Investigating Waning of Influenza Vaccine Induced Immunity with a Multi-Scale Modeling Approach

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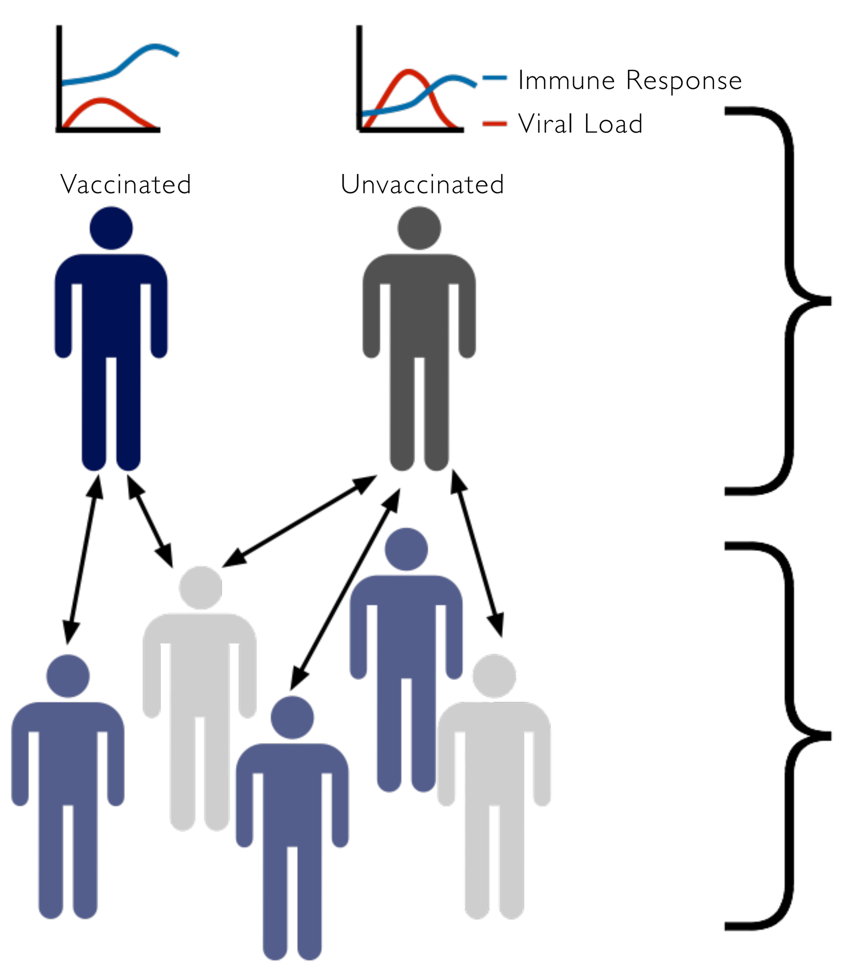
Summary

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. Different levels of prior immunity and vaccination distribution timing complicate interpretation of the results when attempting to estimate vaccine efficacy and its waning in humans.

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.

Multi-Scale Model



Within-Host
- Captures the individual level of response to infection based on prior immunity

Heterogeneity
- In prior immunity
- In immune response and transmission
- In vaccination timing

Between-Host
- SIR-based framework for agent-based model
- Captures population level dynamics of infection

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.

Cox Proportional Hazard Model

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

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

where $h_0(t)$ is the baseline hazard function and β_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.

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.

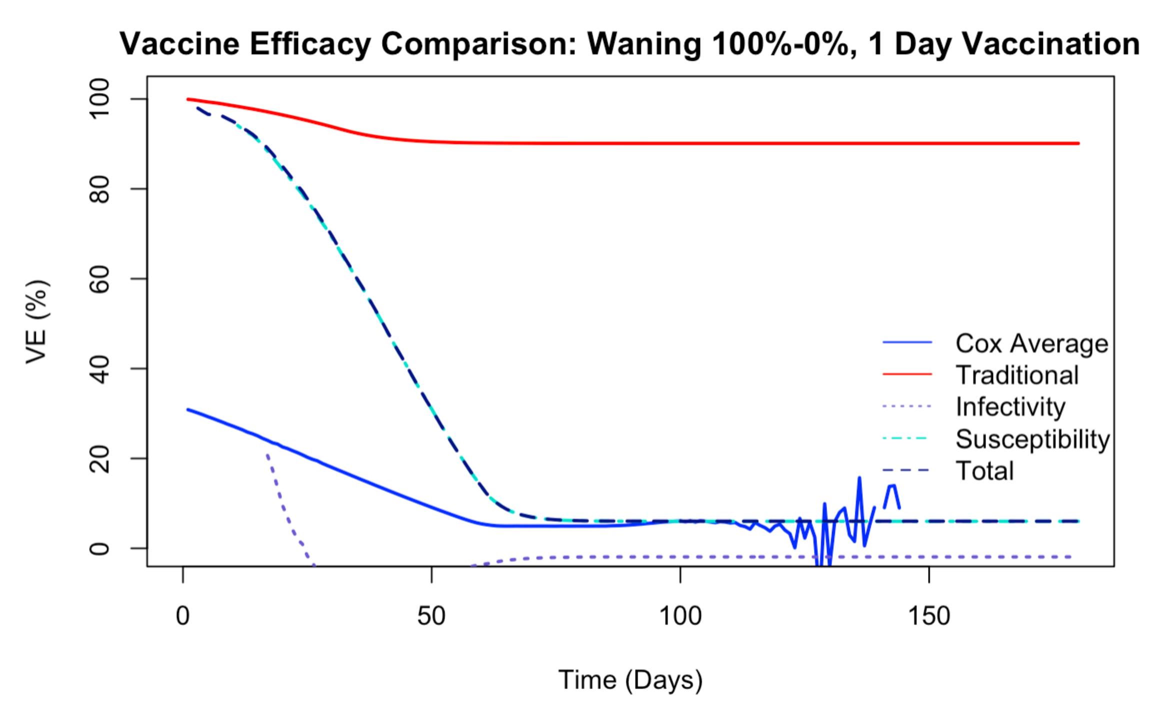
Waning Protection Over 60 Days: 100%- 0%

Waning (100-0%)	1 Day	30 Days	60 Days
Detected Waning (%)	98.3%	100%	100%
Average Vaccine Efficacy	7.0%	37.6%	64.7%
Attack Rate	62,799	52,530	48,4723

- **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]:



True (Traditional) vaccine efficacy:

$$VE = \left(1 - \frac{AR_V}{AR_U}\right) * 100$$

Vaccine efficacy for susceptibility:

$$VE_S = \left(1 - \frac{Inf_{VV}}{Exp_{VV}} / \frac{Inf_{VU}}{Exp_{VU}}\right) * 100$$

Vaccine efficacy for infectivity:

$$VE_I = \left(1 - \frac{Inf_{VV}}{Exp_{VV}} / \frac{Inf_{UV}}{Exp_{UV}}\right) * 100$$

Vaccine efficacy total:

$$VE_T = \left(1 - \frac{Inf_{VV}}{Exp_{VV}} / \frac{Inf_{UU}}{Exp_{UU}}\right) * 100$$

Here AR_i is the attack rate in group *i* (vaccinated or unvaccinated), Inf_{ij} is the infection of group *j* by group *i*, and Exp_{ij} is the exposure of group *j* to group *i*

While waning was statistically determined to exist in almost all simulations, the vaccine efficacy over time as estimated by the Cox model **underestimates** early season vaccine efficacy.

Additional Scenarios

Control: Constant Complete Protection

Control	1 Day	30 Days	60 Days
Detected Waning (%)	0%	0%	0%
Average Vaccine Efficacy	100%	100%	100%
Attack Rate	626	8,971	31,066

Leaky Protection: 80%

	1 Day	30 Days	60 Days
Detected Waning (%)	5.2%	99.9%	100%
Average Vaccine Efficacy	80.0%	81.6%	82.2%
Attack Rate	12,416	21,301	40,560

Waning Protection Over 60 Days: 80%- 50%

Waning (80-50%)	1 Day	30 Days	60 Days
Detected Waning (%)	92.6%	100%	100%
Average Vaccine Efficacy	51.9%	65.3%	72.4%
Attack Rate	37,128	33,493	45,265

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

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.

For leaky vaccine-induced protection, waning can be spuriously detected using the Cox proportional hazard model; however, the average vaccine efficacy estimate was accurate regardless of timing.

- We will further refine our within-host model to combine our previously published work [3,4].
- We intend to fit this model to existing data, to determine the amount of influenza vaccine waning in humans.
- While the focus of our model is influenza vaccination, this framework is easily generalizable for use with other communicable diseases.

References

1. Coleclough et al. *Scandinavian Journal of Immunology.* 62: 2005
2. Halloran et al. *American Journal of Epidemiology.* 146(10): 1997
3. Zarnitsyna et al. *PLoS Pathogens.* 12(6): e1005692, 2016.
4. Zarnitsyna et al. *Frontiers in Immunology.* 7(165): 2016.

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