“Intra-Seasonal Waning” as Methodological Artifact

Ivo M. Foppa

10/10/2018

Waning VE

- Since 2015, there have been numerous reports, from the US, Europe and beyond, suggesting that influenza Vaccine effectiveness (VE) declines over the season
- ...

Petrie JG et al., “Modest waning of influenza vaccine efficacy and antibody titers during the 2007-2008 influenza season”, *JID* 2016;214(8):

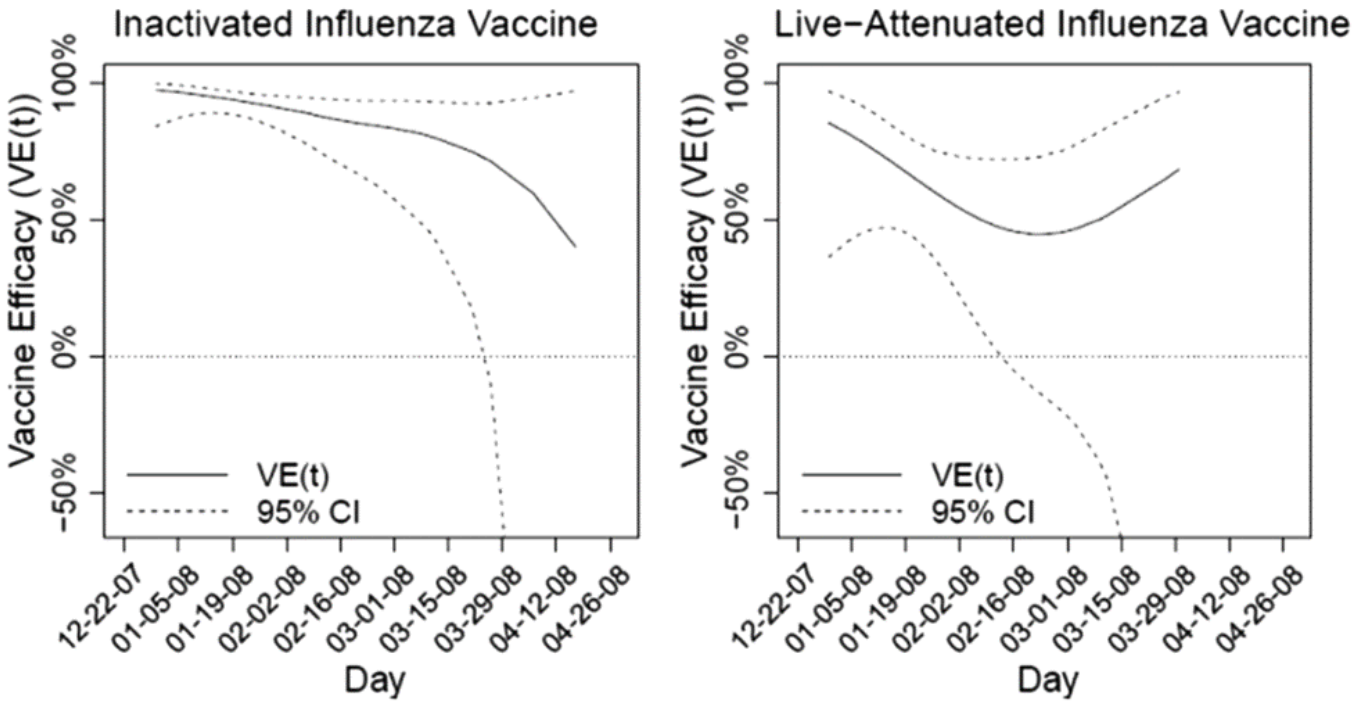
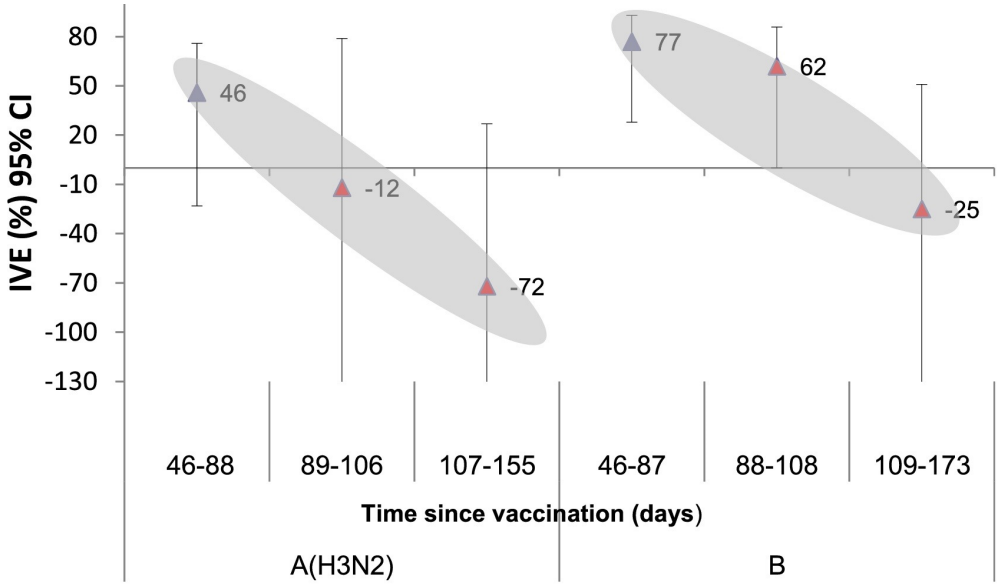


Figure 2. Influenza Vaccine Effectiveness by Time

Gherasim A et al., “Waning protection of influenza vaccine against mild laboratory confirmed influenza A (H3N2) and B in Spain, season 2014-15”, *Vaccine* 2016;34(20):



[1] IVE adjusted by sex, age (0-14; 15-64; >64 years), chronic condition, sentinel network, period of swabbing (pre-epidemic -weeks 50/2014-01/2015; epidemic - weeks 2-11/2015, post-epidemic- weeks 12-16/2015), obesity, severity, sentinel physicians visits and smoking (pregnancy not included due to low sample size: one and two pregnancies in the A(H3N2) and B analysis respectively)
[2] IVE modeled with the time since vaccination divided by tertiles and using non-vaccinated as the reference group.

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> 3. What if the vaccine is not leaky?

Vaccine models

- “Leaky” model: Those susceptible before vaccination have a risk of $\lambda_0 k$ of becoming infected during a contact if an unvaccinated susceptible has risk λ_0.

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- Implement two scenarios (“leaky”, ”all-or-none” with two viruses)
- Use numerical solutions to ODEs to generate TND data
- Calculate VE “estimates” and true VE

“Leaky” vaccine: The instantaneous infection risk of those vaccinated is reduced by a constant factor (e.g. difference in infectious dose):

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- Risk at time t in those **not vaccinated**:

$$\lambda_0(t)$$

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- $\text{VE} = 1 - \frac{\lambda_1(t)}{\lambda_0(t)} = 1 - \frac{\lambda_0(t)\,\alpha}{\lambda_0(t)} = 1 - \alpha$

Deterministic transmission modeling, refresher

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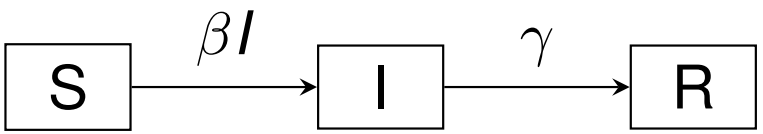
- Basic SIR model



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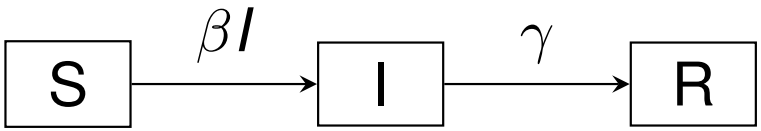

- Differential equation representation (Kermack&McKendrick, 1927):

$$\frac{dS}{dt} = -\beta IS$$
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$$\frac{dR}{dt} = -\gamma I$$

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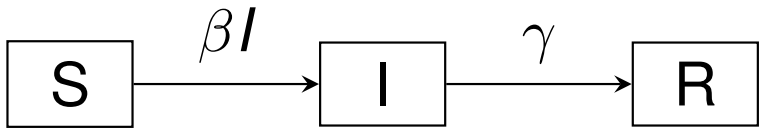

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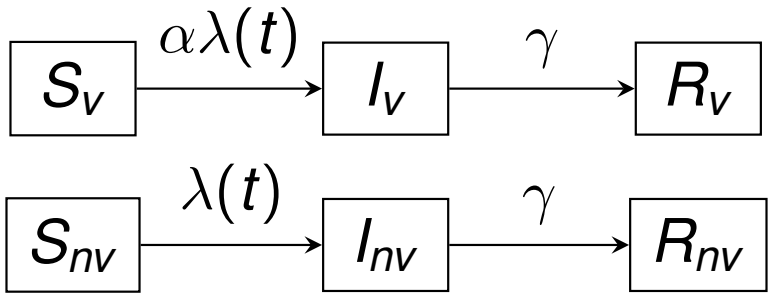
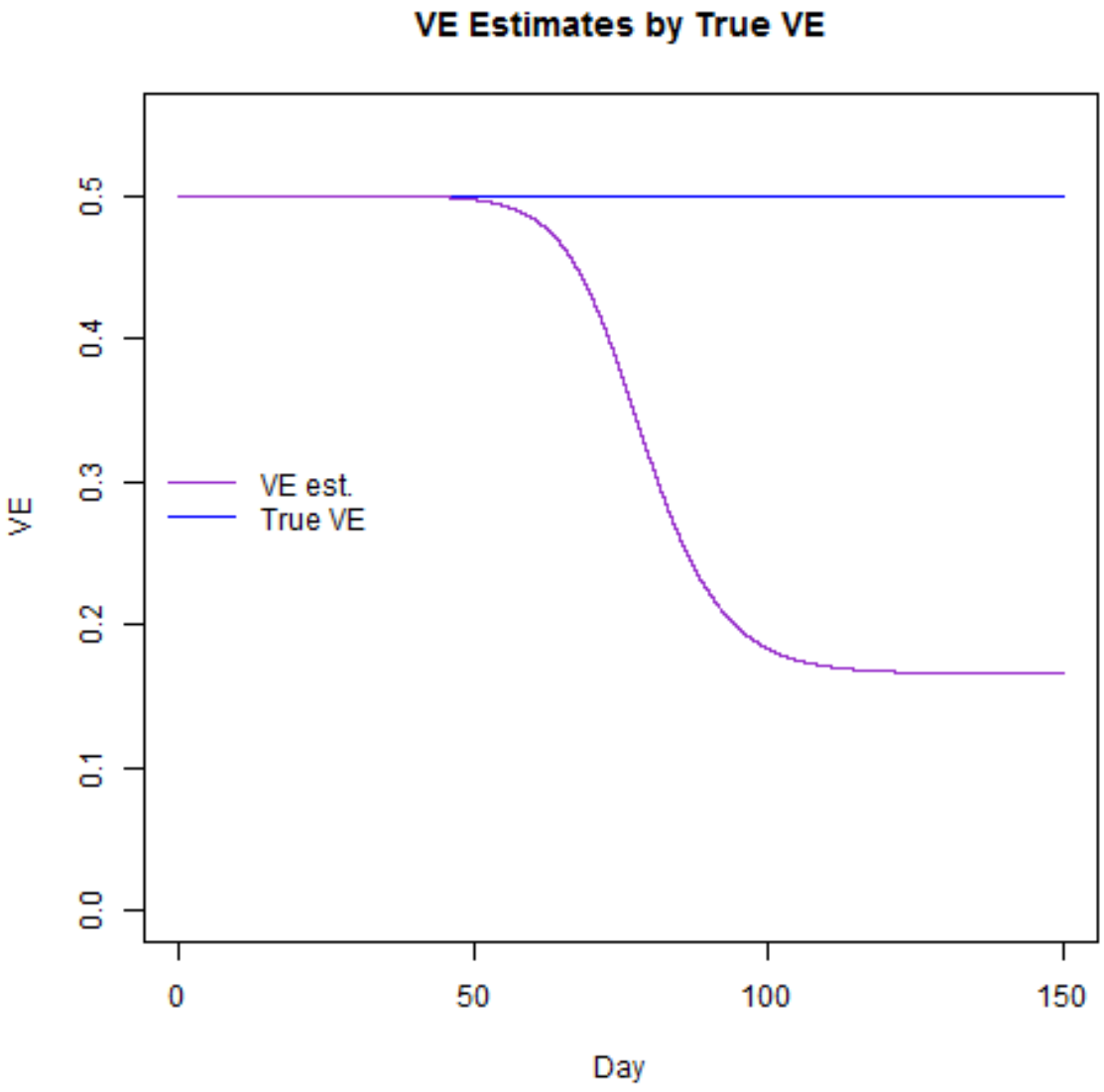
- System of ODEs can be solved (numerically!), makes pretty pictures ...

SIR model, “leaky” vaccine



where $\lambda(t) = \beta(I_v + I_{nv})$.

VE estimates for true VE=50%



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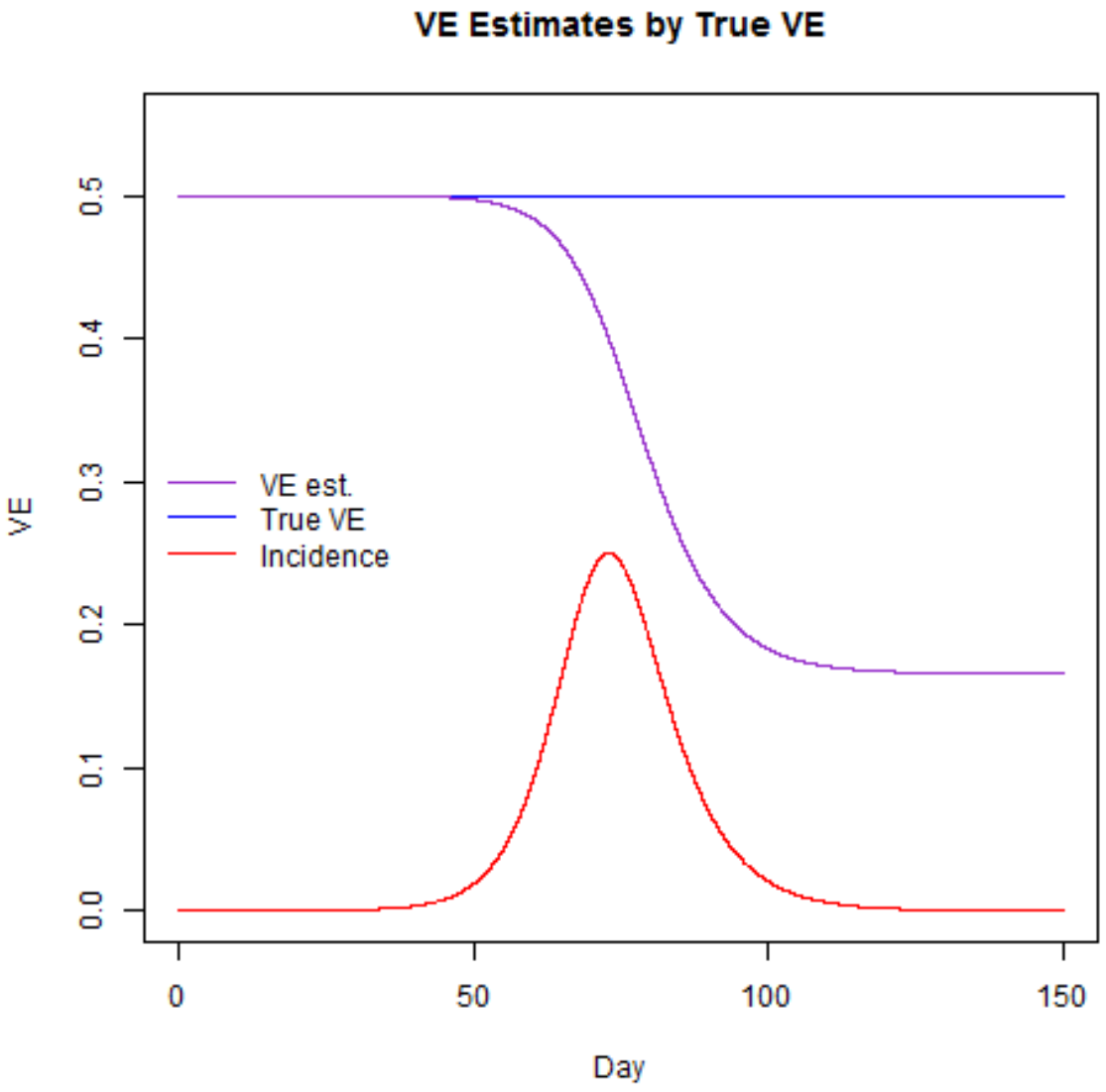
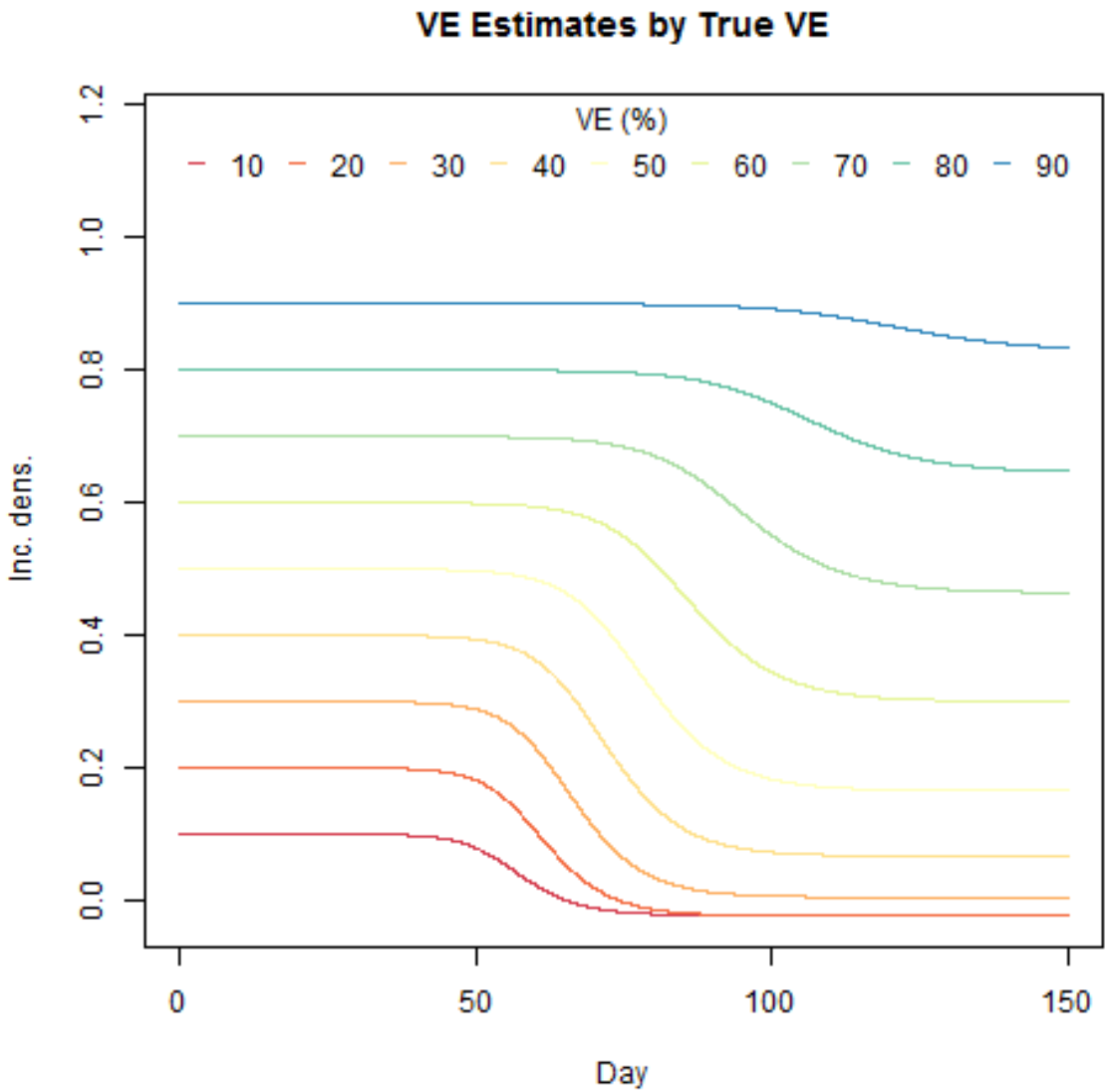


VE estimates for range of true VEs



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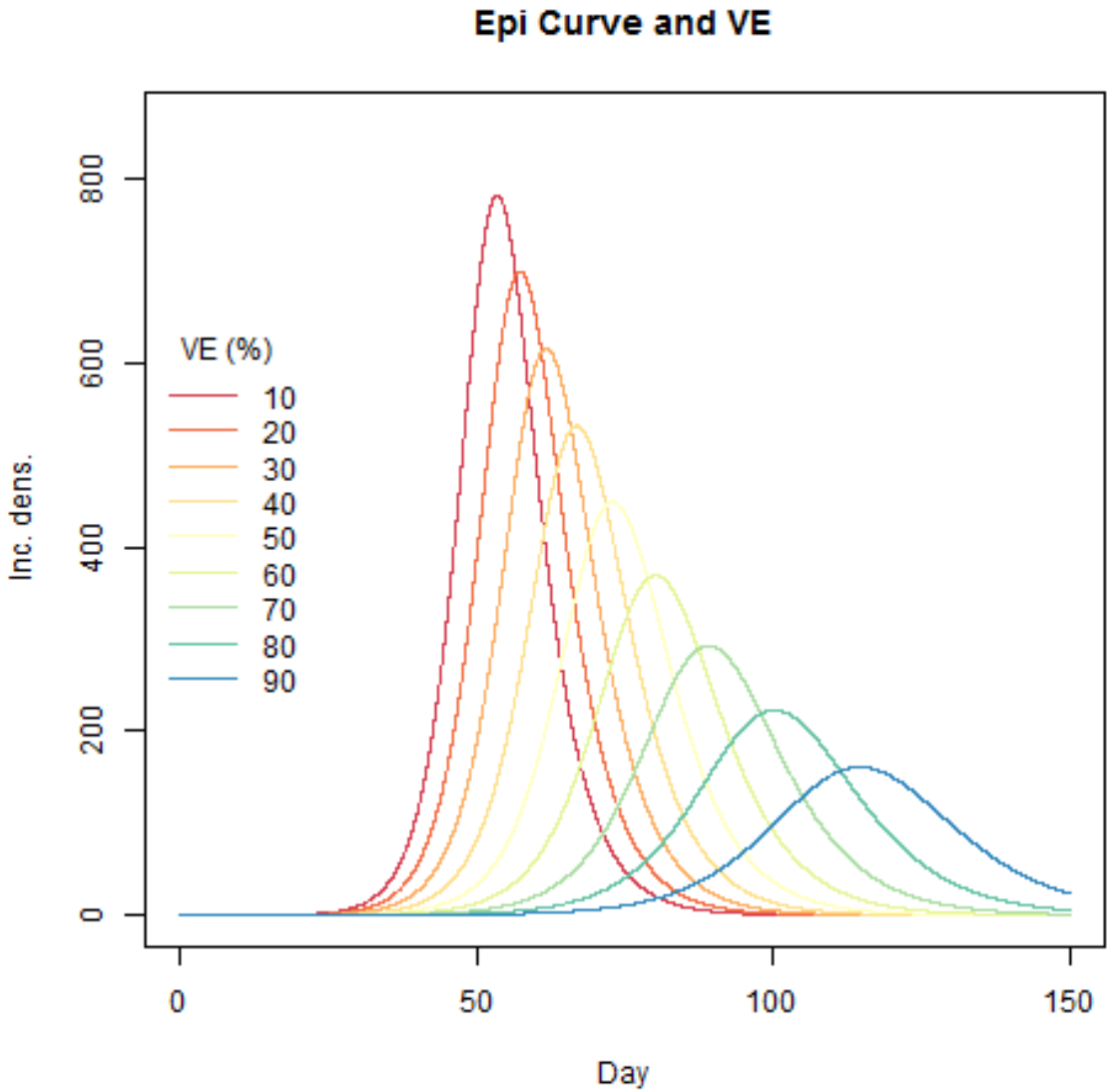

Mechanism for reduced VE over season, “leaky” vaccine

- True VE remains unchanged
- Decrease in VE due to **bias**: Faster depletion of unvaccinated susceptibles, compared to vaccinated susceptibles

“All-Or-None” Vaccine, two viruses: Vaccination fully immunizes against virus 2; infection with either virus immunizes fully:

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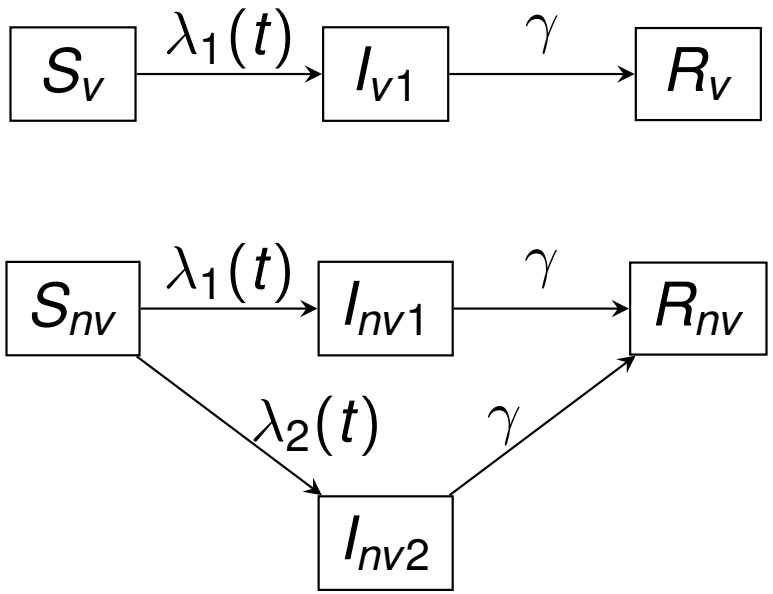

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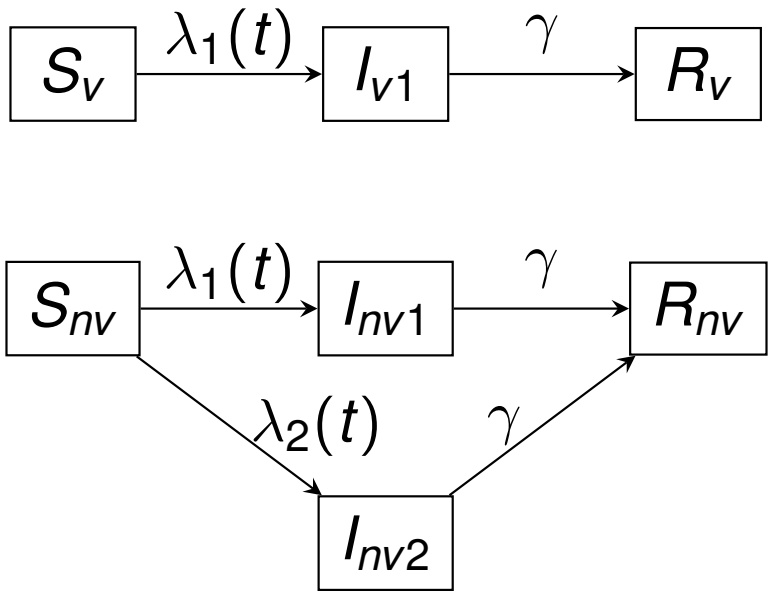
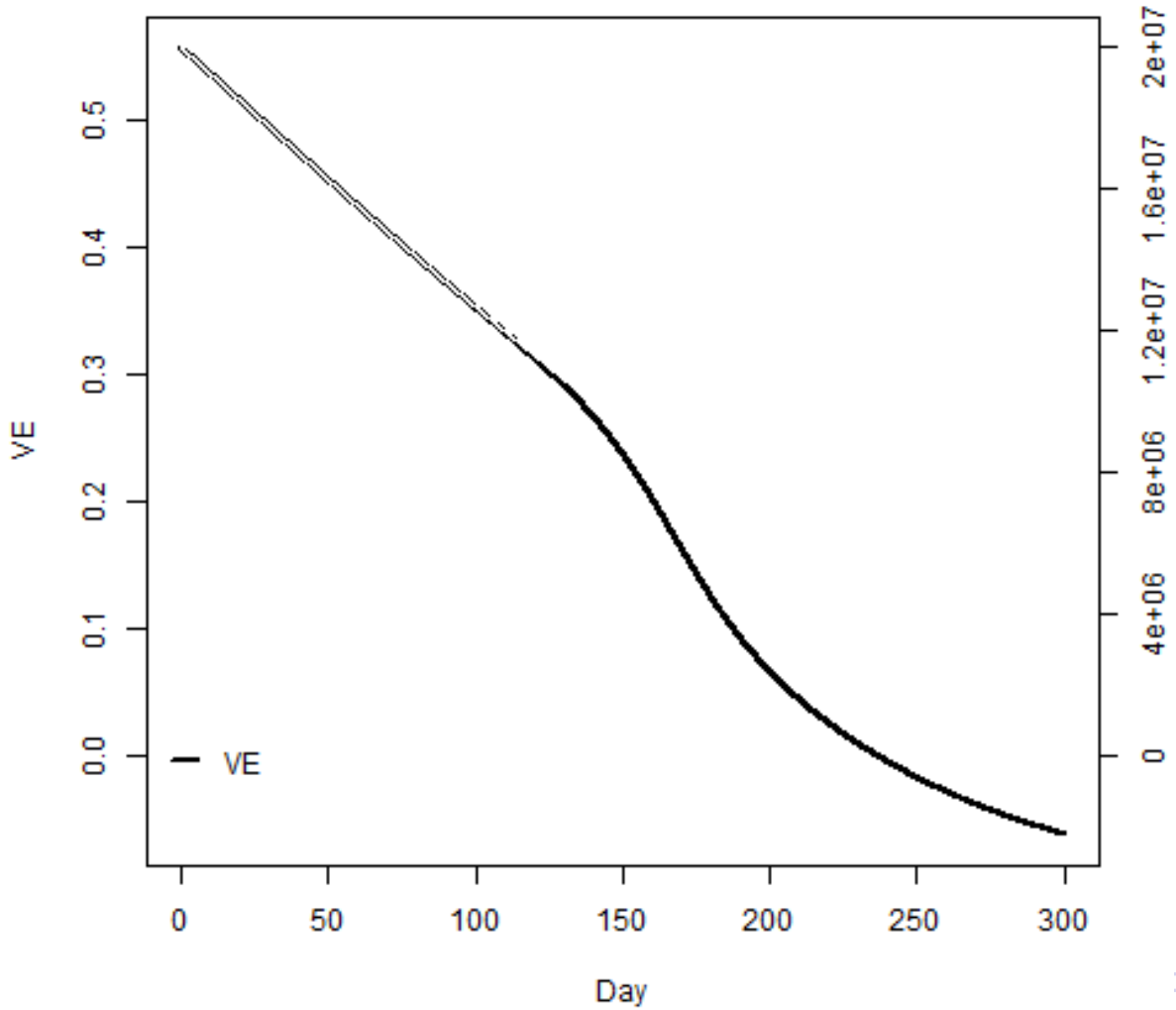


$$\begin{aligned}\mathrm{VE}(t) &= 1 - \frac{\lambda_1(t)}{\lambda_0(t)} \\ &= 1 - \frac{\beta_1\left(I_{v1} + I_{nv1}\right)}{\beta_1\left(I_{v1} + I_{nv1}\right) + \beta_2 I_{nv2}} \rightarrow \text{time dependent; both viruses}\end{aligned}$$

VE estimates over season



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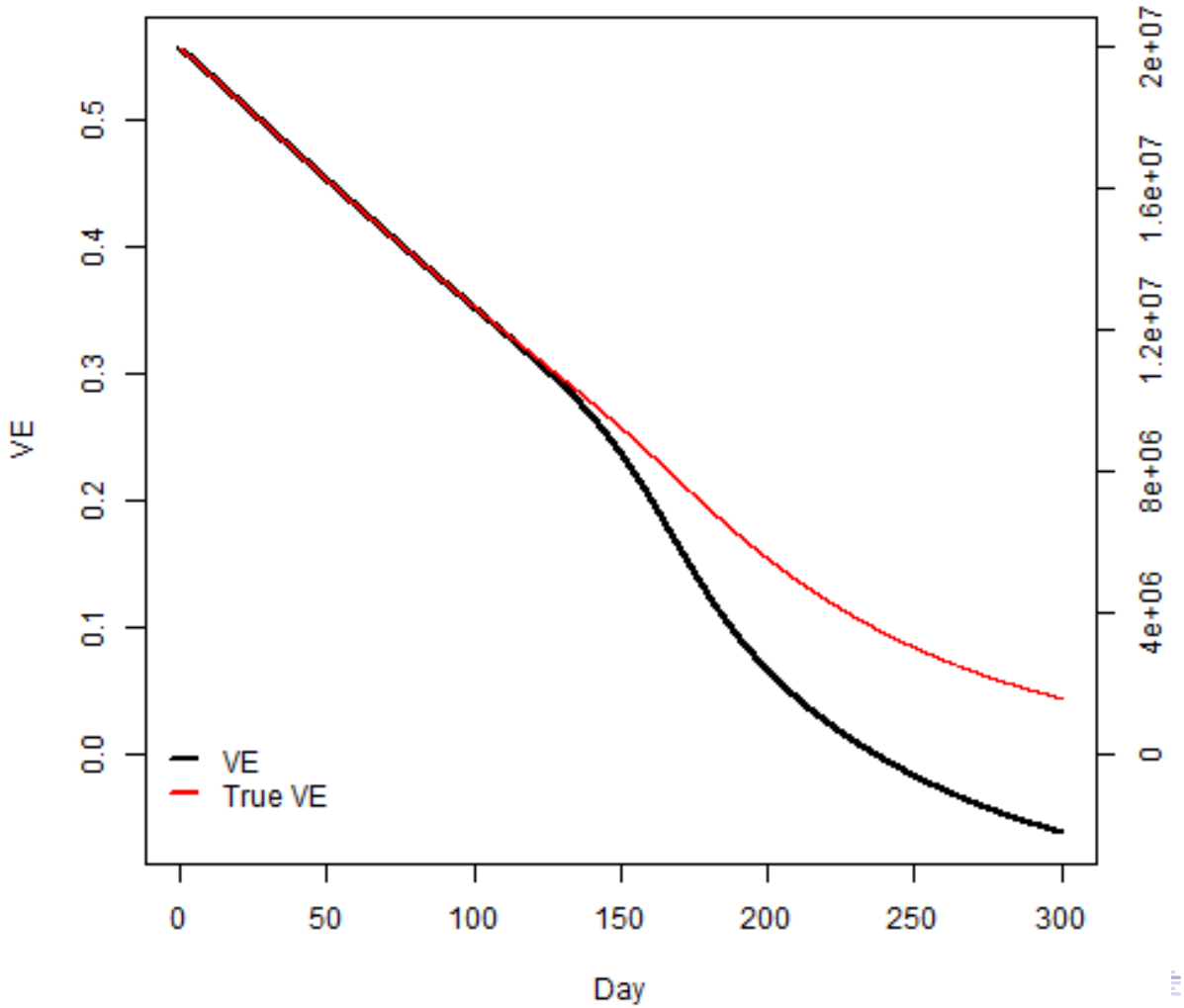

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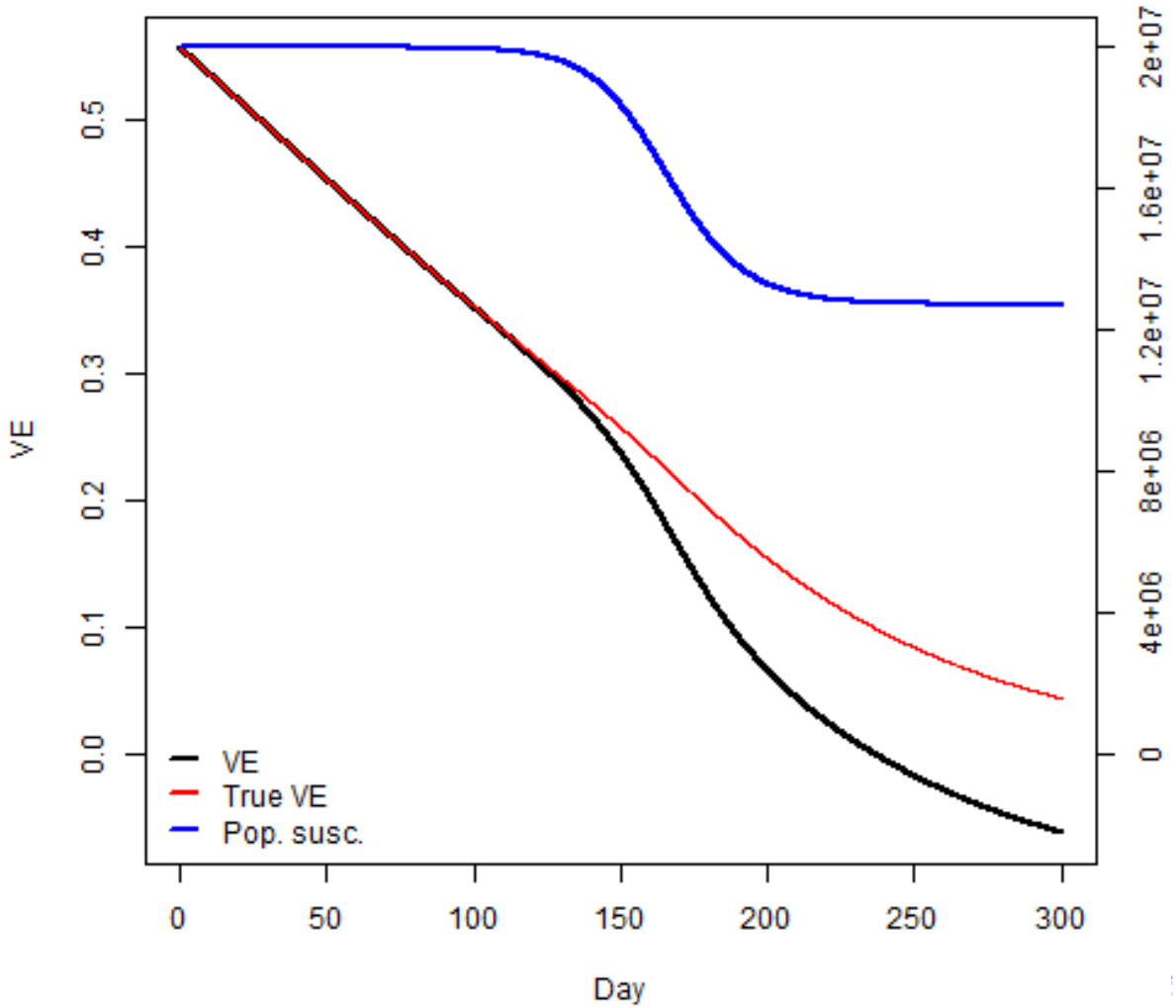
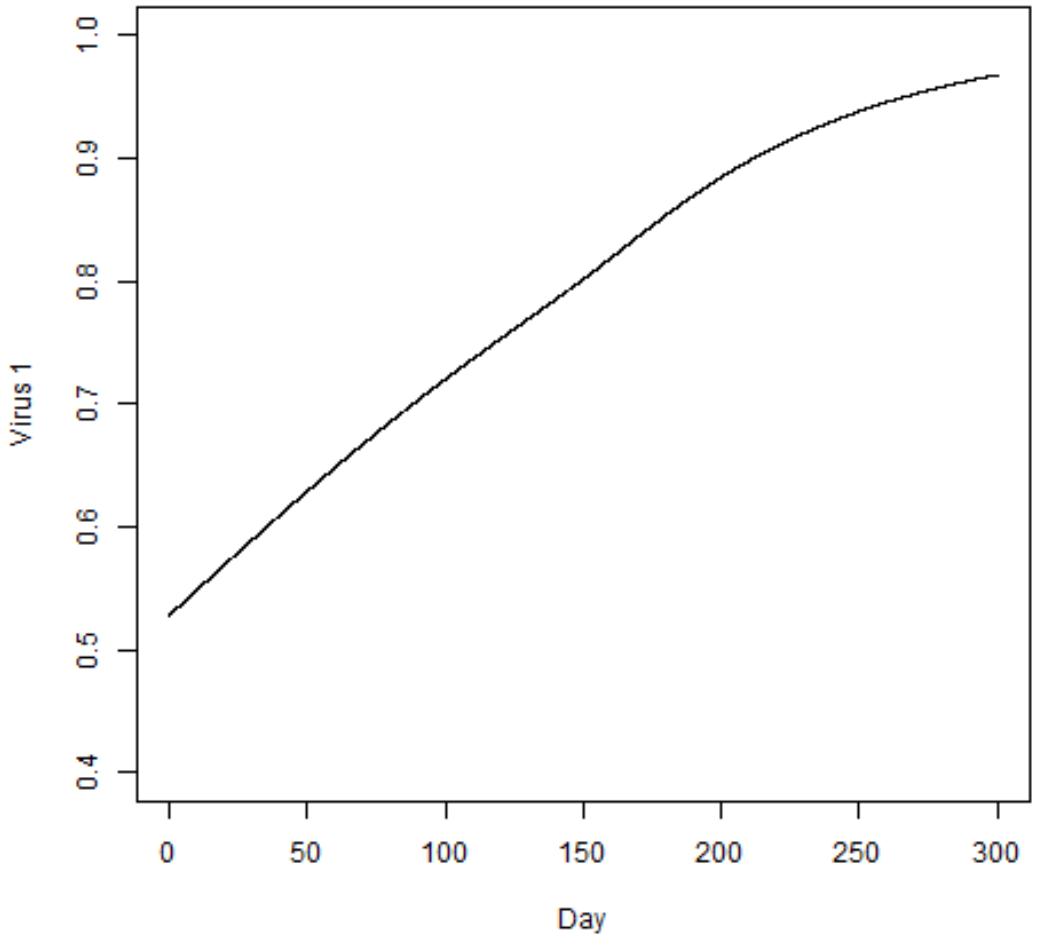


Mechanisms for reduced VE over season, “all-or-none” vaccine, two viruses

- **True decrease** in VE due to evolutionary process, without any decay in individual vaccine protection: Relative distribution of two viruses changes (virus 1 outcompeting virus 2)
- Decrease in VE due to **bias**: Faster depletion of unvaccinated susceptibles, compared to vaccinated susceptibles.

Evolutionary process: Viruse 1 outcompeting virus 2



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