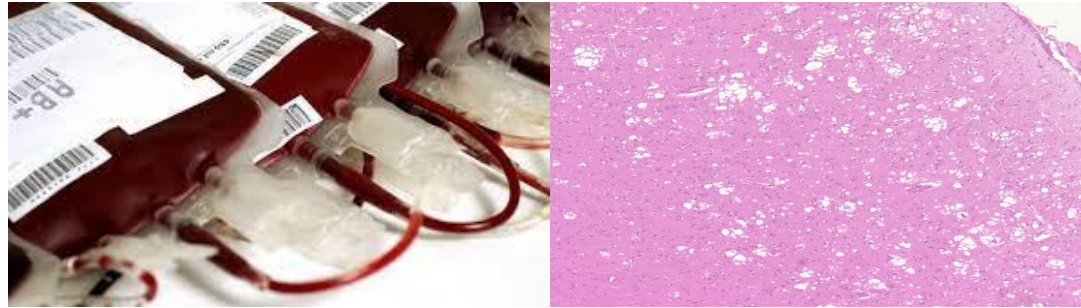


What is the vCJD Risk for Blood Safety in the UK Donor Population?



Richard Knight

UK National CJD Research & Surveillance Unit



TOPICS

BACKGROUND

SOME COMMENTS ON RISK

THE PRESENT SITUATION

WHAT IS THE vCJD RISK ?

TOPICS

BACKGROUND

SOME COMMENTS ON RISK

THE PRESENT SITUATION

WHAT IS THE vCJD RISK ?



BSE

1981

1st calves infected

1985

1st def case

1986:

Recognised



PRIOR TO 1989:

**460,000-482,000
BSE CATTLE**

Valleron et al Science 2001

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.

Findings Ten cases of CJD have been identified in the UK in recent months with a new neuropathological profile. Other consistent features that are unusual include the young age of the cases, clinical findings, and the absence of the electroencephalogram features typical for CJD. Similar cases have not been identified in other countries in the European surveillance system.

Interpretation These cases appear to represent a new variant of CJD, which may be unique to the UK. This raises the possibility that they are causally linked to BSE. Although this may be the most plausible explanation for this cluster of cases, a link with BSE cannot be confirmed on the basis of this evidence alone. It is essential to obtain further information on the current and past clinical and neuropathological profiles of CJD in the UK and elsewhere.

Lancet 1996; **347**: 921–25

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Correspondence to: Dr R G Will

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 death certificates in the UK on which CJD is mentioned are obtained and some cases are identified retrospectively in this way; some are identified from other sources. Clinical details are obtained for all cases, and information on potential risk factors for CJD is obtained with a standard questionnaire, usually administered to a close relative of the case. After obtaining informed consent from the relatives or patients, blood is obtained for DNA analysis in most patients. Information on all known cases of CJD in England and Wales since 1970 and in Scotland and Northern Ireland since 1985 is also available from previous surveys of CJD.¹ Parallel studies of CJD have been carried out in France, Italy, Germany, and the Netherlands between 1993 and 1995 with similar methods.²

Whenever possible, neuropathological examination is carried out on cases and suspect cases notified to the CJD Surveillance Unit. Such examinations have been done on about 70% of cases notified since May, 1990, either by referral for necropsy in Edinburgh or in cooperation with neuropathologists in other centres who refer cases after diagnosis. Blocks from the frontal, temporal, parietal, and occipital cortex; basal ganglia; thalamus; hypothalamus; cerebellum midbrain; pons; and medulla are fixed in formalin. Blocks are immersed in 96% formic acid for 1 hour before routine processing into paraffin wax. Sections are cut at 5 µm and stained by conventional histological techniques and immunocytochemistry for prion protein (PrP). Pretreatments for immunocytochemistry with two monoclonal PrP antibodies (KG9 and 3F4)³ include incubation in 96% formic acid for 5 min, then 4 mol/L guanidine thiocyanate for 2 hours, and hydrated autoclaving at 121°C for 10 min.

Results

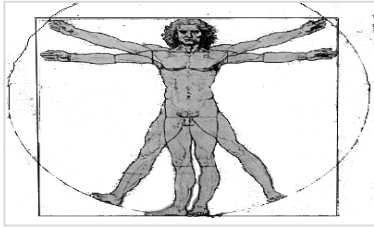
Patients

Of the 207 cases of CJD examined neuropathologically since May, 1990, ten have neuropathological findings that clearly distinguish them from other cases examined by the CJD Surveillance Unit (two have been reported previously^{4,5}).

These ten cases (four male) had disease onset from

1996: A NEW VARIANT OF CJD

ORIGIN:
BSE CONTAMINATION OF DIET



BSE: HUMAN vCJD

Def/Prob cases



vCJD: CURRENT WORLD NUMBERS

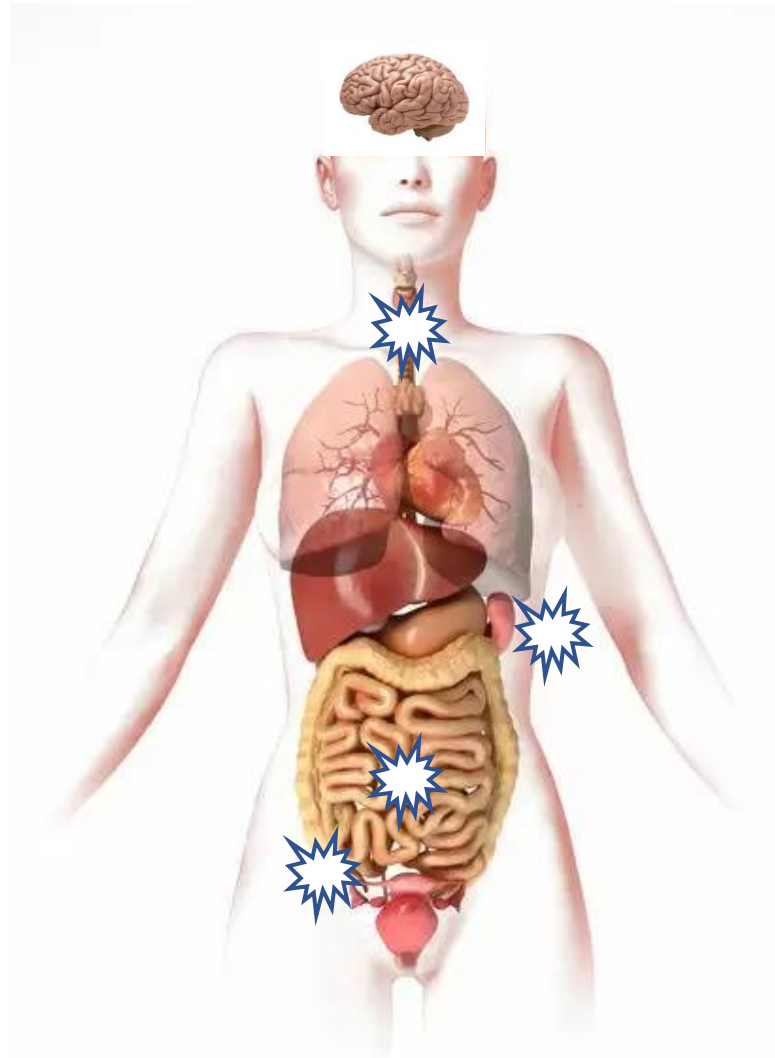
UK	178	[Last case onset 2014]
France	28	[Last case reported 2019]
Spain	5	
Rep of Ireland	4	
USA	4	
Italy	3	
Netherlands	3	
Portugal	2	
Canada	2	
Saudi Arabia	1	
Japan	1	
Taiwan	1	

***NOT NECESSARILY
INFECTED IN
THAT COUNTRY***

Sept 2022

NO KNOWN LIVING CASES

DIETARY VARIANT CJD



BRAIN DISEASE LATER

SYMPTOMATIC ILLNESS



INFECTION BEGINS IN LRS

ASYMPTOMATIC INFECTION

Peyer's Patches

Appendix

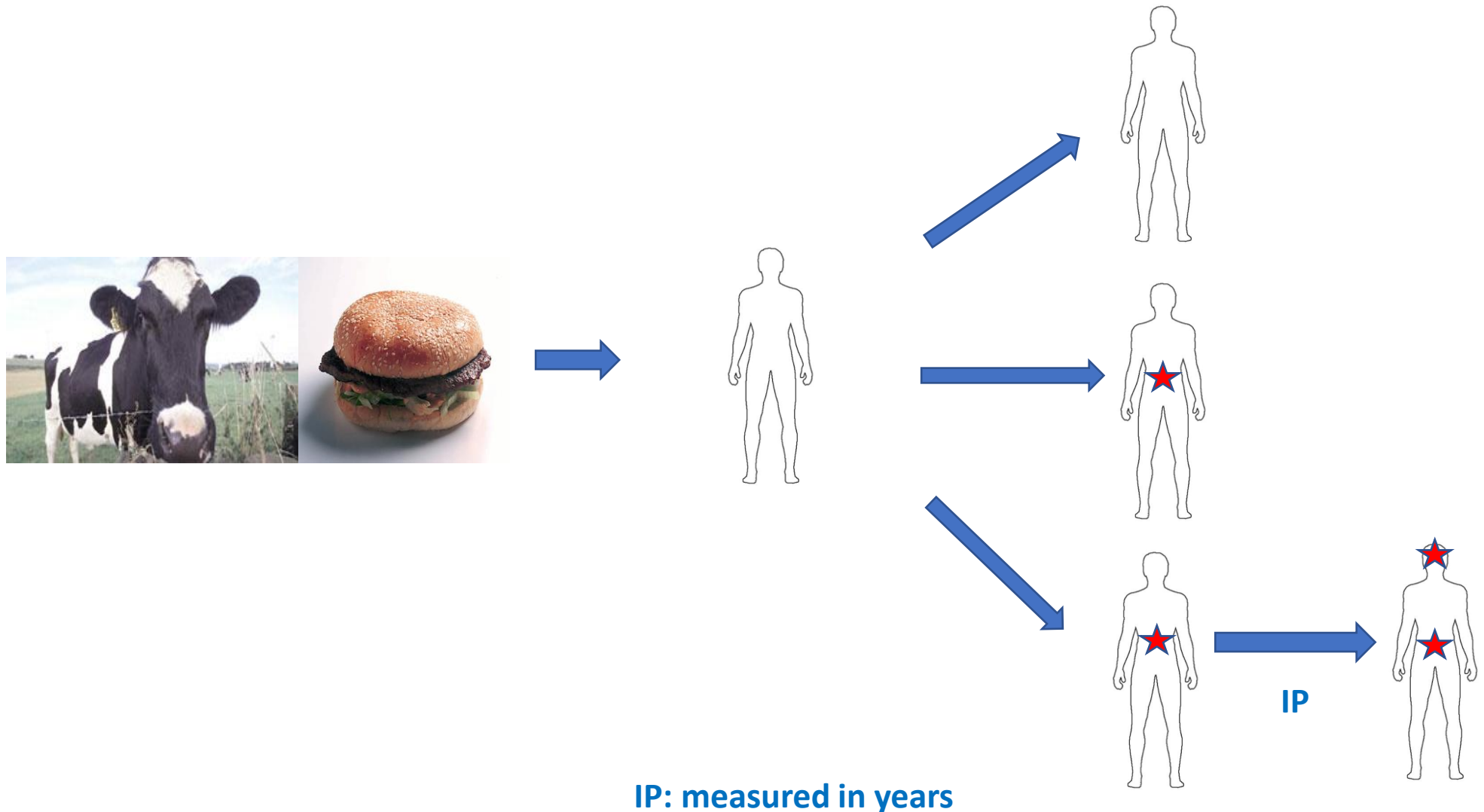
Tonsils

Spleen

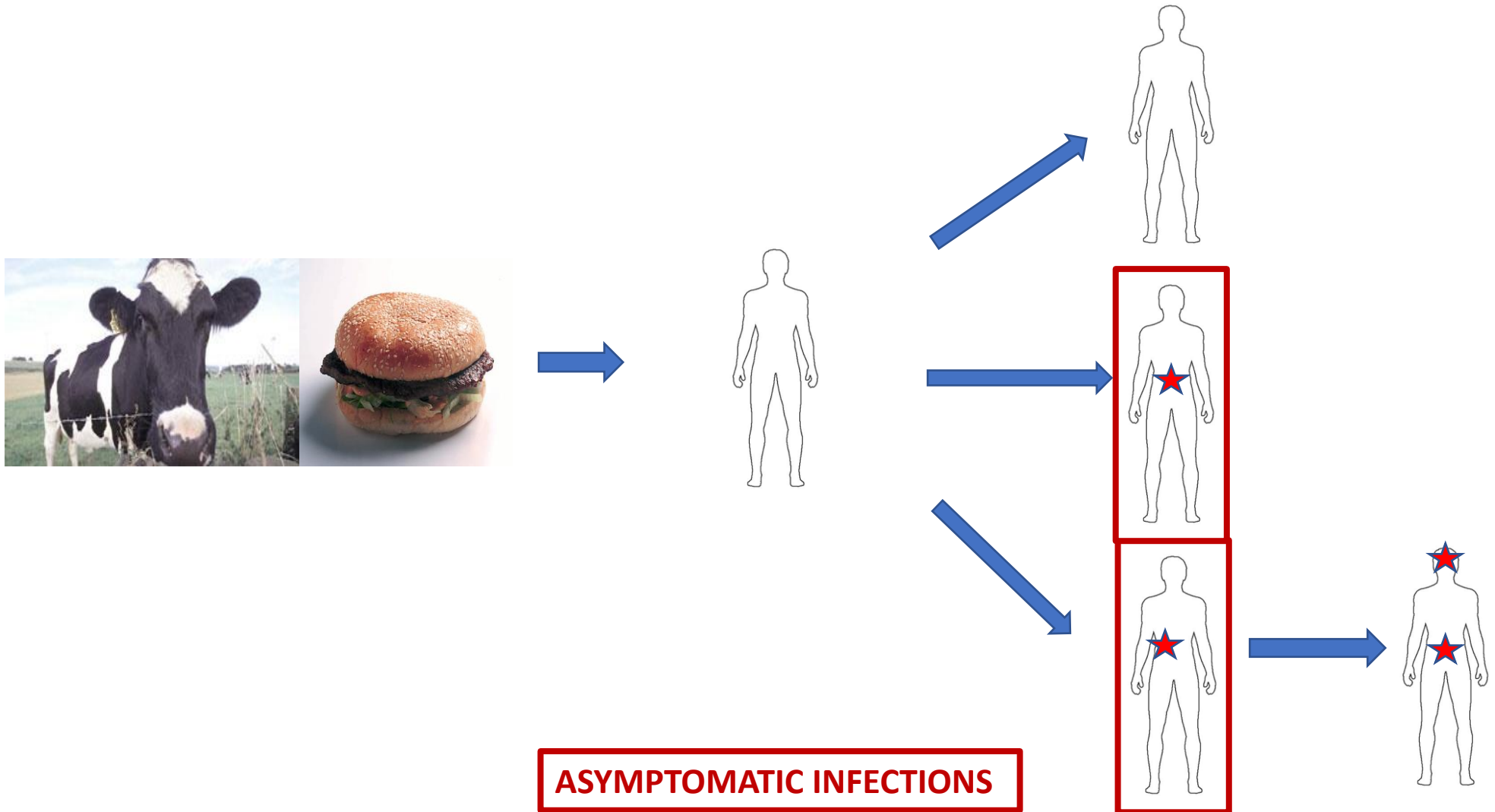
LN's

POSSIBLE OUTCOMES OF EXPOSURE TO INFECTION

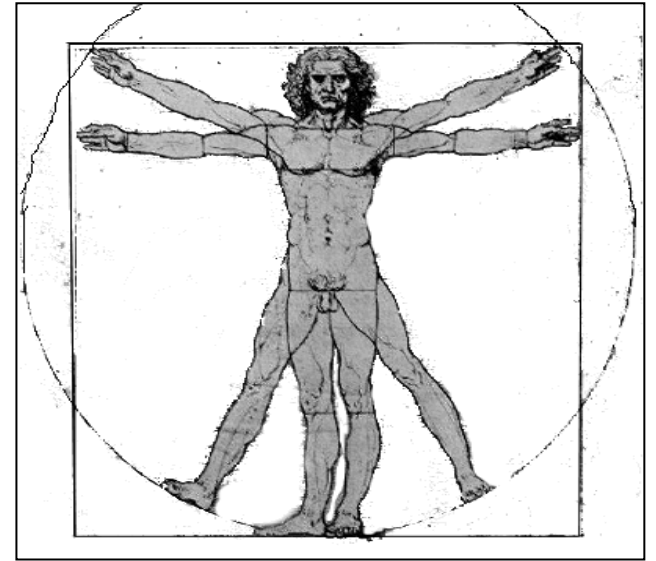
GOOD REASONS FOR THINKING ALL 3 OUTCOMES OCCUR IN BSE



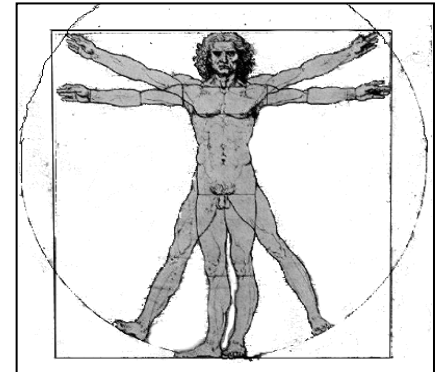
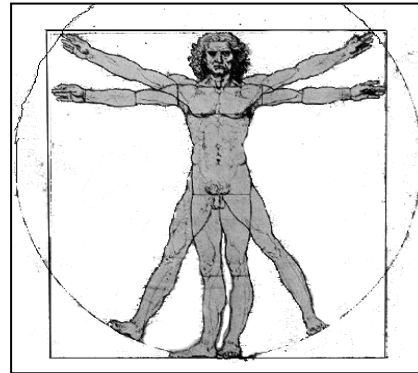
POSSIBLE OUTCOMES OF DIETARY EXPOSURE TO BSE



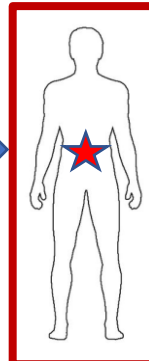
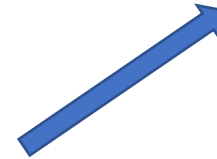
SPECIES BARRIER



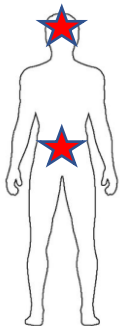
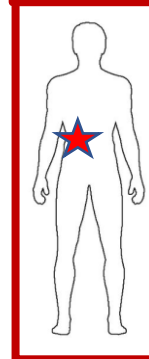
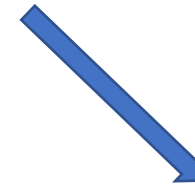
SPECIES ADAPTATION



LRS INVOLVEMENT: BLOOD MIGHT BE A PARTICULAR RISK



**ASYMPTOMATIC
DONORS**





Transfusion Medicine Epidemiological Review 1997: NCJDSU & UK NBServices



4 TRANSFUSION ASSOCIATED vCJD INFECTIONS IN HUMANS

3 CLINICAL CASES

1 ASYMPTOMATIC CASE

ALL NON-LEUCODEPLETED RBCs: 1996-1999

(UK universal leucodepletion: Oct 1999)

+ 1 Asymptomatic infection attributed to a blood product: Factor VIII [exposure 94/96]

TOPICS

BACKGROUND

SOME COMMENTS ON RISK

THE PRESENT SITUATION

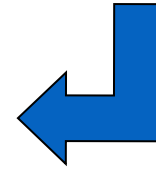
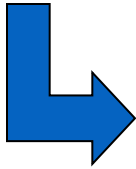
WHAT IS THE vCJD RISK ?

**LEVEL OF
INFECTIVITY
IN BLOOD**

**SUSCEPTIBILITY
OF RECIPIENTS**

RISK OF BLOOD TRANSMISSION

**FREQUENCY OF
INFECTION IN
DONORS**



```
graph TD; A{{LEVEL OF INFECTIVITY IN BLOOD}} --> B(RISK OF BLOOD TRANSMISSION);
```

**LEVEL OF
INFECTIVITY
IN BLOOD**



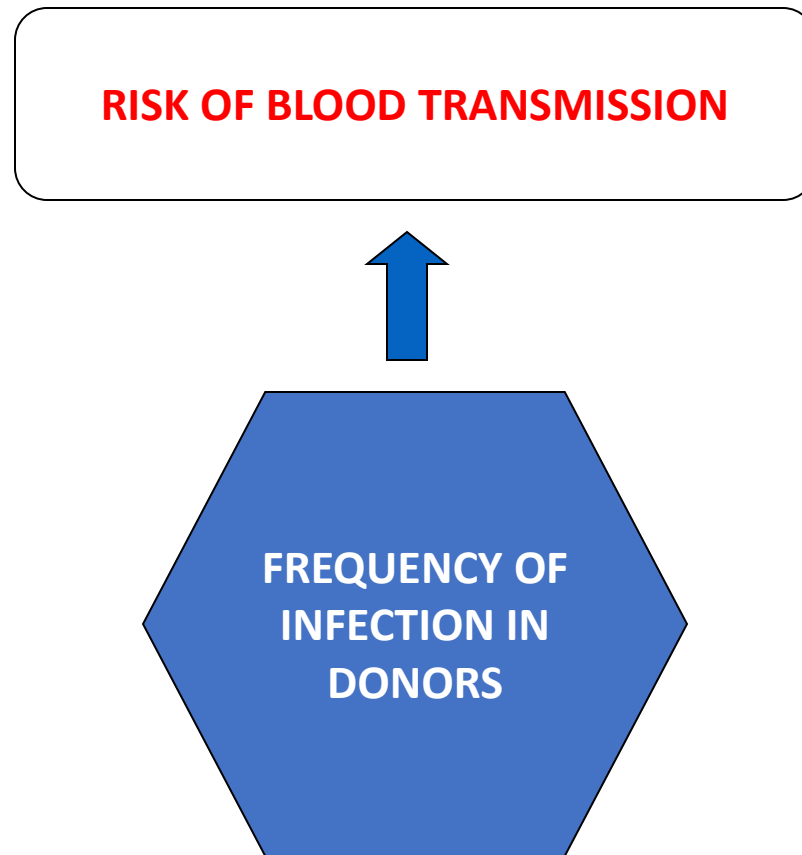
RISK OF BLOOD TRANSMISSION

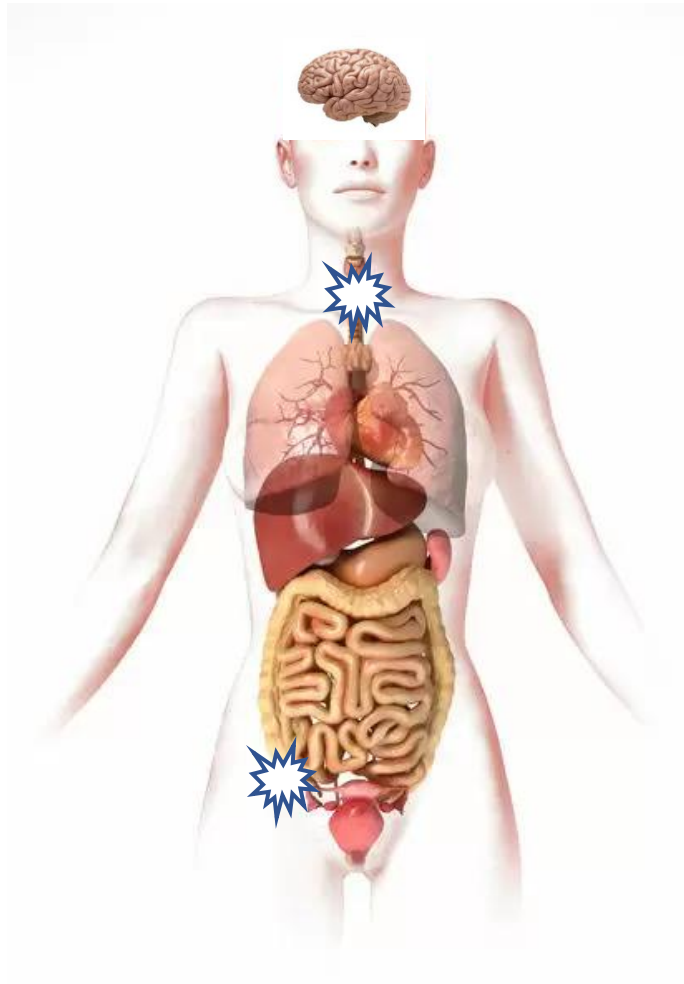
**How much infectivity in their blood ?
How any infectivity in blood varies over time ?
How any infectivity in blood varies for other reasons ?**

**Distribution of infectivity in Blood Components ?
Effectiveness of Leuco-reduction ?
Infectivity in PDMPs ?**

HOW MANY *ASYMPTOMATICALLY* INFECTED IN POTENTIAL DONOR POPULATION ?

[*Symptomatic* individuals would not be accepted]





ROUTINE APPENDICECTOMY* SPECIMENS

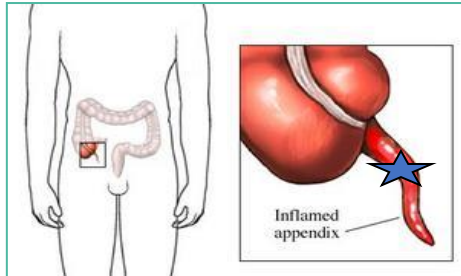
ANONYMISED

TESTED FOR ABNORMAL PRION PROTEIN

* *Some* Tonsillectomy specimens

**Now 3 studies reported
'Appendix I, II, III'**

APPENDIX I & APPENDIX II



STUDY	REPORT YEAR	POSITIVES	TOTAL	RATE / M [95% CI]	'CENTRAL' RATE
APPDX I	2004	3	12,674	237 [49-692]	1:4000
APPDX II	2013	16	32,441	493 [282-801]	1:2000

Hilton et al J Path 2004, Gill et al 2013 BMJ

DISCREPANCY

1:2000 Infected

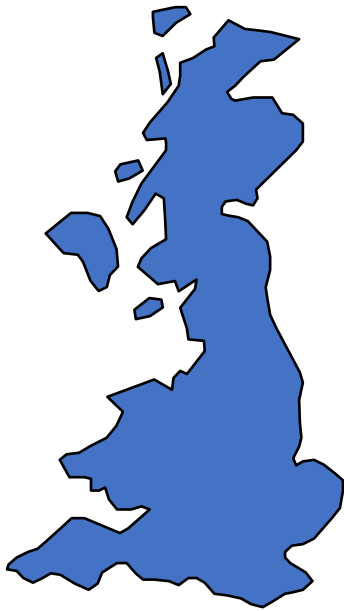
Only 178 cases. No onsets for 8 years

Very few secondary transmissions. None recently.

1:2000 “infected”:

Positive appendix = BSE infection

APPENDIX III



PRE-BSE

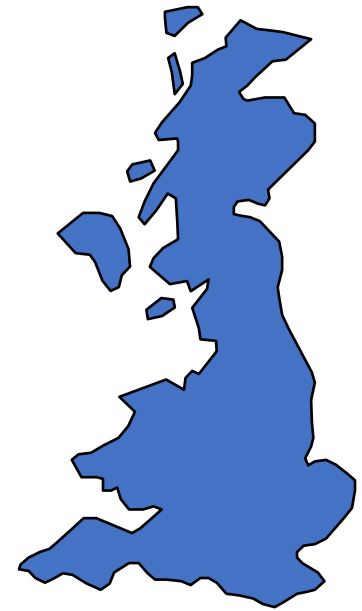
Appdx Sx < 1979



BSE

1980-1996

Appdx I & II



POST-BSE

Appdx in Born $\geq$ 1996

APPENDIX III

Appendix Surgical Specimens

Appdx Sx < 1979

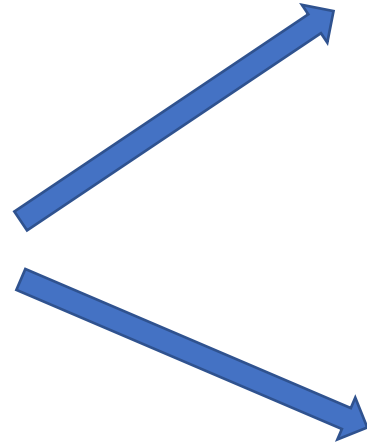
1980-1996

Born $\geq$ 1996

NO STATISTICALLY SIGNIFICANT DIFFERENCE BETWEEN THE PERIODS

POSSIBLE INTERPRETATIONS

APPENDIX III RESULTS

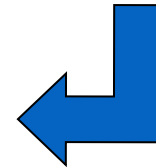


**A POSITIVE APPENDIX
IS NOT NECESSARILY BSE INFECTION**

**THE BSE RISK PERIOD
IS LONGER THAN WAS THOUGHT**

**SUSCEPTIBILITY
OF RECIPIENTS**

RISK OF BLOOD TRANSMISSION



?

ALL UNCERTAIN

**LEVEL OF
INFECTIVITY
IN BLOOD**

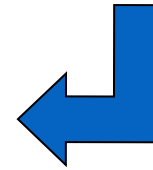
?

**SUSCEPTIBILITY
OF RECIPIENTS**

?



RISK OF BLOOD TRANSMISSION



**FREQUENCY OF
INFECTION IN
DONORS**

?

THE PRECAUTIONARY PRINCIPLE

MODELLING

BASED ON:

MANY ASSUMPTIONS (often 'worst case')

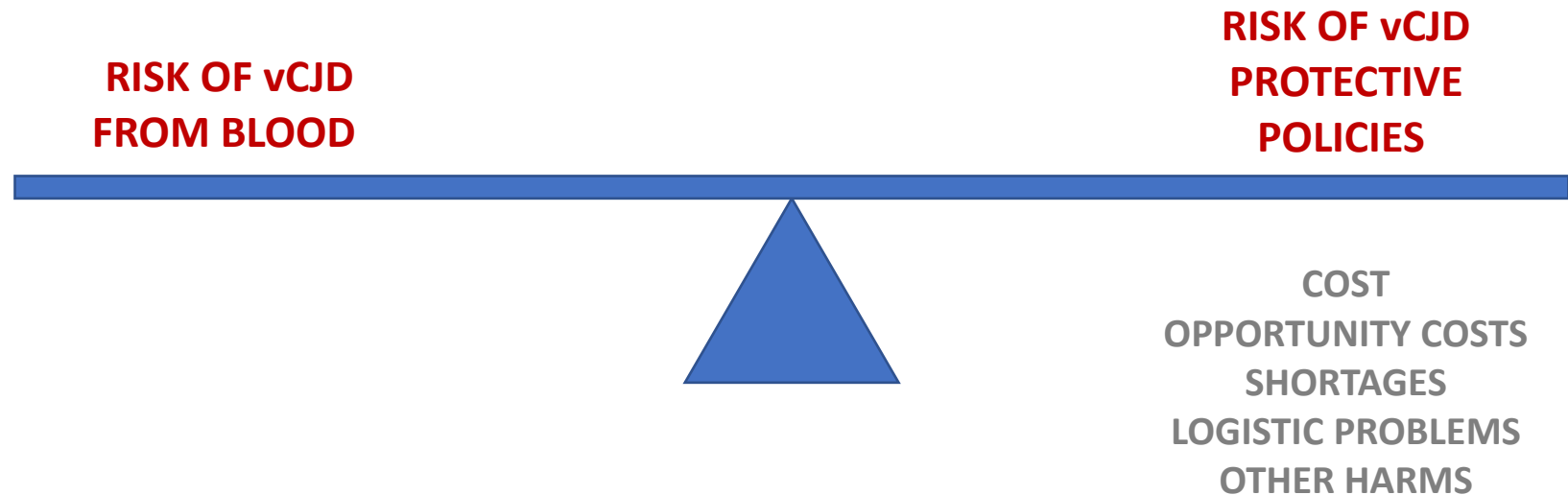
EXPERIMENTAL EVIDENCE (of uncertain translatability)

DECISIONS TAKEN

IN VERY UNCERTAIN CIRCUMSTANCES

OFTEN VERY PRECAUTIONARY

RISK ANALYSIS & RISK MANAGEMENT



TOPICS

BACKGROUND

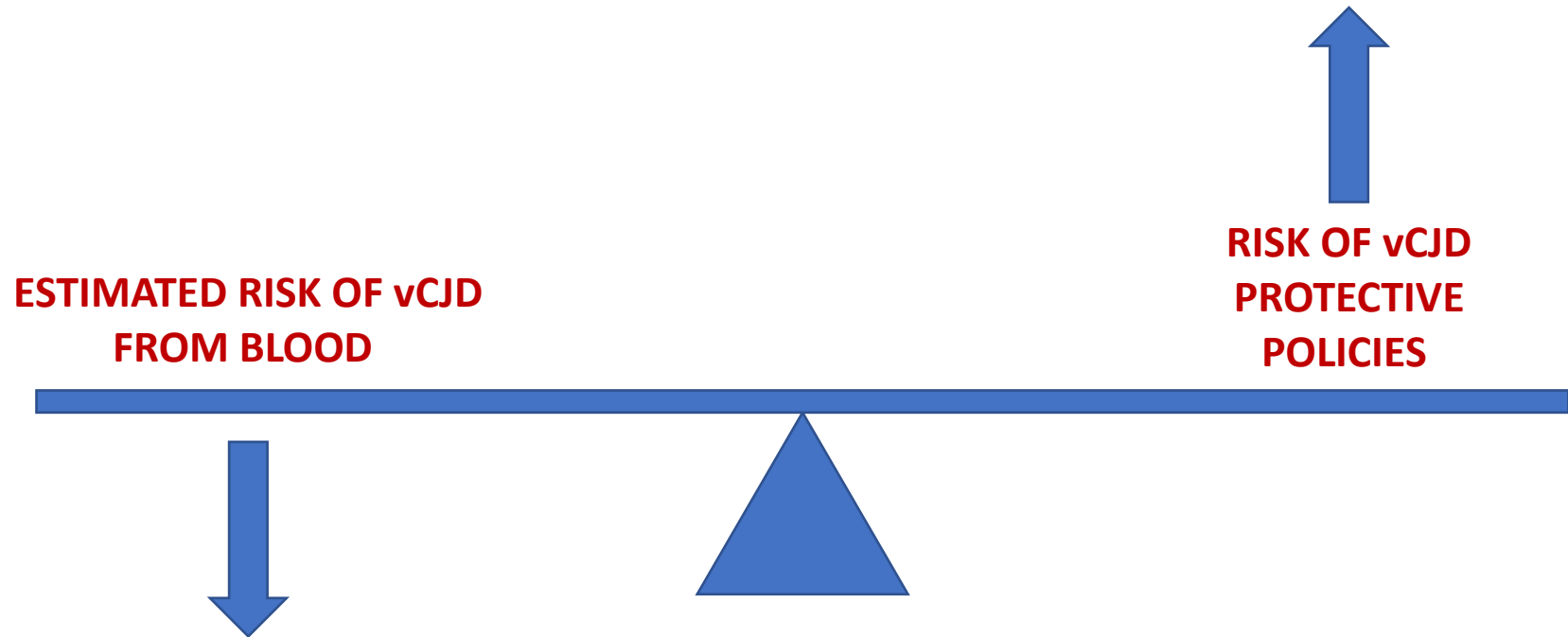
SOME COMMENTS ON RISK

THE PRESENT SITUATION

WHAT IS THE vCJD RISK ?

RISK ANALYSIS & RISK MANAGEMENT

Recent Considerations





September 2021



**Removal of need to use:
Imported Fresh Frozen Plasma (FFP) & apheresis platelets
for patients born after 1996.**

**Following 2019 Risk Assessment Modelling
UK SaBTO review: extremely low risk**

[Also Risk Management considerations]



February 2021



Lifting of ban on the use of UK plasma for manufacture of immunoglobulin for use in the UK

**CHM/MHRA consideration that vCJD risk would be negligible
[Also noting the clinical need for immunoglobulin]**



May 2022



Removed recommendations to defer blood donors who

- **Spent time in the UK from 1980-1996**
- **Received a blood transfusion in the UK 1980 onwards**

Recommended requalification of individuals previously deferred for these reasons

**Based on UK SaBTO & MHRA risk assessments
evaluated by FDA: “no or minimal additional risk of vCJD”**



April 2022



Overtaken its ban on former UK residents donating blood in Australia due to the perceived risk of vCJD.

“no negative effect on the safety of the blood supply”



2019



**Overturning of deferral of donors at risk
of vCJD exposure in the UK 1980-1996
(via residence, surgery or blood transfusion)**

**Following review of possible risk by the IBTS Medical
Advisory Committee**

SEVERAL RECENT POLICY CHANGES BY DIFFERENT BODIES

Based On:

**MAINLY
REDUCED RISK**

**SOME
RISK MANAGEMENT CONSIDERATIONS**

TOPICS

BACKGROUND

SOME COMMENTS ON RISK

THE PRESENT SITUATION

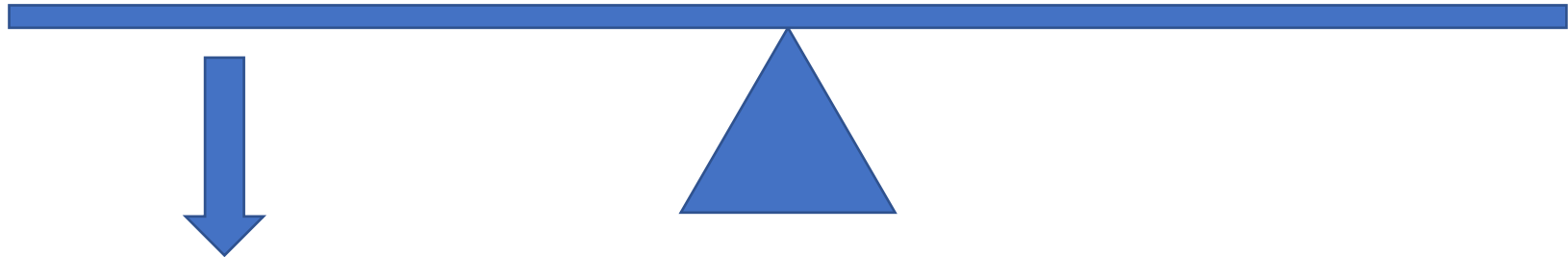
WHAT IS THE vCJD RISK ?

RISK ANALYSIS & RISK MANAGEMENT



**ESTIMATED RISK OF vCJD
FROM BLOOD**

**RISK OF vCJD
PROTECTIVE
POLICIES**



**BUT STILL.....
ESTIMATIONS BASED ON UNCERTAINTIES
DISAGREEMENTS THAT CANNOT BE RESOLVED**

IN THE GAME OF MODELLING (Predicting) EPIDEMIOLOGICAL DATA (Observation) ARE TRUMPS



EPIDEMIOLOGY DATA RELIABLE ?

UK CJD SURVEILLANCE SYSTEM: Expert assessment of all suspected cases

DEATH CERTIFICATE STUDIES

PIND [Paediatric] STUDY

OVER 65 STUDY

UK TMER STUDY

ANALYSES BASED ON TMER DATA

PRIMARY IMMUNODEFICIENCY STUDY

HIGHLY-TRANSFUSED STUDY

HAEMOPHILIA CENTRE STUDY

Variant CJD Summary

No known living cases in the world

Last recorded death in UK: 2016

vCJD not identified in UK in anyone born after 1989

No UK Blood/Blood Product-related cases with exposure after 1999

Only 1 PDMP implicated & not certain



**No reports of vCJD transmission despite:
Issue of >40 million* UK-derived blood components**

No reports of plasma or platelet transfusions transmissions

[*allowing for an 8-year IP, post leuco-reduction]



Second highest vCJD case number



Domestic plasma collection & fractionation continued

No reported

Transfusion-transmitted cases

Cases related to plasma products

Garske & Ghani 2010

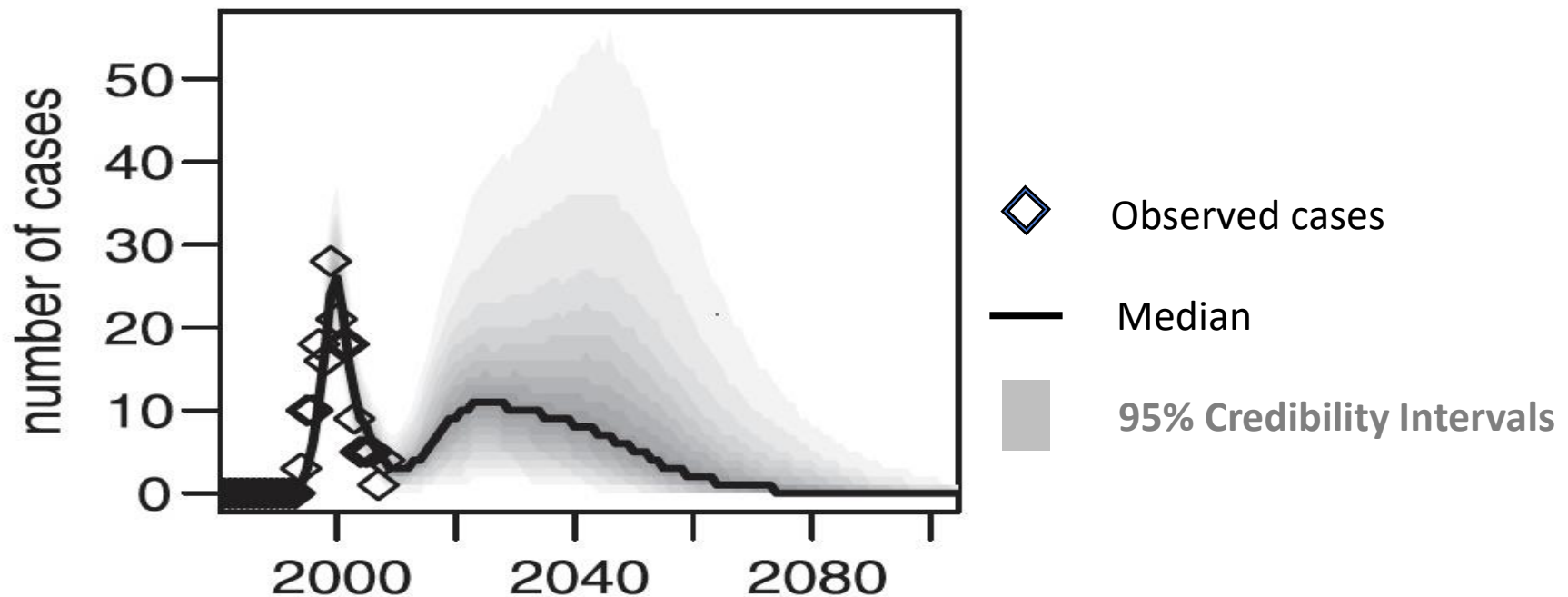
2010-2179:

Predictions: ALL cases of vCJD (Dietary & Blood-related)

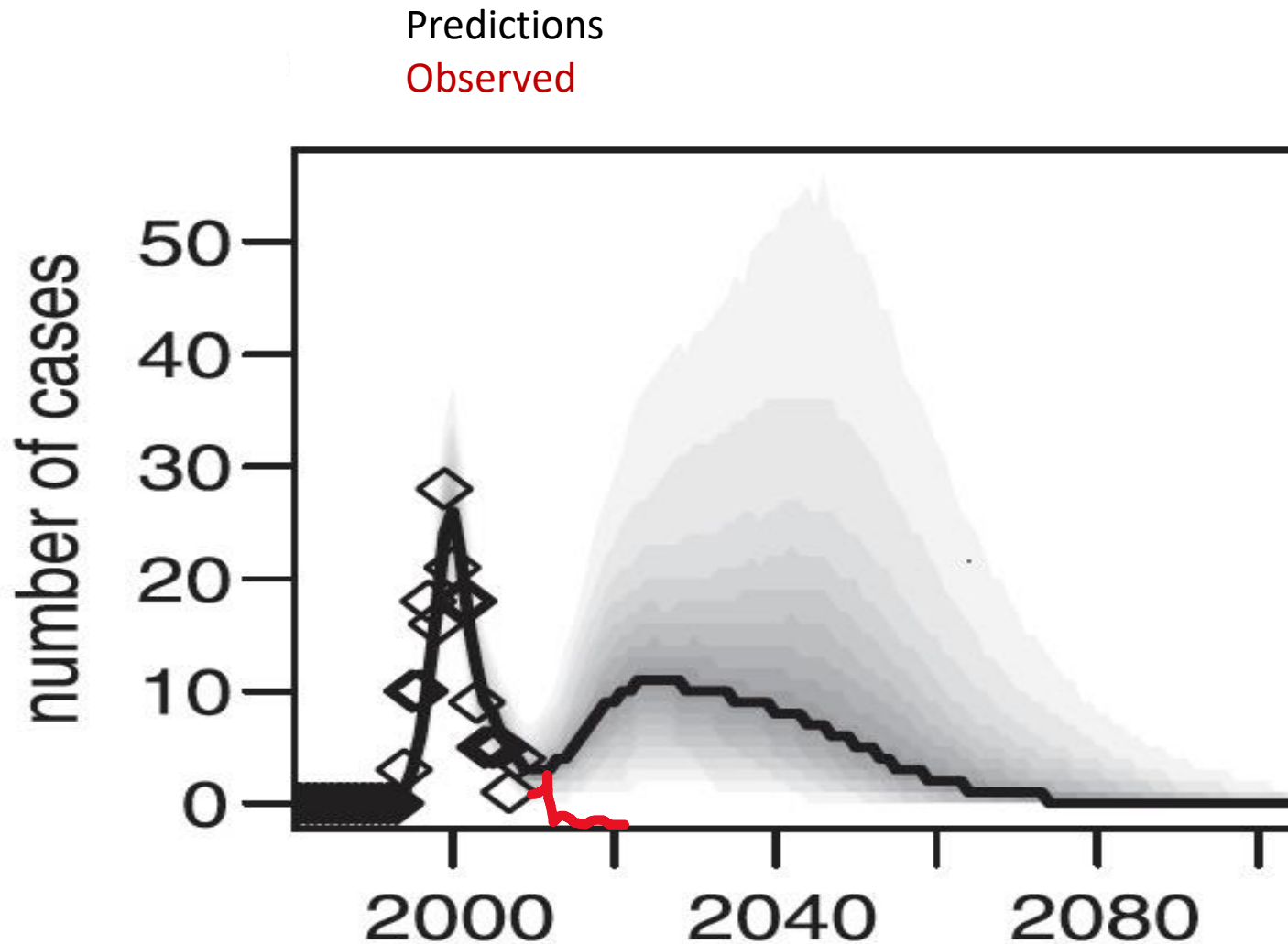
TOTAL: median 390 [95% CI: 84-3000]

Primary: median 100

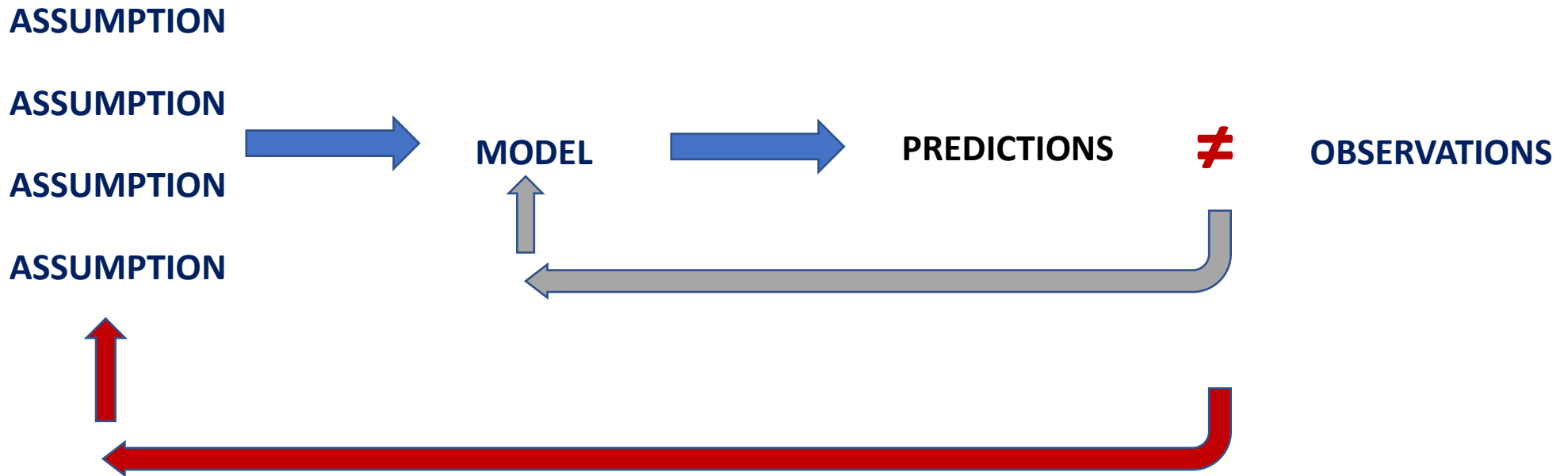
Identified Blood cases: median 17



Garske & Ghani 2010 & Present Position 2022



PREDICTIONS & OBSERVATIONS



Which assumptions are wrong?
But from a policy viewpoint-Does it matter?

WHAT IS THE RISK ?

ACCORDING TO THE OBSERVATIONS:

BLOOD COMPONENTS with Leuco-reduction: EXTREMELY LOW

PDMPs: NEGLIGIBLE

[With increasing need for some PDMPs]

[Stop Press: The UK Plasma Risk Assessment Working Group Paper]

Thanks to:

**STAFF AT NCJDRSU, NPC & ELSEWHERE
LOCAL MEDICAL TEAMS
BTS**

RESEARCH FUNDERS

PATIENTS & FAMILIES

