

# INFLUENZA VACCINE EFFICACY TRIALS: A SIMULATION APPROACH TO UNDERSTAND FAILURES FROM THE PAST

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# Seasonal influenza and vaccine

Seasonal

Infectious disease

5% of the population (yearly)

Severe complications

Multi-strains disease

Spatial and temporal heterogeneity



**FAILURE OF  
RECENT VE TRIALS**

Vaccine

Immunogenicity response

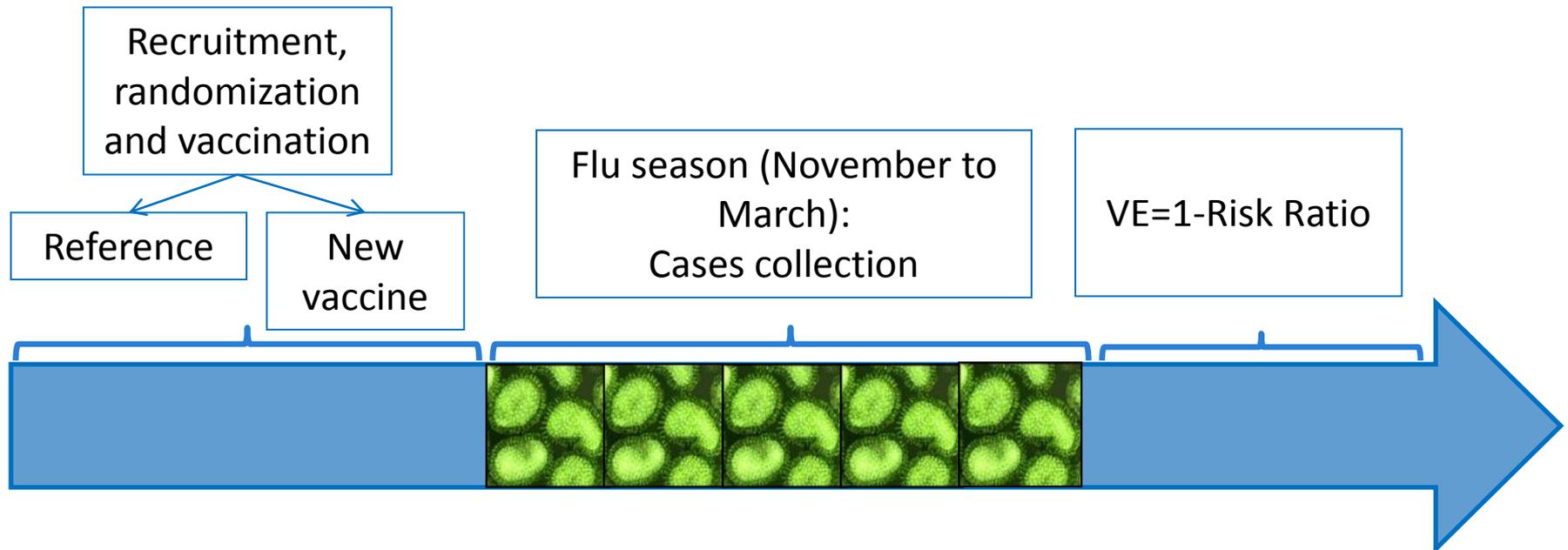
Decreased risk of getting infected

Updated yearly

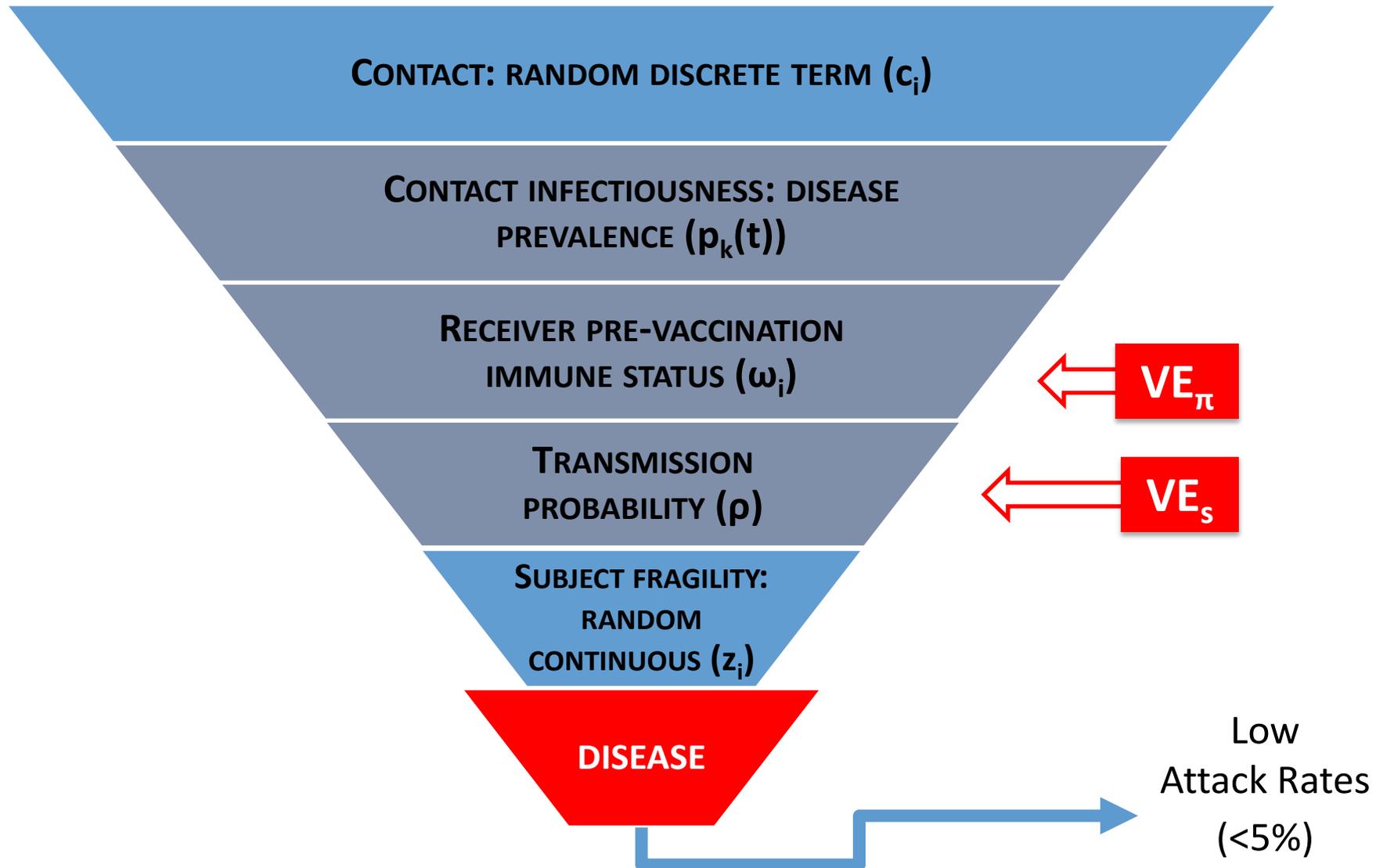
Clinical trials  
Immunogenicity (yearly)  
Efficacy (once)

# Seasonal influenza vaccine development

- Phase I: safety
- Phase II: immunogenicity
- **Phase III: efficacy**



# Data generation model



# Data generation model

$$\begin{cases} S_{0,i}(t) = \exp \left( - (1 - \omega_i) \left( z_i c_i \rho \sum_k \left( \int_0^t p_k(u) du \right) \right) \right) \\ S_{1,i}(t) = \exp \left( - (1 - \omega_i) \left( (1 - \boxed{VE_s}) z_i c_i \rho \sum_k \left( \int_0^t p_k(u) du \right) \right) \right) \end{cases}$$

Leaky

$$i = 1, \dots, n_g \text{ with } g = 0, 1$$

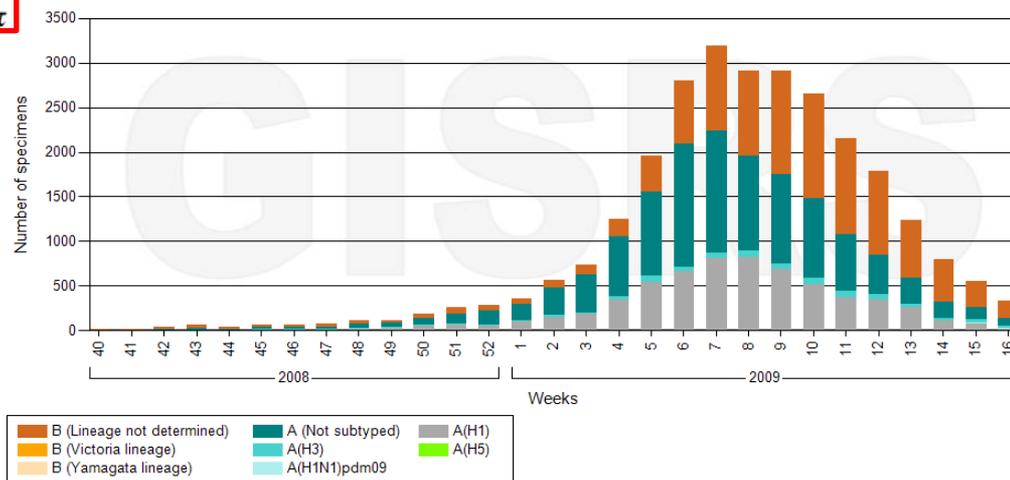
$$t = 1, \dots, T$$

$$k = 1, \dots, K$$

$$\omega_i \sim \text{Bernoulli}(\pi_g) \text{ with } \pi_1 = \pi_0 + \boxed{VE_\pi}$$

All-or-none

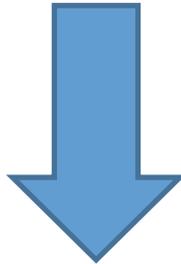
Number of specimens positive for influenza by subtype



# Influenza 65 trial

## Hypotheses:

- **Relative VE of 30%**
- **Cross-protection**
- Expected AR of 2%



## Primary objective:

- Relative **VE > 0** (Cox regression model)



# Simulations: setting and parameterization

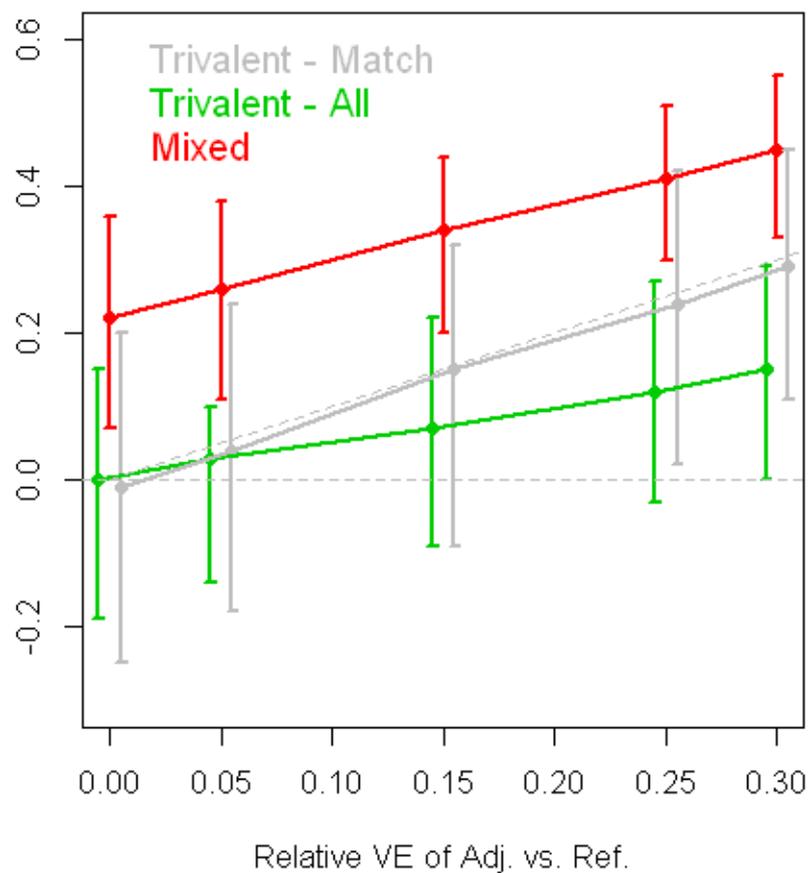
- 500 trials simulated for each scenario
- Contact rates based on country and age category (from Mossong & al. 2008)
- Fragility levels: gamma distribution parameterized based on immunogenicity data
- Transmission probability based on the literature (0.01)
- All susceptible or 20% naturally immune
- Relative VE from 0 to 30%
  
- Prevalence data from FluNet (same countries as original trial)
- 3 vaccine strains as in the original trial

# Simulations: VE scenarios

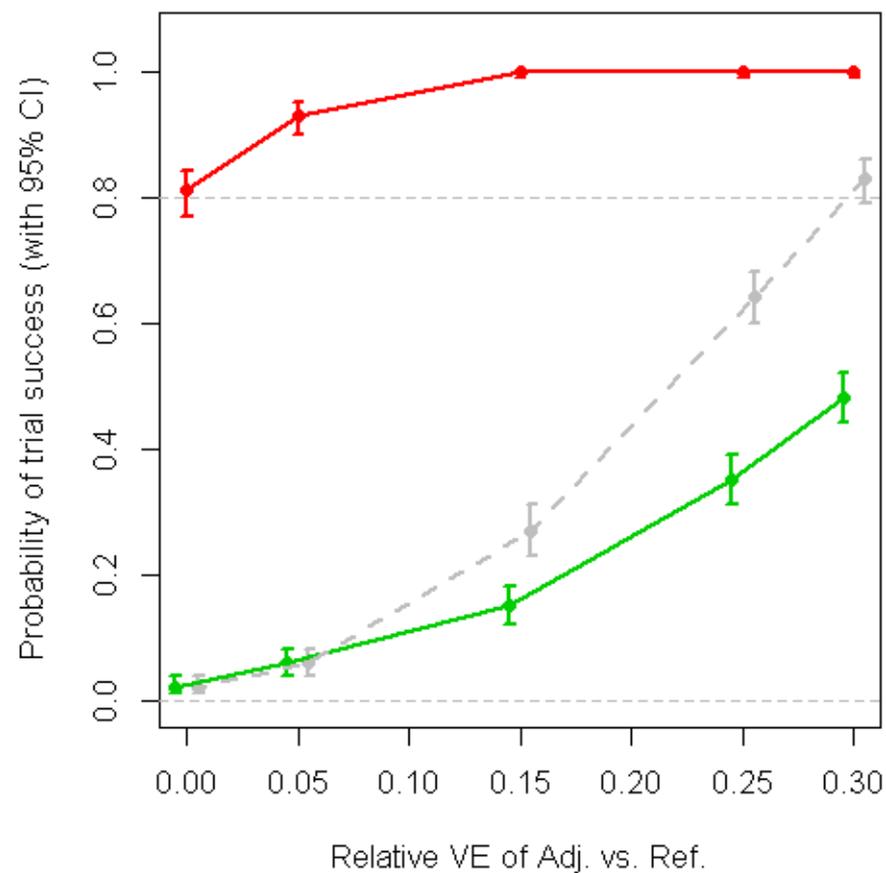
Scenario	Cross-protection	Cases considered for the computation of VE
Trivalent – matching cases	No	<b>Matching</b> vaccines strains
Trivalent – all cases	No	All cases
Mixed	Yes	All cases

# Results

## Median estimated relative VE



## Probability of trial success



# Discussion and conclusions

- Small departures from protocol hypotheses can rapidly lead to smaller probabilities of success
- Strains matching is crucial → quadrivalent vaccines
- Sensitivity analyses should be performed when designing efficacy trials in the context of heterogeneous diseases
- Historical data are freely available and under-used
- Our model is flexible and powerful tool to help design a trial

# References

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