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

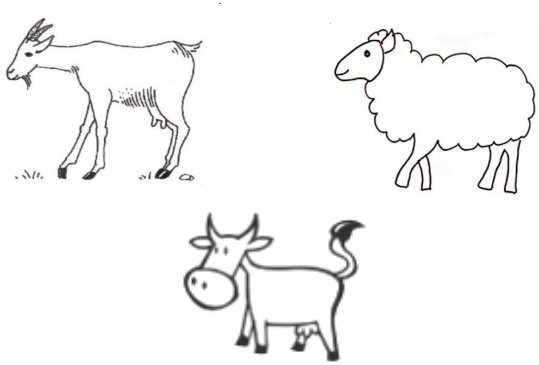
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UMR 0346 EPIA [1], USC 1233[2,] LBBE[3], ANSES LNR fièvre Q[4]

Q fever, a zoonotic disease transmitted by domestic ruminants

- *Coxiella burnetii* is responsible of acute and persistant 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%)



⇒Their 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

$$VPP = \text{Proba}\left(D^{+} \mid T^{+}\right)$$

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

Objectives of the thesis

1- Assess the diagnostic accuracy of the tests in the absence of **Gold standard**

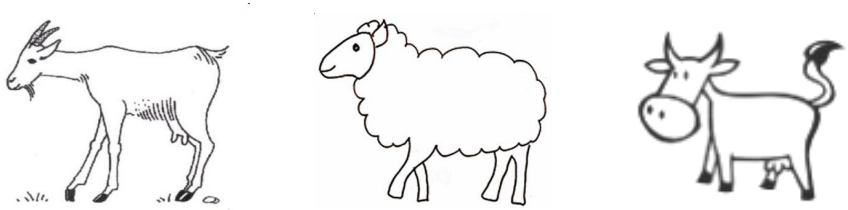
2- Assess within-herd seroprevalence levels accounting for test **diagnostic uncertainty**

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



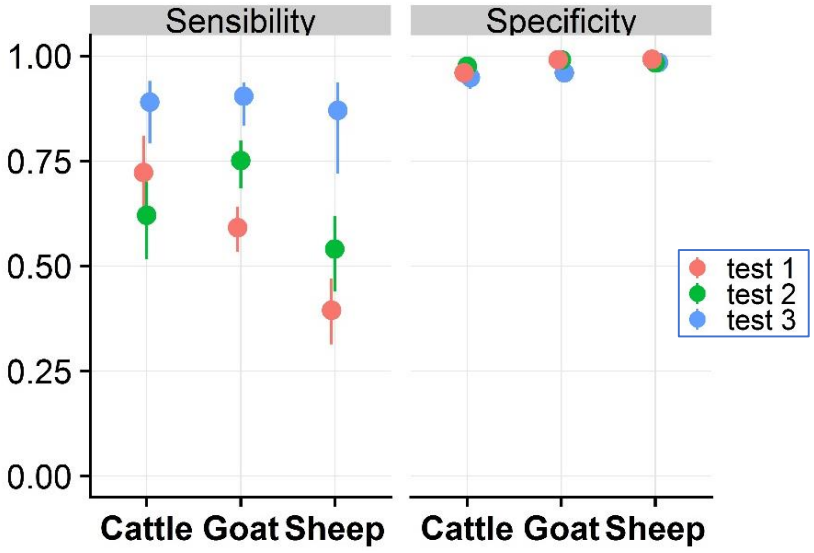
Lurier *et al. Vet Res* (2021) 52:56
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VETERINARY RESEARCH

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

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Cf. poster #59 in the Congress!

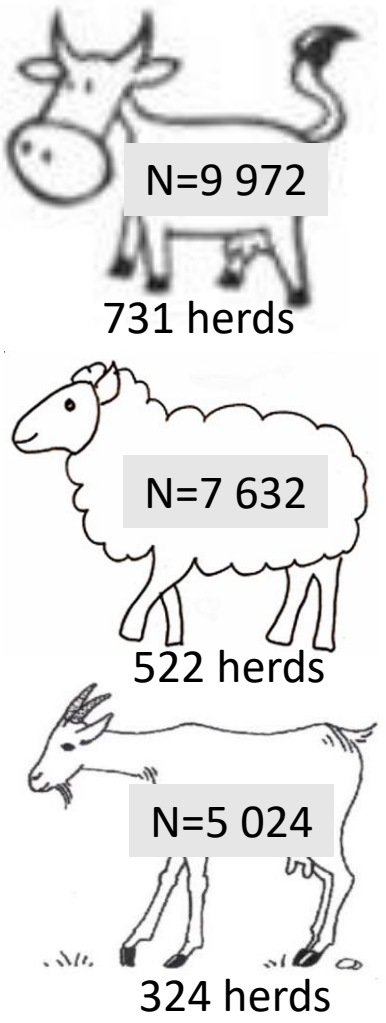
Within (WHP) and between (BHP) herd seroprevalence in France

- 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% => False negative individuals

  ⇒**Underestimation of the WHP**
  - Sp <100% => False positive animals

  ⇒**Overestimation of the BHP**

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



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)?

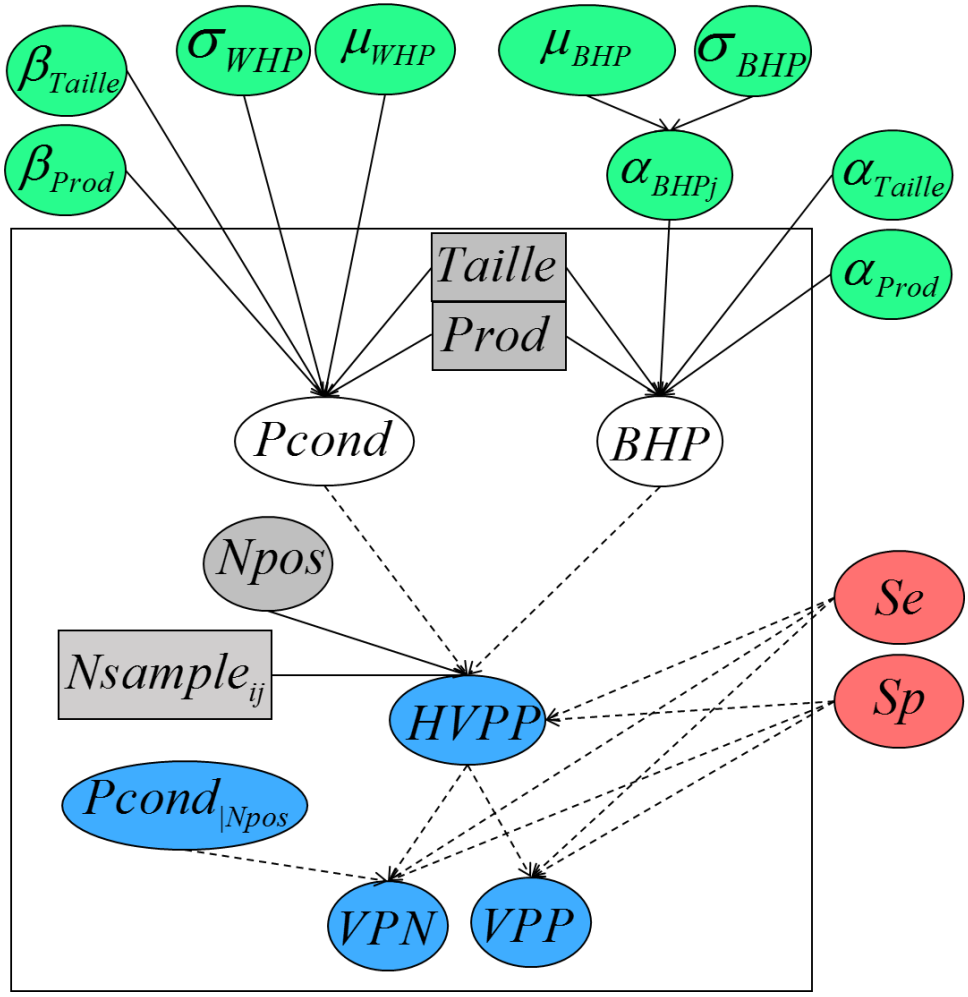
$$VPP = \frac{Se \times WHP}{Se \times WHP + (1 - Sp) \times (1 - WHP)}$$

- 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**

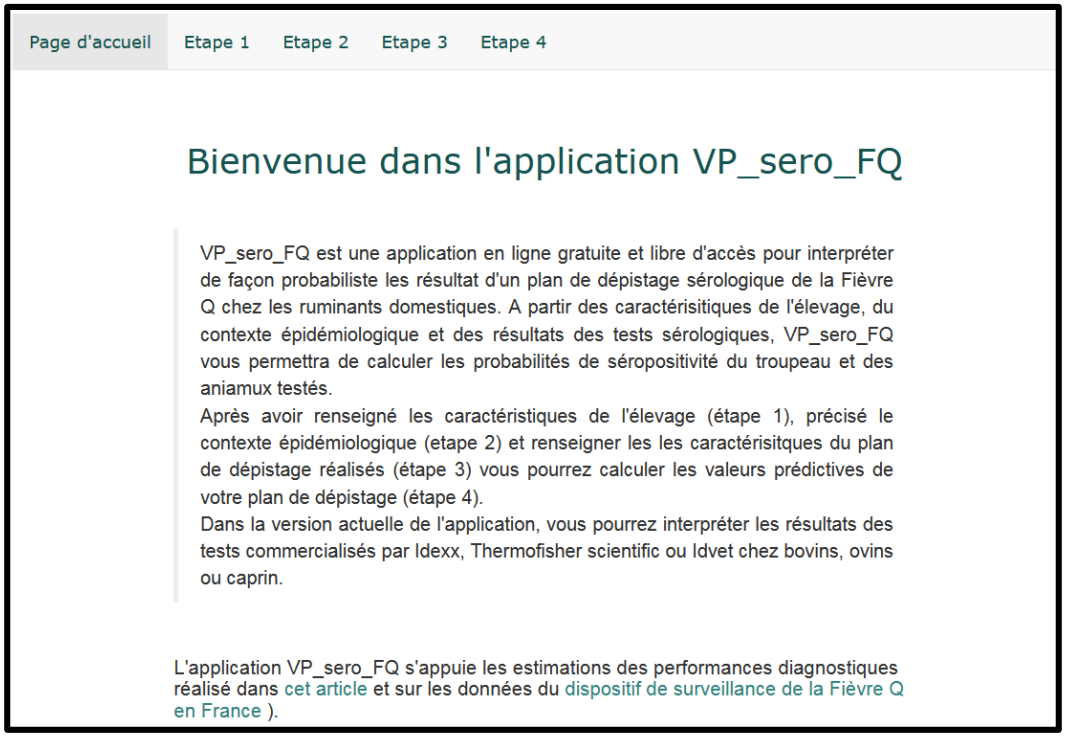
Model

- **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**

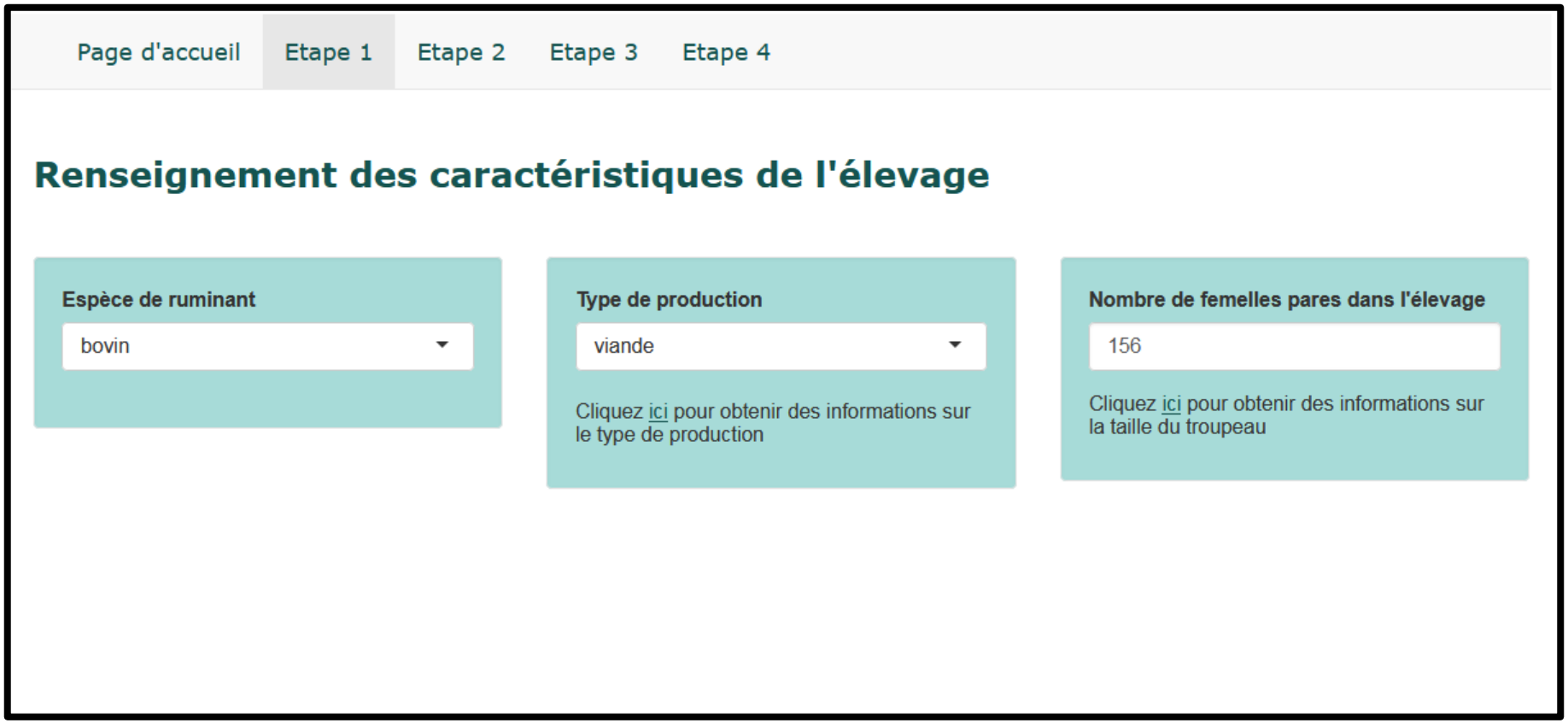


Shiny app

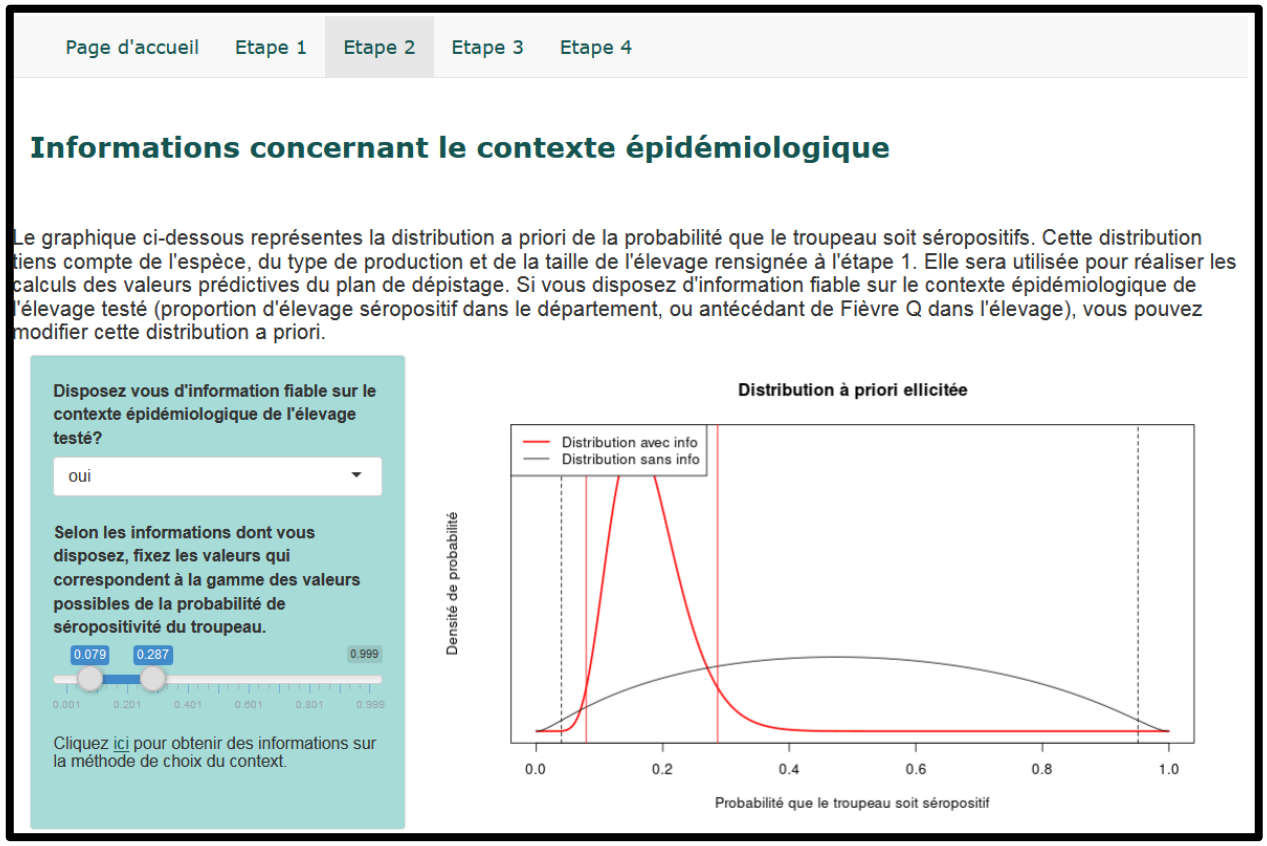
- Creation of a step by step online and open access Shiny application : Demo



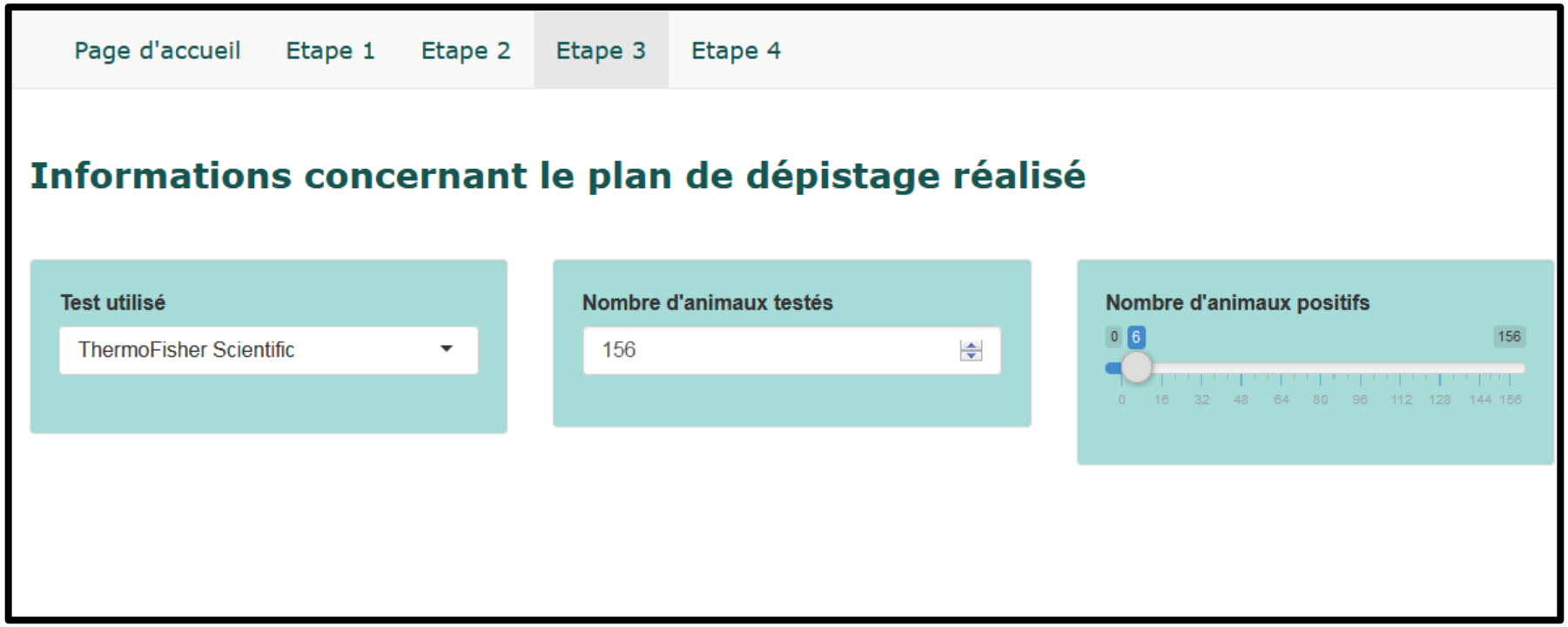
Step 1 : herd characteristics



Step 2 : Epidemiologic context



Step 3 : Results of the diagnostic test



Step 4 : Fit of the model



Calculs et résultats

Cliquez sur ce boutton 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 séroprévalence 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

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  - ANSES
  - DGAL
  - GDS France
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  - VetAgro Sup
- **Acknowledgment**
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  - The veterinarians who collected the samples
  - The Departmental Veterinary laboratories that performed the analyses
  - Animal Health Farmers' Organizations that coordinated the study locally













