

# CWD & PUBLIC HEALTH

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# Overview

- Overview of human prion diseases
- Epidemiology of CJD in USA and Wyoming
- Review of scientific literature about transmission of CWD to humans

# HUMAN PRION DISEASES



# Human Prion Diseases

- Recognized in animals since 1700s, but only recognized in humans since 1920s.
- Creutzfeld-Jakob Disease (CJD)
- Variant Creutzfeld-Jakob Disease (vCJD)
- Gerstmann-Straussler-Scheinker Syndrome
- Fatal Familial Insomnia
- Kuru

# Creutzfeldt-Jakob Disease (CJD)

- Also called Classic CJD or sporadic CJD
- Most common human prion disease
- Neurodegenerative disorder
- Rapidly progressive and always fatal
- Disease usually leads to death within 1 year of onset
- Symptoms include:
  - *Dementia, balance and coordination problems, numbness, dizziness, slurred speech, vision problems, anxiety, irritability, insomnia, depression, confusion, and more.*

# Variant CJD (vCJD)

- “Mad Cow Disease”
- First described in 1996 in UK
- Linked to eating meat infected with Bovine Spongiform Encephalopathy (BSE) in the UK between 1986 and 1996.
- Cases peaked in 2000
- 4 cases in USA, last in 2014 (229 cases in Europe)



Photo Credit: NBC News

# Classic CJD ≠ Variant CJD

Characteristic	Classic CJD	Variant CJD
Median age at death	68 years	28 years
Median duration of illness	4-5 months	13-14 months
Clinical signs and symptoms	Dementia; early neurologic signs	Psychiatric/behavioral problems
Periodic sharp waves on electroencephalogram	Often present	Often absent
“Pulvinar sign” on MRI	Not reported	Present in >75% of cases
Immuno-histochemical analysis of brain tissue	Variable accumulation	Marked accumulation of protease-resistance prion protein
Presence of agent in lymphoid tissue	Not readily detected	Readily detected
Increased glycoform ratio on immunoblot analysis of protease-resistance prion protein	Not reported	Marked accumulation of protease-resistance prion protein

# Kuru

- Historically significant
- Affected Fore people of Papua New Guinea
- Kuru – “to shake from fear”
- First described in 1950s
- Mainly infected young women and children
- Transmitted via ritualistic cannibalism
- Largely stopped after government banned ritualistic cannibalism
- Still saw cases up into 2000s, showing latency periods of 50+ years.



<https://sciencelife.uchospitals.edu/2009/11/19/evolution-via-cannibalism-the-case-of-kuru/>

# Management and treatment of human prion diseases

- No proven treatment for any type of CJD
- All types are managed the same
  - *Palliative care to help them be comfortable*
- Very little research is being done on CJD treatments

# EPIDEMIIOLOGY OF CJD



# Challenges of diagnosing & studying CJD

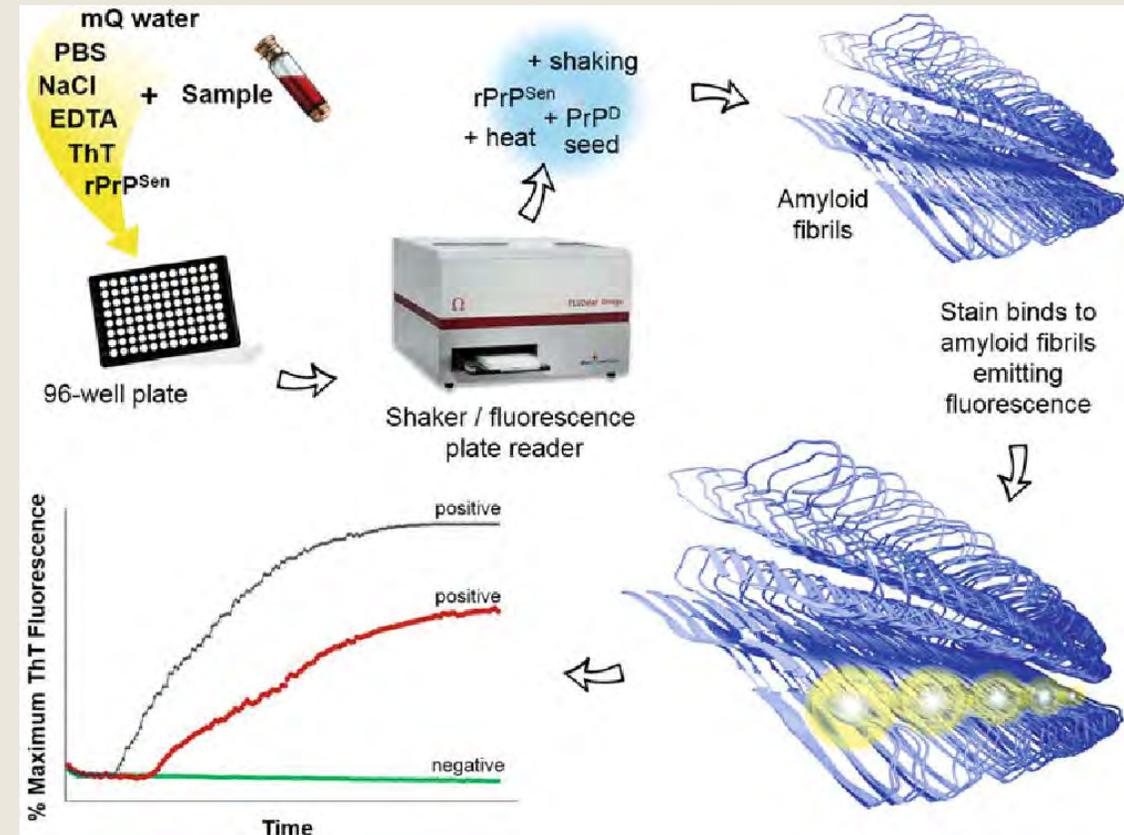
- Definitive diagnosis requires autopsy
- Very rare, low incidence
- Precise time of disease onset uncertain
- Long latent period, unknown incubation period
  - *Estimated to be decades*

# CJD Case Definition

Definite	Probable	Possible
<p>Diagnosed by standard neuropathological techniques; and/or immunocytochemically; and/or Western blot confirmed protease-resistant PrP; and /or presence of scrapie-associated fibrils.</p>	<p>Neuropsychiatric disorder <u>plus</u> positive RT-QuIC in CSF or other tissues  <b>OR</b>            Rapidly progressive dementia; <b>and</b> at least 2 out of the following 4 clinical features:                Myoclonus                Visual or cerebellar signs                Pyramidal/extrapyramidal signs                Akinetic mutism  <b>AND</b> a positive result on at least 1 of the following laboratory tests:            - a typical EEG (periodic sharp wave complexes) during an illness of any duration            - a positive 14-3-3 CSF assay in patients with a disease duration of less than 2 years            - High signal in caudate/putamen on magnetic resonance imaging (MRI) brain scan or at least two cortical regions (temporal, parietal, occipital) either on diffusion-weighted imaging (DWI) or fluid attenuated inversion recovery (FLAIR)  <b>AND</b> without routine investigations indicating an alternative diagnosis.</p>	<p>Progressive dementia; <b>and</b> at least two out of the following four clinical features:                Myoclonus                Visual or cerebellar signs                Pyramidal/extrapyramidal signs                Akinetic mutism  <b>AND</b> the absence of a positive result for any of the four tests above that would classify a case as “probable”  <b>AND</b> duration of illness less than two years  <b>AND</b> without routine investigations indicating an alternative diagnosis.</p>

# RT-QUIC

- Real-time Quaking Induced Conversion Assay
- Diagnose CJD with a cerebrospinal fluid (CSF) Sample
- “This technique exploits the ability of the misfolded pathological form of prion protein ( $\text{PrP}^{\text{Sc}}$ ) found in CSF to induce conversion of normal PrP to the misfolded form, which subsequently aggregates. The formation of these aggregates of misfolded PrP is monitored in real time using fluorescent dyes.”
- Sensitivity 92%, Specificity 100%

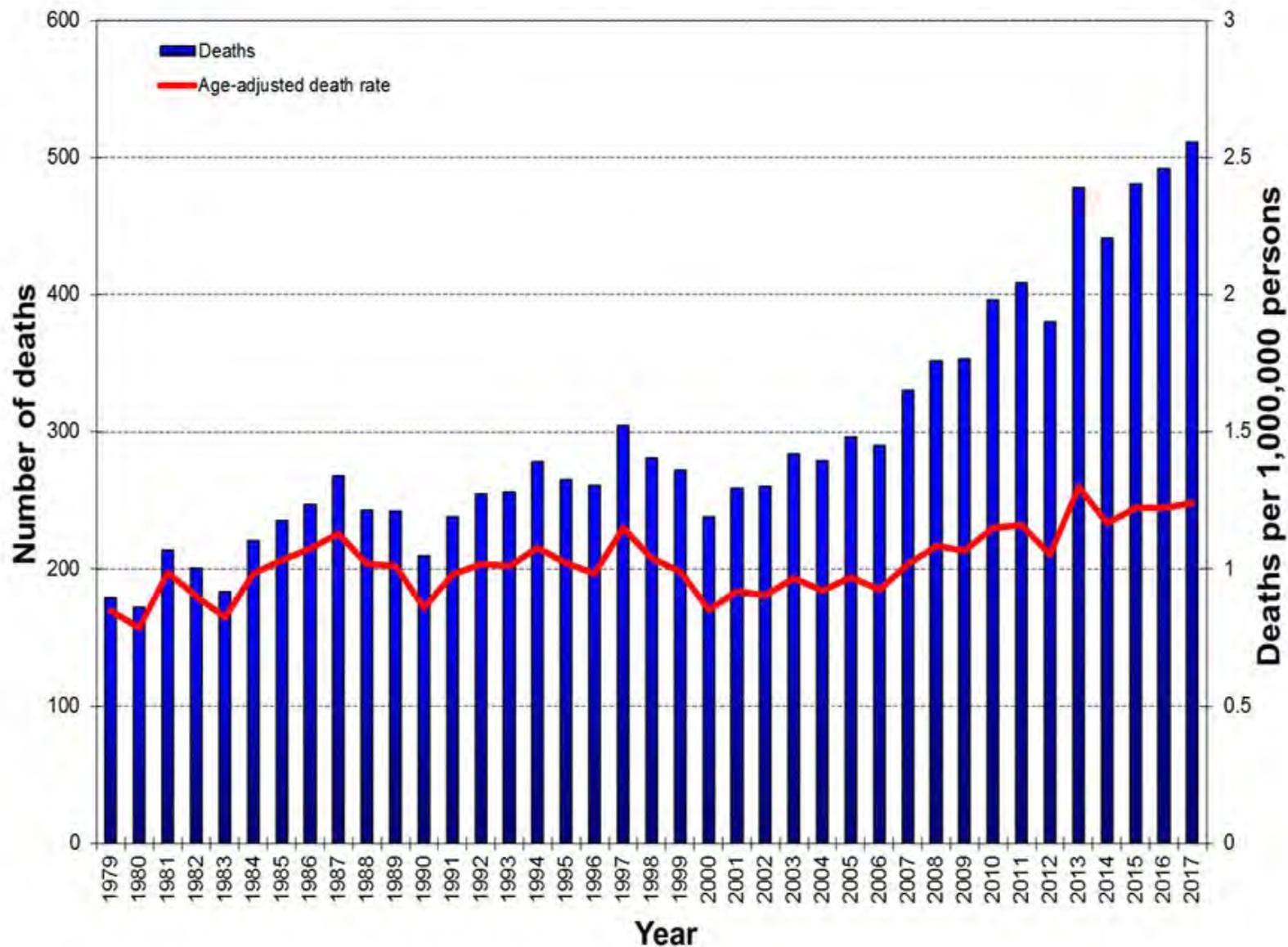


<https://www.semanticscholar.org/paper/RT-QuIC-Assays-for-Prion-Disease-Detection-and-Or%C3%BA-Groveman/055b630a0c6821874ad869e212b78bbcd469ee55/figure/0>

# Epidemiology of CJD

- Occurs sporadically worldwide at the same rate
  - 85-95% *sporadic*
  - 5-15% *genetic*
  - <1% *acquired*
- No recognizable pattern of transmission for sporadic cases
- Risk of disease increases with age
  - Average incidence rate of 1-1.5 per million worldwide (although up to 2 per million is observed in some places)
  - Average rate increases to **3.5 cases per 1 million people among those age 50+**
  - In USA, highest rates in Northeast, Lowest rates in South and West

# Creutzfeldt-Jakob Disease Deaths and Age-Adjusted Death Rate, United States, 1979-2017\*



# CJD in Wyoming

- 13 Cases from 2010-2019
- Wyoming rate: 2.3 cases per 1 million
- Median age at death: 68 years (Range: 56-81 years)
- 62% Male, 38% Female

# Wyoming Case Follow-Up

- Cases are reported several ways
  - *Physicians, Vital Statistics office, National Prion Disease Pathology Surveillance Center (NPDPSC)*
- Encourage autopsy when possible
- Educate about testing available through NPDPSC
- Review medical records to determine case classification
- Interview family to determine potential exposures and risk factors
  - *Occupation, food history, hunting/game meat exposure, medical exposures, travel history, family medical history*

# SCIENTIFIC RESEARCH ON CWD TRANSMISSION



# Inter-species transmission

- The ultimate CWD question
- We know there are species barriers to some prion diseases, but not all
  - *BSE vs Scrapie*
  - *Where do cervids fall?*
- Three main ways to study this:
  - *Epidemiologic*
  - *In vitro*
  - *In vivo*

# Hunter Registry Project

- Joint Collaboration between WDH, Colorado Department of Health and Environment, and CDC.
- Trying to determine if hunters are affected by CJD at a greater rate than the general population.
  - *Hunters are most likely to be exposed to CWD*
- No significant increase in CJD has been found among hunters at this time
- Still ongoing, not published yet



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Journal of  
Virology®

# Lack of Transmission of Chronic Wasting Disease to Cynomolgus Macaques

Brent Race,<sup>a</sup> Katie Williams,<sup>a</sup> Christina D. Orrú,<sup>a</sup> Andrew G. Hughson,<sup>a</sup> Lori Lubke,<sup>a</sup> Bruce Chesebro<sup>a</sup>

- Published July 2018

# Methods

- Study began in 2003
- Cynomolgus macaques (CM) are considered good surrogates for humans (90-93% genetic similarity)
- Obtained CWD-infected elk and deer from Wyoming, Colorado, and South Dakota
- 6 CM were injected intracerebrally
  - *500  $\mu$ l of brain homogenate containing 5 mg of CWD-positive cervid brain.*
- 9 nine CM were inoculated orally using a rubber gastric tube.
  - *Doses were given at 2- to 6-day intervals for a total of 5 doses.*
  - *Each dose contained 0.8 g of brain homogenate for a total of 4 g of CWD-infected cervid brain containing up to  $2.0 \times 10^9$  infectious doses.*

# Methods (cont.)

- As a negative control, one CM was inoculated i.c. with a normal elk brain homogenate.
- Monitored for 13.4 years, before euthanized
- Monitored 2x daily for physical signs of prion disease
- Tissues were collected and analyzed using RT-QUIC, immunohistochemistry, and immunoblotting

# Results

- 5 monkeys developed weight loss
  - *4 of those had diabetes*
- All tests were negative for prion disease.
- “No clinical, pathological, or biochemical evidence suggested that CWD was transmitted from cervids to CM.”
- Limitations:
  - *Different strains of CWD may be more/less infective and may affect humans differently*
  - *CM are still different than humans*

# Prion 2017 Presentation

- Presented by Stephanie Czub of Alberta Prion Research Institute
- 18 macaques exposed to CWD in various ways (+3 controls)
- 3 of 5 CM fed CWD-infected white-tailed deer meat tested positive for prion disease
  - *“Equivalent of a 7 oz. steak once a month”*
- Not completed yet, not published or peer reviewed
- Study is unlikely to be repeated due to cost

# Challenges in interpreting these studies

- Are they comparable to the way humans would consume meat?
  - *Does that matter?*
- Was the incubation period long enough?
- Dose-response?
- What is the infective dose?
- Differences in CWD strain?
- How is human physiology different than animal models?

# EMERGING INFECTIOUS DISEASES™



[Emerg Infect Dis.](#) 2006 Oct; 12(10): 1527–1535.

PMCID: PMC3290936

doi: [10.3201/eid1210.060019](https://doi.org/10.3201/eid1210.060019)

PMID: [17176567](https://pubmed.ncbi.nlm.nih.gov/17176567/)

## Human Prion Disease and Relative Risk Associated with Chronic Wasting Disease

[Samantha MaWhinney](#),<sup>✉\*</sup> [W. John Pape](#),<sup>†</sup> [Jeri E. Forster](#),<sup>\*</sup> [C. Alan Anderson](#),<sup>‡§</sup> [Patrick Bosque](#),<sup>‡¶</sup> and [Michael W. Miller](#)<sup>#</sup>

“The relative risk (RR) of CJD for CWD-endemic county residents was not significantly increased (RR 0.81, 95% confidence interval [CI] 0.40–1.63), and the rate of CJD did not increase over time (5-year RR 0.92, 95% CI 0.73–1.16). In Colorado, human prion disease resulting from CWD exposure is rare or nonexistent. However, given uncertainties about the incubation period, exposure, and clinical presentation, the possibility that the CWD agent might cause human disease cannot be eliminated.”



REVIEW ARTICLE



Open Access



## Current evidence on the transmissibility of chronic wasting disease prions to humans—A systematic review

L. Waddell , J. Greig, M. Mascarenhas, A. Otten, T. Corrin, K. Hierlihy

First published: 30 January 2017 | <https://doi.org/10.1111/tbed.12612> | Cited by: 15

# Methods

- Systematic review of 23 studies
  - *From 4 countries*
  - *Published between 2000 and 2017*
  - *Looked at studies with different designs: epidemiologic, in vitro and in vivo experiments.*

# Results

- 5 epidemiologic studies
  - 2 studies on macaques
  - 7 studies on transgenic mice
- Found no evidence of CWD transmission to humans
- CWD has been found transmissible to Squirrel Monkeys
  - Several others studies were still ongoing
  - Difficult to determine how in vitro studies extrapolate to human risk

Volume 10, Number 6—June 2004

*Perspective*

## Chronic Wasting Disease and Potential Transmission to Humans

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[Cite This Article](#)

# KEY TAKEAWAYS



# Key Takeaways

- Currently, no direct evidence that CWD can be transmitted to humans
  - *No unusual cases of CJD*
  - *No increase of CJD in WY and CO*
  - *Negative/inconclusive experimental evidence*
- BSE/vCJD experience suggests risk is still possible
  - *Human exposure may increase as CWD spreads*
- Due to long incubation periods, convincing negative results will likely require years of follow-up

# Public Health Recommendations

- Do not consume meat from animals that test positive for CWD
- Do not consume meat from animals that appear sick
- Consider having deer or elk tested for CWD before you eat the meat.

# QUESTIONS?

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