

# Explaining the heterogeneous scrapie surveillance figures across Europe: a meta-regression approach

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## Abstract

Active surveillance for scrapie in sheep by surveillance of slaughtered animals and found-dead sheep was introduced in 2002 throughout the EU. The homogeneous implementation of these surveys should produce similar prevalence ratios across the EU Member States. We applied meta-regression techniques to explain the sources of the observed variation between the prevalence ratios. Our results show no reduction in the variability between countries after adjustment for the baseline risk (the log odds of the abattoir survey group). The inclusion of country-specific covariates did not reduce the variability except for one variable: the proportion of the total population sampled as fallen stock by each country. The meta-analysis framework allowed us to make informed comparisons and to explore the reasons for variation in the observed effect between countries.

## Introduction

Throughout Europe, scrapie has acquired increased interest because it is considered a potential threat to public health after the successful experimental transmission of BSE to sheep (Foster et al., 2001) and the likely exposure of sheep to concentrate feed contaminated with the BSE agent (Hunter, 2003). In order to obtain better estimates of the prevalence of scrapie throughout the EU, active surveillance for scrapie in small ruminants was introduced in 2002. The surveillance comprised both slaughtered and found-dead animals with the target numbers calculated for each country based upon the adult sheep and goat populations. The homogeneous implementation of these surveys should produce similar prevalence ratios (the prevalence estimate obtained from the fallen stock survey (FS) over the prevalence estimate from the abattoir survey (AS)) across the EU Member States. That is, broadly speaking, if i) the sensitivity of the tests applied in both surveys across the countries were similar, ii) the relative risk of having scrapie in the respective target populations between countries were similar and, iii) the methodology in the set up and implementation of the surveys between countries were similar. The 2003 results, reported by the EU Commission (Anon, 2004), showed large variation in the prevalence ratio estimates between countries.

Meta-analysis methodology, and more specifically, meta-regression techniques, are well suited to explain the variability between countries in this particular context. Traditionally, meta-analysis techniques are applied to synthesize evidence to provide a quantitative pooled effect of an intervention, generally a drug, a device or a service. The application of the diagnostics tests on the different target populations constitutes our intervention. The objective of this study is to investigate the sources of between-

country heterogeneity by taking into account country-level covariates and the effect of the underlying risk.

## Material and Methods

Data for 2003 from 18 European countries on the number of sheep tested and confirmed by each surveillance source were collected (Anon, 2004). The number of positive and negative samples for each survey can be represented in the form of a 2 x 2 table per country. Odds ratios (OR) between the FS and the AS were calculated and applied in their logarithmic form: logOR.

To study the presence of heterogeneity we compared the logORs of the different countries under the assumption of exchangeability, in effect, conducting a random effects meta-analysis of the logOR in Stata 8.2 (Stata Corporation, College Station, Texas). The heterogeneity is given in the form of the Q statistic which has a Chi-square distribution with  $k-1$  ( $k$ =number of countries) degrees of freedom. The random effects model was run using the method of DerSimonian and Laird, with the estimate of heterogeneity being taken from the Mantel-Haenszel approach. One of the major limitations of the traditional approach to the meta-analysis, modelling the logORs as normally distributed, is the need for continuity corrections for those countries with zero counts in either of the surveillance sources. A further limitation in our case is that all those countries with zero counts in both surveys had to be excluded from this part of the analysis as, otherwise, all the observed effects would have come from the continuity correction applied. This restricted the analysis to 14 countries. To overcome these limitations we also analysed the data under a Bayesian framework, assuming a binomial likelihood for our data (Smith et al., 1995). Finally, we conducted a meta-regression analysis adding country-specific covariates (“test” (the proportion of ELISA screening tests over all samples), “repreAFS”, “repreFS” and “repreAS” (indicating the proportion of the country population sampled by the two surveys, the fallen stock and the abattoir survey, respectively)) and adjusting for the baseline (the risk in the abattoir population). We ran all models in WinBugs 1.4.1 (Spiegelhalter et al., 2004) using a burn-in period of 10,000 iterations and 30,000 further iterations to derive, from the marginal posterior distributions of our parameters of interest, medians, standard deviations and 95% credible intervals. We checked the Gelman-Rubin plots for convergence.

## Results

The test for heterogeneity, from the Stata output, was significant ( $Q=108.59$ ,  $df = 13$ ,  $p\text{-value}<0.0001$ ). The Higgins and Thompson (2002) statistic suggested that most of the total variation in the estimates of effect was due to the heterogeneity between countries ( $I^2 = 88\%$  (82 – 92), 95% confidence intervals (CI)). The pooled effect of the intervention, the exponentiated logOR, was 3.3 (1.57 - 7.08) (95% CI). Ireland, The Netherlands and Germany were the countries that contributed the most to the between-country heterogeneity.

The results after the inclusion of the covariates and adjustment for the baseline showed that only the proportion of the country population sampled by the FS appeared significantly related to the outcome in all univariate models. This covariate explained more than 20% of the between-country heterogeneity in the normal models

and 18% in the binomial models. Whereas the AS-baseline was significantly related to the outcome in the normal models reducing the heterogeneity by 17%, when the data was modelled as binomial, the AS-baseline became non-significant.

## Discussion

We have shown the application of a proven methodology, the meta-analysis framework, in an unusual setting. The large heterogeneity of the logOR has demonstrated the differences between the EU countries in the way the surveys have been conducted and/or in the populations examined. As a by product, we obtained the overall intervention effect, the pooled OR across Europe. Under a random effects model, this can be interpreted as the average effect of the intervention on the target populations. Our results show that scrapie-affected sheep were, on average, 3.3 times more likely to be detected by the FS than by the AS throughout Europe. However, the presence of significant heterogeneity prevents one from drawing conclusions on an overall effect.

From the meta-regression approach, the negative slope of the regression coefficient for repreFS indicates that the greater the proportion of the total adult sheep population sampled by the FS, the lesser the ability of this source in detecting cases of scrapie, relative to that of the AS. Some animals that did not fall within the scope of the FS group, in effect a selection bias, might have been reported under this title. This would produce a dilution effect, a reduction of the “high risk” nature of this group, bringing down the prevalence estimates observed. Furthermore, we can also conclude that the differences in the risk of scrapie in the slaughtered population between countries did not contribute significantly to the model’s heterogeneity.

## References

- Anon. (2004). Report on the monitoring and testing of ruminants for the presence of transmissible spongiform encephalopathy (TSE) in the EU in 2003, including the results of the survey of prion protein genotypes in sheep breeds. Available at [http://europa.eu.int/comm/food/food/biosafety/bse/annual\\_report\\_tse2003\\_en.pdf](http://europa.eu.int/comm/food/food/biosafety/bse/annual_report_tse2003_en.pdf). Accessed on June 2005.
- Editor: Margaret McPike. AVC Inc., Prince Edward Island, Canada, pp 544-560.
- Foster, J.D., Parham, D., Chong, A., Goldman, W. & Hunter, N. (2001). Clinical signs, histopathology and genetics of experimental transmission of BSE and natural scrapie to sheep and goats. *Veterinary Record*, 148, 165-171.
- Higgins, J. P. T. & Thompson, G. (2002). Quantifying heterogeneity in a meta-analysis. *Statistics in Medicine*, 21, 1539-1558.
- Hunter, N. (2003). Scrapie and experimental BSE in sheep. *British Medical Bulletin*, 66, 171-183.
- Smith, T. C., Spiegelhalter, D. J. & Thomas, A. (1995). Bayesian approaches to random-effects meta-analysis. A comparative study. *Statistics in Medicine*, 14, 2685-2699.
- Spiegelhalter, D. J., Thomas, A., Best, N. & Lunn, D. (2004). WinBugs Version 1.4.1 User Manual. Cambridge: MRC Biostatistics Unit and Imperial College School of Medicine, London.