Estimation of the variability of the specificity of gamma interferon tests used for bovine tuberculosis surveillance in France

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To cite this version:

T. Lurier, María-Laura Boschiroli, Kristel Gache, Carole Forfait-Dubuc, Sophie Carles, et al.. Estimation of the variability of the specificity of gamma interferon tests used for bovine tuberculosis surveillance in France. SBED Conference 2024: Insights in Action, SBED: Society for Bayesian Methods in Epidemiology and Diagnostics, Jan 2024, Bruxelles, Belgium. hal-04513113

HAL Id: hal-04513113
https://hal.inrae.fr/hal-04513113v1

Submitted on 20 Mar 2024

Estimation of the variability of the specificity of gamma interferon tests used for bovine tuberculosis surveillance in France

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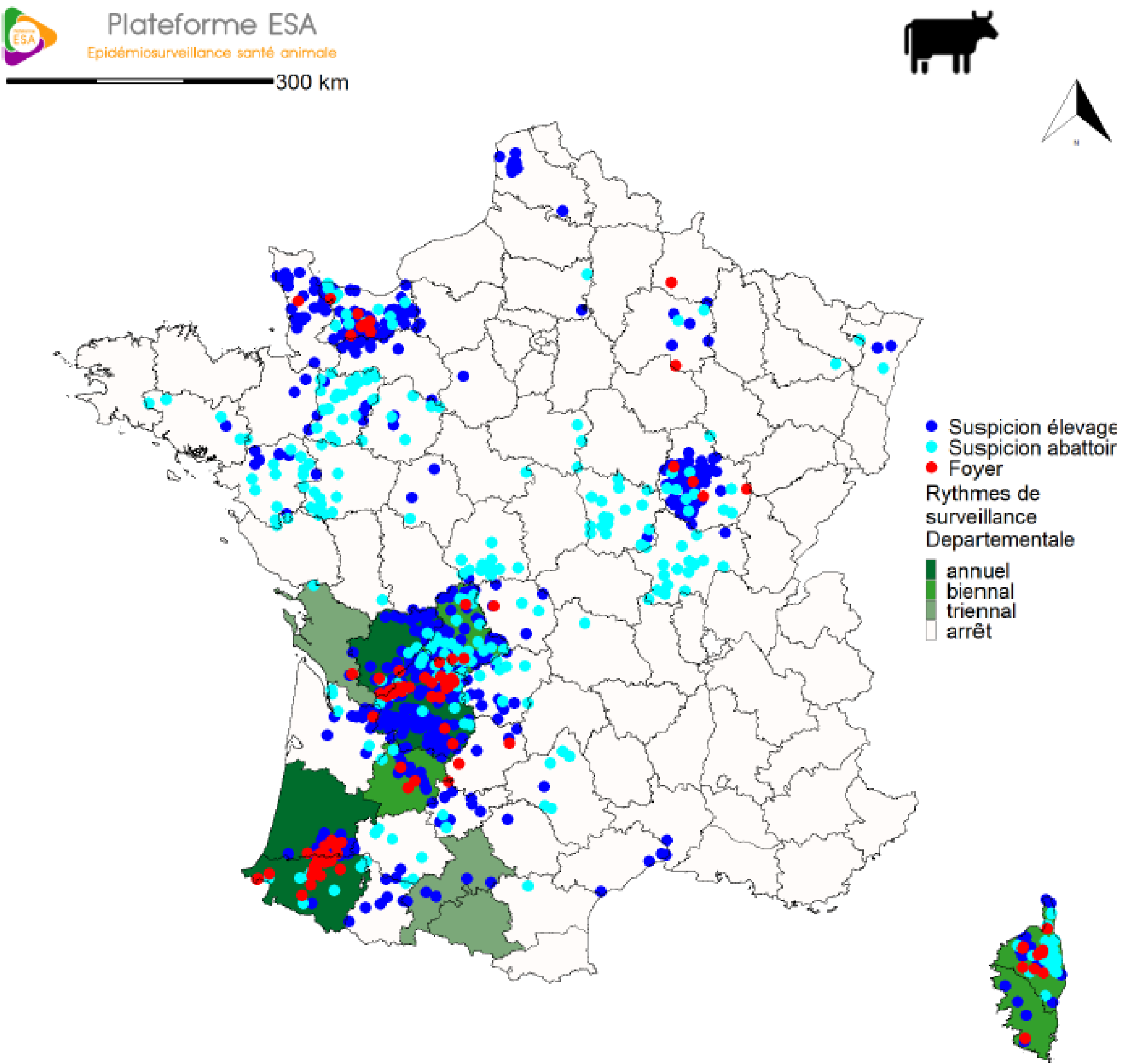
UMR EPIA Vetagro Sup-Inrae, LNR Tuberculose, GDS France, Unité EAS Anses, DGAL, LDAR24

HARMONY
Novel tools for test evaluation and disease prevalence estimation
cost
EUROPEAN COOPERATION IN SCIENCE & TECHNOLOGY
Funded by the European Union
anses
INRAE
L'action sanitaire ensemble
GDS France
Plateforme ESA
VetAgro Sup
RÉPUBLIQUE FRANÇAISE
Liberté
Égalité
Fraternité

Context : Bovine tuberculosis in France

- France is officially free from bovine tuberculosis at the country level (<0.1% of infected herds)
- But
  - **99 outbreaks Identify** in 2021
  - Persistence of the infection in some geographic area
  - Incidence rate that does not decrease anymore.

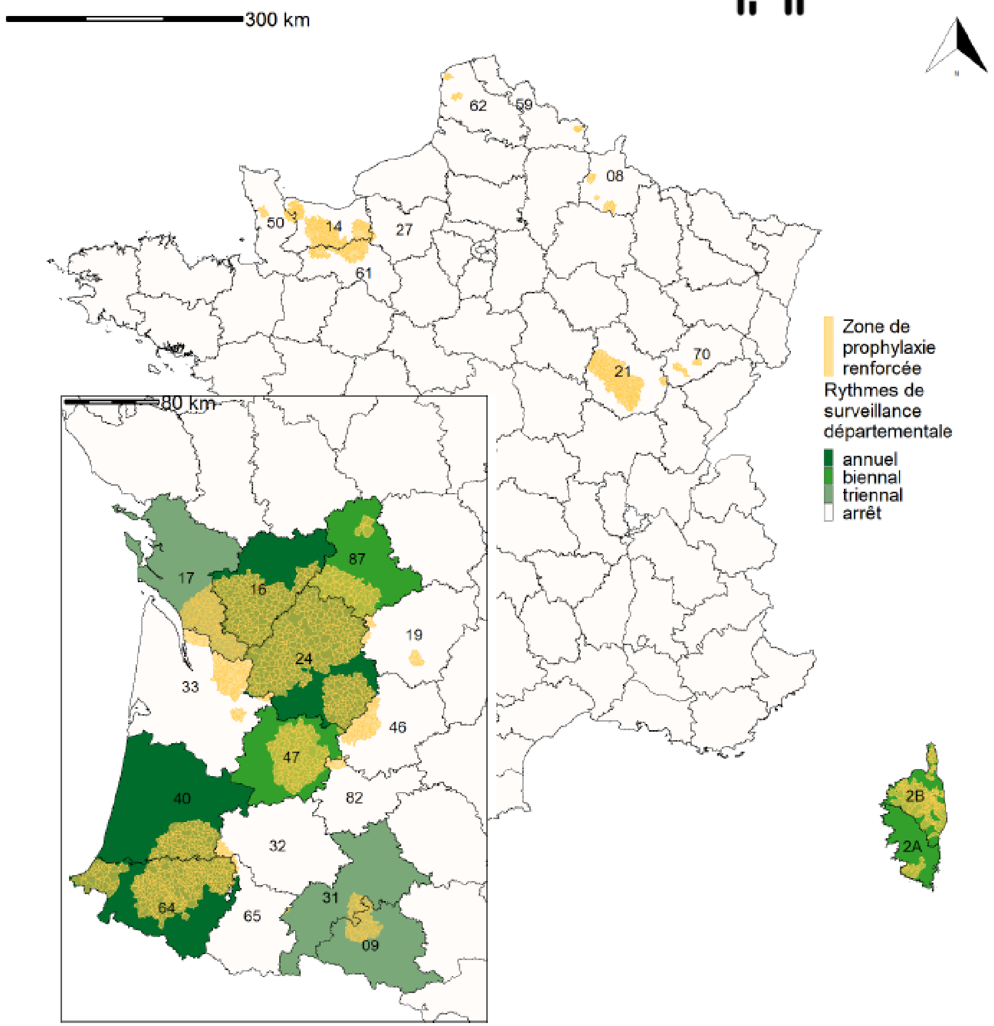


Forfait et al. 2023

Context : Bovine tuberculosis surveillance

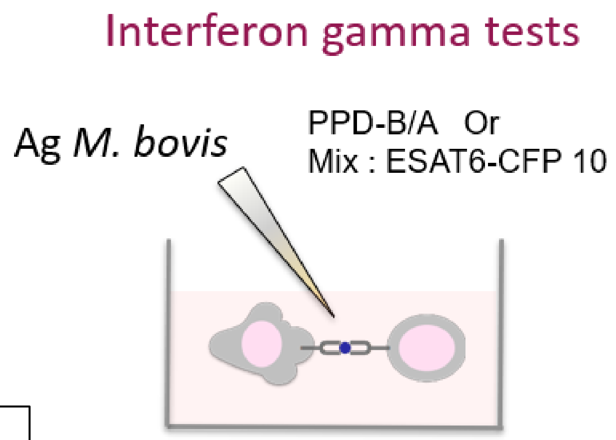
- Passive surveillance program
  - Post-mortem examination at slaughterhouse
- Active surveillance program in infected area
  - Scheduled (every 1-2 or 3 year) SICCT on all cattle (>1 year old)
- In strengthened surveillance area **since 2021**
  - CICCT and interferon gamma tests in parallel

Plateforme ESA
Epidémiosurveillance santé animale

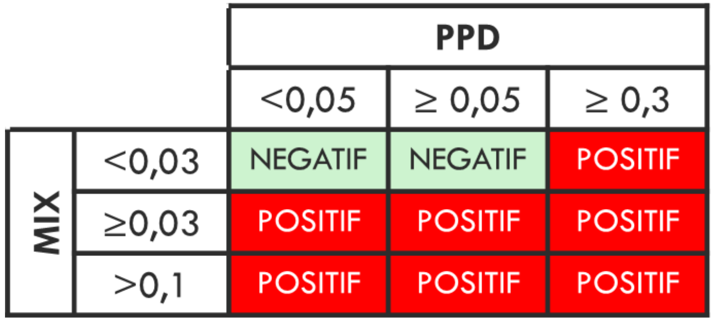


Forfait et al. 2023

Context : Interferon gamma tests in France



- Two different interferon gamma test
  - Stimulation of the blood with either purified (PPD) or recombinant antigen (MIX)
- Results are interpreted jointly



		PPD		
		<0,05	≥ 0,05	≥ 0,3
MIX	<0,03	NEGATIF	NEGATIF	POSITIF
	≥0,03	POSITIF	POSITIF	POSITIF
	>0,1	POSITIF	POSITIF	POSITIF

Performances of the joined test
Se = 58% [44 ; 74]
Sp = 98% [97,8 ; 98,1]

If the joined test is positive
⇒ Cattle are sent to the slaughterhouse to confirm or refute the suspicion
⇒ Performance of the confirmatory test (PCR, histology and culture) :

Se = 90,4% Sp = 100% *(Courcoul et al 2014)*

Problematic

During the mandatory surveillance program in 2021-2022

Many herds tested positive at interferon gamma test with potentially many individuals in tested positives in these herds (until 50% of the animals in some herds)

Few of them were confirmed positive with the confirmation diagnostic

⇒Suspicion of a lack of specificity of the interferon gamma tests

Data from one veterinary laboratory between 2021 et 2022

- All IFNg realised identified by individuals and herd
- + results from the confirmatory test at slaughterhouse

139 herds sampled from **November 2021** with **more than 10 animals** sampled

=> **11665 cattle** tested by IFN including

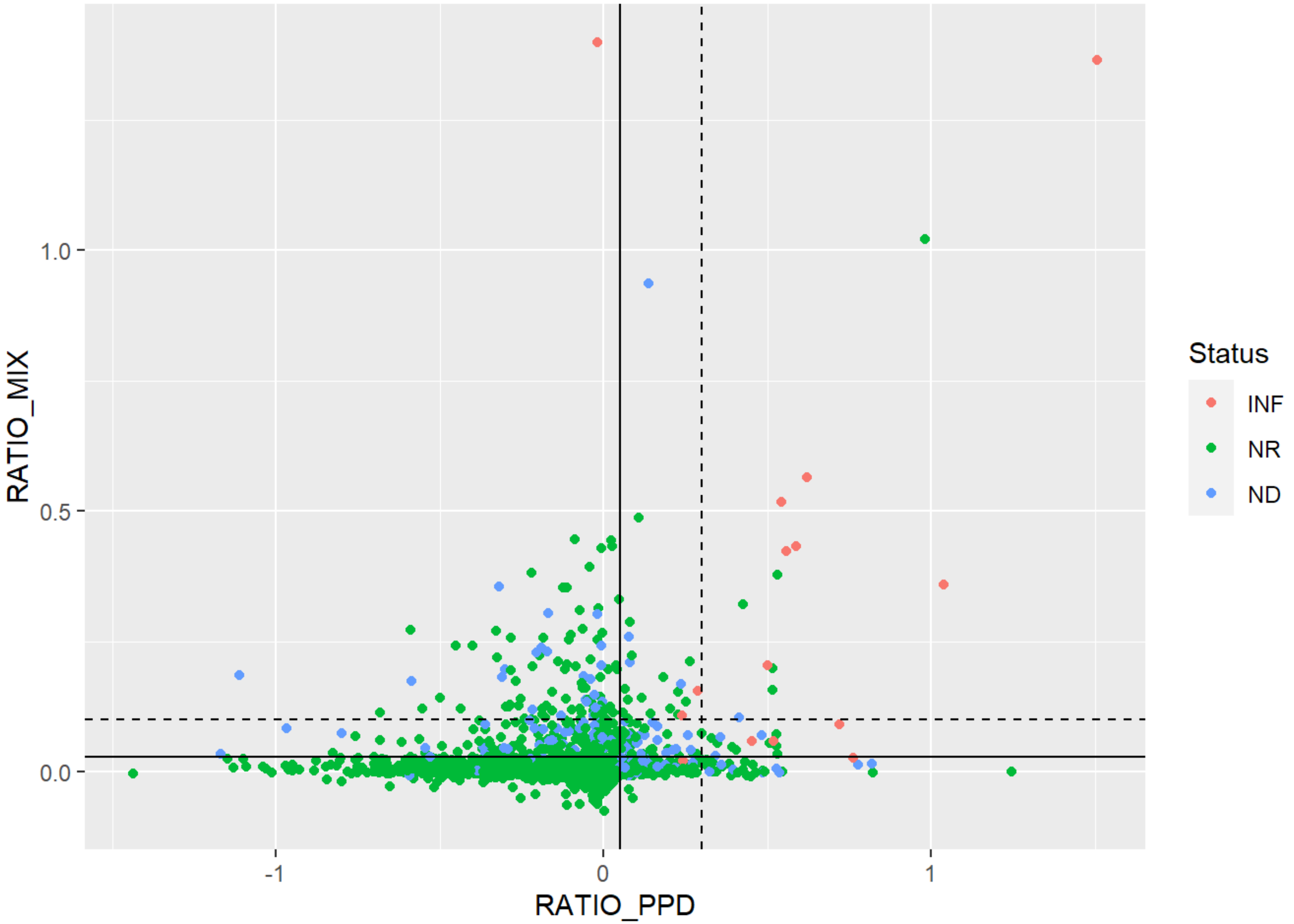
17 confirmed at slaughterhouse

169 not detected

11 479 not slaughtered

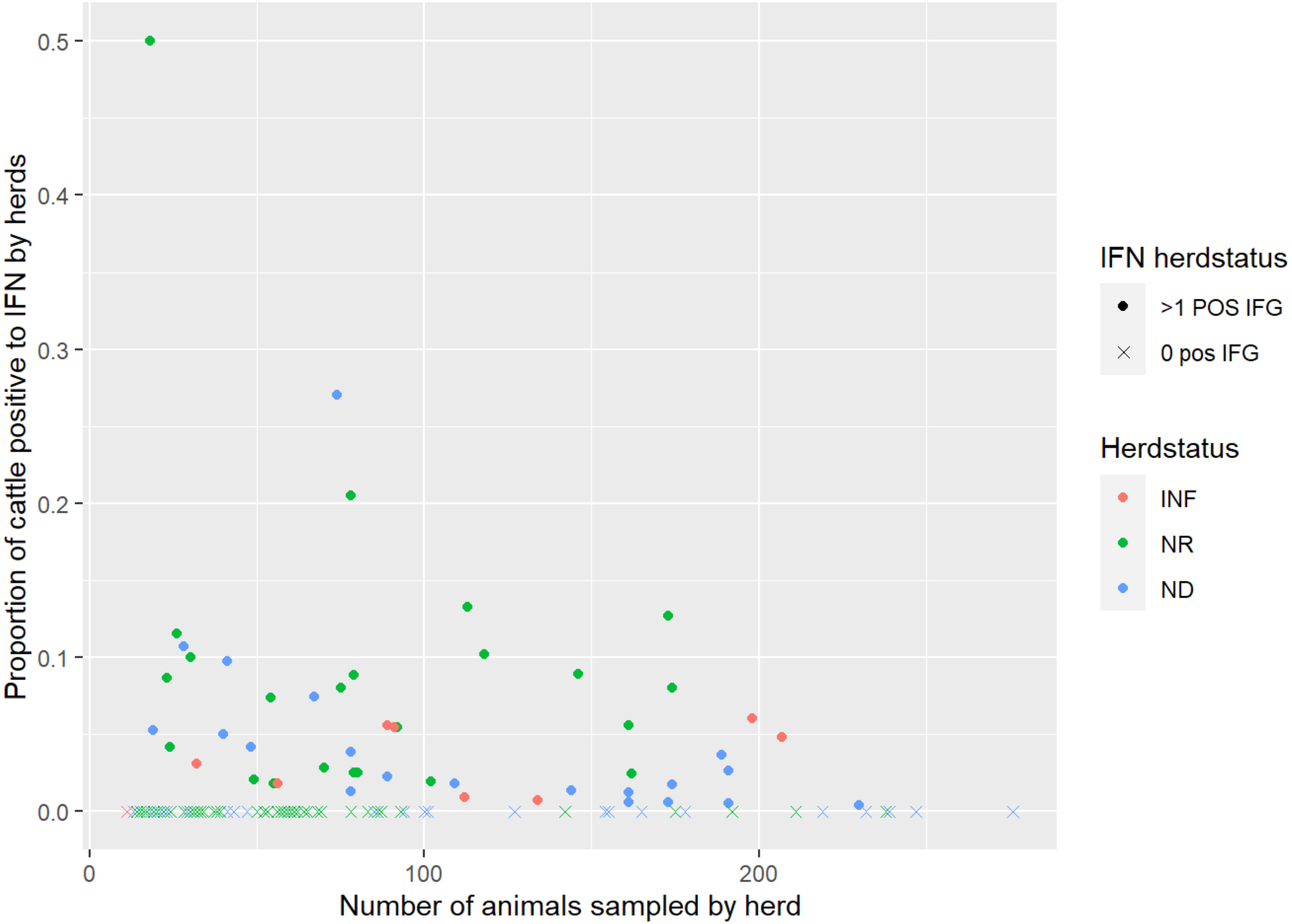
Visualisation of the data at the individual level

- 17 confirmed infected
  - 13 MIX positive (>0,03)
  - 15 PPD positive (>0,05)
  - 14 positive with the joined test
- 169 Not detected with confirmation test
  - 92 MIX positive (>0,03)
  - 59 PPD positive (>0,05)
  - 65 positive with the joined test
- 11 479 not sent to the slaughterhouse
  - 254 MIX positive (>0,03)
  - 282 PPD positive (>0,05)
  - 182 positive with the joined test



Data visualisation at the herd level

- 87/139 herds without any positive
  - ⇒ 6 371 negative cattle..!
- 52/139 herds with at least one positive
  - ⇒Including 8/52 confirmed infected
  - ⇒With proportion of positive ranging from 1 to 50%



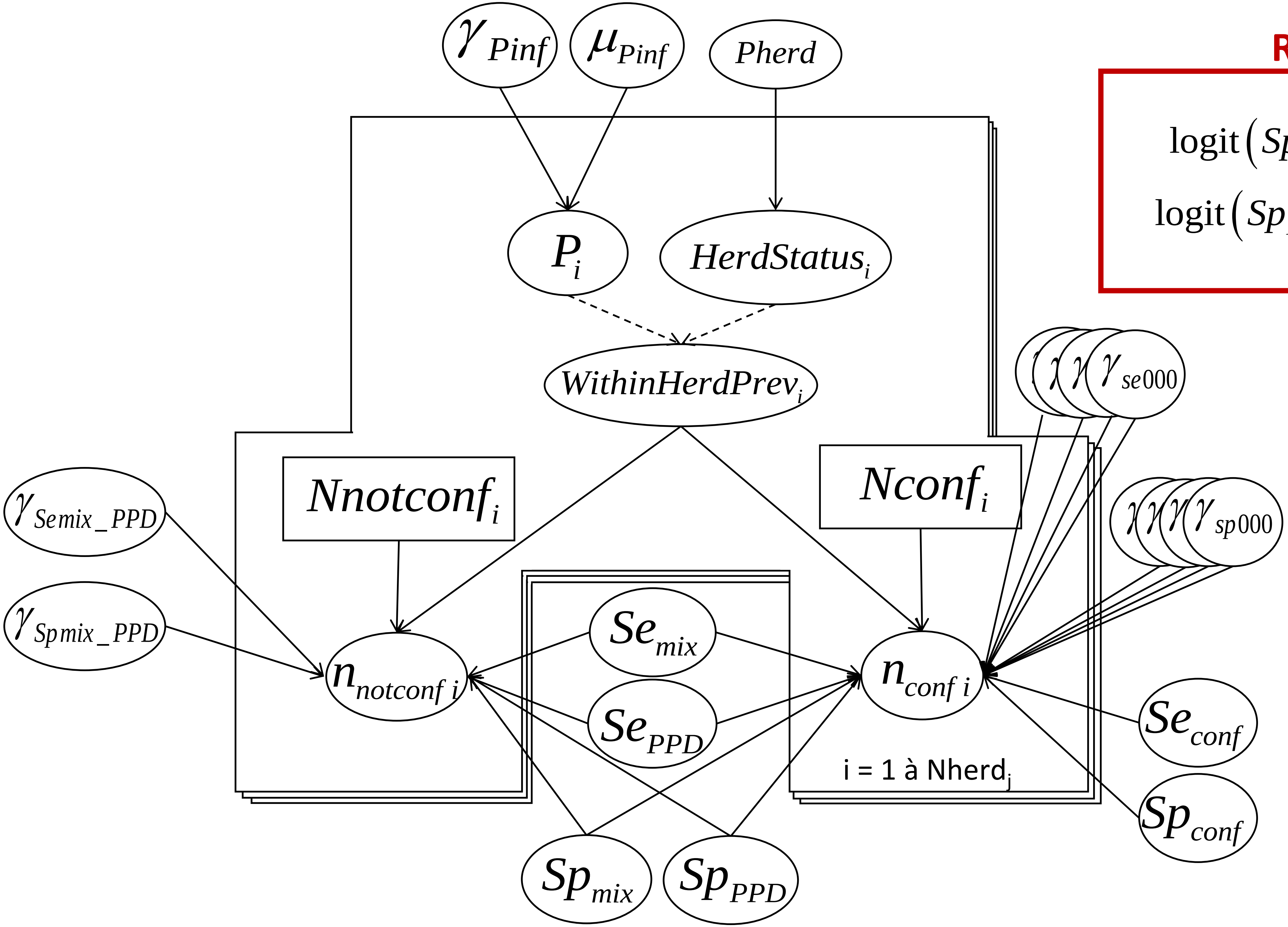
Latent class model

- Modelling of the cross-classified results of the two IFN tests and the confirmatory test when performed
- Informative prior used for the Se and Sp of the three tests
- Modelling of the **proportion of infected herds** (Pherd) and the distribution of the **within herd prevalence** (MuP, gamma)
- 2 versions of the model tested
    - **Sp of IFN tests constant** in all herds
    - **Sp of IFN variable** in each herd (random effect following a logit normal distribution)

Random model

$$\operatorname{logit}\left(Sp_{mix,i}\right) \sim N\left(\mu_{Sp_{mix}}, \sigma_{Sp_{mix}}\right)$$

$$\operatorname{logit}\left(Sp_{PPD,i}\right) \sim N\left(\mu_{Sp_{PPD}}, \sigma_{Sp_{PPD}}\right)$$



Model estimates

- **Model with Sp constant**
  - Pherd = 18% [10 ; 31]
  - MuP = 10% [3 ; 19]

  - MIX :
    - Se = 0.55 [0.46 ; 0.64]
    - Sp = 0.96 [0.96 ; 0.97]
  - PPD :
    - Se = 0.46 [0.37 ; 0.55]
    - Sp = 0.96 [0.96 ; 0.97]

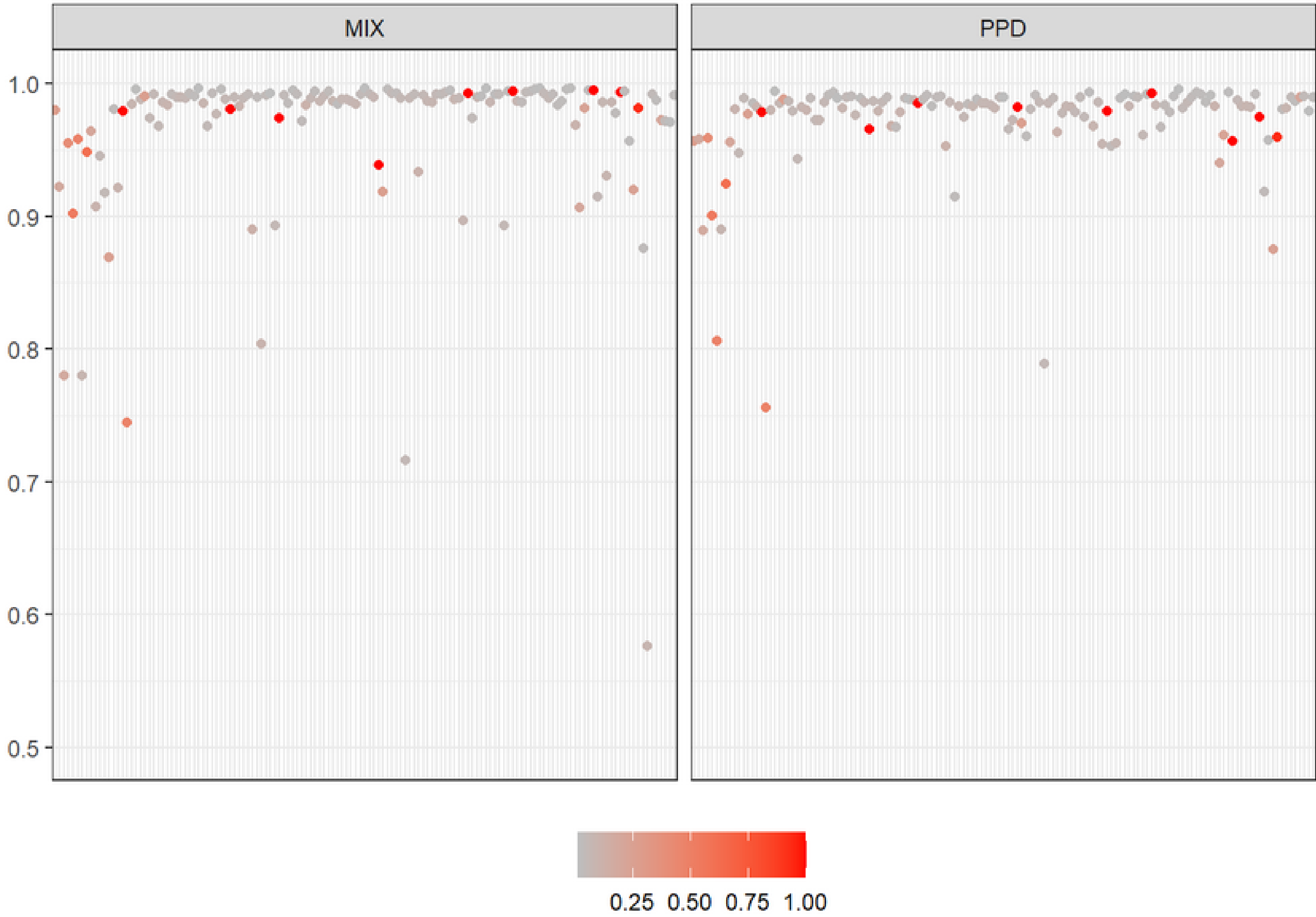
- **Model with Sp variable**
  - Pherd = 12% [6 ; 21]
  - MuP = 3% [1 ; 6]

  - MIX :
    - Se = 0.63 [0.52 ; 0.73]
    - Sp mean = 0.96 [0.96 ; 0.96]
  - PPD :
    - Se = 0.76 [0.63 ; 0.86]
    - Sp mean = 0.96 [0.96 ; 0.97]

Variability of the Sp in the 2nd model

- Sp>97% in most herds
- Sp could be low in some herds
- It seems similar between MIX and PPD

Posterior median of the Sp estimated in each herd, each dot is coloured according to its probability to be infected (herdstatus)



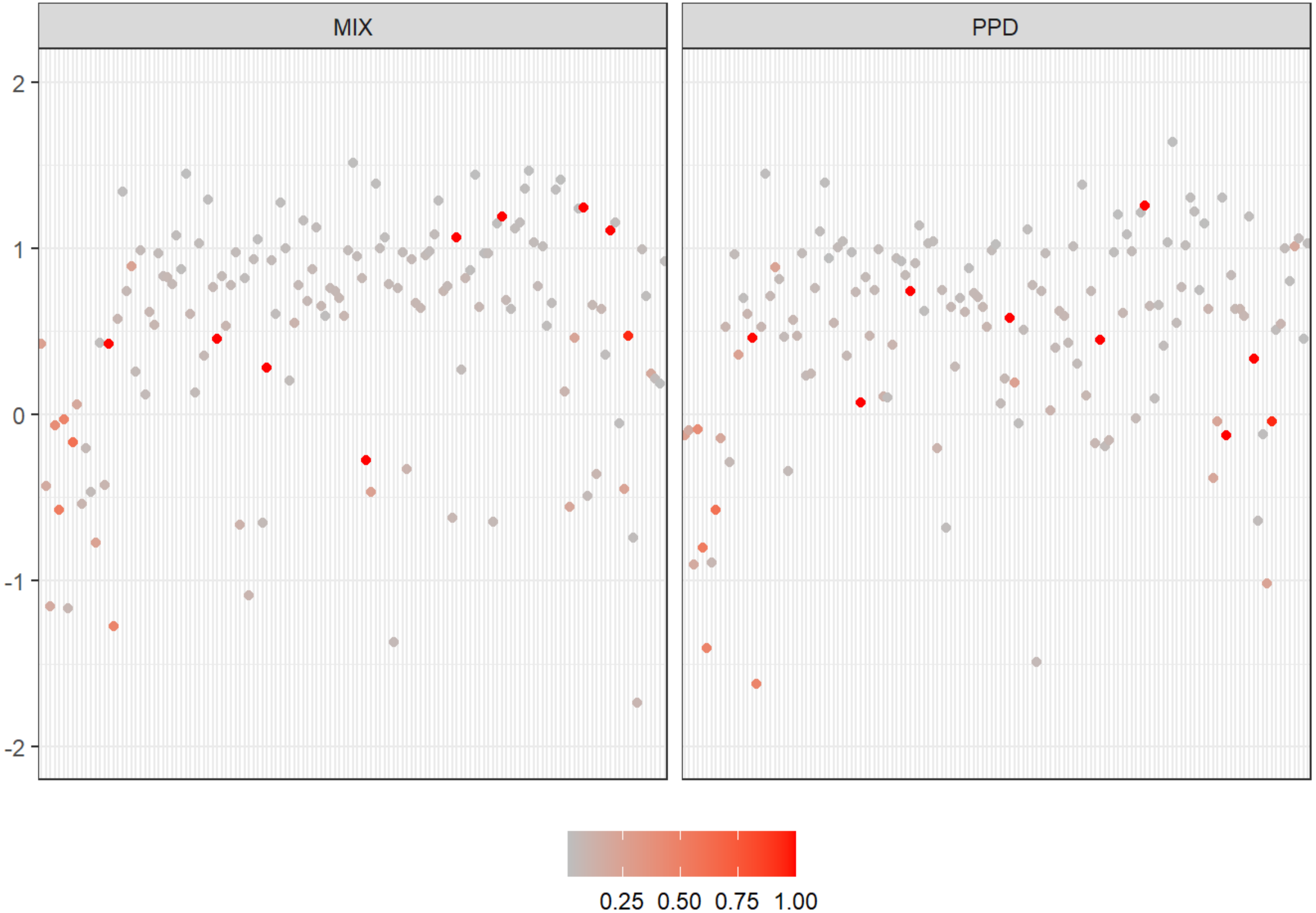
Model « validation » /selection

Normality of the random effects

Random effects are not well centred onto 0

Distribution not really « normal »

Posterior median of standardised random effects on specificity estimated for each farm



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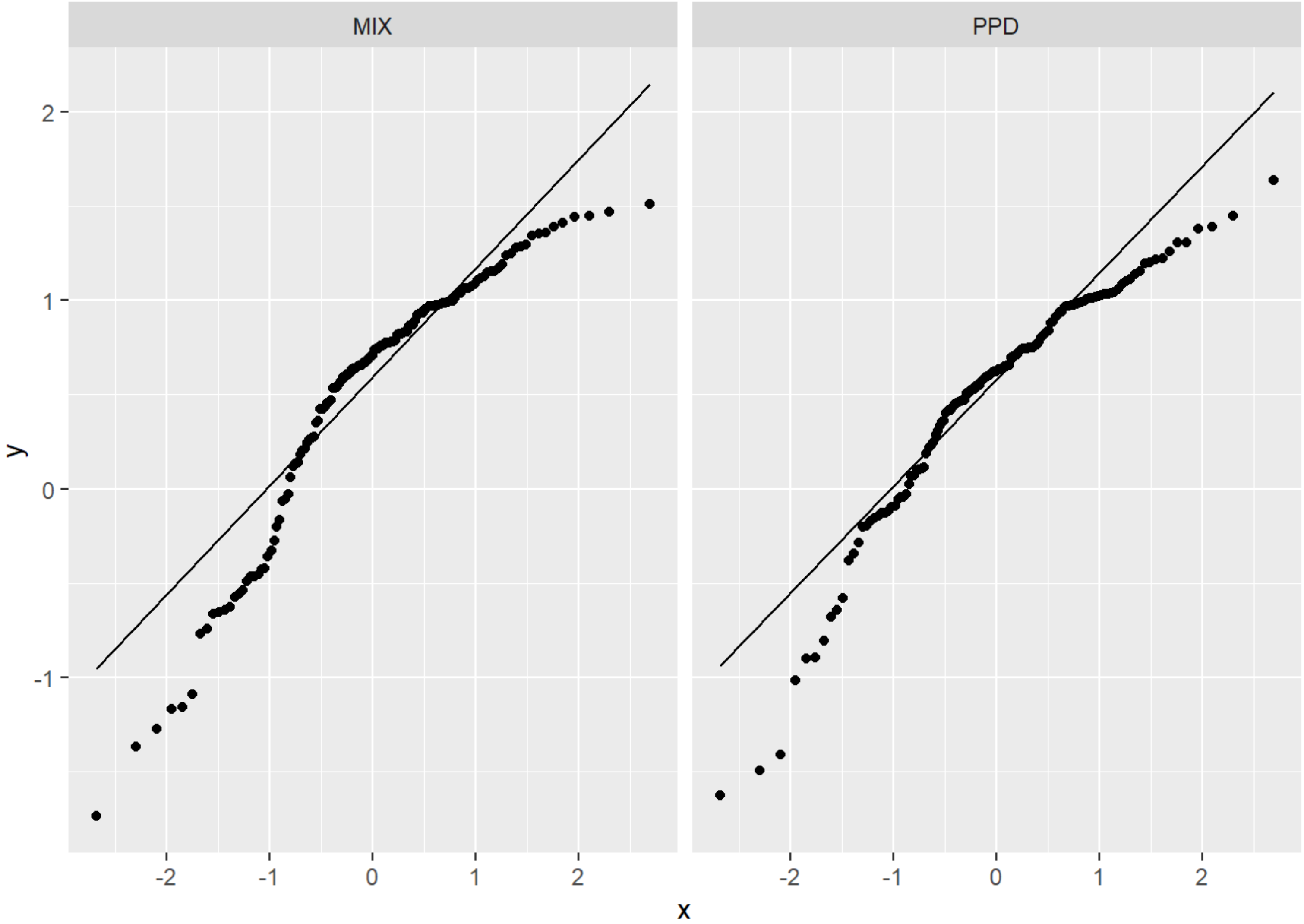
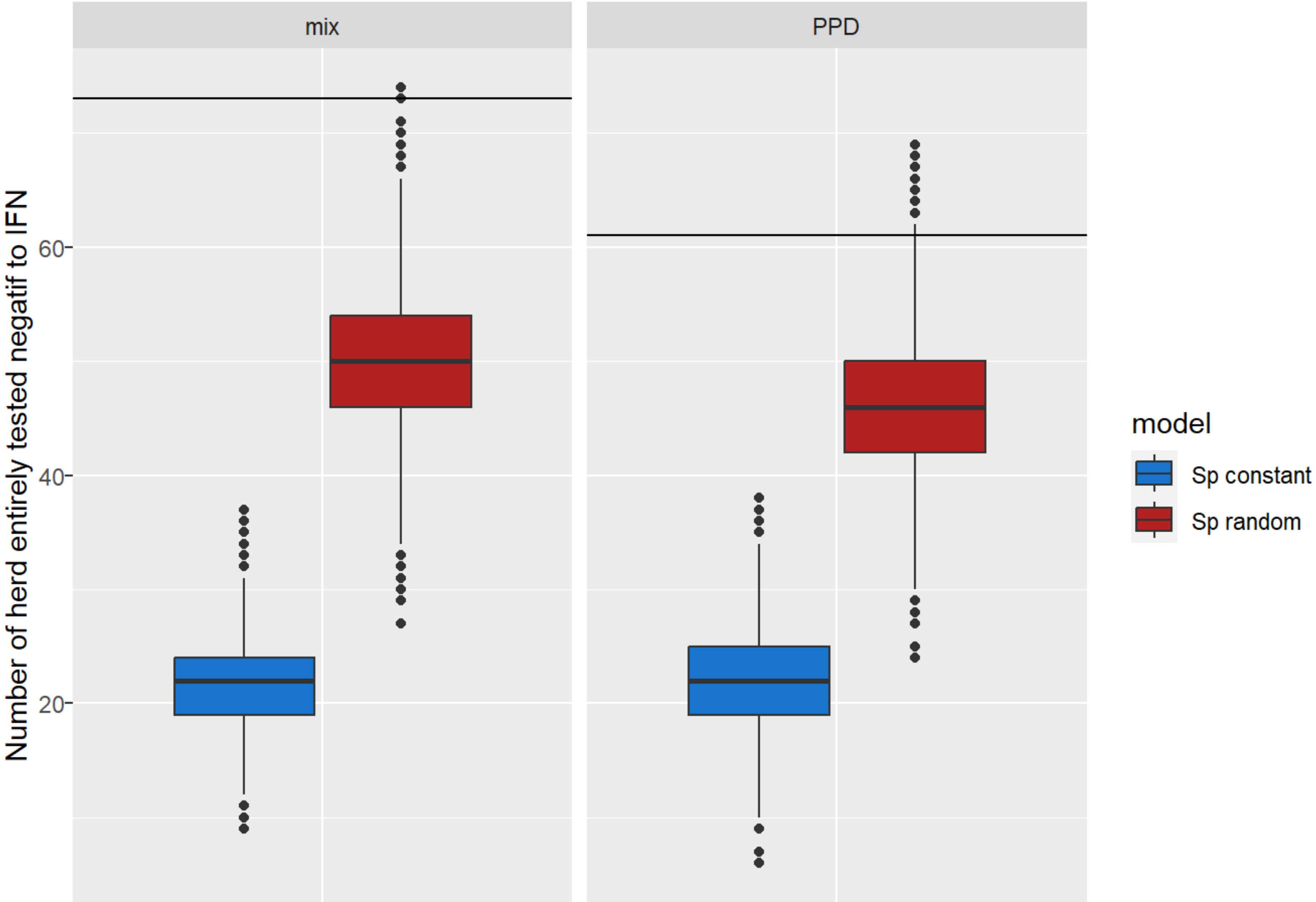


Posterior predictive check : number of negative herds

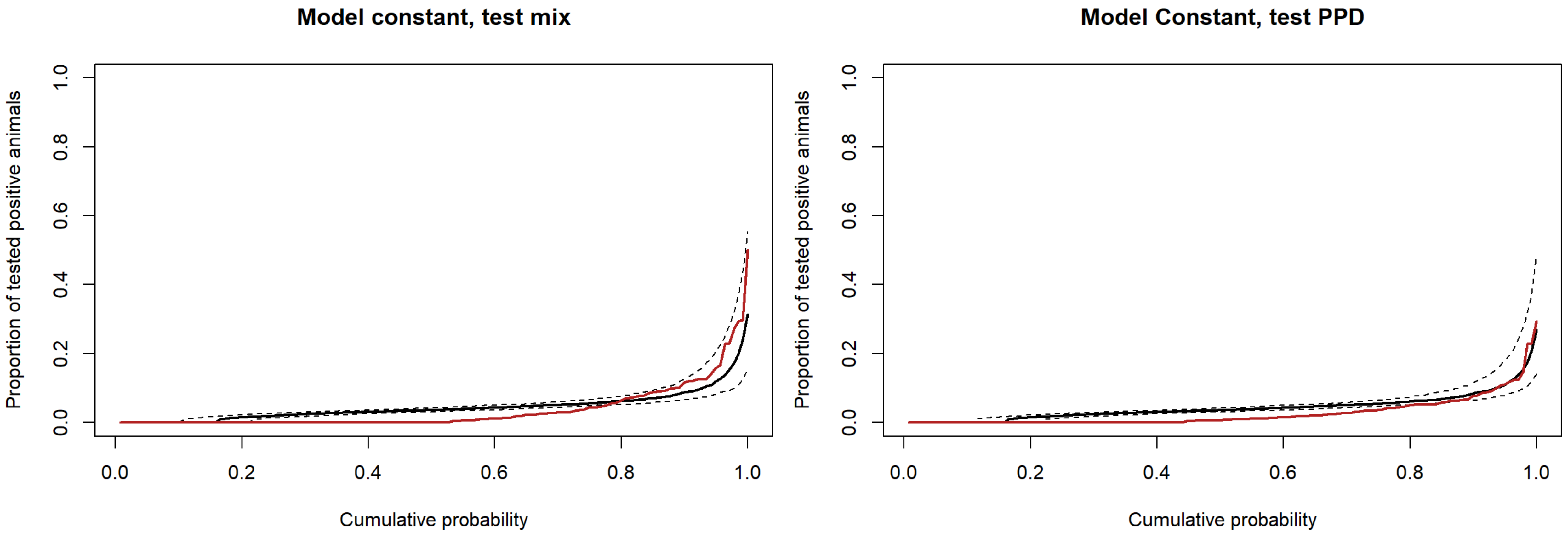
Number herd entirely negative simulated for each MCMC sample (boxplot) and compared with the observed one (plain line)

⇒Models with **Sp random is closest to the observed value**

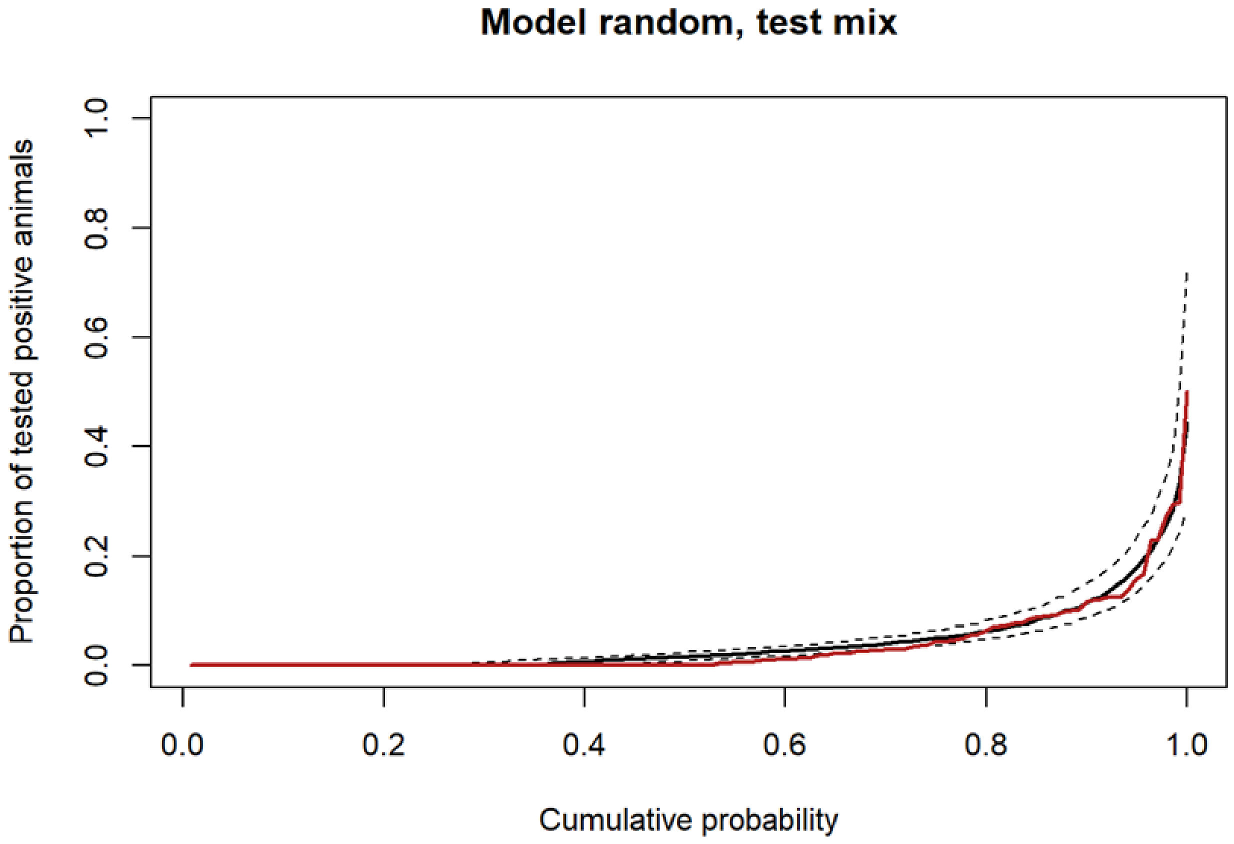
Posterior distribution of the number of entirely negative herds to IFN

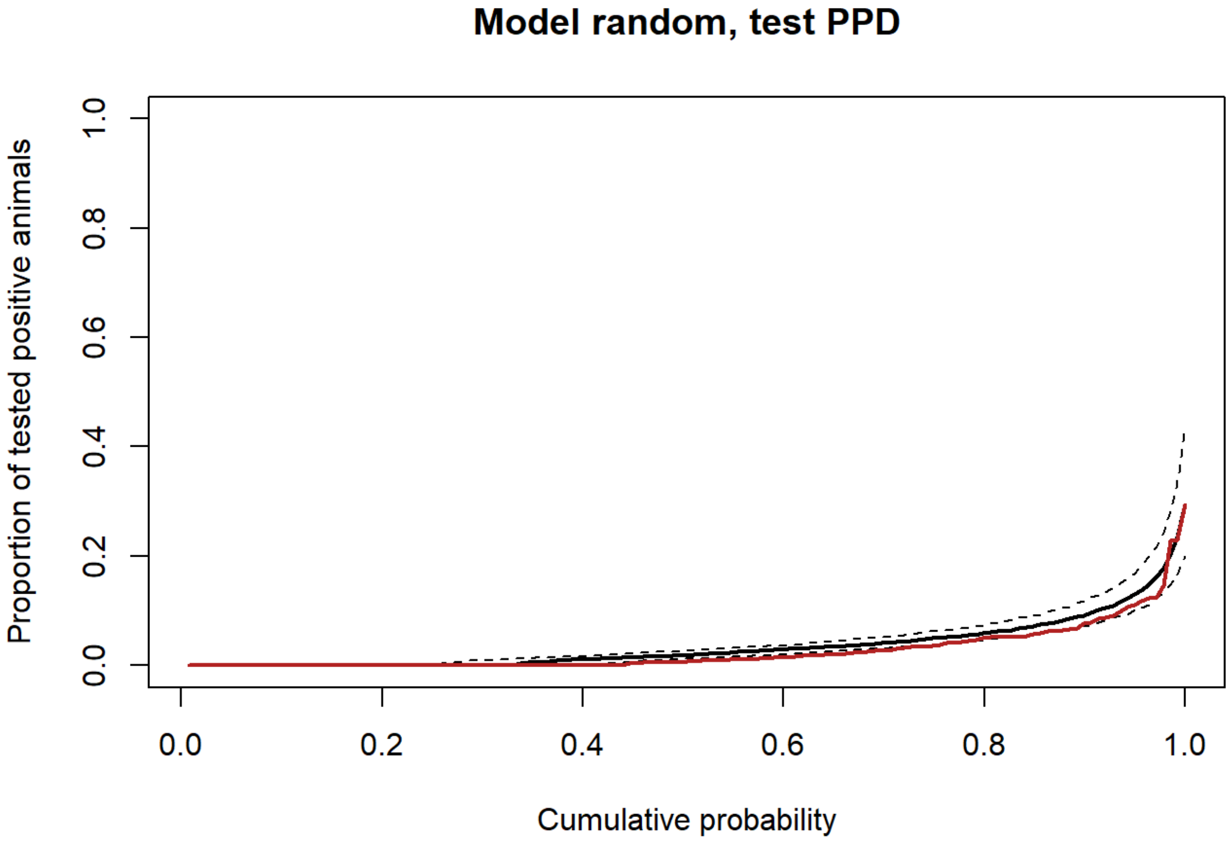


Posterior predictive check : cumulative distribution function of the proportion of positive animals



Posterior predictive check : cumulative distribution function of the proportion of positive animals





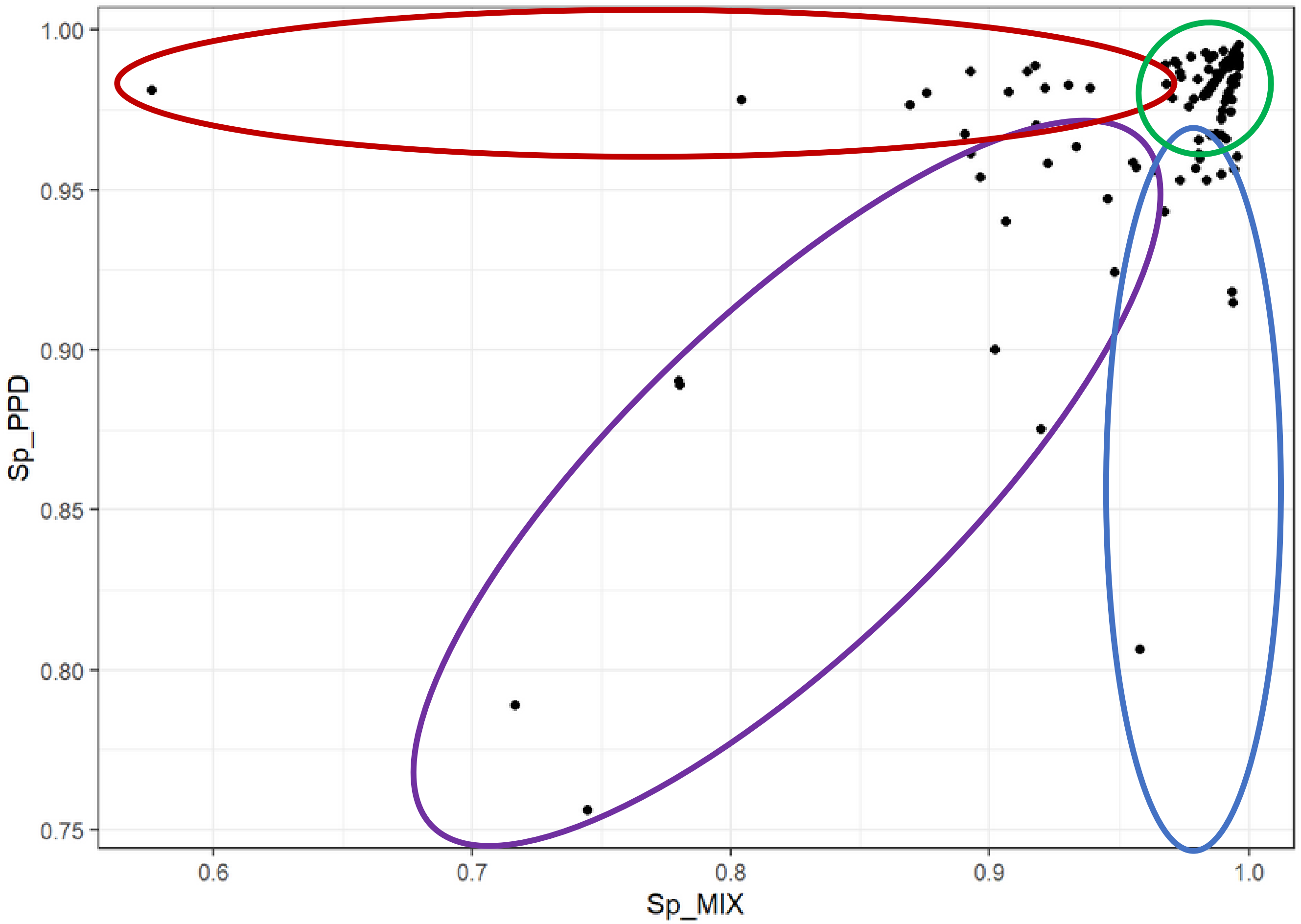
Validity/selection of the models

⇒Model not perfect but better than the model with constant Sp

Sp are variable from one herd to another but why???

Is the specificity issue common to both tests?

- Most herds in which **both IFN tests are highly specific**
- Some in which **only mix** has a low specificity
- Some in which **only PPD** has a low specificity
- Some in which **both** had a low specificity

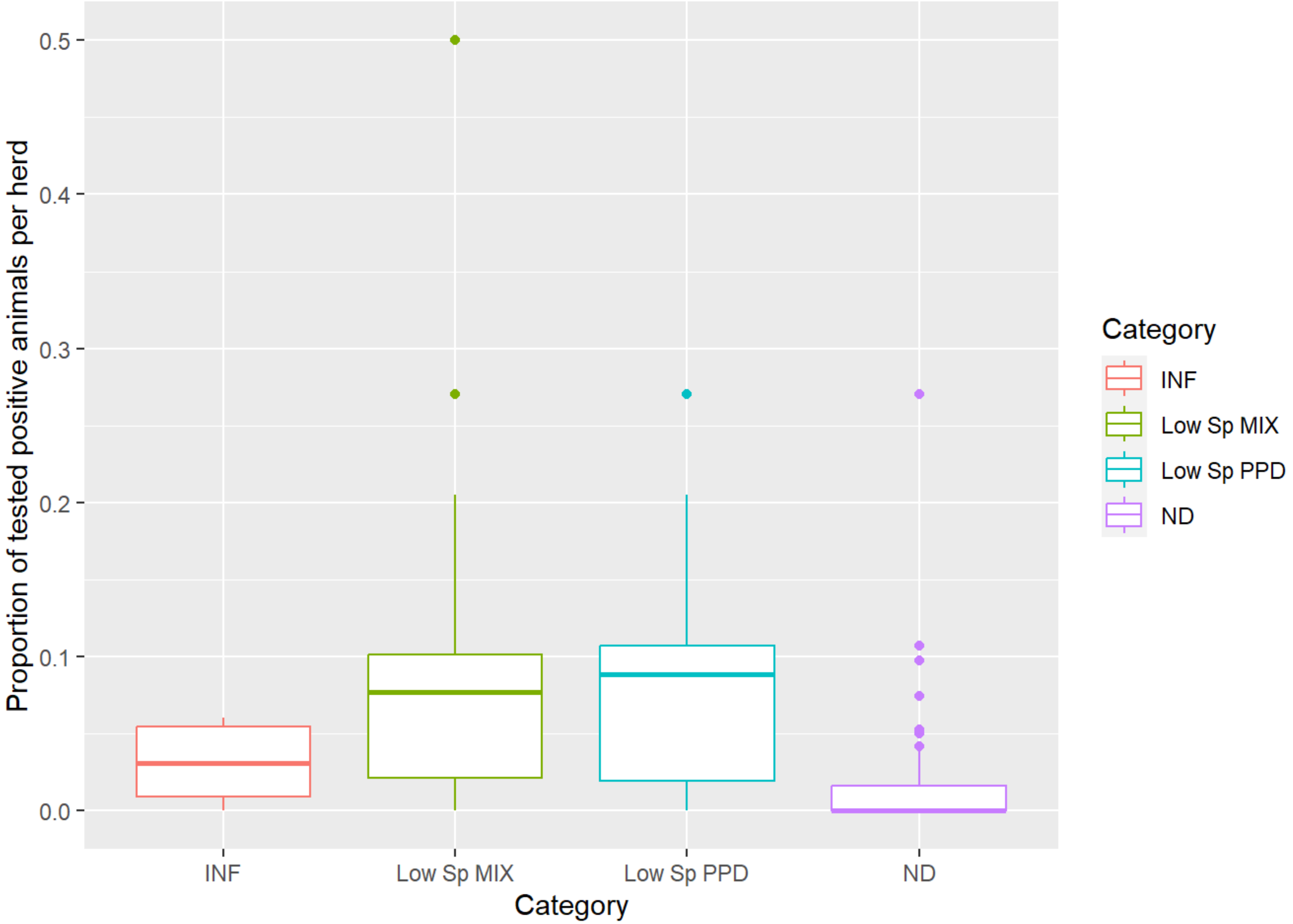


How to discriminate false positive from true positive?

- Classification of herds as :
  - Infected if at least one confirmed infected animal
  - « Low Spmix » if median ($Sp_{mix} < 0.95$) without infected animals
  - « Low SpPPD » if median ($Sp_{PPD} < 0.95$) without infected animals
  - Not detected : not positive to IFN and with confirmed negative animals at slaughterhouse
- Classification of animals
  - Infected if confirmed infected animal
  - « Low Spmix » if tested positive to IFNmix in a « Low Spmix » herd
  - « Low SpPPD » if tested positive to IFNPPD in a « Low SpPPD » herd
  - Not detected : if confirmed negative at slaughterhouse, not positive to IFN

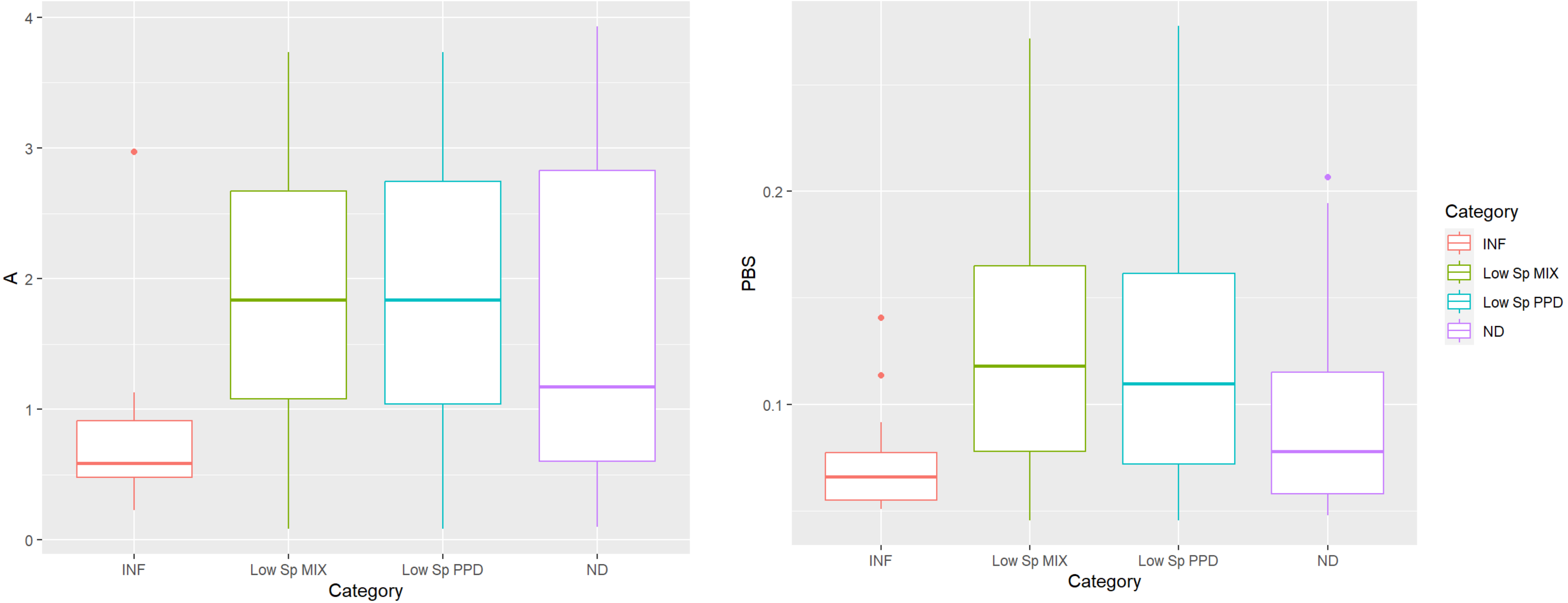
Proportion of tested positive animals in the herd

- Lower proportion of tested positive animals in confirmed infected herds than in « lowSp herds »
- If more than 6-7% of positive in a herd = false positive?



Other measures made during IFN testing

IFNg response after stimulation by PPD-A or PBS higher in false positive animals



Limits and perspective

- Some assumption of the model are not well respected
  - Only a proportion of herds in which the Sp is variable?
  - Another type of random distribution?
- Better description of the reality
  - Confirmed with the posterior predictive check
  - Enables to understand and investigate part of the problem

- Potential « trick » to identify false positive results helpful to stakeholders

Acknowledgment

- All actors involved in the tuberculosis surveillance in France
- ESA platform
- COST and Harmony the organisation and invitation to this meeting
- A special thanks to Eleftherios

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