NECTM9 Northern European Conference on Travel Medicine Denmark Copenhagen May 22-24 2024

# Factors influencing the immunogenicity of rabies vaccines, evaluation of time effect over several decades

*A literature review and meta-regression*

**Authors:** Fernando Morelli[1], Christèle Augard[1], Laurent Coudeville[1], Catherine Bravo[1], Hervé Bourhy[2], Beatriz Quiambao[3], Sergio Recuenco[4], Susan Moore[5]

**Affiliations:** 1. Global Medical Department, Sanofi, Lyon, France; 2. Lyssavirus Epidemiology and Neuropathology Unit, Institut Pasteur, Paris, France; 3. Research Institute for Tropical Medicine, Research Drive, Filinvest Corporate City, Alabang, Muntinlupa City, Metro Manila, Philippines; 4. Facultad de Medicina San Fernando, Universidad Nacional Mayor de San Marcos, Lima, Peru; 5. Veterinary Medical Diagnostic Laboratory/One Health Laboratory, College of Veterinary Medicine, University of Missouri, Columbia, Missouri, USA

# Conflicts of Interest

Fernando Morelli, Christele Augard, Laurent Coudeville and Catherine Bravo are Sanofi employees and may hold share/stock options. Hervé Bourhy receives funding from Humabs BioMed SA on the project PCT/EP2014/003076;18/11/2014 “Antibodies that potentially neutralize rabies virus and other lyssaviruses and uses thereof”. Beatriz Quiambao, Sergio Recuenco, Susan Moore declare no conflict of interest.

Sanofi supported this work.

Rabies causes approximately **59,000 deaths** annually worldwide, with a significant under-reporting likely, affecting both individuals from endemic areas as well as **travellers**.

# Background

Rabies prevention has a long history of effective interventions, mainly due to vaccine access, either with **pre-exposure prophylaxis** (PrEP) or **post-exposure prophylaxis** (PEP). Currently, multiple rabies vaccines are available. They are based on similar viral strains, but prepared using different substrates, such as:

**Human Tissue Culture**
human diploid cell vaccine
(HDCV)

**Primate Tissue Culture**
purified Vero cell vaccine
(PVRV)

**Avian Tissue Culture**
purified chick embryo cell vaccine
(PCECV)

images: Flaticon.com

NECTM9

# NECTM9

Northern European
Conference on Travel Medicine
Denmark Copenhagen May 22-24 2024

NECTM

# Background

In a previous systematic literature search and corresponding meta-analysis on these three rabies vaccines (HDCV, PVRV, and PCECV), a trend of **higher Geometric Mean of Rabies Virus Neutralizing Antibody Titers** (GMT RVNA) was observed in studies conducted before the 2000s compared to more recent studies[1].

The objective of the current research was to assess the possible confounding factors related to these decreasing GMT in more recent studies, through a meta-analysis of RVNA, in healthy individuals, after 14 days or 28 following vaccination in a PEP schedule.

**images:** Flaticon.com

**Reference:** 1. Morelli F, Augard C, Bourhy H, Bravo C, Coudeville L, Moore S, Quiambao B, Recuenco S. Immunogenicity of rabies vaccines in postexposure prophylaxis (PEP) or simulated PEP regimens: a systematic literature review and meta-analysis. Presented at: the International Conference on Rabies in the Americas Meeting; 2022 Oct 23–28; Querétaro, Mexico.

# Methods

- This study is a literature review conducted in scientific databases (PubMed, Embase, the Cochrane Library) and internal Sanofi sources, searching publications using **HDCV**, Sanofi **PVRV**, or **PCECV**, presenting **RVNA GMT**, measured using Rapid Fluorescent Focus Inhibition Tests **(RFFIT),** from Jan 1985 to March 2023. Additional studies were also included using a snowballing strategy.

- **Meta-regressions** were conducted using the function 'metareg' in the package 'metafor'[2] in the statistical software environment R[3]. Briefly, this function fits a meta-analytic random-effects model using a linear model framework. The estimator for the amount of heterogeneity in the random-effect model was an empirical Bayes estimator ('method = EB').

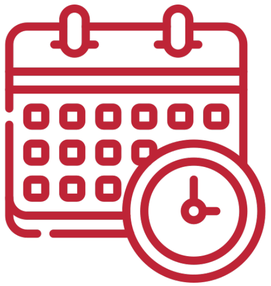
**image:** Generated with AI, powered by **DALL·E 3**

**Reference:** 2. Viechtbauer, W. (2010). Conducting Meta-Analyses in R with the metafor Package. Journal of Statistical Software, 36(3), 1–48. https://doi.org/10.18637/jss.v036.i03
3.R Core Team (2023). _R: A Language and Environment for Statistical Computing_. R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/

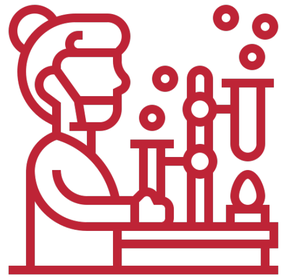
# Methods

The dependent variable for the model was the RVNA GMT. Considering previously known confounding factors for their estimates, **different models** were conducted using the following variables as covariates **separately** and **collectively**

**Vaccine type**

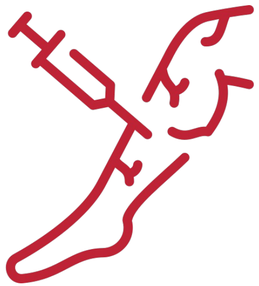


**Year of Titration**



**Laboratory**

**Administration Route**



**Coadministration of rabies immunoglobulin**

images: Flaticon.com

# Results

57 articles were selected representing 90 interventional groups and 5,701 subjects.

| | D14 | | | | D28 | | | |
|---|---|---|---|---|---|---|---|---|
| | **Estimate** | **Standard Error** | **Z-value** | **p-value** | **Estimate** | **Standard Error** | **Z-value** | **p-value** |
| **Model 1** | | | | | | | | |
| **Intercept** | 2.3348 | 0.4349 | 5.3684 | <0.0001 | 2.1706 | 0.4772 | 4.5489 | <0.0001 |
| **Vaccine Type** | -0.1177 | 0.1702 | -0.6913 | 0.4894 | 0.0279 | 0.1839 | 0.1517 | 0.8794 |
| **Model 2** | | | | | | | | |
| **Intercept** | 100.6862 | 17.0069 | 5.9203 | <0.0001 | 81.2657 | 19.5427 | 4.1584 | <0.0001 |
| **Year of Titration** | -0.0492 | 0.0085 | -5.8008 | <0.0001 | -0.0394 | 0.0097 | -4.0452 | <0.0001 |
| **Model 3** | | | | | | | | |
| **Intercept** | 1.3564 | 0.2837 | 4.7814 | <0.0001 | 1.7504 | 0.3316 | 5.2787 | <0.0001 |
| **Laboratory** | 0.0829 | 0.0315 | 26.290 | 0.0086 | 0.0549 | 0.0347 | 1.5843 | 0.1131 |
| **Model 4** | | | | | | | | |
| **Intercept** | 1.1093 | 0.4398 | 2.5222 | 0.0117 | 0.9913 | 0.4428 | 2.2388 | 0.0252 |
| **Administration Route** | 0.5456 | 0.2484 | 21.970 | 0.0280 | 0.7386 | 0.2552 | 2.8948 | 0.0038 |
| **Model 5** | | | | | | | | |
| **Intercept** | 2.3115 | 0.2795 | 8.2706 | <0.0001 | 2.4962 | 0.4031 | 6.1925 | <0.0001 |
| **Coadministration of rabies immunoglobulin** | -0.1227 | 0.1171 | -10.476 | 0.2948 | -0.1021 | 0.1517 | -0.6731 | 0.5009 |

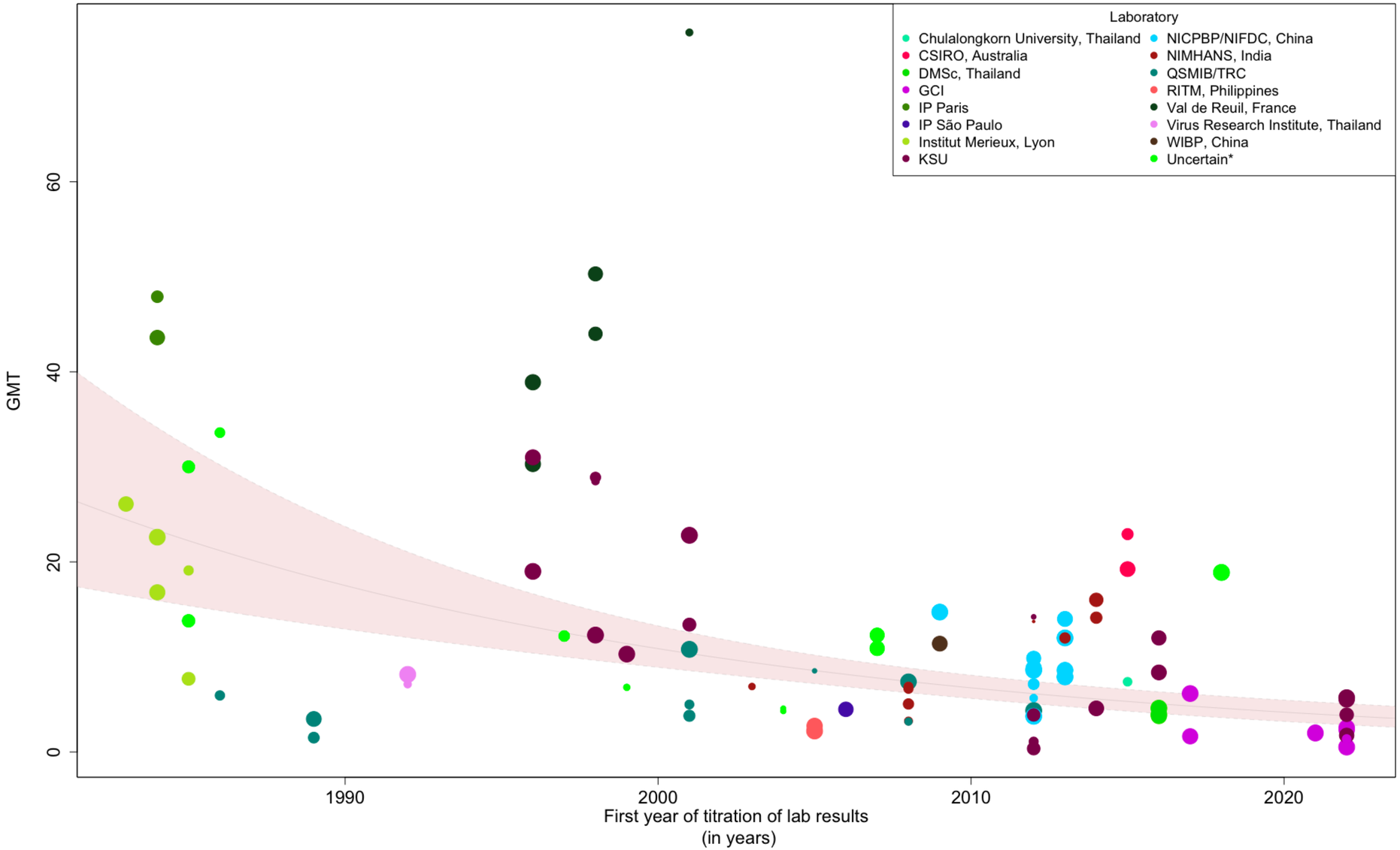
Table. Results of the meta-regressions models for the log of rabies virus neutralizing antibody titers, at 14 and 28 days after vaccination.

# Results

| | D14 | | | | D28 | | | |
|---|---|---|---|---|---|---|---|---|
| | **Estimate** | **Standard Error** | **Z-value** | **p-value** | **Estimate** | **Standard Error** | **Z-value** | **p-value** |
| **Model 6** | | | | | | | | |
| Intercept | 87.4562 | 18.7206 | 4.6716 | <0.0001 | 78.6412 | 23.4155 | 3.3585 | 0.0008 |
| Vaccine Type | -0.1932 | 0.1507 | -12.824 | 0.1997 | 0.0354 | 0.1571 | 0.2255 | 0.8216 |
| Year of Titration | -0.0427 | 0.0092 | -46.356 | <0.0001 | -0.0391 | 0.0116 | -3.3702 | 0.0008 |
| Laboratory | 0.0488 | 0.0290 | 16.843 | 0.0921 | 0.0237 | 0.0347 | 0.6825 | 0.4949 |
| Administration Route | 0.2381 | 0.2377 | 10.015 | 0.3166 | 0.7822 | 0.2402 | 3.2569 | 0.0011 |
| Coadministration of rabies immunoglobulin | -0.0604 | 0.0997 | -0.6062 | 0.5444 | 0.1845 | 0.1386 | 1.3312 | 0.1831 |

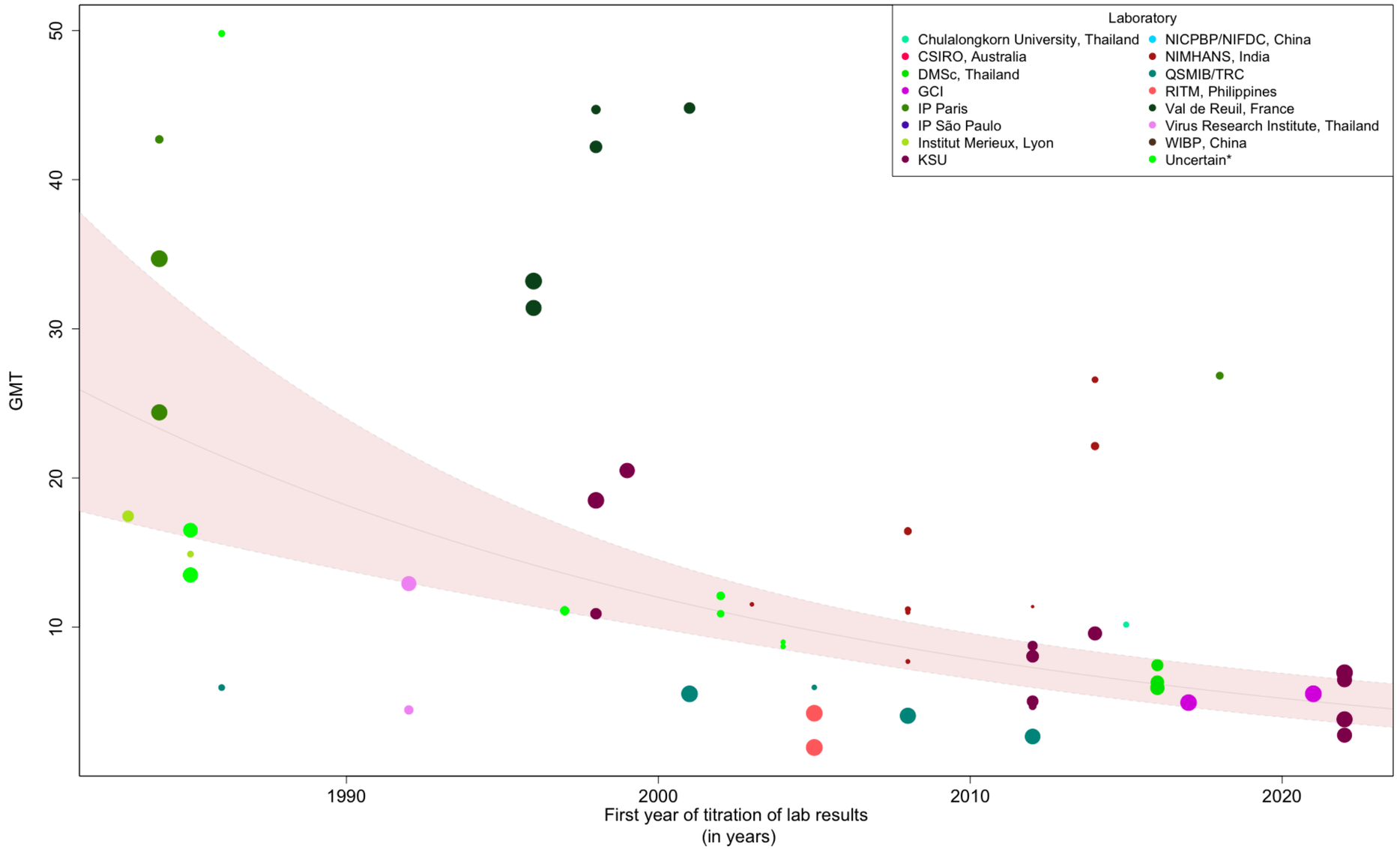
Table. Results of the meta-regressions models for the log of rabies virus neutralizing antibody titers, at 14 and 28 days after vaccination.

Meta-regression estimates for the GMT of RVNA and year of titration, at 14 days after vaccination. Each laboratory is represented by a specific color.



# NECTM9

Northern European
Conference on Travel Medicine
Denmark Copenhagen May 22-24 2024




Meta-regression estimates for the GMT of RVNA and year of titration, at 28 days after vaccination. Each laboratory is represented by a specific color.

# Conclusions

Some of the **limitations** of our study include the fact that incomplete reports or missing data were addressed through mean imputations of missing values according to routes and regimens. Also, **laboratories comparability** may be challenging due to the low number of institutions providing results throughout several years.

- The RVNA GMT results varied when conducted across **different laboratories**, suggesting a potential influence on the results. However, this does not reach statistical significance when controlled for year of titration

- There is a direct correlation between the **year of titration** and the **RVNA GMT**, with the GMT progressively decreasing in more recent years.

# Thank you!