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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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.

HARMONY
Novel tools for test evaluation and disease prevalence estimation

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Conference of the Society for bayesian/advanced methods for epidemiology and diagnostics

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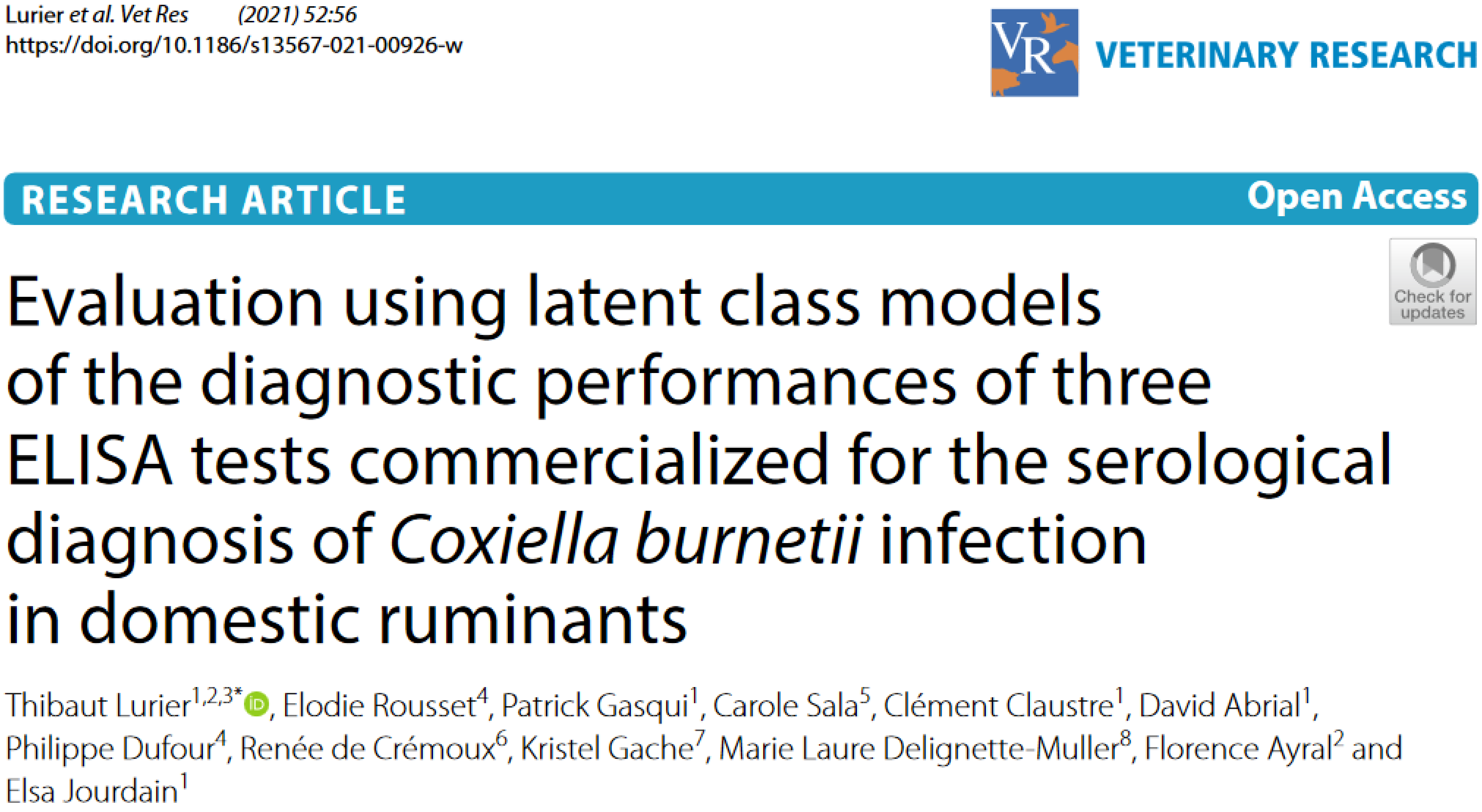

Lurier *et al. Vet Res* (2021) 52:56
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VETERINARY RESEARCH

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

Thibaut Lurier[1,2,3*], Elodie Rousset[4], Patrick Gasqui[1], Carole Sala[5], Clément Claustre[1], David Abrial[1], Philippe Dufour[4], Renée de Crémoux[6], Kristel Gache[7], Marie Laure Delignette-Muller[8], Florence Ayral[2] and Elsa Jourdain[1]

https://doi.org/10.1186/s13567-021-00926-w

Serological diagnosis of *Coxiella burnetii* infection

- **ELISA methods are recommended by the OIE**
- **Three commercialized ELISA tests**
  - Test 1 , commercialized by Idexx
  - Test 2, commercialized by ThermoFisher Scientific
  - Test 3 : commercialized by Innovative Diagnostics Vet
- **Only few studies about their sensitivity and specificity**

→ *Depending on the test, study and species, estimates vary*

- ***sensitivity** from 70 to 100%*
- ***specificity** from 90 to 100%*

- **Not for all tests and/or species**
- **Sometimes with an important risk of bias**

⇒**No Gold Standard (**reference test with 100% Se and Sp)

Conditional dependence between tests

Are the tests frequently wrong/correct at the same time?

False negative/true positive results, more likely to occur simultaneously

- When the level of antibodies is low/high and difficult/easy to detect with any test
- When the tests target closely related antigens of *C burnetii*

False positive results, less likely to occur simultaneously?

- Observed for bacteria that have antigens closely related to the ones of *C. burnetii* (e.g., *Coxiella*-like tick symbionts) → cross reactions

Otherwise, errors are expected to be independent between tests

In our case, conditional dependence between tests are expected
→ has to be taken into account to assess the tests diagnostic performances.

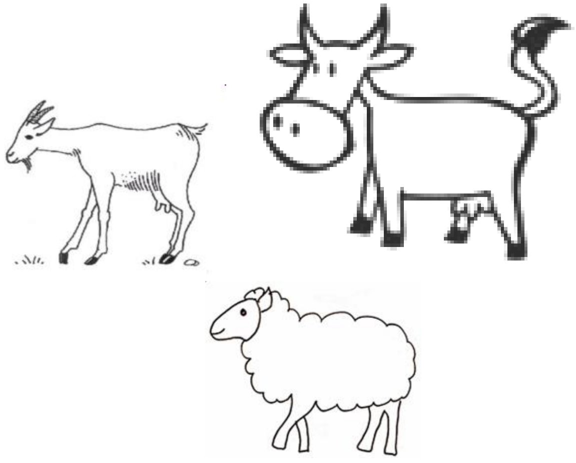
Limits of previous LCM studies

- Five studies which applied LCM with some of the three ELISA tests

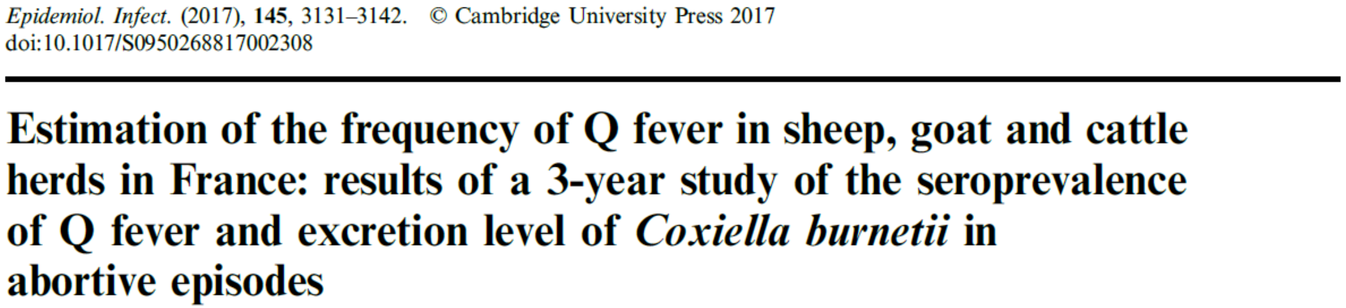
Study	Tests included	Se/Sp of test 1	CONDITIONNAL DEPENDENCE		Prior used	Comment
			Assesment	Results		
Horigan et al. 2011	Tests 1, test 2 et test 3 ,CFT	Se=87%, Sp=99%	**No**	NA	NA	High risk of bias with probable overestimation of Sensitivities
Paul et al. 2013	Test 1 (Blood/Milk)	Se=84% Sp=99%	Yes	“Not significant”	Non Informative	**Only test 1** => Latent status might be « is the animal positive with test 1 » ≠ « is the animal truly seropositive »
Lucchese et al. 2016	Test 1 et test 2, CFT	Se=97%, Sp=92%	Yes	Low (almost null)	Non Informative and Informative	Very High Se and Sp estimate, potential bias if test are conditionally dependent
Muleme et al. 2016	Test 1, CFT, Elisa mod, IFA	Se=70% Sp=96%	Yes	Not shown (but low)	Informative (from Horrigan or human studies)	Prior information from potentially highly biased study (Horrigan et al.) Little information about conditional dependence between tests
Wood et al. 2019	Test 1, IFA	Se =88% Sp= 98%	Yes	Not shown (but low)	Informative (from Muleme and Horrigan)	

Objectives of this study

- **Estimate the sensitivity and specificity values** of the three ELISA tests commercialized for Q fever serodiagnosis in ruminants
    - From serum **samples of unknown status** originating from cattle, sheep and goat herds in France
    - With **latent class models** considering the **cross-classified test results** of the three tests
    - Accounting for the likely **conditional dependence** between tests

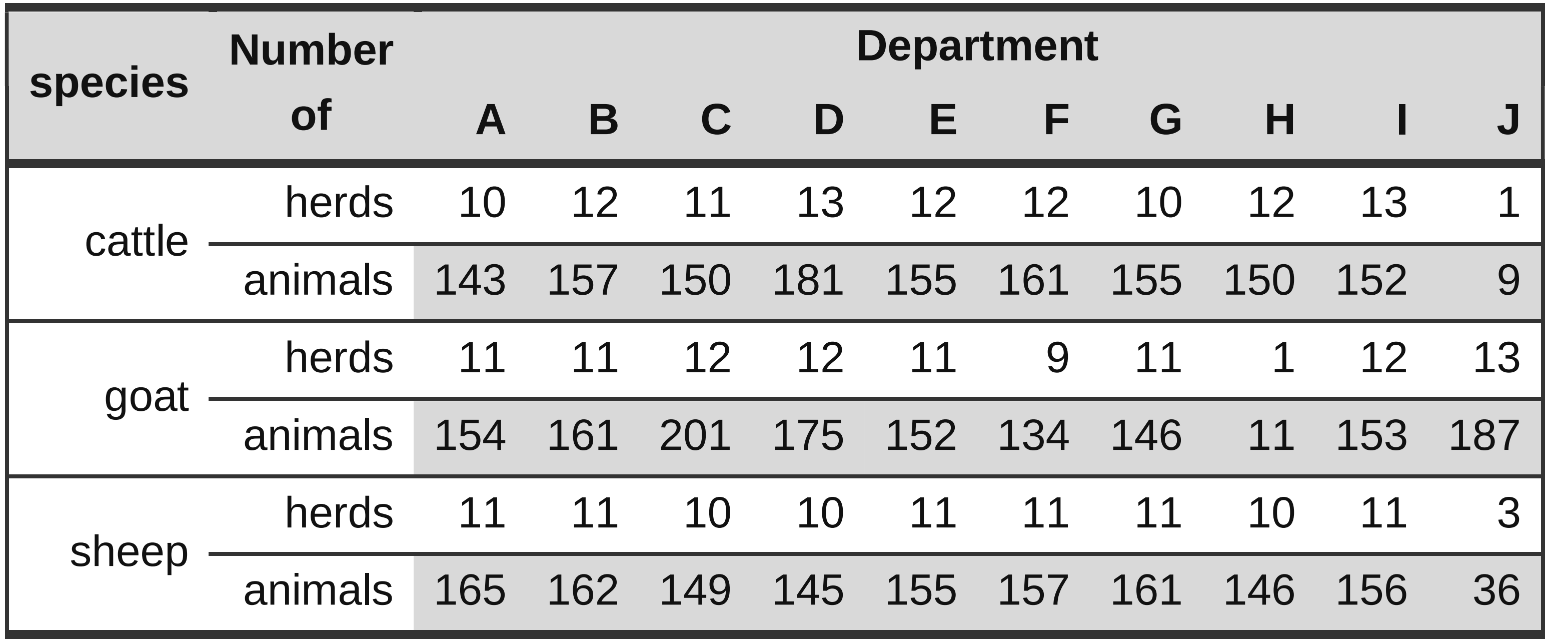


Study sample


Epidemiol. Infect. (2017), **145**, 3131–3142. © Cambridge University Press 2017
doi:10.1017/S0950268817002308

Estimation of the frequency of Q fever in sheep, goat and cattle herds in France: results of a 3-year study of the seroprevalence of Q fever and excretion level of *Coxiella burnetii* in abortive episodes

- Sub-sample of a larger epidemiologic study *(Gache et al. 2017)* of 23,000 animals sampled from 1,500 randomly selected herds with no history of Q fever vaccination
- Inclusion of 150 animals from 10 herds in each *department*
    - 1,413 cows from 106 herds
    - 1,474 goats from 103 herds
    - 1,432 ewes from 99 herds
- Samples collected and analyzed in 2014 with the three ELISA tests at the NRL for Q fever



species	Number of	Department									
		A	B	C	D	E	F	G	H	I	J
cattle	herds	10	12	11	13	12	12	10	12	13	1
	animals	143	157	150	181	155	161	155	150	152	9
goat	herds	11	11	12	12	11	9	11	1	12	13
	animals	154	161	201	175	152	134	146	11	153	187
sheep	herds	11	11	10	10	11	11	11	10	11	3
	animals	165	162	149	145	155	157	161	146	156	36

Latent class model with conditional depence between three test (Wang et al. 2017)

Catégorie	Probabilité
$T_1^- T_2^- T_3^-$	$P \times ((1-Se_1) \times (1-Se_2) \times (1-Se_3) + \gamma_{Se000}) +$ $(1-P) \times (Sp_1 \times Sp_2 \times Sp_3 + \gamma_{Sp000})$
$T_1^- T_2^+ T_3^-$	$P \times ((1-Se_1) \times Se_2 \times (1-Se_3) + \gamma_{Se010}) +$ $(1-P) \times (Sp_1 \times (1-Sp_2) \times Sp_3 + \gamma_{Sp010})$
$T_1^- T_2^- T_3^+$	$P \times ((1-Se_1) \times (1-Se_2) \times Se_3 + \gamma_{Se001}) +$ $(1-P) \times (Sp_1 \times Sp_2 \times (1-Sp_3) + \gamma_{Sp001})$
$T_1^- T_2^+ T_3^+$	$P \times ((1-Se_1) \times Se_2 \times Se_3 + \gamma_{Se011}) +$ $(1-P) \times (Sp_1 \times (1-Sp_2) \times (1-Sp_3) + \gamma_{Sp011})$
$T_1^+ T_2^- T_3^-$	$P \times (Se_1 \times (1-Se_2) \times (1-Se_3) + \gamma_{Se100}) +$ $(1-P) \times ((1-Sp_1) \times Sp_2 \times Sp_3 + \gamma_{Sp100})$
$T_1^+ T_2^+ T_3^-$	$P \times (Se_1 \times Se_2 \times (1-Se_3) + \gamma_{Se110}) +$ $(1-P) \times ((1-Sp_1) \times (1-Sp_2) \times Sp_3 + \gamma_{Sp110})$
$T_1^+ T_2^- T_3^+$	$P \times (Se_1 \times (1-Se_2) \times Se_3 + \gamma_{Se101}) +$ $(1-P) \times ((1-Sp_1) \times Sp_2 \times (1-Sp_3) + \gamma_{Sp101})$
$T_1^+ T_2^+ T_3^+$	$P \times (Se_1 \times Se_2 \times Se_3 + \gamma_{Se111}) +$ $(1-P) \times ((1-Sp_1) \times (1-Sp_2) \times (1-Sp_3) + \gamma_{Sp111})$

- 8 cross classified test results category

$\Rightarrow$7 DL

- Minimum 7 parameters (P, 3xSe, 3xSp)
- Conditional dependences
  - In theory 8 + 8 but :

$$\gamma_{Se100} = \gamma_{Se011} + \gamma_{Se111} - \gamma_{Se000} \qquad \gamma_{Sp100} = \gamma_{Sp011} + \gamma_{Sp111} - \gamma_{Sp000}$$

$$\gamma_{Se101} = -(\gamma_{Se001} + \gamma_{Se011} + \gamma_{Se111}) \qquad \gamma_{Sp101} = -(\gamma_{Sp001} + \gamma_{Sp011} + \gamma_{Sp111})$$

$$\gamma_{Se110} = \gamma_{Se000} + \gamma_{Se001} - \gamma_{Se111} \qquad \gamma_{Sp110} = \gamma_{Sp000} + \gamma_{Sp001} - \gamma_{Sp111}$$

$$\gamma_{Se010} = -(\gamma_{Se000} + \gamma_{Se001} + \gamma_{Se011}) \qquad \gamma_{Sp010} = -(\gamma_{Sp000} + \gamma_{Sp001} + \gamma_{Sp011})$$

  - So 8 more parameters

=> Theoriticaly identifiable with 3 populations

First latent class model

- **One model by ruminant species**
- Conditional dependence between the three tests modeled with a **fixed effect model** (*Wang et al. 2017)*
- Each Department is considered as a population

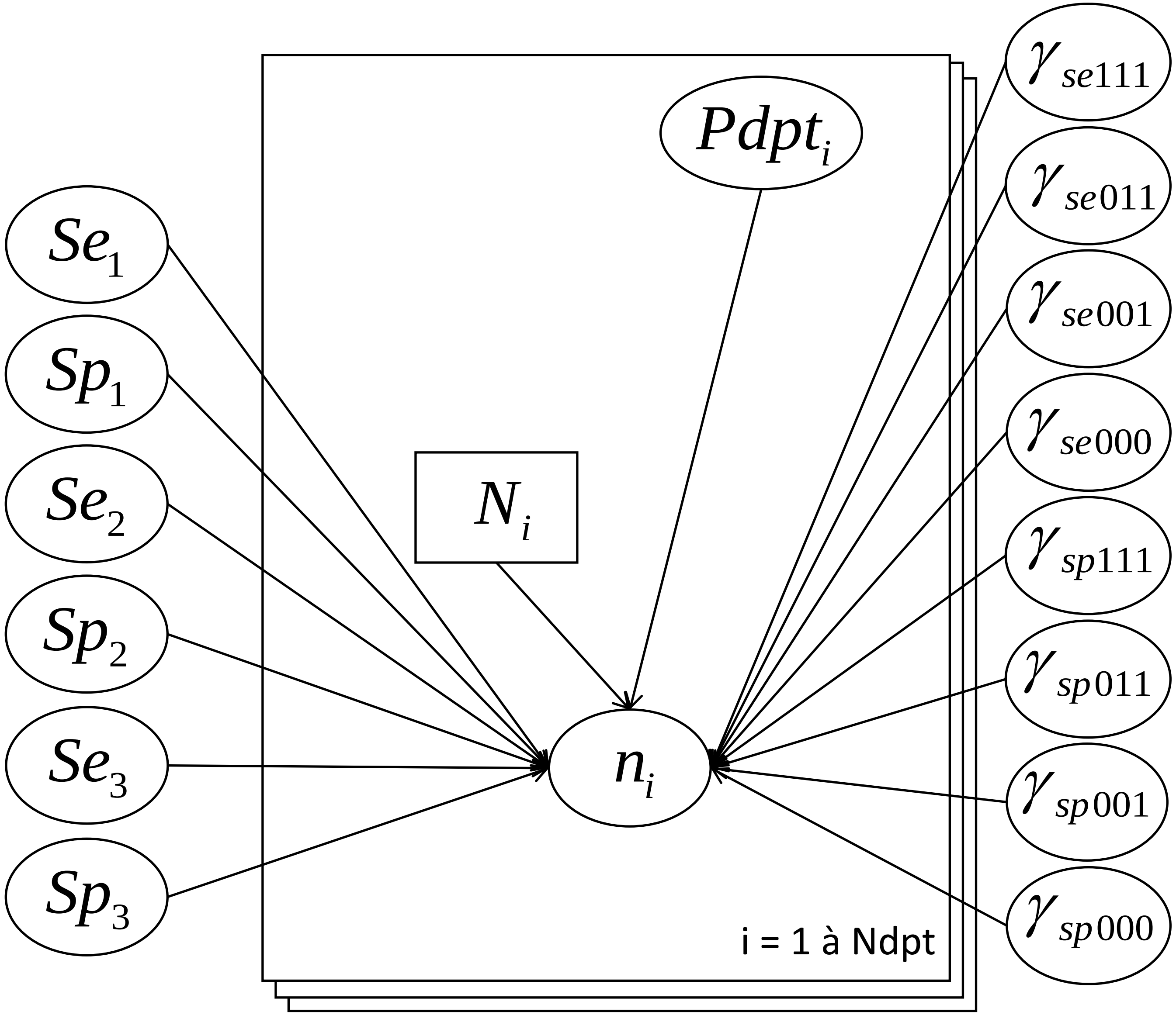
⇒10 populations of approximately 150 individuals each

- Use of **the least informative prior distributions**

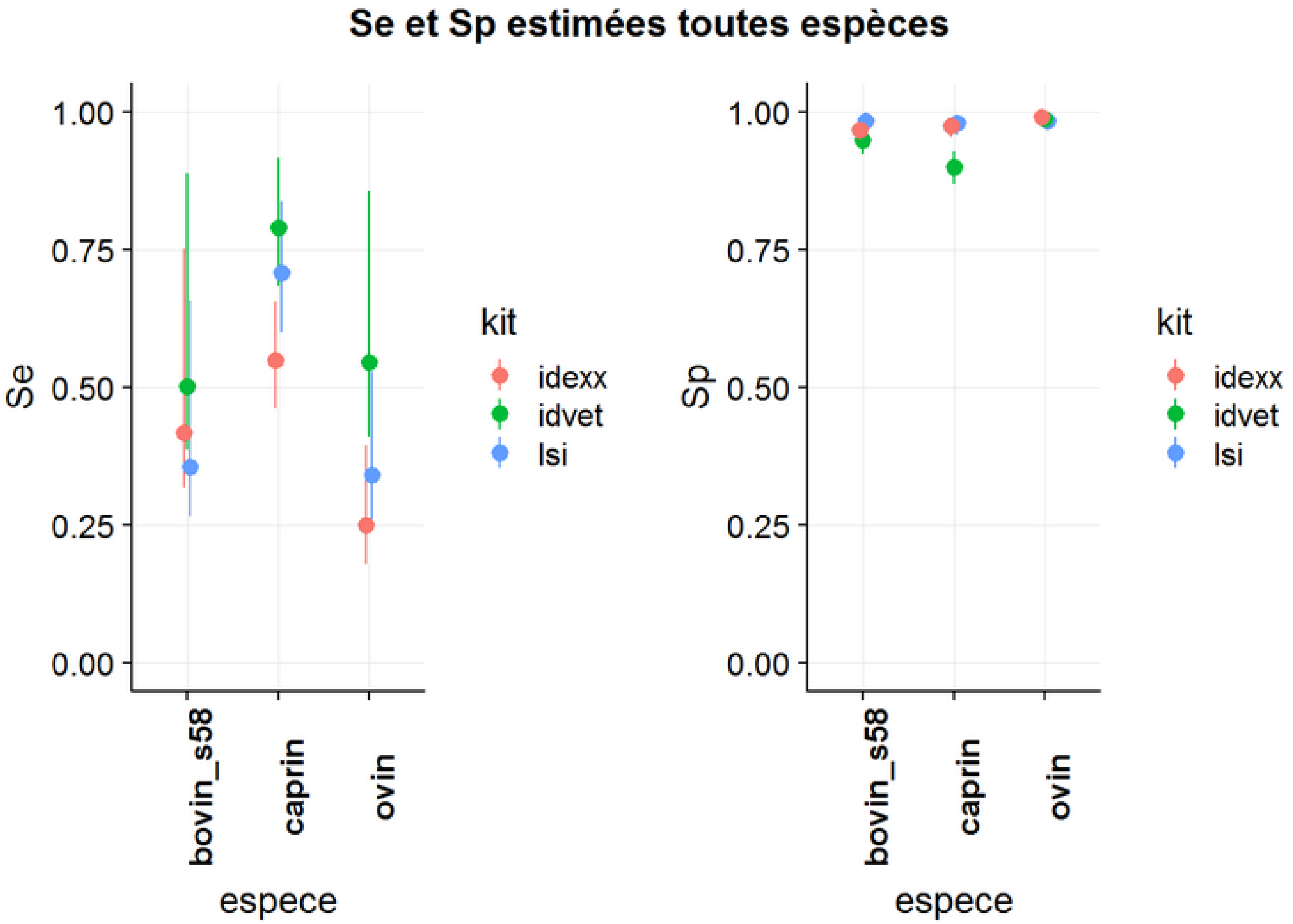
⇒**Beta(0.5, 0.5) for probability parameters**

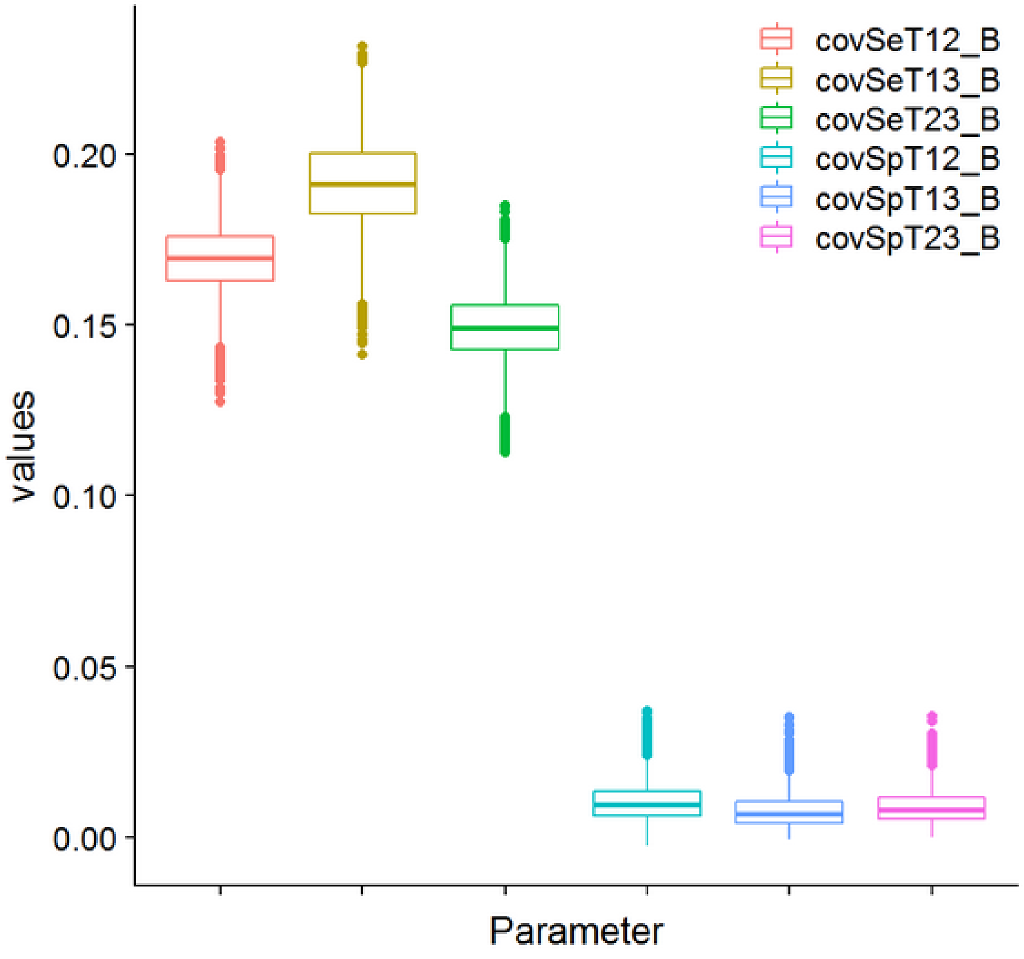
⇒**Uniform(-0.5;0.5) for conditional paramerters**

Directed acyclique graph



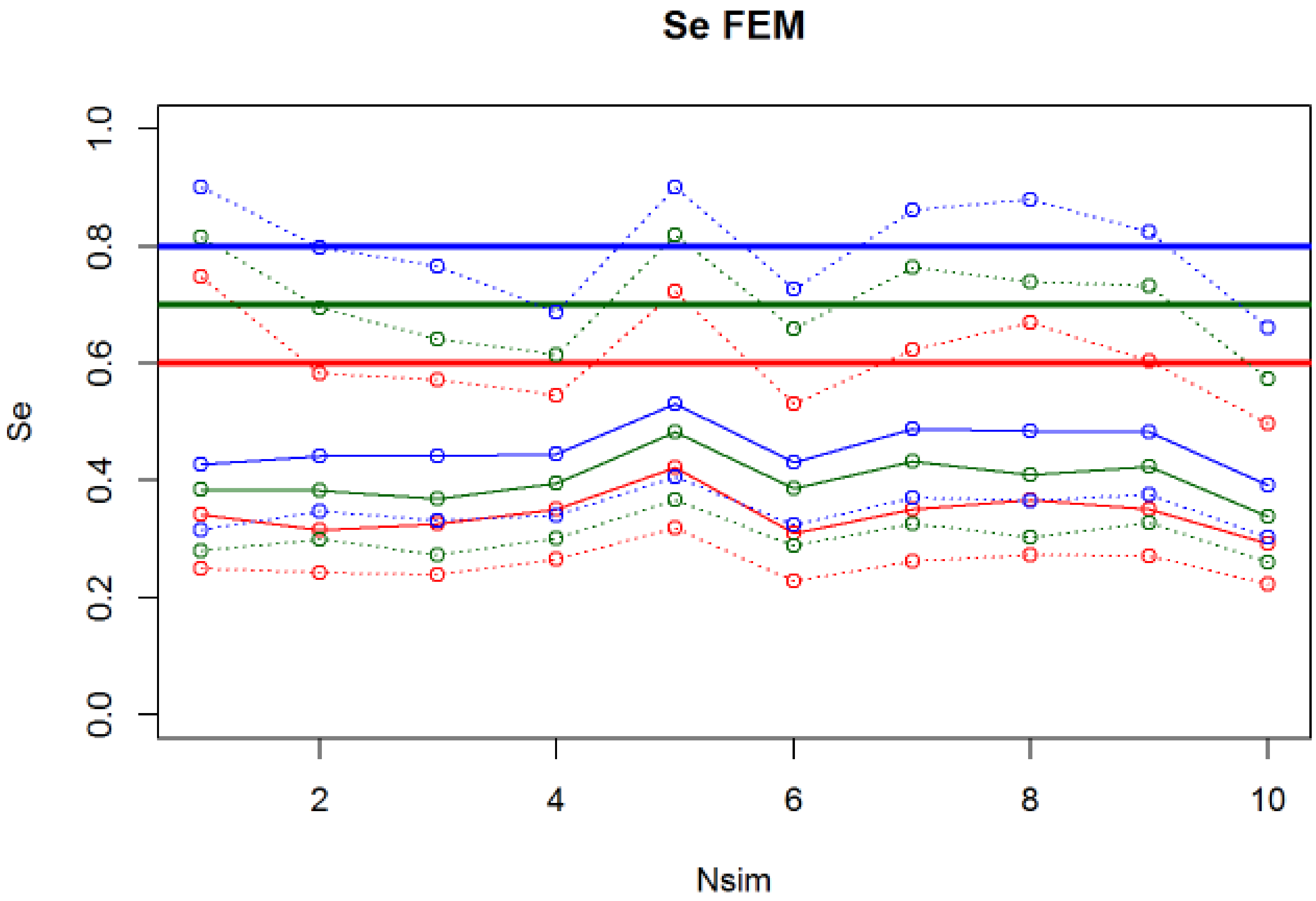
First inference with JAGS





Simulation

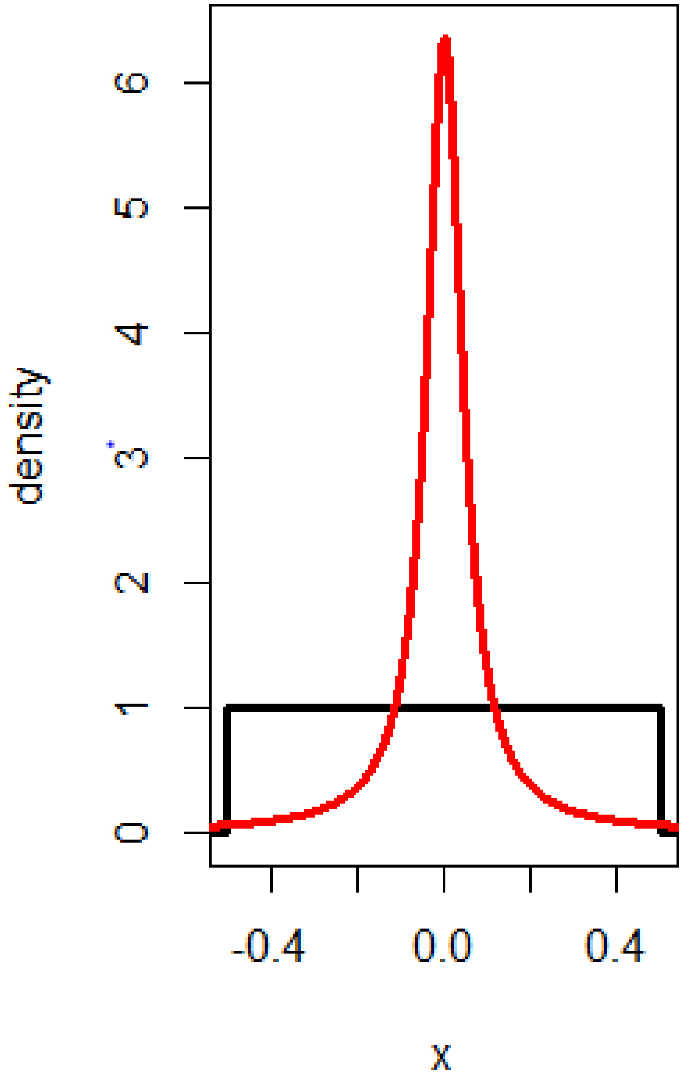
- 10 data set simulating from the estimate obtain with the previous model
- **Important negative biais** with an underestimation of the parameters…



What if we change prior distribution on conditional parameters?

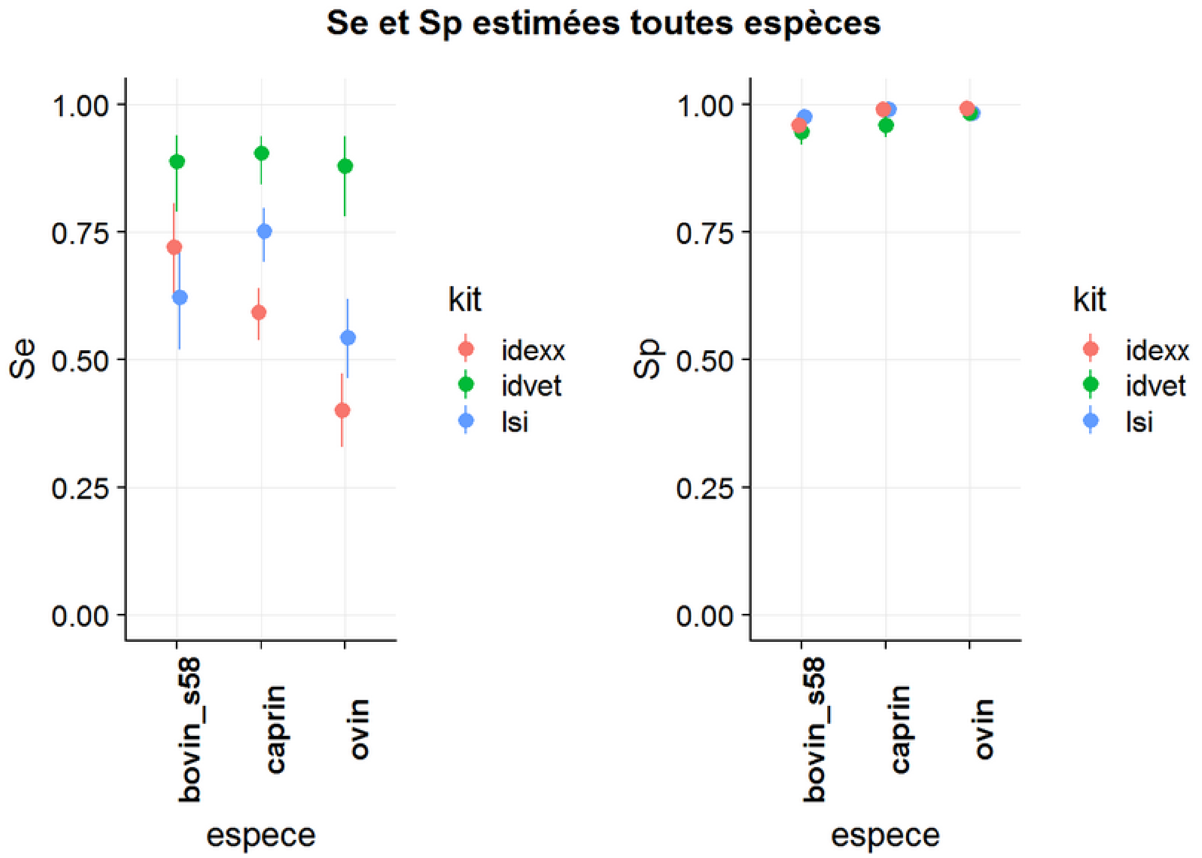
Uniform(-0.5, 0.5)

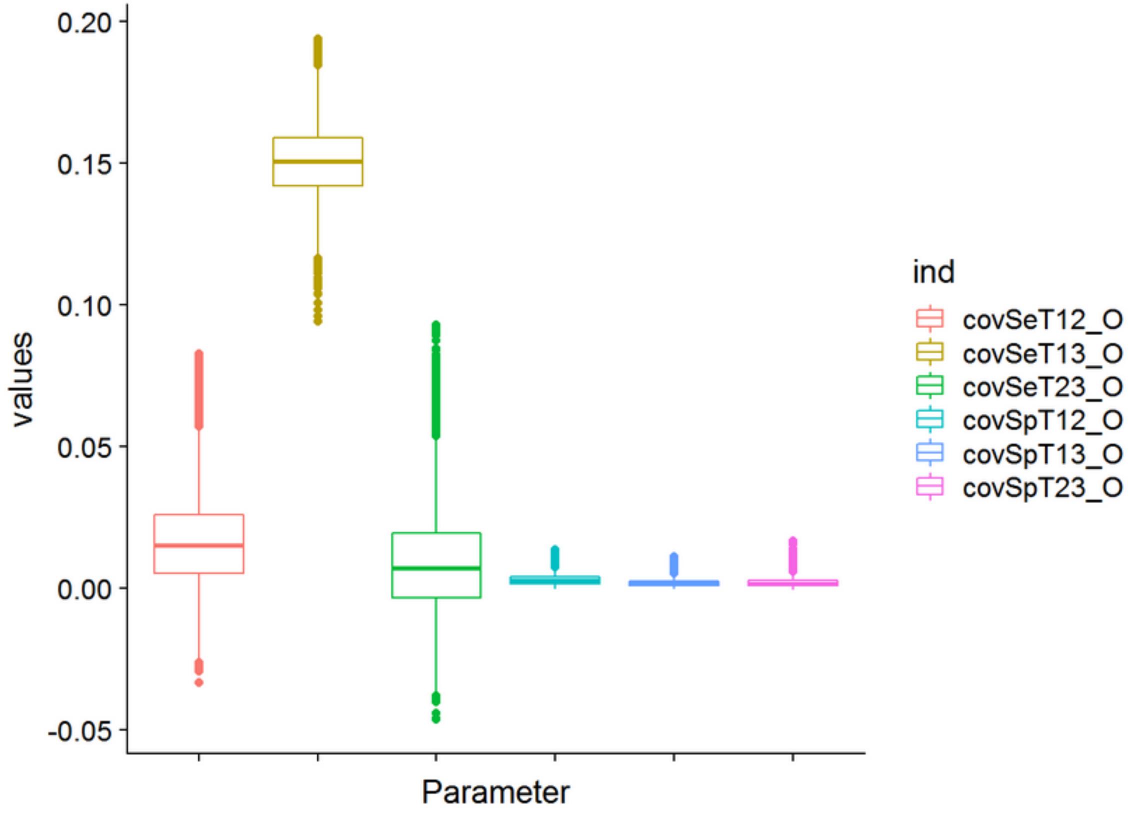
Cauchy (0,0.05)



Second inference with JAGS

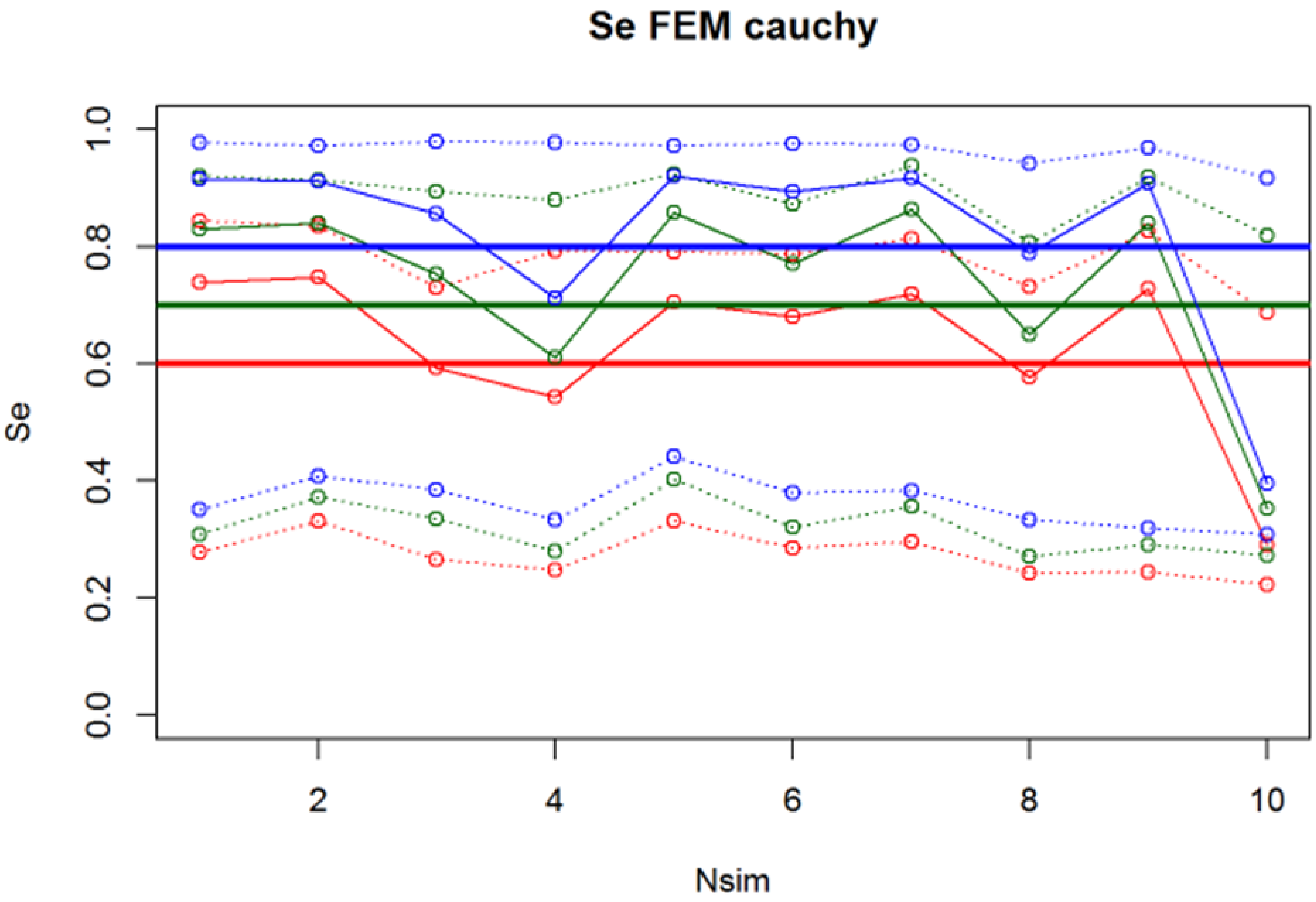
- Priors
  - Loi cauchy (0, 0.039) for conditional dependance parameters


Se et Sp estimées toutes espèces



Simulation

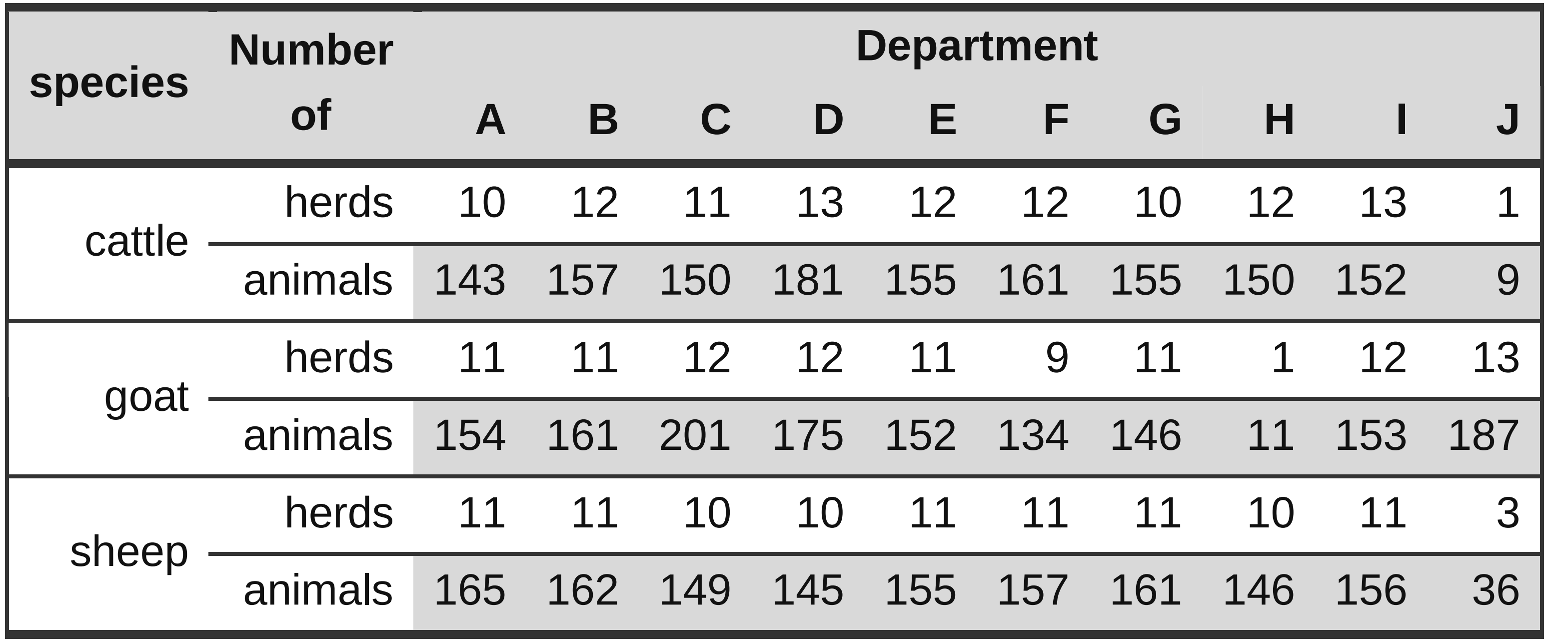
- Much better
- But still a relative bias with an overestimation of the Se and very wide credibility intervals



What if we change the model?

Is the departement level the right scale to create population?

There is 10 to 13 herds by departement, let’s use this information!



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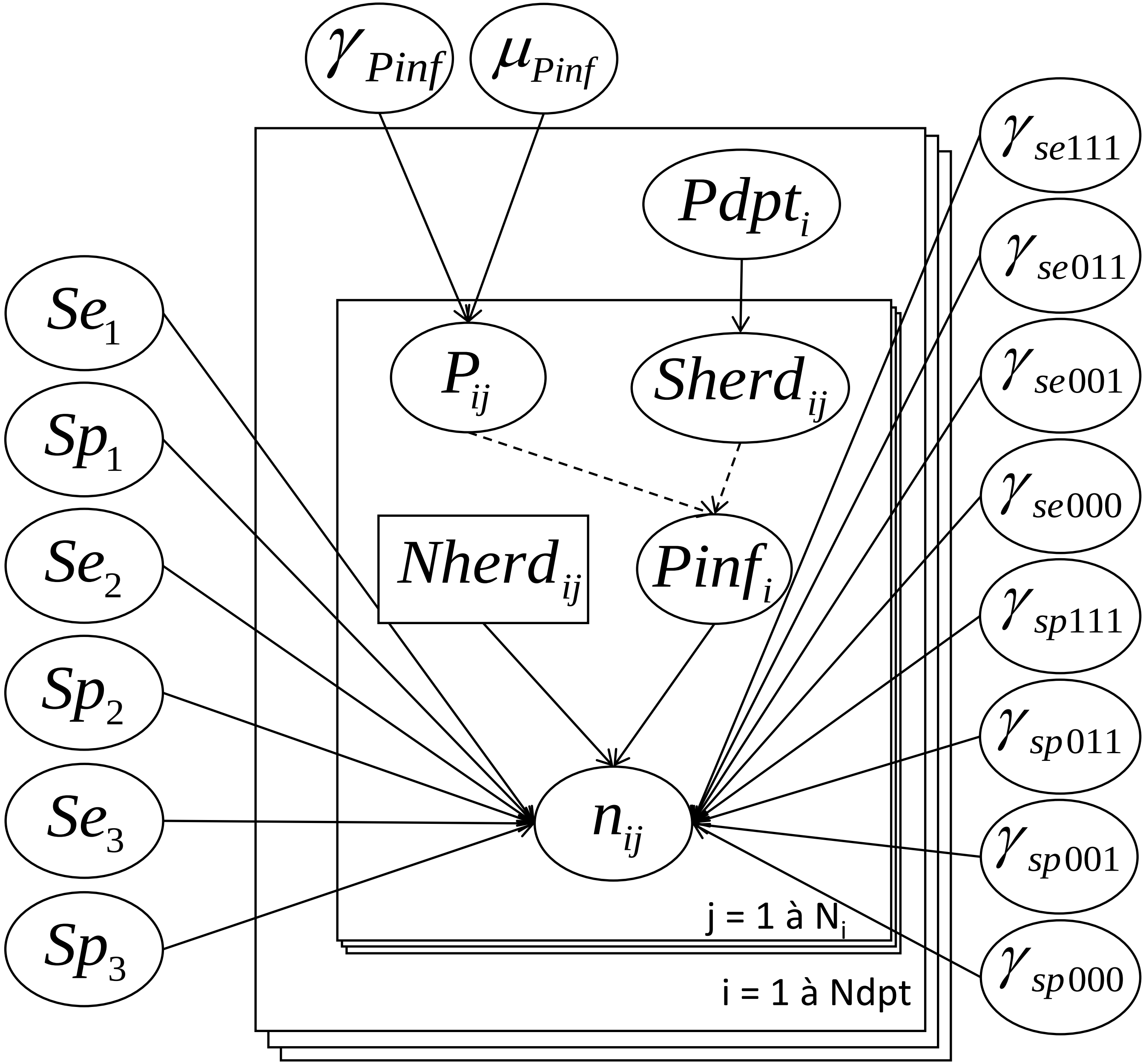
sheep	herds	11	11	10	10	11	11	11	10	11	3
	animals	165	162	149	145	155	157	161	146	156	36

Second model

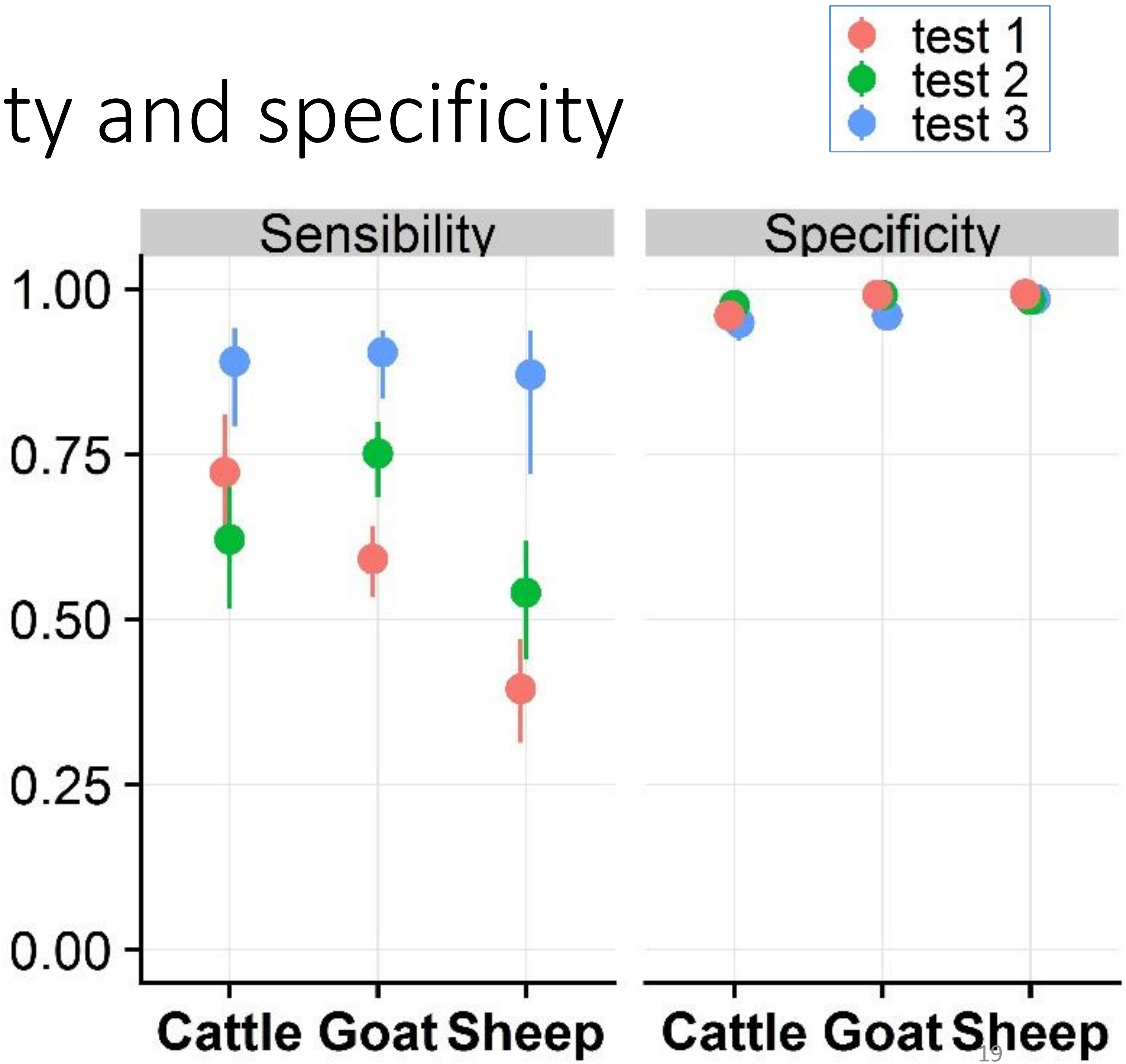
- **One model by ruminant species**
- Conditional dependence between the three tests modeled with a **fixed effect model** (*Wang et al. 2017)*
- **Each herd is considered as a population**
- Modeling of the **within-herd seroprevalence distribution** across all seropositive herds
  - (zero inflated hierarchical beta-binomial distribution)

  ⇒Some herd could be free of *C.burnetii*
- **Between-herd seroprevalence** assessed in each department
- Use of **the least informative prior distributions**


γ_{Pinf}
μ_{Pinf}
$Pdpt_i$
Se_1
Sp_1
Se_2
Sp_2
Se_3
Sp_3
P_{ij}
$Sherd_{ij}$
$Nherd_{ij}$
$Pinf_i$
n_{ij}
j = 1 à N_i
i = 1 à Ndpt
γ_{se111}
γ_{se011}
γ_{se001}
γ_{se000}
γ_{sp111}
γ_{sp011}
γ_{sp001}
γ_{sp000}

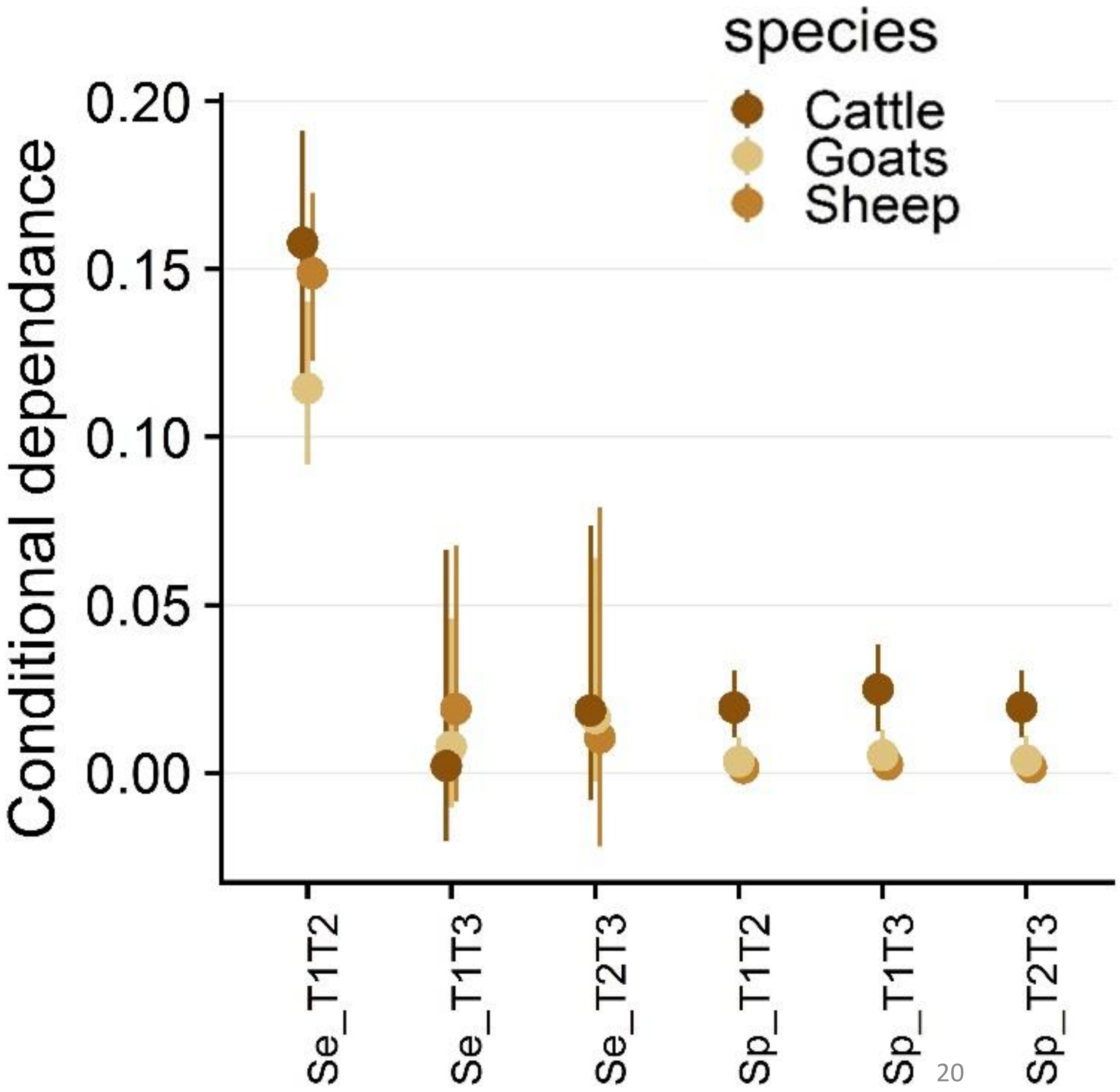
Results : test sensitivity and specificity

- **Sensitivity value are close to the Cauchy prior model** but still low for two test in sheeps!
- **All tests** seem **highly specific**
  - Slightly lower in cattle



Conditional dependence

- **High between T1 and T2** for **truly seropositive** animals
- lower between T3 and T1/T2
- **Negligible for truly seronegative animals** (except in cattle)

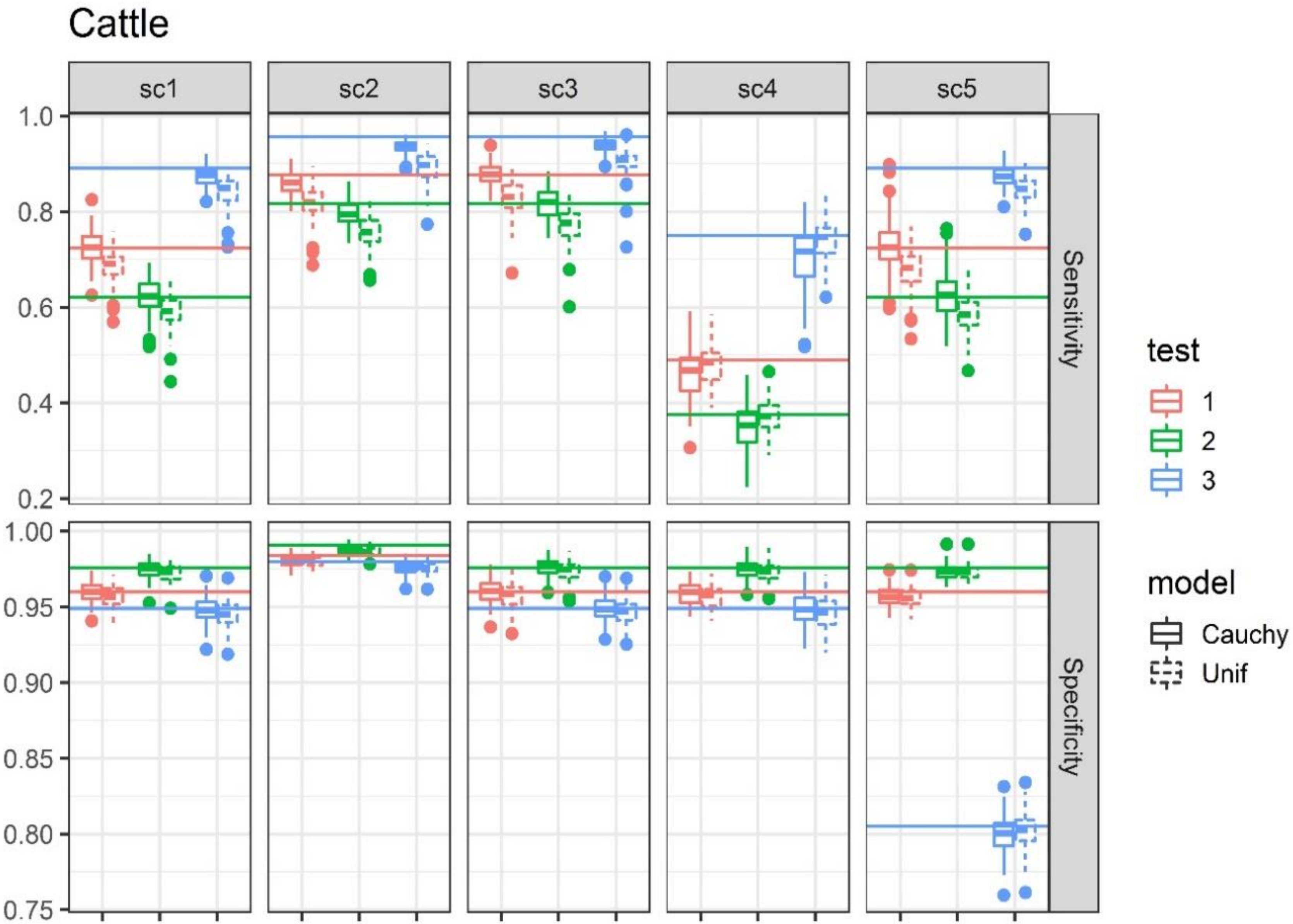


Simulation

- **5 scenario of simulation * two priors**
  - Sc1 = « original » scenario (same as estimated in the data)
  - Sc2 = **High Se and Sp**, no conditional dependency
  - Sc3 = **High Se, original Sp and low conditional dependency**
  - Sc4 = **Low Se, Original Sp** and similar conditional dependency
  - Sc5 = **Low Sp for test 3 only**
- Simulation of 100 dataset similar in size of the one of the study
- Analysis by two model with Cauchy(0,0,049) or uniforme(-0.5;0.5) on conditional dependence terms
- Calcul on the 100 dataset of **Mean relative bias**, **coverage probability** of the 95% CI and the **quadratic error mean**

Result of the simulation study

- Cauchy priori distribution less biased
- **High performances in goats and cattle**
  - Mean bias < -2%
  - Coverage probability > 80%
- Tendency to underestimate the Se and Sp in sheeps (-3 to -7%)
- With an acceptable coverage probability (de 79 à 92%)



Discussion

- **“non informative” prior distribution** do not exist?
- **“vaguely informative” prior distribution** can have an important impact on the results
- Simulation studies may help in identifying the issue
- In this case, complexification of the model structure help us to obtaine unbiased estimates of the parameters of interest

- There is an **important risk of biais** when we use latent class models that need to be assess in each dataset and application?

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  - GDS France
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  - VetAgro Sup
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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

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