**APPEARANCE OF WANING IMMUNITY IN STUDIES OF INFLUENZA VACCINE EFFECTIVENESS DUE TO BIAS**

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**Introduction**

In his enlightening editorial on the challenges faced by observational vaccine effectiveness (VE) studies, Lipsitch {Lipsitch, 2018 #20} spells out two mechanisms causing apparent waning in ``leaky'' vaccines: First, heterogeneous risk of infection will deplete the population of those with higher risk first, among the vaccinated slower than the unvaccinated {Margheri, 2017 #24}. This leads to a relative increase in vaccinated case, resulting in lower VE estimates over time. The second mechanism, due to incomplete case ascertainment {Wu, 2018 #21}, is not further discussed by Lipsitch {Lipsitch, 2018 #20}. Here, we reconsider that mechanism in the context of observational influenza VE studies. Presently, most influenza VE studies are test-negative studies (TNS) and investigate its impact on VE estimates. We also comment on the recent manuscript by Ray et al. {Ray, 2018 #1} to highlight some of these challenges.

**Methods**

Simulation studies

We conducted two simulation studies, which we briefly describe here, providing more technical detail in the Appendix.

*Simulation study 1*

The first simulation study was based on a simple SIR ordinary differential equations (ODE) model, using parameter values shown in the Appendix. Virtual case-control studies were conducted using incident infections as cases and the vaccination uptake in the whole population to inform the vaccination odds in the controls; an “under-ascertainment corrected) VE was calculated by using the vaccination odds in the susceptibles, instead. This simulation resulted in graphs of VE estimates over time, by true VE.

*Simulation study 2*

The second simulation study used a stochastic SIR model that kept track of time since vaccination. We simulated vaccination uptake as an unimodal function, with the total coverage, time of start relative to beginning of transmission and total duration to be chosen. We investigated two scenarios: One in which vaccination was only begun with the start of transmission (maximum overlap) and one without overlap of vaccination uptake and transmission. We generated case-control studies using all incident infection as cases and the remainder of the population as controls. We analyzed the data using conditional logistic regression as described by Ray et al. {Ray, 2018 #1}

**Results**

Theoretical considerations

*Bias in the VE estimate*

Assume that, for the sake of the argument, we conduct a TNS for the assessment of influenza VE, with full ascertainment of all influenza infections, both symptomatic and asymptomatic. Using the notation of {Wu, 2018 #21}, is the probability of infection from a contact which, in the unvaccinated, would have resulted in infection. If the rate of influenza infection in the unvaccinated were to be , the rate in the vaccinated would amount to and the rate ratio of infection, comparing vaccinated to unvaccinated, would be . It is well known that the incidence rate ratio is estimated by the odds ratio, as long as incidence density sampling is followed, controls are drawn from “only actual candidates for the illness” {Miettinen, 1976 #23}, i.e. people susceptible to influenza infection and some other fundamental conditions are met.

VE can then be estimated as

()

where and represent the number of vaccinated and unvaccinated cases and and represent controls. However, if controls are not restricted to “actual candidates”, i.e. subjects susceptible to influenza infection, then the vaccinated pool of susceptible individuals will be depleted more rapidly than the vaccinated (see Appendix 1), “making the rate of new cases in the two groups converge or, in extreme cases, even cross, so that observed incidence is higher in the vaccinated than the unvaccinated group” {Lipsitch, 2018 #20}. Hence, expression (1) will become increasingly biased downwards.

*Bias in vaccinated-only analyses*

Ray et al. {Ray, 2018 #1} proposed an analysis that only includes vaccinated subjects and modeled time since vaccination, as a categorical variable with 28-day increments, to capture a waning effect, implemented using conditional logistic regression analysis, with day of recruitment as sub-setting variable. While this approach, on first sight, appears to solve the problem of differential depletion of susceptibles by vaccination status, the problem persists and the effects associated with the time-since-vaccination variable (the most recently vaccinated as reference category) are expected to be more positive with increasing time since vaccination. This will only be true if vaccination uptake overlaps with transmission and here is the intuitive reason: Those vaccinated most recently had been, until their vaccination, been exposed to the unabated infection pressure, while those having been vaccinated for longer had profited from reduced infection risk for longer. As a result, among those having been vaccinated just recently, a lower proportion than among those who had gotten vaccinated a longer time ago remains susceptible to influenza infection (Appendix 2). Therefore, the case-control ratio shifts increases with increasing time since vaccination, imitating waning immunity.

Simulation studies

*Simulation study 1*

*Simulation study 2*

**Figures**

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Figure 1. VE estimates over time by VE.

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Figure 2. Relative bias in VE estimates over time, by VE.

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