



# *VICI*: a Shiny app for accurate estimation of Vaccine Induced Cellular Immunogenicity with bivariate modeling

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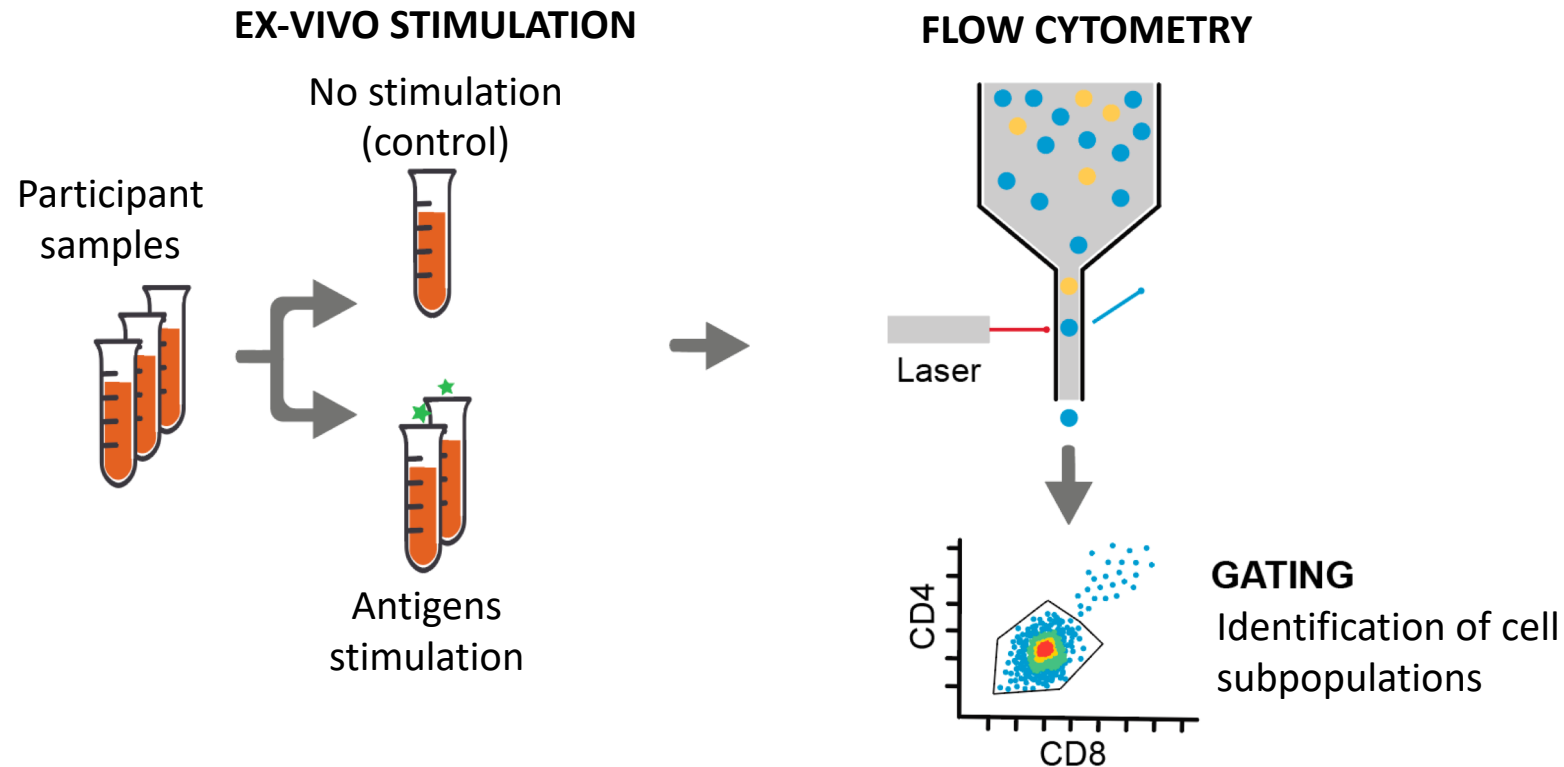
4 Pôle de Santé Publique, CHU de Bordeaux, Bordeaux, F-33000 France

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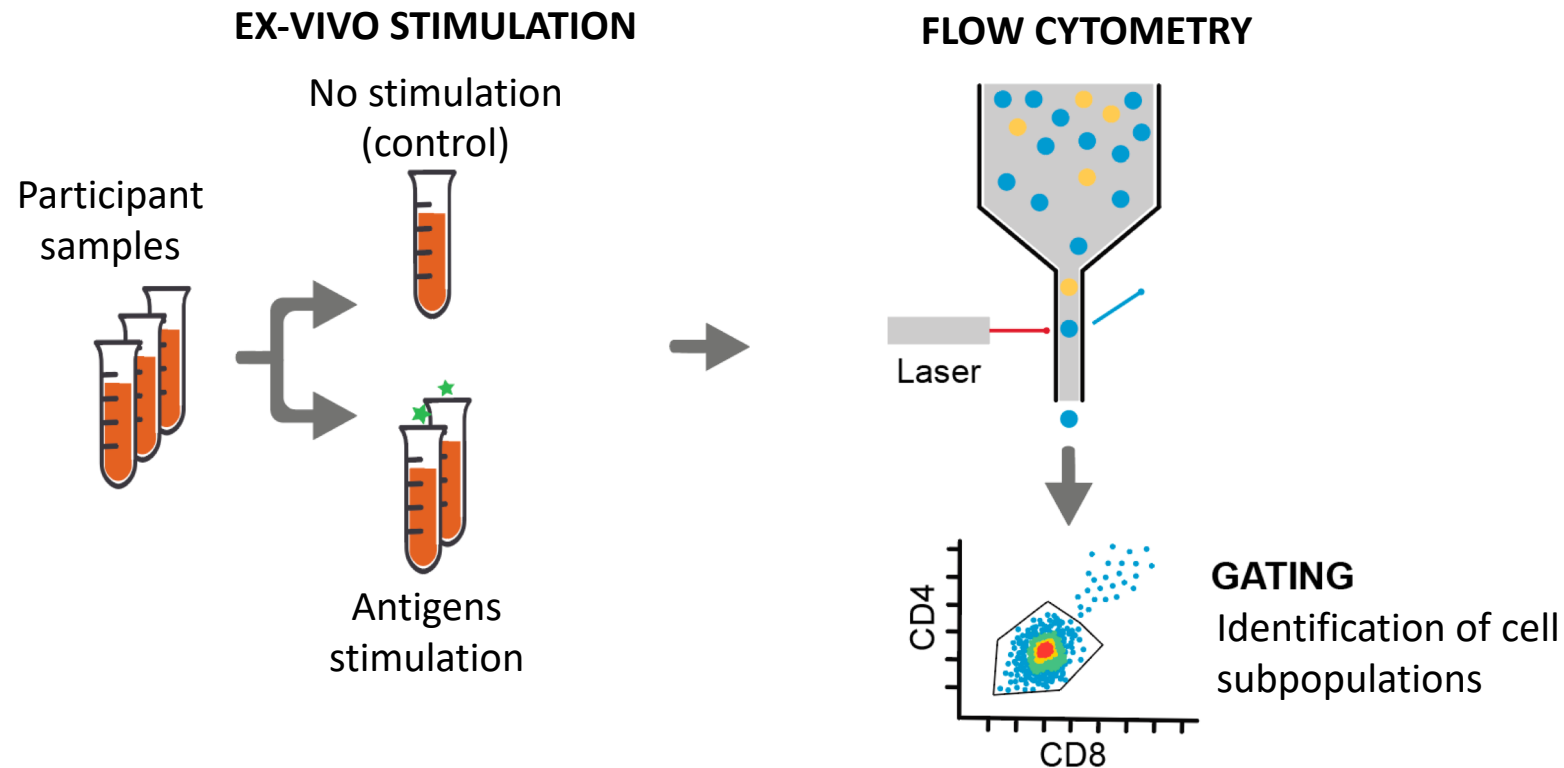
# Context: clinical vaccine development

- **Immunogenicity evaluation:** key step in phase 1 & 2 clinical trials
  - many immunological markers are measured at once, (in particular in the absence of protective correlates — such as in HIV vaccine trials)
  - Cellular response is evaluated with *intracellular cytokine staining* (ICS)



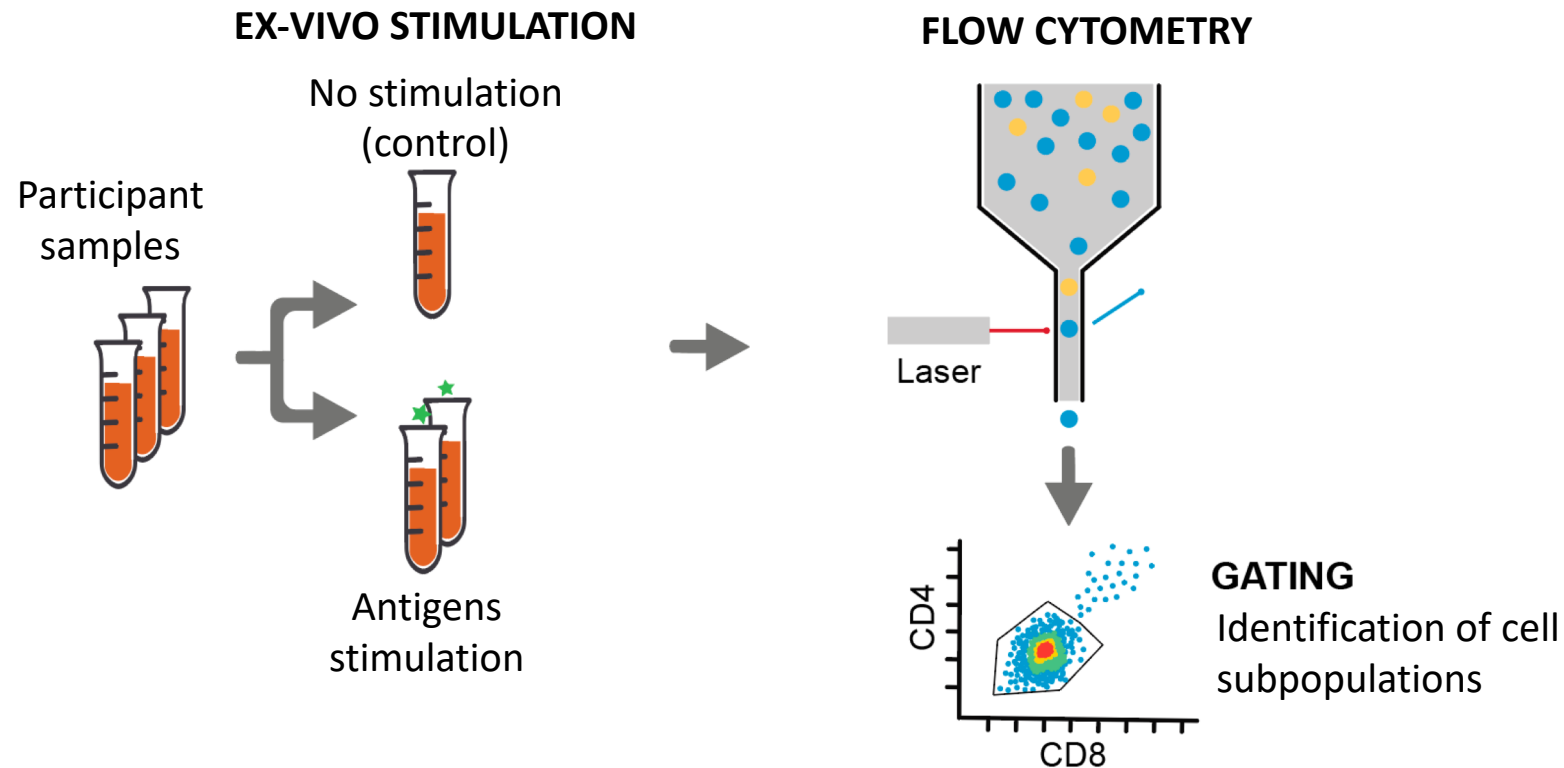
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# Conventional statistical analysis of ICS data

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- Comparing cytokine producing cell proportions between vaccine arms ***after subtracting the non-stimulated response*** (control) in each sample
- **Rational:** subtraction aims for the antigen specific response
- **Issues:** type-I error increase, bias, low statistical power

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NEED FOR A BETTER STATISTICAL APPROACH

# Bivariate linear modeling

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- **Dependent variables:**  $Y_i^{NS}$  the non-stimulated response &  $Y_i^S$  the specific stimulated response(s)

$$\begin{cases} Y_i^{NS} = \beta_0^{NS} + \beta_1^{NS} V_i + \varepsilon_i^{NS} \\ Y_i^S = \beta_0^S + \beta_1^S V_i + \beta_2^S Y_i^{NS} + \varepsilon_i^S \end{cases}$$

- where

- $V_i$  is the vaccine arm (eg vaccine vs placebo)
- $Y_i^{NS} \sim N(\beta_0^{NS} + \beta_1^{NS} V_i, \sigma^{NS})$  and  $\varepsilon_i^{NS} \sim N(0, \sigma^{NS})$
- $Y_i^S \sim N(\beta_0^S + \beta_1^S V_i + \beta_2^S Y_i^{NS}, \sigma^S)$  and  $\varepsilon_i^S \sim N(0, \sigma^S)$

- Estimates

- $\beta_1^S$ : vaccine effect on the stimulated response
- $\beta_1^{NS}$ : vaccine effect on the non stimulated response
- $\beta_2^S$ : non stimulated response effect on the stimulated response

# Bivariate linear modeling

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## code

```
proc mixed data = DATATABLE;  
  
class ID_PATIENT STIMULATION ;  
  
model Y = STIMULATION STIMULATION*VACCINE STIMULATION* Y_NS / cl noint ;  
  
repeated /type=VC grp=STIMULATION sub=ID_PATIENT ;  
  
run ;
```

## code


```
mgls <- nlme::gls(myformul,  
                 data = transformed_data,  
                 weights = nlme::varIdent(value = c("1" = 1), form = ~ 1 | stim),  
                 method="REML"  
)
```




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$$\begin{cases} Y_i^{NS} = \beta_0^{NS} + \beta_1^{NS} V_i + \varepsilon_i^{NS} \\ Y_i^S = \beta_0^S + \beta_1^S V_i + \beta_2^S Y_i^{NS} + \varepsilon_i^S \end{cases}$$

 **for statisticians**

 **for immunologists**

• where

- $V_i$  is the vaccine amount (eg vaccine dose)
- $Y_i^{NS} \sim N(\beta_0^{NS} + \beta_1^{NS} V_i, \sigma^{NS})$
- $Y_i^S \sim N(\beta_0^S + \beta_1^S V_i + \beta_2^S Y_i^{NS}, \sigma^S)$

• Estimates

- $\beta_1^S$ : vaccine effect on the stimulated response
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```
code
proc mixed data=...;
  class STIMULATION;
  model Y_NS = _INTERCEPT_ + VACCINE STIMULATION* Y_NS / cl noint;
  vc grp=STIMULATION sub=ID_PATIENT;
run;
```

```
R code
mgls <- nlme::gls(myformul,
  data = transformed_data,
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```

# VICI: shiny user interface

<https://shiny-vici.apps.math.cnrs.fr>

VICI: accurate estimation of Vaccine Induced Cellular Immunogenicity with bivariate modeling

**Data input**

Choose a CSV/TXT file to import

Browse... No file selected

Header

**Separator**

Comma

Semicolon

Tab

**Input parameters**

**Model choice**

inter-arm

**Variable specification**

**Select the column that identifies the subject ID**

Please select a column name below

**Select the column that identifies the ICS response**

Please select a column name below

**Select the column that identifies the stimulation**

Please select a column name below

**Select the column that identifies the arm**

Please select a column name below

**Run analysis**

Fit model

Results Data view Additional Information

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### Data input

Choose a CSV/TXT file to import

Browse... Light\_ICSDataW28.txt

Upload complete

Header

**Separator**

Comma

Semicolon

Tab

### Input parameters

**Model choice**

inter-arm

**Variable specification**

Select the column that identifies the subject ID

USUBJID

Select the column that identifies the ICS response

ptot\_IFN\_CD4

Select the column that identifies the stimulation

POOL

Select the value that identifies background samples

NS

GAG

NEF

NS

POL\_ENV

### Run analysis

Fit model

Results Data view Additional Information

Show 10 entries

Search:

	USUBJID	VISITNUM	POOL	ptot_IFN_CD4	ptot_IL2_CD4	ptot_TNF_CD4	ptot_IFN_CD8	ptot_IL2_CD8	ptot_TNF_CD8	ARM
1	10001	06	NS	0.00000	0.00017	0.100	0.0100	0.00000	0.0000	Groupe Placebo
2	10001	06	NS	0.00000	0.100	0.000	0.0000	0.100	0.0000	Groupe Placebo
3	10001	06	POL_2000	0.0000	0.0000	0.000	0.0100	0.0000	0.0000	Groupe Placebo
4	10001	06	NS	0.0100	0.0000	0.011	0.0000	0.0000	0.0000	Groupe Placebo
5	10000	06	NS	0.0000	0.0000	0.100	0.0000	0.0100	0.0000	Groupe Placebo
6	10000	06	NS	0.000	0.000	0.001	0.110	0.0000	0.100	Groupe Placebo
7	10000	06	POL_2000	0.0001	0.0100	0.000	0.000	0.0000	0.100	Groupe Placebo
8	10000	06	NS	0.000	0.000	0.000	0.0000	0.0001	0.0000	Groupe Placebo
9	10000	06	NS	0.0100	0.0100	0.0000	0.0000	0.0100	0.0000	Groupe Vaccina
10	10000	06	NS	0.0017	0.0000	0.100	0.111	0.0000	0.0000	Groupe Vaccina

Showing 1 to 10 of 356 entries

Previous 1 2 3 4 5 ... 36 Next

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### Data input

Choose a CSV/TXT file to import

Browse... Light\_ICSdataW28.txt Upload complete

Header

### Separator

Comma  
 Semicolon  
 Tab

### Input parameters

Model choice: inter-arm

### Variable specification

Select the column that identifies the subject ID: USUBJID

Select the column that identifies the ICS response: ptot\_IFN\_CD4

Select the column that identifies the stimulation: POOL

Select the value that identifies background samples: NS

Select the column that identifies the arm: ARM

Select the value that identifies the reference arm: Groupe Placebo

### Run analysis

[Fit model](#)



### Numerical results

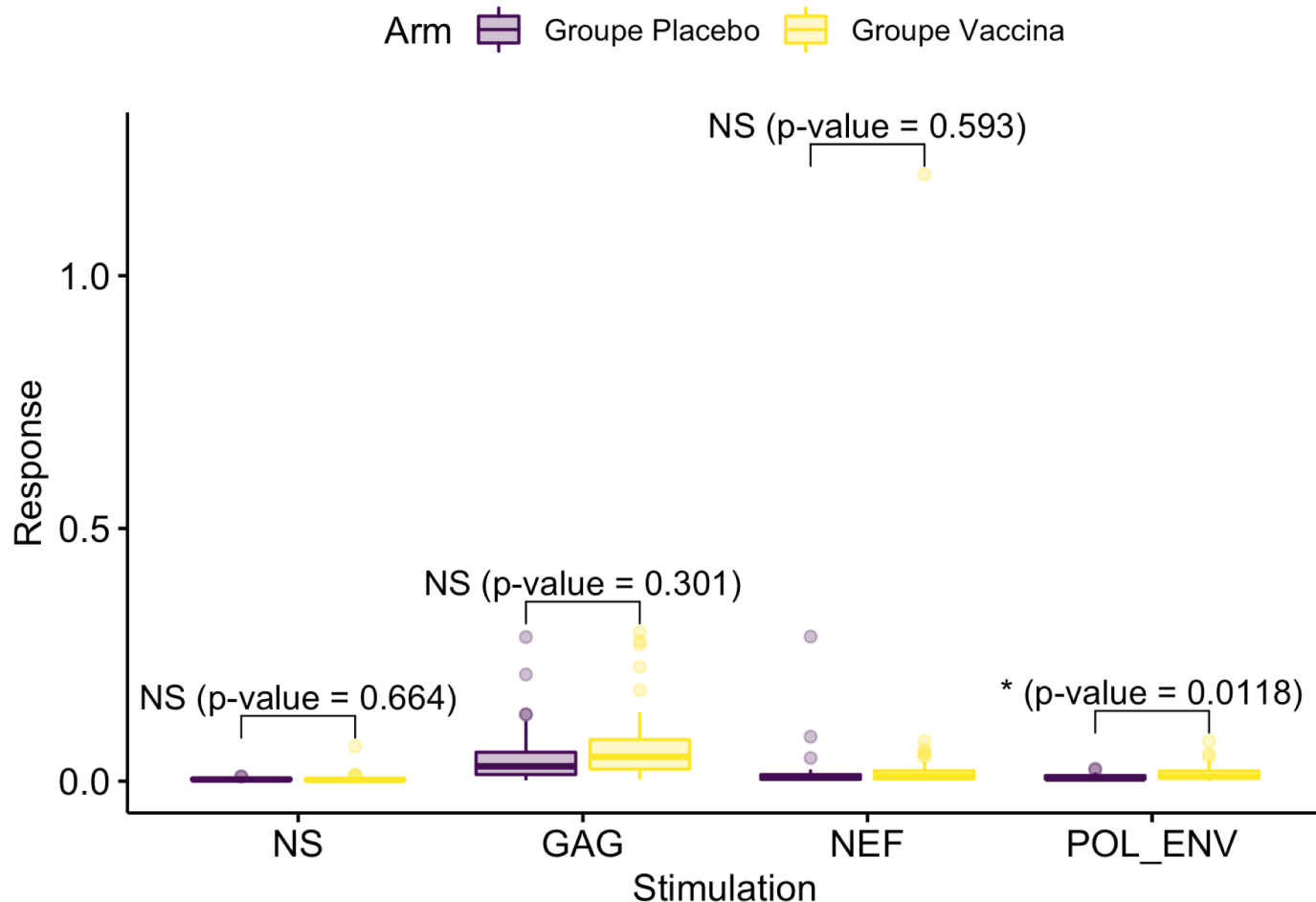
	Estimate	Standard error	p-value
Average response in reference stimulation NS in reference arm Groupe Placebo	0.00375	0.00132	0.00479
Average response in stimulation GAG in reference arm Groupe Placebo	0.04784	0.01221	0.00011
Average response in stimulation NEF in reference arm Groupe Placebo	0.01967	0.02420	0.41693
Average response in stimulation POL_ENV in reference arm Groupe Placebo	0.00655	0.00227	0.00420
Effect of reference stimulation NS on response in stimulation GAG	0.82730	0.94901	0.38395
Effect of reference stimulation NS on response in stimulation NEF	0.20906	1.88061	0.91155
Effect of reference stimulation NS on response in stimulation POL_ENV	0.28485	0.17654	0.10756
Effect of arm Groupe Vaccina on response in reference stimulation NS	0.00072	0.00165	0.66449
Effect of arm Groupe Vaccina on response in stimulation GAG	0.01513	0.01462	0.30146
Effect of arm Groupe Vaccina on response in stimulation NEF	0.01549	0.02896	0.59311
Effect of arm Groupe Vaccina on response in stimulation POL_ENV	0.00689	0.00272	0.01176

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## Arm effect on ICS response

taking into account background response levels



made with VICI

## Dependencies:

- *DT*
- *ggplot2*
- *ggpubr*
- *magrittr*
- *nlme*
- *shiny*

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Select the value that identifies background samples

NS

Select the column that identifies the arm

ARM

Select the value that identifies the reference arm

Groupe Placebo

**Run analysis**

Fit model

Results Data view Additional Information

Statistical model:

$$y_i^{NS} = \beta_0^{NS} + \beta_{GroupeVaccina}^{NS} GroupeVaccina_i + \varepsilon_i^{NS}$$
$$y_i^{GAG} = \beta_0^{GAG} + \beta_{GroupeVaccina}^{GAG} GroupeVaccina_i + \beta_{NS}^{GAG} y_i^{NS} + \varepsilon_i^{GAG}$$
$$y_i^{NEF} = \beta_0^{NEF} + \beta_{GroupeVaccina}^{NEF} GroupeVaccina_i + \beta_{NS}^{NEF} y_i^{NS} + \varepsilon_i^{NEF}$$
$$y_i^{POL_{e}NV} = \beta_0^{POL_{e}NV} + \beta_{GroupeVaccina}^{POL_{e}NV} GroupeVaccina_i + \beta_{NS}^{POL_{e}NV} y_i^{NS} + \varepsilon_i^{POL_{e}NV}$$

Number of estimated model parameters: 15

AIC	-2 Res. loglikelihood
-1402.4379	-1432.4379

	NS	GAG	NEF	POL_ENV
Variance	0.004369	0.017156	0.000056	0.000151

# Conclusion

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- **Bivariate modeling**

- Better statistical performances than conventional approach

- **Shiny app deployed**

<https://shiny-vici.apps.math.cnrs.fr>

- **R package *vici* available**

- GitHub <https://github.com/borishejblum/vici>
- Soon on CRAN

- **User community:**

- VRI Immunologists
- Wider community