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Within-herd prevalence and clinical incidence distributions of *Mycobacterium avium* subspecies *paratuberculosis* infection on dairy herds in Chile

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ABSTRACT

This study aimed to estimate the distributions of the within-herd true prevalence (TP) and the annual clinical incidence proportion (CIp) of *Mycobacterium avium* subsp. *paratuberculosis* (MAP) infection in dairy cattle herds in Chile. Forty two commercial herds with antecedents of MAP infection were randomly selected to participate in the study. In small herds (≤30 cows), serum samples were collected from all animals present. Whereas, in larger herds, milk or serum samples were collected from all milking cows with 2 or more parities. Samples were analysed using the Pourquier® ELISA PARATUBERCULOSIS (Insitute Pourquier, France) test. Moreover, a questionnaire gathering information on management practices and the frequency of clinical cases, compatible with paratuberculosis (in the previous 12 months), was applied on the sampling date. A Bayesian latent class analysis was used to obtain TP and clinical incidence posterior distributions. The model adjusts for uncertainty in test sensitivity (serum or milk) and specificity, and prior TP & CIp estimates.

A total of 4963 animals were tested, with an average contribution of 124 samples per herd. A mean apparent prevalence of 6.3% (95% confidence interval: 4.0–8.0%) was observed. Model outputs indicated an overall TP posterior distribution, across herds, with a median of 13.1% (95% posterior probability interval (PPI); 3.2–38.1%). A high TP variability was observed between herds. CIp presented a posterior median of 1.1% (95% PPI; 0.2–4.6%). Model results complement information missing from previously conducted epidemiological studies in the sector, and they could be used for further assessment of the disease impact and planning of control programs.

1. Introduction

Paratuberculosis (Ptb) is a chronic wasting disease of domestic and wild ruminants, caused by *Mycobacterium avium* subspecies *paratuberculosis* (MAP). In the dairy industry, MAP infection has been associated to significant economic losses (Ott et al., 1999) and several countries have implemented control schemes to reduce its impact (Geraghty et al., 2014). However, due to a long incubation period, prolonged survival of viable MAP in the environment, and limited performance of available diagnostic tests, control has shown limited success (Nielsen and Toft, 2008). Additionally, those characteristics have also precluded the proper estimation of basic health measures, like prevalence and incidence. In recent years, the introduction of Bayesian latent class analysis have allowed the estimation, with a better degree of accuracy, of Ptb prevalence distributions at animal and herd levels (Nielsen and Toft, 2009). This technique permits the incorporation of the sensitivity (Se) and specificity (Sp) distributions of the diagnostic tests, into a flexible framework, where complex surveillance strategies and co-variables can be jointly modelled (Nielsen et al., 2013). Conversely, a reduced number of incidence estimations has been published (Norton et al., 2009; Raizman et al., 2011), possibly due to the chronic nature of the disease, which makes the data collection at population level difficult. The lack of prevalence and incidence estimates not only limits our capacity to assess the real impact of the disease, but also limits our capacity to allocate sufficient resources for its control, and precludes an adequate monitoring of the effectiveness of control measures. For these reasons, the estimation of these parameters is relevant for any disease.

In Chile, Ptb was originally described more than 50 years ago in a dairy cattle herd, by Grinbergs and Caorsi (1958). Since then, the infection has been described in sheep, goats and wild animals, as well as South American camelids, deer and hares (Salgado et al., 2011). However, few population based epidemiological studies have been conducted. Kruze et al. (2013), using bulk-tank milk samples, estimated

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the between-herd true prevalence (HTP) of MAP infection in the Chilean dairy cattle sector, showing evidence of MAP circulation in around 87% of herds. On the other hand, van Schaik et al. (2007), assessed the performance of different diagnostic assays used on Chilean dairy herds at the field level. Despite this, currently neither the industry nor the government have estimates on the within-farm true prevalence (TP) or clinical incidence (CI) distributions between the infected dairy herds. Therefore, the objective of this research was to estimate the TP and CI of MAP infection in the Chilean dairy sector, to complete the missing data from previous population-based studies.

2. Materials and methods

2.1. Study population and target conditions

In Chile, the dairy cattle industry is geographically clustered, where 78% of the production occurs in the regions of De Los Rios and De Los Lagos, located in the southern part of the country (ODEPA, 2017). In this way, the objective population included commercial dairy herds (at least one milk delivery to a processing plant per week) located in these two regions, and with records of MAP infection (at least one laboratory confirmed diagnosis by ELISA, culture, or PCR) in the last five years. Considering the high HTP reported in the country, the chronic nature of the infection, and the lack of Ptb control/surveillance programmes. It was assumed that a herd found positive within the last five years, will continue to be infected on the sampling date. In particular, the source population corresponded a list of 131 commercial dairy farms with antecedents of MAP infection. This list was mainly drawn from Kruze et al. (2013) study, in addition to information provided by processing plants, veterinary practitioners, and producer cooperatives. The representativeness of this population is considered in the discussion section. A total of 42 herds were randomly selected from the compiled list, and owners or farm-managers were contacted to explain the scope of the project and to request participation consent.

The selected farms were sampled from February to November 2015. In herds with ≤ 30 cows, all animals were individually sampled through puncture of the coccygeal vein, collecting 2–5 ml of blood. In larger herds (> 30 cows) all milking cows with ≥ 2 parities were individually sampled. In this group, and depending on the infrastructure available at each farm, 5–10 ml of milk were collected during milking, or 2–5 ml of blood were collected through coccygeal vein puncture (only one type of sample was collected at each farm). Samples were analysed using a commercial ELISA test (Pourquier® ELISA PARATUBERCULOSIS, Insitute Pourquier, France), following manufacturer recommendations for milk or blood-serum samples, respectively, with a cut-off of 0.50 sample-to-positive (S/P). Additionally, the equations proposed by Humphry et al (2004) were used to calculate the sample size for TP estimation, when an imperfect test was used. Assuming a Se of 0.26, a Sp of 0.98, and an expected TP of 0.11, a minimum sample size of 1181 animals would be required to estimate the TP distribution, with a precision of 5% and a confidence of 95%.

At the sampling date, a structured questionnaire was applied by means of a personal interview with the farm manager. The questionnaire gathered information on herd demographics and management, as well as the number of compatible clinical Ptb cases in the last 12 months. This particular question was accompanied by a statement describing the common clinical signs of Ptb and supported by printed colour-photographs of those signs. In particular, a compatible clinical Ptb case was defined as a cow (older than 2 years) that was alert and with good appetite but presented a chronic diarrhoea that does not respond to treatment, leading to emaciation and finally to culling or death. The supporting photographs presented to farmers during the personal interview, showed signs of diarrhoea and scouring, ventral and inter-mandibular edema, and emaciated cows with lordosis. Those photographs were taken from previous local Ptb cases, confirmed by fecal culture and PCR.

The target was to estimate the mean TP (*mTP*), which is the distribution of the mean TP in an average infected herd. The overall TP (*oTP*), which corresponds to the TP distribution across all infected herds, and the annual incidence proportion of compatible clinical Ptb cases (*CIp*).

2.2. Statistical analysis

2.2.1. Analytical model

Based on the models proposed by Branscum et al (2004). The total count of positive test results for each herd (y_{ij}) were assumed to be distributed as binomial, that is:

$$y_{ij} \sim binomial(n_i, q_{ij})$$

where n_i is the number of animals sampled in the *ith* herd, and q_{ij} is the probability of a positive test result for the animals sampled from the herd i using sample type j (1 = milk & 2 = blood serum), modelled as:

$$q_{ij} = TP_i \times Se_j + (1 - TP_i) \times (1 - Sp)$$

being Se_j & Sp the animal level sensitivity and specificity, respectively. A mixture of point mass at zero with a continuous distribution on (0, 1) was used to model TP_i, where

$TP_i = Z_i \times TP_i^*$, with:

$TP_i^* = beta\ (a, b)$, $Z_i \sim bernoulli\ (HTP)$, $a = mTP \times vTP$, and $b = (1 - mTP) \times vTP$ where vTP is the variability associated to TP_i. Moreover, oTP was calculated as the average distribution among TP_i estimates from the sampled herds. Finally, the total count of compatible clinical Ptb cases (CC_i) in the last 12 months, was assumed to be binomially distributed, that is:

$$CC_i \sim binomial\ (herd\ size_i, CIp_i)$$

2.2.2. Model priors, computation, and sensitivity analysis

Independent beta distributions were used to model Se_j, Sp, HTP, mTP, and CIp_i, whereas a gamma distribution was used to model vTP. Information on the model parameters prior distributions were elicited through scientific literature review (Se_j & Sp) and expert opinion (mTP & vTP). The expert, and co-author of this research (MS), has more than 10 years working on the microbiology and diagnostic of MAP in Chile, with a particular emphasis on the dairy sector, and he has published more than 25 peer-reviewed papers on the subject. In particular, the expert was requested to provide an estimation for mode and upper 95% limit of mTP. Whereas, in the case of vTP, the expert was requested to provide the median and upper 95% limit of the 90th percentile of the distribution of TP conditional on the elicited mTP. Then, based on the methodology proposed by Hanson et al. (2003), the variability of the $beta(a = mTP \times vTP, b = (1 - mTP) \times vTP)$ distribution was estimated, assuming that mTP was known. Additionally, the expert was required to provide the mode and 95% upper limit of the number of clinical cases in an average infected herd, with a herd size of 100 cows. In the particular case of HTP, this probability was assumed to be very high, with a mode of 0.97 and an upper 95% limit of 0.99, because samples were collected from known MAP infected herds. Finally, Se differences between blood serum and milk samples were modelled, assuming a lower performance of the ELISA test when milk samples were used. Van Weering et al. (2007) reported a Se ratio of 0.87 of milk ELISA relative to serum ELISA. Conversely, no Sp differences were assumed between serum and milk samples (van Weering et al., 2007). Prior beta distribution parameters were fitted using the function "beta.select" from the "LearnBayes" package for R.3.1.2 (R_Core_Team, 2014). On the other hand, gamma distribution parameters were fitted using an R-code developed by Nielsen et al. (2011). Prior distribution parameters are presented in Table 1.

Model convergence was assessed through visual inspection of the Gelman-Rubin-Brooks plot for two parallel chains with different initial