Commentary: Predicting the unpredictable: the future incidence of variant Creutzfeldt-Jakob disease

Azra C Ghani

Following publication of the report from the bovine spongiform encephalopathy (BSE) inquiry into the handling of the BSE epidemic in the UK, there has been a considerable loss of public trust in the safety of food products and in the handling of disease outbreaks more generally, highlighted by intense public and media reaction to E. coli, salmonella, foot-and-mouth, and most recently severe acute respiratory syndrome (SARS). Perhaps for this reason, and despite the relatively small numbers of cases, there continues to be substantial public interest in the future course of the variant Creutzfeldt-Jakob disease (vCJD) epidemic. In addition, and again perhaps in part stimulated by the precautionary principle proposed by the BSE inquiry report, there is an ongoing need for updated estimates of the future incidence of vCJD so that public health safety measures (such as the Over Thirty Months Scheme which prevents older cattle from entering the human food supply) can be constantly evaluated. Thus there is a growing number of publications providing such predictions based on the limited case numbers (135 cases to the end of May 2003) in the UK.

Predicting the future incidence of new diseases is always fraught with difficulty, as epidemiologists are hampered by limited data on the cases, the absence of reliable diagnostic tools and often a poor understanding of key properties of the disease such as its mode of transmission. A good example is the emergence of human immunodeficiency virus (HIV)/AIDS in the 1980s, for which a range of predictions was made using different methods based on the incidence of new cases before diagnostic tools, better data on sexual behaviour, and unlinked anonymous testing became available. Following on from the experience gained from the HIV/AIDS epidemic, early predictions of the vCJD epidemic in the UK highlighted the great uncertainty with wide bounds on future incidence. As the epidemic has progressed and understanding of the biology and epidemiology of the disease has improved, the bounds on these estimates have gradually narrowed, such that current predictions made by a number of groups all now suggest a relatively small epidemic.

However, many of the key epidemiological markers of this disease remain unknown, including the pattern of exposure of the population to BSE-infected material, the incubation period distribution, and the mechanisms resulting in the observed excess of cases in young individuals. In the paper in this issue of the International Journal of Epidemiology by Cooper and Bird, some of these issues are addressed, in the first analysis combining dietary exposure data into prediction models. Whilst dietary exposure data are notoriously difficult to collect (given problems with recall and the inconsistency of data from different sources), Cooper and Bird in a previous publication highlighted an interesting discrepancy. By calculating the exposure of the population to mechanically recovered meat (MRM) and head meat of bovines (the parts of BSE-infected cattle thought to be more infectious), they discovered that the older cohort (born between 1940 and 1969) was exposed to a greater extent than the young (born from 1969 onwards). This is in contrast to the excess of vCJD cases observed in the younger cohort. These results suggest that either the younger cohort were much more susceptible to infection and/or have shorter incubation periods. In the paper in this issue, the authors develop models to explore these hypotheses. Their results suggest that the younger cohort were both more susceptible to infection (demonstrated by the lower transmission barrier estimated for this cohort) and that their incubation period is much shorter.

As the years have progressed, it has become apparent that the future case incidence is likely to remain low (Cooper and Bird predict 163 future onsets between 2001 and 2005 and 88 onsets between 2006 and 2010). This low incidence suggests the existence of a significant species barrier between cattle and humans. However, as noted by Cooper and Bird, it is not possible to estimate the number of people who have become infected with the disease but do not display clinical symptoms from case incidence alone. Thus, they coin the term ‘transmission barrier’ to represent the inverse of the average number of clinical cases arising per dietary exposure unit. Their results demonstrate that, even for what appears to be a simple term, great uncertainty still exists in this value depending on the assumptions made regarding the relative infectivity of BSE-infected bovines over the course of their incubation period and the mean incubation period in humans—with higher transmission barriers estimated for short incubation periods and vice versa.

Despite the relatively small number of cases, continued surveillance will be required over the coming years to identify any changes in the incidence both of vCJD and other human transmissible spongiform encephalopathies, the emergence of cases in other genotypes (all cases to date have been in those who are methionine-homozygous at codon 129 of the prion protein gene—a trait shared by approximately 40% of the population), and any social, demographic, or geographical clustering of cases. In addition, there remains the theoretical possibility of secondary transmission from human-to-human through blood products or surgery. This latter point continues to remain uncertain, not only because of our improving but still limited
understanding of the biology and modes of transmission of these diseases, but also because any estimates of the risk from these routes can only be made with accurate information on the prevalence of asymptomatic infection in the population. One recent study provided the first estimate of asymptomatic infection in the UK population through testing approximately 8000 appendix tissues for the presence of abnormal PrP protein (one tissue was found to be positive). Additional studies in tonsil tissues are currently underway, with a national archive centre for tonsil tissues currently being established. It is hoped that these studies will improve the precision of estimates of the prevalence of asymptomatic infection. However, the development of a simple diagnostic test (for example, a blood-based assay) that can be applied anonymously at a population level remains a high priority.

References