Investigating Waning of Influenza Vaccine Induced Immunity with a Multi-Scale Modeling Approach
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Summary
Vaccination is the best way to protect against influenza, and studies in mice show we can achieve a high level of protection but it wanes over time[1]. Although it is unknown how this waning time scale translates from mice to humans, studies of influenza vaccine efficacy suggest that protection may wane intra-seasonally. Many studies attempt to estimate influenza vaccine efficacy and waning but the results are contradictory. A common method of determining vaccine efficacy and whether it wanes is the Cox proportional hazard model:

\[ h(t) = h_0(t)e^{\beta_1 x_1 + \beta_2 x_2 + \ldots + \beta_n x_n} \]

where \( h_0(t) \) is the baseline hazard function and \( \beta_i \) is the \( i \)-th covariate. Waning is determined by calculating the Schoenfeld residuals and determining if they statistically significantly varied from the linearity assumption.

We aim to investigate the accuracy of vaccine efficacy estimates using common statistical methods on a simulated set of data obtained with a multi-scale model of influenza transmission.

Cox Proportional Hazard Model
A common method of determining vaccine efficacy and whether it wanes in human studies is the Cox proportional hazard model:

\[ h(t) = h_0(t)e^{\beta_1 x_1 + \beta_2 x_2 + \ldots + \beta_n x_n} \]

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Example of Waning Detection
We modeled a scenario of waning vaccine-induced protection from 100% to 0% protection over 60 days since vaccination under 3 different vaccination strategies: 1 day pulse, 30 day spread, or 60 day spread.

Waning Protection Over 60 Days: 100%-0%

- Waning is accurately identified
- Optimal vaccination strategies for waning vaccines would be spread over time

Comparing Vaccine Efficacy & Waning Over Time
Working within the vaccine efficacy framework developed in [2]:

\[ VE = \left( 1 - \frac{AR}{AR_{inf}} \right) \times 100 \]

True (Traditional) vaccine efficacy:

\[ VE = \left( 1 - \frac{AR}{AR_{inf}} \right) \times 100 \]

Vaccine efficacy for susceptibility:

\[ VE_S = \left( 1 - \frac{AR_{sus}}{AR_{inf}} \right) \times 100 \]

Vaccine efficacy for infectivity:

\[ VE_I = \left( 1 - \frac{AR_{inf}}{AR_{sus}} \right) \times 100 \]

Vaccine efficacy total:

\[ VE_T = \left( 1 - \frac{AR_{sus}}{AR_{inf}} \right) \times 100 \]

In this model, one of the key parameters is the waning of vaccine efficacy due to loss of immune memory. We compared the waning of true and observed vaccine efficacy by simulating different potential immune response levels and vaccination study types analyzed with the Cox proportional hazard model.

All parameters are based on available influenza data. All scenario information shown is based on the average of 1,000 simulations each with a population size of 100,000.

Discussion
For waning vaccine-induced protection, vaccine efficacy estimates will underestimate the vaccine efficacy during the early season and vaccine distribution timing affects the average estimate.

- Waning is accurately identified
- Optimal vaccination strategies for waning vaccines would be spread over time

We repeated this analysis for several other scenarios to determine if waning is ever spuriously detected and to compare vaccine efficacies. Scenarios where vaccine protection is incomplete but constant are defined as "leaky."

Optimal vaccination strategy for non-waning vaccines would be a single day pulse.

References

Acknowledgements
NIH grant U01HL139483

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