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T. Lurier, Marie Laure Delignette-Muller, Elsa Jourdain, Florence Ayrat,
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➤ Interpretation of the results of Q fever ELISA tests in domestic ruminants: a user-friendly Shiny application based on latent class models in a Bayesian framework

2022 International intracellular bacteria meeting, Lausanne

Thibaut Lurier^{1,2}, Marie Laure Delignette Muller³

Elsa Jourdain¹, Florence Ayrat², Elodie Rousset⁴

UMR 0346 EPIA ¹, USC 1233², LBBE³, ANSES LNR fièvre Q⁴



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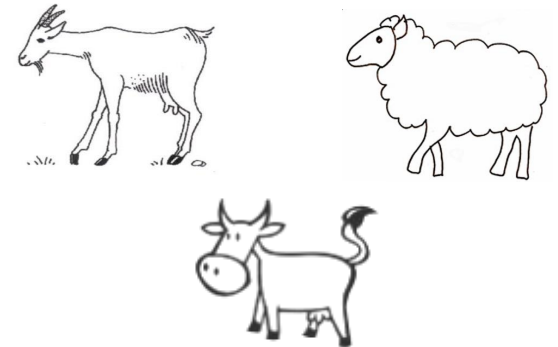
Shinycox : Q fever serological tests in domestic ruminants

24/08/2022 / LURIER Thibaut

p. 1

➤ Q fever, a zoonotic disease transmitted by domestic ruminants

- *Coxiella burnetii* is responsible of acute and persistent infection in Human
- Main reservoir = Domestic ruminant
 - **Reproductive issues** (abortion)
- Diagnostic limitations
 - Direct diagnosis (PCR)
 - Sp = 100% but **low Se** except after abortion
 - Indirect diagnosis (ELISA)
 - **Unknown but imperfect Se and Sp** (<100%)



⇒ There is some potential **diagnostic errors** (either false negative or false positive)

⇒ We need **tools to interpret the results** of diagnostic tests in domestic ruminants

➤ Context: risk of Q fever introduction in a herd

Case study in France, 2019

- Herd A bought a bull from herd B
 - The bull was **tested and seropositive** for Q fever
 - **Is it a true seropositive?**
- ⇒ 5 additional animals from herd B were tested

All were seronegative

⇒ Then, the whole herd B (n=149) was tested using serum samples previously collected for the IBR prophylaxis

5/149 seropositive



➔ **Estimate of the positive predictive value (VPP) is required**

$$VPP = \text{Proba}(D^+ | T^+)$$
$$VPP = \frac{Se \times WHP}{Se \times WHP + (1 - Sp) \times (1 - WHP)}$$

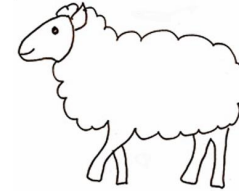
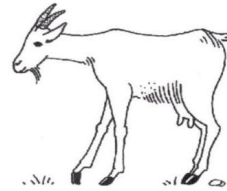
Objectives of the thesis

- 1- Assess the **diagnostic accuracy** of the tests in the absence of **Gold standard**
- 2- Assess **within-herd seroprevalence levels** accounting for test **diagnostic uncertainty**
- 3- Develop and make an online tool available to professionals to **calculate predictive values**

$$VPP = \frac{Se \times WHP}{Se \times WHP + (1 - Sp) \times (1 - WHP)}$$

➤ Diagnostic accuracy of the commercialized ELISA serological tests

- Absence of a gold standard test
- Assessment of the **sensitivity** and **specificity** of the three ELISA tests with latent class models



Lurier et al. *Vet Res* (2021) 52:56
<https://doi.org/10.1186/s13567-021-00926-w>



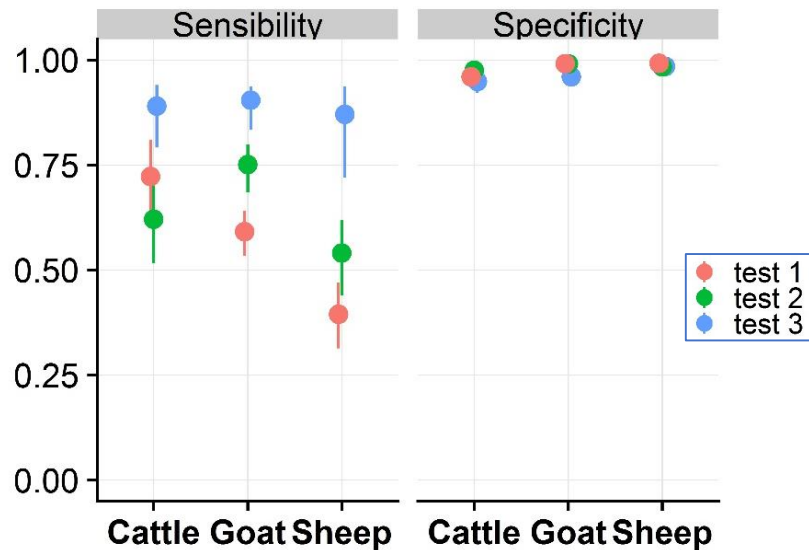
RESEARCH ARTICLE

Open Access



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

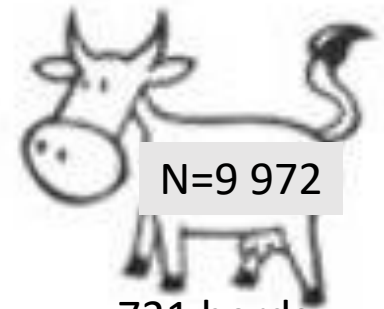
Thibaut Lurier^{1,2,3*}, Elodie Rousset⁴, Patrick Gasqui¹, Carole Sala⁵, Clément Claustre¹, David Abrial¹, Philippe Dufour⁴, Renée de Crémoux⁶, Kristel Gache⁷, Marie Laure Delignette-Muller⁸, Florence Ayrat² and Elsa Jourdain¹



➤ Within (WHP) and between (BHP) herd seroprevalence in France

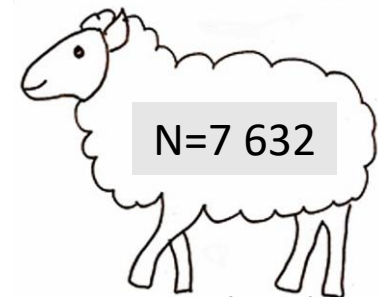
- Serosurvey in France in 2014 using ELISA test 2 (Gache et al. 2017)
 - Diagnostic accuracy assumed as $Se = 100\%$ and $Sp = 100\%$
 - Herd positive as soon as 1 animal tests positive
- **Potential bias :**
 - $Se = 50-60\% \Rightarrow$ False negative individuals
 \Rightarrow **Underestimation** of the **WHP**
 - $Sp < 100\% \Rightarrow$ False positive animals
 \Rightarrow **Overestimation** of the **BHP**

\Rightarrow **Necessity of a reassessing BHP and WHP accounting for diagnostic uncertainty**



N=9 972

731 herds



N=7 632

522 herds



N=5 024

324 herds

Cf. poster #60 in the Congress!



➤ Results in cattle

- In France
 - ⇒ Median of the BHP in meat herd = 5.7%
 - ⇒ 8 times higher in dairy herds
- If the herd is seropositive
 - ⇒ The median of the WHP = 39.4%
 - ⇒ With a tendency to increase with the herdsize

Scale	Risk factor	Risk ratio [95% CI]
Between herd	Herd size	1.39 [0.91;2.11]
	Meat	*Réf : 5,7 % [1,5 ; 19,5]
	Dairy	7.97 [3.44;22.22]
Within herd	Herd size	1.17 [0.97;1.34]
	Meat	*Réf : 39,4 % [27,3 ; 57,0]
	Dairy	0.98 [0.67;1.46]

➤ How to calculate the probability of being a true seropositive animal (e.g., the bull)?

$$VPP = \frac{Se \times WHP}{Se \times WHP + (1 - Sp) \times (1 - WHP)}$$

• We assessed

- (part 1) the test **sensitivity and specificity** with some uncertainty
 - Se = 0.619 [0.517; 0.718]
 - Sp = 0.975 [0.962; 0.987]
- (part 2) **within-herd seroprevalence** in seropositive herds
 - from 13.7% to 81.2%

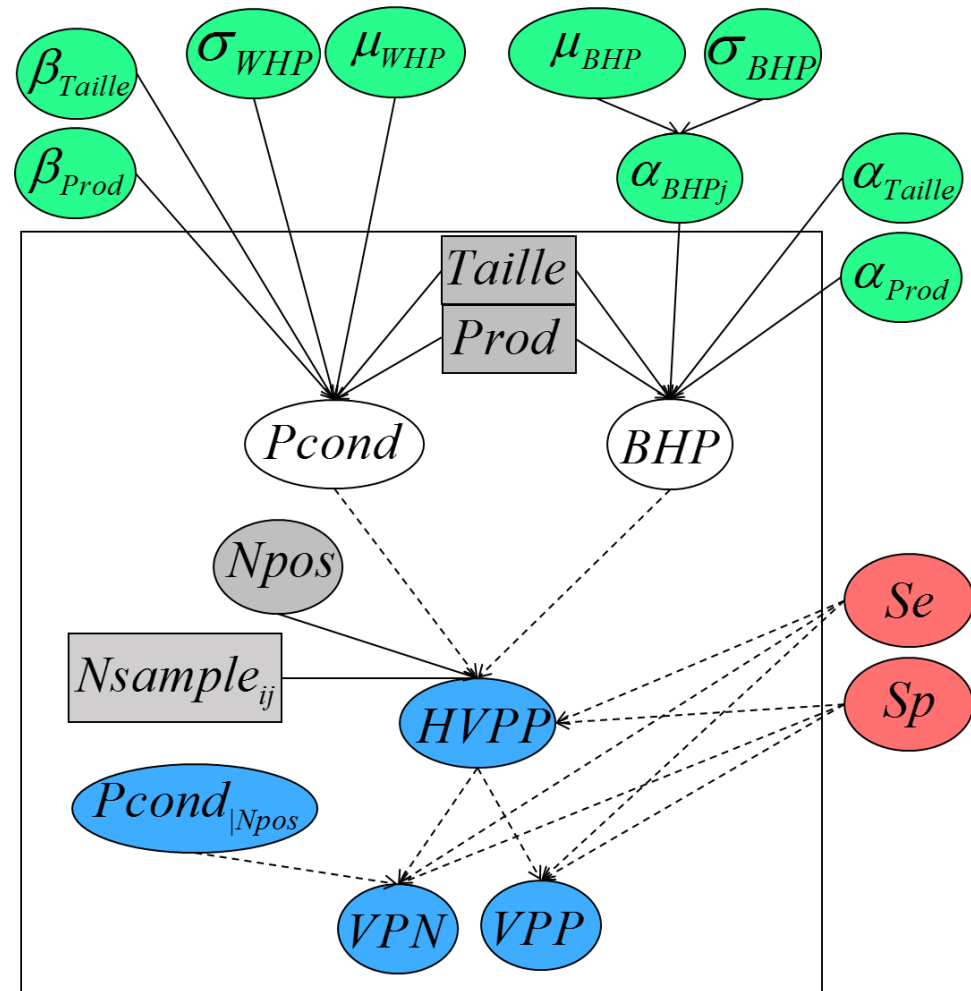
• Because predictive values may strongly differ depending on the epidemiological situation

⇒ We have to implement a model to also **assess the uncertainty of the predictive values**



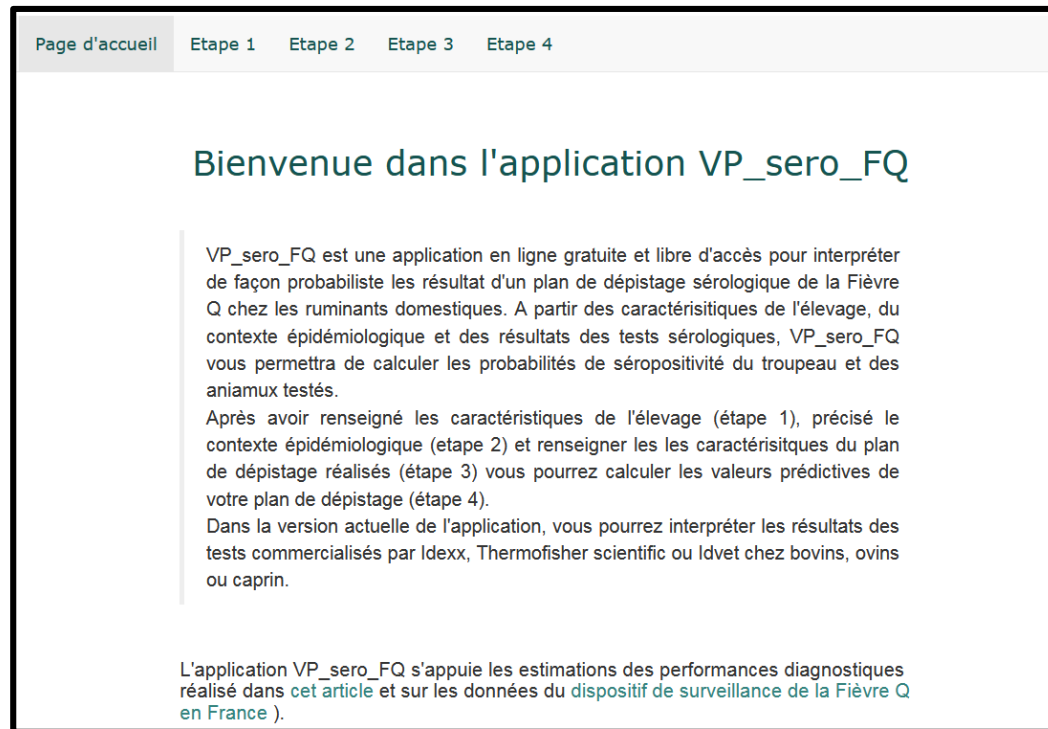
➤ Model

- **Se and Sp (study 1)**
- **Parameters corresponding to the within and between herd seroprevalences (study 2)**
- Results obtained in the herd (number of animals sampled, number of animals tested positive)
- **Predictive values**



➤ Shiny app

- Creation of a step by step online and open access Shiny application : [Demo](#)



The screenshot shows the user interface of the VP_sero_FQ Shiny application. At the top, there is a navigation bar with five tabs: 'Page d'accueil' (selected), 'Etape 1', 'Etape 2', 'Etape 3', and 'Etape 4'. The main content area features a heading 'Bienvenue dans l'application VP_sero_FQ' followed by a detailed introductory text. The text explains that the application is a free, open-access online tool for interpreting serological screening results for Q fever in domestic ruminants. It describes the workflow: users provide breeding characteristics (step 1), epidemiological context (step 2), and screening plan details (step 3) to calculate predictive values (step 4). It also notes that the current version uses commercialized tests from Idexx, Thermofisher scientific, or Idvet for bovine, ovine, and caprine species. At the bottom, a note states that the application is based on diagnostic performance estimates from a specific article and data from the Q fever surveillance device in France.

➤ Step 1 : herd characteristics

Page d'accueil **Etape 1** Etape 2 Etape 3 Etape 4

Renseignement des caractéristiques de l'élevage

<p>Espèce de ruminant</p> <input type="text" value="bovin"/>	<p>Type de production</p> <input type="text" value="viande"/> <p>Cliquez ici pour obtenir des informations sur le type de production</p>	<p>Nombre de femelles paires dans l'élevage</p> <input type="text" value="156"/> <p>Cliquez ici pour obtenir des informations sur la taille du troupeau</p>
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➤ Step 2 : Epidemiologic context

Page d'accueil Etape 1 **Etape 2** Etape 3 Etape 4

Informations concernant le contexte épidémiologique

Le graphique ci-dessous représente la distribution a priori de la probabilité que le troupeau soit séropositifs. Cette distribution tiens compte de l'espèce, du type de production et de la taille de l'élevage renseignée à l'étape 1. Elle sera utilisée pour réaliser les calculs des valeurs prédictives du plan de dépistage. Si vous disposez d'information fiable sur le contexte épidémiologique de l'élevage testé (proportion d'élevage séropositif dans le département, ou antécédant de Fièvre Q dans l'élevage), vous pouvez modifier cette distribution a priori.

Disposez vous d'information fiable sur le contexte épidémiologique de l'élevage testé?

Selon les informations dont vous disposez, fixez les valeurs qui correspondent à la gamme des valeurs possibles de la probabilité de séropositivité du troupeau.

Cliquez [ici](#) pour obtenir des informations sur la méthode de choix du contexte.

Distribution à priori elicitée

— Distribution avec info
— Distribution sans info

Densité de probabilité

Probabilité que le troupeau soit séropositif

0.0 0.2 0.4 0.6 0.8 1.0

➤ Step 3 : Results of the diagnostic test

Page d'accueil Etape 1 Etape 2 **Etape 3** Etape 4

Informations concernant le plan de dépistage réalisé

Test utilisé
ThermoFisher Scientific ▼


Nombre d'animaux testés
156

Nombre d'animaux positifs
0 6 156

➤ Step 4 : Fit of the model

Calculs et résultats

Cliquez sur ce bouton à chaque fois que vous modifier les informations des étapes précédentes :

 Calcul

Cliquez [ici](#) pour obtenir des informations sur la méthode de calcul

⚠ Attention, le calcul peut prendre quelques dizaines de secondes, les valeurs calculées peuvent varier très légèrement d'un calcul à l'autre.

Interprétation des résultats du plan de dépistage réalisé

Sachant que 6 animaux ont été testés positifs avec le test ThermoFisher Scientific parmi les 156 prélevés dans un élevage bovin de type de production viande et de taille 156

La probabilité que le troupeau soit réellement séropositif est de :

0 IC à 95% [0; 0.67]

Si le troupeau est séropositifs, sa séoprévalence est estimée à :

0.06 IC à 95% [0.02; 0.13]

La valeur prédictive positive (probabilité que les individus testés positifs soient réellement seropositifs) est de :

0 IC à 95% [0; 0.67]

La valeur prédictive négative (probabilité que les individus testés négatifs soient réellement séronégatifs) est de :

1 IC à 95% [0.98; 1]

➤ Conclusion

- Concerning the bull :
 - PPV knowing that 1 out of 6 animals sampled were seropositive : 0.85 [0.14; 0.98]
 - PPV knowing that 5 out of 149 animals were sampled positive : 0 [0; 0.59]
- We developed a complete framework to **interpret the results of the serological tests** based on:
 - **Unbiased estimates of the diagnostic performances** of the test
 - The assessment of **true** between and within herd seroprevalences
- We will make it available to professionals (veterinarians, laboratories, ...)



➤ Thank you for your attention

• Funding

- ANSES
- DGAL
- GDS France
- INRAE
- VetAgro Sup

• Acknowledgment

- the French platform for epidemiological surveillance in animal health (ESA platform)
- The farmers who took part in this study
- The veterinarians who collected the samples
- The Departmental Veterinary laboratories that performed the analyses
- Animal Health Farmers' Organizations that coordinated the study locally



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France



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