Prediction of human results based on trials from rat models in the field of vaccines

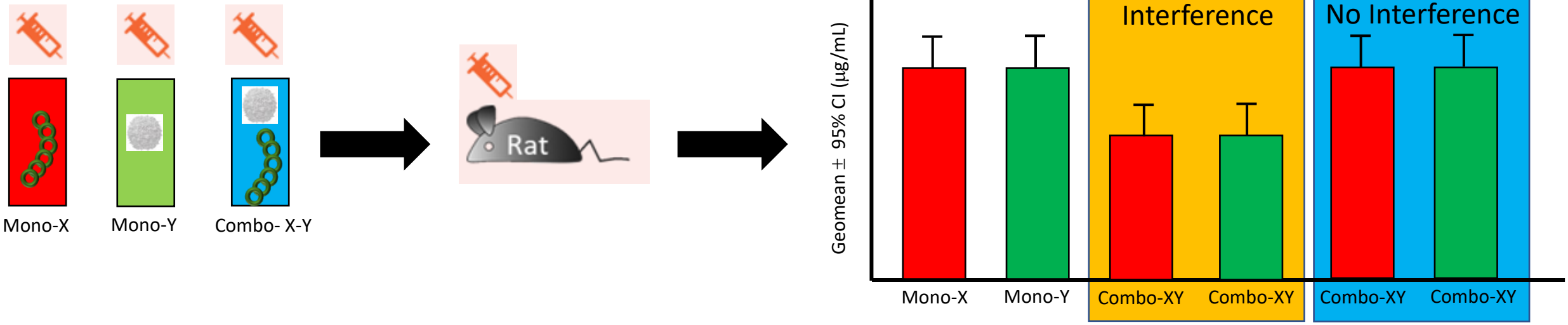
Callegaro - D2 - 20m

The data and the challenge - interference

Vaccines with antigens

Vaccination

Impact of Vaccination



Concept of translational statistics

Rat model developed and optimized (1)

Animal model validated

New candidates tested with
Control groups (2)

Improved formulations

Translational stat modelling
Prediction of results in human (3)

Prediction (GO/NO GO in human)

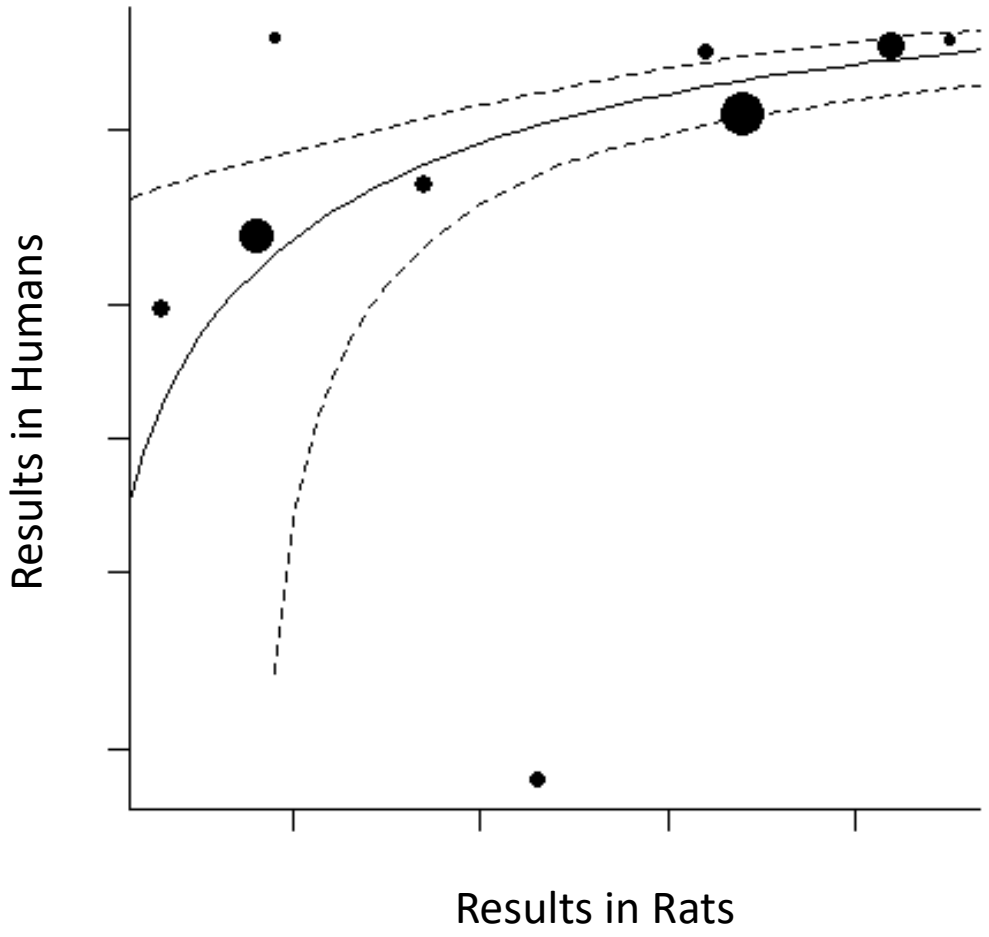
Predict human interference from animal results - model

- **AIM**: predict human immunological results from animal immunological results
- IDEAL DATA: data available in different conditions (such as different doses), where we fit meta-analytical approaches (see figure).

- ***Anti-X interference: multiple*** **data-sets but in only one condition.**
  - **Only one parameter can be estimated: we will consider the multiplicative model**

$$log(GMR_h) = \delta + log(GMR_a)$$

  - **extensions of the model including elicited parameters (e.g. slope) can be considered in the future.**



Model: meta-analysis on treatment effect

Let's model the observed log10GMRs (treatment effect) of the i-th study $Y_{k,i}$ (i=1,…, N_k) on species k (k =*h*uman; k =*r*at), using a random effect meta-analysis (hierarchical) model

$$Y_{ki} \sim N\left(\theta_{ki}, s_{ki}^2\right)$$

where

$$\theta_{ki} \sim N\left(\theta_k, \tau_k^2\right)$$

and τ_k^2 represents the between-trial variability.

It follows that $D_i = Y_{hi} - Y_{ri} \sim N\left(\delta_i, s_{hi}^2 + s_{ri}^2\right)$ where $\delta_i \sim N(\delta, \tau^2)$ with $\delta = \theta_h - \theta_r$ and $\tau^2 = \tau_h^2 + \tau_r^2$.

Prediction of human results based on new rat results

A rat study has been conducted using a new formulation of the vaccine $Y_{r,new} \sim N\left(\theta_{r,new}, s^2_{r,new}\right)$. Our aim is to predict the corresponding results in humans using the following model

$$E(Y_{h,new}) = \delta + E(Y_{r,new})$$

The parameter δ is estimated on historical data using a Meta-Analytic-Predictive (MAP) approach

$$\hat{\delta}_{MAP} \sim N\left(\hat{\theta}_h - \hat{\theta}_r, Var\left(\hat{\theta}_h\right) + Var\left(\hat{\theta}_r\right) + \tau_h^2 + \tau_r^2\right)$$

which is the difference of the MAP parameters estimated in humans and in rats.

Prediction of human results based on new rat results

The predictive distribution of human results in the new condition is given by

$$\hat{\theta}_{h,new} \sim N\left(\hat{\delta}_{MAP} + \hat{\theta}_{r,new}, Var\left(\hat{\delta}_{MAP}\right) + s^2_{h,new} + s^2_{r,new}\right)$$

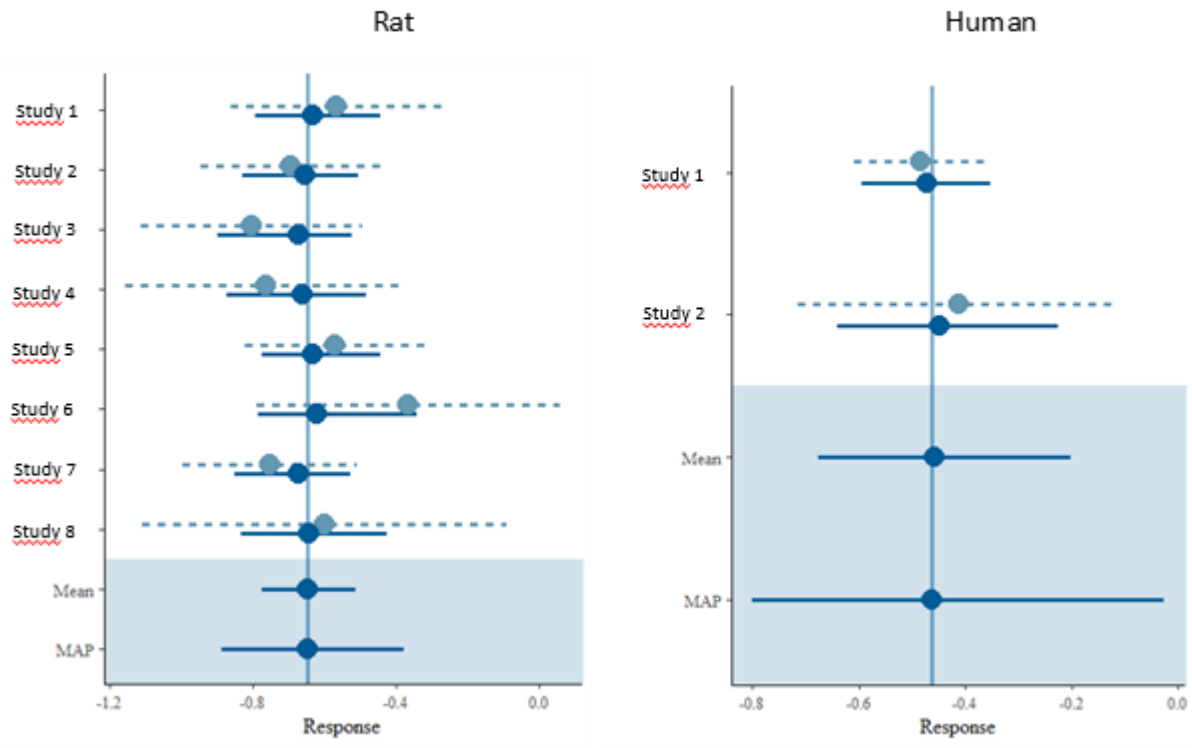
where and $s^2_{h,new} = \frac{2\sigma^2_h}{N_{h,new}}$ and $\hat{\theta}_{r,new} = Y_{r,new}$ (non-informative prior of the new formulation).

With this distribution we can compute the ***Probability of Success*** **(PoS)** (Spiegelhalteret al.1986, O'Hagan et al. 2005) of the new formulation in the human study

$$PoS = \int \Pr\left(R \middle| \theta_{h,new}\right) \Pr(\theta_{h,new}) d\theta_{h,new}$$

which is an average of the Power $\Pr\left(R \middle| \theta_{h,new}\right)$ over the predictive distribution.

Interference results



	$\hat{\theta}_k$	$\sqrt{var(\hat{\theta}_k) + \tau_k^2}$	τ_k
Rat	-0.644	0.122	0.079
Human	-0.452	0.183	0.105

$\hat{\delta}$	$\sqrt{var(\hat{\delta})}$
0.192	0.2199

Prediction of human GMR from rat log10(GMR)

$Y_{a,new}$	$\widehat{GMR}_h^{pred}$	LL	UL	PoS $Pr(\widehat{GMR}_h^{pred} > 0.8)$
-0.66	0.34	0.09	1.28	0.10
…	…	…	…	…
-0.05	1.40	0.38	5.22	0.80

Conclusions

The ideal setting to predict human results based on animal data is where historical data (humans and animals) is available in multiple conditions (e.g. different doses).

In our real case study (interference), the historical data was available in only one condition, so we used a simplistic model $\left(log(GMR_h) = \delta + log(GMR_a)\right)$

- not a problem if the assumptions are explicit; Mathematical (mechanistic) models should play a key role in the future

The proposed model can be extended in different ways, for example

- Bivariate meta-analysis (Houwelingen et al. 2002) by treatment group
- The parameter $\hat{\theta}_{r,new}$ could be dynamically combined with historical data using *Bayesian Dynamic Borrowing* (see for example Schmidli et al, 2014).

The proposed approach allowed us to compute the Probability of Succsess (PoS) of a hypothetical human study using a new formulation evaluated in rats.

References

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- Schmidli, H., Gsteiger, S., Roychoudhury, S., O'Hagan, A., Spiegelhalter, D., & Neuenschwander, B. (2014). Robust meta-analytic-predictive priors in clinical trials with historical control information. *Biometrics*, 70(4), 1023−1032
- Spiegelhalter D, Reedman L, Blackburn P. Monitoring clinical trials: conditional power or predictive power? *Control Clin Trials*. 1986;7(1):8-17.
- Van Houwelingen, H. C., Arends, L. R., & Stijnen, T. (2002). Advanced methods in meta-analysis: multivariate approach and meta-regression. *Statistics in medicine*, 21(4), 589-624.

Andrea Callegaro is an employee of and holds shares in the GSK group of companies.
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