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T. Lurier, María-Laura Boschioli, Kristel Gache, Carole Forfait-Dubuc, Sophie Carles, Céline Dupuy, Fabrice Chevalier, Jean-Louis Moyen

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

Thibaut Lurier, María Laura Boschioli, Kristel Gache, Carole Forfait, Sophie Carles, Celine Dupuy, Fabrice Chevalier, Jean Louis Moyen

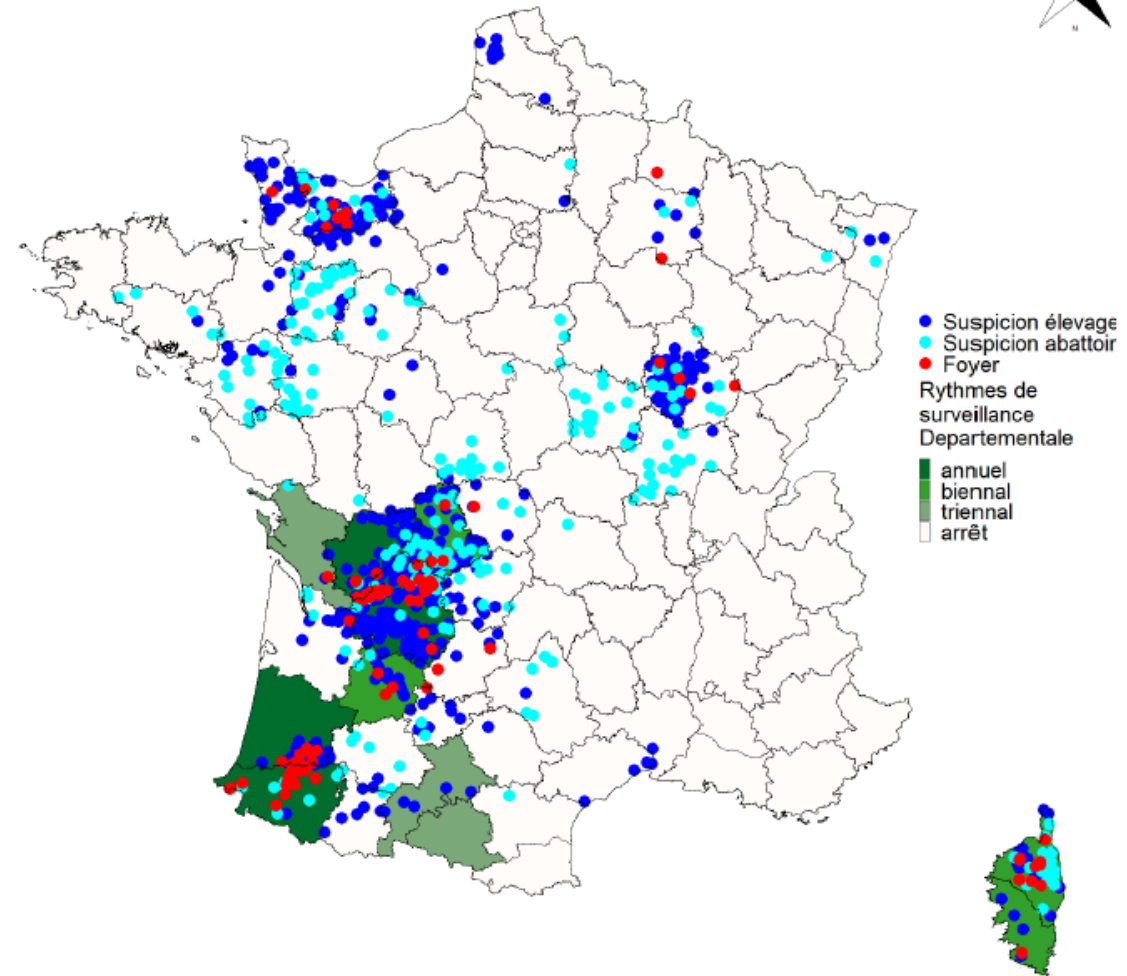
UMR EPIA Vetagro Sup-Inrae, LNR Tuberculose, GDS France, Unité EAS Anses, DGAL, LDAR24



Context : Bovine tuberculosis in France

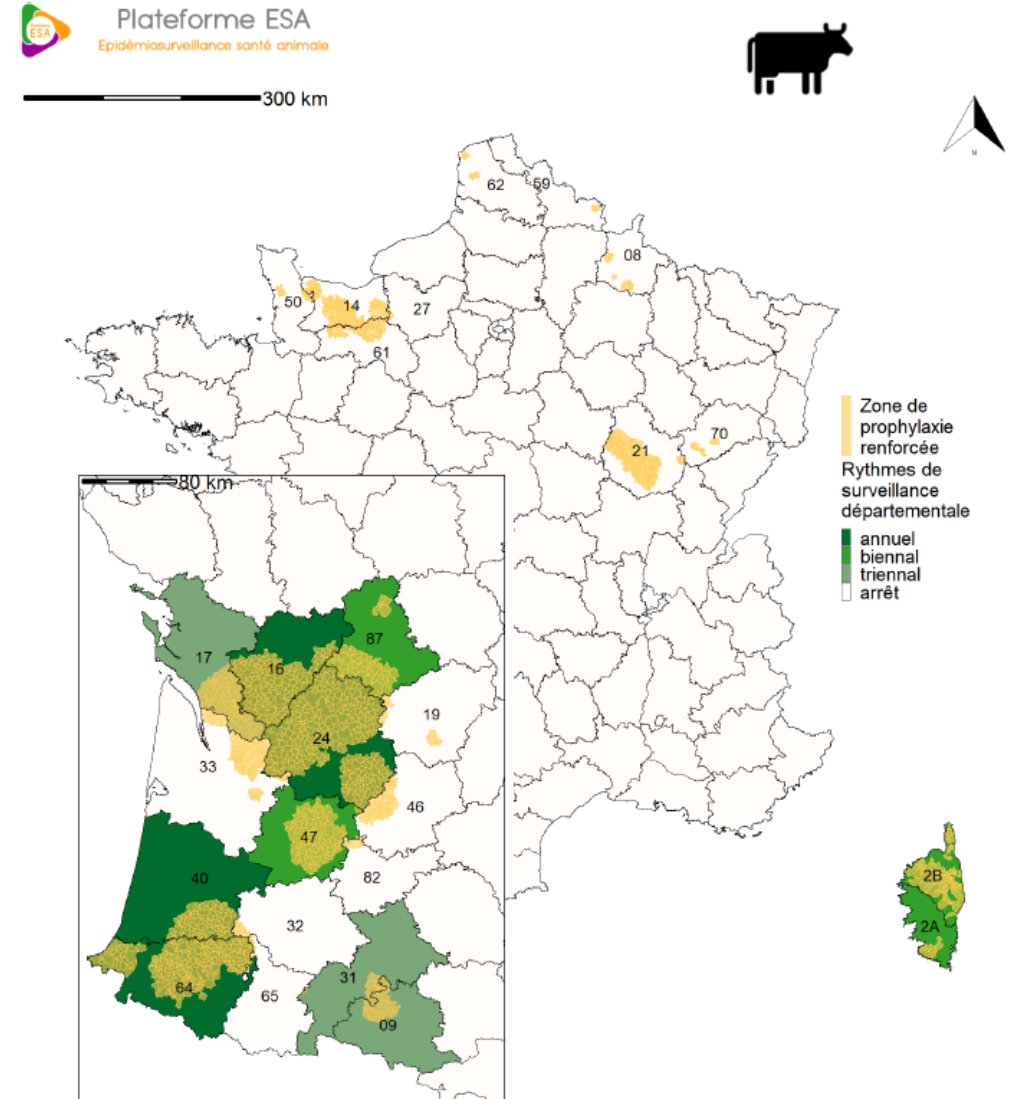
- France is officially free from bovine tuberculosis at the country level (<0.1% of infected herds)
- But
 - **99 outbreaks Identify** in 2021
 - Persistence of the infection in some geographic area
 - Incidence rate that does not decrease anymore.

Plateforme ESA
Epidémiosurveillance santé animale
300 km



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



Forfait et al. 2023

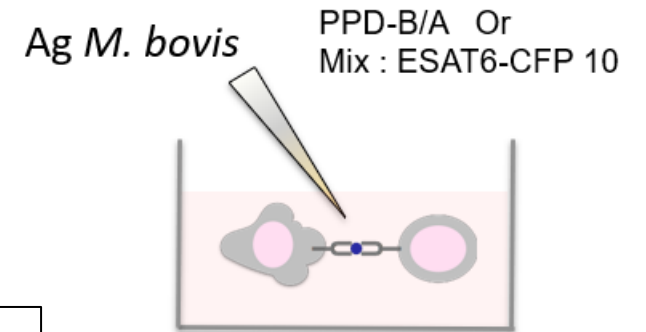
Context : Interferon gamma tests in France

- 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]

Interferon gamma tests



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

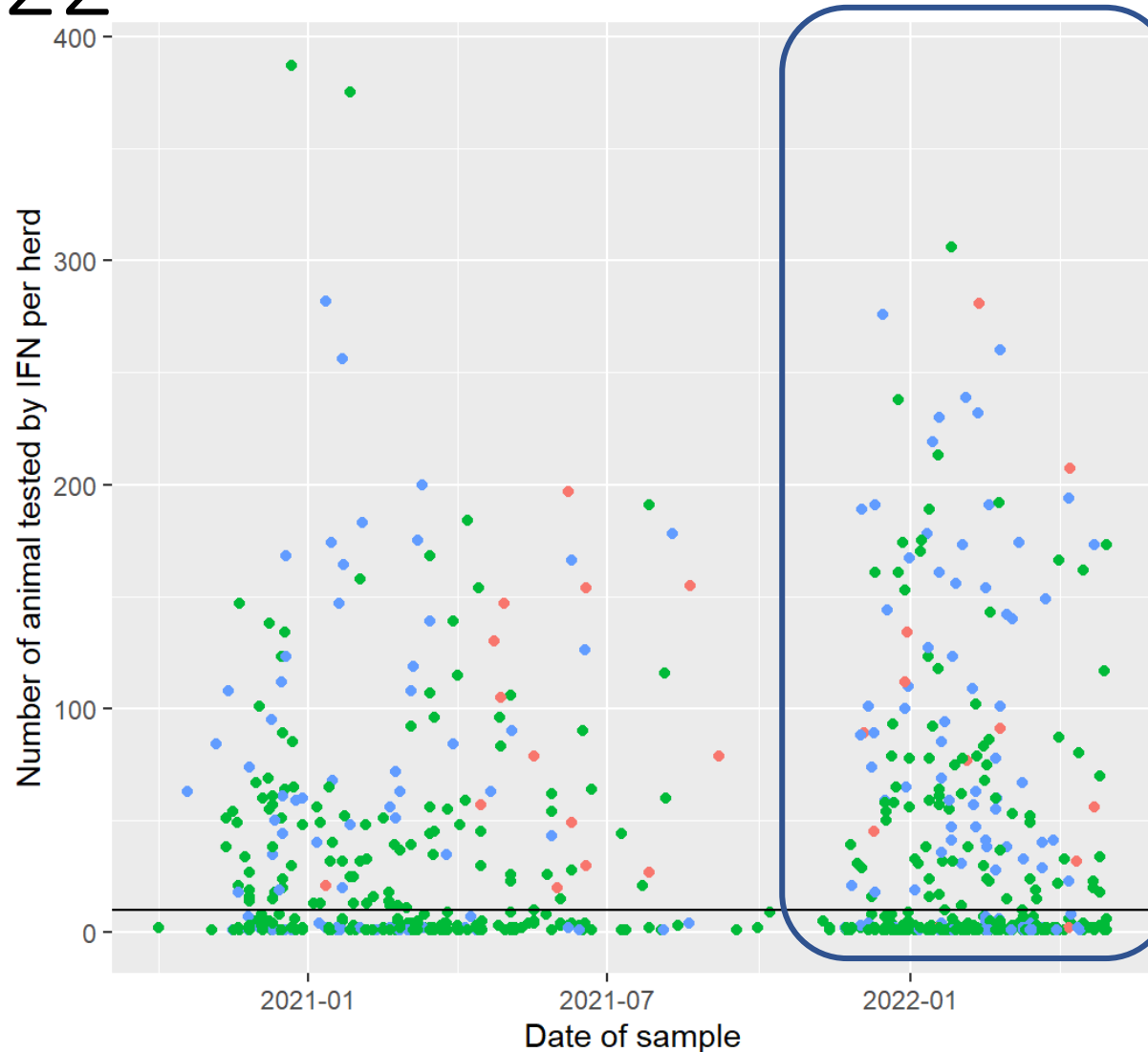
Many herds tested positive at interferon gamma test with potentially many individuals in tested positives in these herds (until 50% of the animals in some herds)

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



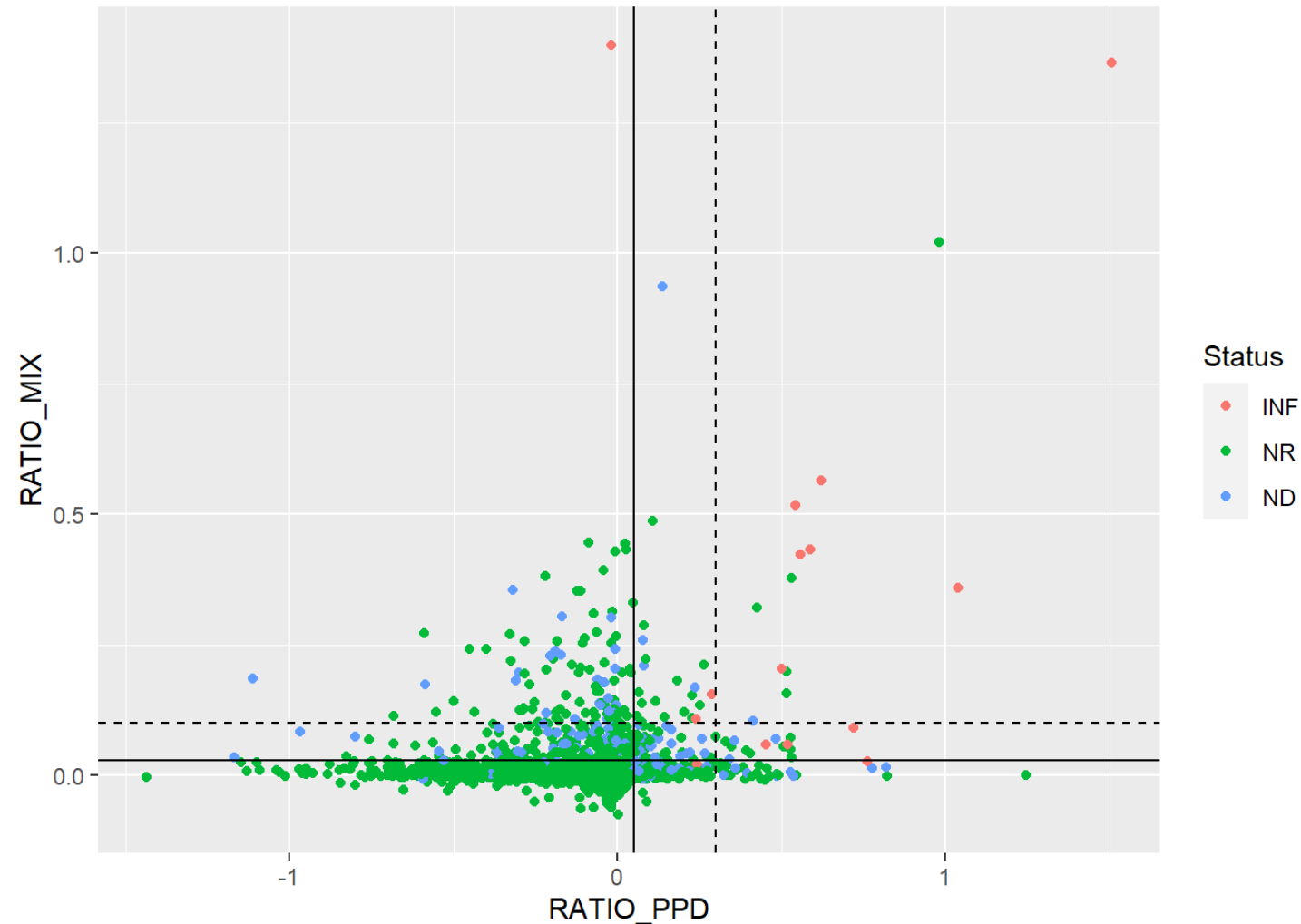
Status of the herd

- INF
- NR
- ND

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

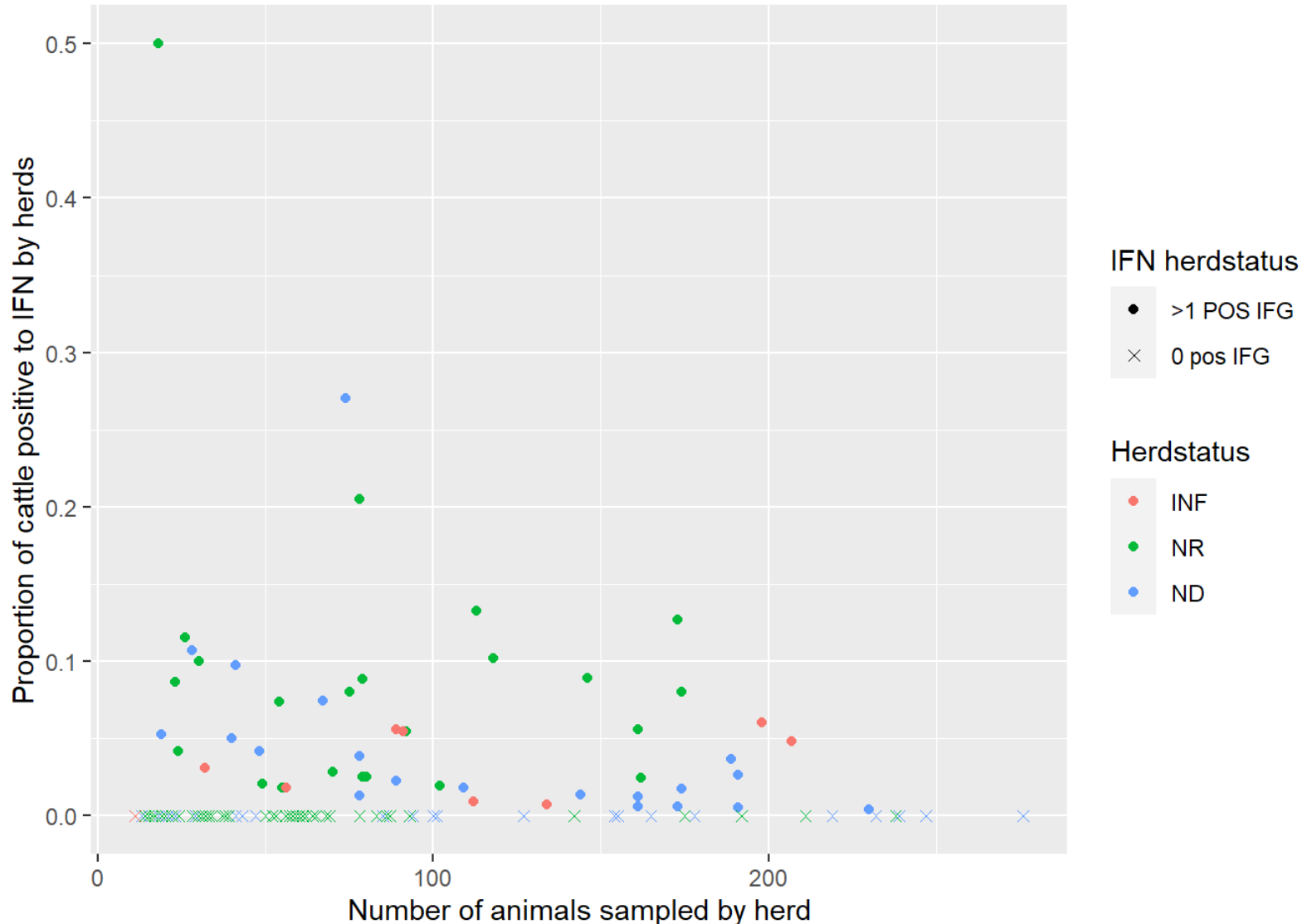
Visualisation of the data at the individual level

- **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%



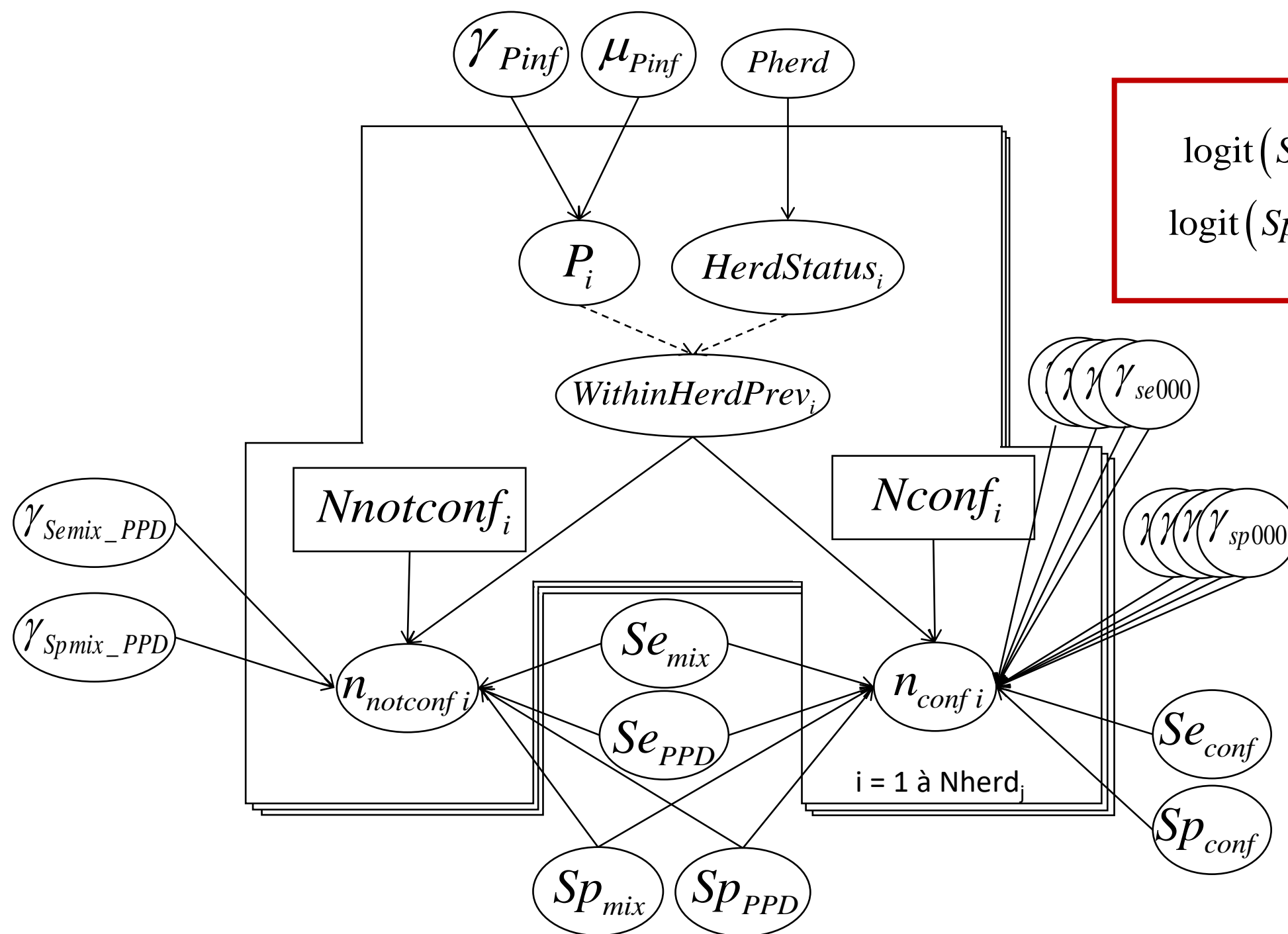
Latent class model

- 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

$$\text{logit}(Sp_{mix,i}) \sim N(\mu_{Sp_{mix}}, \sigma_{Sp_{mix}})$$

$$\text{logit}(Sp_{PPD,i}) \sim N(\mu_{Sp_{PPD}}, \sigma_{Sp_{PPD}})$$



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 S_p in the 2nd model

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

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



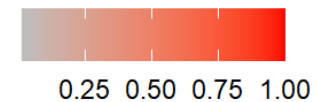
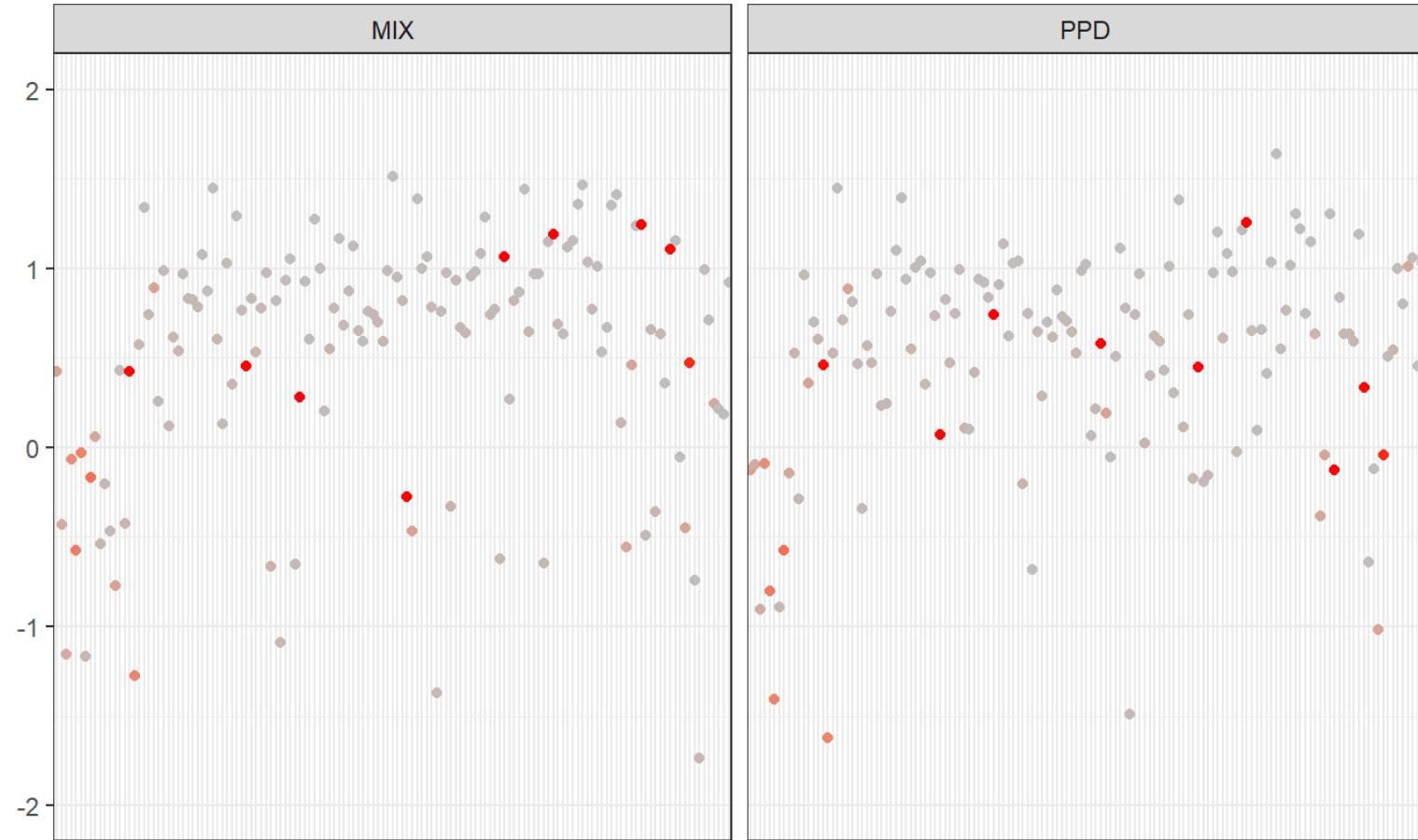
Model « validation » /selection

Normality of the random effects

Random effects are not well centred onto 0

Distribution not really « normal »

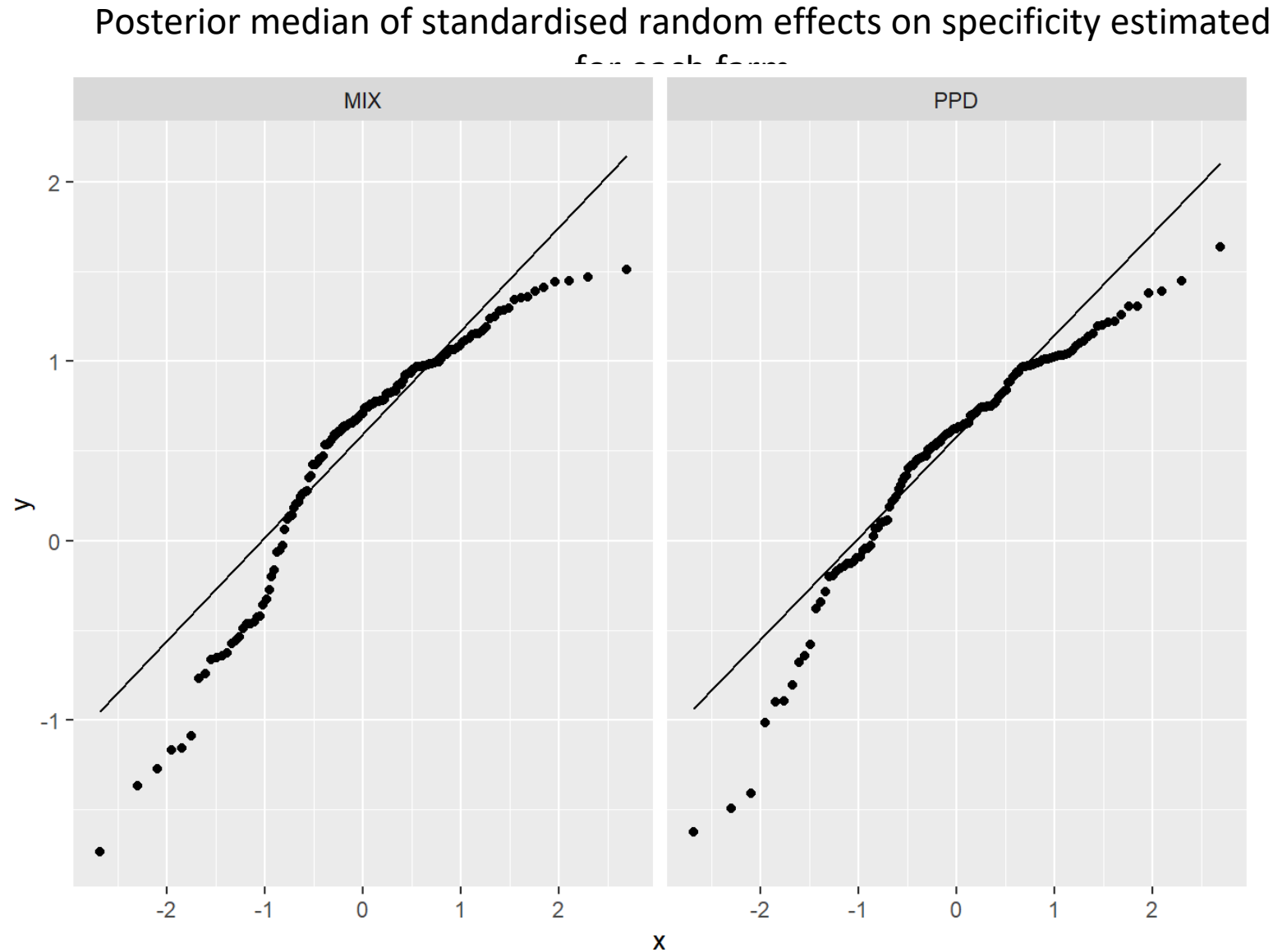
Posterior median of standardised random effects on specificity estimated for each farm



Normality of the random effects

Random effects are not well centred onto 0

Distribution not really « normal »

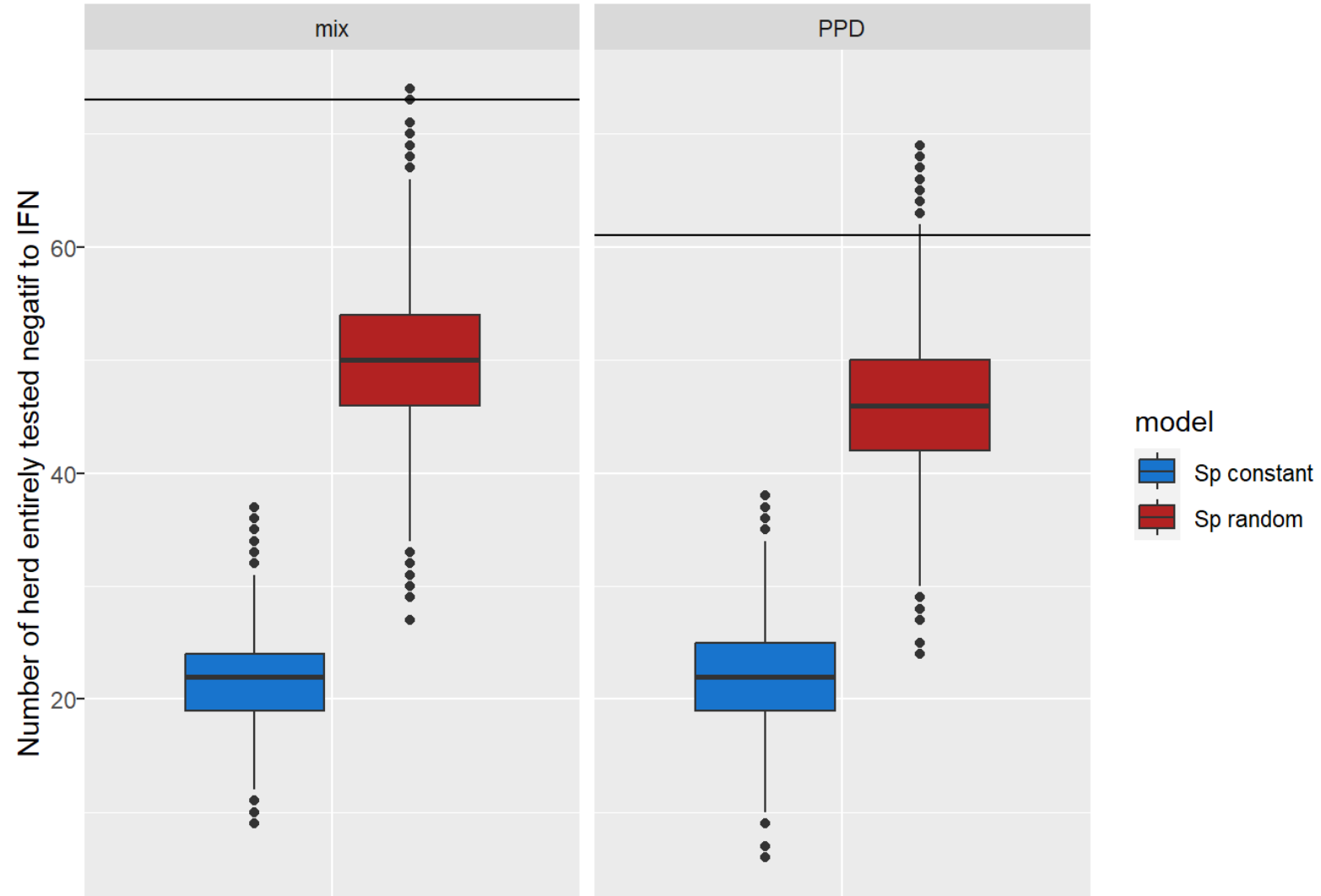


Posterior predictive check : number of negative herds

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

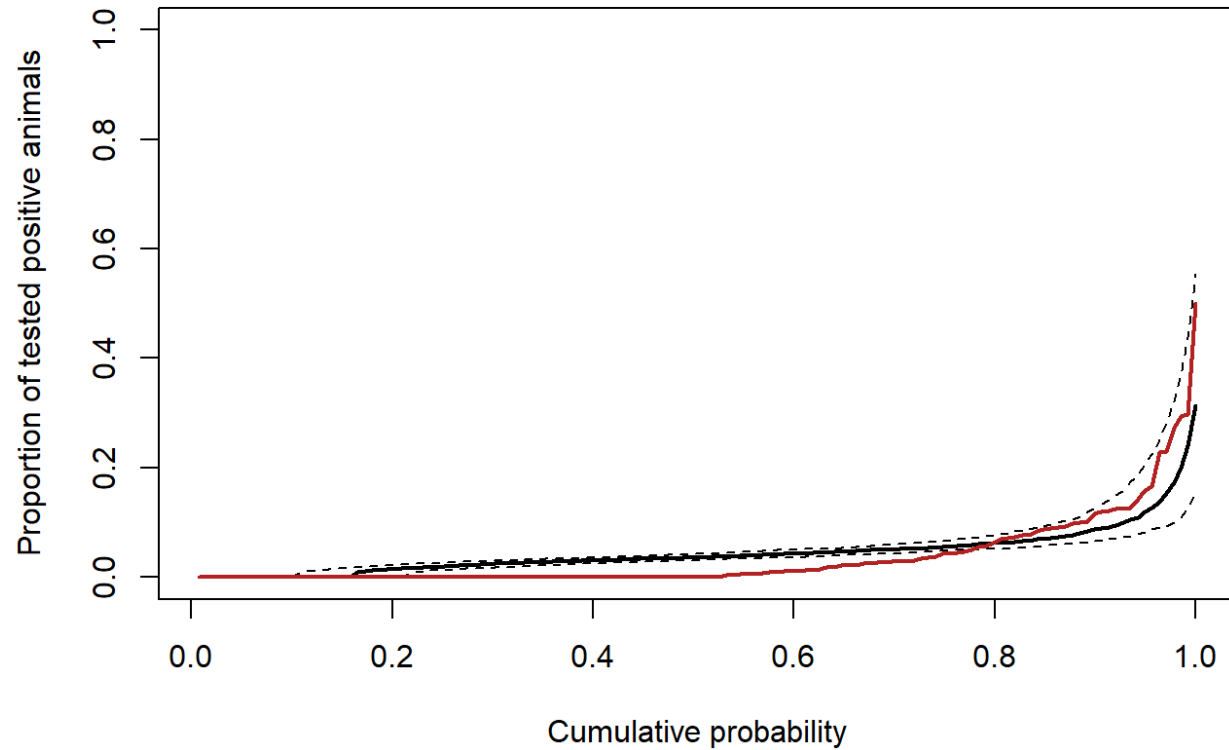
⇒ Models with **Sp random** is closest to the observed value

Posterior distribution of the number of entirely negative herds to IFN

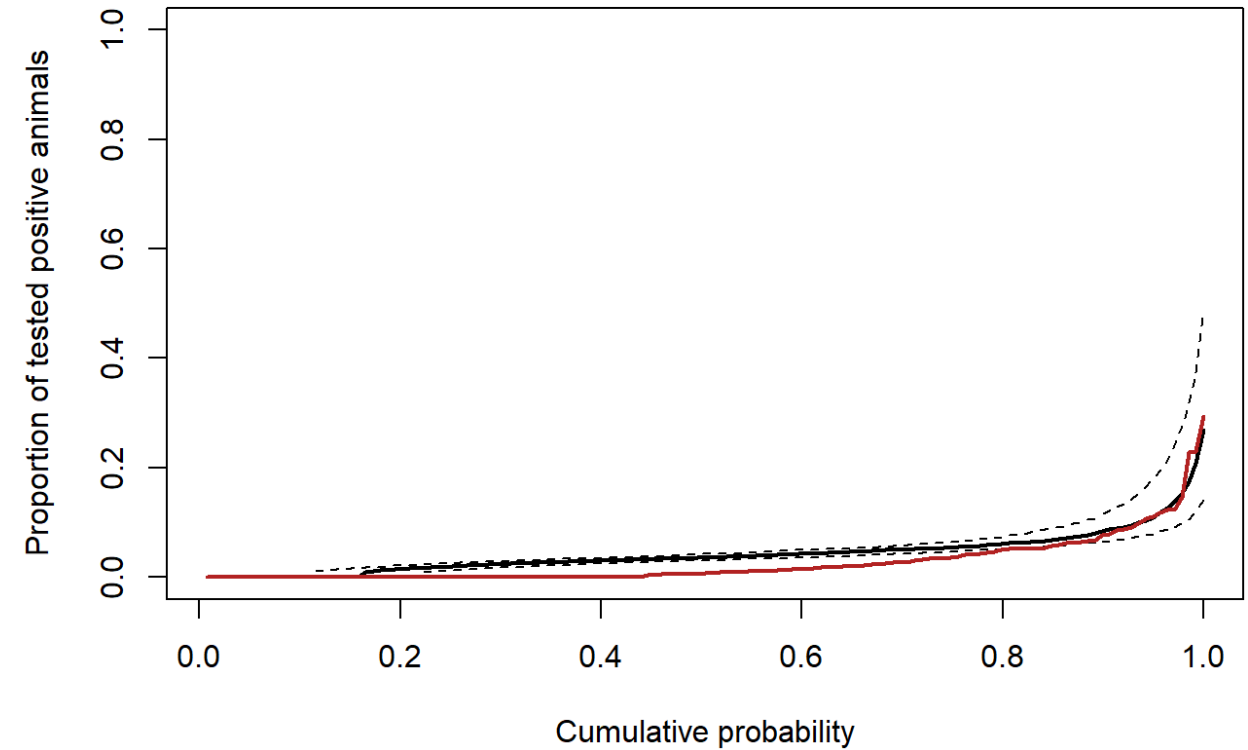


Posterior predictive check : cumulative distribution function of the proportion of positive animals

Model constant, test mix

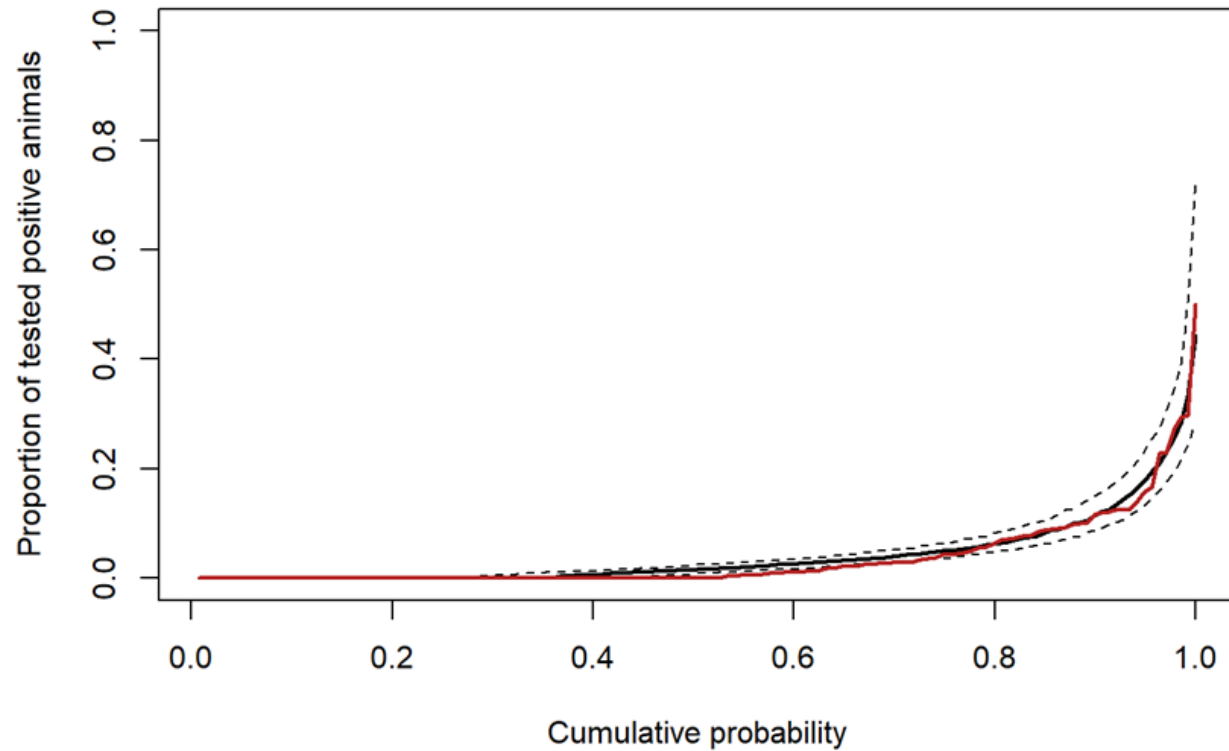


Model Constant, test PPD

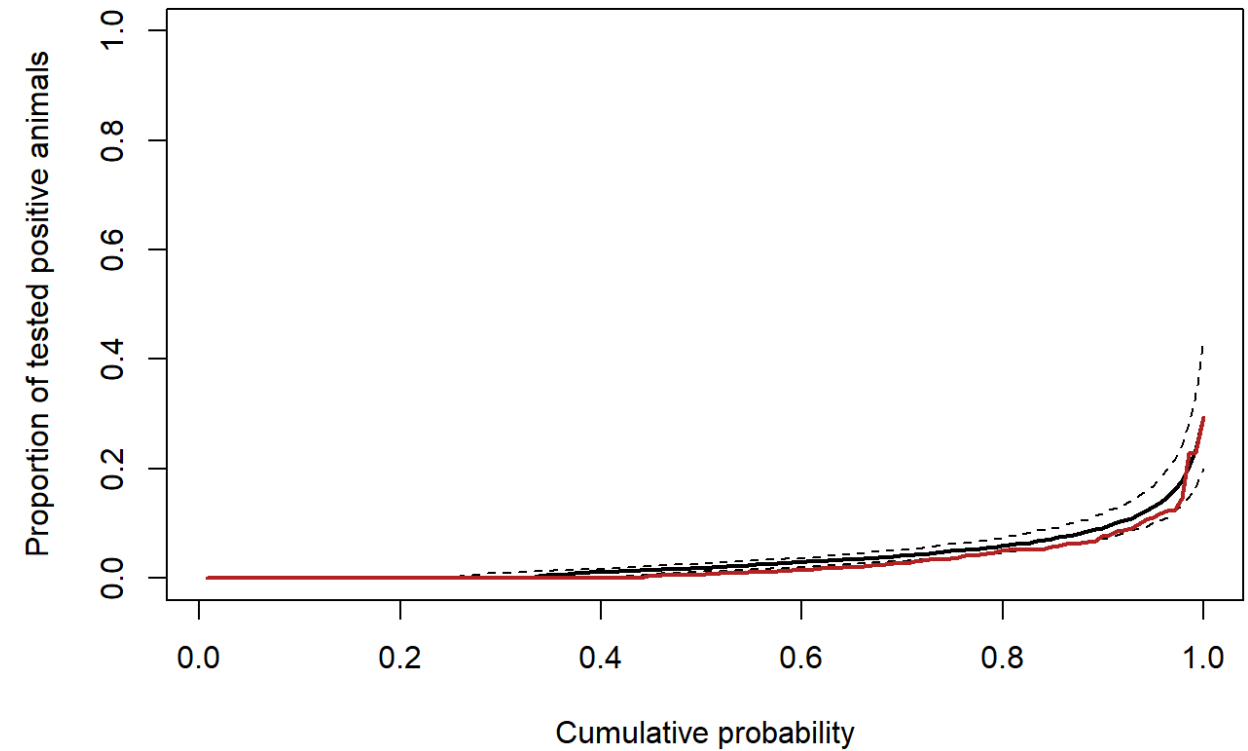


Posterior predictive check : cumulative distribution function of the proportion of positive animals

Model random, test mix



Model random, test PPD



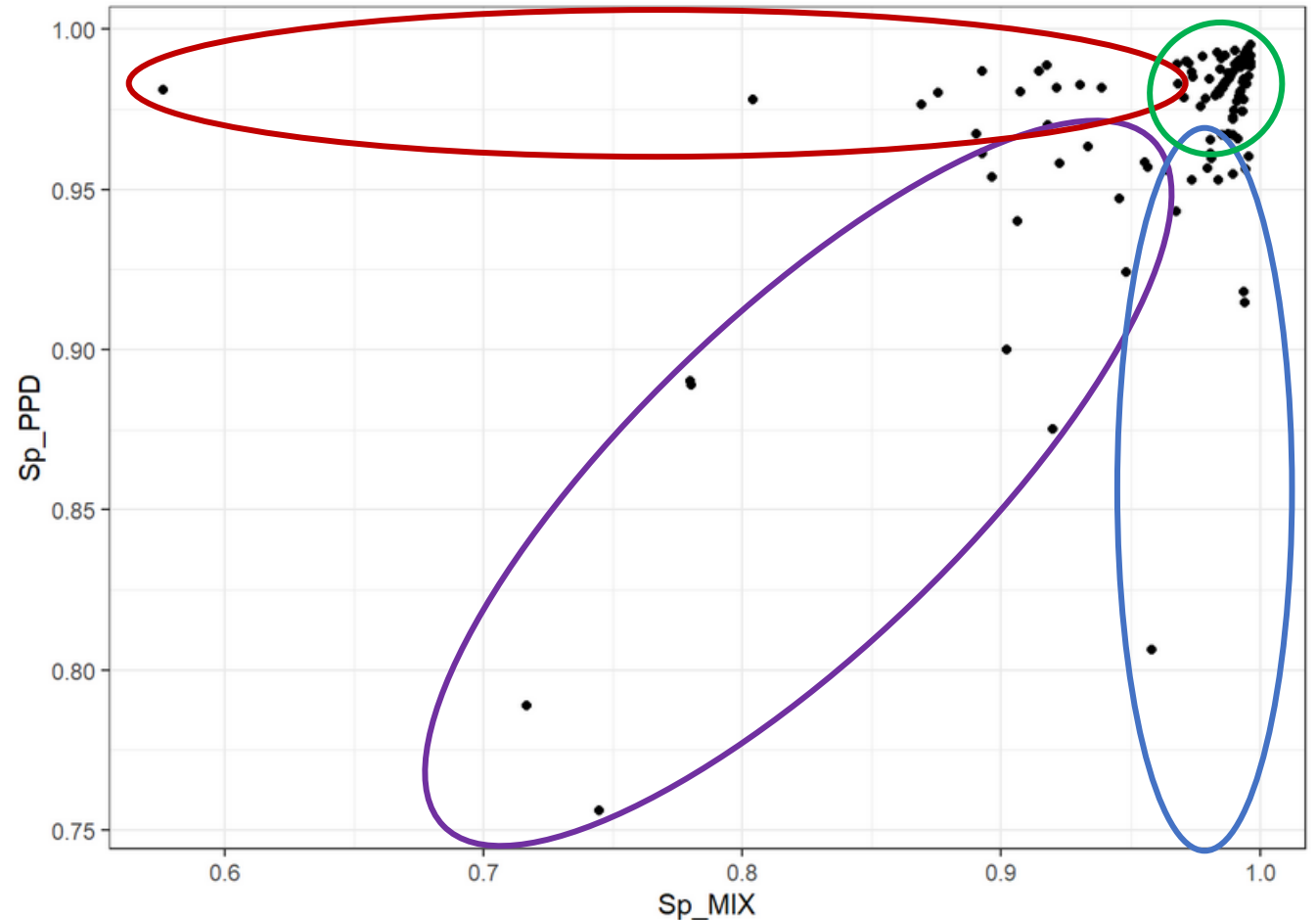
Validity/selection of the models

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

S_p 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

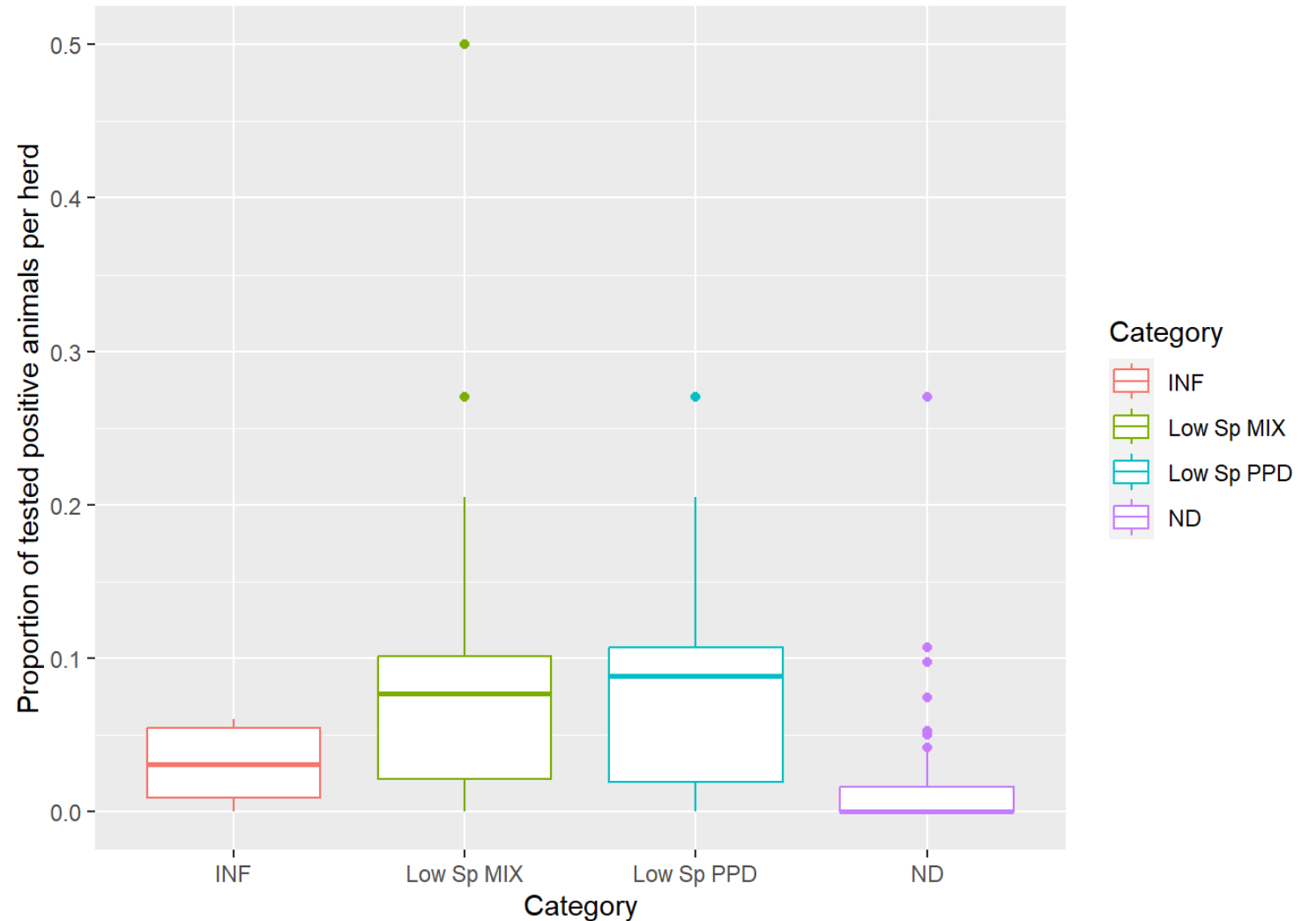


How to discriminate false positive from true positive?

- 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

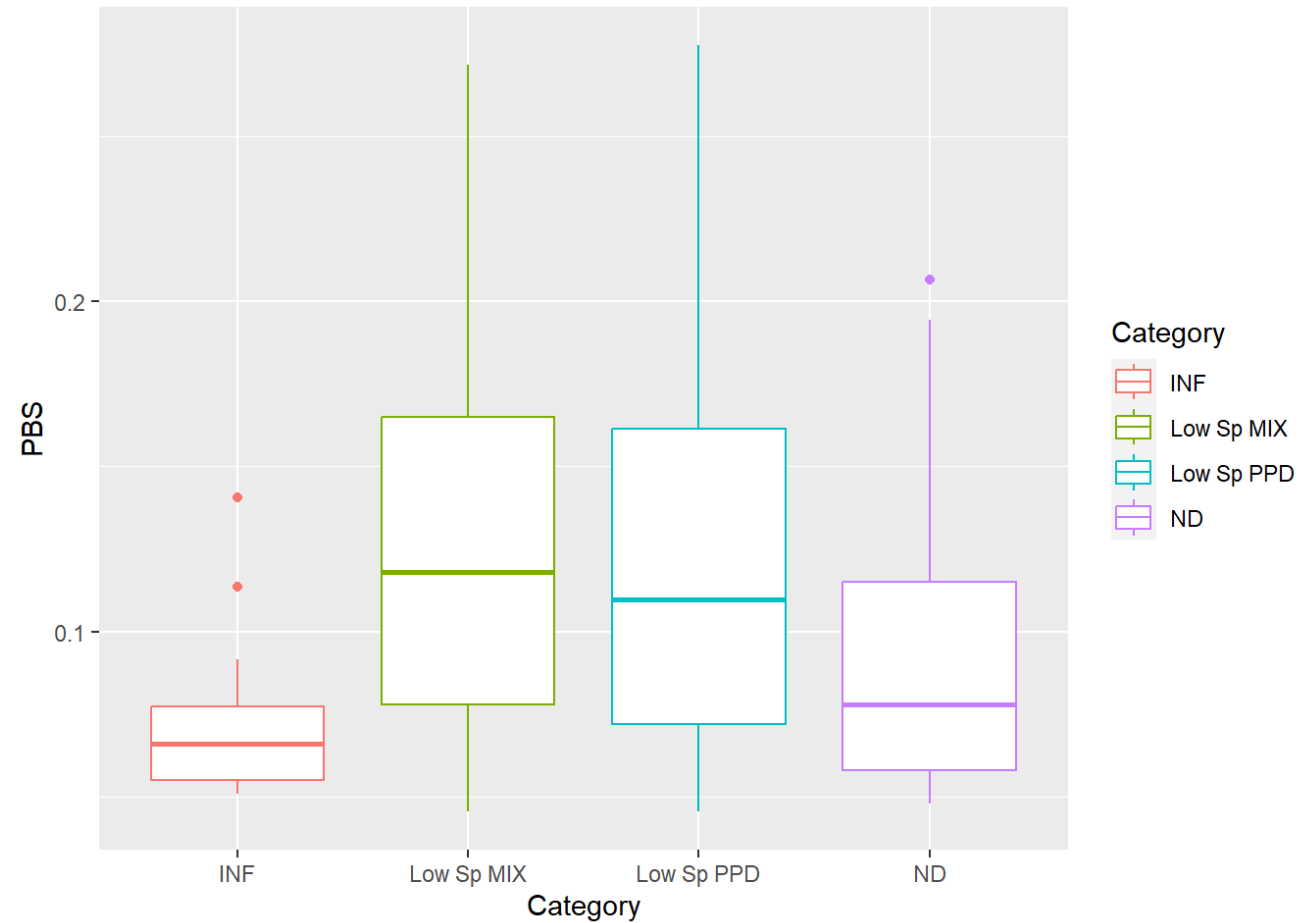
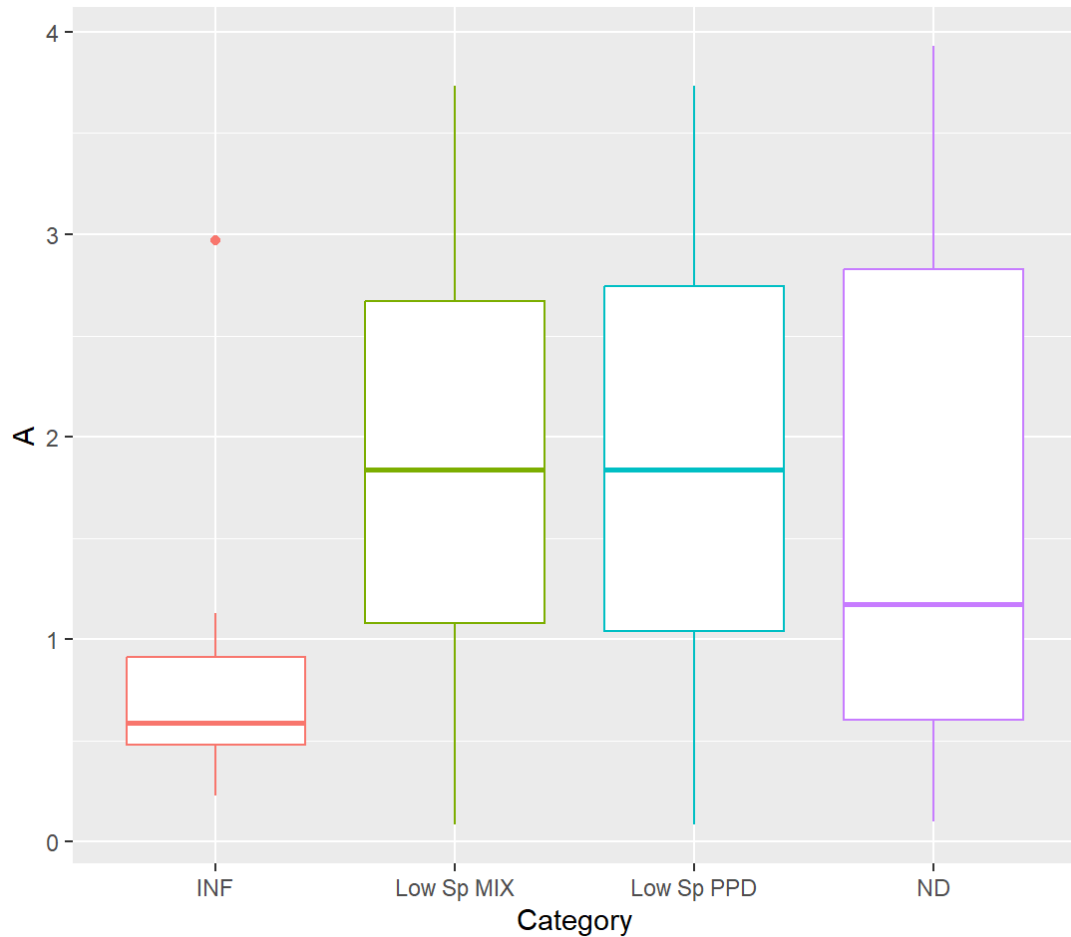
Proportion of tested positive animals in the herd

- 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

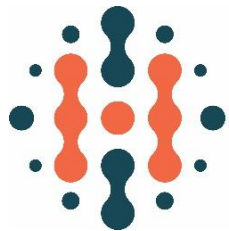


Limits and perspective

- Some assumption of the model are not well respected
 - Only a proportion of herds in which the S_p 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
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HARMONY

Novel tools for test evaluation and
disease prevalence estimation



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