Reviewer’s report

Title: Epidemiological evidence of higher susceptibility to vCJD in the young

Version: Date: 10 March 2004

Reviewer: Simon Cousens

Reviewer’s report:

General

-----------------------------------------------------------------------------------

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

The equation presenting the model (Pi(a,t) = ...) is unclear to me. The authors mention a “planar Poisson process in a lexis diagram”. This is jargon with which I am unfamiliar. What does this mean? The "lexis diagram" part of the statement suggests that discrete time intervals were used (see comment below). I presume that Pi() represents the mean of a Poisson distribution. What is beta exactly? A measure of the relative exposure of males and females? Where does the size of the birth/gender cohort appear in the model?

The authors define the “likelihood” which they maximize. This appears to be a Poisson log likelihood rather than a likelihood. The authors should clarify whether they really mean the likelihood or they mean the log likelihood. I am also unclear why the second part of the likelihood is a double integral rather than a double summation. Was this really based on continuous time or on discrete time intervals. If the latter then it would be more correct to show a double summation and it would also be less confusing for the reader. The males and females could then be dealt with as a third summation or will need to be enclosed in parentheses (missing at the moment.

The authors present 95% confidence intervals for their estimates but nowhere describe how these were obtained. I would expect that the parameter estimates may be quite strongly correlated and it will therefore be important that the confidence intervals were obtained from the profile log likelihood. The authors must describe the approach they used to obtain confidence intervals.

One caveat that needs to be raised in the discussion is that all of the work presented is based on the premise that humans were infected through diet. While this remains the most plausible explanation for all except perhaps one of the observed UK cases, there is rather little direct evidence to support this hypothesis. I'm not sure if this is what the authors are trying to say at the end of the discussion ("still there is no evidence..."). If so, this could be expressed more clearly.

-----------------------------------------------------------------------------------

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

At the end of paragraph 1 of the results Figure 2 is referred to as showing good agreement between the age distribution of observed cases and model predicted cases. This reference should be to (current) Figure 3. The subsequent reference to figure 3 is actually to Figure 2. The figures need to be switched.
In the model “Diet alone” we are told that the expression $f(a) = f_0(e(a) – \min(e(a)))$ is used to examine the effect of a threshold dose. All this does is to set $f(a)$ to 0 in the age group with the lowest consumption. I do not think this results in an illuminating examination of the existence of a threshold dose. The authors could drop this from the paper.

Discretionary Revisions (which the author can choose to ignore)

$\Pi()$ is commonly used to represent a binomial probability and it may confuse some readers to see it here used to represent the mean of a Poisson process. $\mu()$ might be less confusing notation.

In their model the authors assume that exposure to infection increased exponentially over time from 1980 to 1989 and then declined exponentially between 1989 and 1996. In the introduction they refer to the age/gender specific exposure estimates of Cooper and Bird, and the opportunity this provides for disentangling exposure and susceptibility effects. They use these estimates to produce relatively complex (5 parameter) age/exposure patterns. It is therefore slightly surprising that they have chosen a relatively crude representation of the pattern of exposure over time. Some discussion of/justification for this exposure pattern would be helpful.

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No

Declaration of competing interests:
None