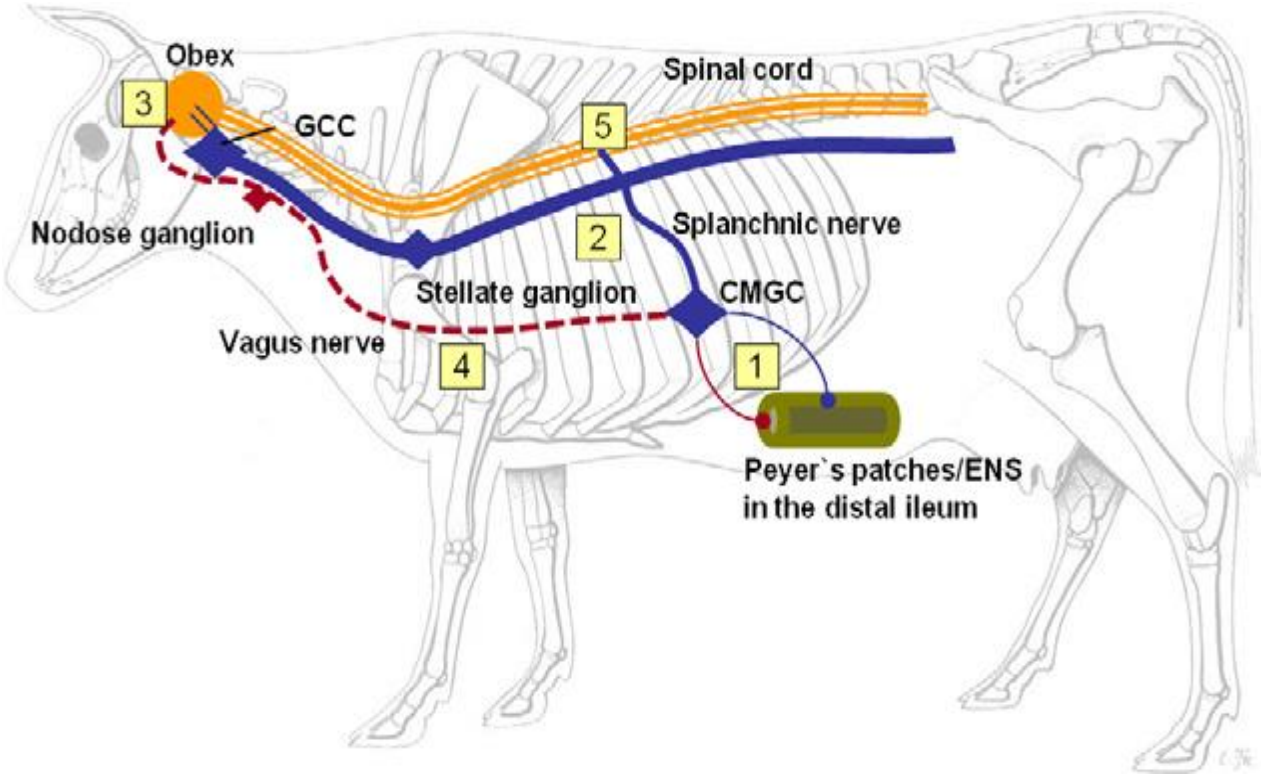
- More macaques /mice to be tested; bank vole challenges; second passage 2 tg lines
- Assays repeated in partner labs (PMCA, PET-BLOT, IHC, RT-QuiC, IHC)
- Post mortems of remaining animals in 2019 (in absence of clinical disease)

- *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



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- K. Colwell, Y. Fang, T. Pickles, K. Santiago Mateo: histology group

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Canadian Food Inspection Agency
Agence canadienne d'inspection des aliments

UNIVERSITY OF CALGARY VETERINARY MEDICINE

prion

ALBERTA PRION RESEARCH INSTITUTE
ALBERTA INNOVATES

ALMA
Alberta Livestock and Meat Agency Ltd.

Bigger context:

Epidemiology: no evidence ?
in vitro assays: no/(yes) (PMCA, RT-QuIC)
tg mouse models: no (1 exception?)
non-human primates: no/yes

JOURNAL OF VIROLOGY, Nov. 2005, p. 13794–13796 Vol. 79, No. 21
0022-538X/05/$08.00+0 doi:10.1128/JVI.79.21.13794–13796.2005

NOTES

Interspecies Transmission of Chronic Wasting Disease Prions to Squirrel Monkeys (*Saimiri sciureus*)

Richard F. Marsh,[1]† Anthony E. Kincaid,[2] Richard A. Bessen,[3] and Jason C. Bartz[4]*

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Received 3 May 2005/Accepted 10 August 2005

Chronic wasting disease (CWD) is an emerging prion disease of deer and elk. The risk of CWD transmission to humans following exposure to CWD-infected tissues is unknown. To assess the susceptibility of nonhuman primates to CWD, two squirrel monkeys were inoculated with brain tissue from a CWD-infected mule deer. The CWD-inoculated squirrel monkeys developed a progressive neurodegenerative disease and were euthanized at 31 and 34 months postinfection. Brain tissue from the CWD-infected squirrel monkeys contained the abnormal isoform of the prion protein, PrP-res, and displayed spongiform degeneration. This is the first reported transmission of CWD to primates.

Chronic Wasting Disease Agents in Nonhuman Primates

Brent Race, Kimberly D. Meade-White, Katie Phillips, James Striebel, Richard Race, and Bruce Chesebro

Chronic wasting disease, a prion disease of cervids, may infect humans, but this is unproven. Primates from 2 genera were observed for 9–10 years after intracerebral or oral inoculation. Cynomologus macaques were completely resistant. However, squirrel monkeys were highly susceptible to the pathogen, which adapted more quickly on second passage.

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

Differences between Canadian & RML CWD macaques study

	Canadian	RML	Impact
Age	4 years at challenge (18/18 animals)	Variation in age at challenge (3 – 12 years)	Tighter & more controlled animal cohort
Clinpath (Glucose)	Yes (5/10) 50%	Yes (4/14) 28.5%	Higher frequency of Type 2 diabetes in female cyn. macaques.
Inocula:			
Origin	Different sources: 1) Canadian (SK & AB) 2) US (Iowa, Wisc, Wyo, Colorado)	?	Individual & species strain variations (McKenzie, Beekes)
High titre	Yes (ic, po, skin) No (po, iv)	yes	
Different CWD types	Yes CWD1 & CWD 2 in elk challenge material	?	Individual & species strain variations (McKenzie, Beekes)
Frequency of challenge	IC = 10 mg PO 5x (2gr each) = 10 gr brain PO 24 X (200gr) muscle each)	IC= 5 mg PO 5x200mg= 1 gr brain PO muscle = Not Done	Significant differences in challenge dose! No po challenge with muscles
Amount	PO : 5 kg		Impact of repeated low dose versus 3x high dose
Steel wire i.c.	YES	NO	Greater retention of input material
Assays:			
Histopathology	74 different tissues & organs	5 different tissues & organs	

Prions – Past, Present, Policy and What May Lie Ahead

10/16/2018

Faculty Disclosures

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

The following faculty have a relevant financial relationship:

- Robert Will

  Ferring Pharma: Consultant

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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

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VoxSanguinis
The International Journal of Transfusion Medicine
ISBT International Society of Blood Transfusion

Volume 113, Issue 3
April 2018
Pages 220-231

Review Article

Creutzfeldt-Jakob disease and blood transfusion safety

C. R. Seed ✉, P. E. Hewitt, R. Y. Dodd, F. Houston, L. Cervenakova

- 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

Policy Option*		Total percentage risk reduction			Annual number of donors potentially reentered
	Donor deferral only	Donor deferral plus 71.3% RBC LR	Donor deferral plus 95% RBC LR	Donor deferral plus universal RBC LR	
Option 1	79.0%	87.1%	89.8%	90.4%	-
Option 2	78.0%	86.5%	89.3%	89.9%	~100,000

*Option 1. Current donor deferral policy (U.K. >3 months, 1980-1996; other countries in Europe >5 years, 1980-present)

Option 2. Modified donor deferral policy (U.K. >3 months, 1980-1996; France and Ireland: >5 years, 1980-2001)

Summary from the 2015 TSE Advisory Committee

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

Summary of Current and Proposed Geographical vCJD Blood Donor Deferrals

Current deferrals	Proposed deferrals
Donors who spent cumulatively ≥ 3 months in the U.K. from 1980 to 1996	Unchanged
Donors who spent cumulatively ≥ 5 years in France or other countries in Europe from 1980 to present	Donors who spent cumulatively ≥ 5 years in France or Ireland from 1980 to 2001
Donors with a history of blood transfusion in the U.K. and France from 1980 to the present	Donors with a history of blood transfusion in the U.K., France, or Ireland from 1980 to the present
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.	Unchanged

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?

Whitney R. Steele, PhD, MPH
Director, Epidemiology
Scientific Affairs
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Rockville, MD
Whitney.Steele@redcross.org

Prions – Past, Present, Policy and What May Lie Ahead

AABB 2018
Tuesday, October 16, 2018
Whitney R. Steele, PhD, MPH

American Red Cross

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

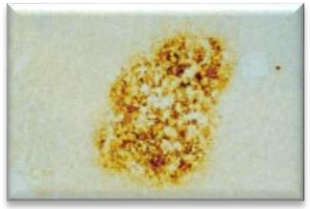
Bovine Spongiform Encephalopathy (mad cow disease)

Kuru (Human)

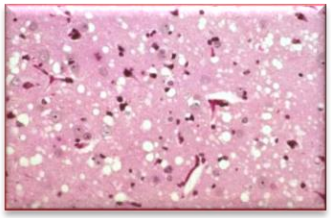
TSEs

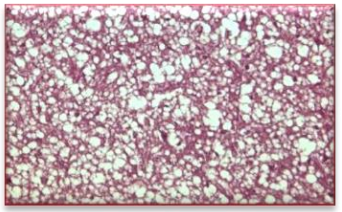
Scrapie

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?
  - **Pro**tein and **in**fectious
  - -***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

TRANSFUSION

BRIEF REPORT

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

Lauren A. Crowder,[1] Lawrence B. Schonberger,[2] Roger Y. Dodd,[3] and Whitney R. Steele[1]

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

VoxSanguinis
The International Journal of Transfusion Medicine

ISBT International Society of Blood Transfusion

Vox Sanguinis (2015)

ORIGINAL PAPER

DOI: 10.1111/vox.12371

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

P. J. M. Urwin,[1] J. M. Mackenzie,[1] C. A. Llewelyn,[2] R. G. Will[1,a] & P. E. Hewitt[3,a]

[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*

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 – 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

	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)

Variant Creutzfeldt-Jakob disease

AABB Boston, 16th October 2018

RG Will
University of Edinburgh, UK

Articles

A new variant of Creutzfeldt-Jakob disease in the UK

R G Will, J W Ironside, M Zeidler, S N Cousens, K Estibeiro, A Alperovitch, S Poser, M Pocchiari, A Hofman, P G Smith

Summary

Background Epidemiological surveillance of Creutzfeldt-Jakob disease (CJD) was reinstituted 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.

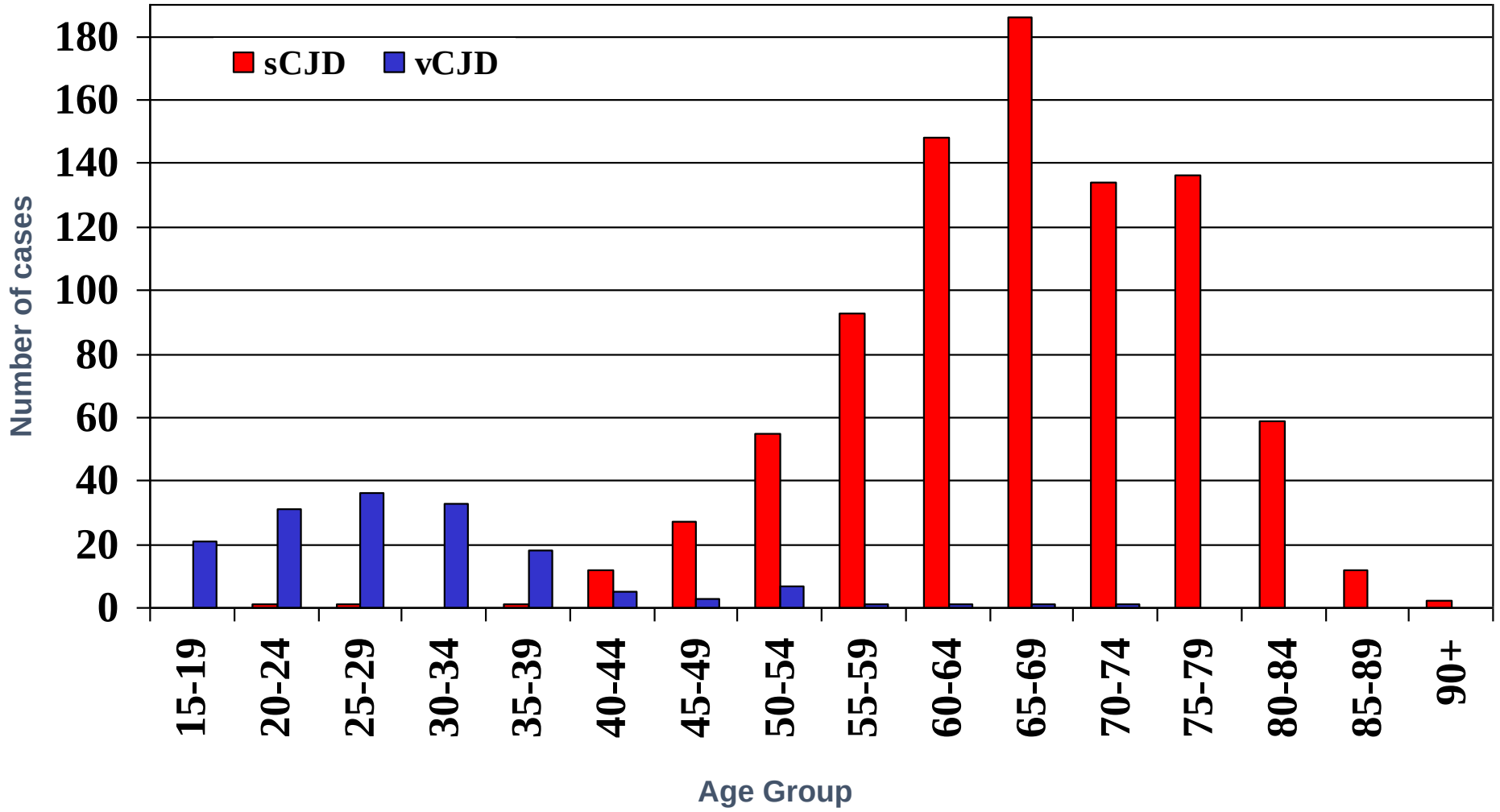
Introduction

Because of the epidemic of bovine spongiform encephalopathy (BSE) in cattle, surveillance of Creutzfeldt-Jakob disease (CJD) in the UK was reinstituted 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.

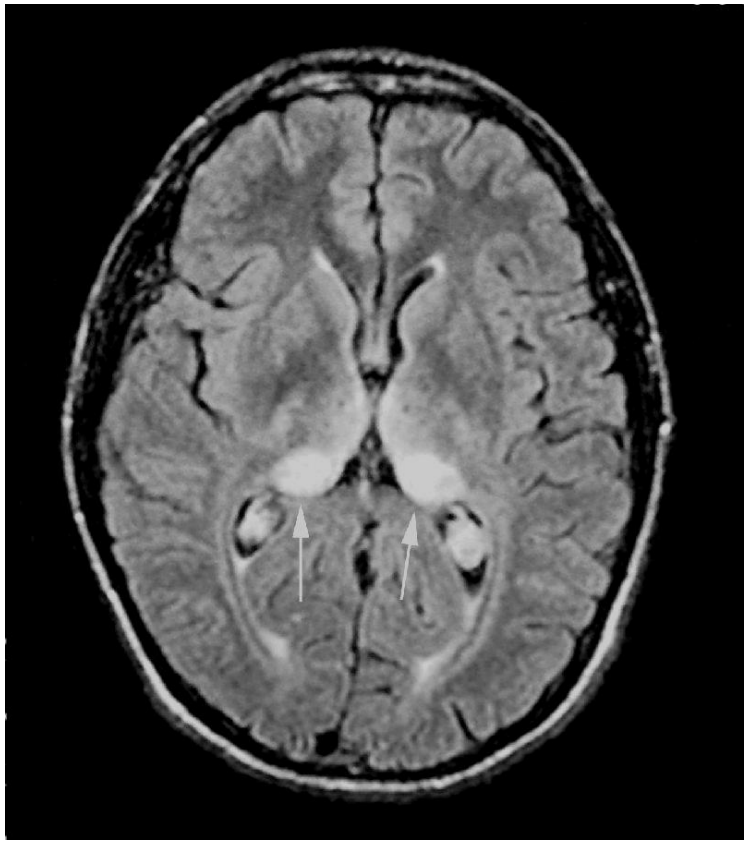
Methods

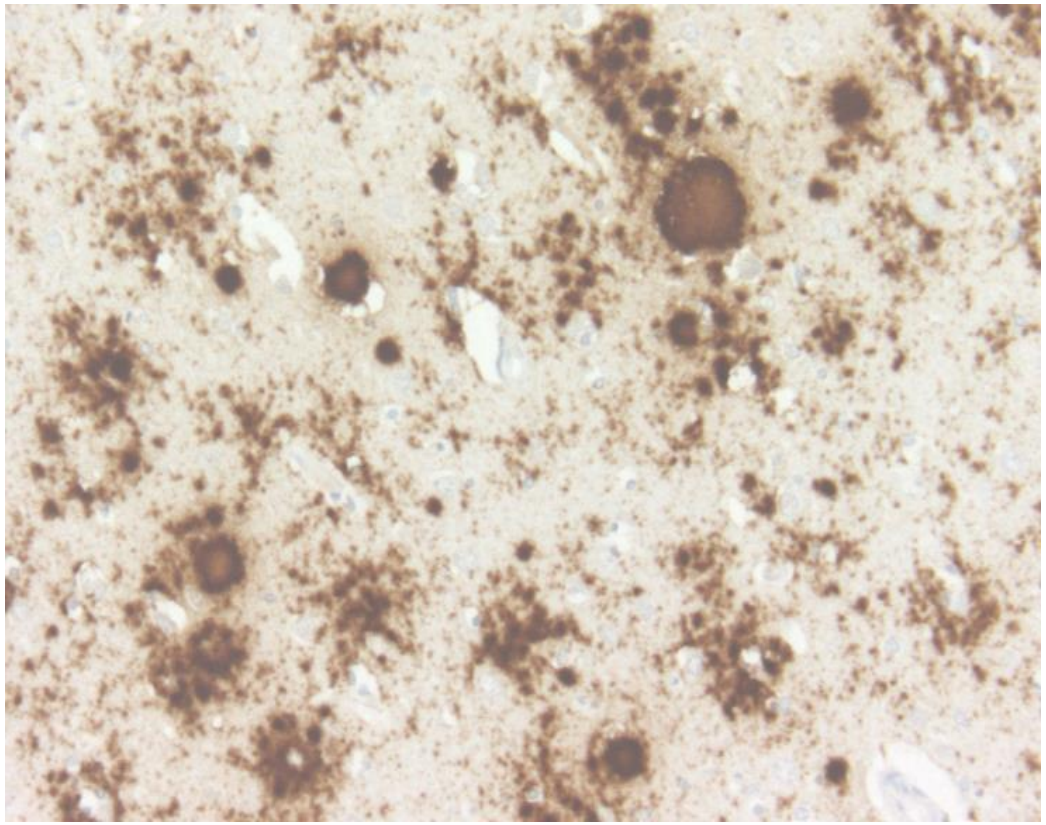
Since May, 1990, cases of CJD have been identified to the CJD Surveillance Unit, usually by direct referral from professional groups, which include neurologists and neuropathologists. All

AGE AT DEATH FOR SPORADIC CJD CASES AND vCJD CASES BY 5-YEAR AGE GROUP

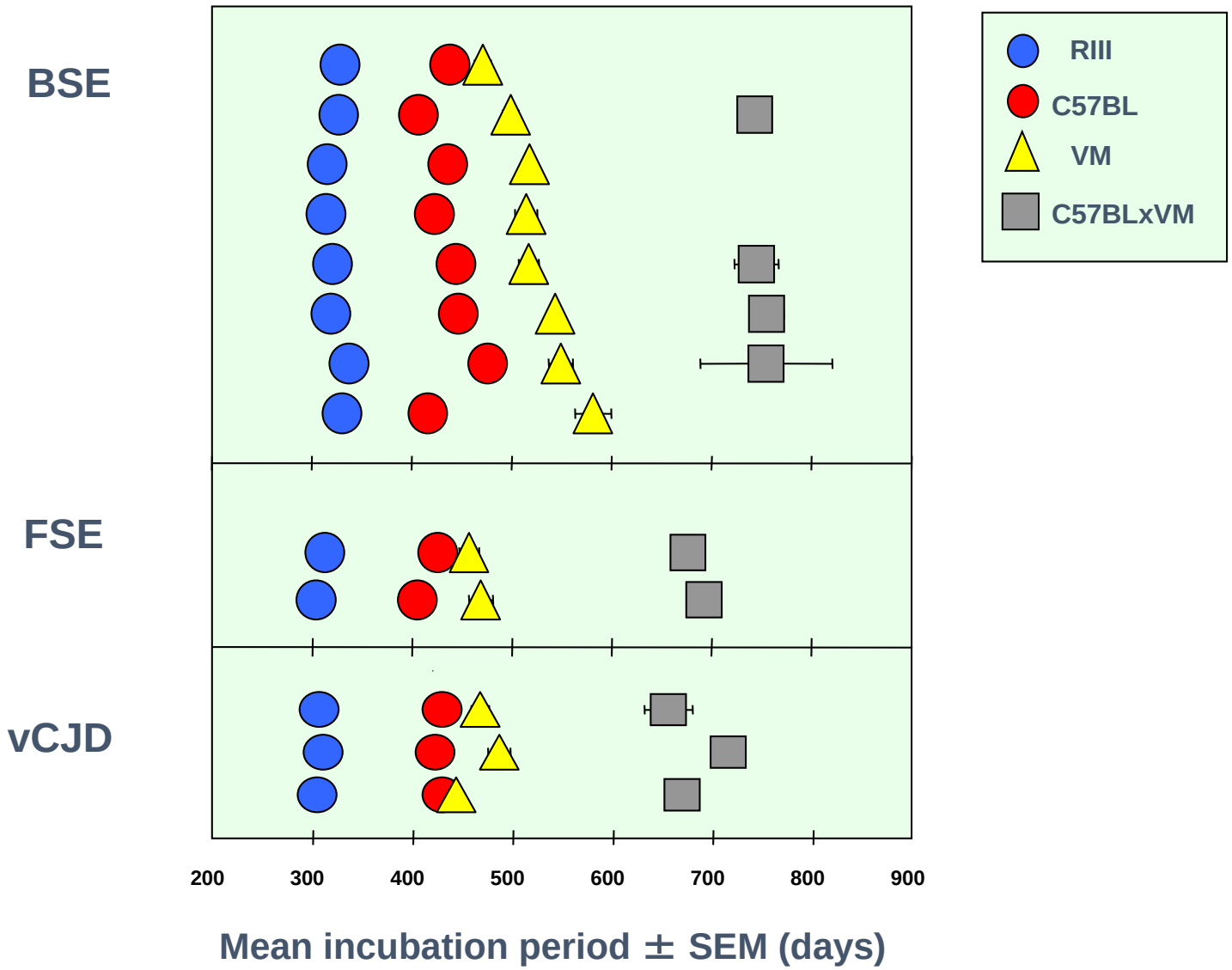


MRI scan and brain immunocytochemistry in variant CJD

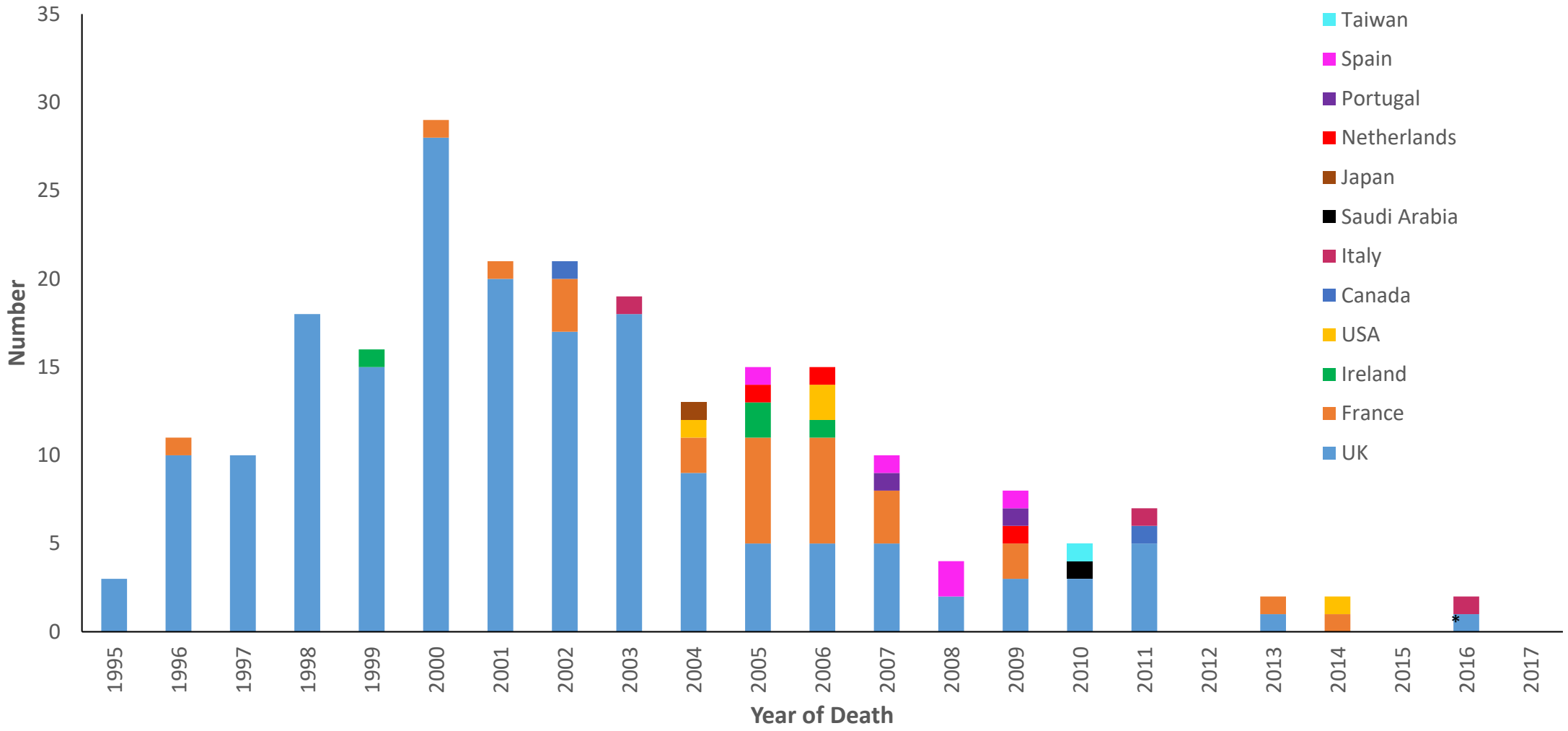




Transmission of TSEs to mice



vCJD CASES BY YEAR AND COUNTRY
1994-2017 (n=230)



Estimation of the Exposure of the UK Population to the Bovine Spongiform Encephalopathy Agent through Dietary Intake During the Period 1980 to 1996

Chu-Chih Chen*, Yin-Han Wang

Division of Biostatistics and Bioinformatics, Institute of Population Health Sciences, National Health Research Institutes, Zhunan, Taiwan

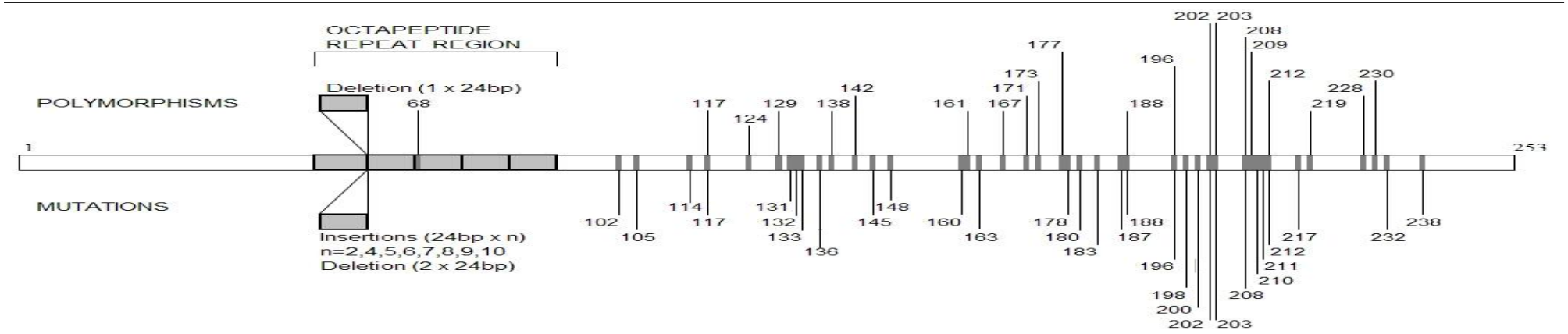
Furthermore, the threshold dose estimate of approximately 12 bID_{50} with an equivalent weight of 1.2g of a BSE infected bovine brain also appears reasonable, which may alternatively be interpreted as the species barrier between bovine and human.

PLOS One April 2014
Volume 9 Issue 4 e94020

Codon 129 genotype in vCJD

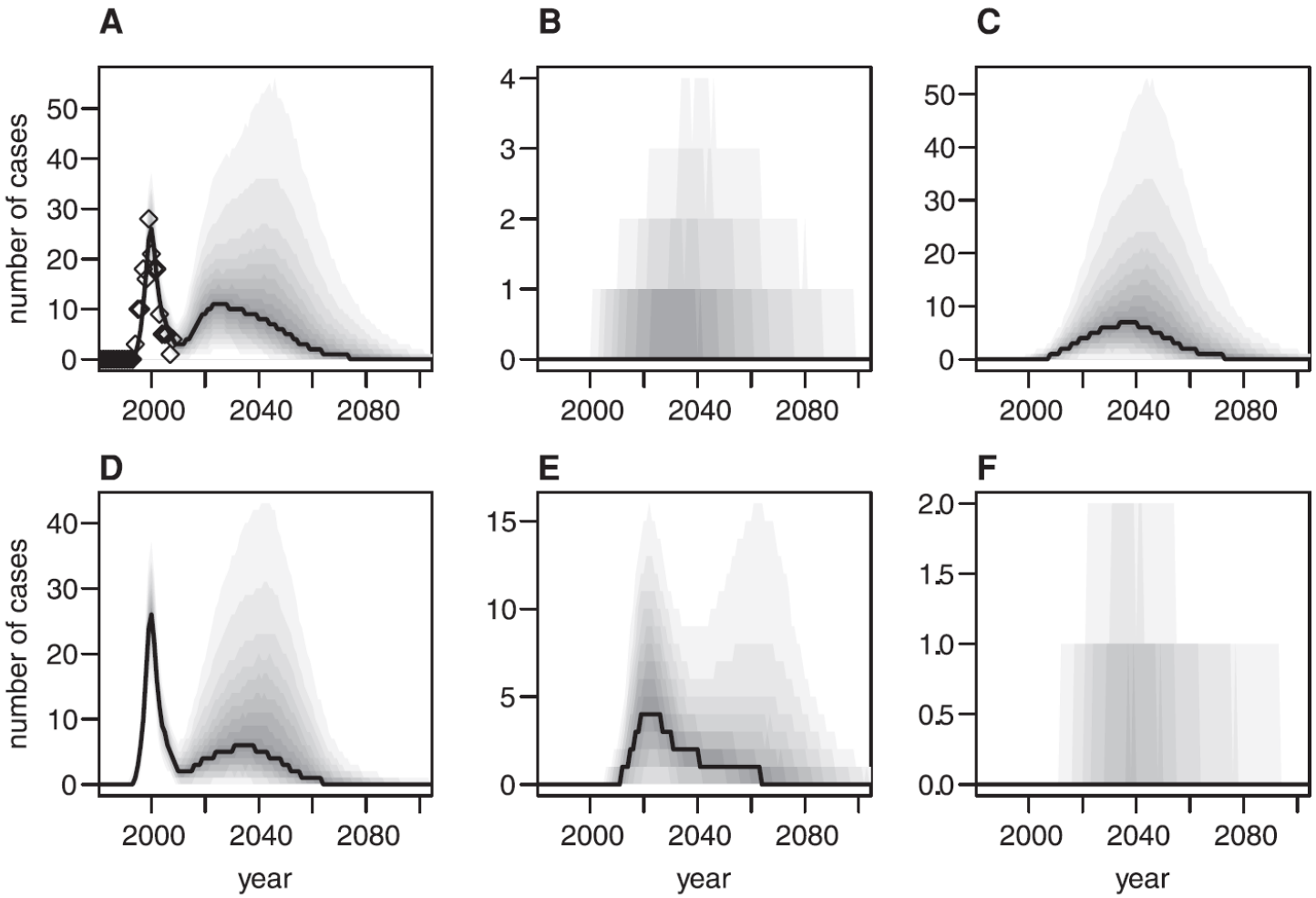
- 160/161 tested cases in UK : MM
- 1/161 tested cases in UK : MV
- 52/52 cases outside UK: MM

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



PLoS one

Median and posterior distributions of projected time series



Cases:

A: Total number

B: Transfusion associated

C: Unidentifiable transfusion associated

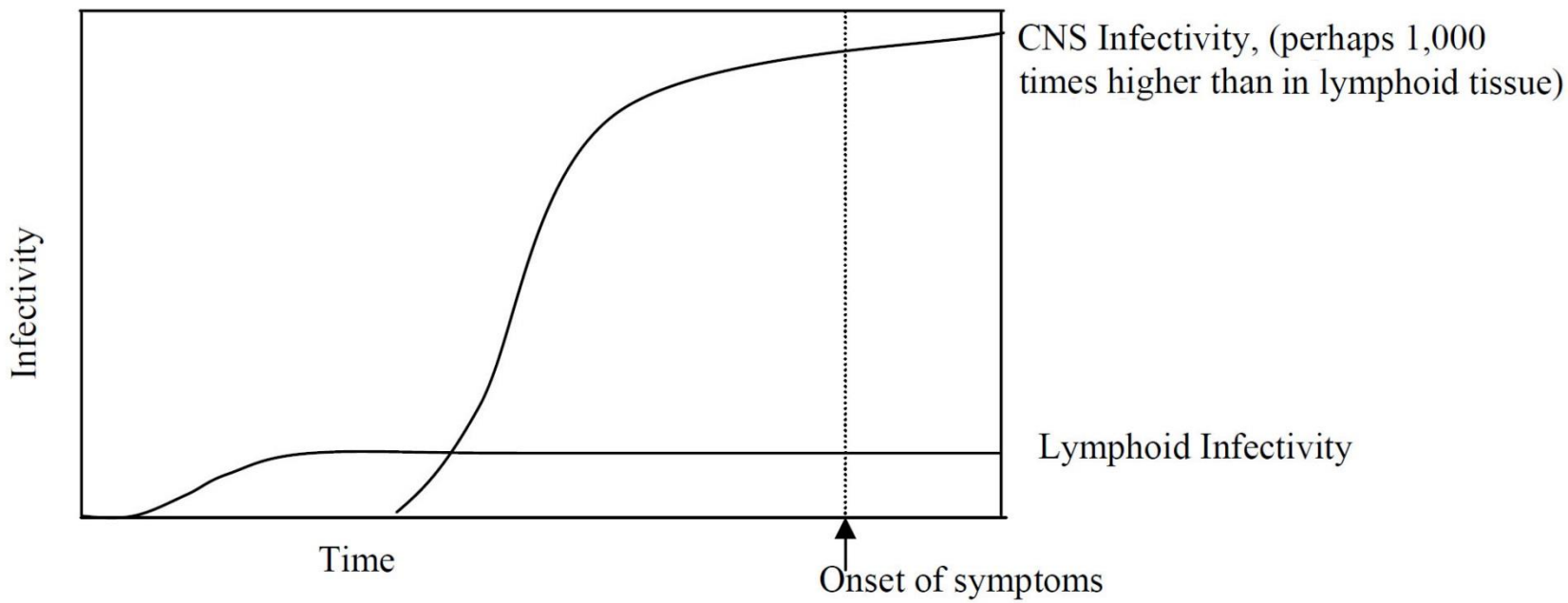
Genotypes:

D: MM

E: MV

F: VV

Probable pattern of tissue infectivity in variant CJD, based on scrapie models

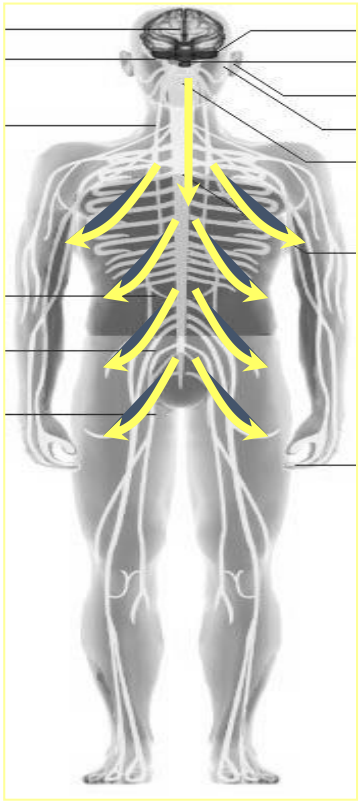


Tissue Infectivity in CJD

sCJD ***centrifugal spread***

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

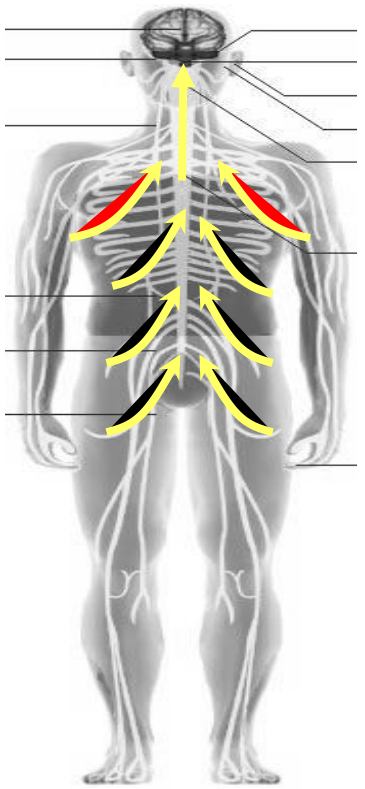
MEDIUM
Spinal ganglia
Olfactory epithelium



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

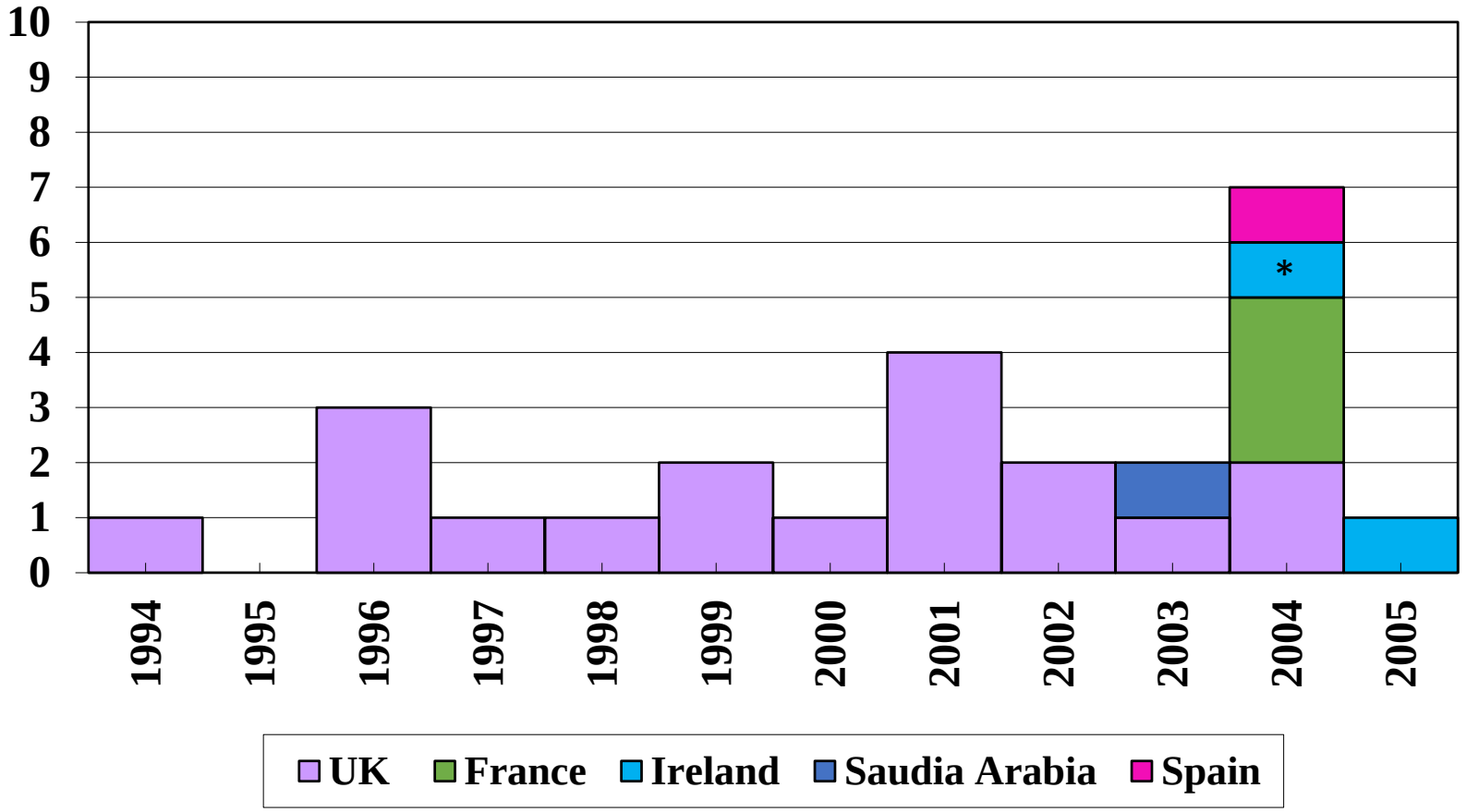
vCJD - Blood Donors

Year Death	Total vCJD cases	Total eligible to donate	Number reported to be blood donors	Number registered with UK Blood Services[1]	Number with donations[2]
1995-1999	56	54	11	7	6
2000-2004	92	84	17	12	10
2005-2009	20	20	3	5	2
2010-2014	9	9	1	0	0
2015-2018	1	1	0	0	0
Total	178	168	32	24	18

[1]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.

[2] Donors 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

Articles

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

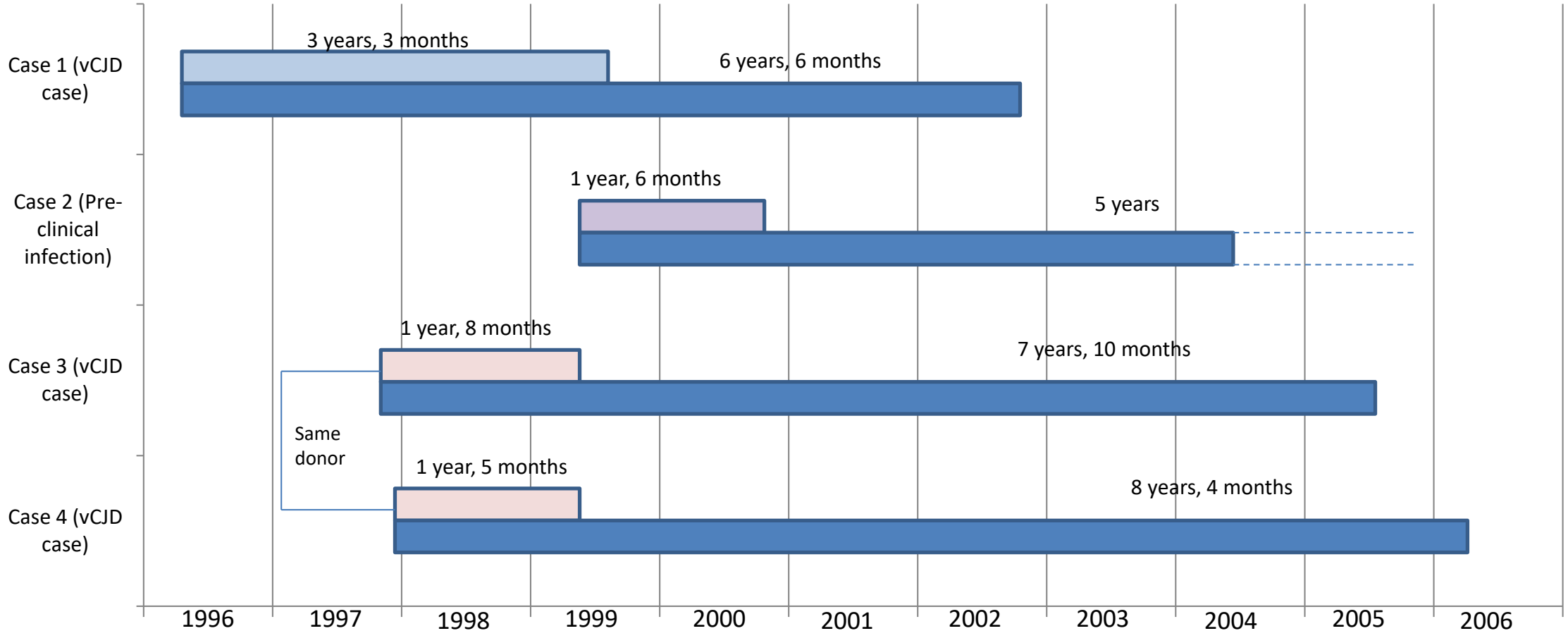
Summary

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-

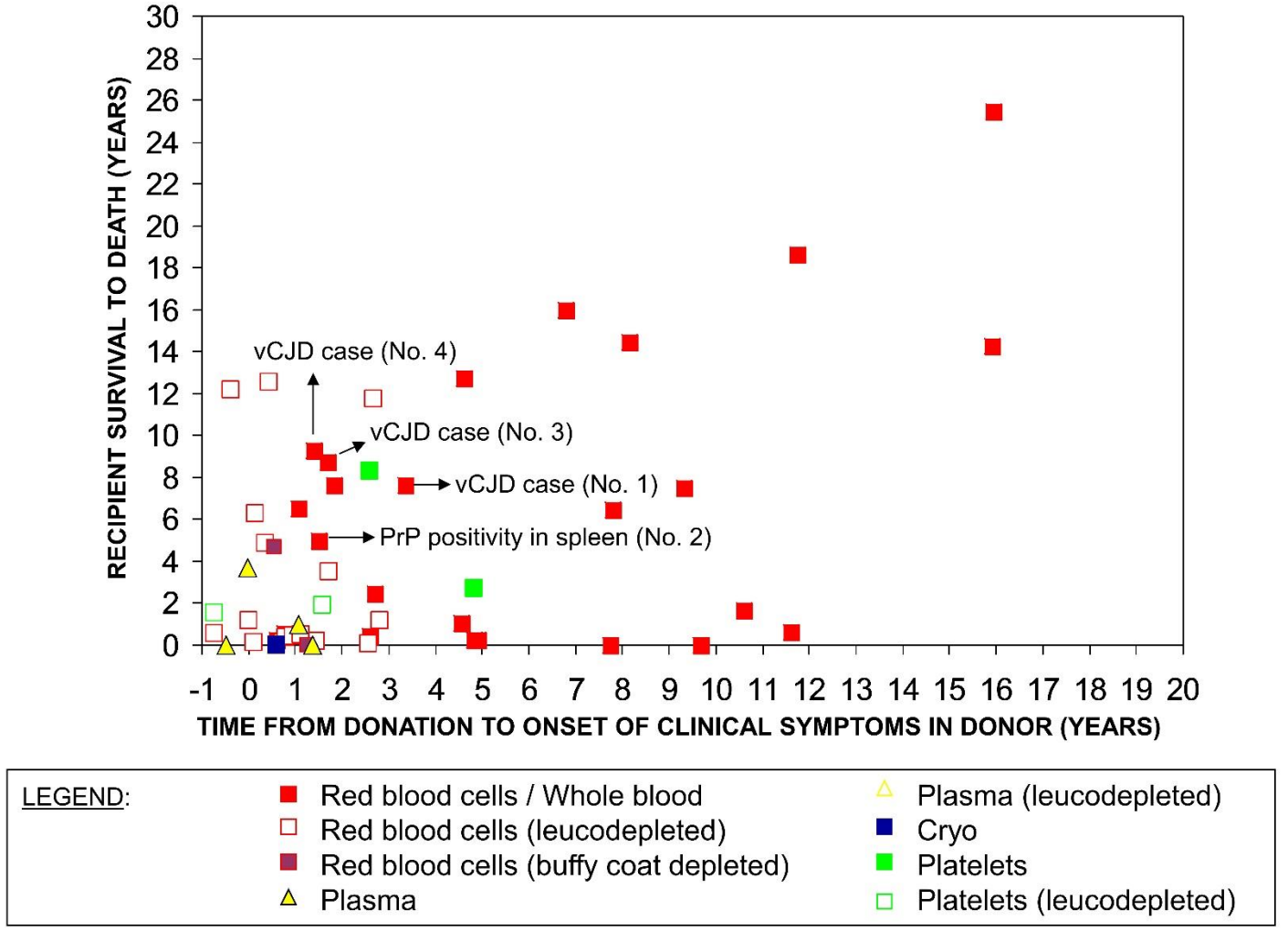
TRANSFUSION TRANSMISSION OF vCJD



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)

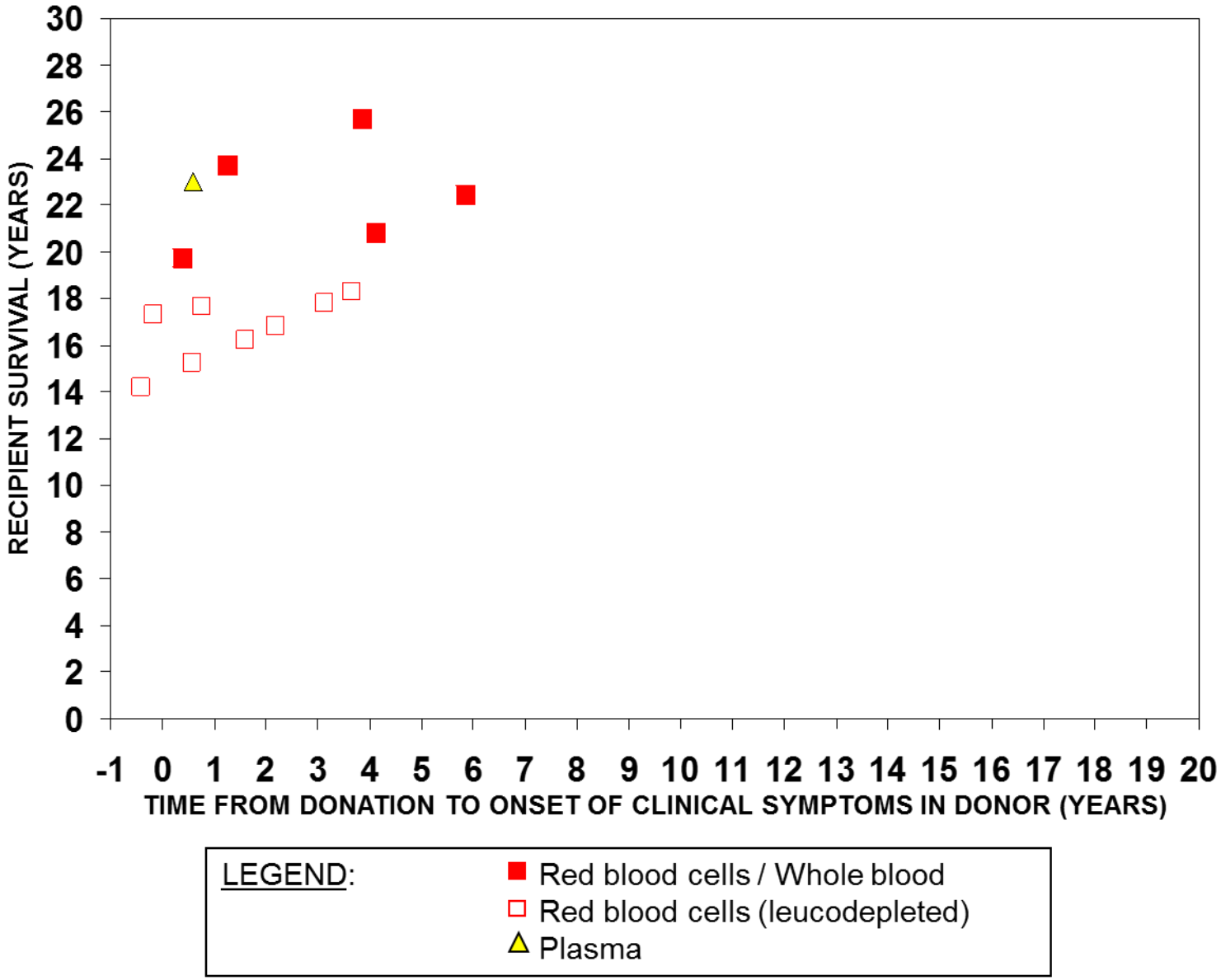
FOR RECIPIENTS OF vCJD COMPONENTS ACCORDING TO INTERVAL BETWEEN DONATION AND ONSET OF CLINICAL SYMPTOMS IN THE DONOR



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)

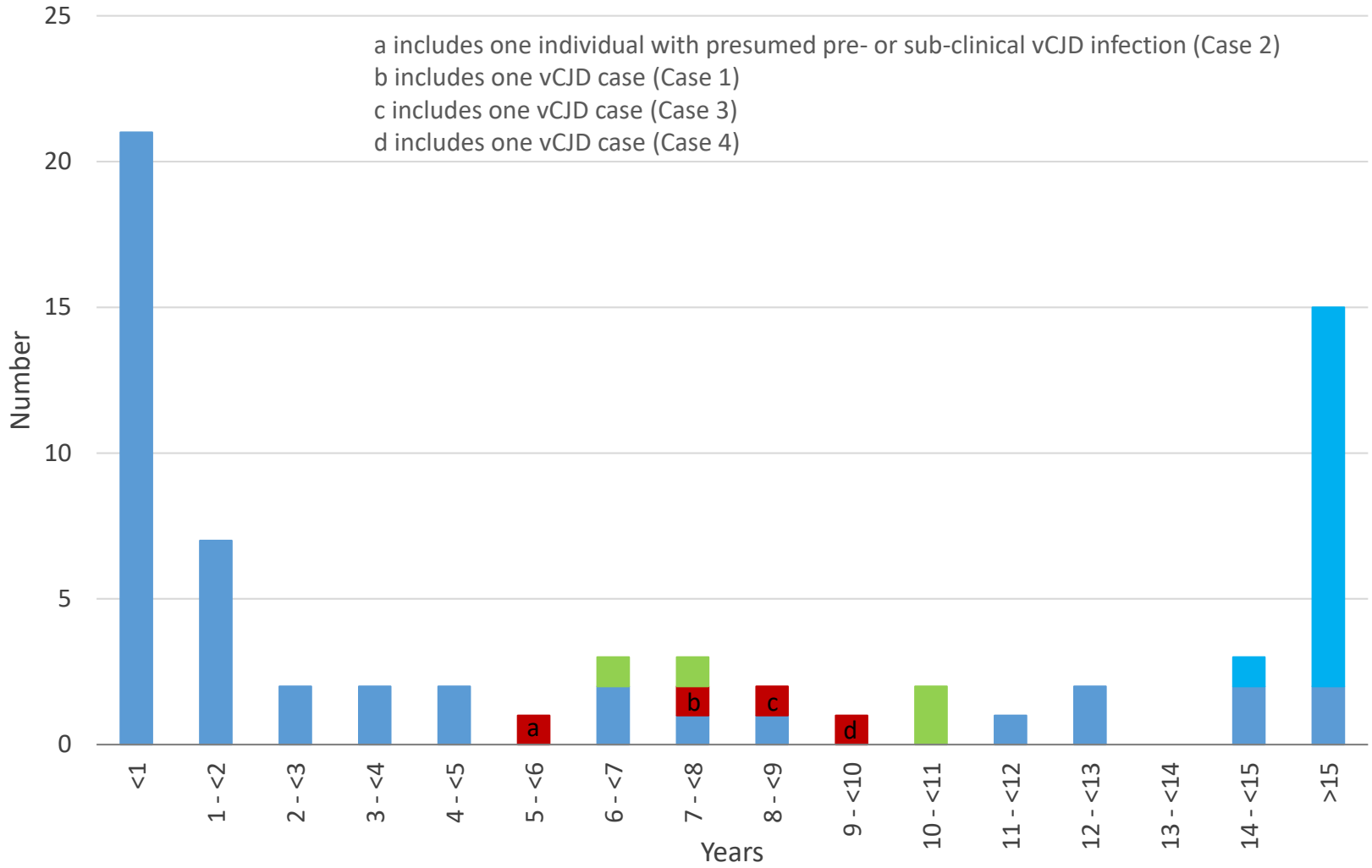


RECIPIENTS ALIVE WITH CODON 129 STATUS AVAILABLE

Age	Codon 129	Component	Time since transfusion to 30 September 2018	Donation to onset in donor
80	MV	RBC	25+ years	3.85 years
62	MV	RBC	23+ years	1.25 years
46	MM	Cyro-depleted plasma	23+ years	7 months
87	MV	RBC	22+ years	5.83 years
55	MV	RBC	19+ years	5 months[1]
77	MM	RBC (LD)	18+ years	3.65 years
45	MV	RBC (LD)	17+ years	9 months
70	MM	RBC (LD)	16+ years	1.6 years
51	MM	RBC (LD)	15+ years	7 months

[1]same donor as 2 of the transfusion transmission cases (tonsil biopsy negative – June 2008)

RECIPIENTS OF LABILE BLOOD COMPONENTS DONATED BY vCJD CASES (n=67)

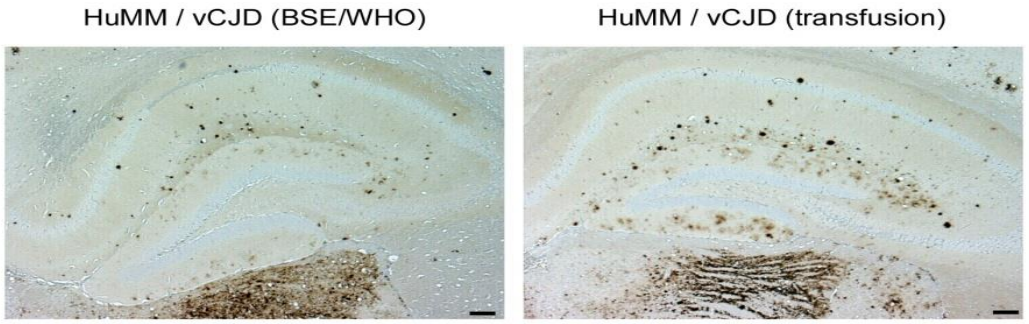


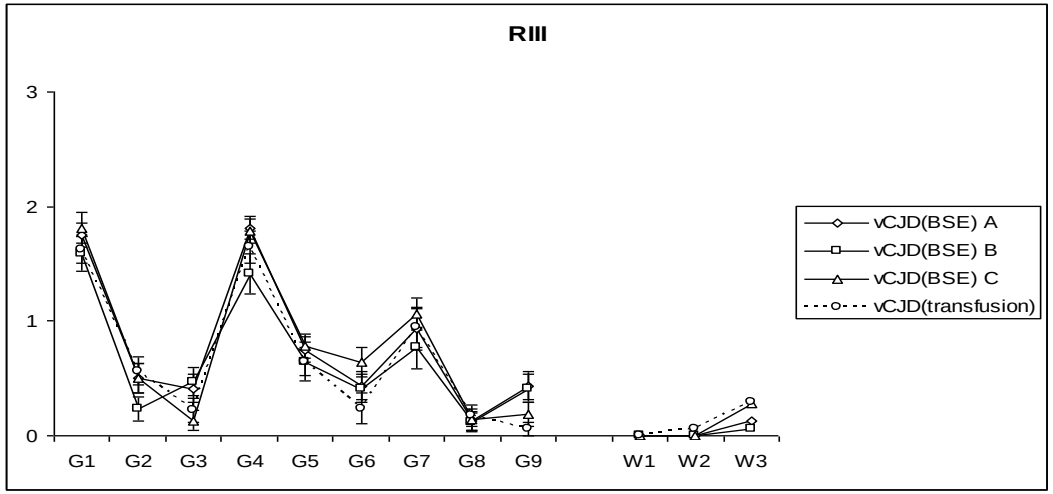
DEAD, n=53
(interval from transfusion to death)
- Dead – untested
- Dead – tested positive for PrP deposition at PM
- Dead – tested negative for PrP deposition at PM

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

Science Translational Medicine AAAS

Sci. Transl. Med. **8**, 370ra183 (2016)

PRION DISEASES

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,[4] Paul E. Schulz,[1] Claudio Soto[1,2]*

Table 1. Blood samples and PrP^{Sc} detection by PMCA.

Clinical diagnosis	Total patients	PrP^{Sc} detected in blood
vCJD	14	14/14
sCJD*	16	0/16
Other neurodegenerative diseases†	62	0/62
Other neurological diseases‡	26	0/26
Healthy controls	49	0/49

*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.

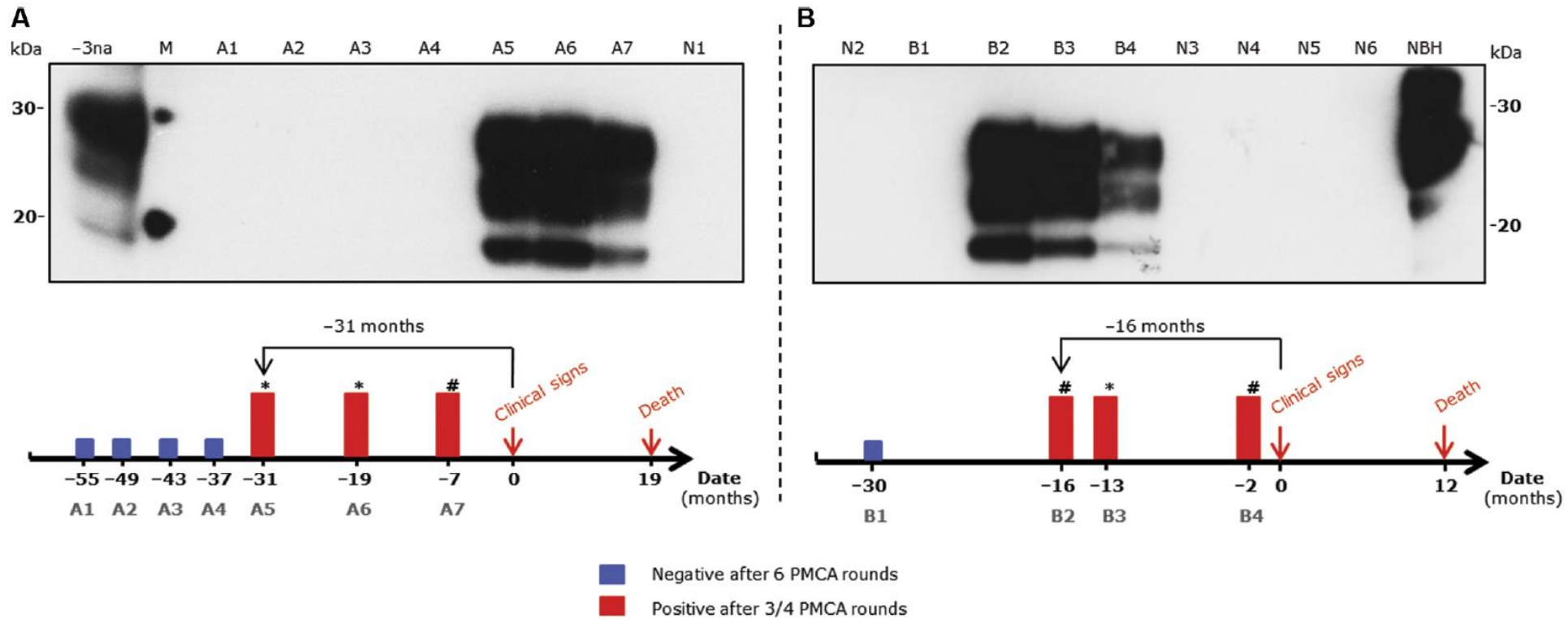
Science Translational Medicine
AAAS

Sci. Transl. Med. **8**, 370ra182 (2016)

PRION DISEASES

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,[4,7] Charly Mayran,[1] Simon Nicot,[1] Alison Green,[8] Arlette Welaratne,[3] David Narbey,[9] Chantal Fournier-Wirth,[1] Richard Knight,[8] Robert Will,[8] Pierre Tiberghien,[9,10] Stéphane Haïk,[2,3,4] Joliette Coste[1,9]*



BMJ

BMJ 2013;347:f5675 doi: 10.1136/bmj.f5675

RESEARCH

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

O Noel Gill *head of department*[1], Yvonne Spencer *head of pathology*[2], Angela Richard-Loendt *senior research histologist*[3], Carole Kelly *senior CJD scientist*[1], Reza Dabaghian *senior scientific and technical manager*[4], Lynnette Boyes *histologist*[3], Jacqueline Linehan *senior research histologist*[5], Marion Simmons *veterinary research pathologist, head of EU Reference Laboratory for TSE*[2], Paul Webb *pathology research scientist*[2], Peter Bellerby *pathology research scientist*[2], Nick Andrews *senior statistician*[1], David A Hilton *consultant neuropathologist*[6], James W Ironside *professor of clinical neuropathology*[7], Jon Beck *research scientist*[5], Mark Poulter *research scientist*[5], Simon Mead *reader in neurology, consultant neurologist*[5], Sebastian Brandner *professor of neuropathology, honorary consultant neuropathologist*[3]

- 16/32,441 samples positive
- 493 per million (95%CI: 282-801)
- **1 in 2,000**
- Codon 129: MM 8, MV 4, VV 4

BLOOD-BORNE TRANSMISSION OF vCJD
RE-EXAMINATION OF SCENARIOS

Summary of issues by UK Blood Services 1999-2009 (SHOT, 2010)

Year	Red Blood Cells	Platelets	FFP	Cryoprecipitate	Totals
1999–2000	2,737,572	249,622	365,547	94,114	**3,446,855**
2000–2001	2,706,307	250,259	374,760	95,456	**3,426,782**
2001–2002	2,679,925	251,451	385,236	88,253	**3,404,865**
2002–2003	2,678,098	251,741	377,381	92,768	**3,399,988**
2003–2004	2,607,410	264,539	372,855	95,417	**3,340,221**
2004–2005	2,428,934	258,528	313,019	102,719	**3,103,200**
2005–2006	2,316,152	259,654	320,852	106,139	**3,002,797**
2006–2007	2,235,638	255,474	306,444	116,672	**2,914,228**
2007–2008	2,174,256	258,419	295,085	117,699	**2,845,459**
2008–2009	2,209,153	266,312	306,740	121,555	**2,903,760**

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)

Public Health England

Health Protection Report
weekly report

Infection report
Volume 10 Number 26 Published on: **12 August 2016**

Summary results of the third national survey of abnormal prion prevalence in archived appendix specimens

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.

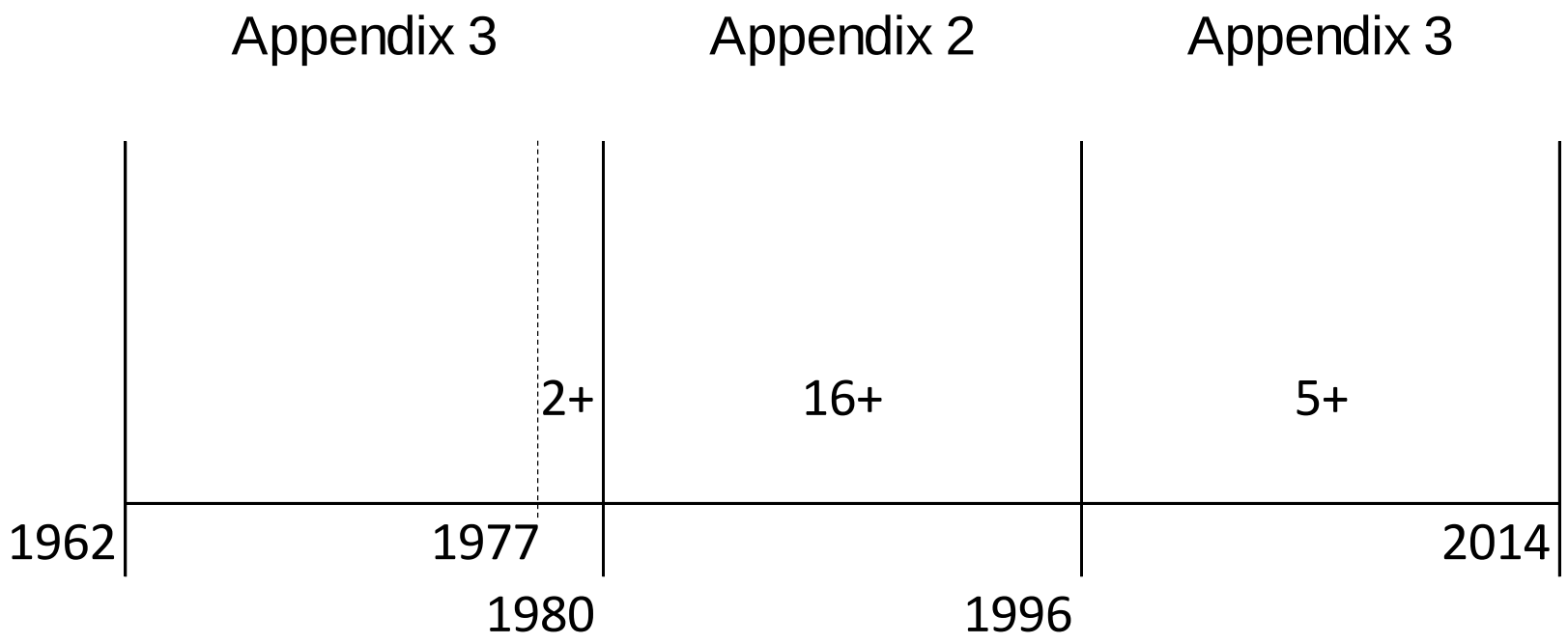
Public Health England

Health Protection Report
weekly report

Infection report

Volume 10 Number 26 Published on: **12 August 2016**

Summary results of the third national survey of abnormal prion prevalence in archived appendix specimens



Public Health England

Health Protection Report
weekly report

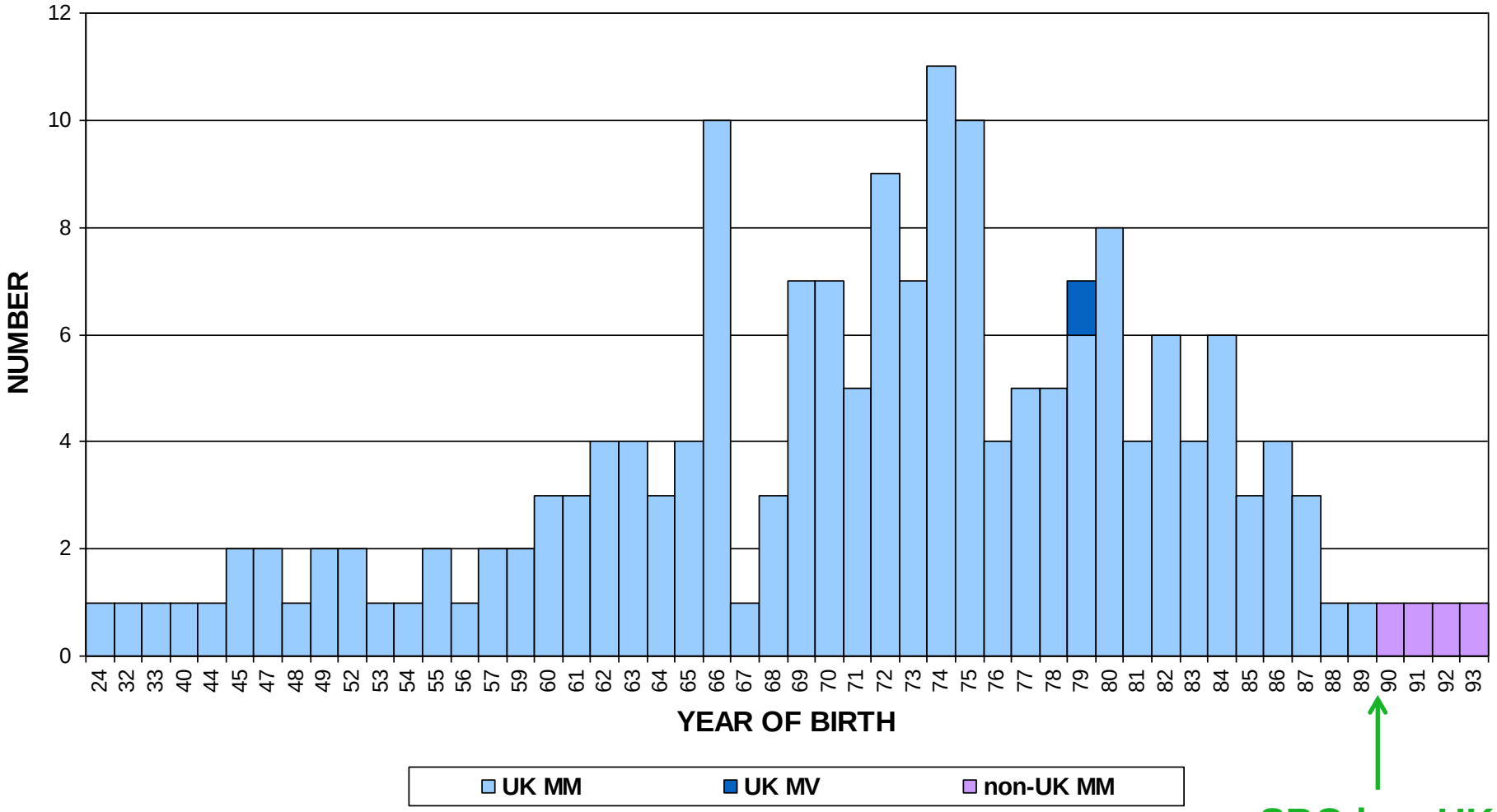
Infection report
Volume 10 Number 26 Published on: **12 August 2016**

Summary results of the third national survey of abnormal prion prevalence in archived appendix specimens

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



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