Estimates of the vCJD epidemic in the UK
Azra Ghani, Paul Clarke, Tini Garske
London School of Hygiene & Tropical Medicine

vCJD Risk Assessment – Primary Infection

- Dose/age/genotype dependent
- Survivorship
- Infectivity - by tissue & incubation stage
- Dose response - linear/non-linear/cumulative
- Susceptibility heterogeneity
- Consumption rates - per individual/per product
- Heterogeneity - by age/time - consumers per bovine
- Tissue types used for food - by time/type of bovine
- SBO ban effectiveness
- Estimation of infected animals slaughtered through time

Back-calculation
- Use case numbers and knowledge about the incubation period distribution to estimate numbers infected ‘backwards’ in time
- Infection rates close to current time given by those with ‘shorter’ incubation periods
- These infection rates can be used to make short-term predictions about cases arising from those infected at this time but with longer incubation periods

Back-calculation in words
Suppose we have a case of disease observed in 2005. Then under our simple model the probability that we observe this case is:
- number infected in 2004 x prob. incubation period = 1 year
- number infected in 2003 x prob. incubation period = 2 years
- number infected in 2002 x prob. incubation period = 3 years
- number infected in 1982 x prob. incubation period = 23 years
- number infected in 1981 x prob. incubation period = 24 years
- number infected in 1980 x prob. incubation period = 25 years

Parameters in primary risk models
- Estimates of numbers of infected bovines by time and disease stage at slaughter
- Function which relates stage of disease of animal to infectivity
- Incubation period – time from infection to onset of disease or death
- Age-dependent susceptibility/exposure – allows younger individuals to be at higher risk
- Effect of control measures – SBO ban in mid-1989 removed highest risk material from food supply but may not have been totally effective
- Transmission probability
- Competing causes of survival/birth cohort size

Predictions of future clinical cases or deaths
- Models are able to produce statistically robust estimates of future cases once the epidemic has peaked (in UK in 2000)
- All published models now give similar estimates
- Predictions only valid within populations studied:
  - to date UK cases do not include cases assigned to other countries
  - consider all cases but one to be acquired from consumption of BSE-infected beef
  - only consider the MM-homozygous population to be at risk
  - assume a uni-modal incubation period
  - majority assume no age-dependency in incubation period
Updated case predictions for primary epidemic

- Based on time- and age-stratified vCJD deaths and results from appendix survey
- Include carrier state – proportion of individuals who become infected and are detectable in appendix but do not go on to develop clinical disease (see later)
- Exclude one patient who is thought to have acquired infection via blood
- Predictions only in the MM-homozygote population (40% of UK population)

Long-term estimates & 95% bounds/prediction intervals for vCJD mortality

<table>
<thead>
<tr>
<th>Year of data</th>
<th>vCJD case data alone / with carrier state</th>
<th>vCJD case data plus appendix data</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999</td>
<td>(83-136,000)</td>
<td>136 (45-175,000)</td>
</tr>
<tr>
<td>2000</td>
<td>(50-50,000)</td>
<td>100 (10-7,000)</td>
</tr>
<tr>
<td>2001</td>
<td>80 (10-7,000)</td>
<td>101 (10-2,800)</td>
</tr>
<tr>
<td>2002</td>
<td>40 (9-640)</td>
<td>100 (10-2,800)</td>
</tr>
<tr>
<td>2003</td>
<td>69 (12-189)</td>
<td>133 (32-3,780)</td>
</tr>
<tr>
<td>2004</td>
<td>37 (10 - 105)</td>
<td>-</td>
</tr>
</tbody>
</table>

- Change in methodology to statistical fitting from 2000 onwards – from this point onwards projections are future cases; prior to this projections are total epidemic size
- *Note: 2002 estimates are based on 1/8318 appendix results, 2003/2004 based on 1/312,674 appendix results*

Age-dependent susceptibility/exposure

Uniform distribution with gamma-distributed tails fitted to age-classified deaths

Mean incubation period for primary infection

Incubation period in this model is defined as the time from infection to death – mean incubation period approximately 9-11 years

Estimates of prevalence of infection

- Models fitted to clinical cases alone are unable to estimate prevalence of infection
- If survey data are included they can predict prevalence in a wider age-group consistent with survey results
- For clinical cases & survey to be consistent, need to include possibility of a carrier state
- Survey results are scaled to apply only to the MM population

Inclusion of carrier state

- A proportion of those infected do not develop clinical disease
- Projections of future cases are the same as fitting to clinical cases alone
- Estimates that 10%-15% of infections go on to develop clinical disease (95% confidence interval <5%-30%)
Estimates of prevalence by age-group

Prevalence in 20 year olds over calendar time

Note: Depends on assumptions made about sensitivity of the test on appendix tissues over the course of the incubation period – here test sensitive for last 75% of incubation period

Past, Current and Future Prevalence – Primary Infection

Note: 84% of infections are carriers and hence persist for many years

Genotypes

- Codon 129 frequency in population: Approx. 40% methionine (MM) homozygous, 10% valine homozygous (VV) and 50% heterozygous (MV)
- All tested clinical cases are MM
- One patient with PrP detected in spleen was MV
- Data suggest non-MM individuals are either less susceptible to infection and/or have longer incubation periods – these two possibilities were explored in sensitivity analyses to assess impact on projections of future cases

Extension of models to incorporate wider genetic susceptibility

- Genetic model explores MM versus non-MM (ie VV and MV)
- Mean incubation period in non-MM is scaled from that in MM – shape parameters remain the same for both genotypes
- Model fitting simplified – fits MM case data stratified by time/age and zero clinical cases in non-MM to end of 2004
- Also fitted to appendix survey results in simplified form assuming draw from random sample of the population
- Sensitivity analysis – in mean incubation period for non-MM and susceptibility

Cases in non-MM genotypes

- Given no cases in non-MM genotypes, it is not possible to predict what will happen in this group
- However, sensitivity analyses can look at assumptions regarding increased incubation period and reduced susceptibility in this group to explore potential size of epidemics.
- Future case estimates can be up to 5-fold higher

Risks to blood transfusion recipients in the UK

- 27 of the 154 vCJD cases are known to have been blood donors – 18 of these were traced at blood centres.
- 49 components of blood transfused to named recipients
- 15 individuals known to have received blood transfusions from these 27 individuals are currently being followed
- 1 of these individuals developed vCJD 6.5 years after receiving the transfusion – the probability that this would occur by chance (i.e. that there was no link between the two cases) is very low.
- 1 further individual died of other causes but had detectable PrPSc in his spleen, but not his appendix or tonsil tissue.
Measures in place to reduce the risk of transmission in the UK
• Several measures have been put in place to reduce the risk of transmission:
  – 1997: All probable vCJD cases reported to NBS and any remaining blood donated is destroyed
  – July 98/Oct 99 – Leuco-depletion phased in
  – Nov 98/Dec 99 – Phase-out use of UK-sourced plasma in manufacture of blood products
  – Apr 04 – Recipients of blood transfusions after 1/1/1980 in the UK excluded from donating blood
  – Aug 04 – Donors unsure about whether they have had a blood transfusion and apheresis donors who have had a blood transfusion excluded
• Recent research suggests that leuco-depletion reduces infectivity by no more than 50%

What determines the potential scale of transfusion-associated transmission?
Chains of transmission between hosts

R₀ and the scale of the epidemic

Factors determining R₀
• The infectious dose – what is the probability that an individual given x units of infected blood will become infected
• The number of donations and recipients of transfusions ie. the magnitude of the blood supply:
  – Donations:
    National Blood Service Figures for 1996/97 – 1,907,000 donors donated 2,215,000 units of blood – 4300 units donated per 100,000 population per year (Source: DNV)
  – Red-cell transfusions
    – Wallis et al. BMJ 2002: 4274 units per 100,000 population per year

Summary
• vCJD clinical cases remain low
• Predictions based on clinical cases or including a carrier state are low (upper 95% CI – 200)
• Prevalence estimated from appendix survey is higher than would be expected from epidemic observed so far.
• Inclusion of carrier state to explain the discrepancy estimates that only 10% of those infected become clinical cases
• Possibility that appendix samples are in other genotypes – worst-case scenario is that non-MM genotypes have similar susceptibility and longer incubation periods. In worst-case, total projected case numbers are 5-fold higher.
• Remaining uncertainty – blood transmission & secondary epidemic
Acknowledgements

Department of Infectious Disease Epidemiology, Imperial College
Neil Ferguson, Christl Donnelly, Roy Anderson

vCJD Surveillance Unit, Edinburgh
Bob Will, Hester Ward & James Ironside

Derriford Hospital, Plymouth
David Hilton

Department of Infectious & Tropical Diseases, LSHTM
Simon Cousens, Peter Smith

Funding: Department of Health, The Royal Society

Key Model References