



## Estimating diagnostic accuracy of fecal culture in liquid media for the detection of *Mycobacterium avium* subsp. *paratuberculosis* infections in Québec dairy cows: A latent class model



Juan Carlos Arango-Sabogal<sup>a</sup>, Gilles Fecteau<sup>a</sup>, Julie Paré<sup>b</sup>, Jean-Philippe Roy<sup>a</sup>, Olivia Labrecque<sup>c</sup>, Geneviève Côté<sup>d</sup>, Vincent Wellemans<sup>a</sup>, Ian Schiller<sup>e</sup>, Nandini Dendukuri<sup>e</sup>, Sébastien Buczinski<sup>a,\*</sup>

<sup>a</sup> Département de sciences cliniques, Faculté de médecine vétérinaire, Université de Montréal, Saint-Hyacinthe, Québec, J2S 8H5, Canada

<sup>b</sup> Groupe de recherche en épidémiologie des zoonoses et santé publique (GREZOSP), Faculté de médecine vétérinaire, Université de Montréal, Saint-Hyacinthe, Québec, J2M 2M1, Canada

<sup>c</sup> Laboratoire de santé animale du Québec, Saint-Hyacinthe, Québec, J2S 2M2, Canada

<sup>d</sup> Direction générale des laboratoires et de la santé animale, Ministère de l'Agriculture, des Pêcheries et de l'Alimentation du Québec, Québec, G1P 4S8, Canada

<sup>e</sup> Centre for Outcomes Research, McGill University Health Centre – Research Institute, Montreal, Québec, H3H 2L9, Canada

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### ABSTRACT

A latent class model fit within a Bayesian framework was used to estimate the sensitivity and specificity of individual fecal culture (IFC) in liquid medium (Para TB culture liquid medium and BACTEC MGIT 960 system) for the detection of *Mycobacterium avium* subsp. *paratuberculosis* (MAP) infections in Québec dairy cows. As a secondary objective, the within-herd paratuberculosis prevalence was estimated. A dataset including 21 commercial Québec dairy herds participating in previous research projects was retrospectively analyzed. In total, 1386 adult cows on which both IFC and serum-ELISA were available were included. The selected latent class model assumed conditional dependence between the tests. Non-informative priors for IFC accuracy and paratuberculosis prevalence were used while informative priors, obtained from the literature, were used for serum-ELISA accuracy. The WinBUGS statistical freeware was used to obtain posterior estimates (medians and 95% Bayesian credibility intervals (95% BCI)) for each parameter. The sensitivity and specificity estimates for IFC were 34.4% (95% BCI: 20.3–66.1) and 99.5% (95% BCI: 98.6–100), respectively. Sensitivity and specificity for serum-ELISA were 27.3% (95% BCI: 18.1–38.3) and 97.4% (95% BCI: 96.6–98.0). Median paratuberculosis within herd prevalence was estimated to be 0.3% (0–3.3). In conclusion, a higher sensitivity of IFC compared to serum-ELISA was observed both in the unconditional and conditional dependent models. Since the sensitivity of both IFC and serum-ELISA was relatively low, conditional dependence between the tests is more likely in the true disease positive animals. We hypothesize that conditional dependence arises because an unmeasured covariate influences the performance of both tests among disease positive animals causing both tests to incorrectly misclassify the animal as negative. One limitation of this study was the very low within herd prevalence of the participant herds.

### 1. Introduction

Paratuberculosis is a chronic, incurable and contagious enteric disease of ruminants associated with significant economic losses to the dairy industry (Hendrick et al., 2005; Lombard et al., 2005; Kudahl and Nielsen, 2009; McAloon et al., 2016). The zoonotic potential of *Mycobacterium avium* subsp. *paratuberculosis* (MAP; the etiologic agent of paratuberculosis) has been previously suggested (Scanu et al., 2007; Waddell et al., 2008, 2016), however the causal link between MAP and

human Crohn's disease has not been proven (Qual et al., 2010; Waddell et al., 2015). Diagnostic tests for paratuberculosis can be classified in 2 categories: organism detection tests (e.g. bacterial culture and PCR assay) and immune response detection tests (e.g. ELISA and IFN- $\gamma$ ). Bacterial culture has a major advantage over PCR and immunologic tests given that a positive result confirms the presence of viable MAP (Collins et al., 2006). However, bacterial culture has a longer turn-around laboratory time and is more expensive than PCR and ELISA. The main disadvantage of immune response detection tests is that a positive

\* Corresponding author.

E-mail address: [s.buczinski@umontreal.ca](mailto:s.buczinski@umontreal.ca) (S. Buczinski).

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result might indicate MAP exposure and not necessarily infection (Nielsen, 2010). Regardless of the diagnostic test used, the identification of MAP infected animals can be challenging for 3 reasons: 1) the low accuracy of available diagnostic tests, especially in the earlier phases of the disease (Nielsen and Ersboll, 2006; Nielsen and Toft, 2006; Nielsen, 2008), 2) the passive shedding phenomena (Fecteau and Whitlock, 2010), and 3) the presence of intermittent shedders (Nielsen, 2008; Mitchell et al., 2015). It has been suggested that the accuracy of available diagnostic tests for paratuberculosis increases with the age of the animal (Nielsen and Toft, 2006). The latent period of the disease (silent phase) can be long (Nielsen and Ersboll, 2006) and available diagnostic tests do not perform well during that period (Nielsen and Toft, 2008). Given that the incubation period for paratuberculosis is even longer than the latent period, it is also possible to observe infected asymptomatic shedders (subclinical phase of the disease). Paratuberculosis diagnostic tests' accuracy for identifying these subclinical animals is also limited (Sockette et al., 1992; Collins et al., 2006). The highest accuracy of diagnostic tests is observed during the clinical phase of the disease when they can be used to confirm an infected animal showing clinical signs (Nielsen and Toft, 2008). However, from a disease control perspective, detecting animals at the subclinical phase of the disease is more valuable than detecting clinical animals (Nielsen and Toft, 2008). Subclinical animals (infected asymptomatic shedders) are a source of MAP for the environment of the farm and young stock, while they go unnoticed (Nielsen and Toft, 2006, 2008).

A perfect reference test accurately classifies all the diseased animals within a population (Dohoo et al., 2009). In the case of paratuberculosis, none of the available diagnostic tests can be considered perfect as they have near perfect specificity but low sensitivity (Enøe et al., 2000; Collins et al., 2006). Latent class models fit within a Bayesian framework are an interesting alternative for estimating test accuracy in the absence of perfect reference test (Enøe et al., 2000) given that it is possible to model the sensitivity and specificity of all tests as unknown parameters and incorporate (when available) prior scientific information about test accuracy and population prevalence (Branscum et al., 2005). Thus, latent class models are suitable for comparing the diagnostic accuracy of paratuberculosis diagnostic tests. In spite of its imperfect accuracy, bacteriologic culture is still considered the definitive antemortem diagnostic test to confirm paratuberculosis (Whittington, 2010). The bacterial culture process includes three steps: a purification (or decontamination) of the samples to reduce microbial overgrowth, an incubation period in a selective medium to promote MAP growth, and the identification of MAP by phenotypic or genotypic methods (Whittington, 2010). The incubation step can be performed in either solid or liquid media. The latter having a better analytical sensitivity and a faster MAP growth (8–12 weeks) than the solid media (10–20 weeks; Whittington, 2010). The Para TB culture liquid medium and BACTEC MGIT 960 system is a non-radiometric system for growth and detection of mycobacteria. It has been suggested that the BACTEC MGIT 960 has a similar sensitivity and a better specificity than the ESP Culture system (another non-radiometric system for growth of mycobacteria; ESP II; Trek Diagnostics, Inc., Westlake, Ohio) for the detection of mycobacteria in human samples (Williams-Bouyer et al., 2000). The accuracy of individual fecal culture in solid media, using latent class models fit within a Bayesian framework, has been reported previously (Scott et al., 2007; van Schaik et al., 2007; Norton et al., 2010). In those studies, the estimated sensitivity of fecal culture in solid medium varied from 32% (Scott et al., 2007) to 74% (Norton et al., 2010) and the specificity was estimated to be > 98% (van Schaik et al., 2007; Norton et al., 2010). However, to the best of our knowledge, the diagnostic accuracy of the bacteriological culture of bovine feces in liquid medium (Para TB culture liquid medium and BACTEC MGIT 960 system) using a latent class model approach has not been reported. The main objective of this study was to estimate the sensitivity and specificity of the fecal culture in liquid medium for the detection of MAP infections in dairy cows using a latent class model fit within a Bayesian

framework. Secondly, we aimed to estimate the true within-herd paratuberculosis prevalence in Québec dairy herds. This manuscript was written following the Standards for the Reporting of Diagnostic accuracy studies that use Bayesian Latent Class Models (Kostoulas et al., 2017).

## 2. Materials and methods

### 2.1. Study design and sampling strategy

Existing databases from previous studies of the paratuberculosis research group of the Université de Montréal were retrospectively analyzed. Data included individual fecal culture (IFC) and serum-ELISA results of cows from paratuberculosis positive Québec dairy herds enrolled in the Québec Voluntary Paratuberculosis Prevention and Control Program (QVPPCP). Producers enrolled voluntarily in this program. Upon enrollment, producers complete a risk assessment questionnaire to identify the risk of introduction and transmission of MAP. Then, the veterinarian recommended better management practices according to the critical points identified during the risk assessment. In the first year of enrollment, no sampling was performed. The second and subsequent years, a follow up of the implementation of the better practices recommended by the veterinarian during the last visit was performed as well as herd-level testing using environmental sampling.

Sampling strategy was described elsewhere (Arango-Sabogal et al., 2016, 2017). Briefly, it included a cluster sampling strategy using the herd as the primary sampling unit and the adult cow as the unit of interest. All the adult cows present in the herds at the moment of the visit were sampled. The target population was the Québec dairy herds and the source population was the dairy herds enrolled in the QVPPCP. An adult cow was defined as a cow of at least 24 months of age, which had given birth at least once.

### 2.2. Sample collection and eligible participants

Samples were collected between summer 2011 and fall 2015 from 21 Québec dairy herds as a part of a cross-sectional and a cohort study (Arango-Sabogal et al., 2016, 2017). For the present study, available data were merged in a single database. Only the cows sampled during the first available sampling of each herd were analyzed ( $n = 1398$ ). Cows were finally included in the study if they had available results for both fecal culture and ELISA tests, otherwise they were not considered ( $n = 12$ ).

### 2.3. Test methods

Isolation of MAP was achieved using the MGIT Para TB culture liquid media and the BACTEC MGIT 960 system (Becton, Dickinson and Company) as described previously (Arango-Sabogal et al., 2016). The entire culture process includes a 3-day decontamination period followed by 3 steps performed in series: 1) incubation in the automated system, 2) acid fast bacilli (AFB) staining, and 3) confirmatory PCR. Sera were processed using the IDEXX Pourquier MAP antibody test kit according to the manufacturer's instructions (IDEXX Laboratories, Westbrook, Maine, USA).

Sample collectors or laboratory personnel were not aware of the infection status of cows before sampling. However, all cows originated from positive MAP herds enrolled in the QVPPCP. The positive MAP herd status was determined by a positive result to IFC, environmental culture or histopathology between 2009 and 2011 (Arango-Sabogal et al., 2016, 2017).

#### 2.3.1. Rationale for choosing the test under evaluation in relation to its purpose

Even if the accuracy of available diagnostic tests for detecting MAP

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