An economic assessment of high-dose influenza vaccine

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AN ECONOMIC ASSESSMENT OF HIGH-DOSE INFLUENZA VACCINE

Estimating the vaccine-preventable burden of disease

in the United States using real-world data

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For Emily and Eleanor.

Messieurs, c'est les microbes qui auront le dernier mot.
Louis Pasteur

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GLOSSARY OF ABBREVIATIONS

aIIV3	adjuvanted Inactivated Influenza Vaccine, trivalent
aIIV4	adjuvanted Inactivated Influenza Vaccine, quadrivalent
ARR	Absolute Risk Reduction
CAN	Care Assessment Need
CBOC	Community-Based Outpatient Clinic
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
CMS	Centers for Medicare & Medicaid Services
CPT	Current Procedural Terminology
CTL	Cytotoxic T Cell
ED	Emergency Department
EMR	Electronic Medical Record system
FDA	Food and Drug Administration
GEE	Generalized Estimating Equations
HA	Hemagglutinin
HD	HD-IIV3: High-Dose Inactivated Influenza Vaccine, trivalent
HD-IIV4	High-Dose Inactivated Influenza Vaccine, quadrivalent
HIPAA	Health Insurance Portability and Accountability Act
HTA	Health Technology Assessment
ICD-10	ICD-10-CM: International Classification of Diseases, Tenth Revision, Clinical Modification
ICD-9	ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification
IV	Instrumental Variable
MCA	Managerial Cost Accounting system
MDCK	Madin–Darby Canine Kidney
NA	Neuraminidase
NDI	National Death Index
NNT	Number Needed to Treat
NNV	Number Needed to Vaccinate
PEHR	Prior Event Hazard Ratio
PERD	Prior Event Rate Difference
PERR	Prior Event Rate Ratio

PHI	Protected Health Information
QALY	Quality-Adjusted Life Year
RCT	Randomized Clinical Trial
RIV4	Recombinant Influenza Vaccine, quadrivalent
RR	Rate Ratio
RSV	Respiratory Syncytial Virus
rVE	relative Vaccine Effectiveness or relative Vaccine Efficacy
RWD	Real-World Data
RWE	Real-World Evidence
SD	IIV3: Standard-Dose Inactivated Influenza Vaccine, trivalent
SD-IIV4	Standard-Dose Inactivated Influenza Vaccine, quadrivalent
US	USA: United States of America
VA	Veterans Affairs
VAMC	White River Junction VA Medical Center
VE	Vaccine Effectiveness or Vaccine Efficacy
VHA	Veterans Health Administration
VINNE	Veteran's Institutional Review Board of Northern New England
WHO	World Health Organization

GENERAL INTRODUCTION

Background

Influenza is a frequent, contagious, acute respiratory disease caused by influenza virus infection. The public at large is quite familiar with outbreaks of the "flu" but may not always realize that influenza is a major cause of morbidity and mortality. Classic symptoms of flu include cough, fever, sore throat and muscle ache, but influenza infection can also cause pneumonia, sepsis, and inflammation of the heart (myocarditis) and brain tissue (encephalitis) [1].

This thesis addresses the role of vaccination in prevention of the disease with an emphasis on clinical and economic aspects, as well as challenges of estimating vaccination effects. Understanding these challenges requires some basic knowledge of the virus, its rapidly changing character, and the various influenza vaccine types currently available for viral control and disease prevention. Here, we introduce relevant aspects of the virus, the vaccines and vaccine effectiveness studies and outline important questions that this thesis will address.

The influenza virus

The influenza virus attacks the mucosal lining of the respiratory system [2]. This occurs because of its ability to bind via a characterizing surface protein (antigen) hemagglutinin (HA). In response, the host cell engulfs the virus by endocytosis. The virus is now able – using the replicative armamentarium of the host cell – to reproduce itself. Newly produced viruses can leave the host cell using another characterizing antigen neuraminidase (NA) and immediately start infecting other host cells. The host cell is killed in the process.

Influenza viruses comprise a large group of slightly different variants that are each classified by antigenic differences in HA and NA. There are four main virus types: A, B, C and D. Almost every winter, in both the Northern and Southern hemispheres, human influenza A and B viruses cause seasonal epidemics of disease. The influenza A virus has 18 different HA subtypes and 11 different NA subtypes, which can be further broken down into strains. Current season influenza A subtypes found in humans are mostly H3N2 and H1N1 [3]. Influenza B viruses are not divided into subtypes, but broken down into lineages and strains. Current influenza B lineages found in humans

are Yamagata and Victoria. Lineages and subtypes were created by exchange of gene segments between avian, swine, and human influenza viruses: a process called antigenic *shift*. Such a shift may change the virulence of the virus and can be the cause of a new disease outbreak that rapidly spreads worldwide. Examples are the devastating influenza pandemics of 1918 (Spanish flu) and 2009 (Swine flu). A subtler process of antigenic *drift* continues to produce novel influenza strains each year, and as a result, contributes to the yearly influenza epidemic.

Human immune response

The human immune response to influenza infection has an innate and adaptive component. The innate response attacks the virus during the initial phase of the influenza virus infection. Alveolar macrophages and monocytes are activated, resulting in a proinflammatory cytokine response with classic 'fever' symptoms [4]. The adaptive immune system has a humoral and a cellular component. The humoral immune system, mediated by B and helper-T cells in extracellular body fluids, not only attacks the virus, but also produces antibodies against different influenza antigens (including HA and NA). The HA-specific antibody is the most important by preventing virus attachment to the host cell, and thus, preventing infection. The cellular immune system, mediated by T cells, is the last line of defense and cleans up infected host cells.

As the result of a process called "immunosenescence", the ability to fight infections deteriorates with age. At a cellular level, immunosenescence is a combination of a diminished number of immune cells (e.g., phagocytes, B and T cells) and function, coupled with a less controlled inflammatory response resulting in chronic low-grade inflammation [4]. Immunosenescence is an important reason why adults aged 65 years and older (hereinafter referred to as seniors) carry the majority of the annual influenza disease burden. In the 2017–18 respiratory season, seniors in the United States (U.S.) were estimated to have incurred over 650,000 influenza-associated hospitalizations and 65,000 influenza-associated deaths – 69% and 86% of the total number of influenza-associated hospitalizations and deaths, respectively [5]. Other risk factors for complications after an influenza infection also tend to increase with age. Examples are chronic lung disease, heart disease, liver disorders and endocrine disorders like diabetes mellitus [6].

VACCINATION

Introduction

Vaccination aims to improve or strengthen the adaptive immune response against HA antigens. Vaccination activates a humoral response to build memory B cells and antibodies, which results in preventing or slowing down the virus to enter the host cell, and a cellular response to build cytotoxic T cells (CTLs). Immunosenescence not only reduces the ability to fight infections with age, it also reduces the benefit from vaccination. Even so, vaccination is the best preventive strategy against influenza infection [7].

Vaccine Types

There are different types of influenza vaccines available to the US population. It is important to note that these differences go beyond the fact that manufacturers produce a new (different) vaccine each year, composed of (slightly) different strains, to counter antigenic drift.

One way to distinguish influenza vaccines is by the number of strains they include (Table 1). *Trivalent* vaccines include antigens of three strains (one A/H3N2, one A/H1N1, and one B strain). *Quadrivalent* vaccines include antigens of four strains (those in the trivalent vaccine plus another B strain).

Table 1. Differentiating Influenza Vaccines

Differentiating Element	Vaccine Type
Number of Strains	Trivalent
	Quadrivalent
Growth Medium	Chicken Egg
	Mammalian cell culture
	Insect cell culture
Virus Resemblance	Live attenuated – highest resemblance
	Virus-like particle (VLP)
	Inactivated – lowest resemblance
Dose	Standard-dose
	High-dose
	Other doses

Table 1 (continued). Differentiating Influenza Vaccines

Differentiating Element	Vaccine Type
Delivery	Intermuscular
	Intradermal
	Nasal
	Jet injector
Advanced Technology	Recombinant RNA technology
Additives	Preservatives
	Adjuvants

Vaccine manufacturers do not decide which strain to include in their annual influenza vaccine. The World Health Organization (WHO) collects and analyzes virological and epidemiological influenza surveillance data from around the world and uses these data to predict which strains are likely to become virulent during the typical influenza season in the northern and southern hemisphere. WHO then issues a "recommendation" to the manufacturers detailing which strains to include [8].

Influenza vaccines can be distinguished by method of manufacturing. The most common method to manufacture influenza vaccines is to grow the influenza virus in fertilized chicken eggs. Virus-containing allantoic fluid is extracted from the eggs. The virus is then killed for inactivated influenza vaccines (the "flu shot") or weakened for live attenuated vaccines (the "nasal spray"). Last, the vaccines are purified and tested [9]. The influenza virus can also be grown in a mammalian cell culture: Madin–Darby canine kidney (MDCK) cells; or in an insect cell culture for the production of recombinant influenza vaccine [10].

Additives to the influenza vaccines may vary. Adjuvants are added with the intention to increase the immune response and improve vaccine efficacy [11]. Currently the only adjuvant used in commercially available influenza vaccines is an oil-in-water emulsion of squalene oil (MF59).

Vaccines can also be distinguished by the amount (micrograms, μg) of HA antigen it contains. Where standard-dose inactivated vaccines contain 15 μg of HA per strain (45 μg total in trivalent, 60 μg total in quadrivalent), a recombinant inactivated influenza vaccine contains *three times* the amount, or 45 μg of HA per strain (135 μg total in

trivalent, 180 μg total in quadrivalent) and a high-dose inactivated vaccine contains *four times*, or 60 μg of HA per strain (180 μg total in trivalent).

Finally, influenza vaccines can be distinguished by method of delivery: intramuscular, intradermal or intranasal. The most common influenza vaccination is administered intramuscularly (typically via a needle in the deltoid muscle). Intradermal vaccines are administered with a very small needle in the skin; nasal sprays are inhaled through the nose.

The high-dose vaccine (Fluzone High-Dose, Sanofi Pasteur, PA) that we studied in this thesis is an egg-grown inactivated, trivalent influenza vaccine (HD-IIV3), and administered intramuscularly. This high-dose vaccine was specifically developed to address reduced immunogenicity and effectiveness of influenza vaccines in older adults by increasing antigen dose to provoke a stronger immune response and therefore improve protection in seniors. In 2009, the US Food and Drug Administration approved the use of HD-IIV3 in adults 65 years and older. Fluzone High-Dose is the only HD-IIV3 vaccine commercially available in the US.

Efficacy and effectiveness against influenza infection

Randomized studies that estimate the protective effect of influenza vaccines are called efficacy studies, while retrospective cohort studies and other non-randomized observational studies are called effectiveness studies. By convention, vaccine efficacy estimates are considered stronger evidence (less biased) than vaccine effectiveness estimates, potentially at the cost of generalizability outside the randomized controlled trial (RCT) population [12]. When the vaccine of interest is not compared to a placebo, but to another vaccine (often the standard of care), a comparative efficacy study estimates the *relative* vaccine efficacy, and a comparative effectiveness study estimates the *relative* vaccine effectiveness. In the US, RCTs that use placebo as a control are not deemed ethical because of the established benefits of vaccination and clear recommendations in place, and as a result, vaccine efficacy estimates of recently approved and available influenza vaccines, like HD-IIV3 in the US population, are not available. The US Centers for Disease Control and Prevention (CDC) publish annual vaccine effectiveness (VE) rates using a test-negative, case-controlled design [12]. People who seek medical care for a "new cough" and who are tested for influenza (enrolled in the study) are categorized in vaccinated versus unvaccinated and positive

versus negative for influenza. For 2018/19, CDC published an average (over all age groups and strains) VE of 29% (95 CI: 21%-35%) [13]. This can be interpreted as the proportion of positive tests in the vaccinated group to be 29% less than the proportion of positive test in the unvaccinated group. Interestingly, the rates published by CDC are not stratified by vaccine type.

In earlier seasons, average VE rates ranged between 10% in 2004/5 and 60% in 2010/11 [14]. These rates are much lower than vaccines with the highest VE, like polio (99% VE after three doses) or measles (97% after 2 doses), and has resulted in people questioning the premise of influenza vaccination and therefore, contributed to suboptimal vaccination rates [15-17]. Low influenza VE may have multiple causes. To name a few: 1) a low performing vaccine (e.g., strain mismatch, insufficient immune response); 2) insufficient or lack of herd immunity; and 3) a biased VE estimate: bias *inherent* in the test-negative case-control design may result in VEs that are not generalizable to the general population or risk groups, and are not generalizable to other outcomes like asymptomatic influenza infection (typical in seniors) and hospitalizations [18].

Another way to measure vaccine performance is to compare recipients of two different vaccines and estimate the relative vaccine efficacy or effectiveness. This design makes it possible to study other outcomes than a positive laboratory test – at the cost of being less specific, but potentially more sensitive to influenza infection [12]. As mentioned earlier, efficacy studies have to be comparative because of ethical considerations. For HD-IIV3, a relative vaccine efficacy (rVE) of 24% was estimated for laboratory confirmed influenza in symptomatic patients seeking care at an outpatient clinic, compared to the standard of care at the time: an egg-grown, standard-dose trivalent inactivated influenza vaccine (SD-IIV3) [19]. For this RCT, almost 32 thousand participants were enrolled to ensure sufficient statistical power for the primary outcome. Studying more severe complications, but even less frequent outcomes like hospitalizations, would need an even bigger study cohort, making the study logistically challenging and prohibitively expensive. In the US, the availability of large databases with de-identified health insurance claims data and the electronic medical records of millions of patients makes retrospective cohort studies of severe complications after an influenza infection possible. Multiple comparative effectiveness studies have reported an association between HD-IIV3 and reduced influenza-associated hospitalizations, emergency room visits and mortality, compared to SD-IIV3 [20]. These retrospective

studies in large databases have their own unique challenges, of course. Missing data and misclassification of comorbid conditions; treatment and outcomes (information bias and confounding); and the tendency to reserve better treatment for sicker patients (selection bias) are among the hardest to overcome [12].

Real-world data

Health insurance claims and electronic medical records are often referred to as "real-world data" (RWD) and are the primary source for generating "real-world evidence" (RWE) – a term introduced in the 2016 signed Cures Act allowing the use of RWE for regulatory purposes in the US [21, 22]. The regulatory body in the US, the Food and Drug Administration (FDA) is currently developing a framework for evaluating RWD and RWE in regulatory decisions [22]. Given the high cost of RCTs, opening up the regulatory process to RWE is an exciting development. The FDA has not (yet) published guidelines to generate RWE from data based on non-randomized treatment assignment, but it is to be expected that the potential sources in retrospective cohort studies mentioned earlier need to be addressed convincingly: information bias, confounding, and selection bias.

Economic assessment

Many experts in the field of health economics recommend taking a societal perspective when assessing the value of a certain treatment or health technology [23, 24]. Not including societal elements like "days missed from work" and "quality adjusted life years (QALY) lost" will likely underestimate the value of the treatment or technology [25]. These cost-effectiveness or health technology assessments (HTA) work on the premise of scarcity: when funding is limited, a choice between two vaccination strategies must be made – or in case no substitute exists, if the treatment should be reimbursed. This is, maybe perversely, not true for the largest payer in the US healthcare system: The Centers for Medicare & Medicaid Services (CMS). CMS is, by law, not authorized to select one treatment over the other based on cost-effectiveness. One of the most important challenges of using cost-effectiveness studies for policy decisions is that these studies report a price per QALY for a certain treatment – for instance drug A, a novel cancer treatment, will buy you one QALY ("one extra year to live") for $600,000. The challenge, of course, is to decide what price per QALY is still reasonable, or to put it differently, put a price on a human life [25, 26]. In my thesis, I only include direct

medical costs in the economic assessments because of the difficulty to estimate deaths prevented, and to report conservative estimates of the economic benefit of HD-IIV3.

CONTRIBUTION TO THE LITERATURE

Study population

This thesis describes the economic impact of HD-IIV3 in two specific sub-populations in the United States: Veterans receiving care through the Veterans Health Administration (VHA) and members of a large national managed care company affiliated with Optum [27, 28]. Both organizations have in common that they share some of the financial risks with the payers of healthcare. In other words, they do not get fully reimbursed for all of the care they provide. This financial arrangement is an incentive to prevent healthcare utilization. Vaccination policy and programs support this objective. In the United States, healthcare for seniors gets funded through commercial insurers or taxpayers (through the federal government and individual states). For seniors, the most important government funded payer is Medicare. Medicare has a fee-for-service program and a risk-sharing program (Medicare Advantage). VHA receives funds directly from the federal government to pay for their operation, but VHA enrollees (Veterans) can receive care in non-VHA facilities as well. In that case, this care would get funded by Medicare fee-for-service or Medicare Advantage. Only a very small number of Veterans who are eligible for VHA care are also commercially insured [29]. A managed care company (like the one affiliated with Optum) manages Medicare Advantage funds. It negotiates risk-bearing contracts with hospitals or private practices and measures and/or tracks the performance of these healthcare providers.

Research question

HD-IIV3 is often offered at a price premium compared to SD-IIV3 and adjuvanted SD-IIV3 (aIIV3). Payers of healthcare are generally interested in the economic impact of various vaccination strategies like vaccinating with HD-IIV3 versus aIIV3 or SD-IIV3. We will answer this question using RWD: insurance claims data and electronic medical records from VHA, Medicare and Optum. The overall approach is to first estimate the burden of disease in the population, then estimate the relative vaccine effectiveness of HD-IIV3 in that population, and lastly, to assess the economic impact of switching vaccine recipients over to HD-IIV3. The main reason for not including

unvaccinated patients in this study is twofold: first, when using insurance claims, it is impossible to tell if missing a vaccination record means that the patient did not receive a vaccine, or received care outside of the observable healthcare system (resulting in missing data), and second, patients who get vaccinated are very different from patients who do not choose to get vaccinated [30]. Healthy vaccinee bias and confounding by indication are major concerns in observational cohort studies of vaccine effectiveness, and including a non-vaccinated group would exacerbate this issue [31].

Specific aims

1. Assess the economic impact of switching SD-IIV3 vaccine recipients over to HD-IIV3 in Veterans receiving care through VHA using real-world data.

2. Assess the economic impact of switching aIIV3 vaccine recipients over to HD-IIV3 in members of a large national managed care company affiliated with Optum using real-world data.

Outline of the thesis

In chapter 1, we estimate the burden of disease associated with influenza infection in the VHA population. Chapter 2 addresses the effectiveness of HD-IIV3 versus SD-IIV3 in reducing lab-confirmed influenza, influenza-associated hospitalizations and urgent care visits in VHA hospitals and outpatient clinics. Chapter 3 compares the economic impact between HD-IIV3 and SD-IIV3 on the cost of (the aggregate of) cardiovascular or respiratory hospitalizations in the VHA population. Chapter 4 breaks this analysis down into an economic impact on cost of hospitalizations for cardiovascular and respiratory disease, separately. In chapter 5, we compare the effectiveness between HD-IIV3 and aIIV3 in reducing influenza-associated hospitalizations in a large national managed care company affiliated with Optum. In chapter 6 we discuss the causal interpretation and workings of the previous event rate ratio (PERR) method that we used in chapters 2 and 5 to adjust for unmeasured confounding factors. Chapter 7 uses some of these insights to evaluate the direct medical cost of both vaccines in the population studied in chapter 6.

This thesis concludes with an assessment of the extent the research question has been answered; a review of important limitations of the methods that were used; and finally, outlines potential future directions to address these limitations.

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