Distribution Agreement

In presenting this thesis or dissertation as a partial fulfillment of the requirements for an advanced degree from Emory University, I hereby grant to Emory University and its agents the non-exclusive license to archive, make accessible, and display my thesis or dissertation in whole or in part in all forms of media, now or hereafter known, including display on the world wide web. I understand that I may select some access restrictions as part of the online submission of this thesis or dissertation. I retain all ownership rights to the copyright of the thesis or dissertation. I also retain the right to use in future works (such as articles or books) all or part of this thesis or dissertation.

Signature:

Meng Shi	Date

Estimates of Influenza Vaccine Effectiveness from Observational Studies

By

Meng Shi

Doctor of Philosophy

Biostatistics

Michael J. Haber, Ph.D.
Advisor

Robert Lyles, Ph.D.
Committee Member

Eugene Huang, Ph.D.
Committee Member

Ben Lopman, Ph.D.
Committee Member

Accepted:

Lisa A. Tedesco, Ph.D.
Dean of the James T. Laney School of Graduate Studies

Date

Estimates of Influenza Vaccine Effectiveness from Observational Studies

By

Meng Shi
MSPH, Emory University, 2013

Advisor: Michael J. Haber, Ph.D.

An abstract of
A dissertation submitted to the Faculty of the
James T. Laney School of Graduate Studies of Emory University
in partial fulfillment of the requirements for the degree of
Doctor of Philosophy
in Biostatistics
2020

Abstract

Estimates of Influenza Vaccine Effectiveness from Observational Studies

By

Meng Shi

Influenza is an infectious disease caused by influenza virus. Due to the variety of influenza viruses, a new vaccine must be developed each season, and the influenza vaccine effectiveness (VE) has to be re-estimated in every season. As annual influenza vaccination is now widely recommended, randomized clinical trials for estimating VE are no longer ethical in many populations, and observational studies based on patients seeking care for acute respiratory illnesses (ARI) remain the only option.

In the first topic, we developed a probability model for comparing the bias of VE estimates from two popular case-control designs: traditional case-control (TCC) design and test-negative (TN) design, under non-random vaccination. Our model allows non-random vaccination and confounding. In addition, we consider two outcomes of interest: symptomatic influenza (SI) and medically-attended influenza (MAI). Since the bias of VE estimates depends on the outcome against which the vaccine is supposed to protect, it is important to specify the outcome of interest when evaluating the bias.

In a stochastic agent-based model, the disease transmission process is governed by the behavior of each individual, and incorporates elements of random processes into the system. In topic 2, we present a stochastic agent-based simulation program, SimFlu, for the transmission of influenza in a stratified population, and use it to evaluate bias and precision of estimates of VE from 4 observational study designs (two case-control studies and two cohort studies). Besides that, we proposed several methods to correct the bias for test negative study.

The exact timing and duration of flu season can vary. Most of the time, the influenza activity peaks between December and February, and the duration of the annual influenza epidemic can last as late as May. However, influenza vaccines are now available as early as July. As a result, there may be relatively long periods between vaccination and potential exposure, raising concerns about the possibility of waning vaccine efficacy over a single season. In this study, we analyze data generated from SimFlu using three different methods for the evaluation of waning vaccine efficacy in both cohort and test negative studies.

Estimates of Influenza Vaccine Effectiveness from Observational Studies

By

Meng Shi
MSPH, Emory University, 2013
BS, Nankai University, 2011

Advisor: Michael J. Haber, Ph.D.

A dissertation submitted to the Faculty of the
James T. Laney School of Graduate Studies of Emory University
in partial fulfillment of the requirements for the degree of
Doctor of Philosophy
in Biostatistics
2020

Contents

List of Figures

List of Tables

Chapter 1

Introduction

1.1 Epidemiology of Influenza

Influenza is an infectious disease caused by influenza viruses, it is the most frequent cause of acute respiratory illness (ARI) requiring medical intervention because it affects all age groups and because it can recur in any individual. Influenza viruses belong to the family Orthomyxoviridae, which includes four genera: influenza virus A, influenza virus B, influenza virus C and thogotovirus. Influenza A viruses and influenza B viruses are the primary cause of influenza disease, and they are spread from person to person by respiratory droplets and fomites (Cox and Subbarao (1999)).

Influenza pandemics are usually caused by influenza A viruses, which is the most feared type of influenza viruses. These influenza A viruses can infect humans and several types of animals, including wild birds, pigs, horses and whales. They are further classified into subtypes depending on which versions of two different proteins are present on the surface of the virus. These proteins are called hemagglutinin (HA) and neuraminidase (NA). 17 subtypes of HA and 10 subtypes of NA has been identified. Although many different combinations of the HA and NA proteins are possible, viruses with only a few of the possible combinations circulate through the human population at any given time. Currently, subtypes H1N1 and H3N2 are in general circulation in people. The subtypes that exist within a population change over time. For example, the H2N2 subtype, which infected people between 1957 and 1968, is no longer found in humans.

Influenza B viruses are only known to infect humans and seals, this limited host and range is the main reason for the lack of influenza virus B-caused influenza pandemics in contrast with those caused by the influenza virus A, but they still cause outbreaks of seasonal flu. Influenza viruses B are not defined with subgroups but rather are defined by lineages and strains. Currently circulating influenza B viruses belong to one of two lineages: B/Yamagata and B/Victoria.

Influenza virus has a rounded shape and has a layer of spikes on the outside (Figure

1.1). There are two different kinds of spikes, each made of one type of protein, HA or NA. The HA protein allows the virus to stick to a cell, so that it can enter into a host cell and start the infection process. The NA protein is needed for the virus to exit the host cell, so that the new viruses that were made inside the host cell can go on to infect more cells. Because these proteins are present on the surface of the virus, they are "visible"to the human immune system. Inside the layer of spikes, there are eight single-stranded, negative-sense RNA segments that encode at least ten polypeptides, of which eight are structural viral proteins, and two are found in infected cells. When new viruses are made inside the host cell, all eight segments need to be assembled into a new virus particle, so that each virus has the complete set of instructions for making a new virus. The danger occurs when there are two different subtypes of influenza A virus inside the same cell, and the segments become mixed to create a new virus.

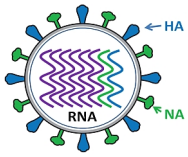


Figure 1.1: Influenza particle showing the HA and NA spikes on the outside an dRNA segments inside.

Influenza virus is one of the most changeable viruses known. The epidemiological success of influenza viruses is largely due to two types of antigenic variation that occur primarily in the HA and NA antigens: antigenic drift and antigenic shift. Antigenic drift is a gradual, continuous evolution that involves the accumulation of mutations within the genes. This will result in a slightly difference in the HA or NA proteins. The antibodies cannot inhibit this new strain of virus particles effectively, so the virus spread throughout a population more easier. This is the reason why individuals may repeatedly get influenza and influenza vaccines must be administered each year to combat the current circulating strains of the virus. Antigenic drift occurs in both

influenza A viruses and influenza B viruses. Antigenic shift is defined as an abrupt, major change in the virus, resulting from the recombination of the HA and NA proteins, which occurs only among influenza A viruses. This is typically the result of reassortment of animal and human influenza A viruses (Figure 1.2). When the newly created subtype can be transmitted easily from person-to-person, a pandemic could occur (Morens and Fauci (2007)).

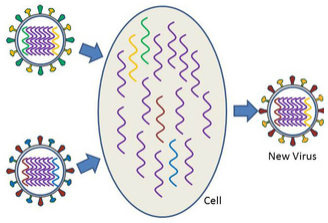


Figure 1.2: Reassortment of the genetic material of two different influenza subtypes within an infected cell to produce a new virus subtype.

Influenza viruses are unique in their ability of causing both recurrent annual epidemics and more serious pandemics that spread rapidly and may affect all or most age-groups. Individuals at increased risk for complications of influenza virus infection include children < 5 years of age, pregnant women, the elderly, and individuals with chronic health conditions such as chronic heart or lung disease, asthma, and HIV/AIDS. Children < 5 years of age have about 90 million new cases of influenza episodes, about 20 million cases of influenza-associated acute lower respiratory infections, and 1-2 million cases of influenza-associated severe acute lower respiratory infections (Nair et al. (2011)), causing 200-300 thousand deaths annually (Rolfes MA (n.d.)). Pregnant women have an increased risk of severe illness due to influenza (Omer et al. (2011)). The elderly have the highest rates of influenza-associated hospitalizations and deaths of any age group and account for up to 90% of influenza-associated deaths from seasonal influenza viruses(Rolfes MA (n.d.)).

1.2 Influenza Vaccination

Influenza vaccines are the mainstay of efforts to reduce the substantial health burden from seasonal influenza. Vaccination against influenza began in the 1930s with large scale availability in the U.S. beginning in 1945 when the first commercial vaccines were approved for use. An influenza vaccine was of particular interest to the U.S. military and civilian populations following the 1918-1919 influenza pandemic during the late stages of World War I.

Two main types of influenza vaccine are currently available: inactivated influenza vaccine (IIV) and live attenuated influenza vaccine (LAIV). The first IIV was monovalent and was protective against the influenza A (H1N1) strain. In 1940, influenza B virus was isolated and the first bivalent vaccine was subsequently tested in healthy adults (Hannoun (2013)). At the end of the 1970s, a new strain of influenza A (H3N2) was identified. In 1978, the first trivalent influenza vaccine including two influenza A strains (H1N1 and N3N2 subtypes) and one influenza B strains was created. The first trivalent LAIV was licensed in North America in 2003. The aim of vaccination with a LAIV is to induce a secretory and systemic immune response that more closely resembles the immune response detected after natural infection (Gasparini et al. (2011)), although the immunological mechanisms of action and correlates of protection remain largely unclear (Sridhar et al. (2015)). LAIV was administered via drops rather than via an injection. However, CDC's Advisory Committee on Immunization Practices (ACIP) voted that LAIV should not be used during the 2016-2017 flu season in U.S. in 2016. In 2009, Europe authorized a particular intradermal trivalent influenza vaccine which act alternative routes of delivery, and licensed for adults older than 60 years in the 2010/11 season in Europe. This vaccine was approved by the Food and Drug Administration (FDA) on 2011 in the U.S., and has been available since 2011/12 influenza season for people older than 64 years. In 2013, the WHO recommendations included a second influenza B strain in the vaccine composition, allowing member

countries to make their own decision on the possibility to recommend a trivalent influenza vaccine or a quadrivalent influenza vaccine in their immunization programs. Quadrivalent influenza vaccines contain both influenza B lineages for each season have been available. These offer the potential to improve protection by overcoming the drawbacks of wrongly predicting which B lineage will predominate in a given year (Barberis et al. (2016)).

Based on the recommendation of definition of the criteria for identifying risk groups targeted for vaccination issued by WHO, as the elderly are at high risk of complications such as morbidity, hospitalization and mortality, vaccination is recommended for the elderly worldwide. In U.S., annual influenza vaccination is now recommended for all persons aged 6 months or older. Studies have shown that influenza vaccine reduced children's risk of influenza-related pediatric intensive care unit admission by 75% during influenza seasons from 2010-2012 (Ferdinands et al. (2014)), and that people 50 years and older who got an influenza vaccine reduced their risk of hospitalizing resulting from influenza by 57% (Havers et al. (2016)). Influenza vaccination also has been shown to be associated with reduced hospitalizations among people with diabetes by 79% (Colquhoun et al. (1997)) and chronic lung disease by 52% (Nichol et al. (1999)).

1.3 Evaluation of the Effects of Vaccines

In order to determine whether to introduce a new vaccine in a population, there are two general considerations. The first consideration is the burden of disease that is potentially preventable by vaccination. The second consideration is the expected performance of the vaccine in practice. This can be assessed through RCTs, which allow the estimation of vaccine efficacy, and through observational studies that evaluate vaccine effectiveness.

Vaccine efficacy and vaccine effectiveness, VE, are generally estimated as one minus some measure of relative risk (RR), in the vaccinated group compared to the unvaccinated group:

$$VE = 1 - RR. \tag{1.1}$$

1.3.1 Vaccine Efficacy

Vaccine efficacy is the percentage reduction of disease incidence in a vaccinated group compared to an unvaccinated group under ideal circumstances.

$$VE = 1 - \frac{ARV}{ARU} \tag{1.2}$$

where ARV is the attack rate, or cumulative incidence, in the vaccinated population and ARU is the attack rate in the unvaccinated population.

Vaccine efficacy was defined and calculated by Greenwood and Yule in 1915 for the cholera and typhoid vaccines (Greenwood and Yule (1915)). Ideal vaccine efficacy studies are double-blind randomized controlled trails starting with a sample of susceptible individuals, where half the subjects receive vaccines and half receive placebo (Orenstein et al. (1985)). These studies are typically undertaken for pre-licensure vaccines, since once a vaccine has been shown to be effective and is licensed, it is unethical to use placebo. Observational studies are being increasingly used to evaluate vaccine effectiveness.

1.3.2 Vaccine Effectiveness (VE)

Vaccine effectiveness (VE) is the reduced risk of disease among vaccinated persons attributed to vaccination under real-life conditions. In vaccine effectiveness studies, the decision to be vaccinated is made by the individual or her/his physician.

A number of observational methodologies can be used in the assessment of vaccine

effectiveness, including case-control studies, cohort studies, the screening method and case-cohort studies. In cohort studies, the vaccine effectiveness is estimated by one minus the ratio of attack rates in vaccinated group and unvaccinated group, while in case-control studies, the relative risk is approximated by the odds ratio, comparing the odds of vaccination in cases and controls.

There are many potential biases in all observational vaccine effectiveness studies which we will introduce later.

1.4 Outcomes of Interest for influenza Vaccine Effectiveness Studies

A number of outcomes have been used for influenza vaccine effectiveness (VE) studies, reflecting the morbidity and mortality caused by influenza virus infection. Selecting appropriate VE outcomes involves a trade-off between providing information that is of greatest interest to policy makers and identifying outcomes that can be determined with a minimum of misclassification, or other type of bias. It is important to clearly define the outcomes of interest when designing a study to estimate VE, since incorrectly determining the occurrence of the outcomes for a study subject, such as falsely considering a diseased person to be disease-free, or falsely considering a disease-free person to be diseased will lead to wrong VE estimates.

There are two main categories of clinical outcomes: non-specific outcomes and laboratory-confirmed outcomes, that could be used as endpoints for influenza VE studies. VE estimates against non-specific outcomes are generally lower, depending on what proportion of the outcome measured is attributable to influenza. Bridges et al. showed that among healthy adults, vaccine was 86% effective against laboratory-confirmed influenza, but only 10% effective against influenza-like illness (ILI) in the same population and season (Bridges et al. (2000)).

1.4.1 Non-specific Outcomes

For any non-specific outcomes, the estimated VE is likely to be much lower than the estimated VE against lab-confirmed influenza.

1.4.1.1 Severe Acute Respiratory Infection (SARI)

SARI, defined by the WHO Global Epidemiological Surveillance Standards for influenza, is an acute respiratory infection (ARI) with history of fever or documented fever of $\geq 38C^{o}$, cough, onset within the last ten days, and required hospitalization. Since the existence of SARI surveillance system and severe illnesses are much more interest to policy maker, SARI is an attractive outcome for influenza VE studies. However, using SARI as endpoint for observational influenza VE studies requires a large sample size to achieve effectiveness with adequate precision, and influenza vaccine may be used disproportionately by persons with a different risk for SARI than unvaccinated persons, which can cause strong confounding of VE estimates in observational studies.

1.4.1.2 All-cause pneumonia requiring hospitalization

As SARI, all-cause pneumonia requiring hospitalization is of high interest to policy makers, and the existing surveillance system for hospitalized pneumonia cases can be used in influenza VE studies. However, the existing surveillance systems for hospitalized pneumonia cases focus on children less than 5 years of age, while many of the influenza-associated pneumonia cases occur in adults 50 years of age and older. If influenza VE studies want to use hospitalized pneumonia as an outcome, new surveillance systems need to be developed. Also, the probability of influenza to pneumonia is low which will lead to low VE in observational VE studies.

1.4.1.3 Influenza-like Illness (ILI)

The WHO define ILI as an ARI with measured fever of $\geq 38C^{o}$, cough, and onset within the last seven days. There are several advantages of using ILI as outcome in VE studies. Firstly, the case definition is easy to apply. Secondly, in one influenza epidemic, the number of subjects with ILI is more than the number of subjects with SARI or pneumonia, in order to detect statistically significant VE, the relative sample size is smaller than previous two outcomes. The limitation for ILI as an endpoint for observational influenza VE studies is ILI does not emphasis on serious outcomes. While demonstrating VE against ILI would indicate that the vaccine can reduce the risk of influenza-associated illness, VE against ILI is not generalizable to VE against more serious outcomes without making assumptions that are difficult to validate.

1.4.1.4 All-cause Mortality

All-cause mortality was formerly a common endpoints in observational influenza VE studies among older adults. Jackson et al. (2006) showed that healthy seniors are more likely to receive influenza vaccine than seniors at higher risk for death which will lead strong confounding in VE estimates. All-cause mortality is not recommended as endpoint for VE studies.

1.4.1.5 Adverse Birth Outcomes

Evidence that influenza vaccination during pregnancy is safe and effective at preventing influenza disease in women and their children through the first months of life is increasing. Influenza virus infection in pregnant woman may sometimes result in preterm birth, or cause poor birth outcome. But evidence that influenza itself cause adverse pregnancy outcomes is inconsistent and limited in quality (Savitz et al. (2015)). If a reduction in adverse birth outcomes wanted to be used as endpoints of observational influenza VE studies, it must be used in caution.

1.4.2 Laboratory-confirmed Outcomes

Reverse transcriptase polymerase chain reaction (RT-PCT) is the standard for laboratory confirmation of influenza virus infection during acute illness. RT-PCR and other commercially available molecular diagnostic tests are both highly sensitive and highly specific for detecting influenza viruses.

Laboratory-confirmed outcomes are much more specific for influenza virus infections than outcomes based on clinical signs and symptoms only. It is generally preferred than non-specific outcomes in observational VE studies. Laboratory-confirmed outcomes as a VE endpoint has several challenges as well. The first one is the need for laboratory capacity, molecular assay technology and reagents. All of these activities require well trained clinical staff to ensure standardized specimen collection, proper processing, and testing. Improper specimen collection or handling can lead to false negative results. In addition, using laboratory-confirmed outcomes restricted to subjects who seek medical care within around seven days of illness onset. Furthermore, study protocol should specify the symptoms, duration of illness, and all eligibility criteria for attempting to enroll and test subjects for influenza. These criteria should then be applied to all eligible subjects regardless of clinical testing preferences. Although the available molecular diagnostic tests are high sensitive and high specific, the diagnostic test for influenza viruses are not 100% sensitive and specific, which will lead misclassification bias into the estimation of VE.

Laboratory-confirmed outcomes are becoming standard for VE studies in high-resource countries, and WHO recommends the use of laboratory-confirmed outcomes whenever possible due the benefits associated with use of outcomes specific to influenza.

1.4.3 Symptomatic Influenza and Medically-attended Influenza

In this study, we evaluate estimates of VE based on the outcomes that the vaccine is supposed to protect, i.e. symptomatic influenza (SI) or medically-attended influenza (MAI).

During the influenza season, a person may become infected with an influenza virus and develop ARI. This outcome is referred to as "influenza ARI" (FARI), where "F" stands for flu. A person may also develop an ARI not resulting from influenza infection. This outcome is referred to as "non-influenza ARI" (NFARI). Therefore, a person's influenza status can be categorized into 3 categories: no ARI, NFARI, and FARI.

SI is the outcome of interest lead by the person's influenza status, FARI. In observational influenza VE studies, surveillance for SI is needed in the entire study population, and for persons ill with compatible illnesses, samples of influenza are taken for verification. A true case of SI is a person has ARI and is infected by an influenza virus. SI is more appropriate from the public health perspective. MAI is defined as a truly influenza-infected person who seeks medical care because of her/his ARI. Once a person decides to seek medical care in clinic, the health care provider may ask the person to be tested for influenza viruses. If the person agrees then a swab is taken and sent to a laboratory for testing.

1.5 Observational Studies to Estimates VE

Observational studies are important category of study designs, which examine conditions and events that already occurred or will occur anyway. As annual influenza vaccination is recommended for all U.S. persons ages 6 months or older, it is unethical to conduct randomized clinical trials to estimate influenza VE. Observational studies may be the next best method to address the estimation of influenza VE. Case-control

studies and cohort studies are two primary types of observational studies that aid in evaluating associations between influenza and vaccination.

1.5.1 Case-control Studies

1.5.1.1 Traditional Case-control Studies

Traditional case-control studies (TCC) were historically borne out of interest in disease etiology. Smith (Smith (1982)) argued for the conduct of case-control studies to assess the effect on the incidence of tuberculosis of mass BCG campaigns that had been conducted in numerous countries in Asia and Africa beginning in the 1950s. Prior to that, case-control studies had not been widely used for evaluating vaccines. In TCC, cases of the disease are ascertained, and information on various covariates collected. In influenza VE studies, vaccination status is the most important factor. Then a comparison group of individuals who did not experience the outcome of interest is selected as controls. In TCC study, VE is estimated from odds ratio, which is the ratio of the vaccinated cases to the unvaccinated cases is divided by the ratio of vaccinated controls to unvaccinated controls:

$$VE = 1 - OR = 1 - \frac{O_{\text{Cases}}}{O_{\text{Controls}}}, \tag{1.3}$$

where O_{Cases} is the odds of vaccination among the cases, and O_{Controls} is the odds of vaccination among the controls.

TCC studies can be more feasible than the follow-up of large cohorts. They are more efficient than cohort studies, in terms of the number of study subjects required, cost of budget, and study duration. Orenstein et al. (Orenstein et al. (1988)) argue that TCC studies allow large amounts of resources to be directed at a small number of cases and controls to assess vaccination status and history of disease most accurately, decreasing errors due to misclassification.

However, TCC studies also present some methodological issues. One is the selection of cases. In a TCC study, it is imperative that the investigator has explicitly defined inclusion and exclusion criteria prior to the selection of cases, e.g. outcome of interest in this study design. In addition, selecting a proper group of controls can be one of the most demanding aspects of a TCC study. The controls should be chosen so that the distribution of vaccination among the controls is the same as the distribution of vaccination in the target population that gave rise to the cases. The investigator may also consider the control group to be an at-risk population, with the potential to develop the outcome. One common approach is to randomly select asymptomatic and disease-free individuals from the target population. One method used in an attempt to ensure comparability between cases and controls and reduces variability and systematic differences due to background variables that are not of interest of the investigator is matching. Each case is typically individually paired with one or more control subjects with respect to the background variables by time. Meanwhile, a TCC study is susceptible to various sources of bias, which we will introduce later. These biases will affect the estimation of VE in TCC studies.

1.5.1.2 Test-negative Studies

The test-negative (TN) design is a special case of TCC design, it is increasingly used for annual influenza VE estimation. The first TN study was published for influenza VE estimation in Canada in 2007 (Skowronski (2005); Skowronski et al. (2007)). Since then, this approach has been widely used within existing surveillance structures annually in Canada. Investigators in Europe (Kissling et al. (2009, 2013); Pebody et al. (2013); McMenamin et al. (2013)), the Unites States (Belongia et al. (2009); Treanor et al. (2012); Centers for Disease Control and Prevention (CDC) (2013)) and Australia (Kelly et al. (2009); Fielding et al. (2012)) also began to publish VE findings based on TN study from 2009 following a publication on the methodological

validity of the TN study (Orenstein et al. (2007)). In TN study, the target population for enrollment consists of all persons who seek care for a defined set of symptoms, typically ARI; cases are those with positive tests for influenza, and controls are those with negative tests. VE is calculated as:

$$VE = 1 - OR = 1 - \frac{O_{\text{pos}}}{O_{\text{neg}}}, \tag{1.4}$$

where O_{pos} is the odds of vaccination among those testing positive for influenza, and O_{neg} is the odds of vaccination among those testing negative.

The TN study is predicated on the core assumption that influenza vaccine only protects against influenza, and has no effect on other non-influenza causes of ILI (Jackson and Nelson (2013); Foppa et al. (2013)), a core premise that has been validated through randomized controlled trial data sets (De Serres et al. (2013)). It has several advantages. Firstly, cases and controls in TN studies come from the same communities since they have sought medical care at the same communities, which will reduce the bias. Secondly, cases and controls seek medical care for ARI symptoms. This reduces confounding due to differences in healthcare seeking behavior between cases and controls. Although imperfect sensitivity and specificity of influenza testing cause bias in VE estimation, in the context of RT-PCR whose sensitivity is as low as 70% and near-perfect specificity, outcome misclassification has been shown to have trivial impact on VE estimates derived by the TN study (Jackson and Rothman (2015)).

The TN study need to be used in caution while it has lots of important strengths. Validation of core assumption is inevitable. Also, since TN study only select subjects who seek medical care, this may not reflect the entire community or population accurately. VE estimates from TN studies seem to be appropriate for estimating VE against MAI, but their performance as estimates of VE against SI has not been

studied yet. In this dissertation, we will compare VE estimates from TCC and TN studies with respect to their bias and precision for each of the outcomes of interest.

1.5.2 Cohort Studies

The term "cohort" is derived from the Latin word *cohors*, the modern epidemiological definition of the word now means a "group of people with defined characteristics who are followed up to determine incidence of, or mortality from, some specific disease, all causes of death, or some other outcome"(Morabia (2004)). Cohort studies are also commonly used to estimate influenza VE. In a cohort study, a disease-free study population is first identified by the vaccination status, and separated into vaccinated or unvaccinated groups. These individuals are then followed up for a given time period (usually until the end of the influenza season). Because vaccination status is identified before the beginning of the study, cohort studies have a temporal framework to assess causality and thus have the potential to provide strong scientific evidence. The cohort study can be thought of as a source population that gives rise to the cases, and a case-control study can also be thought of as a sample of data from a hypothetical cohort study.

Cohort studies can be categorized into two categories based on the types of surveillance: active surveillance or passive surveillance. In a cohort study with active surveillance, every subject who develops ARI is identified and tested for influenza infection; this is usually called monitored cohort study. The other type of cohort study is an unmonitored study which is based on passive surveillance; only those who seek medical care for ARI are test. In a monitored cohort study, participants will be reminded weekly to report ARI symptoms to the study coordinator. When a participant has reported a symptom that can be attributed to influenza, a swab is taken and sent to a laboratory for testing. In an unmonitored cohort study, when a participant has decided to seek medical care for an ARI, s/he will be tested for influenza infection. In

both studies, a person who tests positive for influenza infection is eligible to be considered as a case. In cohort study, VE is estimated from risk ratio, which is the ratio comparing the cumulative incidence rate of the outcome of interest among vaccinated and unvaccinated persons,

$$VE = 1 - RR = 1 - \frac{CI_{\mathrm{v}}}{CI_{\mathrm{u}}}, \tag{1.5}$$

where CI_{v} is the cumulative incidence rate in the vaccinated persons and CI_{u} is the cumulative incidence rate in the unvaccinated persons.

Comparing to other observational studies, the results of cohort studies are relatively easy to communicate to policy maker, and due to the fact that cohort studies can directly estimate incidence rate, these studies can be used to estimate the burden of influenza in the vaccinated and unvaccinated and to estimate the number of cases averted by vaccination provided that unvaccinated population is available for a comparison.

Cohort studies also present important challenges in estimating influenza VE. First, investigators need to be able to enumerate cohorts of vaccinated and unvaccinated subjects, and identify the study outcomes in both the vaccinated and unvaccinated cohorts. In addition, as with all other observational studies, the confounding due to differences, such as behavior of seeking medical care, health condition, and risk of severe disease, in vaccinated subjects compared to unvaccinated subjects must be taken into consideration.

Meanwhile, since the overall incidence of influenza in a given season is quite low (5% - 10%), cohort studies will have to involve a large number of subjects in order to achieve a statistically significant effect of vaccination. The expense of a well-design cohort study is generally high. One of the objectives of this dissertation is to compare bias and precision between cohort and case-control studies.

1.5.3 Main Sources of Bias in Observational Studies

In the face of a lack of random sampling and random vaccination, observational studies designed to estimate influenza VE may be subject to numerous sources of bias.

(a) Probabilities of non-influenza ARI may depend on vaccination status: In TN studies, individuals with non-influenza ARI serve as controls. Therefore, TN studies may produce biased estimates of VE unless vaccinees and non-vaccinees are equally likely to develop non-influenza ARI. The validity of this assumption has not yet been confirmed. De Serres et al. (De Serres et al. (2013)) used data from randomized clinical trials to argue that this assumption is usually satisfied. However, a randomized influenza vaccine trial (Cowling et al. (2012)) found that vaccinees had a significantly increased risk of virologically-confirmed non-influenza infection (that may lead to ARI) as compared to those who received the placebo.

(b) Ascertainment of cases (selection bias): A person who develops an ARI may or may not seek medical care. In both TCC and TN studies, only persons seeking medical care for ARI may be tested and considered cases. This subset of cases who seek care for ARI may not be a representative sample of all cases.

(c) Confounding by propensity of seeking medical care: The likelihood of seeking medical care may be related to (1) a person's vaccination status, as vaccinated individuals may be more health-conscious so that their probability of seeking care for ARI may be different from that of unvaccinated persons, and (2) a person's probability of becoming a case when the outcome of interest is MAI.

(d) Other confounders: Health status, age, exposure, education, and socioeconomic status, may be associated with both the likelihood of being vaccinated and the likelihood of becoming influenza-infected, developing ARI and seeking medical care.

(e) Misclassification bias: Diagnostic tests for influenza viruses are not 100% sensitive and specific. Vaccination status may also be misclassified.

Several sources of bias may be present in some or all of the four observational study designs (Table 1.1).

Source of Bias	Description	Study Designs Affected
1	Vaccination affect the probability of NFAIR	TN, PSC
2	Selection Bias	TN, TCC, PSC
3	Vaccination affects the probability of seeking medical care	TN, TCC, PSC
4	Covariates associated with the probability of vaccination, NFARI, and FARI	All
5	Covariates associated with the probability of vaccination and seeking medical care	TN, TCC, PSC
6	Misclassification of influenza status and vaccination status	All

Table 1.1: Sources of bias and the corresponding study designs that are impacted by each source of bias.

1.6 Objectives of this dissertation

This study is motivated by several challenges in the estimation of influenza VE. (1) As we discuss before, influenza VE must be re-estimated every season due to the antigenic variation of influenza virus. (2)RCTs for estimating influenza VE are no longer ethical since annual vaccination is now widely recommended. (3) Observational studies have been increasingly used in VE estimation, but they are prone to multiple sources of bias. (4) In influenza VE estimation, it is significant to specify the outcome of interest, since the bias of the VE estimates depends on the outcome, against which the vaccine is supposed to protect.

This dissertation aims to evaluate the effects of various sources of bias and the effect of different outcomes of interest in VE estimates in observational studies, and to develop new study designs to produce improved estimates of influenza VE.

Topic 1: A Comparison of the Test-Negative and the Traditional Case-Control Study Designs for Estimation of Influenza Vaccine Effectiveness under Nonrandom Vaccination

In the first topic, we evaluated the impact of the sources of bias in VE estimates against two outcomes of interest in two popular case-control study designs by developing a probability model. By detailed comparison, we can help provide guidance on choosing outcomes of interest and study designs under different circumstances.

Topic 2: Estimation of Influenza Vaccine Effectiveness Using Agent-based Stochastic Simulation Model in Observational Studies

In the second topic, we evaluated the bias and the precision for 4 observational study designs (two case-control study designs and two cohort study designs) using the data generated from our agent-based stochastic simulation model. Also, we can use this model to validate our results in Topic 1. Besides that, we proposed several methods to correct the bias for test negative study.

Topic 3: Waning of Influenza Vaccine Effectiveness in Cohort and Test-Negative Studies

In the third topic, since the influenza activity usually peaks between December, but influenza vaccines are available as early as July. As a result, there can be relative long periods between vaccination and potential exposure, raising concerns about the probability of waning vaccine efficacy over a single season. We analyze data generated from SIMFLU using three different methods evaluate waning vaccine efficacy in both cohort study and test negative study.

Chapter 2

A Comparison of the Test-Negative and the Traditional Case-Control Study Designs for Estimation of Influenza Vaccine Effectiveness under Nonrandom Vaccination

2.1 Introduction

Influenza vaccine effectiveness (VE) has to be re-estimated in every season because predominant influenza virus types, subtypes and phenotypes change from one season to the next, necessitating a new vaccine targeting different strains in most seasons. As annual influenza vaccination is now widely recommended, randomized clinical trials for estimating VE are no longer ethical in many populations, and observational studies based on patients seeking medical care for acute respiratory illnesses (ARI) remain the only option. However, observational studies for estimating VE are prone to multiple sources of bias.

In this chapter we present a new probability model for comparing the bias and precision of VE estimates from two popular case-control study designs under nonrandom vaccination, i.e., vaccination probabilities may depend on a covariate. In both study designs, ARI patients seeking medical care who test positive for influenza infection are considered cases. In the test-negative (TN) design, ARI patients seeking medical care who test negative for influenza infection serve as controls, while in the traditional case-control (TCC) design, individuals who did not develop an ARI are randomly selected from the study population to serve as controls.

The goal of this topic is to evaluate and compare the bias and precision of estimates of VE resulting from TN and TCC studies. As we will see, the bias of VE estimates may depend on the outcome of interest, i.e., the outcome against which the vaccine is expected to protect. We consider two outcomes of interest, symptomatic influenza (SI) and medically-attended influenza (MAI). In both the TN and TCC study designs, only influenza patients seeking medical care are considered cases. Therefore, one expects these study designs to produce estimates of VE against MAI. However, lay persons may interpret these estimates as VE against *any influenza illness*, i.e., VE against SI.

We will (a) evaluate the bias of each of the VE estimates for each of the outcomes

by comparing the expected value of the estimate with the true VE, and (b) evaluate the standard errors of the VE estimates. To perform these evaluations and comparisons, we developed a detailed stepwise probability model of the process involved in collecting data in these studies and deriving VE estimates. The model includes a covariate, health status, that may be associated with the likelihood of being vaccinated, of developing ARI, of seeking medical care against ARI. This allows us to assess the effects of nonrandom vaccination on the bias of VE estimates.

2.2 Methodology

We first describe the real-life process involved in conducting the two types of case-control studies and obtaining the estimates of VE. We then describe the model we developed to mimic this process.

2.2.1 The study population

The source population for both types of case-control studies consists of all individuals receiving most of their medical care at a single clinic or at a specific network of clinics. Since influenza VE varies by age, we can assume that the model pertains to a subpopulation corresponding to a single age group.

2.2.2 The study designs

When a member of the study population develops an ARI, s/he may decide to report to a clinic for treatment. At the clinic, the health care provider may ask the person to be tested for influenza viruses. If the person agrees then a swab is taken and sent to a laboratory for testing. In both study designs, a person who tests positive is eligible to be considered a case. In a TN study, an individual who tests negative is eligible to be considered a control. In a TCC study, controls are randomly selected members

of the study population who have not developed ARI prior to their inclusion in the study. Usually, one or more controls are selected right after a case is identified. In both study designs, the vaccination status of every case or control is determined from manual or electronic records, or from oral histories.

2.2.3 Outcome of interest and true VE

In this chapter we evaluate estimates of VE when the outcome of interest is either SI or MAI. SI is sometimes called 'influenza illness' or 'influenza ARI'. Surveillance for SI is needed in the entire study population, and for a person who develops compatible symptoms, a throat swab is taken for testing. A person is considered a true case of SI if s/he has an ARI and is infected by an influenza virus. For MAI, a true case is defined as a person who is influenza-infected, develops an ARI, and seeks medical care. In both cases, the true VE is defined as one minus the ratio of the probability of the outcome of interest in vaccinees and non-vaccinees.

2.2.4 Estimation of VE and bias of VE estimates

We only consider estimates of VE that are not adjusted for possible confounders. In case-control studies, VE is usually estimated as one minus the odds ratio (OR) of being vaccinated in cases vs. controls. The bias of the estimate is defined as the difference between the expectation of the estimated VE and the true VE.

2.2.5 The model

The model we developed for comparing the estimates from the two study designs follows the scheme described above with a few simplifications. We assume that (a) when a person seeks medical care for ARI then her/his probability of being tested for influenza viruses does not depend on vaccination status, health status, or on the

actual cause of ARI (influenza/non-influenza); (b) given a person's symptoms and influenza infection status, the sensitivity and specificity of the test do not depend on the tested person's vaccination or health status; (c) a person's vaccination status is determined without error; and (d) controls in a TCC study are selected at random from all asymptomatic individuals in the study population (See section: The study population).

Our model includes a covariate, health status, and we assume that a person's probabilities of being vaccinated, developing an ARI, and seeking medical care against ARI may be associated with her/his health status. In this way, the model generates possible confounding effects linking vaccination status with the probabilities of being included in the study and of becoming a case or a control.

The model consists of five steps, where the value of a single variable is determined at each step. The probability distribution of this variable may depend on the values of the variables from the previous steps. Below we define the five steps, the associated variables, and the probabilities determining each variable's distribution.

Step 1: Health Status.

A person can be classified as "healthy" or "frail". Define a binary variable X, where $X = 1$ for a "healthy" person and $X = 0$ for a "frail" person. Denote $\pi = P(X = 1)$.

Step 2: Vaccination.

A person may be vaccinated against influenza. Define a binary variable V, where $V = 1$ for a vaccinated person. The probability of being vaccinated may depend on health status; therefore, denote $\alpha_x = P(V = 1|X = x)$, $x = 0, 1$.

Step 3: Influenza infection and ARI.

During the influenza season, a person may become infected with an influenza virus and develop an ARI. This outcome is referred to as "influenza ARI" (FARI), where "F" stands for flu. A person may also develop an ARI not resulting from influenza infection. This outcome is referred to as "non-influenza ARI" (NFARI). We therefore define an outcome variable Y with 3 categories as follows: $Y = 0$ for no ARI, $Y = 1$ for NFARI, and $Y = 2$ for FARI. The distribution of Y depends on the person's vaccination status, V, and health status, X. We denote $\beta_{vx} = P(Y = 1|V = v, X = x)$, $v = 0, 1$, $x = 0, 1$ and $\gamma_{vx} = P(Y = 2|V = v, X = x)$ for $v = 0, 1$, $x = 0, 1$ with $\beta_{vx} + \gamma_{vx} \leq 1$ for all v, x. Here we assume the "leaky vaccine" model, in which the vaccine provides a reduction in the probability of influenza transmission to the vaccinated person, rather than complete immunity(Haber et al. (1991)). Under this model, a vaccinee has a lower probability of becoming infected than a non-vaccinee, but is not rendered completely immune from influenza infection.

Step 4: Seeking medical care for ARI.

A person with ARI may seek medical care and, in this case, be tested for influenza viruses. We define a binary variable M with $M = 1$ for a person seeking medical care for her/his ARI. The probability of this event depends on Y (only individuals with ARI seek medical care), and it may be different for FARI and NFARI patients. In addition, the conditional distribution of M given Y may depend on X and V. We therefore define $\delta_{yvx} = P(M = 1|Y = y, V = v, X = x)$, where $y = 1, 2$, $v = 0, 1$ and $x = 0, 1$.

In order to reduce the number of parameters, we make two simplifying assumptions regarding the probabilities of seeking medical care: (1) the effect of health status on probability of seeking medical care does not depend on vaccination status or type of ARI; (2) the effect of vaccination status on probability of seeking medical care does

not depend on health status (but it may depend on type of ARI).

Define a "standard person" as a person with X = 0 and V = 0. For a "standard person", we define δ_{SN}, δ_{SF} as follows:

- $\delta_{SN} = P(M = 1|Y = 1, V = 0, X = 0) = \delta_{100}$
- $\delta_{SF} = P(M = 1|Y = 2, V = 0, X = 0) = \delta_{200}$

In addition, we define two multipliers:

- λ = multiplier for x = 1; λ does not depend on V and Y.
- Ψ_F = multiplier for v=1 only when y=2; Ψ_F does not depend on X.

Then, $\{\delta_{yvx}\}$ can be written in terms of δ_{SN}, δ_{SF} and the multipliers λ, Ψ_F as follows:

- $\delta_{100} = \delta_{SN}$, $\delta_{101} = \delta_{SN} * \lambda$, $\delta_{110} = \delta_{SN}$, $\delta_{111} = \delta_{SN} * \lambda$.
- $\delta_{200} = \delta_{SF}$, $\delta_{201} = \delta_{SF} * \lambda$, $\delta_{210} = \delta_{SF} * \Psi_F$, $\delta_{211} = \delta_{SF} * \lambda * \Psi_F$.

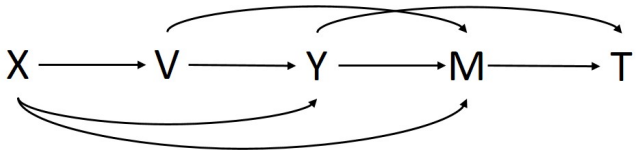
Note: The multiplier Ψ_F reflects the effect of severity of ARI in an influenza infected person. We assume that vaccination may reduce severity of symptoms, hence a vaccinated influenza patient may be less likely to seek care than an unvaccinated patient.

Step 5: Testing for influenza infection.

Although only individuals who seek medical care for an ARI are tested for influenza infection, it will be convenient to define a binary variable T as the (possibly unobserved) test result for any person with an ARI. Define $T = 1$ ($T = 0$) if a person would test positive (negative) for influenza if tested. Because of assumption (b) above, the probability of testing positive given the person's influenza infection status does not depend on X, V, or M. Denote $\tau_y = P(T = 1|Y = y)$ for $y = 1, 2$. Note that τ_1 is one minus the test's specificity and τ_2 is the test's sensitivity. In this study, we assume

the test has 100% sensitivity and 100% specificity, i.e. $P(T = 1|Y = 1) = \tau_1 = 0$ and $P(T = 1|Y = 2) = \tau_2 = 1$.

Figure 2.1 shows the directed acyclic graph (DAG) of the model. Recent papers by Sullivan *et al.* (Sullivan et al. (2016)) and Lipsitch *et al.* (Lipsitch et al. (2016)) discuss the use of DAGs to explore sources of bias of VE estimates from TN studies. A summary of the variables and parameters in our model is given in Table A.1.



X = Health status V = Vaccination Y = Outcome (type of ARI)
M = Seeking medical care T = Result of test for influenza infection

Figure 2.1: DAG of the model

2.2.6 True VE in our model

When we evaluate the true VE, we assume that vaccination is done *at random*, i.e. for true VE we assume that vaccination status does not depend on health status X ($\alpha_0 = \alpha_1 = \alpha$).

The true VE against SI is:

$$VET_{SI} = 1 - RRT_{SI} \quad \text{where} \quad RRT_{SI} = \frac{P(Y = 2|V = 1)}{P(Y = 2|V = 0)}.$$

The true VE against MAI is:

$$VET_{MAI} = 1 - RRT_{MAI} \quad \text{where} \quad RRT_{MAI} = \frac{P(Y = 2, M = 1|V = 1)}{P(Y = 2, M = 1|V = 0)}.$$

Using the parameters defined above, VET_{SI} and VET_{MAI} can be written as:

$$VET_{SI} = 1 - RRT_{SI} = 1 - \frac{\gamma_{10}(1-\pi) + \gamma_{11}\pi}{\gamma_{00}(1-\pi) + \gamma_{01}\pi} \tag{2.1}$$

$$VET_{MAI} = 1 - RRT_{MAI} = 1 - \frac{\Psi_F[\gamma_{10}(1-\pi) + \lambda\gamma_{11}\pi]}{\gamma_{00}(1-\pi) + \lambda\gamma_{01}\pi}. \tag{2.2}$$

The proofs of these results can be found in Appendix 1.

2.2.7 Estimates of VE in our model

Although the true VEs against SI and MAI may differ, most VE studies use the same estimate regardless of the outcome of interest. Therefore, we only consider a single VE estimate for each study design, namely 1 minus the odds ratio (OR) in the $C \times V$ table cross-classifying the individuals included in the study, where C is a binary indicator of case/control status with $C = 1$ for a case. For convenience, the TN and TCC studies will be represented by the letters A and B, respectively. In a TN study, the case/control variable is denoted C_A, where $(C_A = 1) = (M = 1, T = 1)$ and $(C_A = 0) = (M = 1, T = 0)$. Then the estimate of VE is: $VE_A = 1 - OR_A$, where

$$OR_A = \frac{P(C_A = 1, V = 1|M = 1)P(C_A = 0, V = 0|M = 1)}{P(C_A = 1, V = 0|M = 1)P(C_A = 0, V = 1|M = 1)}.$$

Note that all the probabilities condition on $M = 1$ as only individuals who seek medical care for ARI are included in the TN study.

In a TCC study, the case/control variable is denoted C_B. Cases are defined in the same way as in the TN study, i.e., $(C_B = 1) = (M = 1, T = 1) = (C_A = 1)$. Controls are individuals included in a random sample drawn from all the asymptomatic individuals in the study population. In other words, $(C_B = 0)$ is a random subset of $(Y = 0)$. In addition, we define a binary variable B indicating whether or not a person is included in the TCC study, i.e., $(B = 1) = (C_B = 1$ or $C_B = 0)$. The VE

estimate is based on the OR in the $C_B \times V$ table when all the probabilities condition on $B = 1$: $VE_B = 1 - OR_B$, where

$$OR_B = \frac{P(C_B = 1, V = 1|B = 1)P(C_B = 0, V = 0|B = 1)}{P(C_B = 1, V = 0|B = 1)P(C_B = 0, V = 1|B = 1)}.$$

Note that in a real-life study, the odds ratios are estimated from the relative frequencies of the corresponding events, rather than from their (unknown) probabilities. Therefore, the model-based estimates of VE defined above are actually the expected values of the observed estimates. For convenience we will continue to refer to them as "the VE estimates".

Using the parameters defined above, VE_A and VE_B can be written as follows:

$$VE_A = 1 - \frac{\Psi_F[\gamma_{10}\alpha_0(1-\pi) + \lambda\gamma_{11}\alpha_1\pi][\beta_{00}(1-\alpha_0)(1-\pi) + \lambda\beta_{01}(1-\alpha_1)\pi]}{[\gamma_{00}(1-\alpha_0)(1-\pi) + \lambda\gamma_{01}(1-\alpha_1)\pi][\beta_{10}\alpha_0(1-\pi) + \lambda\beta_{11}\alpha_1\pi]}, \quad (2.3)$$

$$VE_B = 1 - \frac{\Psi_F[\gamma_{10}\alpha_0(1-\pi) + \lambda\gamma_{11}\alpha_1\pi][(1-\gamma_{00}-\beta_{00})(1-\alpha_0)(1-\pi) + (1-\gamma_{01}-\beta_{01})(1-\alpha_1)\pi]}{[\gamma_{00}(1-\alpha_0)(1-\pi) + \lambda\gamma_{01}(1-\alpha_1)\pi][(1-\gamma_{10}-\beta_{10})\alpha_0(1-\pi) + (1-\gamma_{11}-\beta_{11})\alpha_1\pi]}. \quad (2.4)$$

The proofs can be found in Appendix 2.

2.2.8 Bias and standard errors of estimates

The bias of an estimate of VE is the difference between the expected value of the estimate and the true VE.

In Appendix 3 we use approximations based on the "Delta method" for the standard errors (SEs) of odds ratios (Agresti (2013)) to derive expressions for the SEs of both VE estimates in terms of the parameters and the corresponding sample size(s).

For evaluating the SEs we consider the observed odds ratios, where the probabilities are replaced by the corresponding observed relative frequencies.

2.2.9 Probability Ratios

Next, we define a few probability ratios comparing vaccinees and non-vaccinees or healthy and frail individuals. These ratios will be helpful in the presentation of the results (see Table A.1 for a full list of the notations used in this paper).

- $\rho_\beta = \frac{\beta_{1x}}{\beta_{0x}}$, the ratio of the probabilities of NFARI comparing a vaccinated and an unvaccinated person of the same health status.

- $\eta_\beta = \frac{\beta_{v1}}{\beta_{v0}}$, the ratio of the probabilities of NFARI comparing a healthy and a frail person of the same vaccination status.

- $\rho_\gamma = \frac{\gamma_{1x}}{\gamma_{0x}}$, the ratio of the probabilities of FARI comparing a vaccinated and an unvaccinated person of the same health status.

- $\eta_\gamma = \frac{\gamma_{v1}}{\gamma_{v0}}$, the ratio of the probabilities of FARI comparing a healthy and a frail person of the same vaccination status.

The parameters λ and Ψ_F defined earlier are also probability ratios:

- $\lambda = \frac{\delta_{yv1}}{\delta_{yv0}}$ The ratio of the probabilities of seeking medical care comparing a healthy and a frail person of the same vaccination status. We assume that this ratio is the same for FARI and NFARI patients.

- $\Psi_F = \frac{\delta_{21x}}{\delta_{20x}}$ The ratio of the probabilities of seeking medical care comparing a vaccinated and an unvaccinated FARI patient of the same health status.

2.3 Results

2.3.1 Sources of Bias

Table A.2 presents the main sources of bias that can be identified from our model. The absence of bias A is essential for the validity of the TN design, since the VE estimate from this design is based on comparing the odds of being vaccinated in FARI patients (cases) and NFARI patients (controls). This bias may be a result of virus interference(Cowling et al. (2012)) (if vaccinees are more likely than non-vaccinees to contract NFARI, then the estimated VE will be falsely high). Biases B1 and B2 represent the effects of health status on the probabilities of NFARI and FARI, respectively. These effects, which are sometimes called the '*healthy vaccinee effect*', represent the confounding resulting from association of health status with the probability of exposure (vaccination) and the outcome. Bias BS is a special case of $B1 \cap B2$. It results when health status affects both the probabilities of FARI and NFARI but the risk ratios comparing a healthy and a frail person are the same for the both types of ARIs. Bias C represents the effect of vaccination status on the probability of seeking care in patients with SI. This effect may be due to less severe symptoms in vaccinated persons compared to unvaccinated ones. Bias D represents the effect of health status on the probability of seeking medical care against FARI and NFARI. As stated earlier, we assume perfect sensitivity and specificity of the influenza test ($\tau_1 = 0$, $\tau_2 = 1$), as it is well-known that misclassifications result in negatively-biased estimates of effectiveness.

We first state conditions for the unbiasedness of the VE estimate based on the TN design. The proofs of these results can be found in Appendix 4.

(1) Under random vaccination ($\alpha_0 = \alpha_1$), the estimate of VE when the outcome of interest is SI is unbiased if biases A and C are absent. When the outcome of

interest is MAI, the estimate of VE is unbiased if bias A is absent.

(2) Under non-random vaccination ($\alpha_0 \neq \alpha_1$), the estimate of VE when the outcome of interest is SI is unbiased if biases A, B1, B2, and C are absent. When the outcome of interest is MAI, the estimate of VE is unbiased if biases A, B1, and B2 are absent.

Next we explore the magnitude of the effects of various sources of bias and their combinations. We consider three scenarios for vaccination probabilities (see Table A.3). In Table A.4 we present the range and the maximum absolute value of the bias of VE estimates resulting from TN and TCC studies under the three vaccination scenarios and various combinations of sources of bias. For these results we used the following baseline values of some of the parameters: $\pi = 0.7$, $\beta_{00} = 0.2$, $\gamma_{00} = 0.1$, $\delta_{SN} = 0.2$, $\delta_{SF} = 0.3$, $\rho_\gamma = 0.4$. π is the probability of being 'healthy'; β_{00} and γ_{00} are the probabilities of NFARI and FARI, respectively, for an unvaccinated 'frail' person; δ_{SN} and δ_{FN} are the probabilities of seeking medical care for NFARI and FARI, respectively, for an unvaccinated 'frail' person; ρ_γ is the risk ratio comparing the probability of FARI for a vaccinated and an unvaccinated person - thus, the true VE against SI is 1 - 0.4 = 0.6 (60%). The values of β, γ are based on table A1 in Haber et al. 2015 (Haber et al. (2015)), and the values of δ are from the literature. In all the tables, figures and examples, values of VE are presented as fractions, rather than percentages.

In the calculations for tables A.4 and A.5, when a source of bias was present we used a reasonable range for the corresponding probability ratio. When bias A was present, ρ_β was allowed to vary from 0.5 to 2.0. For biases B1, B2, and BS, we allowed η_β and η_γ to vary between 0.5 and 1.0, since one would not expect frail persons to have lower probabilities of ARI, compared to healthy persons. For bias C, the ratio Ψ_F could vary between 0.5 to 1.0, since one would expect vaccination to reduce the

probability that a person with SI will seek medical care compared to a person with ARI resulting from a different pathogen. For bias D, we let λ vary between 0.5 to 2.0.

For each combination of two or more sources of bias, we calculated the minimum, mean, and maximum of the bias and the absolute values of the bias by allowing the probability ratios that are not fixed to vary independently in the ranges specified above. For example, when biases A, B1, and B2 are absent, we used $\rho_\beta = \eta_\beta = \eta_\gamma = 1$, $0.5 \leq \Psi_F \leq 1$, $0.5 \leq \lambda \leq 2$.

2.3.2 Summary of Results

2.3.2.1 The impact of sources of bias

Our model allows us to evaluate the impact of the sources of bias listed in Table A.2. Each source of bias is a result of a possible effect of vaccination or health status on the probability of FARI or NFARI or seeking care. Below we summarize our results for each of the sources of bias. We also use numerical examples to illustrate the magnitude and direction associated with each source of bias. *Unless otherwise specified, the true VEs against SI and MAI are 0.6 (60%).* In each of these examples we assume that only one source of bias is present.

(1) **Vaccination affects the probability of NFARI (bias A)**

- This bias does not depend on vaccination scenario nor on the outcome of interest (SI or MAI).
- Estimates of VE from TN studies may suffer from severe bias.
- This effect also affects the bias of VE estimates from TCC studies, though to a lesser extent.

- **Example:** As the ratio of the probability of NFARI comparing vaccinated and unvaccinated persons varies from 0.5 to 2.0, VE estimates from TN studies range from 0.2 to 0.8, respectively, while VE estimates from TCC studies range from 0.67 to 0.50, respectively (Figure 2.2).

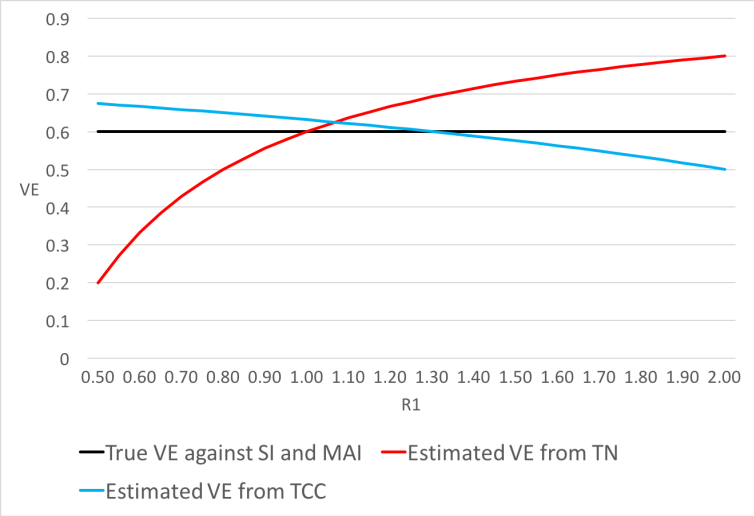


Figure 2.2: True and estimated VEs as a function of R1 = P(NFARI if vaccinated)/P(NFARI if unvaccinated) when only bias A is present.

(2) Health status affects the probabilities of FARI and NFARI (biases B1, B2 - the '*healthy vaccinee effect*')

- The bias does not depend on the outcome of interest (SI or MAI).
- Under non-random vaccination, these effects may result in substantial bias of VE estimates from TN or TCC studies. However, this bias is usually less severe compared to the biases resulting from sources A, C and D.
- If the effect of health status on the probability of ARI is the same for FARI and NFARI, i.e., bias BS is present, then the TN-based estimates of VE are unbiased.
- **Example:** Suppose that the probabilities of vaccination are 0.8 and 0.4 for

healthy and frail persons, respectively. Consider three cases regarding the *risk ratios* P(ARI in a healthy person) / P(ARI in a frail person): (a) When these risk ratios are 0.5 for NFARI and 0.8 for FARI, then the estimated VEs from TN and TCC studies are 0.51 and 0.67, respectively. (b) When the risk ratios are 0.8 for NFARI and 0.5 for FARI, then estimated VEs from TN and TCC studies are 0.67 and 0.72, respectively. (c) When the risk ratios for NFARI and FARI are equal and their common value ranges from 0.5 to 1.0, then estimated VEs from TN studies are always unbiased (i.e., they equal 0.6), while estimates from TCC studies range from 0.63 to 0.73. In Figures 2.3 and 2.4, we set the risk ratio for NFARI to 0.75 and let the risk ratio for FARI vary between 0.5 to 1.0.

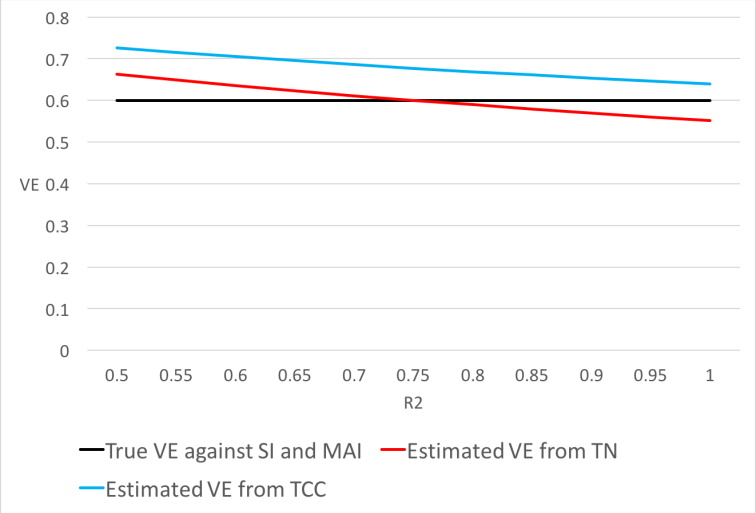


Figure 2.3: True and estimated VEs when only biases B1 and B2 are present. We set the risk ratio P(NFARI if healthy)/P(NFARI if frail) = 0.75 and let the risk ratio R2 = P(FARI if healthy)/P(FARI if frail) vary between 0.5 to 1.0. The probabilities of vaccination are 0.4 and 0.8 for healthy and frail persons, respectively.

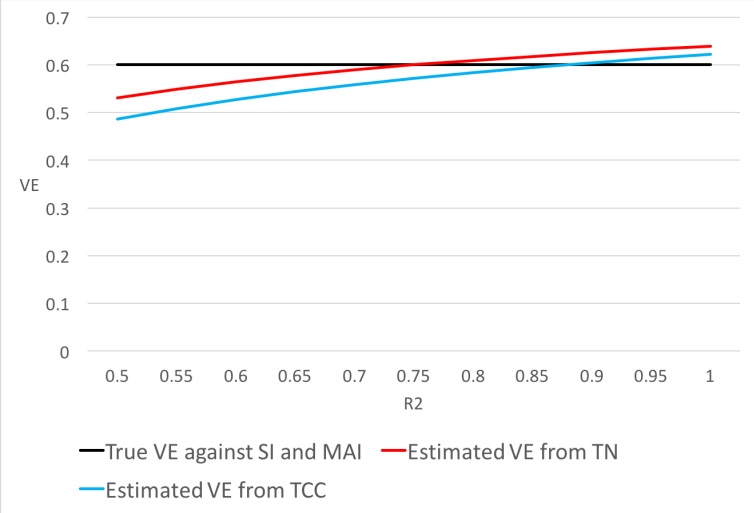


Figure 2.4: True and estimated VEs when only biases B1 and B2 are present. We set the risk ratio P(NFARI if healthy)/P(NFARI if frail) = 0.75 and let the risk ratio R2 = P(FARI if healthy)/P(FARI if frail) vary between 0.5 to 1.0. The probabilities of vaccination are 0.8 and 0.4 for healthy and frail persons, respectively.

(3) **Vaccination affects the probability of seeking medical care for FARI, but it does not affect the probability of seeking care for NFARI (bias C)**

- When this effect is present then the true VEs against SI and MAI may be different, thus the estimates' bias may depend on the outcome of interest.
- If all other sources of bias are absent, the bias of VE estimates does not depend on the vaccination scenario.
- Estimates of VE from TN or TCC studies may be severely biased when the outcome of interest is SI.
- When the outcome of interest is MAI, estimates of VE from TN studies are unbiased, while the bias of estimates from TCC studies is usually small and is not affected by the magnitude of the effect underlying this source of bias.

- **Example:** Let the ratio R = P(seeking medical care against FARI if vaccinated) / P(seeking medical care against FARI if unvaccinated) vary from 0.5 to 1.0. Then the true VE against SI remains fixed at 0.6, while the true VE against MAI varies with R from 0.8 to 0.6. The estimated VEs from TN studies equal the true VE against MAI for all values of R, while the estimated VEs from TCC studies vary from 0.82 to 0.63 (see Figure 2.5). For example, when R=0.5 then the true VE against MAI is 0.80, and the VE estimates from TN and TCC studies are 0.80 and 0.82, respectively. This translates into severe bias when the outcome of interest is SI but small bias when the outcome of interest is MAI, since bases on the true VE against MAI we got (equation 2.2), MAI is a function of R.

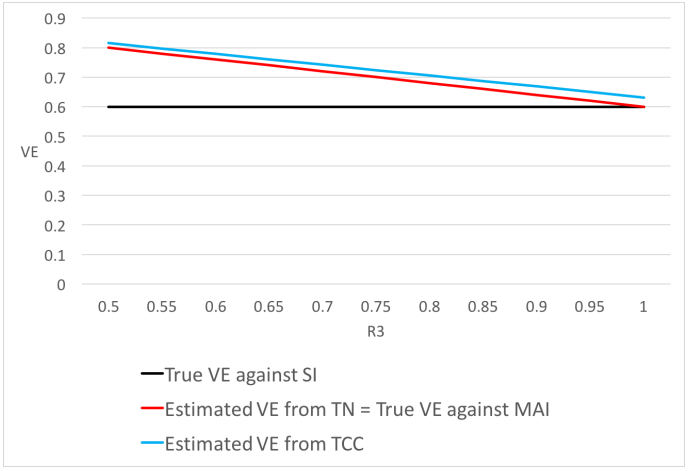


Figure 2.5: True and estimated VEs when only bias C is present as function of R3 = P(seeking medical care against FARI if vaccinated)/P(seeking medical care against FARI if unvaccinated)

(4) Health status affects the probabilities of seeking care against FARI and NFARI (bias D)

- The bias of VE estimates does not depend on the outcome of interest (SI or MAI).

- In the absence of other sources of bias, VE estimates from TN studies are unbiased regardless of the vaccination scenario.
- Under non-random vaccination, this effect may result in substantial bias in VE estimates from TCC studies.
- **Example:** We assume that the probabilities of seeking care do not depend on vaccination status. As the ratio of the probabilities of seeking care comparing healthy and frail individuals varies from 0.5 to 2.0, VE estimates from TN studies remain fixed at 0.6 (i.e., they are unbiased) under both random and non-random vaccination. When the probabilities of vaccination are 0.8 and 0.4 for healthy and frail persons, respectively, the VE estimates from TCC studies vary from 0.72 to 0.53 (Figures 2.6 and 2.7).

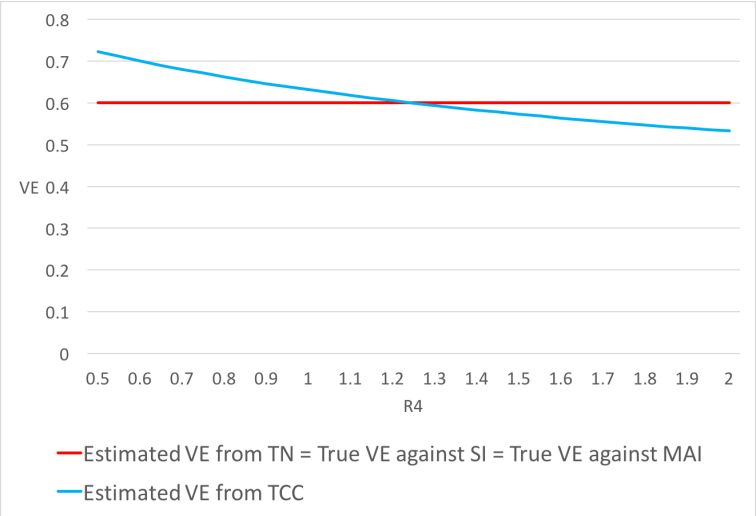


Figure 2.6: True and estimated VEs when only bias D is present as function of R4 = P(seeking medical care if healthy)/P(seeking medical care if frail). Probabilities of vaccination are 0.8 and 0.4 for healthy and frail persons, respectively.

In addition, we found that in some cases the true VEs against SI and MAI are different. Hence, the bias of VE estimates may depend on the outcome against which the vaccine is supposed to protect. For example, if the only sources of bias are

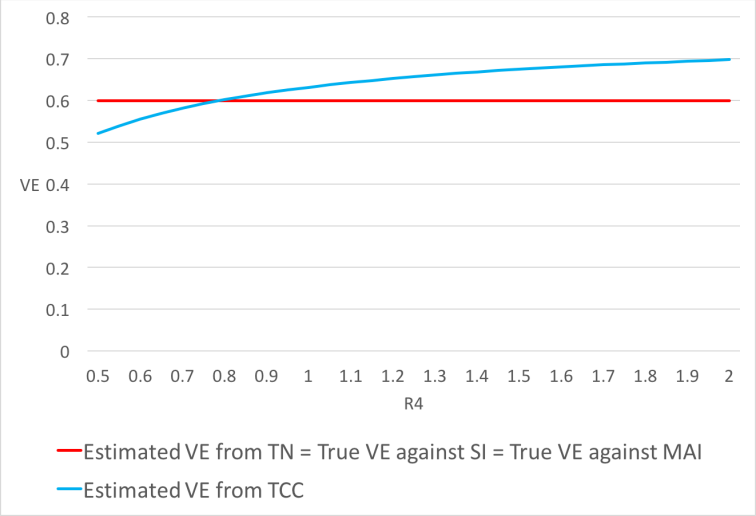


Figure 2.7: True and estimated VEs when only bias D is present as function of R4 = P(seeking medical care if healthy)/P(seeking medical care if frail). Probabilities of vaccination are 0.4 and 0.8 for healthy and frail persons, respectively.

BS, C, and D then, the VE estimate from TN studies is unbiased when considering effectiveness against MAI. The same estimate may overestimate the true VE against SI by 0.20 (i.e. 20%).

2.3.2.2 Comparison of the bias of VE estimates from TN and TCC studies:

- If one is concerned that vaccination may affect the probability of non-influenza ARI, then one should prefer the TCC study design. However, TCC-based VE estimates may still be biased in this case. For example, when the ratio of the probability of NFARI comparing a vaccinated and an unvaccinated person is 0.5, then the bias of VE estimate from TN study is -0.4 while the bias of VE estimate from TCC study is 0.07.

- Under non-random vaccination, effects of health status on probabilities of influenza and non-influenza ARI (the '*healthy vaccinee effect*') may bias VE estimates from both study designs. In general, TN-based estimates perform slightly better than TCC-based estimates when this effect is believed to be the main

source of bias. If the effect of health status is similar for FARI and NFARI then the TN design produces less biased estimates compared to the TCC design. For example, suppose the probabilities of vaccination are 0.4 and 0.8 for healthy and frail persons, respectively. When the risk ratios for NFARI and FARI are both 0.75, then the VE estimate from TN study is unbiased, while the bias of VE estimate from TCC study is 0.07.

- If one assumes that vaccination does not affect the probability of non-influenza ARI but one is concerned that vaccinated influenza patients are less likely to seek care than unvaccinated patients (because of reduced symptoms severity) then VE estimates may suffer from severe bias in both study designs when the outcome of interest is SI. In this case, the bias of TN-based estimates may be somewhat smaller than that of TCC-based estimates. This source of bias does not affect VE estimates when the outcome of interest is MAI! For example, suppose that the ratio comparing vaccinated and unvaccinated FARI cases w.r.t. the probability of seeking medical care is 0.5. When the outcome of interest is SI, then the bias of a VE estimate from TN study is 0.2 and the bias of a VE estimate from TCC study is 0.22. When the outcome of interest is MAI, then the VE estimate from a TN study is unbiased, while the bias of a VE estimate from a TCC study is 0.02.

- Under non-random vaccination, the TN study design is preferable to the TCC design if one is concerned about bias resulting from possible effect of a person's health status on her/his probability of seeking care against ARI. For example, suppose that the probabilities of vaccination are 0.8 and 0.4 for healthy and frail persons, respectively. When the ratio of the probabilities of seeking medical care comparing healthy and frail persons is 0.5, then the VE estimate from TN study is unbiased while the bias of VE estimate is 0.12.

2.3.2.3 Precision of VE estimates

Table A.5 presents the standard errors of VE estimates from TN and TCC studies. From this table we conclude that:

- Non-random vaccination may reduce precision of VE estimates.
- If the probability of NFARI is associated with vaccination status, then VE estimates from TN studies are somewhat less precise compared to VE estimates from TCC studies, although, the differences in precision were small.
- If the probability of NFARI is not associated with vaccination status, then the precision of VE estimates from TN and TCC studies are similar.

2.4 Discussion

We developed a new model for the evaluation of the bias and precision of influenza estimates from case-control studies. The new model is more comprehensive than previously suggested models (De Serres et al. (2013); Orenstein et al. (2007); Ferdinands and Shay (2012); Foppa et al. (2013); Jackson and Nelson (2013); Haber et al. (2015)) for the following reasons:

- It allows assessment of the impact of non-random vaccination.
- It incorporates a confounder (health status) which links vaccination status with the probabilities of ARI and of seeking medical care for these ARIs.
- By including parameters corresponding to the probabilities of seeking medical care, the model allows us to examine the effect of association of these probabilities with vaccination and health status on the bias of VE estimates.
- The model allows evaluating and comparing the precision of VE estimates.

Our calculations confirm earlier findings (Orenstein et al. (2007)) that when the probability of non-influenza ARI depends on vaccination status, VE estimates from test-negative studies may be severely biased. However, even when this probability is not affected by vaccination, VE estimates from the two types of case-control studies considered in this study may suffer from substantial bias. In addition to the well-known '*healthy vaccinee effect*' (probabilities of vaccination and of ARI depend on health status), bias of VE estimates may result from heterogeneities in health-care-seeking behaviors. Specifically, if vaccination reduces the probability that an influenza patient seeks medical care (because her/his symptoms are less severe than those of an unvaccinated influenza patient) then VE estimates from TN or TCC studies may grossly overestimate the true VE against SI. On the other hand, when the outcome of interest is MAI then the biases resulting from vaccine-related reduction in symptoms' severity are very small. Recent papers (castilla et al.(2013); VanWormer et al. (2014); Deiss et al. (2015)) found evidence of vaccine-associated reduction in influenza patient's symptoms severity. The effects of health-care-seeking behaviors on VE estimates from studies in which only ARI patients who seek medical care may become cases need to be further investigated.

The results of this study lead to the following conclusions:

- In general, estimates of influenza VE from case-control studies where only ARI patients seeking medical care are tested for influenza infection may suffer from severe bias, i.e. an absolute bias of 20% or more, especially when the outcome of interest is SI.

- The bias of VE estimates may depend on the outcome against which the vaccine is supposed to protect. Influenza VE estimates from TN studies are usually presented as 'VE against medically-attended influenza'. However, most lay persons interpret this VE estimate in the context of the benefit of vaccination to *any* vaccine recipient. Health authorities and the public should be made

aware of this distinction.

- When the outcome of interest is SI, the TN design provides reliable estimates (i.e., no or small bias) if the following assumptions are satisfied: (a) vaccination does not affect the probability of non-influenza ARI, (b) effects of confounding variables on the probabilities of influenza and non-influenza ARI are similar, and (c) vaccination does not affect the probabilities of seeking medical care for influenza ARI due to reduced severity of symptoms. When the outcome of interest is MAI, then only assumptions (a) and (b) are necessary for obtaining a reliable VE estimate from a TN study.

- Estimates of VE from TCC studies have small bias when the outcome of interest is SI if assumptions (a) and (c) are satisfied, assumption (b) is replaced by the stronger assumption (b*) of no presence of confounding, and the additional assumption (d) that the probabilities of seeking medical care for ARI are not affected by potential confounders is satisfied. When the outcome of interest is MAI, then TCC-based estimates of VE have small bias under assumptions (a), (b*), and (d).

- It is important to collect more data on health-care-seeking behaviors of ARI patients and to study the effects of vaccination and potential confounders on these behaviors.

In summary, the test negative design produces less biased VE estimates, compared to the traditional case-control design provided that vaccination does not modify the probability of non-influenza ARI. However, this very popular study design may still produce biased estimates of influenza VE, especially when the outcome of interest is symptomatic influenza. More reliable estimates of VE against SI can be obtained from *monitored cohort studies*, where every participant reporting an ARI is tested for influenza infection. VE estimates from these cohort studies should be compared with

estimates from TN studies conducted in same population during the same influenza season.

Our study has a few limitations:

- In order to focus on bias associated with the study designs, we ignored bias resulting from misclassification of infection and vaccination status.
- Our model does not account for the dynamics of outbreaks of influenza and other ARI-causing infections.
- We only consider unadjusted VE estimates as we tried to focus on sources of bias rather than on how one can reduce bias using standard or novel statistical techniques (Talbot et al. (2016)).

In the future we plan to improve the model by incorporating dynamics of the related processes. We also plan to use stochastic simulations to assess bias and precision of influenza VE estimates for other study designs (e.g. cohort studies) and to propose new study designs resulting in less biased VE estimates.

Chapter 3

Estimation of Influenza Vaccine Effectiveness Using Agent-based Stochastic Simulation Model in Observational Studies

3.1 Introduction

Together with pneumonia, influenza is the seventh leading cause of death in the U.S. During the past three decades, the estimated number of influenza-associated deaths ranged from 3,000 to 50,000 every year(Centers for Disease Control and Prevention (CDC) (2010)). Among all mitigation interventions (e.g., social distancing, public health measures, antiviral prophylaxis), vaccination provides the most efficient and durable response (Chao et al. (2010); Talbot et al. (2013)).

Mathematical and computer simulation models are increasingly being used to characterize the transmission dynamics of infectious diseases, to evaluate the effectiveness of various intervention strategies and to guide policy decisions on disease outbreak management. In the literature, stochastic agent-based simulation models (Germann et al. (2006); Chao et al. (2010)) are frequently employed to make mitigation plans for influenza pandemics and evaluate the effectiveness of various public health interventions. In a stochastic agent-based model, the disease transmission process is governed by the behavior of each individual, and incorporate elements of random processes into the system. Rules governing disease transmission dynamic are defined at an individual level and the infection and transition of individuals from one state to another is determined probabilistically. Hence, the models can keep track of each individual and add up individuals in each disease state at the end of each time step of the simulation. This helps capture heterogeneity of individual behavior and different sources of variation, which can have important impacts in terms of overall disease transmission dynamics. Meanwhile, the model parameters are specified in the form of probabilities. Although the estimates vary by iteration, stochastic models are typically run many times to obtain a central estimate value. Here, we present a stochastic agent-based simulation program, SimFlu, for the transmission of influenza in a stratified population.

SimFlu performs a set of simulations with fixed values of the input parameters.

Each simulation corresponds to a single outbreak. The population is made up of different strata that have different characteristics. On the first day of the outbreak, a given input number of people are chosen randomly to be infected and infectious. Every day, the program calculates the probability that each person will be infected. These calculations depend on the transmission probabilities, number and distribution of contacts, and the prevalence of infection in the different strata. The vaccination coverage for each month is given as an input parameter, and a person who receives the vaccine during a given month becomes effectively vaccinated on the first day of the following month. The protection afforded by the vaccine depends on the vaccine efficacy parameter. On each day, every person may develop a new episode of Acute Respiratory Infection (ARI), it can be either ARI resulting from influenza infection (FARI) or ARI resulting from non-influenza pathogens (NFARI). A person with FARI or NFARI may decide to visit a clinic to seek care. The decision is made on the first day of an episode of FARI or NFARI. In this program, we considered two covariates: health status and health awareness. These two covariates modify input parameters via multipliers that are specified in the input file, and these multipliers may depend on a person's stratum, but do not change over time. A sample input parameter file is attached in Appendix B.2.

In this chapter, we use the simulation results from SimFlu to help evaluate the bias and precision of estimates of vaccination effectiveness (VE) from different study designs. In addition, we proposed several methods to correct the bias for test negative studies.

3.2 Methodology

3.2.1 Scenario

In this chapter, when assessing the bias of VE estimates from observational studies using the proposed stochastic agent-based simulation model, we assume that vaccination is completed before the onset of the study. Under this scenario, vaccination status does not depend on time. The true VE is defined as one minus the ratio of the cumulative incidence rates (attack rates) in vaccinees and non-vaccinees: $VE = 1 - AR(V)/AR(U)$, where $AR(V)$ stands for the attack rate among vaccinees, and $AR(U)$ stands for the attack rate among non-vaccinees. When vaccination occur before or during the study, vaccination status will vary by time. There is no universally accepted definition of true VE in this case. VE estimates are usually based on hazard ratio (via a Cox regression model) or on person-time considerations.

3.2.2 Outcome of interest

In this chapter, we evaluate estimates of VE based on the outcomes against which the vaccine is supposed to protect, i.e. symptomatic influenza (SI) or medically-attended influenza (MAI).

In observational influenza VE studies, surveillance for SI is needed in the entire study population, and persons with influenza-like illnesses undergo a test for the presence of the influenza virus. A true case of SI is a person has ARI and is infected by an influenza virus. SI is more appropriate from the public health perspective. MAI is defined as an influenza-infected person who seeks medical care because of her/his ARI. Once a person decide to seek medical care in clinic, the health care provider may ask the person to be tested for influenza viruses. If the person agrees then a swab is taken and sent to a laboratory for testing.

3.2.3 Observational Study

In this chapter, we consider two case-control studies: traditional case-control (TCC) study and test-negative (TN) study, and two cohort studies: active surveillance cohort (ASC) study and passive surveillance cohort(PSC) study, which are introduced in Chapter 1.5.

3.2.3.1 Cohort Studies

We have 2 types of cohort studies depending on the type of surveillance: active surveillance and passive surveillance. Under active surveillance, every person who has ARI is tested for influenza infection. It is also called active surveillance study (ASC). If a person tests positive then s/he is considered a case of SI. In this case s/he will not be tested again if develops another ARI later. If a person tests negative then s/he will be tested again if develops another ARI later. Every person who either never had an ARI or had one or more ARIs but always tested negative is considered a non-case. VE is estimated as one minus the ratio of the cumulative incidence rates of SI in vaccinated and unvaccinated.

The other type of cohort study is called passive surveillance study(PSC). In PSC, a person with an ARI decides whether s/he will seek medical care. A person who seeks care and tests positive is considered a case. Everyone else is a non-case. The total number of vaccinated and unvaccinated persons should be the same as in the ASC situation, and their sum should be equal to the cohort size. In both types of cohort studies, the vaccination status of each person, even if s/he is not a case, is known.

3.2.3.2 Case-control Studies

As introduced in Chapter 2, there are 2 types of Case-control studies: (1) the test negative study (TN), and (2) the traditional case control study (TCC).

3.2.4 SimFlu

SimFlu is a stochastic agent-based simulation program, it mimics the transmission process of influenza in a closed population with several strata in one influenza season. The program performs a set of simulations with fixed values of the input parameters, and each simulation corresponds to a single outbreak.

On the first day the outbreak, a given input number of people are chosen randomly to be initially infected and infectious. For every day in the influenza season, a susceptible individual may become infected as a result of a contact with an infectious person, and SimFlu calculates the probability that each susceptible person will be infected. These calculations depend on the transmission probabilities, number and distribution of contacts, and the prevalence of infection in the different strata. When a susceptible individual become infected s/he first enters a latent (exposed) period. During the latent period, the individual is not infectious (to others) and does not have symptoms. Following the latent period, the individual becomes infectious and may have symptoms. On the first day of an episode of symptomatic influenza, a decision is made about whether s/he visit a clinic to seek medical care or not. Covariates, such as the individual's health status and the individual's health awareness, are taken into consideration in SimFlu, but the value of covariates do not change over time. When the infectious period is over, the individual is no longer infectious and cannot become infected again during the same influenza season.

In addition, the person can develop non-influenza ARI (NFARI) according to prespecified probabilities. On the first day of an NFARI episodes, the person may decide to make a visit to clinic.

SimFlu takes a set of input parameters, and for each simulation, SimFlu outputs an "outcomes file" which includes, for each member of the population, information on vaccination status, influenza infection, NFARI, clinic visits and test results. With all this detailed information, we will estimate VE for each of the four study designs

introduced earlier in this Chapter. The bias of a VE estimate for a given study design can be assessed by averaging over all simulated VEs and comparing with the true VE. The standard errors of these estimates can also be calculated from the simulation outcomes.

3.2.5 Covariates: Health Status and Health Awareness

In SimFlu, we defined two covariates: health status(X) and health awareness(U).

We assume that people within the population can be classified with a health status of either "healthy" or "frail". We define a binary variable X, where $X = 1$ stands for a "healthy" person, and $X = 0$ stands for a "frail" person. Let $\pi = \mathbb{P}(X = 1)$, which is the probability of "healthy" persons among the population. Health status may affect the probabilities of being vaccinated, the transmission probabilities, the probability of FARI/NFARI, it may also affect the vaccine efficacy and the probabilities of seeking care for ARIs.

We also assume that people within the population can have either "high" or "low" health awareness. We define an unobserved binary variable U, where $U = 1$ if a person has "high" health awareness, and $U = 0$ if a person has "low" health awareness.

Health awareness may depend on health status, thus we let $\omega_x = \mathbb{P}(U = 1|X = x)$, $x = 0, 1$. Health awareness may affect the probabilities of being vaccinated and the probabilities of seeking care for ARIs. It does not directly affects the probabilities of infections and symptoms.

The covariates health status(X) and health awareness(U) modify input parameters via multipliers that are specified in the SimFlu input file. These multipliers may depend on a person's stratum, but do not change over time. Multipliers must be non-negative numbers.

3.2.6 True VE

When vaccination is done at random, which means the probability of vaccination does not depend on any covariates, the true VE is defined as one minus RR, where RR is the probability of the outcome of interest given vaccination divided by the probability of the outcome of interest given no vaccination. In this chapter, we use SimFlu to calculate the true VE against the two outcomes of interest, SI and MAI.

From the input parameters of SimFlu program, the overall vaccination coverage can be calculated as the weighted average of the probabilities of vaccination over all 4 combinations of X, U. With the calculated overall vaccination coverage, we generated a new set of input parameters corresponding to random vaccination. In this new set of parameters, all the multipliers for vaccination coverage are set to 1.0, and the probability of vaccination is equal to the calculated overall probability. We do not change any other parameters. Using this new modified set of parameters as the input parameter set for SimFlu, we mimic a transmission process of influenza under random vaccination. A person is considered as a true case of SI if he/she had influenza infection with symptoms, and a person is considered as a true case of MAI if he/she had a medical visit for influenza infection with symptoms.

3.2.7 VE Estimates

In ASC and PSC studies, VE is estimated as $\hat{VE} = 1 - \hat{RR}$, where $\hat{RR}$ is based on sample proportions. In TN and TCC studies, VE is estimated as $1 - \hat{OR}$, where $\hat{OR}$ is the estimate of the odds ratio comparing the odds of vaccination in cases and controls.

For ASC study, since every person with ARI is tested for flu infection, so no information for seeking medical care is obtained in this study, our VE estimate is only suitable for SI. In ASC study, if a person tests positive then he/she is considered a case of SI. In this case, he/she will not be tested again if develops another ARI

later. If a person tests negative then he/she will be tested again if develops another ARI later. Every person who either never had an ARI or had one or more ARI's but always tested negative is considered a non-case. VE is estimated as one minus the ratio of the cumulative incidence rates of case in vaccinated and unvaccinated.

For PSC study, a person who had at least one ARI with medical visit and test positive for ARI is considered a case of MAI. Everyone else is a non-case. Hence the total number of vaccinated and unvaccinated persons should be the same as in the ASC study, and the total number should be equal to the cohort size.

The TN study only includes persons with at least one ARI for which there was a visit. A person who tested positive is a case, and a person who tested negative is a control. VE is estimated as one minus the odds ratio in the table cross classifying cases and controls by their vaccination status.

For the TCC study, cases and controls are selected via separate processes. Cases are defined in the same way as in the TN study, i.e. everyone who had at least one ARI with a visit is tested, and if the test result is positive then the person is a case. If the test result is negative then the person is not included in the study. Controls are selected at the end of the study at random among the population who did not have any ARI during the study period. VE is estimated as $1 - \hat{OR}$, where $\hat{OR}$ is the estimated odds ratio in the table cross classifying cases and controls by their vaccination status.

3.2.8 Sources of Bias

Biases are often present in observation studies. The sources of bias that may occur under our model are listed in Table 3.1.

Before discussing the details about the sources of bias, we defined a few parameters and a few probability ratios comparing vaccines and non-vacciness or healthy and frail individuals. Theses ratios will be helpful in the presentation of the results.

- β_{vx}, the probability of NFARI for a person of vaccination status V and health status X, where $V = 0(unvaccinated), 1(vaccinated)$, and $X = 0(frail), 1(healthy)$.

- $\theta_\beta = \frac{\beta_{1x}}{\beta_{0x}}$, the ratio of the probabilities of NFARI comparing a vaccinated and an unvaccinated person of the same health status.

- $\psi_\beta = \frac{\beta_{v1}}{\beta_{v0}}$, the ratio of the probabilities of NFARI comparing a healthy and a frail person of the same vaccination status.

- γ_{vx}, the probability of FARI for a person of vaccination status v and health status x, where $v = 0(unvaccinated), 1(vaccinated)$, and $x = 0(frail), 1(healthy)$.

- $\theta_\gamma = \frac{\gamma_{1x}}{\gamma_{0x}}$, the ratio of the probabilities of FARI comparing a vaccinated and an unvaccinated person of the same health status.

- $\psi_\gamma = \frac{\gamma_{v1}}{\gamma_{v0}}$, the ratio of the probabilities of FARI comparing a healthy and a frail person of the same vaccination status.

- M, binary variable with $M = 1$ for a person seeking medical care for her/his ARI, and $M = 0$ for a person does not seeking medical care for his/her ARI.

- Y, outcome variable. $Y = 0$ for no ARI; $Y = 1$ for NAFRI, and $Y = 2$ FARI.

- δ_{yvu}, the conditional distribution seeking for medical care given outcome Y. It may depend on covariate health status X, and health awareness U.

- $\theta_{\delta_2} = \frac{\delta_{21u}}{\delta_{20u}}$, the ratio comparing vaccinees and non-vaccinees for FARI with respect to the probability of seeking for medical care.

- $\mu_{\delta_1} = \frac{\delta_{1v0}}{\delta_{1v1}}$, the ratio comparing persons with low and high health awareness with respect to the probability of seeking for medical care for NFARI.

- $\mu_{\delta_2} = \frac{\delta_{2v0}}{\delta_{2v1}}$, the ratio comparing persons with low and high health awareness with respect to the probability of seeking for medical care for FARI.

In this chapter, we focused on bias A to bias D listed in Table 3.1. The source of bias A comes from the probabilities of NFARI may depend on vaccination status, since the validity of the assumption that vaccinees and non-vaccinees are equally likely to develop NFARI has not yet been confirmed (Cowling et al. (2012)). We considered two cases: for bias A1, we assume vaccination lowers the probability of NFARI, and that θ_β ranges from 0.5 to 1.0. For bias A2, we assume vaccination increases the probability of NFARI and θ_β ranges from 1.0 to 2.0.

The probabilities of influenza and non-influenza ARIs may depend on confounders, thus covariates such as health status, age, exposure, education and socio-economic status may be associated with both the likelihood of being vaccinated and the likelihood of developing influenza and non-influenza ARIs. In source of bias B, we consider the association between health status and the probabilities of FARI and of NFARI. We consider three situations. For source of bias B1, we assume healthy persons have lower probability of NFARI, and ψ_β ranges from 1.0 to 2.0. For source of bias B2, we assume healthy persons have lower probability of FARI, and ψ_γ ranges from 1.0 to 2.0. For source of bias BS, we assume healthy person have a lower probability of FARI and NFARI, and health status has the same effect on the probabilities of FARI and NFARI ($\psi_\beta = \psi_\gamma$).

Several studies (castilla et al.(2013); VanWormer et al. (2014); Deiss et al. (2015)) suggest that vaccinated individuals who contract influenza may have milder symptoms that unvaccinated influenza patients, and therefore may be less likely to seek medical care. A person with ARI may seek medical care and, in this case, be tested for influenza viruses. The probability of seeking medical care depends on whether this person develop an ARI (only individuals with ARI seek medical care), and it may be different for FARI and NFARI patients. In addition, the conditional distribution seeking for medical care given the type of infection (FARI or NFARI) may depend on health awareness. For source of bias C, we assume vaccination lowers the probability

of seeking medical care in FARI patients, and for source of bias D, we assume ARI patients with high health awareness have a higher probability of seeking medical care. The probability representation for each source of bias are listed in Table 3.2.

Table 3.1: Sources of Bias

Label	Source of Bias
A1	Vaccination lowers the probability of NFARI
A2	Vaccination increases the probability of NFARI
B1	Healthy persons have a lower probability of NFARI
B2	Healthy persons have a lower probability of FARI
BS	Healthy persons have a lower probability of FARI and NFARI. Health status has the same effect on the probabilities of both types of ARI.
C	Vaccination lowers the probability of seeking medical care in FARI patients (because of reduced symptom severity).
D	ARI patients with high health awareness have a higher probability of seeking medical care.
E	Misclassification of influenza infection status.

Table 3.2: Probability ratio corresponding to source of bias

Source of Bias	Probability Ratio	Definition	Symbol	Range
A1	PR_{A1}	$P(NFARI\|Vacc)/P(NFARI\|Unvacc)$	θ_β	0.5 - 1.0
A2	PR_{A2}	$P(NFARI\|Vacc)/P(NFARI\|Unvacc)$	θ_β	1.0 - 2.0
B1	PR_{B1}	$P(NFARI\|Frail)/P(NFARI\|Healthy)$	ψ_β	1.0 - 2.0
B2	PR_{B2}	$P(FARI\|Frail)/P(FARI\|Healthy)$	ψ_γ	1.0 - 2.0
BS	PR_{BS}	Common value PR_{B1} and PR_{B2}	$\psi_\beta = \psi_\gamma$	1.0 - 2.0
C	PR_C	$P(SMC\|FARI, Vacc)/P(SMC\|FARI, Unvacc)$	θ_{δ_2}	0.5 - 1.0
D	PR_D	$P(SMC\|LowHA)/P(SMC\|HighHA)$	$\mu_{\delta_1} = \mu_{\delta_2}$	0.5 - 1.0

PR - Probability ratio, Vacc - Vaccinated, Unvacc - Unvaccinated,
FARI - Influenza ARI, NFARI - Non-influenza ARI,
HA - Health awareness, SMC - Seeking medical care

3.2.9 Calculations

To dive into the impact of different sources on the bias of VE estimates, we used SimFlu to mimic the transmission process of influenza under different sources of bias for 4 cases.

We varied the joint probabilities of health status and health awareness, (X, U), the probabilities of vaccination for given values of (x, u) (Table 3.3).

Table 3.3: Description of Cases

Cases	Association between X and U	Association between X and V
1	X and U are independent	frail persons are more likely to be vaccinated compared to healthy persons;
2	X and U are positively associated	frail persons are more likely to be vaccinated compared to healthy persons;
3	X and U are negatively associated	frail persons are more likely to be vaccinated compared to healthy persons;
4	X and U are independent	frail persons are less likely to be vaccinated compared to healthy persons.

Under each case, we conducted 7 sets of simulations corresponding to the 7 sources of biases mentioned in Table 3.2. If vaccination affects the probability of NFARI, source of bias A1 or A2 will present. If Healthy persons have a lower probability of non-influenza ARI, source of bias B1 will present. If Healthy persons have a lower probability of influenza ARI, source of bias B2 will present. Under the situation that healthy persons have a lower probability of influenza and non-influenza ARI and health status has the same effect on the probabilities of both types of ARI, source of bias BS will present. If vaccination lowers the probability of seeking medical care in influenza ARI patients (because of reduced symptom severity), source of bias C will present. If ARI patients with high health awareness have a higher probability of seeking medical care, source of bias D will present.

In each set of simulation, 1000 simulations are conducted with the same input file. For each set of simulation, we first modified the input file for the SimFlu program. If no source of bias was present, we set the values of all corresponding parameters specified in Table 3.2 to 1.0. When a source of bias was present, we set one or two of the parameters which corresponded to the source of bias to specified values in Table 3.2 and kept the values of all other parameters at 1.0. For each set of simulation, we estimated VE for 4 study designs using the outcomes file from SimFlu, which included

all the detailed information for each member of the population, such as vaccination status, influenza infection, NFARI, clinic visits, test results, etc.

3.2.10 Corrections for Bias for Test Negative Study

The TN study was first used for the estimation of VE in 2005(Skowronski (2005)), and since has been very popular in VE estimation. In this Chapter we try to assess the bias for TN study using the probability model we proposed in Chapter 2 and we proposed different methods to correct the bias for TN study when different sources of bias are present. We only corrected bias A-C in this chapter, since the bias of the VE estimate from the TN design under source of bias D is not severe. In this part, we are using the same parameter definitions as Chapter 2, a list of parameters and notations in Table A.1.

3.2.10.1 Correction for Bias A1 and A2

When vaccination affects the probability of NFARI, which means when bias A1 or bias A2 is present, estimates of VE from TN studies suffer from severe bias based on results from the probability model we proposed in Chapter 2 and the simulation results in Table 3.4 - 3.7. In order to correct the bias when only bias A1 or bias A2 is present, we proposed the following method based on the probability model in Chapter 2:

When only bias A1 or bias A2 is present and all other biases are absent, we have: $\psi_\beta = 1, \psi_\gamma = 1, \theta_{\delta_2} = 1$, and $\mu_{\delta_1} = \mu_{\delta_2} = 1$. Therefore, the true VE can be written as: $VE_{True} = 1 - \theta_\gamma$, and the estimated VE is $\hat{VE} = 1 - \frac{\hat{\theta}_\gamma}{\hat{\theta}_\beta}$.

The corrected VE estimate can be written as:

$$\hat{VE}_C = 1 - \hat{\theta}_\beta(1 - \hat{VE}),$$

where $\hat{\theta}_\beta$ is estimated from data as $\hat{\theta}_\beta = \frac{n_1/N_1}{n_0/N_0}$, where n_i is the number of persons in TN study who has NFARI with vaccination status i, $i = 0, 1$, and N_i is the number of person in the population with vaccination status i, $i = 0, 1$. See detailed calculation in Appendix B.1.

3.2.10.2 Correction for Bias B1, B2 and BS

When health status affects the probabilities of FARI and NFARI, which means when bias B1, B2 or BS is present, substantial bias may result from TN study. To correct the bias result from bias B1, B2 or BS, we proposed three methods: (1) logistic regression, (2) propensity score and (3) matching control to cases.

Logistic Regression

Logistic regression is typically used to calculate the adjusted odds ratios to estimate VE, which is generally defined by:

$$logitPr(Y = 1|M, X, U) = \alpha + \beta_1 * M + \beta_2 * X + \beta_3 * U$$

where Y is the outcomes status of the patients, α is the parameter for the intercept. In this chapter, we assessed the bias using logistic regression with covariates: month of onset of illness(M), health status(X), and health awareness(U). Also, we compared models with different combinations of these three covariates.

Propensity Score

The propensity score is the probability of treatment assignment conditional on observed baseline characteristics (covariates). In observational studies, treatment selection is often influenced by subject characteristics. As a result, baseline characteristics of subjects to receive treatment often differ systematically from those of untreated

subjects. Therefore, systematic differences in baseline characteristics between treated and untreated subjects when estimating the effect of treatment on outcomes must be taken into consideration.

The propensity score was defined by Rosenbaum and Rubin (1983) to be the probability of treatment assignment conditional on observed baseline covariates: $e_i = Pr(Z_i = 1|X_i)$, where Z is a indicator variable for treatment,Z_0 for control treatment and Z_1 for active treatment. Since the propensity score is a balancing score, so conditioning on the propensity score, the distribution of measured baseline covariates is similar between treated and untreated subjects. Thus, for subjects with same propensity score, the distribution of observed baseline covariates will be the same between the treated and untreated subjects.

In randomized experiments the true propensity score is known and is defined by the study design. In observational studies, the true propensity score is not, in general, known. However, it can be estimated using the data. In practice, the propensity score is most often estimated using a logistic regression model, in which treatment status is regressed on observed baseline characteristics.

In this chapter, we used logistic regression model to estimate the propensity score for vaccinated group and unvaccinated group, then we used three different propensity score methods to remove the effects of confounding when estimating the effects of vaccination on FARI: propensity score matching, stratification of the propensity score and inverse probability of treatment weighting using the propensity score.

Propensity score matching entails forming matched sets of treated and untreated subjects who share a similar value of the propensity score (Rosennbaum and Rubin, 1983a, 1985). The most common implementation of propensity score matching is one-to-one or pair matching, in which pairs of treated and untreated subjects are formed, such that matched subjects have similar values of the propensity score. Once a matched sample has been formed, the treatment effect can be estimated by directly

comparing outcomes between treated and untreated subjects in the matched sample, and the effect of treatment can also be described using the relative risk.

Stratification on the propensity score involves stratifying subjects into mutually exclusive subsets based on their estimated propensity score. Subjects are ranked according to their estimated propensity score. Subjects are then stratified into subsets based on previously defined thresholds of the estimated propensity score. A common approach is to divide subjects into five equal-size group using the quintiles of the estimated propensity score. Within each propensity score stratum, treated and untreated subjects will have roughly similar values of the propensity score. Therefore, when the propensity score has been correctly specified, the distribution of measured baseline covariates will be approximately similar between treated and untreated subjects within the same stratum.

Inverse probability of treatment weighting (IPTW) using the propensity score uses weights based on the propensity score to create a synthetic sample in which the distribution of measured baseline covariates is independent of treatment assignment. IPTW was first proposed by Rosebaum (1987a) as a form of model-based direct standardization.

Let Z_i be the indicator variable denoting whether or not the ith subject was treated, and let e_i denote the propensity score for the ith subject. Weights can be defined as $w_i = \frac{Z_i}{e_i} + \frac{1-Z_i}{1-e_i}$. A subject's weight is equal to the inverse of the probability of receiving the treatment that the subject actually received.

Match Cases in TN Study

In many epidemiological studies subjects are matched to make the study groups comparable. While there are no methods that can guarantee comparability, individual cases are often matched on important characteristics to provide assurances that the groups are comparable. We matched the subjects with same health status in cases

and controls to correct the bias resulting from health status.

3.2.10.3 Correction for Bias C

When vaccination affects the probability of seeking medical care for FARI, which means when bias C is present, this may result from reduced severity of symptoms in vaccinated influenza patients.

To correct the bias C, we assume only bias C is present, and all other biases are absent. Then we have:

$\theta_\beta = 1, \psi_\beta = 1, \psi_\gamma = 1$, and $\mu_{\delta_1} = \mu_{\delta_2} = 1$. So, $\beta_{00} = \beta_{10} = \beta_{01} = \beta_{11}, \gamma_{v1} = \gamma_{v0}$.

Therefore, the model-based estimates from TN study when only bias C is present can be written as:

$$\begin{aligned} VE_E &= 1 - \frac{\theta_{\delta_2}[\gamma_{10}\alpha_0(1-\pi) + \mu_{\delta_1}\gamma_{11}\alpha_1\pi][\beta_{00}(1-\alpha_0)(1-\pi) + \mu_{\delta_1}\beta_{01}(1-\alpha_1)\pi]}{[\gamma_{00}(1-\alpha_0)(1-\pi) + \mu_{\delta_1}\gamma_{01}(1-\alpha_1)\pi][\beta_{10}\alpha_0(1-\pi) + \lambda\beta_{11}\alpha_1\pi]} \\ &= 1 - \theta_{\delta_2}\frac{[\gamma_{11}\alpha_0(1-\pi) + \gamma_{11}\alpha_1\pi][(1-\alpha_0)(1-\pi) + (1-\alpha_1)\pi]}{[\gamma_{01}(1-\alpha_0)(1-\pi) + \gamma_{01}(1-\alpha_1)\pi][\alpha_0(1-\pi) + \alpha_1\pi]} \\ &= 1 - \theta_{\delta_2}\frac{\gamma_{11}}{\gamma_{01}} \\ &= 1 - \theta_{\delta_2}\theta_\gamma \end{aligned}$$

We know the true VE against SI is : $VET_{SI} = 1 - \theta_\gamma$. So the bias of the VE estimate when only bias C is present is:

$$\begin{aligned} bias &= VE_E - VET_{SI} \\ &= 1 - \theta_{\delta_2}\theta_\gamma - (1 - \theta_\gamma) \\ &= \theta_\gamma(1 - \theta_{\delta_2}) \end{aligned}$$

The corrected estimate of VE is:

$$VE_{EC} = 1 - \frac{1}{\theta_{\delta_2}}(1 - VE_E)$$

In order to correct the bias result from bias C, we need to get the estimate of θ_{δ_2}, which is the ratio of the probabilities of seeking medical care comparing a vaccinated and an unvaccinated FARI patient of the same health status. Since in the TN study, we only take consideration of the patients who seek for medical care, we proposed a method combining a small ASC study and a TN study. In this method, we try to conduct simultaneously a TN study and an ASC study to obtain the corrected VE. In the ASC study, we can get an estimate of θ_{δ_2}, and use this estimation to correct our VE estimate for TN study when bias C is present.

3.3 Results

3.3.1 Bias of VE Estimate from Observational Studies

We evaluated bias of VE estimates from cohort and case-control studies in the presence of the sources of bias listed in Table 3.2 for 4 cases.

Under case 1(Table 3.4), we assume health status and health awareness are independent, and fail persons are more likely to be vaccinated compared to healthy persons. In set 0, when no source of bias is present, the absolute values of the biases of VE estimates from all study designs except the TCC are smaller than 0.01. When bias A1 or bias A2 is present, the absolute values of the bias of VE estimates from both cohort studies are all very small, while the estimates of VE from case-control studies suffer from severe bias. Comparing the results from bias A1 with the results from bias A2, we can conclude ASC and TCC produce smaller absolute value of bias of VE estimates and TN produce larger absolute value of bias of VE estimates. When

bias B1 is present, the absolute values of the biases of VE estimates from two cohort studies are very small (< 0.01). Under the two case-control studies, the absolute values of the biases of VE estimates from TN are substantially larger than those from TCC. When bias B2 is present, the absolute values of the biases of VE estimates from all 4 study designs are larger than 0.01. The absolute values of the biases of VE estimates from TCC are substantially smaller than those from other three studies. When bias BS is present, the absolute values of the biases of VE estimates from all 4 study designs are larger than 0.01. The absolute values of the biases of VE estimates from TCC are substantially smaller than those from other three studies. When bias C is present, the VE estimates against MAI are much better than the VE estimates against SI. When bias D is present, the absolute values of the biases of VE estimates from ASC and TN are smaller than 0.01.

Under case 2(Table 3.5), we assume health status and health awareness are positively associated, and fail persons are more likely to be vaccinated compared to healthy persons. When bias B1 is present, the absolute values of the biases of VE estimates from PSC are larger than those in case 1, while the absolute values of the biases of VE estimates from TN and TCC are smaller than those in case 1. When bias B2 is present, the absolute values of the biases of VE estimates are smaller than those in case 1, except those from TCC. When bias BS is present, the absolute values of the biases of VE estimates from TCC are smaller than those in case 1. When bias C is present, the absolute values of the biases of VE estimates from cohort studies are smaller than those in case 1, but the absolute values of the biases of VE estimates from case-control studies are larger than those in case 1. When bias D is present,

Under case 3(Table 3.6), we assume health status and health awareness are negatively associated, and fail persons are more likely to be vaccinated compared to healthy persons. When bias B1 is present, the absolute values of the biases of VE estimates from PSC, TN and TCC are all larger than those in case 1. When bias B2

is present, the absolute values of the biases of VE estimates are smaller than those in case 1, except those from TCC. When bias BS is present, only the absolute values of the biases of VE estimates from TCC against MAI are smaller than those in case 1. When bias C is present, except from the PSC against MAI, the absolute values of the biases of VE estimates are larger than those in case 1. When bias D is present, the absolute values of the biases of VE estimates are larger than those in case 1.

Under case 4(Table 3.7), we assume health status and health awareness are independent, and fail persons are less likely to be vaccinated compared to healthy persons. When bias B1 is present, the absolute values of the biases of VE estimates from TN and TCC studies are quite similar, while under case 1 the absolute values of the biases of VE estimates from TN are substantially larger than those from TCC. The absolute values of the biases of VE estimates from TCC are larger than those in case 1, while the absolute values of the biases of VE estimates from PSC and TN are smaller than those in case 1. When bias B2 is present, the absolute values of the biases of VE estimates are smaller than those in case 1, except those from TCC. When bias BS is present, only the absolute values of the biases of VE estimates from TCC are larger than those in case 1. When bias C is present, except from PSC against MAI, the absolute values of the biases of VE estimates are larger than those in case 1. When bias D is present, the absolute values of the biases of VE estimates from PSC and TN are smaller than those in case 1, but the absolute values of the biases of VE estimates from ASC and TCC are larger than those in case 1.

Under case 1 and case 4, where health status and health awareness are independent, the absolute values of the biases of VE estimates in TN studies are not significantly affected by the association between health awareness and vaccination status. Under case 2 and case 3, when health status and health awareness are independent, and frail persons are more likely to be vaccinated compared to healthy persons, the absolute values of the bias of estimates from all 4 study designs under

case 3 are in general larger than the ones under case 2. Under all 4 cases, when source of bias A1 or A2 present, which is the vaccination lowers or increase the probability of NFARI, the absolute values of the bias of estimates from TN study are severe. When source of bias B present, which is health status affect the probability of NFARI or FARI or both, the VE estimates suffer differ level of bias. When source of bias C, vaccination lower the probability of seeking medical care for FARI, the VE estimates from TN against symptomatic influenza suffer severe bias, but the VE estimates from TN against MAI have little bias. When source of bias D present, the bias of VE estimates from TN study are very small.

Table 3.4: Bias of VE Estimates for Case 1

Set	Source of Bias	Value of Parameter(s)	ASC SI	PSC MAI	PSC SI	TN SI	TN MAI	TCC SI	TCC MAI
0	None	All parameters = 1.0	-0.0006	-0.00929	-0.00916	0.00235	0.00248	0.01792	0.01805
1	A1	$\theta_\beta = 0.5$	-0.00013	-0.00433	-0.0042	-0.54641	-0.54628	0.125	0.12513
2	A2	$\theta_\beta = 2.0$	-0.00137	-0.00287	-0.0032	0.2839	0.28357	-0.26243	-0.26276
3	B1	$\psi_\beta = 2.0$	0.00004	-0.0022	0.00075	0.06699	0.06994	-0.00704	-0.00409
4	B2	$\psi_\gamma = 2.0$	-0.11769	-0.11944	-0.11931	-0.10029	-0.10016	-0.03387	-0.03374
5	BS	$\psi_\beta = \psi_\gamma = 2.0$	-0.0531	-0.0542	-0.05228	-0.03754	0.03946	0.00252	0.00444
6	C	$\theta_{\delta_2} = 0.5$	-0.00061	0.27805	-0.00305	0.28324	0.00214	0.28832	0.00722
7	D	$\mu_{\delta_1} = \mu_{\delta_2} = 0.5$	-0.00061	-0.15219	-0.15009	0.00105	0.00315	-0.11656	-0.11446

Table 3.5: Bias of VE Estimates for Case 2

Set	Source of Bias	Value of Parameter(s)	ASC SI	PSC SI	PSC MAI	TN SI	TN MAI	TCC SI	TCC MAI
0	None	All parameters = 1.0	-0.00031	-0.00164	-0.00111	0.00539	0.00592	0.02136	0.02189
1	A1	$\theta_\beta = 0.5$	0.00088	-0.00442	-0.00504	-0.54836	-0.54898	0.12394	0.12332
2	A2	$\theta_\beta = 2.0$	-0.00161	-0.00586	-0.00326	0.2836	0.2862	-0.26255	-0.25995
3	B1	$\psi_\beta = 2.0$	0.00113	-0.00472	-0.00404	0.03755	0.03823	0.0041	0.00478
4	B2	$\psi_\gamma = 2.0$	-0.02857	-0.02936	-0.02877	-0.00979	-0.0092	0.06203	0.06262
5	BS	$\psi_\beta = \psi_\gamma = 2.0$	-0.02769	-0.02575	-0.02495	0.0313	0.0321	0.04889	0.04969
6	C	$\theta_{\delta_2} = 0.5$	-0.00031	0.27969	-0.00001	0.28515	0.00545	0.29199	0.01229
7	D	$\mu_{\delta_1} = \mu_{\delta_2} = 0.5$	-0.00031	-0.1275	-0.12662	0.00395	0.00483	-0.09092	-0.09004

Table 3.6: Bias of VE Estimates for Case 3

Set	Source of Bias	Value of Parameter(s)	ASC SI	PSC SI	PSC MAI	TN SI	TN MAI	TCC SI	TCC MAI
0	None	All parameters = 1.0	-0.00187	-0.00159	-0.00074	0.00651	0.00736	0.02051	0.02136
1	A1	$\theta_\beta = 0.5$	-0.00183	-0.00742	-0.00599	-0.55347	-0.55204	0.11772	0.11915
2	A2	$\theta_\beta = 2.0$	-0.00416	-0.00658	-0.00742	0.28065	0.27981	-0.26504	-0.26588
3	B1	$\psi_\beta = 2.0$	-0.00284	-0.00797	-0.00577	0.11631	0.11851	-0.03861	-0.03641
4	B2	$\psi_\gamma = 2.0$	-0.10932	-0.10781	-0.10821	-0.0947	-0.0951	-0.04342	-0.04382
5	BS	$\psi_\beta = \psi_\gamma = 2.0$	-0.1092	-0.11101	-0.10982	0.0515	0.05269	-0.10055	-0.00119
6	C	$\theta_{\delta_2} = 0.5$	-0.00187	0.27909	0.00075	0.2838	0.00546	0.28771	0.00937
7	D	$\mu_{\delta_1} = \mu_{\delta_2} = 0.5$	-0.00187	-0.17935	-0.17859	0.00546	0.00622	-0.14044	-0.13968

3.3.2 Corrections for Bias for TN Study

The results of bias after correction for Bias A - C are shown in Table 3.9 - 3.15.

Table 3.7: Bias of VE Estimates for Case 4

Set	Source of Bias	Value of Parameter(s)	ASC SI	PSC SI	PSC MAI	TN SI	TN MAI	TCC SI	TCC MAI
0	None	All parameters = 1.0	-0.00223	-0.00319	-0.00231	0.00817	0.00905	0.03842	0.0393
1	A1	$\theta_\beta = 0.5$	-0.00205	-0.00229	-0.00279	-0.56248	-0.56298	0.13847	0.13797
2	A2	$\theta_\beta = 2.0$	-0.00307	-0.00481	-0.00444	0.2918	0.29217	-0.24458	-0.24421
3	B1	$\psi_\beta = 2.0$	0.00125	-0.00038	0.00005	-0.06667	-0.06624	0.06618	0.06661
4	B2	$\psi_\gamma = 2.0$	0.04854	0.0496	0.04916	0.07775	0.07731	0.17393	0.17349
5	BS	$\psi_\beta = \psi_\gamma = 2.0$	0.04929	0.04782	0.04772	0.00603	0.00593	0.19174	0.19164
6	C	$\theta_{\delta_2} = 0.5$	-0.00223	0.28921	-0.00039	0.29451	0.00491	0.30809	0.01849
7	D	$\mu_{\delta_1} = \mu_{\delta_2} = 0.5$	-0.00223	-0.12108	-0.12055	0.00623	0.00676	-0.06453	-0.064

In all 4 cases, after the correction of bias A, the corrected VE estimates is very close to the true VE (Table 3.9 - 3.10).

For the correction for Bias B, we compared the results from 10 different methods listed in Table 3.8, and results are shown in Table 3.11 - 14.

Table 3.8: Methods for Bias B Correction

	Methods
1	Logistic Regression with No Covariates
2	Logistic Regression with Covariate: M
3	Logistic Regression with Covariate: X
4	Logistic Regression with Covariate: M and X
5	Logistic Regression with Covariates: X and U
6	Logistic Regression with Covariates: M, X and U
7	Covariate Adjustment Using the Propensity Score Based on M, X, U
8	Stratification on the Propensity Score Based on M, X, U
9	Inverse Probability of Treatment Weighting Using the Propensity Score Based on M, X, U
10	1:1 Match X for cases and controls unadjusted VE estimate

Under Case 1, when source of bias B1 is present, method 7 and method 10 give better estimates for VE than other methods. Method 7 tends to overestimate VE whereas method 10 tends to underestimate VE. When source of bias B2 is present, all methods tend to underestimate VE. The absolute values of bias from method 10 are much smaller than the ones from all other methods. Among the methods, method 10 give the best estimate of VE. When source of Bias BS is present, Method 2 gives the closest estimate.

Under Case 2, when source of bias B1 is present, method 7 gives better estimates for VE than other methods. While method 9 performs better than other methods when source of bias B2 or BS present.

Under Case 3, when source of bias B1 is present, if using method 3, 5, or 8, the corrected bias for bias B1 is very similar. In order to get better corrected results when bias b2 is present, we will prefer method 4 or 9. And to better correct the VE estimates when bias BS is present, we will prefer method 2.

Under Case 4, when source of bias B1 is present, method 7 gives better estimates. When source of bias B2 is present, method 2 performs better than other methods. When source of bias BS is present, method 3 performs better than other methods.

Under all 4 cases, when bias B1 is the main concern, method 7 gives better estimates for VE in general. When B2 is the main concern, method 9, in general, gives better estimates. When BS is the main concern, method 2 or method 9 may be an option.

For the correction for Bias C, we tried to vary the sample size of ASC study from 200 to 1000, and vary the sample size of the TN study from 2000 to 10000 to compare the corrected VE estimate. The results for ASC and TN study for case 1 are based on 1000 simulations and are present in Table 3.15. The true VE under case 1 is 0.438. Under different study sizes, due to the number of persons who visit and test positive is small, the corrected estimated VE based on the TN study also has a large SE. If we only conduct the ASC study, we get an estimate of VE that has less bias and a smaller SE compared to the corrected estimate from the TN study even the cohort study size is not very large. When bias C is the main concern, ASC study can help correct the VE estimate from TN study, but the standard error of the corrected VE estimate is relatively large.

Table 3.9: Bias A1 Correction for TN Study for Case 1 - Case 4

Case	True VE	Corrected VE for Bias A1
1	0.43835	0.43832
2	0.43766	0.43749
3	0.44346	0.43885
4	0.42352	0.42260

Table 3.10: Bias A2 Correction for TN Study for Case 1 - Case 4

Case	True VE	Corrected VE for Bias A2
1	0.43893	0.43938
2	0.43764	0.43641
3	0.44239	0.44005
4	0.42395	0.42083

Table 3.11: Bias B Correction for TN Study for Case 1 when True VE is 0.43835.

Method	Corrected VE for Bias B1	Corrected VE for Bias B2	Corrected VE for Bias BS
1	0.50575	0.33806	0.41277
2	0.50589	0.34229	0.41544
3	0.44487	0.39950	0.39624
4	0.44597	0.40452	0.40072
5	0.44501	0.39992	0.39688
6	0.44592	0.40497	0.40123
7	0.44382	0.36720	0.36905
8	0.44751	0.33781	0.35494
9	0.44633	0.40527	0.40127
10	0.43388	0.40908	0.38416

Method 1: Logistic Regression with No Covariates
Method 2: Logistic Regression with Covariate: M
Method 3: Logistic Regression with Covariate: X
Method 4: Logistic Regression with Covariate: M and X
Method 5: Logistic Regression with Covariates: X and U
Method 6: Logistic Regression with Covariates: M, X and U
Method 7: Covariate Adjustment Using the Propensity Score Based on M, X, U
Method 8: Stratification on the Propensity Score Based on M, X, U
Method 9: Inverse Probability of Treatment Weighting Using the Propensity Score Based on M, X, U
Method 10: 1:1 Match X for cases and controls unadjusted VE estimate

3.4 Discussion

SimFlu is a stochastic agent-based simulation model of influenza epidemics, it helps to understand and to mimic the spread of transmission of influenza in a stratified population. It performs a set of simulations with fixed values of parameters. Each

Table 3.12: Bias B Correction for TN Study for Case 2 when True VE is 0.43886.

Method	Corrected Bias for Bias B1	Corrected Bias for Bias B2	Corrected Bias for Bias BS
1	0.47527	0.36447	0.40453
2	0.47586	0.36817	0.33977
3	0.44185	0.39745	0.35218
4	0.44289	0.40182	0.34842
5	0.44218	0.39734	0.35198
6	0.44310	0.40162	0.34839
7	0.43717	0.36198	0.36491
8	0.45088	0.32484	0.34173
9	0.44396	0.40315	0.40039
10	0.44075	0.30005	0.39194

Method 1: Logistic Regression with No Covariates
Method 2: Logistic Regression with Covariate: M
Method 3: Logistic Regression with Covariate: X
Method 4: Logistic Regression with Covariate: M and X
Method 5: Logistic Regression with Covariates: X and U
Method 6: Logistic Regression with Covariates: M, X and U
Method 7: Covariate Adjustment Using the Propensity Score Based on M, X, U
Method 8: Stratification on the Propensity Score Based on M, X, U
Method 9: Inverse Probability of Treatment Weighting Using the Propensity Score Based on M, X, U
Method 10: 1:1 Match X for cases and controls unadjusted VE estimate

simulation corresponds to a single outbreak. In the simulation, it explicitly represents every individual, so the simulated epidemic can be studied in detail, even tracking individual transmission events. With the help of detailed computer simulations, more topics in evaluating containment and mitigation strategies can be explored in future research. However, models created with SimFlu are stochastic, so results may vary from run to run, and some events, especially early in an epidemic, may depend on random choices such as the identity of the initial cases.

By incorporating stochastic simulations to assess bias and precision of influenza VE estimates for four observational study designs, we are able to compare these study designs in detail. In this chapter, we explored the performance of four observational study designs in VE estimating with the impact of different sources of bias under various confounding assumptions. Under all four cases, which means regardless the

Table 3.13: Bias B Correction for TN Study for Case 3 when True VE is 0.44248.

Method	Corrected Bias for Bias B1	Corrected Bias for Bias B2	Corrected Bias for Bias BS
1	0.55814	0.28170	0.42807
2	0.55731	0.28709	0.42932
3	0.44613	0.40623	0.40292
4	0.44682	0.41222	0.40838
5	0.44603	0.40574	0.40229
6	0.44673	0.41160	0.40762
7	0.45123	0.37857	0.38022
8	0.44567	0.37787	0.35673
9	0.44721	0.40930	0.40523
10	0.40583	0.13703	0.35242

Method 1: Logistic Regression with No Covariates
Method 2: Logistic Regression with Covariate: M
Method 3: Logistic Regression with Covariate: X
Method 4: Logistic Regression with Covariate: M and X
Method 5: Logistic Regression with Covariates: X and U
Method 6: Logistic Regression with Covariates: M, X and U
Method 7: Covariate Adjustment Using the Propensity Score Based on M, X, U
Method 8: Stratification on the Propensity Score Based on M, X, U
Method 9: Inverse Probability of Treatment Weighting Using the Propensity Score Based on M, X, U
Method 10: 1:1 Match X for cases and controls unadjusted VE estimate

association between heath status and health awareness, and the relationship between vaccination and health status, estimates from TCC studies performs worst among all four observational study designs when no bias is present. When the probability of non-influenza ARI depends on vaccination status, the two cohorts study designs give better estimates of VE than the two case-control study designs, which confirms our previous findings in Chapter 2 that VE estimates from test-negative study may be severely biased. When vaccination increases the probability of non-influenza ARI, test-negative study tends to severely overestimate vaccination efficiency while traditional case-control study tends to severely underestimate vaccination efficiency. If vaccination reduces the probability that an influenza patient seeks medical care because her/his symptoms are less severe than those of an unvaccinated influenza patient, then only active surveillance cohort study can provide reliable VE estimates

Table 3.14: Bias B Correction for TN Study for Case 4 when True VE is 0.42225.

Method	Corrected Bias for Bias B1	Corrected Bias for Bias B2	Corrected Bias for Bias BS
1	0.35556	0.44084	0.36959
2	0.36042	0.43817	0.36732
3	0.42956	0.39776	0.39346
4	0.43251	0.39536	0.39046
5	0.42978	0.39728	0.39304
6	0.43270	0.39458	0.39004
7	0.41887	0.33960	0.33617
8	0.39412	0.33910	0.31109
9	0.43334	0.39310	0.38785
10	0.41861	0.52978	0.33756

Method 1: Logistic Regression with No Covariates
Method 2: Logistic Regression with Covariate: M
Method 3: Logistic Regression with Covariate: X
Method 4: Logistic Regression with Covariate: M and X
Method 5: Logistic Regression with Covariates: X and U
Method 6: Logistic Regression with Covariates: M, X and U
Method 7: Covariate Adjustment Using the Propensity Score Based on M, X, U
Method 8: Stratification on the Propensity Score Based on M, X, U
Method 9: Inverse Probability of Treatment Weighting Using the Propensity Score Based on M, X, U
Method 10: 1:1 Match X for cases and controls unadjusted VE estimate

against SI. Hereby, when the outcome of interest is MAI, then the vaccine-related reduction in symptoms's severity will not have a serious impact on the VE estimates from test-negative study design and traditional case-control study design. If ARI patients with high health awareness have a higher probability of seeking medical care, active surveillance cohort study and test-negative study can both provide VE estimates with small absolute values of bias(< 0.01).

Compared to the probability model we proposed in Chapter 2, we incorporated dynamics of the transmission of infectious in the SimFlu model, so it mimics the real transmission process of influenza in a closed population. With the help of the detailed simulation data generated by SimFlu, we get a chance to study the details of influenza transmission and evaluate the performance of different observational studies under various situations.

Table 3.15: Bias C Correction for TN Study for Case 1 when True VE is 0.43835.

TN Size \ Cohort Size		200	500	1000
2000	Number of ARI in ASC	88	220	439
	Estimate of VE from ASC	0.361	0.397	0.411
	SE of the VE estimate from ASC	0.452	0.333	0.199
	Number of ARI and visited patients in TN	262	262	262
	Corrected VE estimate from TN	0.542	0.335	0.295
	SE of the corrected VE estimate from TN	0.380	0.562	0.629
5000	Number of ARI in ASC	88	221	439
	Estimate of VE from ASC	0.389	0.390	0.406
	SE of the VE estimate from ASC	0.469	0.348	0.204
	Number of ARI and visited patients in TN	654	654	654
	Corrected VE estimate from TN	0.543	0.366	0.329
	SE of the corrected VE estimate from TN	0.334	0.476	0.464
10000	Number of ARI in ASC	88	220	440
	Estimate of VE from ASC	0.344	0.389	0.427
	SE of the VE estimate from ASC	0.529	0.346	0.171
	Number of ARI and visited patients in TN	1308	1308	1308
	Corrected VE estimate from TN	0.550	0.378	0.321
	SE of the corrected VE estimate from TN	0.306	0.431	0.450

However, due to the stochastic processes in the SimFlu model, the data we generated may depend on random choices such as the identity of the initial cases, especially in an early stage of an outbreak of epidemic.

In this chapter, beside health status, we incorporated another confounder, health awareness, into the model, so the association between health status and health awareness is also taken into consideration.

In this chapter, we considered 4 cases (Table 3.3). In Case 1-3, the association between health status and vaccination is the same with one in Scenario 2 in Chapter 2, and the association between health status and vaccination is the same for Case 4 in this chapter and Scenario 3 in Chapter 2, despite the effect of health awareness. We compared the absolute value of bias under various combinations of sources of bias for Traditional Case-control study and Test-negative study (Table 3.1 and Table 3.2 below).

Here are several differences in the setup of situations: 1. In this chapter, we separated the two direction of the association between vaccination and the probability of NFARI. A1 stands for the source of bias when vaccination lowers the probability of NFARI, and A2 stands for the source of bias when vaccination increases the probability of NFARI. While in Chapter 2, we considered these two situations as one source of bias. 2. In this chapter, source of bias D is defined as ARI patients with high health awareness have a higher probability of seeking medical care, but in Chapter 2, source of bias D is defined as Health status affects the probability of seeking medical care against FARI and NFARI. The results for source of bias D from this chapter and the ones from Chapter 2 are not comparable. Thus, we do not include them in the tables below (Table 3.16 and Table 3.17).

In general, the results are consistent, except the situation when source of bias B present.

In addition, we investigated the situations when the associations among health status, health awareness and vaccination status are varied. When health status and health awareness are independent, the absolute bias of VE estimates from test-negative study will not be affected by the association between health status and vaccination status. When health status and health awareness are positively associated, the absolute bias of VE estimates from test-negative study are smaller compared to the ones when health status and health awareness are independent, while the absolute bias of VE estimates are larger compared to the ones when health status and health awareness are independent when health status and health awareness are negatively associated. When health status and health awareness are negatively associated or when frail persons are less likely to be vaccinated compared to healthy persons, the absolute bias of VE estimates from traditional case-control study are larger than the ones based on the situation that health status and health awareness are independent and frail persons are more likely to be vaccinated compared to healthy persons. If

Table 3.16: Comparison of Absolute Value of Bias under Various Combinations of Source of Bias from Chapter 2 Scenario 2 and Chapter 3 Case 1-3 for Traditional Case-Control Study and Test-negative Study

Type of Bias	Chapter 2 Scenario 2 Result				Chapter 3 Case 1 Result				Chapter 3 Case 2 Result				Chapter 3 Case 3 Result			
	TN SI	TN MAI	TCC SI	TCC MAI	TN SI	TN MAI	TCC SI	TCC MAI	TN SI	TN MAI	TCC SI	TCC MAI	TN SI	TN MAI	TCC SI	TCC MAI
None	0.00	0.00	0.03	0.03	0.00	0.00	0.02	0.02	0.01	0.01	0.02	0.02	0.01	0.01	0.02	0.02
A1	0.40	0.40	0.10	0.10	0.55	0.55	0.13	0.13	0.55	0.55	0.12	0.12	0.55	0.55	0.12	0.12
A2					0.28	0.28	0.26	0.26	0.28	0.29	0.26	0.26	0.28	0.28	0.27	0.27
B1	0.13	0.13	0.05	0.05	0.07	0.07	0.01	0.00	0.04	0.04	0.00	0.00	0.12	0.12	0.04	0.04
B2	0.10	0.10	0.12	0.12	0.10	0.10	0.03	0.03	0.01	0.01	0.06	0.06	0.09	0.10	0.04	0.04
BS	0.00	0.00	0.13	0.13	0.04	0.04	0.00	0.00	0.03	0.03	0.05	0.05	0.05	0.05	0.10	0.00
C	0.20	0.00	0.22	0.03	0.28	0.00	0.29	0.01	0.28	0.01	0.29	0.01	0.28	0.01	0.29	0.01

the study assumptions are that healthy persons have a lower probability of FARI and health status and health awareness are either independent or negatively associated, then neither active surveillance cohort study nor passive surveillance cohort study can provide accurate estimates for VE.

Table 3.17: Comparison of Absolute Value of Bias under Various Combinations of Source of Bias from Chapter 2 Scenario 3 and Chapter 3 Case 4 for Traditional Case-Control Study and Test-negative Study

Type of Bias	Chapter 2 Scenario 3 Result				Chapter 3 Case 4 Result			
	TN SI	TN MAI	TCC SI	TCC MAI	TN SI	TN MAI	TCC SI	TCC MAI
None	0.00	0.00	0.03	0.03	0.01	0.01	0.04	0.04
A1	0.40	0.40	0.10	0.10	0.56	0.56	0.14	0.14
A2					0.29	0.29	0.24	0.24
B1	0.09	0.09	0.03	0.03	0.07	0.07	0.07	0.07
B2	0.12	0.12	0.10	0.10	0.08	0.08	0.17	0.17
BS	0.00	0.00	0.12	0.12	0.01	0.01	0.19	0.19
C	0.20	0.00	0.22	0.03	0.29	0.01	0.31	0.02

Meanwhile, in this chapter, we assessed the bias for test-negative study and proposed different methods to correct the bias for TN study when different sources of bias are present. When vaccination affect the the probability of non -influenza ARI, the bias of VE estimates can be corrected using the probability model we proposed in Chapter 2. If health status affects the probability of non-influenza ARI or influenza ARI, we proposed three methods: (1) logistic regression, (2) propensity score and (3) matched control to cases. Under different situation, different methods are preferred. Additionally, we combined test-negative study with a small active surveillance cohort study in order to correct the bias caused by vaccination lowering the probability of seeking medical care for influenza ARI patients.

We did not find a universal solution to correct the bias introduced by different sources of bias, however, when the main concern comes from different sources of bias, we proposed different approaches to correct the bias. When source of bias A1/ A2 is the main concern, the VE estimate can be corrected using the numbers of vaccinated and unvaccinated persons in TN study who has NFARI based on the probability we proposed in Chapter 2. When source of bias B is the main concern, covariate adjustment using the propensity score based on seeking for medical care,

health status and health awareness method will help correct the bias, in general. If you have clear knowledge about the association between health status and health awareness under your situation, methods such as matching health status for cases and controls and logistic regression with different covariates can also help you get better results under specific situations. When source of bias C is the main concern, we proposed a method that combining a small ASC and a TN study. In this method, a small ASC study is suggested to conduct simultaneously with the TN study, the ratio of probability of seeking for medical care in FARI patients between vaccinated patients and unvaccinated patients estimated from the ASC study can help correct the bias from TN study.

Our study has a few limitations: (a) We assume that the tests sensitivity and specificity do not depend on vaccination status or on the propensity of seeking medical care. (b) We assume that vaccination status is determined without an error. (c) We assume vaccination is complete before the onset of study, so the vaccination status remain unchanged throughout the study and the true VE can be defined as one minus the ratio of the cumulative incidence rates in vaccinees and non-vaccinees. (d) When combining test-negative study and active surveillance study, although the bias VE estimates are smaller from the combined study design comparing with the bias of the VE the from the test-negative study design, the standard errors are large.

Chapter 4

Waning of Influenza Vaccine Effectiveness in Cohort and Test-Negative Studies

chapter

4.1 Introduction

Influenza viruses can cause pandemics, and rates of illness and death from influenza-related complications can increase worldwide. It is a highly contagious respiratory illness that is responsible for significant morbidity and mortality. Since 2010, influenza has resulted in between 9 million − 45 million illnesses, between 140,000 − 810,000 hospitalizations and between 12,000 − 61,000 deaths annually. In the 2019/20 U.S. flu season, the Centers for Disease Control and Prevention (CDC) estimates that there are 39,000,000 − 56,000,000 flu illnesses, 410,000 − 740,000 flu hospitalizations and 24,000 − 62,000 flu deaths in the U.S.A (Centers for Disease Control and Prevention (CDC) (2020b)). Since influenza viruses can results in serious illness, hospitalization, and death in all age groups, the United States Advisory Committee on Immunization Practices recommends that US residents aged >= 6 months receive annual influenza vaccination by October of each year to allow sufficient time for development of immune protection prior to onset of influenza activity (Centers for Disease Control and Prevention (CDC) (2019)).

While seasonal influenza(flu) viruses are detected year-round in the United States, flu virus is most commonly circulating from late fall through early spring. CDC collects, compiles, and analyzes information on influenza activity year-round in the United States. The exact timing and duration of flu season can vary, but in the United State, the annual influenza activity is typically beginning in October. Most of the time, the influenza activity peaks between December and February, and the duration of the annual influenza epidemic can last as late as May (Centers for Disease Control and Prevention (CDC) (2020a)).

In the 2011/12 influenza seasons various studies in Europe reported a decrease

in influenza vaccine effectiveness (VE) against A(H3N2) over time within the season (Kissling et al. (2013), Pebody et al. (2013), Castilla et al. (2013), Jiménez-Jorge et al. (2013)). The I-MOVE multicenter case-control study suggested a low vaccine effectiveness against medically attended A(H3) influenza in that season. In a pooled analysis, the adjusted vaccine effectiveness against A (H3N2) was 46.8% and 10.5%, respectively, among patients with illness onset less than 93 days after vaccination and those with illness beginning 93 days or more after vaccination. Because of the late arrival of the 2011/12 influenza season, persons presenting with influenza had a long delay between onset of symptoms and the vaccination. The observed fall in influenza vaccine effectiveness may be due to the intraseason waning of influenza vaccine effectiveness (Kissling et al. (2013)).

An observational study of influenza vaccine effectiveness against laboratory-confirmed influenza infection in primary care in the United Kingdom 2011/12 winter season found that the 2011/12 seasonal influenza vaccine was overall poorly protective in preventing influenza A(H3N2) infection, and the vaccine protection was moderate in the first three months of the season, but reduced in the second three months. The adjusted vaccine effectiveness was 53% for individuals vaccinated less than three months before illness onset, and 12% for those vaccinated three months or more before illness onset ($p = 0.02$, test for trend). And they suggested that there was evidence of waning protection against influenza A(H3N2) three months after vaccination (Pebody et al. (2013)).

In the Navarre region of Spain, a test-negative study was conducted to evaluate the influenza vaccine effectiveness in preventing laboratory-confirmed cases in the 2011/12 season. The adjusted vaccine effectiveness against influenza A (H3N2) was 61% in the first 100 days after vaccination, 39% between 100 and 119 days, and zero after 120 days. The results suggest that on average, the seasonal influenza vaccine had a low protective effect in preventing laboratory-confirmed influenza during that

season, and the early estimates of the influenza VE for the first part of the season were higher than the complete season, which suggests a decline in vaccine effectiveness over time (Castilla et al. (2013)). This study included both outpatient and hospital cases. If the analysis was limited to the primary care patients, the vaccine effectiveness was maintained, i.e., no waning was found during the season. Another study in Spain also suggested the trend toward a decrease in influenza vaccine effectiveness with time, and the decreasing protective effect of the vaccine in the late part of the season could be related to waning vaccine protection because no viral changes were identified throughout the season (Jiménez-Jorge et al. (2013)).

However, the interpretation of waning immunity for all four studies was complicated by the emergence of antigenic variant A (H3N2) viruses in Europe as the season progressed.

In the United States, the data from an observational study of influenza vaccine effectiveness that was performed during the 2008/09 influenza season was reanalyzed to assess evidence for waning protection against influenza A(H3N2) in a community cohort. A significant association between influenza A(H3N2) positive medically attended ARI visits and increasing time since vaccination among young children and elderly adults was identified in the 2007/08 influenza season (Belongia et al. (2015)). In addition, data from a placebo-controlled trial was analyzed to estimate the absolute and relative efficacies of inactivated influenza vaccine (IIV) and live-attenuated influenza vaccine (LAIV). In this study, statistically significant waning was detected for IIV ($p = 0.03$), but not for LAIV ($p = 0.\ 37$). Both vaccines were efficacious, however, IIV efficacy decreased slowly over time (Petrie et al. (2016)).

Pooled data across five post-pandemic seasons were studied by Kissling et al. in 2016, and influenza type/subtype specific VE by time since vaccination for the overall season was measured. Among the five seasons studied (2010/11 to 2014/15), there are four season with influenza A(H3N1), four seasons with influenza A(H1N1)pdm09

and three seasons with influenza B. Influenza seasons varied in terms of start, intensity and duration, evidence of moderate waning of VE against influenza A(H3N2) and mild waning of VE against influenza B were found, and there was no evidence of waning of VE against influenza A(H1N1)pdm09 virus infection (Kissling et al. (2016)). In combined data from four US influenza seasons (2011/12 to 2014/15), decreasing influenza vaccine protection with increasing time since vaccination for influenza A(H3N2), influenza A(H1N1) pdm09, and influenza B virus infections was also observed by Ferdinands et al. in 2017 (Ferdinands et al. (2017)).

These reports have raised concerns that vaccine induced protection against influenza illness may decline over the course of a single season. It has been reported that antibody levels begin to decrease one month after administration of the influenza vaccine, and this loss of immune response is more pronounced in older people (Song et al. (2010)). If vaccine-induced protection wanes during the season, then depending on the start and duration of the influenza season, the decline of the VE may cause increases in overall incidence.

Alternative explanations for the observed decline in vaccine protection during an influenza season include emergency and circulation of a drifted variant less well-matched to the vaccine strain. The change in the viruses circulating during the season, either due to appearance of another virus type or due to antigenic drift of circulating viruses, can result in a loss of the match with the vaccine viruses. However, some study results do not support this mechanism, since Castilla et al observed decreasing in vaccine effectiveness when they evaluated the effectiveness of the vaccine against influenza A(H3) only (Castilla et al. (2013)), and Belongia et al. suggested that they could not assess changes in the prevalence of antigenic variant viruses during the studied season and differential effects by age group should not be expected if virus evolution was the only factor contributing to the changing risk of influenza over time (Belongia et al. (2015)).

The biologic mechanisms that may contribute to the decline in protection against influenza illness over the course of a single season are uncertain, and the evidence for intraseason waning of influenza vaccine protection is growing but inconsistent. The CDC Advisory Committee on Immunization Practices (ACIP) currently recommends that vaccine providers in the United States should begin offering vaccination by the end of July (Centers for Disease Control and Prevention (CDC) (2020c)). As a result, the interval from vaccination to the peak of the influenza season could be as long as 6 months for persons who are vaccinated early. The possibility of waning indicates the need for further studies in different seasons and populations for healthcare organizations to modify the current vaccine recommendations.

In this chapter, we analyze data generated from SimFlu using three different methods to evaluate waning vaccine efficacy under both cohort and test negative studies.

4.2 Methodology

4.2.1 Data

In order to examine waning vaccine efficacy, we present 6 cases. In cases 1-3 the population is homogeneous (everyone is healthy, and everyone has the same probability of getting vaccinated). In cases 4-6 the population is heterogeneous 80% are healthy while 20% are frail, and frail persons are more likely than healthy persons to get vaccinated and they have higher probabilities of becoming infected in each contact. In addition we have 3 levels of waning: (1) no waning (per-contact VE's are 60% every month), (2) moderate waning (per-contact VE's are 60%, 50%, 40% in months 1, 2, 3, respectively, and (3) severe waning (per-contact VE's are 60%, 40%, 20%, respectively).

In case 1, the population is homogeneous and there is no waning, in case 2, the

population is homogeneous and the waning is moderate, in case 3, the population is homogeneous and severe waning is present. In case 4, the population is heterogeneous and there is no waning, in case 5, the population is heterogeneous and the waning is moderate, in case 6, the population is heterogeneous and the waning is severe. Therefore, in our 6 cases, the population is homogeneous in cases 1-3, and is heterogeneous in cases 4-6. There is no waning in cases 1, 4; moderate waning in cases 2, 5; severe waning in cases 3, 6.

4.2.2 Methods

Vaccine efficacy (VE) is generally estimated by $VE = 1 - RR$, where RR is some measure of relative risk in the vaccinated compared with the unvaccinated group. If the VE wanes with time, the relative risk estimates also change with time. In this chapter, we compared 3 approaches to estimate time-varying efficacy for cohort study and test negative study designs.

Although cumulative incidence rate (attack rate) can be used in estimating vaccination effectiveness, when evaluating VE waning, it is not a good idea to use the VE estimate based on attack rates. If the vaccine is leaky, where vaccination is assumed to reduce the probability of infection, the estimate may decrease over time even if the true VE remains fixed (Smith et al. (1984), Zhang and Yu (1998)).

Durham et al. (1998) present a method for nonparametrically estimating $VE(t) = 1 - HR(t)$ from time to event data when the protective effects of the vaccine can change over time, where HR(t) is the ratio of hazard rates of infection, comparing vaccinated and unvaccinated individuals, over time. To estimate HR(t) nonparametrically, Durham et al. used a method based on smoothing scaled residuals from a Cox proportional hazards model,

$$\lambda(t) = \lambda_0(t)exp(\beta V),$$

where V is the binary vaccination status. If VE changes over time, based on this approach, β has to be a function of time and VE is estimated as: $V\hat{E}(t) = 1 - H\hat{R}(t) = 1 - e^{\hat{\beta}(t)}$.

In this method, an ordinary proportional hazards model was fit using the partial likelihood function, and the Schoenfeld residuals were calculated, which are the scaled differences between the actual and expected covariate values at each event time (Schoenfeld (1982)). These residuals were scaled and added to the coefficient from the ordinary proportional hazards model on them, then the time-varying regression coefficient, $\beta(t)$, was estimated by smoothing the sum of the estimated proportional hazards coefficient and the rescaled Schoenfeld residuals over time. Conceptually, they are nonparametrically estimating the instantaneous hazard rate ratio $e^{\beta(t)}$, thus $1 - VE(t)$.

In addition, this method also provided a hypothesis test for departures from the proportional hazards assumption, the null hypothesis is that the vaccine effect does not vary with time, which is: $H_0 : \beta(t) = \beta$ for all t.

Tian et al. (2005) suggested a novel, kernel-weighted partial likelihood technique considered by Valsecchi, Silvestri, and Sasieni (Valsecchi et al. (1996)) and Cai and Sun (Cai and Sun (2003)) to construct a simple estimation procedure for the Cox model with time-varying coefficients. They construct pointwise and simultaneous confidence intervals from the regression parameters over a properly chosen time interval via a simple resampling technique. At each time point, the estimate is obtained by maximizing a smooth concave function of a p x 1 vector of parameters, where p is the dimension of the vector of covariates. In our case, p = 1. Furthermore, they show how to use an integrated function of the estimate for a specific regression coefficient to examine the adequacy of the proportional hazards assumption for the corresponding covariate.

We also performed to use multivariable logistic regression with influenza infection

as the outcome and an interaction of vaccination status and the time between vaccination and symptom onset to examine the association between influenza VE and time since vaccination among patients with medically attended acute respiratory illness.

In a test-negative study, VE is defined as one minus the ratio of the odds of infection in vaccinated and unvaccinated. One can fit a logistic regression model:

$$logit(P(Y = 1)) = \beta_0 + \beta_1 \cdot V + \beta_2 \cdot T + \beta_3 \cdot V \cdot T + \beta_4 \cdot X + \beta_5 \cdot Z$$

where Y is the binary test outcome (0 = negative, 1 = positive), V is the binary vaccination status, T is the time (in days) from vaccination to the day of testing, X is health status, and Z is the prevalence of infection on the day of onset. Then $log(OR) = \beta_1 + \beta_3 \cdot T$. Hence testing the hypothesis of time independent VE is equivalent to testing: $H_0 : \beta_3 = 0$.

4.3 Results

We compared the proportion of simulations where the null hypothesis of no VE waning was rejected ($p < 0.05$) for each case and each method. In a cohort study, we tried methods proposed by Durham (Durham et al. (1998)) and Tian (Tian et al. (2005)) to test the null hypothesis that the vaccine effect does not vary with time, which is: $H_0 : \beta(t) = \beta$ for all t, under 6 cases using data simulated from SimFlu. The results are presented in Table 4.1. Analyses were conducted using R software version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria). For a cohort study, we did not apply the logistic regression method, since the logistic regression model uses the time of event (infection) for the cases, but there is no "time of event" for the non-cases.

For case 1 and case 4, there is no true VE waning. By using Durham's method, among 1000 simulations about 50 simulations have p-value smaller than 0.05, which

means about 5% of simulations where the null hypothesis was rejected at 5% significance level. By using Tian's method, when the population is homogeneous, which is case 1, the null hypothesis was rejected at 5% significance level in about 7% of simulations, and when the population is heterogeneous, the results are very similar to those from Durham's method, in about 5% of simulations the null hypothesis was rejected at 5% significance level.

For case 2 and 5, there is moderate waning, where the per-contact VE's are 60%, 50%, 40% in months 1, 2, 3, respectively. In Durham's method, in about 20% to 25% of simulations, the null hypothesis was rejected at 5% significance level, and by using Tian's method, about 17% of simulations rejected the null hypothesis at the 5% significance level.

For case 3 and case 6, the true VE is severely waning - per-contact VE's are 60%, 40%, 20%, respectively. By using Durham's method, about 70% of simulations rejected the null hypothesis at the 5% significance level, and by using Tian's Method, in about 45% of simulations, the null hypothesis was rejected at the 5% significance level.

Table 4.1: Proportion of Simulations with p-value < 0.05 in Cohort Study

Test / Count	p value < 0.05	
	Durham' Method	Tian's Method
Case 1	5.5%	7.2%
Case 2	25.8%	17.5%
Case 3	72.1%	46.4%
Case 4	5.4%	5.1%
Case 5	22.2%	16.9%
Case 6	64.4%	44.4%

Our results suggest that in a cohort study, both Durham's Method and Tian's Method are able to detect the waning under different settings. And the number of simulations with $p - value < 0.05$ are both increasing when the severity of waning increases. However, Durham's Method has higher power and smaller Type I error than Tian's Method.

For a TN study, in addition to Durham's and Tian's Methods, we also used the method based on the multivariable logistic regression model. We used the same number of study participants in the cohort and TN studies. Unlike cohort studies, in the TN study we can use the time of testing negative to infection at the time (T) in the logistic regression model for the TN controls. In the logistic regression approach, we tried two models, one includes prevalence and one does not use the prevalence as an explanatory variable. The prevalence of infection on a given day is estimated using the number of study participants who are infectious on that day. In our SimFlu program, the latent and incubation periods coincide and last 2 days, the infectious period is 4 days, and the test is done on the onset day of symptoms. Then a study participant who tested positive on day t will be considered infectious on days t, t + 1, t + 2, t + 3.

The proportion of simulations that rejected the null hypothesis at a 5% significance level in Tian's Method are less than 2% in all six cases. This method has trouble in detecting the waning under a test-negative study design. For Durham's method, when there is no true waning , in case 1 and case 4, the proportion of rejections of the null hypothesis at 5% significant level are about 8%. With the severity of waning increasing, the proportion of simulations rejecting the null hypothesis at the 5% significance level increased in both homogenous population and heterogeneous population conditions. However, the increase in proportions of rejections are not as large as they are in cohort study. For a heterogeneous population, comparing to the case with same waning level in the homogenous population, the proportions of

simulations that rejected the null hypothesis at 5% significance level are smaller.

For the logistic regression method, no matter with or without the pre-calculated prevalence as covariate, the waning in six cases can be detected, but in a weak way. When there is no waning in the population, about 3% of simulations rejected the null hypothesis at the 5% significance level, and when moderate waning is present, the proportion of simulations rejecting the null hypothesis at 5% significance level in the homogeneous population is about over 10%, while in heterogeneous population, only about 5% simulations rejected the null hypothesis at a 5% significance level. When severe waning is present, the proportion of simulations that rejected the null hypothesis at a 5% significance level in the homogeneous population is larger than that in the heterogeneous population. The logistic regression model without prevalence as a covariate, in general, showed higher power and smaller type I error than the logistic regression with prevalence as covariate.

Table 4.2: Proportion of Simulations with p-value < 0.05 in Test-Negative Study

Test / Count	p value < 0.05			
	Durham' Method	Tian's Method	Logistic Regression with Prevalence	Logistic Regression without Prevalence
Case 1	8%	1.7%	2.1%	3%
Case 2	25.2%	1.0%	10.8%	12.5%
Case 3	32.3%	0.2%	14.3%	16.5%
Case 4	6.4%	0.8%	2.7%	3.3%
Case 5	13.7%	0.4%	4.9%	5.9%
Case 6	23.2%	1.3%	11.1%	12.9%

Durham's method is able to detect the waning in both cohort and TN studies, but it has higher power in cohort study than in TN study when there is waning in the population.

4.4 Discussion

In this Chapter, we tried different methods to detect waning under different cases using simulated data for both cohort study and test-negative study designs. In a cohort study, Durham's method and Tian's method can detect VE waning, if it exists, while in a test-negative study, Tian's method fails to detect the waning.

Durham's method was previously applied to estimate time-varying efficacy of a cholera vaccine. In contrast to cholera, influenza virus circulation is generally limited to a well-defined winter season in temperate regions, and vaccination is required on an annual basis, except in the tropical regions where influenza circulates throughout the year. The relatively short influenza season limits power to estimate time-varying vaccine efficacy. For a cohort study, Durham's method displayed higher power than Tian's method. Although Tian's method provides reasonable results in a cohort study, this method has trouble in detecting waning in a test-negative study. For a test-negative study, the logistic regression method detected the waning when severe waning was present, although compared to Durham's method, logistic regression provided less powerful results. This finding is similar to the results of Ferdinands et al. (2017), who observed a decrease in effectiveness of influenza vaccine with increasing time since vaccination for influenza using logistic regression model, but their results showed a somewhat less pronounced rate of decline compared to the studies using other methods. There is no established method for modeling the association between VE and time since vaccination. In order to study the association, a study design with a large cohort in which influenza VE is measured at multiple time points during a season with data sufficiently rich to describe time-varying influenza exposure patterns and allow discrimination between putative mechanisms of vaccine action would be required. Observational studies are currently performed on an annual basis in the United States, Europe, Canada, and elsewhere to evaluate influenza vaccine effectiveness. The most common study design is the test-negative study. However, in

the studies evaluating the duration of influenza vaccine effectiveness using data collected in a test negative study, there are several limitations. In test-negative study, subjects are enrolled over the season, and the timing of enrollment can be associated with the likelihood of both influenza vaccination and influenza infection. In addition, subjects testing negative for influenza virus are susceptible to misclassification of immune status, since there is increasing probability that a test-negative subject may have been previously infected but did not seek medical care, especially as the season progresses. Evidence for intraseason waning of influenza vaccine protection is growing but inconsistent. The causes of the observed pattern of deceasing vaccine protection are complicated. Human serologic studies are consistent with a modest rather than a sharp waning in influenza vaccine protection within a given season. The antibodies to influenza hemagglutinin typically persisted for >=4 months for the influenza A(H3N2) component of the vaccine (Petrie et al. (2015)). Alternative explanations for an observed decline in vaccine protection during an influenza season include emergence and circulation of a drifted variant less well-matched to the vaccine strain, as was observed in 2011-2012 Europe (O'Hagan et al. (2012), White et al. (2010)). Meanwhile, it is possible that the observed decreasing vaccine protection pattern arose from uncontrolled confounding. Delaying vaccination may cause increasing risk of early season infection prior to vaccination, while receiving the influenza vaccine at the earliest opportunity each season may lead to little or no protection at the end of the season. Therefore, the waning of vaccination need to be further studied to help health authorities with the important task of making recommendations for vaccination.

Appendix A

Appendix for Chapter 2

Tables

Table A.1: List of parameters and other notation

Symbol	Definition	Values
X	Health status	0 - frail 1 - healthy
V	Vaccination status	0 - unvaccinated 1 - vaccinated
Y	ARI and influenza infection status	0 - no ARI 1 - NFARI 2 - FARI
M	Seeking medical care for ARI	0 - no 1 - yes
T	Result of test for influenza infection	0 - negative 1 - positive
C_A	Case/control status in TND study	0 - control 1 - case
C_B	Case/control status in TCC study	0 - control 1 - case
B	Participating in TCC study	0 - no 1 - yes
π	Probability of having better health status (i.e. healthy persons)	0.7
α_x	Probability of being vaccinated for a person of health status x	
β_{vx}	Probability of NFARI for a person of vaccination status v and health status x	
$\rho_\beta = \frac{\beta_{1x}}{\beta_{0x}}$	Ratio comparing vaccinees and non-vaccinees w.r.t. probability of NFARI	0.5-2.0
$\eta_\beta = \frac{\beta_{v1}}{\beta_{vo}}$	Ratio comparing healthy and frail persons w.r.t. probability of NFARI	0.5-1.0
γ_{vx}	Probability of FARI for a person of vaccination status v and health status x	
$\rho_\gamma = \frac{\gamma_{1x}}{\gamma_{0x}}$	Ratio comparing vaccinees and non-vaccinees w.r.t. probability of FARI	0.4[1]
$\eta_\gamma = \frac{\gamma_{v1}}{\gamma_{v0}}$	Ratio comparing healthy and frail persons w.r.t. probability of FARI	0.5-1.0
δ_{SN}	Probability of seeking medical care for ARI for an unvaccinated frail person with NFARI	
δ_{SF}	Probability of seeking medical care for ARI for an unvaccinated frail person with FARI	
λ	multiplier for the probability of seeking medical care for FARI or NFARI for a healthy person	0.5-2.0
Ψ_F	multiplier for the probability of seeking medical care for FARI for a vaccinated person	0.5-1.0
τ_e	Probability that a person of illness/infection status e tests positive for influenza infection	$\tau_1 = 0$, $\tau_2 = 1$

[1] Assumes a true VE of 60%. Thus, the probability of FARI in a vaccinee is 40% that of a non-vaccinee.

Table A.2: Sources of Bias

Source of Bias	Description
A	Vaccination affects the probability of NFARI, i.e. $\rho_\beta \neq 1$. This may result from virus interference (Cowling et al. (2012)).
B1	Health status affects the probability of NFARI, i.e. $\eta_\beta \neq 1$.
B2	Health status affects the probability of FARI, i.e. $\eta_\gamma \neq 1$.
BS	Health status affects the probability of FARI and NFARI, and the risk ratios comparing a healthy and a frail person are the same for both types of ARI, i.e. $\eta_\beta = \eta_\gamma \neq 1$. This is a special case of $B1 \bigcap B2$.
C	Vaccination affects the probability of seeking medical care for FARI, while it does not affect the probability of seeking medical care for NFARI, i.e. $\Psi_F \neq 1$. This may result from reduced severity of symptoms in vaccinated influenza patients.
D	Health status affects the probabilities of seeking medical care against FARI and NFARI, i.e. $\lambda \neq 1$.

Table A.3: Three scenarios for vaccination probabilities

Vaccination Scenario	Definition
1	Random vaccination, ${\alpha_0}^2 = {\alpha_1}^3 = 0.6$
2	Healthy individuals are more likely to be vaccinated than frail individuals: $\alpha_0 = 0.4$, $\alpha_1 = 0.8$.
3	Healthy individuals are less likely to be vaccinated than frail individuals: $\alpha_0 = 0.8$, $\alpha_1 = 0.4$.

[1] α_0 is the probability of vaccination for frail persons;
[2] α_1 is the probability of vaccination for health persons.

Table A.4: Estimate of VE against Symptomatic Influenza and Medically-Attended Influenza: Range of Bias and Maximum Absolute Value of Bias under Various Combinations of Sources of Bias

Source of Bias \ Outcome of Interest	Scenario	Symptomatic Influenza (SI)				Medically-attended Influenza (MAI)			
		Test-Negative		Traditional Case-Control		Test-Negative		Traditional Case-Control	
		Range of Bias[4]	Max Abs. Value Bias[5]	Range of Bias	Max Abs. Value Bias	Range of Bias	Max Abs. Value Bias	Range of Bias	Max Abs. Value Bias
None	1	(0.00, 0.00)	0.00	(0.03, 0.03)	0.03	(0.00, 0.00)	0.00	(0.03, 0.03)	0.03
	2	(0.00, 0.00)	0.00	(0.03, 0.03)	0.03	(0.00, 0.00)	0.00	(0.03, 0.03)	0.03
	3	(0.00, 0.00)	0.00	(0.03, 0.03)	0.03	(0.00, 0.00)	0.00	(0.03, 0.03)	0.03
A	1	(-0.40, 0.20)	0.40	(-0.10, 0.07)	0.10	(-0.40, 0.20)	0.40	(-0.10, 0.07)	0.10
	2	(-0.40, 0.20)	0.40	(-0.10, 0.07)	0.10	(-0.40, 0.20)	0.40	(-0.10, 0.07)	0.10
	3	(-0.40, 0.20)	0.40	(-0.10, 0.07)	0.10	(-0.40, 0.20)	0.40	(-0.10, 0.07)	0.10
B1	1	(0.00, 0.00)	0.00	(0.03, 0.03)	0.03	(0.00, 0.00)	0.00	(0.03, 0.03)	0.03
	2	(-0.13, 0.00)	0.13	(0.03, 0.05)	0.05	(-0.13, 0.00)	0.13	(0.03, 0.05)	0.05
	3	(0.00, 0.09)	0.09	(0.01, 0.03)	0.03	(0.00, 0.09)	0.09	(0.01, 0.03)	0.03
B2	1	(0.00, 0.00)	0.00	(0.02, 0.03)	0.03	(0.00, 0.00)	0.00	(0.02, 0.03)	0.03
	2	(0.00, 0.10)	0.10	(0.03, 0.12)	0.12	(0.00, 0.10)	0.10	(0.03, 0.12)	0.12
	3	(-0.12, 0.00)	0.12	(-0.10, 0.03)	0.10	(-0.12, 0.00)	0.12	(-0.10, 0.03)	0.10
B1,B2	1	(0.00, 0.00)	0.00	(0.02,0.03)	0.03	(0.00, 0.00)	0.00	(0.02,0.03)	0.03
	2	(-0.13, 0.10)	0.13	(0.03, 0.13)	0.13	(-0.13, 0.10)	0.13	(0.03, 0.13)	0.13
	3	(-0.12, 0.09)	0.12	(-0.12, 0.03)	0.12	(-0.12, 0.09)	0.12	(-0.12, 0.03)	0.12
BS	1	(0.00, 0.00)	0.00	(0.02, 0.03)	0.03	(0.00, 0.00)	0.00	(0.02, 0.03)	0.03
	2	(0.00, 0.00)	0.00	(0.03, 0.13)	0.13	(0.00, 0.00)	0.00	(0.03, 0.13)	0.13
	3	(0.00, 0.00)	0.00	(-0.12, 0.03)	0.12	(0.00, 0.00)	0.00	(-0.12, 0.03)	0.12
C	1	(0.00, 0.20)	0.20	(0.03, 0.22)	0.22	(0.00, 0.00)	0.00	(0.02, 0.03)	0.03
	2	(0.00, 0.20)	0.20	(0.03, 0.22)	0.22	(0.00, 0.00)	0.00	(0.02, 0.03)	0.03
	3	(0.00, 0.20)	0.20	(0.03, 0.22)	0.22	(0.00, 0.00)	0.00	(0.02, 0.03)	0.03
D	1	(0.00, 0.00)	0.00	(0.03, 0.03)	0.03	(0.00, 0.00)	0.00	(0.03, 0.03)	0.03
	2	(0.00, 0.00)	0.00	(-0.07, 0.12)	0.12	(0.00, 0.00)	0.00	(-0.07, 0.12)	0.12
	3	(0.00, 0.00)	0.00	(-0.08, 0.10)	0.10	(0.00, 0.00)	0.00	(-0.08, 0.10)	0.10
C,D	1	(0.00, 0.20)	0.20	(0.03, 0.22)	0.22	(0.00, 0.00)	0.00	(0.02, 0.03)	0.03
	2	(0.00, 0.20)	0.20	(0.03, 0.22)	0.22	(0.00, 0.00)	0.00	(-0.07, 0.12)	0.12
	3	(0.00, 0.20)	0.20	(0.03, 0.22)	0.22	(0.00, 0.00)	0.00	(-0.08, 0.10)	0.10
B1,B2,C,D	1	(0.00, 0.20)	0.20	(0.02, 0.22)	0.22	(0.00, 0.00)	0.00	(0.01, 0.03)	0.03
	2	(-0.13, 0.25)	0.25	(-0.07, 0.30)	0.30	(-0.13, 0.10)	0.13	(-0.07, 0.20)	0.20
	3	(-0.13, 0.25)	0.25	(-0.30, 0.25)	0.30	(-0.13, 0.10)	0.13	(-0.30, 0.10)	0.30
BS,C,D	1	(0.00, 0.20)	0.20	(0.02, 0.22)	0.22	(0.00, 0.00)	0.00	(0.01, 0.03)	0.03
	2	(0.00, 0.20)	0.20	(-0.07, 0.30)	0.30	(0.00, 0.00)	0.00	(-0.07, 0.20)	0.20
	3	(0.00, 0.20)	0.20	(-0.30, 0.25)	0.30	(0.00, 0.00)	0.00	(-0.30, 0.10)	0.30
A,B1,B2,C,D	1	(-0.40, 0.30)	0.40	(-0.11, 0.24)	0.24	(-0.40, 0.20)	0.40	(-0.11, 0.07)	0.11
	2	(-0.67, 0.33)	0.67	(-0.23, 0.31)	0.31	(-0.67, 0.25)	0.67	(-0.23, 0.21)	0.23
	3	(-0.67, 0.33)	0.67	(-0.50, 0.27)	0.50	(-0.67, 0.11)	0.67	(-0.50, 0.13)	0.50

[1] Bias = estimated VE - true VE. The range of the bias is the interval between the smallest and the largest value of the bias (accounting for the sign) using different combinations of the model parameters. The sign of bias indicates the direction of the difference between the estimated and the true VE. A negative sign corresponds to underestimation while a positive bias indicates overestimation.

[2] Maximum absolute value of bias is largest difference between the estimated and the true VE when the sign of the difference in ignored:
. . . Little or no bias (absolute bias less than 0.05), . . . Moderate bias (absolute bias greater than or equal to 0.05 and less than 0.10), . . . Substantial bias (absolute bias greater than or equal to 0.10 and less than 0.20),
. . . Severe bias (absolute bias 0.20 or more)

Table A.5: Minimum, Mean and Maximum Standard Errors of VE Estimates under Various Combinations of Source of Bias

Source of Bias[1] \ Design	Scenario[2]	Test-Negative			Traditional Case-Control		
		Min	Mean	Max	Min	Mean	Max
None	1	0.06	0.06	0.06	0.05	0.05	0.05
	2	0.06	0.06	0.06	0.05	0.05	0.05
	3	0.06	0.06	0.06	0.05	0.05	0.05
A	1	0.03	0.05	0.11	0.04	0.05	0.06
	2	0.03	0.05	0.10	0.04	0.05	0.06
	3	0.03	0.05	0.11	0.04	0.05	0.07
B1	1	0.05	0.05	0.06	0.05	0.05	0.05
	2	0.06	0.06	0.07	0.05	0.05	0.05
	3	0.04	0.05	0.06	0.05	0.05	0.05
B2	1	0.06	0.06	0.06	0.05	0.05	0.05
	2	0.05	0.05	0.06	0.04	0.04	0.05
	3	0.06	0.07	0.08	0.05	0.06	0.06
B1,B2	1	0.05	0.06	0.06	0.05	0.05	0.05
	2	0.05	0.06	0.07	0.04	0.04	0.05
	3	0.04	0.06	0.08	0.05	0.06	0.07
BS	1	0.06	0.06	0.06	0.05	0.05	0.05
	2	0.06	0.06	0.06	0.04	0.05	0.04
	3	0.06	0.06	0.06	0.05	0.07	0.06
C	1	0.03	0.04	0.06	0.03	0.04	0.05
	2	0.03	0.04	0.06	0.03	0.04	0.05
	3	0.03	0.05	0.06	0.03	0.04	0.05
D	1	0.06	0.06	0.06	0.05	0.05	0.05
	2	0.06	0.06	0.06	0.04	0.05	0.06
	3	0.06	0.06	0.06	0.04	0.05	0.06
C,D	1	0.03	0.04	0.06	0.03	0.04	0.05
	2	0.03	0.04	0.06	0.02	0.04	0.06
	3	0.03	0.05	0.06	0.02	0.04	0.06
B1,B2,C,D	1	0.03	0.04	0.06	0.03	0.04	0.05
	2	0.03	0.04	0.07	0.02	0.03	0.06
	3	0.02	0.05	0.08	0.02	0.04	0.09
BS,C,D	1	0.03	0.06	0.04	0.03	0.05	0.04
	2	0.03	0.06	0.04	0.02	0.06	0.03
	3	0.03	0.06	0.04	0.02	0.09	0.04
A,B1,B2,C,D	1	0.02	0.04	0.11	0.02	0.04	0.07
	2	0.02	0.04	0.14	0.01	0.04	0.08
	3	0.01	0.04	0.15	0.02	0.05	0.12

[1] Source of Bias

A	Vaccination affects the probability of NFARI
B1	Health status affects the probability of NFARI
B2	Health status affects the probability of FARI
BS	Health status affects the probability of FARI and NFARI, and the risk ratios comparing a healthy and a frail person are the same for both types of ARI.
C	Vaccination affects the probability of seeking medical care for FARI, while it does not affect the probability of seeking medical care for NFARI.
D	Health status affects the probabilities of seeking medical care against FARI and NFARI.

[2] Vaccination Scenarios

1	Random vaccination
2	Healthy person more likely than frail persons to be vaccinated
3	Healthy person less likely than frail persons to be vaccinated

Proofs

Appendix 1: True VE's in our model

The true VE against SI is:

$$VET_{SI} = 1 - RRT_{SI} \quad \text{where} \quad RRT_{SI} = \frac{P(Y=2|V=1)}{P(Y=2|V=0)}.$$

Since

$$P(Y=y|V=v) = \sum_x P(Y=y|V=v, X=x)P(X=x|V=v)$$
$$P(V=v) = \sum_x P(V=v|X=x)P(X=x)$$
$$P(X=x|V=v) = \frac{P(V=v|X=x)P(X=x)}{P(V=v)} = \frac{P(V=v|X=x)P(X=x)}{\sum_x P(V=v|X=x)P(X=x)}$$

we have

$$P(X=0|V=0) = \frac{P(V=0|X=0)P(X=0)}{\sum_x P(V=0|X=x)P(X=x)} = \frac{(1-\alpha_0)(1-\pi)}{(1-\alpha_0)(1-\pi)+(1-\alpha_1)\pi} = 1-\pi,$$
$$P(X=0|V=1) = \frac{P(V=1|X=0)P(X=0)}{\sum_x P(V=1|X=x)P(X=x)} = \frac{\alpha_0(1-\pi)}{\alpha_0(1-\pi)+\alpha_1\pi} = 1-\pi,$$
$$P(X=1|V=0) = \frac{P(V=0|X=1)P(X=1)}{\sum_x P(V=0|X=x)P(X=x)} = \frac{(1-\alpha_1)\pi}{(1-\alpha_0)(1-\pi)+(1-\alpha_1)\pi} = \pi,$$
$$P(X=1|V=1) = \frac{P(V=1|X=1)P(X=1)}{\sum_x P(V=1|X=x)P(X=x)} = \frac{\alpha_1\pi}{\alpha_0(1-\pi)+\alpha_1\pi} = \pi.$$

Since, for true VE, we have: $\alpha_0 = \alpha_1$. We can get,

$$P(Y=2|V=1) = \sum_x P(Y=2|V=1,X=x)P(X=x|V=1)$$
$$= P(Y=2|V=1,X=0)P(X=0|V=1) + P(Y=2|V=1,X=1)P(X=1|V=1)$$
$$= \gamma_{10}(1-\pi) + \gamma_{11}\pi$$

$$P(Y=2|V=0) = \sum_x P(Y=2|V=0,X=x)P(X=x|V=0)$$
$$= P(Y=2|V=0,X=0)P(X=0|V=0) + P(Y=2|V=0,X=1)P(X=1|V=0)$$
$$= \gamma_{00}(1-\pi) + \gamma_{01}\pi$$

So that,

$$RRT_{SI} = \frac{P(Y=2|V=1)}{P(Y=2|V=0)} = \frac{\gamma_{10}(1-\pi)+\gamma_{11}\pi}{\gamma_{00}(1-\pi)+\gamma_{01}\pi}$$

Therefore,

$$VET_{SI} = 1 - RRT_{SI} = 1 - \frac{\gamma_{10}(1-\pi)+\gamma_{11}\pi}{\gamma_{00}(1-\pi)+\gamma_{01}\pi} \qquad \text{Q.E.D.}$$

The true VE against MAI is:

$$VET_{MAI} = 1 - RRT_{MAI} \quad \text{where} \quad RRT_{MAI} = \frac{P(Y=2,M=1|V=1)}{P(Y=2,M=1|V=0)}.$$

Since

$$P(Y=2,M=1|V=v,X=x) = P(M=1|Y=2,V=v,X=x) * P(Y=2|V=v,X=x)$$

$$P(Y=2,M=1|V=v)=\sum_x P(Y=2,M=1|V=v,X=x)P(X=x|V=v)$$

we can get,

$$P(Y=2,M=1|V=1)=\sum_x P(Y=2,M=1|V=1,X=x)P(X=x|V=1)$$

$$=\delta_{210}\gamma_{10}(1-\pi)+\delta_{211}\gamma_{11}\pi$$

$$P(Y=2,M=1|V=0)=\sum_x P(Y=2,M=1|V=0,X=x)P(X=x|V=0)$$

$$=\delta_{200}\gamma_{00}(1-\pi)+\delta_{201}\gamma_{01}\pi$$

Therefore,

$$\begin{aligned}RRT_{MAI}&=\frac{P(Y=2,M=1|V=1)}{P(Y=2,M=1|V=0)}\\&=\frac{\delta_{210}\gamma_{10}(1-\pi)+\delta_{211}\gamma_{11}\pi}{\delta_{200}\gamma_{00}(1-\pi)+\delta_{201}\gamma_{01}\pi}=\frac{\delta_{SF}\Psi_F\gamma_{10}(1-\pi)+\delta_{SF}\Psi_F\lambda\gamma_{11}\pi}{\delta_{SF}\gamma_{00}(1-\pi)+\delta_{SF}\lambda\gamma_{01}\pi}\\&=\frac{\Psi_F[\gamma_{10}(1-\pi)+\lambda\gamma_{11}\pi]}{\gamma_{00}(1-\pi)+\lambda\gamma_{01}\pi}\end{aligned}$$

Hence,

$$VET_{MAI}=1-RRT_{MAI}=1-\frac{\Psi_F[\gamma_{10}(1-\pi)+\lambda\gamma_{11}\pi]}{\gamma_{00}(1-\pi)+\lambda\gamma_{01}\pi}.\qquad\text{Q.E.D.}$$

Appendix 2: Model-based estimates of VE

The model-based estimate from TN study is:

$$VE_A = 1 - OR_A, \quad \text{where} \quad OR_A = \frac{P(C_A = 1, V = 1|M = 1)P(C_A = 0, V = 0|M = 1)}{P(C_A = 1, V = 0|M = 1)P(C_A = 0, V = 1|M = 1)}.$$

OR_A can be written as:

$$OR_A = \frac{P(M = 1, T = 1, V = 1)P(M = 1, T = 0, V = 0)}{P(M = 1, T = 1, V = 0)P(M = 1, T = 0, V = 1)}$$

$$P(M = 1, T = 1, V = v) = \sum_x P(M = 1, T = 1, V = v|X = x)P(X = x)$$
$$= \sum_x P(T = 1|M = 1, V = v, X = x)P(M = 1, V = v|X = x)P(X = x)$$
$$= \sum_x P(Y = 2|M = 1, V = v, X = x)P(M = 1|V = v, X = x)P(V = v|X = x)P(X = x)$$
$$= \sum_x P(M = 1|Y = 2, V = v, X = x)P(Y = 2|V = v, X = x)P(V = v|X = x)P(X = x)$$

$$P(M = 1, T = 0, V = v) = \sum_x P(M = 1, T = 0, V = v|X = x)P(X = x)$$
$$= \sum_x P(T = 0|M = 1, V = v, X = x)P(M = 1, V = v|X = x)P(X = x)$$
$$= \sum_x P(Y = 1|M = 1, V = v, X = x)P(M = 1|V = v, X = x)P(V = v|X = x)P(X = x)$$
$$= \sum_x P(M = 1|Y = 1, V = v, X = x)P(Y = 1|V = v, X = x)P(V = v|X = x)P(X = x)$$

So that,

$$\begin{aligned}
P(M=1,T=1,V=0) &= \delta_{200}\gamma_{00}(1-\alpha_0)(1-\pi)+\delta_{201}\gamma_{01}(1-\alpha_1)\pi \\
&= \delta_{SF}[\gamma_{00}(1-\alpha_0)(1-\pi)+\lambda\gamma_{01}(1-\alpha_1)\pi] \\
P(M=1,T=1,V=1) &= \delta_{210}\gamma_{10}\alpha_0(1-\pi)+\delta_{211}\gamma_{11}\alpha_1\pi \\
&= \delta_{SF}\Psi_F[\gamma_{10}\alpha_0(1-\pi)+\lambda\gamma_{11}\alpha_1\pi] \\
P(M=1,T=0,V=0) &= \delta_{100}\beta_{00}(1-\alpha_0)(1-\pi)+\delta_{101}\beta_{01}(1-\alpha_1)\pi \\
&= \delta_{SN}[\beta_{00}(1-\alpha_0)(1-\pi)+\lambda\beta_{01}(1-\alpha_1)\pi] \\
P(M=1,T=0,V=1) &= \delta_{110}\beta_{10}\alpha_0(1-\pi)+\delta_{111}\beta_{11}\alpha_1\pi \\
&= \delta_{SN}[\beta_{10}\alpha_0(1-\pi)+\lambda\beta_{11}\alpha_1\pi]
\end{aligned}$$

Therefore,

$$VE_A = 1-\frac{\Psi_F[\gamma_{10}\alpha_0(1-\pi)+\lambda\gamma_{11}\alpha_1\pi][\beta_{00}(1-\alpha_0)(1-\pi)+\lambda\beta_{01}(1-\alpha_1)\pi]}{[\gamma_{00}(1-\alpha_0)(1-\pi)+\lambda\gamma_{01}(1-\alpha_1)\pi][\beta_{10}\alpha_0(1-\pi)+\lambda\beta_{11}\alpha_1\pi]}. \qquad \text{Q.E.D.}$$

The model-based estimates from TCC study is:

$$VE_B = 1-OR_B, \quad \text{where} \quad OR_B = \frac{P(C_B=1,V=1|B=1)P(C_B=0,V=0|B=1)}{P(C_B=1,V=0|B=1)P(C_B=0,V=1|B=1)}.$$

OR_B can be written as:

$$OR_B = \frac{P(M=1,T=1,V=1)P(Y=0,V=0)}{P(M=1,T=1,V=0)P(Y=0,V=1)}.$$

Since,

$$P(Y=0,V=v) = \sum_x P(Y=0,V=v|X=x)P(X=x)$$
$$= \sum_x P(Y=0|V=v,X=x)P(V=v|X=x)P(X=x)$$

and $P(Y=0|V=v,X=x) = 1-P(Y=1|V=v,X=x)-P(Y=2|V=v,X=x) = 1-\gamma_{vx}-\beta_{vx}$, so we have:

$$P(Y=0,V=0) = (1-\gamma_{00}-\beta_{00})(1-\alpha_0)(1-\pi)+(1-\gamma_{01}-\beta_{01})(1-\alpha_1)\pi$$
$$P(Y=0,V=1) = (1-\gamma_{10}-\beta_{10})\alpha_0(1-\pi)+(1-\gamma_{11}-\beta_{11})\alpha_1\pi$$

Therefore,

$$VE_B = 1-\frac{\Psi_F[\gamma_{10}\alpha_0(1-\pi)+\lambda\gamma_{11}\alpha_1\pi][(1-\gamma_{00}-\beta_{00})(1-\alpha_0)(1-\pi)+(1-\gamma_{01}-\beta_{01})(1-\alpha_1)\pi]}{[\gamma_{00}(1-\alpha_0)(1-\pi)+\lambda\gamma_{01}(1-\alpha_1)\pi][(1-\gamma_{10}-\beta_{10})\alpha_0(1-\pi)+(1-\gamma_{11}-\beta_{11})\alpha_1\pi]}. \quad \text{Q.E.D.}$$

Appendix 3: Standard Errors of the VE Estimates

For TN study, the approximate standard error of VE_A is:

$$SE(VE_A) = SE(OR_A) \approx OR_A * SE(log(OR_A))$$
$$\approx \frac{p_{11}^A(1-p_{01}^A)}{p_{01}^A(1-p_{11}^A)}\sqrt{\frac{1}{N^A}\left[\frac{1}{P_{V1}^A P_{11}^A}+\frac{1}{(1-P_{V1}^A)P_{01}^A}+\frac{1}{P_{V1}^A(1-P_{11}^A)}+\frac{1}{(1-P_{V1}^A)(1-P_{01}^A)}\right]}$$

where N_A is the number of persons who were tested for influenza (M=1), i.e., the total sample size for the TN study. The probabilities (p_{V1}^A, p_{01}^A, p_{11}^A) can be written in terms of the parameters defined earlier.

Base on what we got earlier, we know

$$P(M=1,V=1)=\sum_t P(M=1,V=1,T=t)$$

$$=\delta_{110}\beta_{10}\alpha_0(1-\pi)+\delta_{111}\beta_{11}\alpha_1\pi+\delta_{210}\gamma_{10}\alpha_0(1-\pi)+\delta_{211}\gamma_{11}\alpha_1\pi$$

$$=\alpha_0(1-\pi)[\delta_{SN}\beta_{10}+\delta_{SF}\Psi_F\gamma_{10}]+\alpha_1\pi\lambda[\delta_{SN}\beta_{11}+\delta_{SF}\Psi_F\gamma_{11}]$$

$$P(M=1,V=0)=\sum_t P(M=1,V=0,T=t)$$

$$=\delta_{100}\beta_{00}(1-\alpha_0)(1-\pi)+\delta_{101}\beta_{01}(1-\alpha_1)\pi+\delta_{200}\gamma_{00}(1-\alpha_0)(1-\pi)+\delta_{201}\gamma_{01}(1-\alpha_1)\pi$$

$$=(1-\alpha_0)(1-\pi)[\delta_{SN}\beta_{00}+\delta_{SF}\gamma_{00}]+(1-\alpha_1)\pi\lambda[\delta_{SN}\beta_{01}+\delta_{SF}\gamma_{01}]$$

Thus,

$$\begin{aligned}P(M=1)&=\sum_v P(M=1,V=v)\\&=(1-\alpha_0)(1-\pi)[\delta_{SN}\beta_{00}+\delta_{SF}\gamma_{00}]+(1-\alpha_1)\pi\lambda[\delta_{SN}\beta_{01}+\delta_{SF}\gamma_{01}]\\&+\alpha_0(1-\pi)[\delta_{SN}\beta_{10}+\delta_{SF}\Psi_F\gamma_{10}]+\alpha_1\pi\lambda[\delta_{SN}\beta_{11}+\delta_{SF}\Psi_F\gamma_{11}]\\&=(1-\pi)[(1-\alpha_0)(\delta_{SN}\beta_{00}+\delta_{SF}\gamma_{00})+\alpha_0(\delta_{SN}\beta_{10}+\delta_{SF}\Psi_F\gamma_{10})]\\&+\pi\lambda[((1-\alpha_1))(\delta_{SN}\beta_{01}+\delta_{SF}\gamma_{01})+\alpha_1(\delta_{SN}\beta_{11}+\delta_{SF}\Psi_F\gamma_{11})]\end{aligned}$$

Therefore, we have

$$P_{V1}^A=P(V=1|M=1)=\frac{P(V=1,M=1)}{P(M=1)}$$

$$=\frac{\alpha_0(1-\pi)[\delta_{SN}\beta_{10}+\delta_{SF}\Psi_F\gamma_{10}]+\alpha_1\pi\lambda[\delta_{SN}\beta_{11}+\delta_{SF}\Psi_F\gamma_{11}]}{(1-\pi)[(1-\alpha_0)(\delta_{SN}\beta_{00}+\delta_{SF}\gamma_{00})+\alpha_0(\delta_{SN}\beta_{10}+\delta_{SF}\Psi_F\gamma_{10})]+\pi\lambda[((1-\alpha_1))(\delta_{SN}\beta_{01}+\delta_{SF}\gamma_{01})+\alpha_1(\delta_{SN}\beta_{11}+\delta_{SF}\Psi_F\gamma_{11})]}$$

$$p_{01}^{A} = \frac{P(M=1,T=1|V=0)}{P(M=1|V=0)} = \frac{P(M=1,T=1,V=0)}{P(M=1,V=0)}$$
$$= \frac{\delta_{200}\gamma_{00}(1-\alpha_0)(1-\pi) + \delta_{201}\gamma_{01}(1-\alpha_1)\pi}{\delta_{100}\beta_{00}(1-\alpha_0)(1-\pi) + \delta_{101}\beta_{01}(1-\alpha_1)\pi + \delta_{200}\gamma_{00}(1-\alpha_0)(1-\pi) + \delta_{201}\gamma_{01}(1-\alpha_1)\pi}$$
$$= \frac{\delta_{SF}[\gamma_{00}(1-\alpha_0)(1-\pi) + \lambda\gamma_{01}(1-\alpha_1)\pi]}{(1-\alpha_0)(1-\pi)[\delta_{SN}\beta_{00} + \delta_{SF}\gamma_{00}] + (1-\alpha_1)\pi\lambda[\delta_{SN}\beta_{01} + \delta_{SF}\gamma_{01}]}$$

$$P_{11}^{A} = \frac{P(M=1,T=1|V=1)}{P(M=1|V=1)} = \frac{P(M=1,T=1,V=1)}{P(M=1,V=1)}$$
$$= \frac{\delta_{210}\gamma_{10}\alpha_0(1-\pi) + \delta_{211}\gamma_{11}\alpha_1\pi}{\delta_{110}\beta_{10}\alpha_0(1-\pi) + \delta_{111}\beta_{11}\alpha_1\pi + \delta_{210}\gamma_{10}\alpha_0(1-\pi) + \delta_{211}\gamma_{11}\alpha_1\pi}$$
$$= \frac{\delta_{SF}\Psi_F[\gamma_{10}\alpha_0(1-\pi) + \lambda\gamma_{11}\alpha_1\pi]}{\alpha_0(1-\pi)[\delta_{SN}\beta_{10} + \delta_{SF}\Psi_F\gamma_{10}] + \alpha_1\pi\lambda[\delta_{SN}\beta_{11} + \delta_{SF}\Psi_F\gamma_{11}]}$$

In the TCC study, the approximate standard error of VE_B is:

$$SE(VE_B) = SE(OR_B) \approx OR_B * SE(log(OR_B))$$
$$\approx \frac{p_{11}^{B}(1-p_{10}^{B})}{p_{10}^{B}(1-p_{11}^{B})}\sqrt{\frac{1}{N_{C1}^{B}p_{11}^{B}} + \frac{1}{N_{C1}^{B}(1-p_{11}^{B})} + \frac{1}{N_{C0}^{B}p_{10}^{B}} + \frac{1}{N_{C0}^{B}(1-p_{10}^{B})}}$$

where N_{C1}^{b} is the number of cases and N_{C0}^{b} is the number of controls. The probabilities (p_{10}^{B},p_{11}^{B}) can be written in terms of the parameters defined earlier:

$$p_{10}^{B} = P(V=1|C_B=0,B=1) = \frac{P(Y=0,V=1)}{P(Y=0)} = \frac{P(Y=0,V=1)}{\sum_v P(Y=0,V=v)}$$
$$= \frac{(1-\gamma_{10}-\beta_{10})\alpha_0(1-\pi) + (1-\gamma_{11}-\beta_{11})\alpha_1\pi}{(1-\pi)[(1-\gamma_{10}-\beta_{10})\alpha_0 + (1-\gamma_{00}-\beta_{00})(1-\alpha_0)] + \pi[(1-\gamma_{11}-\beta_{11})\alpha_1 + (1-\gamma_{01}-\beta_{01})(1-\alpha_1)]}$$

$$p_{11}^{B} = P(V=1|C_B=1,B=1) = \frac{P(M=1,T=1,V=1)}{P(M=1,T=1)} = \frac{P(M=1,T=1,V=1)}{\sum_v P(M=1,T=1,V=v)}$$
$$= \frac{\delta_{210}\gamma_{10}\alpha_0(1-\pi) + \delta_{211}\gamma_{11}\alpha_1\pi}{\delta_{200}\gamma_{00}(1-\alpha_0)(1-\pi) + \delta_{201}\gamma_{01}(1-\alpha_1)\pi + \delta_{210}\gamma_{10}\alpha_0(1-\pi) + \delta_{211}\gamma_{11}\alpha_1\pi}$$
$$= \frac{\Psi_F[\gamma_{10}\alpha_0(1-\pi) + \lambda\gamma_{11}\alpha_1\pi]}{[\gamma_{00}(1-\alpha_0)(1-\pi) + \lambda\gamma_{01}(1-\alpha_1)\pi] + \Psi_F[\gamma_{10}\alpha_0(1-\pi) + \lambda\gamma_{11}\alpha_1\pi]}$$

Appendix 4: Unbiasness under Random and Non-random Vaccination

Unbiasness under Random Vaccination

If the vaccination is done at random, then $\alpha_0 = \alpha_1$. The VE estimates can be written as:

$$VE_A = 1 - \frac{\Psi_F[\gamma_{10}(1-\pi) + \lambda\gamma_{11}\pi][\beta_{00}(1-\pi) + \lambda\beta_{01}\pi]}{[\gamma_{00}(1-\pi) + \lambda\gamma_{01}\pi][\beta_{10}(1-\pi) + \lambda\beta_{11}\pi]}$$

$$VE_B = 1 - \frac{\Psi_F[\gamma_{10}(1-\pi) + \lambda\gamma_{11}\pi][(1-\gamma_{00}-\beta_{00})(1-\pi) + (1-\gamma_{01}-\beta_{01})\pi]}{[\gamma_{00}(1-\pi) + \lambda\gamma_{01}\pi][(1-\gamma_{10}-\beta_{10})(1-\pi) + (1-\gamma_{11}-\beta_{11})\pi]}$$

(1) If $\rho_\beta = \Psi_F = 1$, and one of the following conditions is satisfied, then $VE_A = VET_{SI}$.

(a) $\lambda = 1$;

(b) $\eta_\gamma = 1$.

Proof:

Since $\rho_{\beta_x} = \Psi_F = 1$, then $\frac{\beta_{10}}{\beta_{00}} = \frac{\beta_{11}}{\beta_{01}} = \Psi_F = 1$. We have:

$$\beta_{10} = \beta_{00} \quad \text{and} \quad \beta_{11} = \beta_{01}.$$

So,

$$\begin{aligned} VE_A &= 1 - \frac{\Psi_F[\gamma_{10}(1-\pi) + \lambda\gamma_{11}\pi][\beta_{00}(1-\pi) + \lambda\beta_{01}\pi]}{[\gamma_{00}(1-\pi) + \lambda\gamma_{01}\pi][\beta_{00}(1-\pi) + \lambda\beta_{01}\pi]} \\ &= 1 - \frac{\gamma_{10}(1-\pi) + \lambda\gamma_{11}\pi}{\gamma_{00}(1-\pi) + \lambda\gamma_{01}\pi} \end{aligned}$$

If (a) $\lambda = 1$ is satisfied, so

$$VE_A = 1 - \frac{\gamma_{10}(1-\pi) + \gamma_{11}\pi}{\gamma_{00}(1-\pi) + \gamma_{01}\pi} = VET_{SI}.$$

If (b) $\eta_\gamma = 1$ is satisfied, then $\gamma_{01} = \gamma_{00}$ and $\gamma_{11} = \gamma_{10}$. Thus,

$$VET_{SI} = 1 - \frac{\gamma_{10}(1-\pi) + \gamma_{11}\pi}{\gamma_{00}(1-\pi) + \gamma_{01}\pi} = 1 - \frac{\gamma_{11}}{\gamma_{01}}.$$

Hence,

$$\begin{aligned} VE_A &= 1 - \frac{\gamma_{10}(1-\pi) + \lambda\gamma_{11}\pi}{\gamma_{00}(1-\pi) + \lambda\gamma_{01}\pi} = 1 - \frac{\gamma_{11}(1-\pi) + \lambda\gamma_{11}\pi}{\gamma_{01}(1-\pi) + \lambda\gamma_{01}\pi} = 1 - \frac{\gamma_{11}[(1-\pi) + \lambda\pi]}{\gamma_{01}[(1-\pi) + \lambda\pi]} \\ &= 1 - \frac{\gamma_{11}}{\gamma_{01}} = VET_{SI} \qquad \text{Q.E.D.} \end{aligned}$$

(2) If $\rho_\beta = 1$,then $VE_A = VET_{MAI}$

Proof:

Since $\rho_\beta = 1$, then $\frac{\beta_{10}}{\beta_{00}} = \frac{\beta_{11}}{\beta_{01}} = 1$.

So,

$$\begin{aligned} VE_A &= 1 - \frac{\Psi_F[\gamma_{10}(1-\pi) + \lambda\gamma_{11}\pi][\beta_{00}(1-\pi) + \lambda\beta_{01}\pi]}{[\gamma_{00}(1-\pi) + \lambda\gamma_{01}\pi][\beta_{00}(1-\pi) + \lambda\beta_{01}\pi]} \\ &= 1 - \frac{\Psi_F[\gamma_{10}(1-\pi) + \lambda\gamma_{11}\pi]}{\gamma_{00}(1-\pi) + \lambda\gamma_{01}\pi} \\ &= VET_{MAI} \qquad \text{Q.E.D.} \end{aligned}$$

(3) If $\lambda = 1$ and $1 - \gamma_{1x} - \beta_{1x} = \Psi_F(1 - \gamma_{0x} - \beta_{0x})$, where $x = 0, 1$,then $VE_B = VET_{SI}$

Proof:

Since $1 - \gamma_{1x} - \beta_{1x} = \Psi_F(1 - \gamma_{0x} - \beta_{0x})$, where $x = 0, 1$, and $\lambda = 1$, then

$$\begin{aligned} VE_B &= 1 - \frac{\Psi_F[\gamma_{10}(1-\pi) + \lambda\gamma_{11}\pi][(1-\gamma_{00}-\beta_{00})(1-\pi) + (1-\gamma_{01}-\beta_{01})\pi]}{[\gamma_{00}(1-\pi) + \lambda\gamma_{01}\pi][\Psi_F(1-\gamma_{00}-\beta_{00})(1-\pi) + \Psi_F(1-\gamma_{01}-\beta_{01})\pi]} \\ &= 1 - \frac{\gamma_{10}(1-\pi) + \lambda\gamma_{11}\pi}{\gamma_{00}(1-\pi) + \lambda\gamma_{01}\pi} \\ &= 1 - \frac{\gamma_{10}(1-\pi) + \gamma_{11}\pi}{\gamma_{00}(1-\pi) + \gamma_{01}\pi} \\ &= VET_{SI} \qquad \text{Q.E.D.} \end{aligned}$$

(4) If $\gamma_{1x} + \beta_{1x} = \gamma_{0x} + \beta_{0x}$, where $x = 0, 1$,then $VE_B = VET_{MAI}$

Proof:

Since $\gamma_{1x} + \beta_{1x} = \gamma_{0x} + \beta_{0x}$, $x = 0, 1$, then

$$1 - \gamma_{1x} - \beta_{1x} = 1 - \gamma_{0x} - \beta_{0x}, \quad \text{where } x = 0, 1$$

So:

$$\begin{aligned} VE_B &= 1 - \frac{\Psi_F[\gamma_{10}(1-\pi) + \lambda\gamma_{11}\pi][(1-\gamma_{00}-\beta_{00})(1-\pi) + (1-\gamma_{01}-\beta_{01})\pi]}{[\gamma_{00}(1-\pi) + \lambda\gamma_{01}\pi][(1-\gamma_{00}-\beta_{00})(1-\pi) + (1-\gamma_{01}-\beta_{01})\pi]} \\ &= 1 - \frac{\Psi_F[\gamma_{10}(1-\pi) + \lambda\gamma_{11}\pi]}{\gamma_{00}(1-\pi) + \lambda\gamma_{01}\pi} \\ &= VET_{MAI} \qquad \text{Q.E.D.} \end{aligned}$$

Unbiasness under Non-random Vaccination

If the vaccination is not done at random, then $\alpha_0 \neq \alpha_1$.

(5) If $\rho_\beta = \eta_\beta = \eta_\gamma = \Psi_F = 1$, then $VE_A = VET_{SI}$.

Proof:

Since $\rho_\beta = \eta_\beta = \eta_\gamma = 1$, then $\beta_{00} = \beta_{10} = \beta_{01} = \beta_{11} \stackrel{\Delta}{=} \beta$, $\gamma_{01} = \gamma_{00}$ and $\gamma_{11} = \gamma_{10}$. Thus,

$$VET_{SI} = 1 - \frac{\gamma_{10}(1-\pi) + \gamma_{11}\pi}{\gamma_{00}(1-\pi) + \gamma_{01}\pi} = 1 - \frac{\gamma_{11}}{\gamma_{01}}.$$

So,

$$\begin{aligned} VE_A &= 1 - \frac{\Psi_F[\gamma_{10}\alpha_0(1-\pi) + \lambda\gamma_{11}\alpha_1\pi][\beta_{00}(1-\alpha_0)(1-\pi) + \lambda\beta_{01}(1-\alpha_1)\pi]}{[\gamma_{00}(1-\alpha_0)(1-\pi) + \lambda\gamma_{01}(1-\alpha_1)\pi][\beta_{10}\alpha_0(1-\pi) + \lambda\beta_{11}\alpha_1\pi]} \\ &= 1 - \frac{[\gamma_{11}\alpha_0(1-\pi) + \lambda\gamma_{11}\alpha_1\pi][(1-\alpha_0)(1-\pi) + \lambda(1-\alpha_1)\pi]}{[\gamma_{01}(1-\alpha_0)(1-\pi) + \lambda\gamma_{01}(1-\alpha_1)\pi][\alpha_0(1-\pi) + \lambda\alpha_1\pi]} \\ &= 1 - \frac{\gamma_{11}[\alpha_0(1-\pi) + \lambda\alpha_1\pi][(1-\alpha_0)(1-\pi) + \lambda(1-\alpha_1)\pi]}{\gamma_{01}[(1-\alpha_0)(1-\pi) + \lambda(1-\alpha_1)\pi][\alpha_0(1-\pi) + \lambda\alpha_1\pi]} \\ &= 1 - \frac{\gamma_{11}}{\gamma_{01}} = VET_{SI} \qquad \text{Q.E.D.} \end{aligned}$$

(6) If $\rho_\beta = 1$ and $\eta_\beta = \eta_\gamma$, then $VE_A = VET_{MAI}$.

Proof:

Since $\eta_\beta = \eta_\gamma$, so $\frac{\beta_{01}}{\beta_{00}} = \frac{\beta_{11}}{\beta_{10}} = \frac{\gamma_{01}}{\gamma_{00}} = \frac{\gamma_{11}}{\gamma_{10}}$. Then we have: $\frac{\gamma_{11}}{\beta_{11}} = \frac{\gamma_{10}}{\beta_{10}} \stackrel{\Delta}{=} a$, $\frac{\gamma_{00}}{\beta_{00}} = \frac{\gamma_{01}}{\beta_{01}} \stackrel{\Delta}{=}$

b, and $\frac{\beta_{10}}{\beta_{00}} = \frac{\beta_{11}}{\beta_{01}} = 1$. Then:

$$\begin{aligned} VE_A &= 1 - \frac{\Psi_F[\gamma_{10}\alpha_0(1-\pi) + \lambda\gamma_{11}\alpha_1\pi][\beta_{00}(1-\alpha_0)(1-\pi) + \lambda\beta_{01}(1-\alpha_1)\pi]}{[\gamma_{00}(1-\alpha_0)(1-\pi) + \lambda\gamma_{01}(1-\alpha_1)\pi][\beta_{10}\alpha_0(1-\pi) + \lambda\beta_{11}\alpha_1\pi]} \\ &= 1 - \frac{\Psi_F[a\beta_{10}\alpha_0(1-\pi) + a\lambda\beta_{11}\alpha_1\pi][\beta_{00}(1-\alpha_0)(1-\pi) + \lambda\beta_{01}(1-\alpha_1)\pi]}{[b\beta_{00}(1-\alpha_0)(1-\pi) + b\lambda\beta_{01}(1-\alpha_1)\pi][\beta_{10}\alpha_0(1-\pi) + \lambda\beta_{11}\alpha_1\pi]} \\ &= 1 - \Psi_F \cdot \frac{a}{b} \end{aligned}$$

and,

$$\begin{aligned} VET_{MAI} &= 1 - \frac{\Psi_F[\gamma_{10}(1-\pi) + \lambda\gamma_{11}\pi]}{\gamma_{00}(1-\pi) + \lambda\gamma_{01}\pi} = 1 - \frac{\Psi_F[a\beta_{10}(1-\pi) + a\lambda\beta_{11}\pi]}{b\beta_{00}(1-\pi) + b\lambda\beta_{01}\pi} \\ &= 1 - \Psi_F \cdot \frac{a}{b} \end{aligned}$$

So, $VE_A = VET_{MAI}$.

Appendix B

Appendix for Chapter 3

B.1 Correction for Bias A

When only bias A is present and all other biases are absent, we have: $\psi_\beta = 1, \psi_\gamma = 1, \theta_{\delta_2} = 1$, and $\mu_{\delta_1} = \mu_{\delta_2} = 1$. So, $\beta_{v1} = \beta_{v0}, \gamma_{v1} = \gamma_{v0}$. Therefore, the true VE can be written as: $VE_{True} = 1 - \theta_\gamma$.

Based on the calculation in Chapter 2, we know that:

$$P(Y = 1|V = v) = \beta_{v0}(1 - \pi) + \beta_{v1}\pi$$
$$P(Y = 2|V = v) = \gamma_{v0}(1 - \pi) + \gamma_{v1}\pi$$

where $\pi = P(X = 1)$ is the probability of "healthy" persons among the population.

Assuming the observed 2x2 table of V by Y(V = 0, 1 and Y = 1, 2) is:

Then, the conditional probabilities of Y = 1 given vaccination status can be writ-

	$V = 0$	$V = 1$
$Y = 1$	a	b
$Y = 2$	c	d

ten as:

$$P(Y=1|V=0) = \beta_{00}(1-\pi) + \beta_{01}\pi = \frac{a}{a+c}$$
$$P(Y=1|V=1) = \beta_{10}(1-\pi) + \beta_{11}\pi = \theta_\beta(\beta_{00}(1-\pi) + \beta_{01}\pi) = \frac{b}{b+d}$$

So, $\theta_\beta = \frac{b(a+c)}{a(b+d)}$. Similarly, we can get $\theta_\gamma = \frac{d(a+c)}{c(b+d)}$.

Therefore, the model based estimates from TN study when only bias A present can be written as:

$$\begin{aligned} VE &= 1 - \frac{\frac{\delta_{210}}{\delta_{200}}[\gamma_{10}\alpha_0(1-\pi) + \lambda\gamma_{11}\alpha_1\pi][\beta_{00}(1-\alpha_0)(1-\pi) + \lambda\beta_{01}(1-\alpha_1)\pi]}{[\gamma_{00}(1-\alpha_0)(1-\pi) + \lambda\gamma_{01}(1-\alpha_1)\pi][\beta_{10}\alpha_0(1-\pi) + \lambda\beta_{11}\alpha_1\pi]} \\ &= 1 - \frac{[\gamma_{11}\alpha_0(1-\pi) + \gamma_{11}\alpha_1\pi][\beta_{01}(1-\alpha_0)(1-\pi) + \beta_{01}(1-\alpha_1)\pi]}{[\gamma_{01}(1-\alpha_0)(1-\pi) + \gamma_{01}(1-\alpha_1)\pi][\beta_{11}\alpha_0(1-\pi) + \beta_{11}\alpha_1\pi]} \\ &= 1 - \frac{\gamma_{11}\beta_{01}}{\gamma_{01}\beta_{11}} = 1 - \frac{\theta_\gamma}{\theta_\beta} \end{aligned}$$

The estimated VE when only bias A is present is:

$$\hat{VE} = 1 - \frac{\hat{\theta}_\gamma}{\hat{\theta}_\beta}.$$

The corrected VE estimate can be written as:

$$\hat{VE}_C = 1 - \hat{\theta}_\beta(1 - \hat{VE}),$$

where $\hat{\theta}_\beta$ is estimated from data and is estimated as $\hat{\theta}_\beta = \frac{n_1/N_1}{n_0/N_0}$, where n_i is the number of persons in TN study who has NFARI with vaccination status i, $i = 0, 1$, and N_i is the number of person in the population with vaccination status i, $i = 0, 1$.

B.2 Sample Parameter File for SimFlu

Title (alphanumeric)	Case 10H Leaky	
Number of simulations	100	
Seed	1943	
All-or-none vaccine (Leaky vaccine if 'no')	no	
Output files ('yes' or 'no' for each)		
Input and calculated parameters	yes	
Vaccination *	no	
Detailed *	no	
Contacts *	no	
Prevalence *	no	
Incidence-daily each simulation	no	
Incidence-monthly each simulation	no	
Incidence-season each simulation	no	
Incidence-daily overall	no	
Incidence-monthly overall	yes	
Incidence-season overall	yes	
Outcomes file	no	
Add timestamp to output file names	yes	
Year of beginning of study	2010	
Month of beginning of study	10	
Number of months in the study	3	
Number of strata	2	
Sizes of strata	600	400
Probability of X=1	0.8	0.4
Probability of U=1 given X=1	0.7	0.5
Probability of U=1 given X=0	0.6	0.3
Vaccination incremental coverage for X=1, U=1 (matrix - rows for months, columns for strata) **		
0	0.5	0.4
1	0.2	0.1
2	0.1	0.05
3	0	0
Vaccination incremental coverage multiplier for X=0	0.9	0.8
Vaccination incremental coverage multiplier for U=0	0.7	0.6
Initial number of infected persons	10	
Number of contacts per day for each person	10	15
Distribution of contacts - K by K matrix (rho)		

1	0.7	0.3
2	0.4	0.6
Length of latent period (days)	2	2
Length of infectious period (days)	4	4
Probability of illness given infection	0.67	0.67
Relative infectiousness if not ill	0.4	0.4
Transmission probabilities to unprotected for X=1 (matrix - rows for months, columns for strata)		
1	0.025	0.03
2	0.025	0.03
3	0.05	0.1
Transmission probabilities multipliers for X=0 in unvaccinated or unprotected	1.5	2
Vaccine efficacy for X=1 (matrix - rows for months, columns for strata) ***		
1	0.6	0.6
2	0.6	0.6
3	0.6	0.6
Vaccine efficacy multipliers for X=0	0.7	0.7
Length of NFARI episode (days)	5	8
Daily probabilities of onset of NFARI for X=1 in unvaccinated or unprotected persons		
1	0.02	0.03
2	0.04	0.06
3	0.05	0.07
NFARI probabilities multipliers for vaccinated or protected persons	0.7	0.8
NFARI probabilities multipliers for X=0	1.5	1.8
Probability of visit for a case of FARI:		
For unvaccinated or unprotected with X=1 and U=1	0.6	0.4
Multiplier for vaccinated	0.7	0.5
Multiplier for X=0	1.3	1.6
Multiplier for U=0	0.8	0.6
Probability of visit for a case of NFARI:		
For unvaccinated or unprotected with X=1 and U=1	0.5	0.3
Multiplier for vaccinated	0.7	0.4
Multiplier for X=0	1.3	1.6
Multiplier for U=0	0.8	0.6

Comments:		
* For debugging purposes		
** Fractions based on initial stratum size		
*** Based on ratio of transmission probabilities		
X: Health status; Healthy: 1, Frail: 0		
U: Health awareness; High: 1, Low: 0		
FARI: Influenza Acute Respiratory Illness		
NFARI: Non-Influenza Acute Respiratory Illness		

Bibliography

Agresti, A. (2013), Categorical data analysis, Vol. 792 of Wiley series in probability and statistics, 3rd ed edn, Wiley, Hoboken, NJ.

Barberis, I., Martini, M., Iavarone, F. and Orsi, A. (2016), 'Available influenza vaccines: immunization strategies, history and new tools for fighting the disease', J Prev Med Hyg **57**(1), E41–6.

Belongia, E. A., Kieke, B. A., Donahue, J. G., Greenlee, R. T., Balish, A., Foust, A., Lindstrom, S., Shay, D. K. and Marshfield Influenza Study Group (2009), 'Effectiveness of inactivated influenza vaccines varied substantially with antigenic match from the 2004-2005 season to the 2006-2007 season', J Infect Dis **199**(2), 159–67.

Belongia, E. A., Sundaram, M. E., McClure, D. L., Meece, J. K., Ferdinands, J. and VanWormer, J. J. (2015), 'Waning vaccine protection against influenza a (h3n2) illness in children and older adults during a single season', Vaccine **33**(1), 246–51.

Bridges, C. B., Thompson, W. W., Meltzer, M. I., Reeve, G. R., Talamonti, W. J., Cox, N. J., Lilac, H. A., Hall, H., Klimov, A. and Fukuda, K. (2000), 'Effectiveness and cost-benefit of influenza vaccination of healthy working adults: A randomized controlled trial', JAMA **284**(13), 1655–63.

Cai, Z. and Sun, Y. (2003), 'Local linear estimation for time-dependent coefficients in cox's regression models', Scandinavian Journal of Statistics **30**(1), 93–111.
URL: *http://www.jstor.org/stable/4616751*

Castilla, J., Godoy, P., Domínguez, Á., Martínez-Baz, I., Astray, J., Martín, V., Delgado-Rodríguez, M., Baricot, M., Soldevila, N., Mayoral, J. M. et al. (2013), 'Influenza vaccine effectiveness in preventing outpatient, inpatient, and severe cases of laboratory-confirmed influenza', Clinical infectious diseases **57**(2), 167–175.

Castilla, J., Martínez-Baz, I., Martínez-Artola, V., Reina, G., Pozo, F., García Cenoz, M., Guevara, M., Morán, J., Irisarri, F., Arriazu, M., Albéniz, E., Ezpeleta, C., Barricarte, A., Primary Health Care Sentinel Network and Network for Influenza Surveillance in Hospitals of Navarre (2013), 'Decline in influenza vaccine effectiveness with time after vaccination, navarre, spain, season 2011/12', Euro Surveill **18**(5).

Centers for Disease Control and Prevention (CDC) (2010), 'Estimates of deaths associated with seasonal influenza — united states, 1976-2007', MMWR Morb Mortal Wkly Rep **59**(33), 1057–62.

Centers for Disease Control and Prevention (CDC) (2013), 'Early estimates of seasonal influenza vaccine effectiveness — united states, january 2013'.

Centers for Disease Control and Prevention (CDC) (2019), 'Recommendations of the advisory committee on immunization practices (acip)—united states, 2019-20'.

Centers for Disease Control and Prevention (CDC) (2020a), 'Centers for disease control and prevention. seasonal influenza (flu) : Flu season'.

Centers for Disease Control and Prevention (CDC) (2020b), 'Centers for disease control and prevention. seasonal influenza(flu) : Disease burden of influenza'.

Centers for Disease Control and Prevention (CDC) (2020c), 'Seasonal influenza vaccine supply and distribution'.

Chao, D. L., Halloran, M. E., Obenchain, V. J. and Longini, Jr, I. M. (2010), 'Flute, a publicly available stochastic influenza epidemic simulation model', PLoS Comput Biol **6**(1), e1000656.

Colquhoun, A. J., Nicholson, K. G., Botha, J. L. and Raymond, N. T. (1997), 'Effectiveness of influenza vaccine in reducing hospital admissions in people with diabetes', Epidemiol Infect **119**(3), 335–41.

Cowling, B. J., Fang, V. J., Nishiura, H., Chan, K.-H., Ng, S., Ip, D. K. M., Chiu, S. S., Leung, G. M. and Peiris, J. S. M. (2012), 'Increased risk of noninfluenza respiratory virus infections associated with receipt of inactivated influenza vaccine', Clin Infect Dis **54**(12), 1778–83.

Cox, N. J. and Subbarao, K. (1999), 'Influenza', Lancet **354**(9186), 1277–82.

De Serres, G., Skowronski, D. M., Wu, X. W. and Ambrose, C. S. (2013), 'The test-negative design: validity, accuracy and precision of vaccine efficacy estimates compared to the gold standard of randomised placebo-controlled clinical trials', Euro Surveill **18**(37).

Deiss, R. G., Arnold, J. C., Chen, W.-J., Echols, S., Fairchok, M. P., Schofield, C., Danaher, P. J., McDonough, E., Ridoré, M., Mor, D., Burgess, T. H. and Millar, E. V. (2015), 'Vaccine-associated reduction in symptom severity among patients with influenza a/h3n2 disease', Vaccine **33**(51), 7160–7.

Durham, L. K., Longini, Jr, I. M., Halloran, M. E., Clemens, J. D., Nizam, A. and Rao, M. (1998), 'Estimation of vaccine efficacy in the presence of waning: application to cholera vaccines', Am J Epidemiol **147**(10), 948–59.

Ferdinands, J. M., Fry, A. M., Reynolds, S., Petrie, J., Flannery, B., Jackson, M. L. and Belongia, E. A. (2017), 'Intraseason waning of influenza vaccine protection:

Evidence from the us influenza vaccine effectiveness network, 2011-12 through 2014-15', Clin Infect Dis **64**(5), 544–550.

Ferdinands, J. M., Olsho, L. E. W., Agan, A. A., Bhat, N., Sullivan, R. M., Hall, M., Mourani, P. M., Thompson, M., Randolph, A. G. and Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network (2014), 'Effectiveness of influenza vaccine against life-threatening rt-pcr-confirmed influenza illness in us children, 2010-2012', J Infect Dis **210**(5), 674–83.

Ferdinands, J. M. and Shay, D. K. (2012), 'Magnitude of potential biases in a simulated case-control study of the effectiveness of influenza vaccination', Clin Infect Dis **54**(1), 25–32.

Fielding, J. E., Grant, K. A., Tran, T. and Kelly, H. A. (2012), 'Moderate influenza vaccine effectiveness in victoria, australia, 2011', Euro Surveill **17**(11).

Foppa, I. M., Haber, M., Ferdinands, J. M. and Shay, D. K. (2013), 'The case test-negative design for studies of the effectiveness of influenza vaccine', Vaccine **31**(30), 3104–9.

Gasparini, R., Amicizia, D., Lai, P. L. and Panatto, D. (2011), 'Live attenuated influenza vaccine–a review', J Prev Med Hyg **52**(3), 95–101.

Germann, T. C., Kadau, K., Longini, Jr, I. M. and Macken, C. A. (2006), 'Mitigation strategies for pandemic influenza in the united states', Proc Natl Acad Sci U S A **103**(15), 5935–40.

Greenwood, M. and Yule, G. U. (1915), 'The statistics of anti-typhoid and anti-cholera inoculations, and the interpretation of such statistics in general', Proc R Soc Med **8**(Sect Epidemiol State Med), 113–94.

Haber, M., An, Q., Foppa, I. M., Shay, D. K., Ferdinands, J. M. and Orenstein, W. A. (2015), 'A probability model for evaluating the bias and precision of influenza vaccine effectiveness estimates from case-control studies', Epidemiol Infect **143**(7), 1417–26.

Haber, M., Longini, Jr, I. M. and Halloran, M. E. (1991), 'Measures of the effects of vaccination in a randomly mixing population', Int J Epidemiol **20**(1), 300–10.

Hannoun, C. (2013), 'The evolving history of influenza viruses and influenza vaccines', Expert Rev Vaccines **12**(9), 1085–94.

Havers, F., Sokolow, L., Shay, D. K., Farley, M. M., Monroe, M., Meek, J., Daily Kirley, P., Bennett, N. M., Morin, C., Aragon, D., Thomas, A., Schaffner, W., Zansky, S. M., Baumbach, J., Ferdinands, J. and Fry, A. M. (2016), 'Case-control study of vaccine effectiveness in preventing laboratory-confirmed influenza hospitalizations in older adults, united states, 2010-2011', Clin Infect Dis **63**(10), 1304–1311.

Jackson, L. A., Jackson, M. L., Nelson, J. C., Neuzil, K. M. and Weiss, N. S. (2006), 'Evidence of bias in estimates of influenza vaccine effectiveness in seniors', Int J Epidemiol **35**(2), 337–44.

Jackson, M. L. and Nelson, J. C. (2013), 'The test-negative design for estimating influenza vaccine effectiveness', Vaccine **31**(17), 2165–8.

Jackson, M. L. and Rothman, K. J. (2015), 'Effects of imperfect test sensitivity and specificity on observational studies of influenza vaccine effectiveness', Vaccine **33**(11), 1313–6.

Jiménez-Jorge, S., de Mateo, S., Delgado-Sanz, C., Pozo, F., Casas, I., Garcia-Cenoz, M., Castilla, J., Pérez, E., Gallardo, V., Rodriguez, C., Vega, T., Quiñones, C., Martínez, E., Vanrell, J. M., Giménez, J., Castrillejo, D., Serrano, M. d. C., Ramos,

J. M., Larrauri, A. and Spanish Influenza Sentinel Surveillance System (2013), 'Effectiveness of influenza vaccine against laboratory-confirmed influenza, in the late 2011-2012 season in spain, among population targeted for vaccination', BMC Infect Dis **13**, 441.

Kelly, H., Carville, K., Grant, K., Jacoby, P., Tran, T. and Barr, I. (2009), 'Estimation of influenza vaccine effectiveness from routine surveillance data', PLoS One **4**(3), e5079.

Kissling, E., Nunes, B., Robertson, C., Valenciano, M., Reuss, A., Larrauri, A., Cohen, J. M., Oroszi, B., Rizzo, C., Machado, A., Pitigoi, D., Domegan, L., Paradowska-Stankiewicz, I., Buchholz, U., Gherasim, A., Daviaud, I., Horváth, J. K., Bella, A., Lupulescu, E., O Donnell, J., Korczyńska, M., Moren, A. and I-MOVE case–control study team (2016), 'I-move multicentre case-control study 2010/11 to 2014/15: Is there within-season waning of influenza type/subtype vaccine effectiveness with increasing time since vaccination?', Euro Surveill **21**(16).

Kissling, E., Valenciano, M., Falcao, J., Larrauri, A., Widgren, K., Pitigoi, D., Oroszi, B., Nunes, B., Savulescu, C., Mazick, A., Lupulescu, E., Ciancio, B. and Moren, A. (2009), '"i-move" towards monitoring seasonal and pandemic influenza vaccine effectiveness: lessons learnt from a pilot multi-centric case-control study in europe, 2008-9', Euro Surveill **14**(44).

Kissling, E., Valenciano, M., Larrauri, A., Oroszi, B., Cohen, J. M., Nunes, B., Pitigoi, D., Rizzo, C., Rebolledo, J., Paradowska-Stankiewicz, I., Jiménez-Jorge, S., Horváth, J. K., Daviaud, I., Guiomar, R., Necula, G., Bella, A., O'Donnell, J., Głuchowska, M., Ciancio, B. C., Nicoll, A. and Moren, A. (2013), 'Low and decreasing vaccine effectiveness against influenza a(h3) in 2011/12 among vaccination target groups in europe: results from the i-move multicentre case-control study', Euro Surveill **18**(5).

Lipsitch, M., Jha, A. and Simonsen, L. (2016), 'Observational studies and the difficult quest for causality: lessons from vaccine effectiveness and impact studies', Int J Epidemiol .

Lozano, R., Naghavi, M., Foreman, K., Lim, S., Shibuya, K., Aboyans, V., Abraham, J., Adair, T., Aggarwal, R., Ahn, S. Y., Alvarado, M., Anderson, H. R., Anderson, L. M., Andrews, K. G., Atkinson, C., Baddour, L. M., Barker-Collo, S., Bartels, D. H., Bell, M. L., Benjamin, E. J., Bennett, D., Bhalla, K., Bikbov, B., Bin Abdulhak, A., Birbeck, G., Blyth, F., Bolliger, I., Boufous, S., Bucello, C., Burch, M., Burney, P., Carapetis, J., Chen, H., Chou, D., Chugh, S. S., Coffeng, L. E., Colan, S. D., Colquhoun, S., Colson, K. E., Condon, J., Connor, M. D., Cooper, L. T., Corriere, M., Cortinovis, M., de Vaccaro, K. C., Couser, W., Cowie, B. C., Criqui, M. H., Cross, M., Dabhadkar, K. C., Dahodwala, N., De Leo, D., Degenhardt, L., Delossantos, A., Denenberg, J., Des Jarlais, D. C., Dharmaratne, S. D., Dorsey, E. R., Driscoll, T., Duber, H., Ebel, B., Erwin, P. J., Espindola, P., Ezzati, M., Feigin, V., Flaxman, A. D., Forouzanfar, M. H., Fowkes, F. G. R., Franklin, R., Fransen, M., Freeman, M. K., Gabriel, S. E., Gakidou, E., Gaspari, F., Gillum, R. F., Gonzalez-Medina, D., Halasa, Y. A., Haring, D., Harrison, J. E., Havmoeller, R., Hay, R. J., Hoen, B., Hotez, P. J., Hoy, D., Jacobsen, K. H., James, S. L., Jasrasaria, R., Jayaraman, S., Johns, N., Karthikeyan, G., Kassebaum, N., Keren, A., Khoo, J.-P., Knowlton, L. M., Kobusingye, O., Koranteng, A., Krishnamurthi, R., Lipnick, M., Lipshultz, S. E., Ohno, S. L., Mabweijano, J., MacIntyre, M. F., Mallinger, L., March, L., Marks, G. B., Marks, R., Matsumori, A., Matzopoulos, R., Mayosi, B. M., McAnulty, J. H., McDermott, M. M., McGrath, J., Mensah, G. A., Merriman, T. R., Michaud, C., Miller, M., Miller, T. R., Mock, C., Mocumbi, A. O., Mokdad, A. A., Moran, A., Mulholland, K., Nair, M. N., Naldi, L., Narayan, K. M. V., Nasseri, K., Norman, P., O'Donnell, M., Omer, S. B., Ortblad, K., Osborne, R., Ozgediz, D., Pahari, B., Pandian, J. D., Rivero,

A. P., Padilla, R. P., Perez-Ruiz, F., Perico, N., Phillips, D., Pierce, K., Pope, 3rd, C. A., Porrini, E., Pourmalek, F., Raju, M., Ranganathan, D., Rehm, J. T., Rein, D. B., Remuzzi, G., Rivara, F. P., Roberts, T., De León, F. R., Rosenfeld, L. C., Rushton, L., Sacco, R. L., Salomon, J. A., Sampson, U., Sanman, E., Schwebel, D. C., Segui-Gomez, M., Shepard, D. S., Singh, D., Singleton, J., Sliwa, K., Smith, E., Steer, A., Taylor, J. A., Thomas, B., Tleyjeh, I. M., Towbin, J. A., Truelsen, T., Undurraga, E. A., Venketasubramanian, N., Vijayakumar, L., Vos, T., Wagner, G. R., Wang, M., Wang, W., Watt, K., Weinstock, M. A., Weintraub, R., Wilkinson, J. D., Woolf, A. D., Wulf, S., Yeh, P.-H., Yip, P., Zabetian, A., Zheng, Z.-J., Lopez, A. D., Murray, C. J. L., AlMazroa, M. A. and Memish, Z. A. (2012), 'Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the global burden of disease study 2010', Lancet **380**(9859), 2095–128.

McMenamin, J., Andrews, N., Robertson, C., Fleming, D., Durnall, H., von Wissmann, B., Ellis, J., Lackenby, A., Cottrell, S., Smyth, B., Zambon, M., Moore, C., Watson, J. and Pebody, R. (2013), 'Effectiveness of seasonal 2012/13 vaccine in preventing laboratory-confirmed influenza infection in primary care in the united kingdom: mid-season analysis 2012/13', Euro Surveill **18**(5).

Morabia, A., ed. (2004), A History of Epidemiological Methods and Concepts., number p. 1-405, Birkhaeuser Verlag.

Morens, D. M. and Fauci, A. S. (2007), 'The 1918 influenza pandemic: insights for the 21st century', J Infect Dis **195**(7), 1018–28.

Nair, H., Brooks, W. A., Katz, M., Roca, A., Berkley, J. A., Madhi, S. A., Simmerman, J. M., Gordon, A., Sato, M., Howie, S., Krishnan, A., Ope, M., Lindblade, K. A., Carosone-Link, P., Lucero, M., Ochieng, W., Kamimoto, L., Dueger, E., Bhat, N., Vong, S., Theodoratou, E., Chittaganpitch, M., Chimah, O., Balmaseda,

A., Buchy, P., Harris, E., Evans, V., Katayose, M., Gaur, B., O'Callaghan-Gordo, C., Goswami, D., Arvelo, W., Venter, M., Briese, T., Tokarz, R., Widdowson, M.-A., Mounts, A. W., Breiman, R. F., Feikin, D. R., Klugman, K. P., Olsen, S. J., Gessner, B. D., Wright, P. F., Rudan, I., Broor, S., Simões, E. A. F. and Campbell, H. (2011), 'Global burden of respiratory infections due to seasonal influenza in young children: a systematic review and meta-analysis', Lancet **378**(9807), 1917–30.

Nichol, K. L., Baken, L. and Nelson, A. (1999), 'Relation between influenza vaccination and outpatient visits, hospitalization, and mortality in elderly persons with chronic lung disease', Ann Intern Med **130**(5), 397–403.

O'Hagan, J. J., Hernán, M. A., Walensky, R. P. and Lipsitch, M. (2012), 'Apparent declining efficacy in randomized trials: examples of the thai rv144 hiv vaccine and south african caprisa 004 microbicide trials', AIDS **26**(2), 123–6.

Omer, S. B., Goodman, D., Steinhoff, M. C., Rochat, R., Klugman, K. P., Stoll, B. J. and Ramakrishnan, U. (2011), 'Maternal influenza immunization and reduced likelihood of prematurity and small for gestational age births: a retrospective cohort study', PLoS Med **8**(5), e1000441.

Orenstein, E. W., De Serres, G., Haber, M. J., Shay, D. K., Bridges, C. B., Gargiullo, P. and Orenstein, W. A. (2007), 'Methodologic issues regarding the use of three observational study designs to assess influenza vaccine effectiveness', Int J Epidemiol **36**(3), 623–31.

Orenstein, W. A., Bernier, R. H., Dondero, T. J., Hinman, A. R., Marks, J. S., Bart, K. J. and Sirotkin, B. (1985), 'Field evaluation of vaccine efficacy', Bull World Health Organ **63**(6), 1055–68.

Orenstein, W. A., Bernier, R. H. and Hinman, A. R. (1988), 'Assessing vaccine efficacy in the field. further observations', Epidemiol Rev **10**, 212–41.

Pebody, R. G., Andrews, N., McMenamin, J., Durnall, H., Ellis, J., Thompson, C. I., Robertson, C., Cottrell, S., Smyth, B., Zambon, M., Moore, C., Fleming, D. M. and Watson, J. M. (2013), 'Vaccine effectiveness of 2011/12 trivalent seasonal influenza vaccine in preventing laboratory-confirmed influenza in primary care in the united kingdom: evidence of waning intra-seasonal protection', Euro Surveill **18**(5).

Petrie, J. G., Ohmit, S. E., Johnson, E., Truscon, R. and Monto, A. S. (2015), 'Persistence of antibodies to influenza hemagglutinin and neuraminidase following one or two years of influenza vaccination', J Infect Dis **212**(12), 1914–22.

Petrie, J. G., Ohmit, S. E., Truscon, R., Johnson, E., Braun, T. M., Levine, M. Z., Eichelberger, M. C. and Monto, A. S. (2016), 'Modest waning of influenza vaccine efficacy and antibody titers during the 2007-2008 influenza season', J Infect Dis **214**(8), 1142–9.

Rolfes MA, Foppa IM, G. S. F. B. B. L. S. J. e. a. (n.d.), 'Estimated influenza illnesses, medical visits, hospitalizations, and deaths averted by vaccination in the united states'.

Savitz, D. A., Fell, D. B., Ortiz, J. R. and Bhat, N. (2015), 'Does influenza vaccination improve pregnancy outcome? methodological issues and research needs', Vaccine **33**(47), 6430–5.

Schoenfeld, D. (1982), 'Partial residuals for the proportional hazards regression model', Biometrika **69**(1), 239–241.
URL: *http://www.jstor.org/stable/2335876*

Skowronski, D. M. (2005), 'Effectiveness of vaccine against medical consultation due

to laboratory-confirmed influenza: results from a sentinel physician pilot project in british columbia, 2004-2005', Can Commun Dis Rep **31**(18), 181–91.

Skowronski, D. M., Masaro, C., Kwindt, T. L., Mak, A., Petric, M., Li, Y., Sebastian, R., Chong, M., Tam, T. and De Serres, G. (2007), 'Estimating vaccine effectiveness against laboratory-confirmed influenza using a sentinel physician network: results from the 2005-2006 season of dual a and b vaccine mismatch in canada', Vaccine **25**(15), 2842–51.

Smith, P. G. (1982), 'Retrospective assessment of the effectiveness of bcg vaccination against tuberculosis using the case-control method', Tubercle **63**(1), 23–35.

Smith, P. G., Rodrigues, L. C. and Fine, P. E. (1984), 'Assessment of the protective efficacy of vaccines against common diseases using case-control and cohort studies', Int J Epidemiol **13**(1), 87–93.

Song, J. Y., Cheong, H. J., Hwang, I. S., Choi, W. S., Jo, Y. M., Park, D. W., Cho, G. J., Hwang, T. G. and Kim, W. J. (2010), 'Long-term immunogenicity of influenza vaccine among the elderly: Risk factors for poor immune response and persistence', Vaccine **28**(23), 3929–35.

Sridhar, S., Brokstad, K. A. and Cox, R. J. (2015), 'Influenza vaccination strategies: Comparing inactivated and live attenuated influenza vaccines', Vaccines (Basel) **3**(2), 373–89.

Sullivan, S. G., Tchetgen Tchetgen, E. J. and Cowling, B. J. (2016), 'Theoretical basis of the test-negative study design for assessment of influenza vaccine effectiveness', Am J Epidemiol **184**(5), 345–53.

Talbot, H. K., Nian, H., Chen, Q., Zhu, Y., Edwards, K. M. and Griffin, M. R. (2016), 'Evaluating the case-positive, control test-negative study design for influenza vaccine effectiveness for the frailty bias', Vaccine **34**(15), 1806–9.

Talbot, H. K., Zhu, Y., Chen, Q., Williams, J. V., Thompson, M. G. and Griffin, M. R. (2013), 'Effectiveness of influenza vaccine for preventing laboratory-confirmed influenza hospitalizations in adults, 2011-2012 influenza season', Clin Infect Dis **56**(12), 1774–7.

Tian, L., Zucker, D. and Wei, L. J. (2005), 'On the cox model with time-varying regression coefficients', Journal of the American Statistical Association **100**(469), 172–183.
URL: *http://www.jstor.org/stable/27590527*

Treanor, J. J., Talbot, H. K., Ohmit, S. E., Coleman, L. A., Thompson, M. G., Cheng, P.-Y., Petrie, J. G., Lofthus, G., Meece, J. K., Williams, J. V., Berman, L., Breese Hall, C., Monto, A. S., Griffin, M. R., Belongia, E., Shay, D. K. and US Flu-VE Network (2012), 'Effectiveness of seasonal influenza vaccines in the united states during a season with circulation of all three vaccine strains', Clin Infect Dis **55**(7), 951–9.

Valsecchi, M. G., Silvestri, D. and Sasieni, P. (1996), 'Evaluation of long-term survival: use of diagnostics and robust estimators with cox's proportional hazards model', Stat Med **15**(24), 2763–80.

VanWormer, J. J., Sundaram, M. E., Meece, J. K. and Belongia, E. A. (2014), 'A cross-sectional analysis of symptom severity in adults with influenza and other acute respiratory illness in the outpatient setting', BMC Infect Dis **14**, 231.

White, M. T., Griffin, J. T., Drakeley, C. J. and Ghani, A. C. (2010), 'Heterogeneity in malaria exposure and vaccine response: implications for the interpretation of vaccine efficacy trials', Malar J **9**, 82.

Zhang, J. and Yu, K. F. (1998), 'What's the relative risk? a method of correcting the odds ratio in cohort studies of common outcomes', JAMA **280**(19), 1690–1.