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Within- and between-herd prevalence variation of *Mycobacterium avium* subsp. *paratuberculosis* infection among control programme herds in Denmark (2011–2013)

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ABSTRACT

This study aimed to estimate the between- (HTP) and within- (TP) herd true prevalence distribution of *Mycobacterium avium* subsp. *paratuberculosis* (MAP) infection in dairy cattle herds participating in the Danish MAP control programme. All herds enrolled in the programme between 2011 and 2013 were included in the analysis, and one annual milk-ELISA test of all lactating cows present in such herds was considered. A Bayesian latent class model was used to obtain HTP and TP posterior distributions for each year. The model adjusts for uncertainty in age-specific test sensitivity and prior prevalence estimates. Bayesian posterior probabilities were computed in order to compare prevalence between the years.

A total of 665,700 samples were included in the study, from 221,914, 224,040, and 220,466 cows sourced from 1138, 1112, and 1059 herds in years 2011, 2012, and 2013, respectively. In that period, HTP estimates of 0.92 (95% posterior probability interval (PPI), 0.87–0.96), 0.78 (95% PPI, 0.74–0.83), and 0.75 (95% PPI, 0.71–0.78) were recorded, respectively. Low TP were observed, with population mean estimates of 0.08 (95% PPI, 0.07–0.08), 0.07 (95% PPI, 0.07–0.08), and 0.07 (95% PPI, 0.06–0.07) for the three consecutive years. Statistically-important differences were recorded for HTP and population mean TP estimates between years, indicating a trend for a decreasing level of MAP infection at both herd and animal level. Model results showed that MAP infection was widespread among the Dairy cattle herds participating in the Danish control programme, though in general it was kept at very low levels.

1. Introduction

Mycobacterium avium subsp. *paratuberculosis* (MAP) causes chronic infections in cattle and other ruminants. MAP infections may lead to significant losses to the dairy industry (Ott et al., 1999) and consequently, several dairy-producing countries have initiated control programmes to reduce the prevalence (Geraghty et al., 2014). However, due to slow pathogenesis of the MAP infections, the most commonly used diagnostic tests lack sensitivity (Nielsen and Toft, 2008), although the test-sensitivity does increase with age (Nielsen and Toft, 2006). Furthermore, false-positive reactions are common for both immunological and agent-based tests (Nielsen and Toft, 2008; Kralik et al., 2014).

Both false-positive and false-negative reactions pose a challenge when declaring herds free from MAP infection. However, Cameron and Baldock (1998) proposed a method to determine freedom from infection in a population where diagnostics were imperfect. Their method requires a design prevalence, below which the herd is considered free-from infection. The low accuracy of MAP diagnostics renders their approach inadequate in confirming freedom from MAP, unless the herd in question is large or the design prevalence is high. Sergeant et al. (2008) proposed an alternative, where herd classification was based directly on an estimate of the probability of having a low MAP prevalence. A more direct measure can be used in Bayesian analysis, where the probability of a herd being infected (or non-infected) can be estimated directly from model outputs, as described for *Salmonella dublin* in calf-rearing herds (Nielsen et al., 2011). In the Bayesian model, we can include prior information about sensitivity, specificity and prevalence, for example. *S. dublin* diagnostics may provide relatively high herd sensitivity, whereas herd sensitivity for a MAP diagnosis is dependent on the herd size

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and age-distribution. This information can also be included in the Bayesian framework, in order to estimate the posterior probability of a herd or an animal being infected. The resulting estimates can be used to determine freedom from infection, while simultaneously providing both within- and between-herd prevalence estimates of MAP infection, which can be used to monitor progress in the Danish MAP control programme.

Consequently, the objectives of this research were to estimate the distributions of between-herd true prevalence (*HTP*) and within-herd true prevalence (*TP*) of MAP infection, along with the probability of the individual herds participating in the Danish control programme being free from MAP infection.

2. Material and methods

2.1. Study population and target condition

All dairy cattle herds enrolled in the Danish control programme on MAP during the years 2011–2013 were included in the study (Nielsen and Krogh, 2014). Lactating cows in the enrolled herds were automatically screened between one and four times per year, using the commercial milk ELISA ID-Screen for MAP antibody detection (ID-Vet, Grabels, France). For the yearly prevalence estimations, one sample was randomly selected from each cow every year. Thereby, inclusion of animals providing different numbers of samples (and their associated clustering) were avoided.

The target was to estimate the overall *TP* (*oTP*), which represents the *TP* distribution across all infected herds. The mean *TP* (*mTP*), understood as the average *TP* distribution between infected herds. And the proportion of herds with at least one truly MAP infected animal (*HTP*).

2.2. Statistical analysis

2.2.1. Analytical model

Test results (y_{ijk}) included in the study were assumed to be distributed as Bernoulli, namely:

$y_{ijk} \sim \text{Bernoulli}(q_{ijk})$,

with q_{ijk} being the probability of a positive test result for animal i belonging to herd j during the year k, modelled as:

$$q_{ijk} = TP_{jk} \times Se_i + (1 - TP_{jk}) \times (1 - Sp)$$

where TP_{jk} is the true within-herd prevalence in a given herd during a given year, and Se_i and Sp are the animal-level test sensitivity and specificity, respectively. Based on Nielsen et al. (2013), the Se_i was assumed to be age-specific and therefore specific to the individual, whereas Sp presented a limited variability between individuals. Considering the current test interpretation protocol used in the Danish control programme, where animals with a sample-to-positive (S/P) ratio ≥0.2 are deemed positive, the Se_i was computed as:

$$Se_i = \frac{e^{1.32-9.38\times e^{-0.7\times \text{age}_i}}}{1 + e^{1.32-9.38\times e^{-0.7\times \text{age}_i}}}$$

where age_i was the age in years of the individual. A mixture of point mass at zero with a continuous distribution on (0,1) was used to model TP_{jk}

$TP_{jk} = Z_{jk} \times TP^*_{jk}$, with:

$TP^*_{jk} = \text{beta}(a_k, b_k)$, $z_{jk} \sim \text{Bernoulli}(HTP_k)$, $a_k = mTP_k \times vTP_k$, and $b_k = (1 - mTP_k) \times vTP_k$ where vTP_k is the between herd variability of mTP_k.

Posterior distributions for HTP_k and mTP_k for the different years were compared through computation of posterior probabilities (POPR), determining the probability that a given year presented a higher prevalence (either within or between herd) than the next available year. For example, $\Pr(HTP_{2011} > HTP_{2012})$ is the probability that *HTP* was higher in 2011 compared to 2012. This comparison approach was based on the hypothesis that control activities are effective, and that a reduction in prevalence could therefore be expected. A POPR is the proportion of Monte Carlo (MC) samples out of all iterations, where the hypothesis tested was true (Okura et al., 2010), thus representing the direct probability of the event occurrence. A difference was regarded as statistically important if the POPR ≥0.95.

2.2.2. Model priors, computation, and sensitivity analysis

The model uses four variable parameters (Sp, HTP_k, mTP_k, and vTP_k) and one fixed parameter (Se_i). Independent beta distributions were used to model Sp, HTP_k and mTP_k, whereas vTP_k were assumed to be gamma distributed. Scientific input to form prior distributions of the variable parameters was elicited through expert opinion. The expert, and co-author in this paper (SSN), has more than 15 years of experience working on epidemiology and MAP infection control in Denmark, and was requested to provide an estimate on the mode and upper 95% limits of HTP_{2011} and mTP_{2011}. Using this information, beta distribution parameters were calculated using the function "beta.select" present in the "LearnBayes" library of R.3.1.1 (R Core Team, 2014). For vTP_{2011}, gamma distributions were fitted using the methodology proposed by Hanson et al. (2003), where the median of mTP_{2011} prior belief distribution was calculated. Then, the expert was requested to provide the median and upper 95% limit of the 90th percentile of the distribution of within-herd prevalence conditional on the elicited mTP_{2011}. Then, the variability associated with these prior beliefs about the median and upper 95% limit of the 90th percentile of the beta $(mTP_{2011} \times vTP_{2011}, (1 - mTP_{2011}) \times vTP_{2011})$ distribution was estimated, considering that mTP_{2011} is known. Finally, the variability estimates were used to fit a Gamma distribution representing vTP_{2011}. Mathematical computation was carried using an R-code developed by Nielsen et al. (2011). Model prior distributions are presented in Table 1.

The incorporation of model priors followed an iterative approach. First, the model was run for the year 2011, and HTP_{2011}, mTP_{2011} and vTP_{2011} posterior distributions were used to form the corresponding prior distributions for the following year. Then, the model was run for the year 2012, with HTP_{2012}, mTP_{2012} and vTP_{2012} posterior distributions being used to form prior distributions for the year 2013. Finally, the model was run for the three years simultaneously in order to compute POPR. The corresponding beta and gamma distributions were fitted from the stated posterior distributions using the package "fitdistrplus_1.0-1", function "fitdist" (Delignette-Muller et al., 2010) for R.3.1.1 (R Core Team, 2014).

Visual inspection of the Gelman–Rubin–Brooks plot for two parallel chains with different starting values was used to assess model convergence. Models were fitted using the WinBUGS software (Spiegelhalter et al., 1996). The posterior median and associated 95% posterior probability interval (PPI) were obtained after running the model for 25,000 iterations (the first 5000 MC samples were discarded as a burn-in period).

Expert-defined prior distributions were considered critical assumptions of the model. A sensitivity analysis was therefore performed by varying the values of HTP_{2011} and mTP_{2011} (as informed by the expert) by +/−10%. Differences were assessed by the computation of POPR following the same methodology described above.

3. Results

A total of 665,700 samples were included in the study, from 221,194 cows in 2011, 224,040 cows in 2012, and 220,466 cows in 2013. For those years, samples were collected from 1138, 1112 and