Author's response to reviews

Title: Comparative evidence for a link between Peyer's patch development and susceptibility to transmissible spongiform encephalopathies

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Author's response to reviews:

Referee 1 has made no suggested revisions

For referee 2, comments have been addressed by first quoting the referee's comment (Referee's comment) and then providing a response (Authors' response). Changes (Changes) made in the manuscript have been underlined.

1. Referee's comment:
The sample sizes analysed for concordance between susceptibility and PP development concern 19 sheep, 94 cattle, and 46 humans. The origin of these samples should be presented in the M and M section.

Authors' response:
The origin of sheep samples have already been presented in the Methods section. However, we have included additional information regarding the origin of sample sizes for cattle and humans.

Change (fourth paragraph of Methods):
The cattle data [18] refer to weight of PP tissue in the small intestine of 94 German beef cattle. The human data [19] refer to the number of PPs in the normal small intestine of 46 individuals between 15 and 96 years of age. The study was limited to necropsies performed within a few hours of death, and to patients with no clinical history or pathological evidence of gastrointestinal tract disease.

2. Referee's comment:
The results rely on the analysis of the correlation between susceptibility and PP development parameters and the "risk of infection". How is the "risk of infection" defined? Is it just f1, f2, f3 (the three values of f(a)) according to age or does it incorporate time (in other words, is it lambda (a,t)?

Authors' response:
The "risk of infection" that we refer to in general in the text, is intended to mean that described by the age-dependent relative susceptibility function f(a) (given by f1, f2, f3 for the different age classes). The function is not time-dependent (i.e. we assume that the relationship between age and relative susceptibility does not change with time) although the per capita rate of infection can change with time.

Change
The term, "instantaneous risk of infection" has been changed (where it has been used in the manuscript) to "per capita rate of infection".
Referee's comment:
For cattle and humans, which models were taken to estimate the risks of infection of a subject of age \( a \) at time \( t \)?

Authors' response:
The models used to estimate risks of infection of a subject of age \( a \), for cattle and humans, have been described in the legend for Figure 2. Description of these models has been moved from the legend to the Methods section. We assume that the age-susceptibility relationship does not change with time (see above).

Change
The following two paragraphs have been added to the Methods section (last two paragraphs under 'Age-susceptibility functions'):

For cattle, estimates of risk of BSE infection were made from \( n=158,550 \) BSE cases in British cattle and were calculated from the cumulative distribution function, defined by Ferguson et al. (1997), corresponding to the age-exposure/susceptibility curve (fitted using maximum likelihood methods).
For humans, estimates of risk of vCJD infection were obtained from a previous study that comprised \( n=129 \) vCJD cases in British people, and were fitted using maximum likelihood methods by Boelle et al. (2004).