Harmonisation of the diagnostic performances of ELISA tests for C. burnetii antibodies in ruminants: optimal positivity thresholds and performance reassessment

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Context

- Several ELISAs are available for the serological diagnosis of *C. burnetii* infection in ruminants.
- **None can be considered as a gold standard** or as a reference test.
- **Differences between their diagnostic performances** (Lurier *et al*. 2021)
  ⇒ decrease the agreement between the test results from different veterinary laboratories, and
  ⇒ limits the comparability of surveillance data.
- **Harmonisation** of the tests is possible by **changing their positivity thresholds**.
  - Proposed ROC curves estimation methods (ordered multinomial model – Wang *et al*. 2007 – and mixture model – Choi *et al.* 2006) are not applicable due to the conditional dependency of the tests and to the non-Gaussian distribution of their quantitative measurement.

Objectives

- Identify the positivity thresholds that maximise the agreement between the tests.
- Estimate the impact of changing the thresholds.

Method

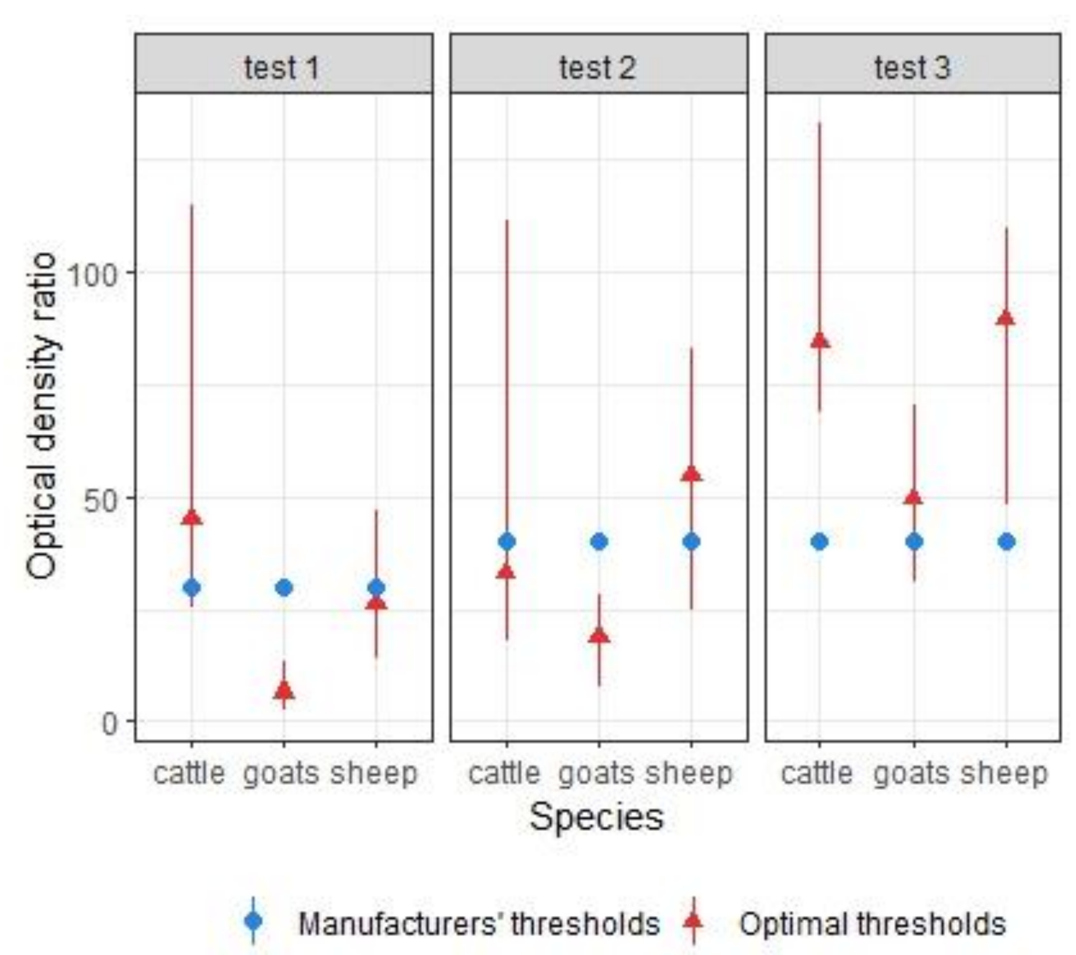
- Data: results of three ELISAs from 1258 cattle, 1474 goats and 1432 sheep.
- **Thresholds maximising Hubert's kappa** were identified using a differential evolution algorithm.
- The uncertainty around these optimal thresholds was estimated by bootstrapping.
- **Sensitivities and specificities** of the tests at the optimal thresholds were estimated by **Bayesian inference** using the hierarchical zero-inflated beta-binomial **latent class model** previously described by Lurier *et al*. (2021).

Results

Optimal positivity thresholds

Optimal thresholds are different (higher or lower) from the manufacturers' thresholds.

The uncertainty around the optimal thresholds is high, but should be interpreted with caution as the coverage of these bootstrap intervals is not guaranteed in this case.

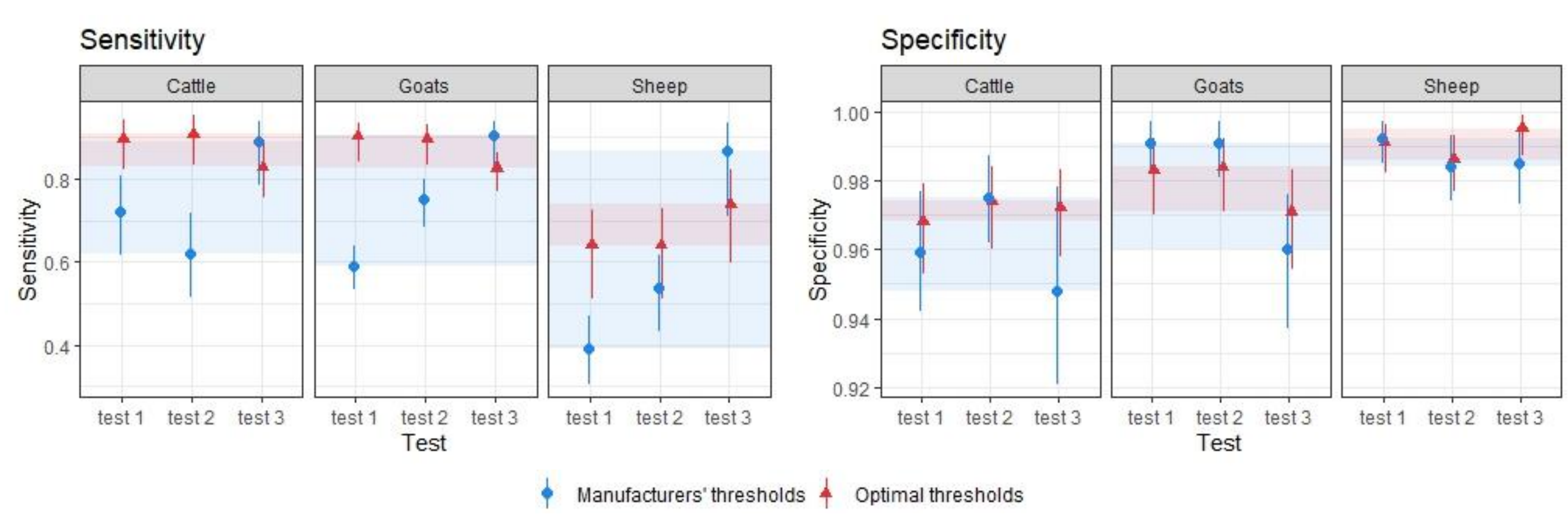


Manufacturers' thresholds and thresholds that maximise Hubert's kappa and their 95% bootstrap intervals

Impact of the threshold change

- **Diagnostic performances**

At the optimal thresholds, the **sensitivities of tests 1 and 2 increased** without major changes in their specificities. The **sensitivity of test 3 decreased** while its **specificity increased**.
The sensitivities and specificities are **closer** from one test to another.



Sensitivity and specificity of the tests at manufacturers' and optimal thresholds and their 95% credibility intervals

- **Observed disagreement**

The proportion of discordant cases is **divided by approximately 2** compared to the manufacturers' thresholds (e.g. from 20 to 12% for goats).

- **Apparent prevalence**

The apparent prevalences are **more similar** from one test to another at the optimal thresholds (e.g. in sheep they range from 7.7 to 17% at the manufacturers' thresholds and from 8.7 to 10.3% at the optimal thresholds).

Findings of the study

Improved harmonisation of the test results and of their diagnostic performances
→ Improved comparability of surveillance data

Discussion and perspective

The increase in sensitivity of tests 1 and 2 estimated in this study is not consistent with the increase in their thresholds compared to the manufacturers' ones.
The development of **methods to evaluate ROC curves in the absence of a gold standard**, especially **considering the conditional dependence** between tests, remains an important area for future research.

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Lurier, Thibaut, Elodie Rousset, Patrick Gasqui, Carole Sala, Clément Claustre, David Abrial, Philippe Dufour, et al. 2021. 'Evaluation Using Latent Class Models of the Diagnostic Performances of Three ELISA Tests Commercialized for the Serological Diagnosis of Coxiella Burnetii Infection in Domestic Ruminants'. Veterinary Research 52 (1): 56. https://doi.org/10.1186/s13567-021-00926-w.

Wang, Chong, Bruce W. Turnbull, Yrjö T. Gröhn, and Søren S. Nielsen. 2007. 'Nonparametric Estimation of ROC Curves Based on Bayesian Models When the True Disease State Is Unknown'. Journal of Agricultural, Biological, and Environmental Statistics 12 (1): 128–46. https://doi.org/10.1198/108571107X178095.