RÉPUBLIQUE FRANÇAISE
Liberté
Égalité
Fraternité

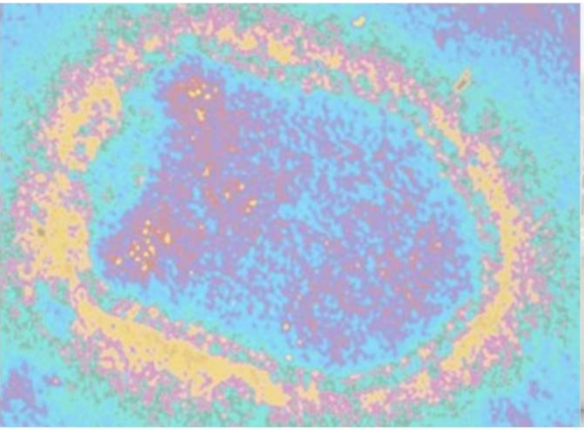
Evaluation of the impact of regulatory measures for rabies prevention by modelling: example of the waiting period issue before dog importations into rabies-free areas

Guillaume Crozet[1], Florence Cliquet[2], Emmanuelle Robardet[2]

[1] Research team EpiMIM, National Veterinary School of Alfort / Anses Maisons-Alfort
[2] Nancy Laboratory for Rabies and Wildlife, Anses (Nancy)

June 22, 2023

École nationale vétérinaire d'Alfort
7, avenue du général de Gaulle
94 704 Maisons-Alfort Cedex
+33 1 43 96 71 00
vet-alfort.fr



Context and objective

Context

Dog importations and rabies risk

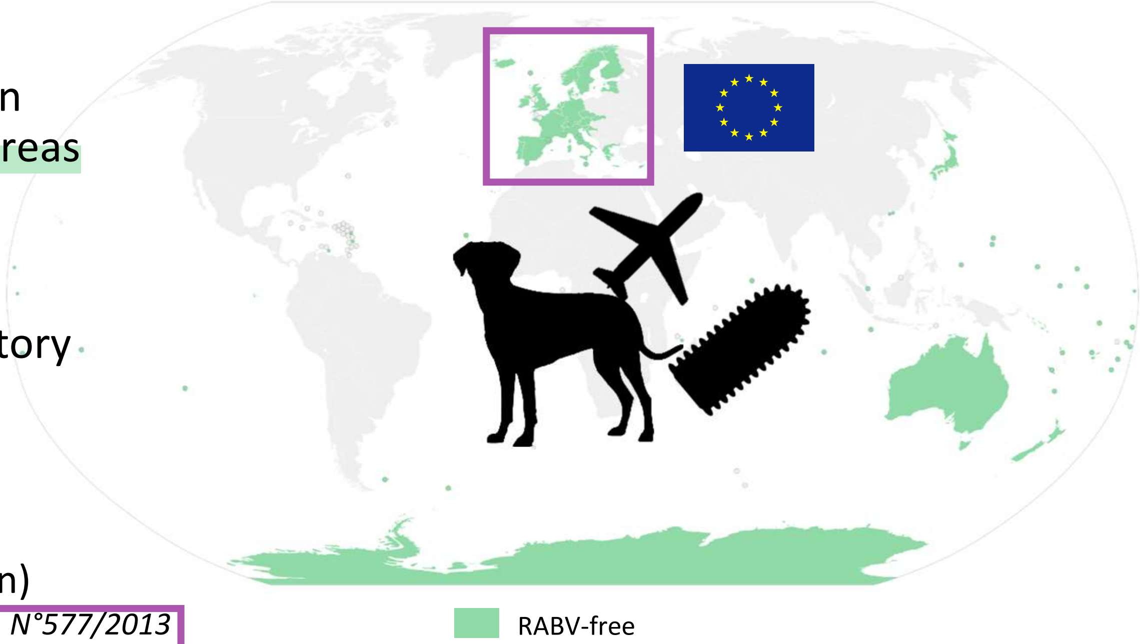
- **Dogs movements** (importations and travel) can contribute to **reintroduce rabies** in RABV-free areas

- Risk linked to:

- **Failure of the prevention measures** = regulatory requirements (Regulations (EU) N°576/2013 and 577/2013)
  - Anti-rabies **vaccination**
  - **Serological testing** (30 days after vaccination)
    for third countries non-listed in Annex II to Regulation (EU) N°577/2013
  - 3-month **waiting period** after the serological test
    for third countries non-listed in Annex II to Regulation (EU) N°577/2013

  ↳ Restrictive: acceptability?

- **Non-compliance** with the prevention measures



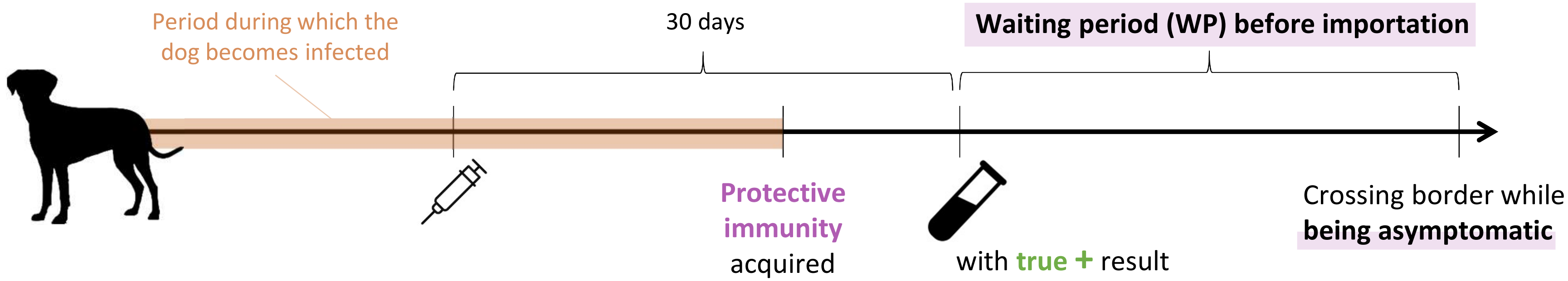
Animal and public health concern

Context

Dog importations and rabies risk : type A and B risks

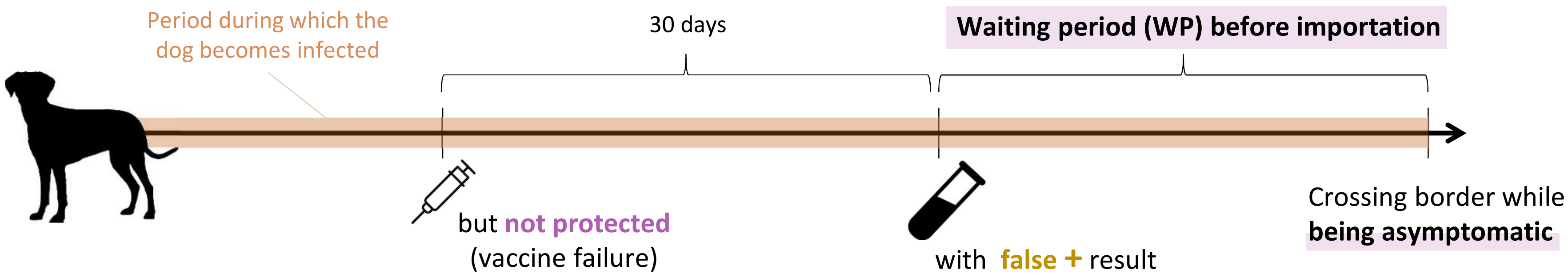
Assuming full compliance with regulations

Type A risk: dogs infected before acquiring vaccine immunity



Type B risk: dogs infected due to vaccine (no protection) and serological test failure (false positive result)

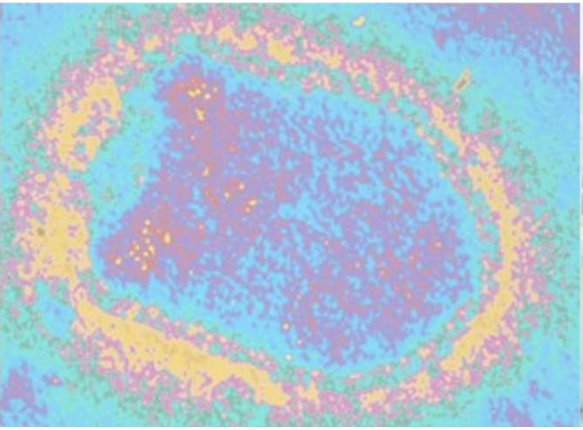
Impact of the WP length on rabies risk ?



Objective

Assess the **impact on rabies risk** of the **reduction of the waiting period** after anti-rabies vaccination and serological testing in the context of **dog importations**

Impact estimated for the **European Union** territory (in terms of the number of dogs imported and their origins)



Material and methods

General framework

- **Risk analysis** using **stochastic scenario tree modelling**

- ***In silico* study**, convenient to study **rare events**

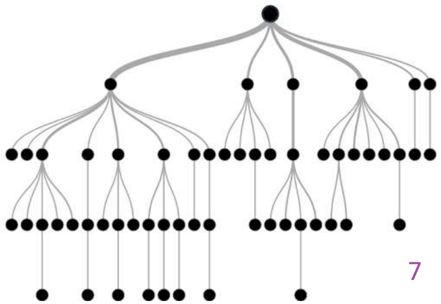
- **Process :**

1. **Risk pathways definition** of RABV introduction through **dog importations**, assuming **full compliance** with regulations

2. Model **parameterisation** using distributions

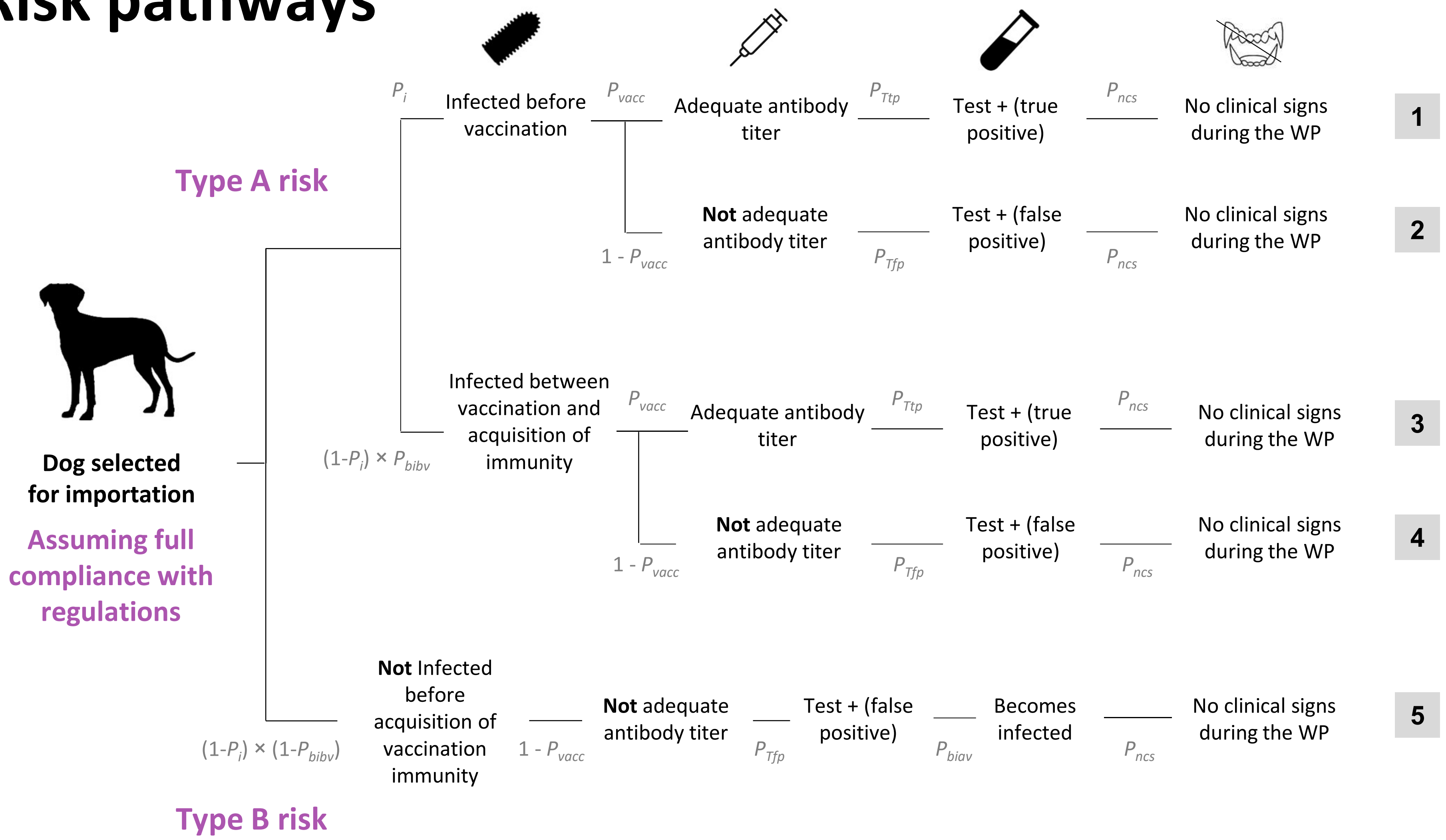
   - For the **European Union**
   - Using different **waiting period lengths**: **3 months**, **2 months**, **1 month**, **none**

3. **Simulations** + **sensitivity analyses**



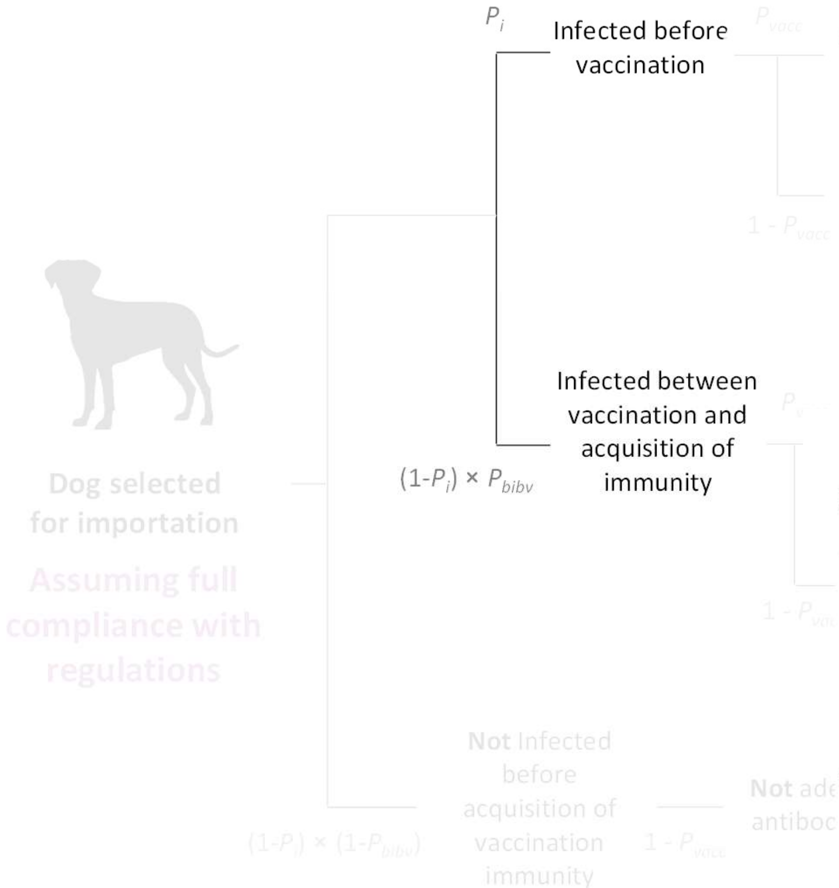
Material and methods

Risk pathways



Material and methods

Risk pathways and parameters

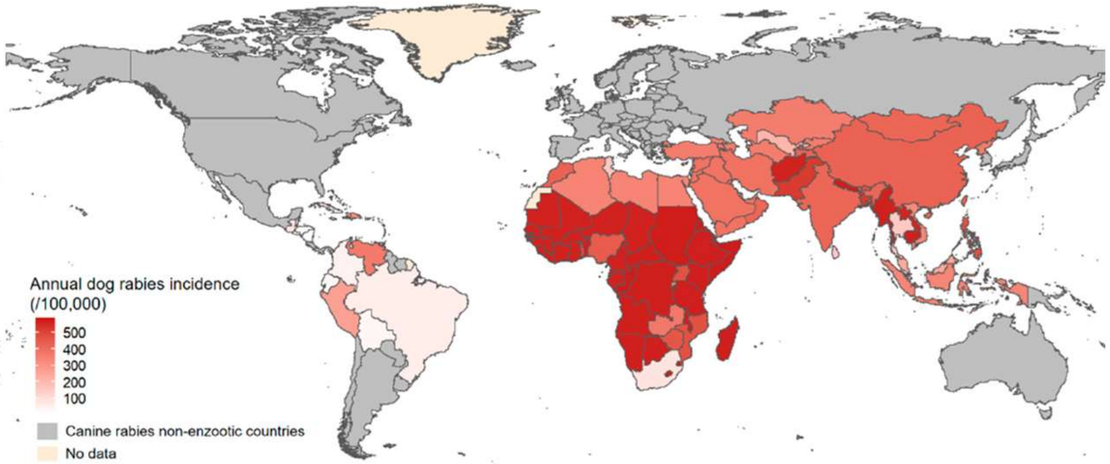


Probability of infection

3 types of rabies incidence levels:

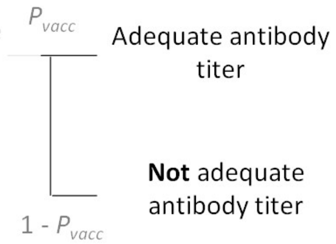
- **High risk areas** (e.g. North Africa)
- **Medium risk areas** (e.g. Caribbean)
- **Low risk areas** (e.g. Eastern Europe)

Dog rabies incidence (mean) in canine rabies enzootic areas



Hampson et al., 2015 (*PLoS Negl Trop Dis*); Crozet et al., 2020 (*Vet Sci*)

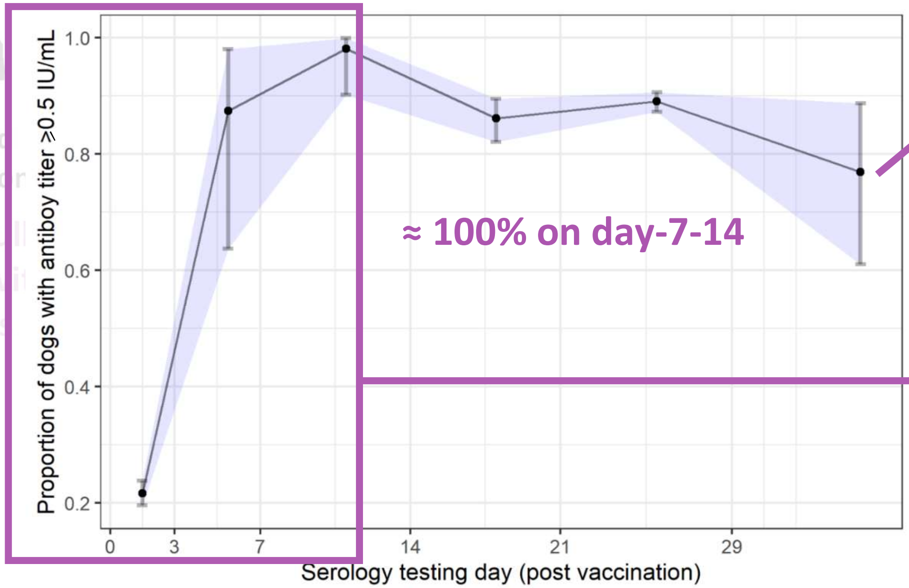
Risk pathways and **parameters**



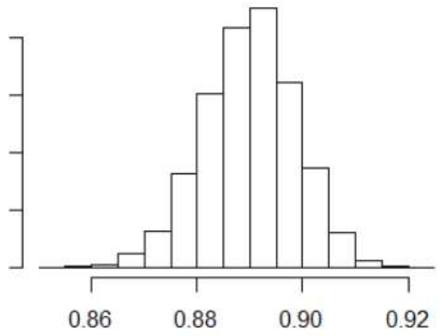
Vaccine immunity

EFSA (2022) dataset :

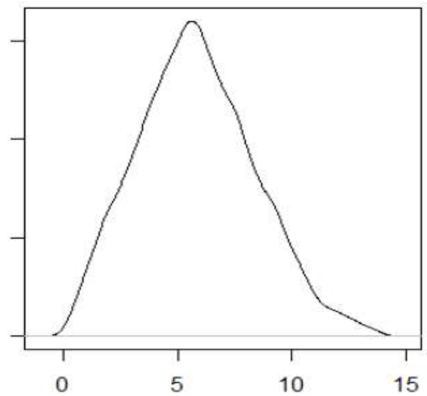
- Only **dogs**
- After **1 injection**
- Using Beta distributions



Probability of having a titer ≥ 0.5 IU/mL on day 30 = « **Vaccination efficacy** »



Delay to acquire immunity (days)
(assumption that 100% of the dogs seroconverted on day 14)



Risk pathways and **parameters**

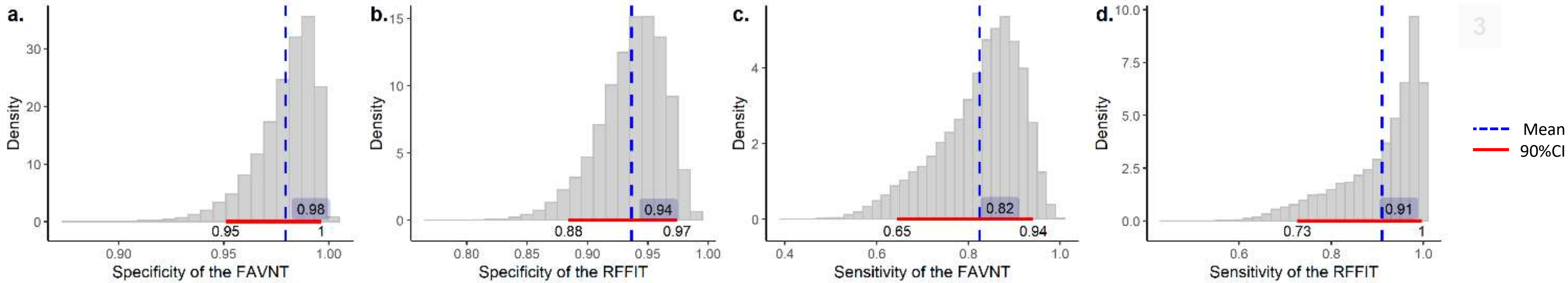
Serological tests

- Cliquet et al. (1998) dataset
- Using bayesian latent class model

P_{Ttp} Test + (true positive)

Test + (false positive) P_{Tfp}

*Posterior distributions of the **Bayesian latent class model** for serological test specificity (a and b) and sensitivity (c and d)*



Crozet et al., 2023 (*Risk Anal.*)

Material and methods

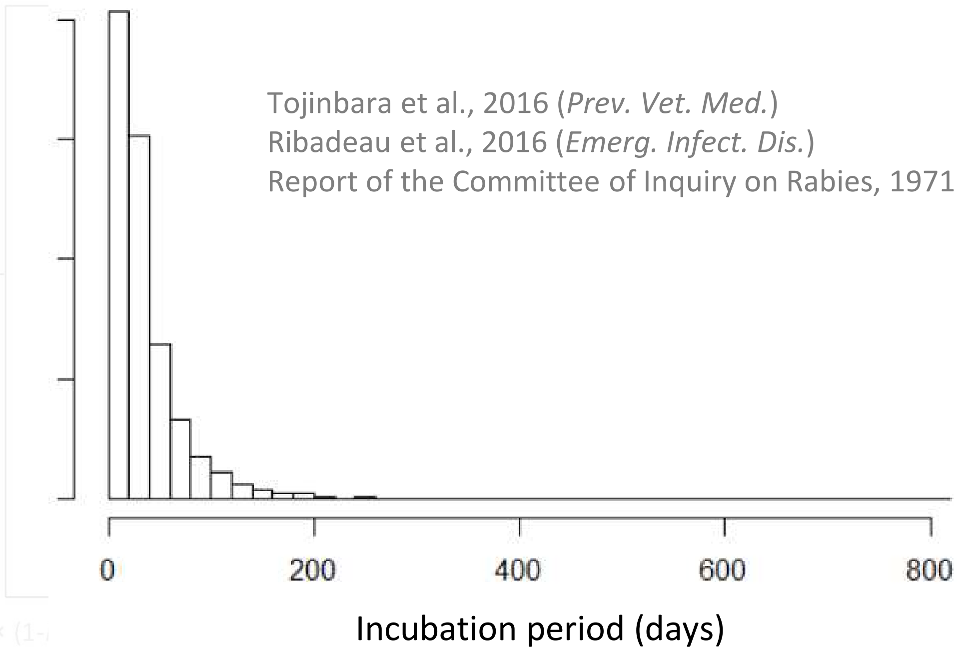
Risk pathways and parameters

Probability of a dog remaining asymptomatic

- Linked to the length of the **incubation period**
- Only **natural infections**

P_{ncs} No clinical signs during the WP

Tojinbara et al., 2016 (*Prev. Vet. Med.*)
Ribadeau et al., 2016 (*Emerg. Infect. Dis.*)
Report of the Committee of Inquiry on Rabies, 1971

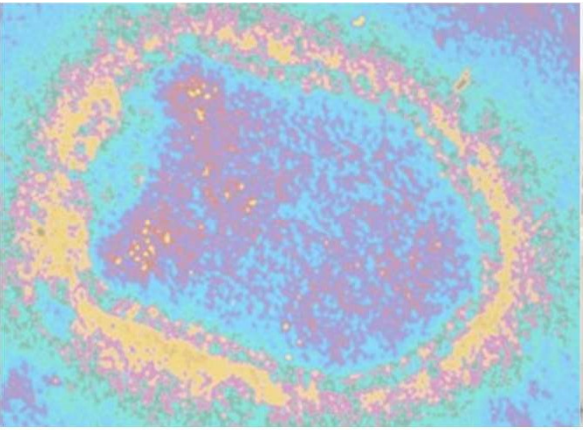


Two modelling approaches

1. **« Classical » scenario tree modelling - Probability calculation** (× 10 000 iterations)
   - **Occurrence probability of each branch**: × of event probabilities
   - **Individual risk (*Ri*):** sum of the occurrence probabilities of each branch
   - **Number of infected imported dogs (*NRabies*) =** *Ri* × Number of imported dogs

2. **Individual-based modelling** (x 10 000 iterations)
   - Events modelled for each imported dog: **0** = no RABV introduction, **1** = RABV introduction
   - Sum of individual trajectories = ***NRabies***

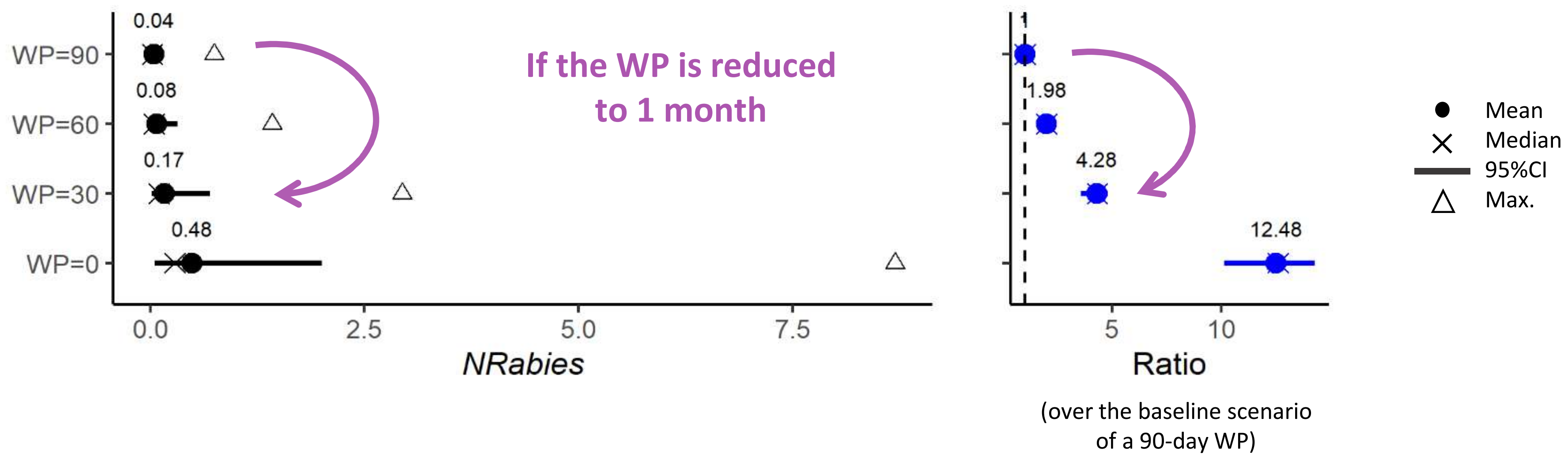
Area of origin	Number of dog importations requiring serological testing in France in 2019 (I-CAD)	Number of dog importations requiring serological testing in the EEA (extrapolation)
High risk countries	811	5746
Medium risk countries	205	1452
Low risk countries	744	**5272**



Results

Risk estimation for each waiting period (WP)

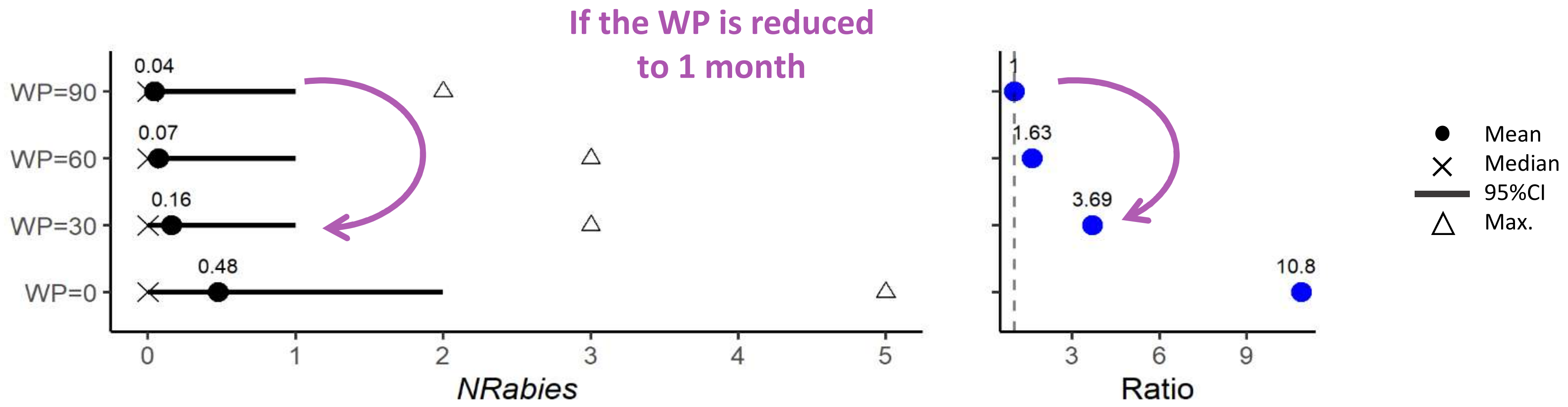
Model 1 results: number of rabies infected dog importations



Results

Risk estimation for each waiting period (WP)

Model 2 results: number of rabies infected dog importations



(over the baseline scenario of a 90-day WP)

Discussion

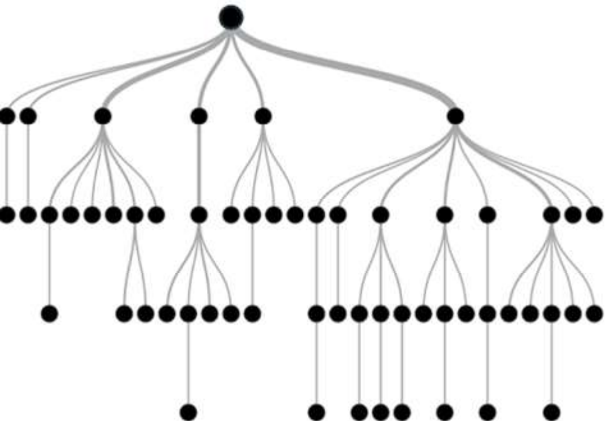
Discussion

Limits

- **Models = simplification**, cannot account for every possible pathway of introduction
- **High uncertainty** on some parameters + potential **bias** (e.g. number of imported dogs = extrapolation)
- **No validation possible**: theoretical situation assuming perfect compliance

Impact of the WP reduction in a « full » scenario (including non compliance) ?

= **negligible impact ?** (Crozet et al., 2023)



Impact of the waiting period on rabies risk

- **Increase in rabies** risk when reducing the WP length (consistent between Model 1 and 2):

≈ 4 fold increase

- Numbers of infected dog importations remain in **low-value ranges**:

e.g. 0.04 introductions per year with a 3-month WP to 0.16 or 0.17 with a 1-month WP

Acceptability?

+ **Similar results in other modelling studies**: increase in risk when reducing the waiting period (Weng et al., 2010; Goddard et al., 2012; Kwan et al., 2017; EFSA, 2022)

+ **Data on experimental infections**: very low increase in risk when reducing the waiting period, but risk at the individual level (not at the population level) (Smith et al., 2021)

Thank you for your attention

Acknowledgments

- **I-CAD:** D. Dorée

References

Cliquet, F., Aubert, M., & Sagné, L. (1998**). Development of a fluorescent antibody virus neutralisation test (FAVN test) for the quantitation of rabies-neutralising antibody**. *Journal of Immunological Methods*, *212*(1), 79–87. https://doi.org/10.1016/s0022-1759(97)00212-3

Crozet, G., Rivière, J., Canini, L., Cliquet, F., Robardet, E., & Dufour, B. (2020). **Evaluation of the Worldwide Occurrence of Rabies in Dogs and Cats Using a Simple and Homogenous Framework for Quantitative Risk Assessments of Rabies Reintroduction in Disease-Free Areas through Pet Movement**s. *Veterinary Sciences*, *7*(4). https://doi.org/10.3390/vetsci7040207

Crozet, G., Rivière, J., Rapenne, E., Cliquet, F., Robardet, E., & Dufour, B. (2023). **Quantitative risk assessment of rabies being introduced into mainland France through worldwide noncommercial dog and cat movements**. *Risk Analysis: An Official Publication of the Society for Risk Analysis*, *43*(5), 896–916. https://doi.org/10.1111/risa.13976

European Food Safety Authority (EFSA), Alvarez, J., Nielsen, S. S., Robardet, E., Stegeman, A., Van Gucht, S., Vuta, V., Antoniou, S.-E., Aznar, I., Papanikolaou, A., & Roberts, H. C. (2022**). Risks related to a possible reduction of the waiting period for dogs after rabies antibody titration to 30 days compared with 90 days of the current EU legislative regime**. *EFSA Journal. European Food Safety Authority*, *20*(6), e07350. https://doi.org/10.2903/j.efsa.2022.7350

Goddard, A. D., Donaldson, N. M., Horton, D. L., Kosmider, R., Kelly, L. A., Sayers, A. R., Breed, A. C., Freuling, C. M., Müller, T., Shaw, S. E., Hallgren, G., Fooks, A. R., & Snary, E. L. (2012). **A quantitative release assessment for the noncommercial movement of companion animals: Risk of rabies reintroduction to the United kingdom**. *Risk Analysis: An Official Publication of the Society for Risk Analysis*, *32*(10), 1769–1783. https://doi.org/10.1111/j.1539-6924.2012.01804.x

Great Britain. Ministry of Agriculture Fisheries and Food. (1971***). Report of the Committee of Inquiry on Rabies: Final report***. HMSO.

Hampson, K., Coudeville, L., Lembo, T., Sambo, M., Kieffer, A., Attlan, M., Barrat, J., Blanton, J. D., Briggs, D. J., Cleaveland, S., Costa, P., Freuling, C. M., Hiby, E., Knopf, L., Leanes, F., Meslin, F.-X., Metlin, A., Miranda, M. E., Müller, T., … Global Alliance for Rabies Control Partners for Rabies Prevention. (2015). **Estimating the global burden of endemic canine rabies**. *PLoS Neglected Tropical Diseases*, *9*(4), e0003709. https://doi.org/10.1371/journal.pntd.0003709

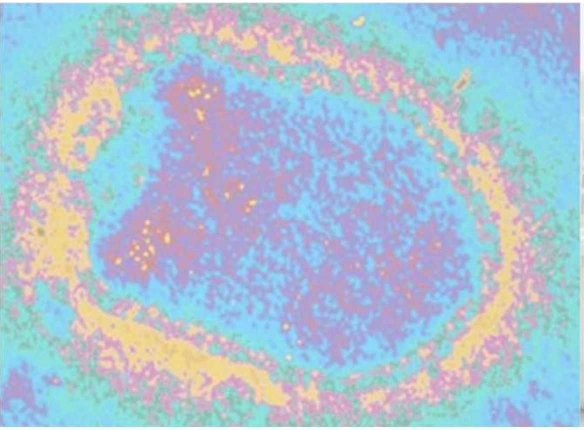
Kwan, N. C. L., Sugiura, K., Hosoi, Y., Yamada, A., & Snary, E. L. (2017). **Quantitative risk assessment of the introduction of rabies into Japan through the importation of dogs and cats worldwide**. *Epidemiology and Infection*, *145*(6), 1168–1182. https://doi.org/10.1017/S0950268816002995

Ribadeau-Dumas, F., Cliquet, F., Gautret, P., Robardet, E., Le Pen, C., & Bourhy, H. (2016). **Travel-Associated Rabies in Pets and Residual Rabies Risk, Western Europe**. *Emerging Infectious Diseases*, *22*(7), 1268–1271. https://doi.org/10.3201/eid2207.151733

Smith, T. G., Fooks, A. R., Moore, S. M., Freuling, C. M., Müller, T., Torres, G., & Wallace, R. M. (2021). Negligible risk of rabies importation in dogs thirty days after demonstration of adequate serum antibody titer. *Vaccine*. https://doi.org/10.1016/j.vaccine.2021.03.064

Tojinbara, K., Sugiura, K., Yamada, A., Kakitani, I., Kwan, N. C. L., & Sugiura, K. (2016). **Estimating the probability distribution of the incubation period for rabies using data from the 1948-1954 rabies epidemic in Tokyo**. *Preventive Veterinary Medicine*, *123*, 102–105. https://doi.org/10.1016/j.prevetmed.2015.11.018

Weng, H.-Y., Wu, P.-I., Yang, P.-C., Tsai, Y.-L., & Chang, C.-C. (2010). **A quantitative risk assessment model to evaluate effective border control measures for rabies prevention**. *Veterinary Research*, *41*(1), 11. https://doi.org/10.1051/vetres/2009059



Supplementary information

Material and methods

Model parameters

Probability of infection

For pet infected when selected for importation

$$P_i = I \times \frac{\text{mean}(Inc)}{365}$$

For pet becoming infected after vaccination and before immunity acquisition

$$P_{bibv} = 1 - (1 - \frac{I}{365})^{DI}$$

For pet becoming infected during the waiting time (when not protected by vaccination)

$$P_{biav} = 1 - (1 - \frac{I}{365})^{WT}$$

Inc: rabies incubation period
DI: delay between vaccination and protective immunity acquisition, only for dogs eliciting a sufficient antibody level (≥ 0.5 IU/mL)
WT: waiting time between dog selection and its importation in a rabies-free country
I: rabies annual incidence

Material and methods

Model parameters

Rabies incidence (annual)

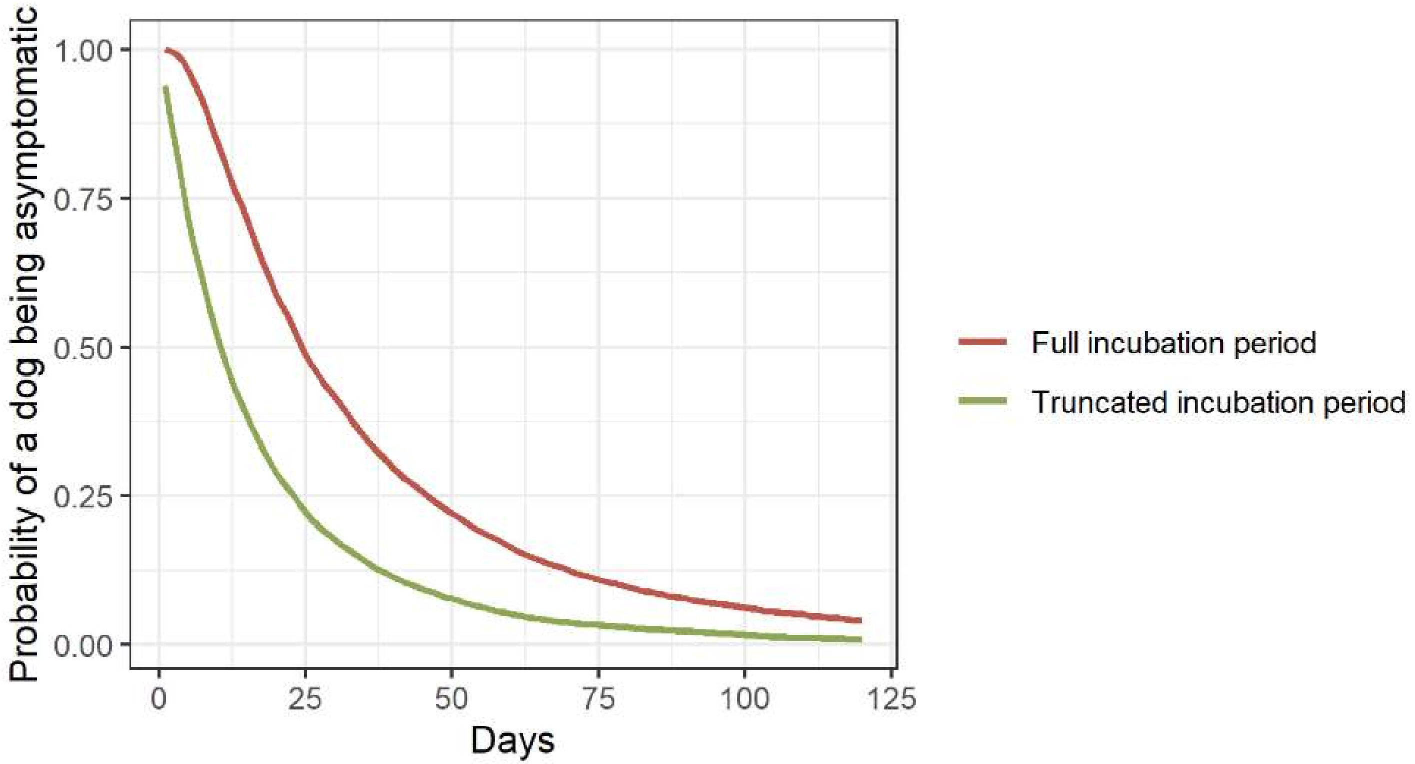
Area type	Annual incidence distribution	Annual incidence values
High risk (e.g. North Africa)	Gamma (shape: 5.56×10^{-1}; scale: mean = 6.09×10^{-3} $[5.03 \times 10^{-3}; 7.23 \times 10^{-3}]_{95\%PI}$)	mean = 3.36×10^{-3}; $[6.38 \times 10^{-6}; 1.67 \times 10^{-2}]_{95\%PI}$
Medium risk area (e.g. Caribbean)	Gamma (shape: 5.56×10^{-1} ; scale: mean = 2.18×10^{-3} $[1.55 \times 10^{-3}; 2.87 \times 10^{-3}]_{95\%PI}$)	mean = 1.20×10^{-3}; $[2.34 \times 10^{-6}; 5.80 \times 10^{-3}]_{95\%PI}$
Low risk area (e.g. Eastern Europe)	$\frac{\text{Annual rabies case number}}{\frac{\text{Human population of the area}}{\text{Human to dog ratio}}}$ With: Annual rabies case number = Gamma (shape: 5.23×10^{3}; scale: 2) Human population of the area = 2.25×10^{8} Human to dog ratio = Uniform (min.: 8.26; max.: 9.49)	mean = 4.22×10^{-4}; $[3.91\times 10^{-4}; 4.53 \times 10^{-4}]_{95\%PI}$

Crozet et al., 2020 (*Vet Sci)*

Material and methods

Model parameters

Probability of a dog being asymptomatic on a given day while infected by rabies virus



Material and methods

Risk estimation - « Classical » scenario tree modelling

Annual number of infected dog imported (*NRabies*)

$$R_1 = (1 - P_i) \times P_{bi} \times P_{vacc} \times Se \times P_{asymp}$$
$$R_2 = (1 - P_i) \times P_{bi} \times (1 - P_{vacc}) \times (1 - Sp) \times P_{asymp}$$
$$R_3 = P_i \times P_{vacc} \times Se \times P_{asymp}$$
$$R_4 = P_i \times (1 - P_{vacc}) \times (1 - Sp) \times P_{asymp}$$
$$R_5 = (1 - P_i) \times (1 - P_{bi}) \times (1 - P_{vacc}) \times (1 - Sp) \times P_{biav} \times P_{asymp}$$

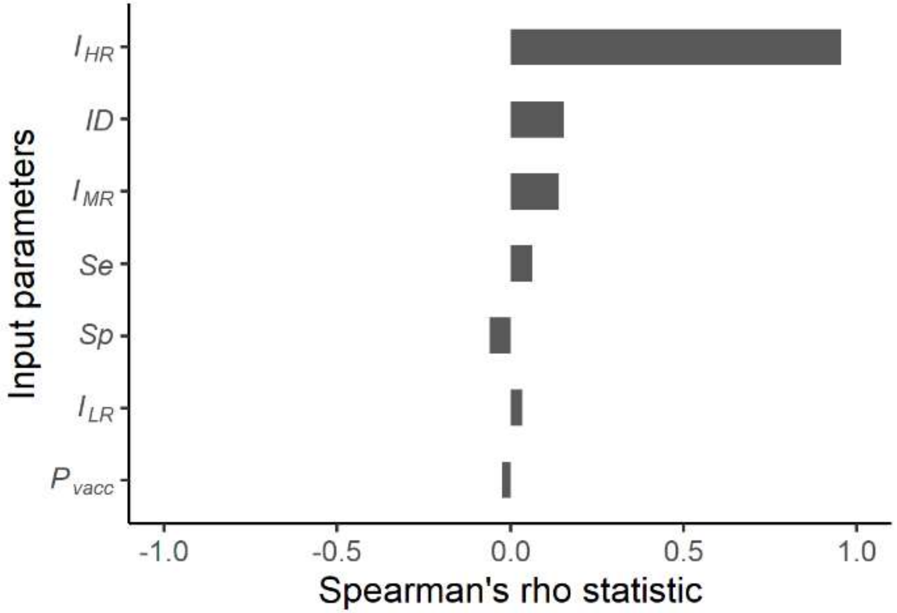
$$PRabies = \sum_{i \in [1;5]} R_i$$

$$NRabies = PRabies \times Nimp$$

Nimp: annual number of imported dogs

Material and methods

Sensitivity analysis - Model 1 (based on Spearman's rho statistic)



Material and methods

Sensitivity analysis - Model 2 (based on Sobol indices)