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

Vaccine
Immunogenicity response
Decreased risk of getting infected
Updated yearly
Clinical trials Immunogenicity (yearly)
Efficacy (once)

FAILURE OF RECENT VE TRIALS
Seasonal influenza vaccine development

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

Recruitment, randomization and vaccination

Reference

New vaccine

Flu season (November to March): Cases collection

VE=1-Risk Ratio

16/09/2015 Flu season (November to March): Cases collection
Data generation model

- Contact: Random Discrete Term ($c_i$)
- Contact Infectiousness: Disease Prevalence ($p_k(t)$)
- Receiver Pre-vaccination Immune Status ($\omega_i$)
- Transmission Probability ($\rho$)
- Subject Fragility: Random Continuous ($z_i$)

Disease

Low Attack Rates (<5%)
Data generation model

\[

case 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) \\
case 1, i(t) = \exp \left( - (1 - \omega_i) \left( 1 - \frac{VE_0}{VE} \right) z_i c_i \rho \sum_k \left( \int_0^t p_k(u) \, du \right) \right)
\]

i = 1, ..., n_g with g = 0, 1

\[ t = 1, ..., T \]

\[ k = 1, ..., K \]

\[ \omega_i \sim \text{Bernoulli}(\pi_g) \text{ with } \pi_1 = \pi_0 + \frac{VE}{\pi} \]

Number of specimens positive for influenza by subtype

- **Leaky**
- **All-or-none**
Influence 65 trial

Hypotheses:

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

Primary objective:

- Relative VE > 0 (Cox regression model)

B strain missmatch
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

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Cross-protection</th>
<th>Cases considered for the computation of VE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trivalent – matching cases</td>
<td>No</td>
<td>Matching vaccines strains</td>
</tr>
<tr>
<td>Trivalent – all cases</td>
<td>No</td>
<td>All cases</td>
</tr>
<tr>
<td>Mixed</td>
<td>Yes</td>
<td>All cases</td>
</tr>
</tbody>
</table>
Results

Median estimated relative VE

Probability of trial success

Trivalent - Match
Trivalent - All
Mixed
Discussion and conclusions

• Small departures from protocol hypotheses can rapidly lead to smaller probabilities of success

• Strains matching is crucial $\rightarrow$ 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


