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Thibaut Lurier^{1, 2}, Elodie Rousset³, Patrick Gasqui¹, Carole Sala⁴, Clément Claustre¹, David Abrial¹, Philippe Dufour³, Renée de Crémoux⁵, Kristel Gache⁶, Marie Laure Delignette-Muller⁷, Florence Ayrat², Elsa Jourdain¹

1- UMR EpiA; 2- USC 1233; 3- Q fever NRL; 4- EAS Unit ; 5- UMT PSR; 6- GDS France; 7- UMR 5558




RESEARCH ARTICLE

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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

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Q fever, a zoonotic disease transmitted by domestic ruminants

- Q fever is a **zoonotic** disease responsible for acute and persistent infection in humans

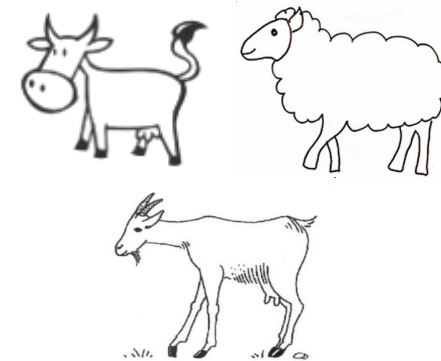


- Main Reservoir = Domestic ruminants : **Reproductive issues**
 - **1st infectious cause of abortion** in Goat herds (27.3%) *(French Oscar network, 2022)*
 - **2nd in Cattle (9.6%) and 3rd in Sheep (19%) herds**

- Aim of the control of *Coxiella burnetii* in ruminants

- **Public health** (zoonotic risk) and **economic** (reproductive issues)

⇒ **Mandatory surveillance** in Europe according to the new animal health law since 2021 (E category)



Diagnostic issues in domestic ruminants

- **Direct diagnostic** : **Intermittent shedding** in milk, vaginal secretions, feces
⇒ PCR : Sp = 100% but **low Se** except after abortion
- **Indirect diagnostic** : 3 ELISA tests commercialized in Europe

No Gold Standard test

- Diagnostic accuracy?
- Not assessed in every species
 - Se considered to vary between 70 and 100%
 - Sp considered to vary between 90 and 100%

⇒ With some **methodological risk of bias**

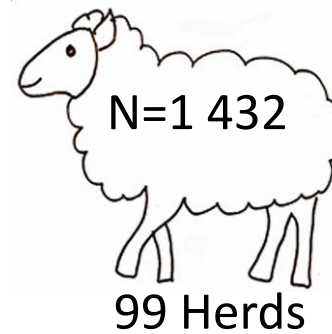
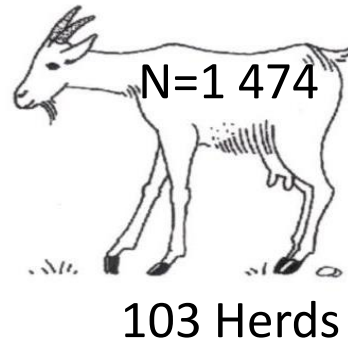
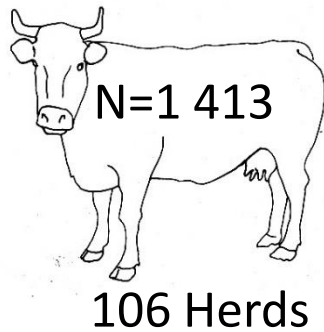
- Comparison to **an imperfect reference test**
- No or inefficient modelling **of the conditional dependence between tests**

Objectives

- To assess **Se and Sp** of the three commercialized ELISA tests for Q fever at the **individual level**
- To assess **Se and Sp** at the **herd level**
- To estimate the **optimal sample size for** detecting Q fever in a herd for each test in each species

Study sample

- Sub-sample of a larger epidemiologic study* of 23 000 animals sampled from 1500 randomly selected herds with no history of Q fever vaccination
- Inclusion of 150 animals from 10 herds in each *department*

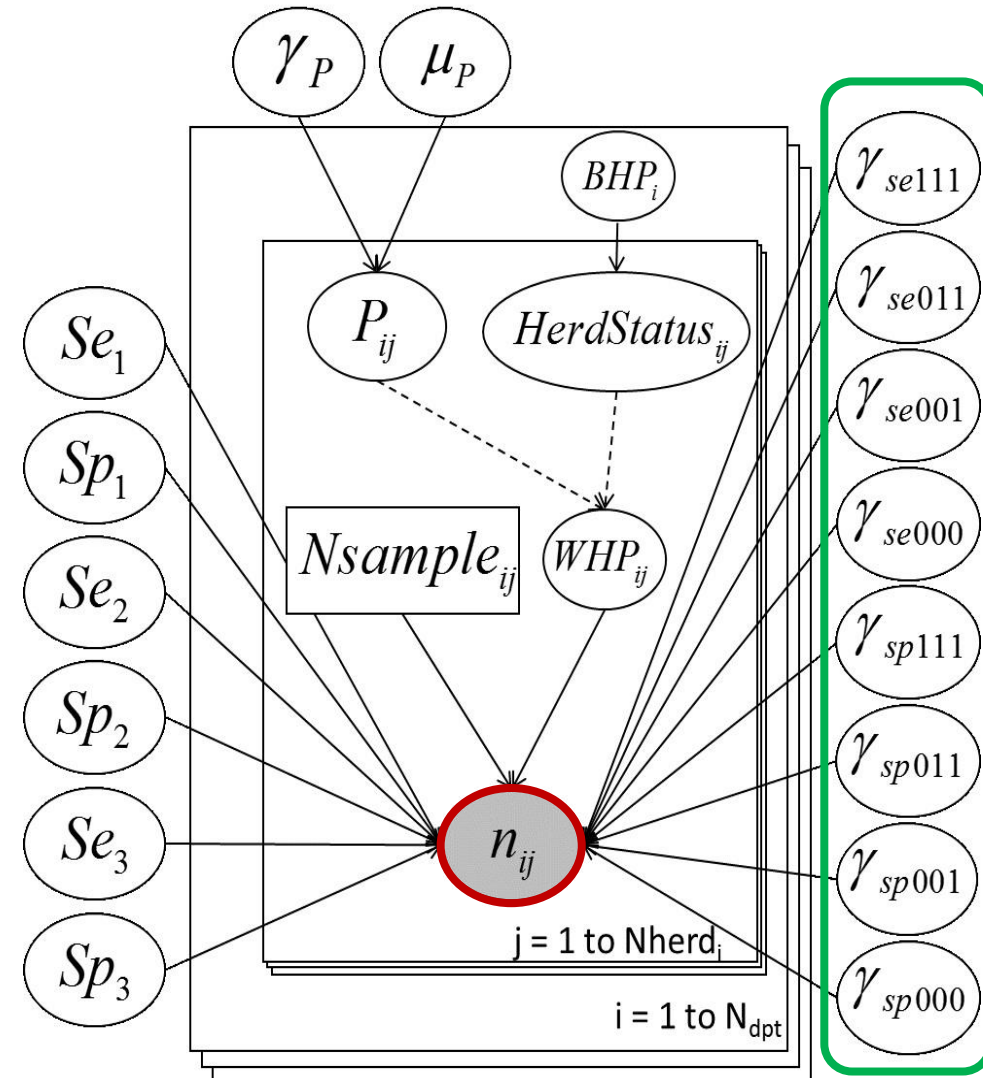


- Serum collected and analysed with the three ELISA tests at the NRL for Q fever in France

(* Gache et al. 2017)

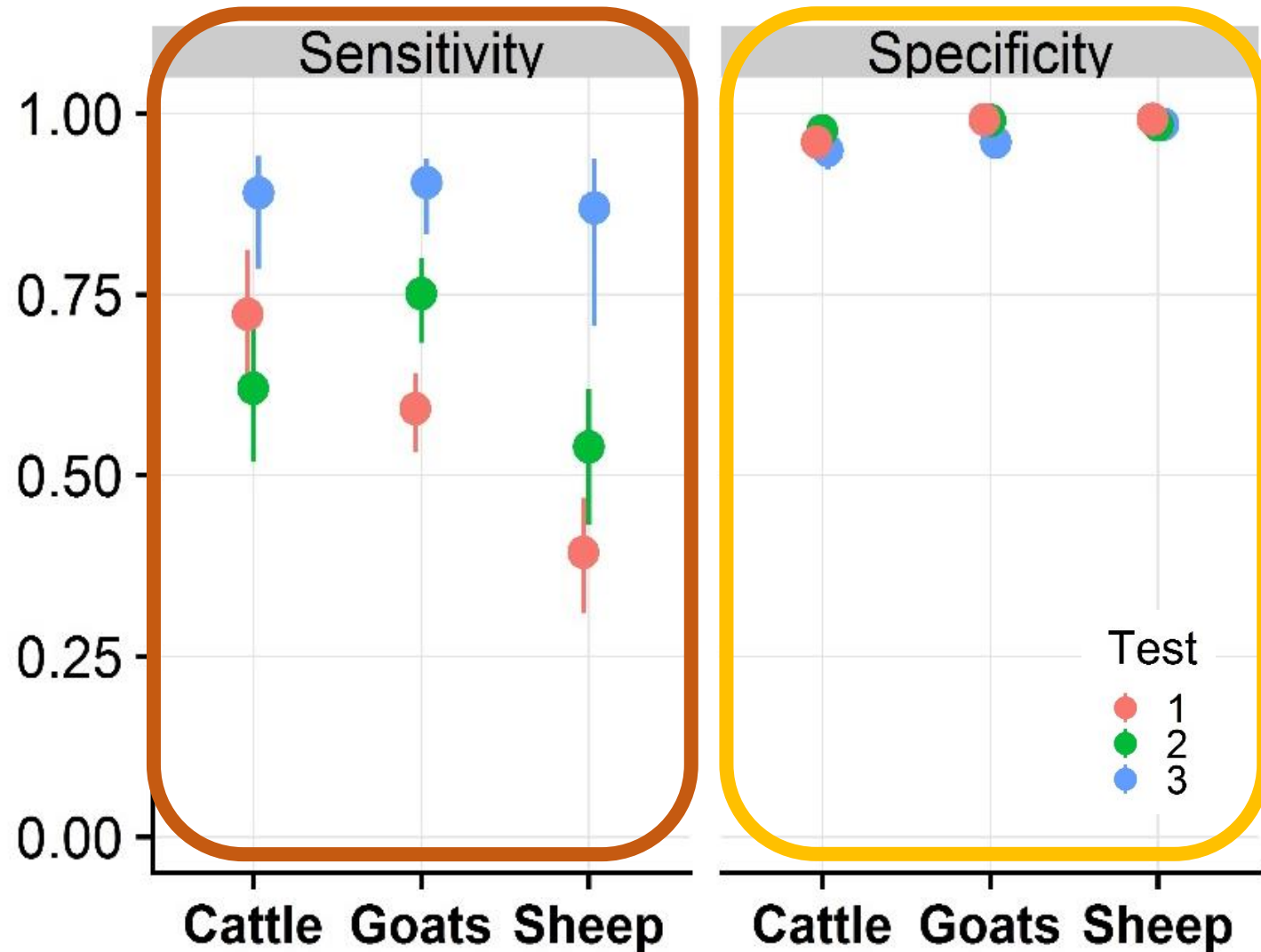
Latent class model

- Modelling the **crossed-classified test results in each herd (n_{ij})**
- Accounting for **conditional dependence** between tests ($\gamma_{Sp\dots}$ and $\gamma_{Se\dots}$)
- One herd = one population
- A unique Between-Herd seroprevalence by department
 - With the possibility that some herds were **free of *C. burnetii*** seropositivity
- **Bayesian inference**
 - JAGS
 - Non informative prior distributions



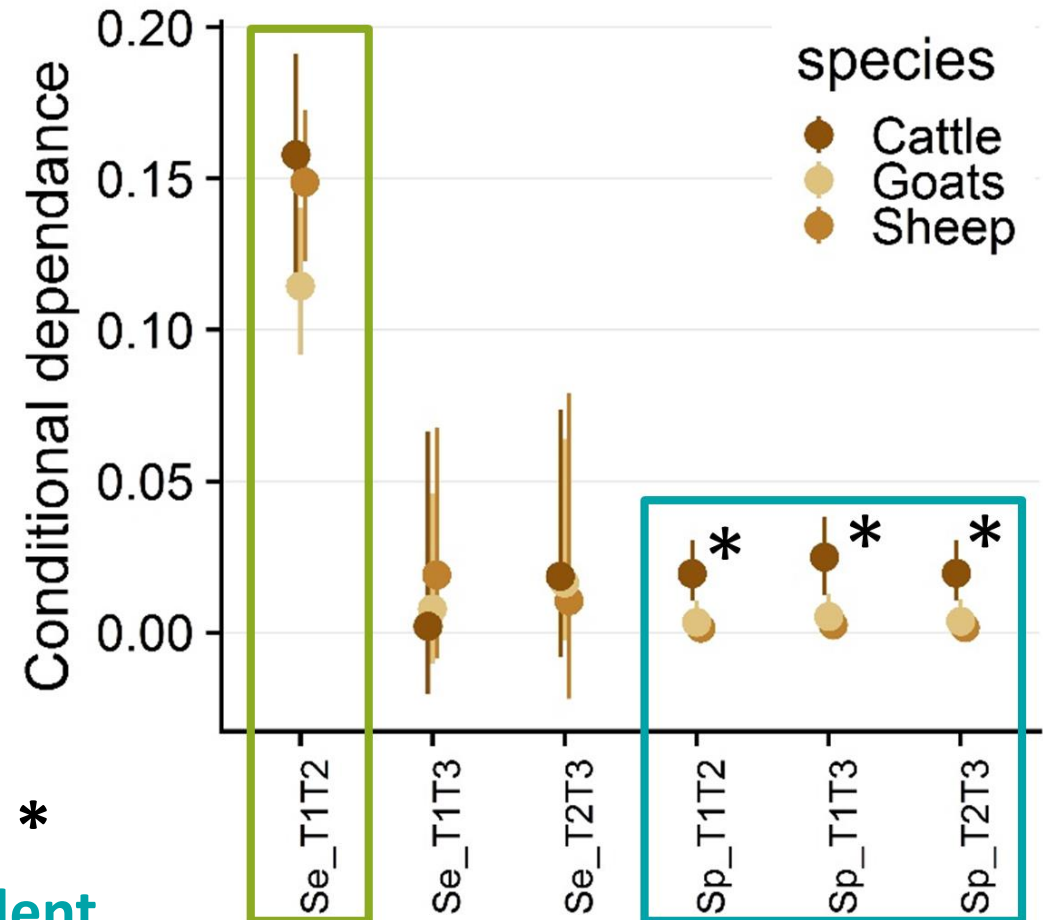
Results : Se and Sp estimates

- **Low Se** especially in sheep
 - **High Sp** (slightly lower in cattle)
 - **Test 3** was the most sensitive in all species but also the least specific
 - Tests were **not equivalent** for each ruminant species
- ⇒ Which test use in each species?



Results : Conditional dependence (CD)

- **High CD between tests 1 and 2** in seropositive animals
⇒ Tests 1 and 2 tended to be **falsely negative at the same time**
- **Negligible CD** in seronegative **sheep** and **goats**
⇒ False positive results were **rare and independent** for the three tests
- **Low but positive CD** in seronegative **cattle** *
⇒ False positive results were **rare but dependent** in **cattle**



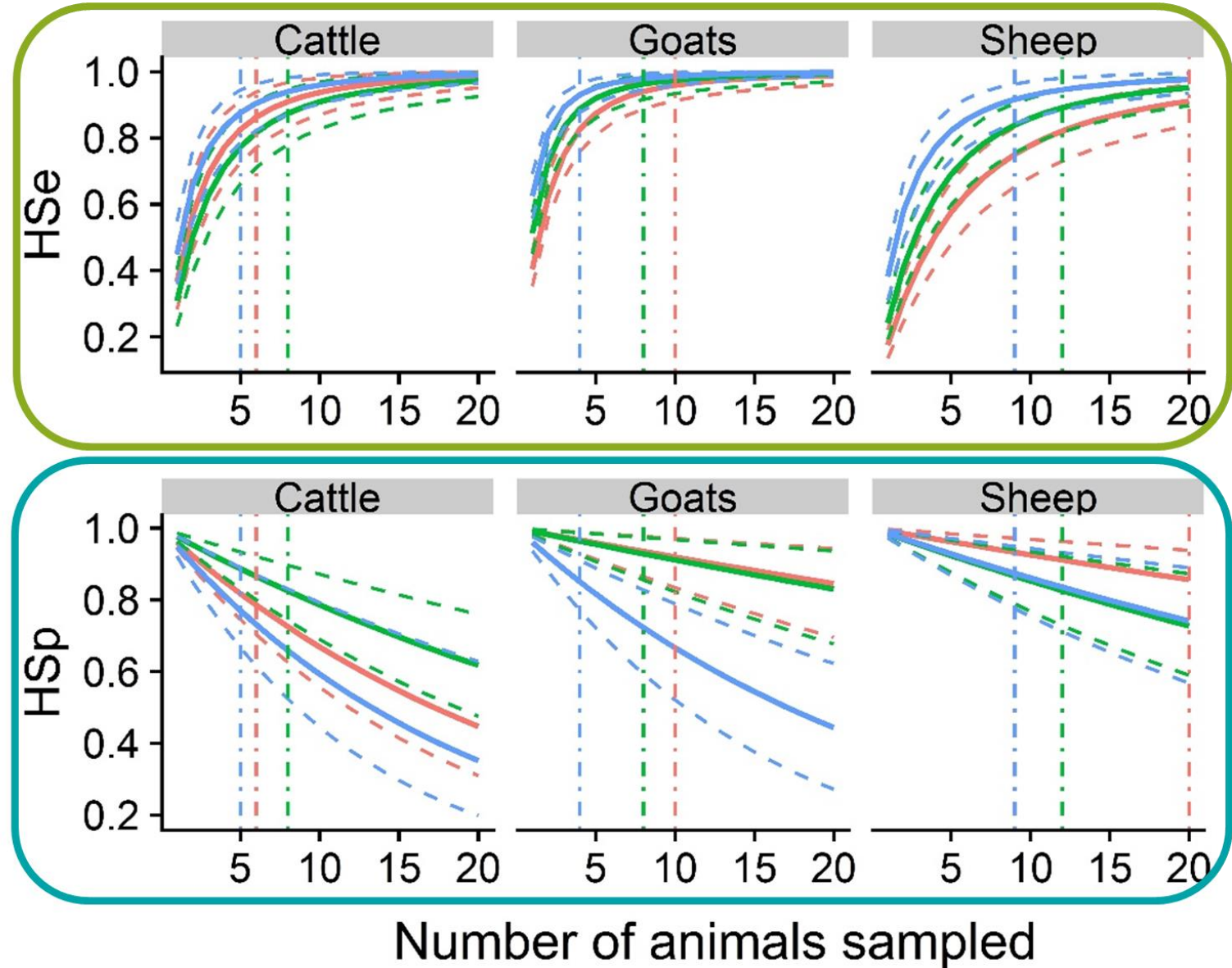
At the herd level : Definitions

- **HSe** = Probability that **at least one** animal sampled is positive using one test in a **truly seropositive herd**
 - **HSp** = Probability that **none** of the animals sampled is positive using one test in a **truly seronegative herd**
- ⇒ Calculated with a sample size varying from **1 to 20** animals
- « Optimal » sample size calculated to maximizing the **HSe + HSp**

At the herd level : Results



- **HSe increased** with the sample size while **HSp decreased**
 - **Test 3** had the worst HSp
- ⇒ The **optimal sample size** maximizing both HSe and HSp **varied from 3 to at least 20** animals depending on the test and ruminant species



Discussion : usefulness and validity of the model

- Unbiased estimation of Se and Sp
 - Did not rely on an imperfect Gold standard
 - Take into account the conditional dependence between tests
- Compared to other studies
 - Similar specificity
 - **Lower sensitivity**

⇒ **Better modelling of conditional dependences** in seropositive animals
- High conditional dependence between tests 1 and 2
 - Only highly seropositive animals are positive with tests 1 and 2
 - Identification of all « seropositive » animals with test 3?
- **Optimal sample size to adapt according to species and tests**

Perspectives

- Necessity to account for ELISA tests Se and Sp to **accurately assess Q fever seroprevalences**
- Need to also assess the respective Se and Sp of the tests corresponding to **abortive contexts**
- Perspectives of harmonization of the 3 tests by changing positivity thresholds

Thank you for your attention

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- INRAE
- VetAgro Sup

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- The Departmental Veterinary laboratories that performed the analyses
- Animal Health Farmers' Organizations that coordinated the study locally



VetAgro Sup



L'action sanitaire ensemble

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