GENETICALLY DETERMINED SUSCEPTIBILITY TO FEED-BORNE INFECTION WITH BOVINE SPONGIFORM ENCEPHALOPATHY: ANALYSIS OF A COHORT STUDY AND DAM IDENTIFICATION DATA

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SUMMARY
We describe analyses of two data sets relating to maternal risk enhancement: data from a seven-year cohort study (Wilesmith et al. 1997, Donnelly et al. 1997a) of the offspring of BSE-affected dams and their matched controls and identification data on the dams of BSE cases born after the introduction of the ruminant feed ban in July 1988 (Donnelly et al. 1997b). Our aim is to characterize the maternal transmission rate (as a function of maternal incubation stage where possible) and genetically variable susceptibility using a range of genetic models including that suggested by the one study to date to find any differences in the PrP gene between BSE-affected and unaffected cows (Neibergs et al. 1994). Results indicate significant heterogeneity in susceptibility to feed infection.

Keywords: Bovine Spongiform Encephalopathy, maternal transmission, cohort study

INTRODUCTION
The epidemic of bovine spongiform encephalopathy (BSE) in the United Kingdom has had enormous consequences for the agriculture industry and political relationships between European member states. The British epidemic of BSE cases peaked in 1992, but public and political attention became more intensely focused on the disease following the announcement in the House of Commons in March 1996 that the most likely explanation for 10 cases of an apparently new variant of Creutzfeldt-Jakob disease (nvCJD) in humans (Will et al. 1996) was exposure to the agent of BSE before regulations were introduced to prevent any part of cattle with clinical signs and specified offal from all cattle from entering human food. This announcement triggered a crisis in consumer confidence in beef and beef products throughout Europe.

The disease BSE was first identified in southern England in November 1986 upon the examination of the brains of two cattle at the Central Veterinary Laboratory (CVL), Weybridge England (Wells et al. 1987). Epidemiological investigations undertaken in 1988 and 1989 revealed that the consumption of meat and bone meal (MBM) from infected cattle was the probable cause of the rapid development of the epidemic in the cattle population within Great Britain (Wilesmith et al. 1988, Wilesmith et al. 1991). The oral route of infection for the BSE agent has since been demonstrated experimentally as it has for the agents of similar diseases (Barlow and Middleton 1990, Fraser et al. 1992, Middleton and Barlow 1993, Wells et al. 1994).
It is well known that host genotype has a major influence on susceptibility to transmissible spongiform encephalopathies in species other than cattle. The evidence of an important role for host genotype in cattle is less clear cut. Martin et al. (1991) genotyped 103 cattle for the prion protein (PrP) gene by length variance, 16 of which subsequently developed BSE, and failed to find an association between genotype and BSE. However, more recent work by Neibergs et al. (1994) suggested that BSE-affected cattle and their relatives are more likely to have a particular homozygous genotype than unrelated unaffected animals of the same breed or animals of different breeds.

Some progeny analyses have been undertaken (Curnow et al. 1994, Curnow and Hau 1996, Hau and Curnow 1996) to examine the possibility of two classes of animals (susceptible and resistant) within five Holstein-Fresian pedigree herds. However, the power of these studies was insufficient to distinguish between alternative genetic models. Until more data becomes available from larger scale pedigree studies, detailed statistical analysis of epidemiological data is needed to shed further light on the question of genetically determined susceptibility to BSE infection.

DAM AND CALF SURVIVAL LIKELIHOOD MODEL

In the analysis of data on maternal transmission, we require the likelihood of all possible dam-calf events (both dam and calf affected; both dam and calf unaffected; only dam affected; only calf affected). Assuming all information is available, a likelihood model can be constructed for the dam-calf events incorporating disease onset ages, dates of birth, genetically enhanced susceptibility to feed-borne infection and a model for the inheritance of susceptibility class.

The maternal transmission rate contributes to the likelihood for dam-calf pairs in which the dam was infected with the etiological agent of BSE by time of the birth of the calf. Data on the age of infection for naturally infected animals is never available since no ante-mortem test has been developed. Thus, the likelihood term for a dam-calf pair in which both animals experience disease onset but the onset in the dam is after the birth of the calf must incorporate the possibility that the dam was infected after the birth and the possibility that the dam was infected prior to the birth and thus capable, at least theoretically, of maternally transmitting the infectious agent. Similarly, a dam not observed to experience the onset of clinical signs of BSE cannot be assumed to have remained uninfected with the etiological agent of the disease. All animals not maternally infected are at risk of feed-borne infection at a level in part determined by their genetic susceptibility.

A survival model is adopted to simultaneously estimate the maternal transmission rate and measures of genetically variable susceptibility to feed-borne infection in the offspring of BSE-affected dams accounting for between-herd differences in feed risk and the duration of exposure of individual animals within pairs. This model is of the form proposed by Donnelly et al. (1997a) generalized to explicitly include genetic variability using models of the forms presented by Ferguson et al. (1997).
THE MATERNAL COHORT STUDY
A cohort study of maternally associated risk factors for BSE was initiated in July 1989 (Wilesmith et al. 1997, Donnelly et al. 1997a). It was designed as a matched exposed-control study to determine whether the risk of BSE is higher in the offspring of BSE-affected dams after controlling for exposure to potentially infectious feed. Maternally exposed animals were recruited from the offspring of dams identified in the main BSE database. For each, a control animal was recruited which was born in the same herd during the same calving period and whose dam had reached at least 6 years of age without developing clinical signs of BSE (but was not necessarily 6 years of age when calving). Both animals in a pair were recruited into the study at the same time. Of the 315 pairs originally recruited into the study, 301 remained after the exclusion of pairs if either animal died before March 1990 or if the dam of the control animal developed BSE at any time.

Animals in both arms of the study were exposed to potentially infectious feed prior to recruitment into the study at on at least one of the three farms used for study animals after recruitment. The magnitude of feed-borne infections depends upon seasonal and age-specific feed usage, feed infectivity which varies over time and between herds, and susceptibility to infection which is believed to vary with age and possibly with host genetic background.

THE DAM-CALF PAIR DATA IN THE CVL DATABASE
The identification data on the dams of BSE cases born after the introduction of the ruminant feed ban in July 1988 yield further information about the extent and pattern of maternal risk enhancement (Donnelly et al. 1997b). While these data provide information on calves born earlier in the dam incubation periods than can be obtained from the maternal cohort study, the data is observational. For this reason, additional uncertainties including survival probabilities arise. Tracing BSE cases born following the introduction of the ban on the use of ruminant material in cattle feed in July 1988 has identified 1346 BSE-affected dam-calf pairs. As before, the continued use of feed contaminated with the etiological agent of BSE after the introduction of the feed ban in July 1988 necessitates a model allowing for feed-borne as well as maternal infections.

We consider the data on BSE cases Born After the introduction of the ruminant feed Ban (cases referred to as BABs) by birth cohort and year of onset of clinical signs of BSE. To make the data from different birth cohorts comparable, we censor the data with respect to the time of onset of clinical signs of BSE both in the BABs and their dams. For each cohort, we therefore consider only confirmed cases in animals and dams with onset of clinical signs within 48 months from the end of the cohort birth year.

RESULTS
Maximum likelihood estimates from analyses of both datasets reveal significant genetic heterogeneity in susceptibility to feed-borne infection as well as significant levels of maternal transmission of the etiological agent of BSE. A range of genetic models are analyzed and their fits compared.
The significant findings point to an urgent need for more genotype information on BSE cases and matched controls from the same herd and time of birth. The results of Neibergs et al. (1994) have not been replicated in the literature. Clearly this is a research priority to contribute to the understanding of the genetic components of susceptibility to infection with BSE and other transmissible spongiform encephalopathies (such as scrapie and new variant Creutzfeldt-Jakob disease (nvCJD)).

REFERENCES