INFLUENZA VACCINE EFFECTIVENESS AMONG PATIENTS ON HEMODIALYSIS: METHODS TO CONTROL THE HEALTHY-USER BIAS

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ABSTRACT

LEAH JILL SIRKUS MCGRATH: Influenza vaccine effectiveness among patients on hemodialysis: methods to control the healthy-user bias
(Under the direction of M. Alan Brookhart)

Background: Patients with end-stage renal disease (ESRD) are at increased risk for several preventable infections. Although vaccines have been recommended for people with ESRD for many years, little is known about the level of vaccine effectiveness (VE) in preventing clinical health outcomes in this population. Observational studies of VE are challenging, however, because vaccinated persons may be healthier than unvaccinated persons. This dissertation aims to estimate influenza vaccine effectiveness among patients on hemodialysis using novel ways to control for bias.

Methods: Using Medicare claims from patients on hemodialysis, a natural experiment was created by using year-to-year variation in the match of the influenza vaccine to the circulating virus. VE for influenza-like illness, influenza/pneumonia hospitalization, and mortality was estimated by comparing matched (1998, 1999, 2001) and mismatched (1997) years among vaccinated patients. An alternate method identified time-varying predictors of vaccination status and used these variables to control for time-varying confounding using a marginal structural model.

Results: Conventional estimates comparing vaccinated patients with unvaccinated patients suggested a large protective effect – influenza vaccine reduced mortality by 30%. The pooled VE estimate from the natural experiment of comparing matched seasons to a placebo was 0% (95% CI: -3,2%) for influenza-like illness, 2% (95% CI: -2,5%) for hospitalization, and 0% (95% CI: -3,3%) for death. Hospitalization and skilled nursing care were highly associated with not being vaccinated, suggesting that these variables could be used to control for the healthy-user bias. The marginal structural model remained biased even after accounting for time-varying confounding, which likely resulted in exaggeration of the protective effect of the vaccine.

Conclusions: Strong confounding bias is present when estimating influenza vaccine effectiveness. Controlling for bias using a natural experiment resulted in estimates of VE for all outcomes that were close to the null. This suggests that the current influenza vaccine strategy may have a smaller effect on morbidity and mortality in the ESRD population than previously thought. Alternate strategies (high dose vaccine, intradermal vaccine, and adjuvanted vaccines) should be investigated to achieve better health outcomes.

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LIST OF ABBREVIATIONS

ACIP	Advisory Committee on Immunization Practices
APCs	Antigen-presenting cells
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
CMS	Centers for Medicare and Medicaid Services
CPT	*Current Procedural Terminology*
ESRD	End-stage renal disease
HCPCS	Health Care Financing Administration Common Procedural Coding System
HMO	Health maintenance organization
HR	Hazard ratio
ICD-9-CM	*International Classification of Diseases, 9th Revision, Clinical Modification*
ILI	Influenza-like illness
I/P	Influenza/pneumonia
IPTW	Inverse probability of treatment weights
RCT	Randomized control trial
TIV	Trivalent, inactivated influenza vaccine
USRDS	United States Renal Data System
VE	Vaccine effectiveness

I. INTRODUCTION

End-stage renal disease (ESRD) is the final stage of kidney disease where kidney function has decreased to less than 15% of normal and patients require a kidney transplant or dialysis to survive. Patients with ESRD are likely to have comorbidities, such as diabetes and hypertension, and are prone to contracting infections. Infection is one of the main causes of morbidity and mortality among patients with ESRD. It is the third leading cause of death, and infection-related hospitalizations have increased 43% since 1993.[1] Vaccinations provide a simple, inexpensive way to protect these high-risk patients from infections such as influenza, pneumococcal pneumonia, and Hepatitis B. Although vaccines have been recommended for people with chronic renal disease for many years,[2] little is known about the characteristics of patients who are vaccinated and the level of vaccine effectiveness in this population. One recent study investigating usage of influenza vaccine among ESRD patients reported less than 50% vaccination rates for both seasons between 1997-99.[3]

Influenza vaccines are recommended by the Advisory Committee on Immunization Practices (ACIP) for people with chronic renal disease; however, there are few studies in this population that investigate the effects of this vaccine in relation to health outcomes. Most vaccine effectiveness studies have considered only the elderly. There has been only one randomized control trial

among the elderly population, which showed that the vaccine reduced lab-confirmed influenza by 50%.[4] It has proven difficult to accurately estimate the effectiveness of flu vaccine among the elderly population in non-experimental studies due to severe confounding by functional status[5] and the "healthy-user effect"[6] that is associated with receiving the vaccine. Although several high-profile studies have suggested that the influenza vaccine may reduce all-cause mortality by as much as 50%,[7-9] more recent studies have suggested that these estimates are due to confounding and the true effect may be small to negligible.[5,10-13] Studies to better elucidate the effects of selection bias as well as the effectiveness of vaccines among the ESRD population are needed.

The United States Renal Data System (USRDS) is a population-based, national system that collects information on all patients with ESRD in the United States. Because all ESRD patients are eligible for Medicare coverage, this system captures a substantial number of ESRD patient encounters, including medication usage, vaccinations, hospitalizations and deaths. Data have been collected from 1989-2007, thus the USRDS is an optimal data source for investigating trends in vaccine use over time, as well as how effective vaccines are in protecting against various health outcomes, such as hospitalization from pneumonia. The number of people with ESRD is expected to continue to grow, especially because of the growth of diabetes, which is a common cause of renal failure. Therefore, it is imperative to understand the current state of vaccine usage as well as the effectiveness of these vaccines in this population.

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II. REVIEW OF THE LITERATURE

A. Overview of End-Stage Renal Disease

Description and epidemiology of ESRD

End-stage renal disease (ESRD) is the final stage of kidney disease where kidney function has decreased to less than 15% of normal and patients require a kidney transplant or dialysis to survive. The kidneys can no longer adequately eliminate nitrogenous waste or fluid and fail to perform other biological processes including regulating pH.

In 2009, there were more than 570,000 patients with ESRD in the U.S.[1] With the rising prevalence of diabetes and hypertension, this number is expected to increase to 774,386 by 2020. The prevalent population has been steadily increasing by ~2% each year since 2003. The incidence of ESRD has been rising since the 1980s, and although the rate dropped slightly in 2007 and 2008, it increased to 355 cases per million population (adjusted for age, gender, and race).[1] Table 1 shows that elderly people aged 75 years and older, and African Americans have the highest rates of ESRD. In fact, the incidence rate of ESRD among African Americans was 3.5 times the rate among Whites. In addition, ESRD affects people with Hispanic ethnicity disproportionally – 13% of all new cases of ESRD were among Hispanics, and the rate of ESRD among Hispanics is 1.5 times that of non-Hispanics.[1]

Table 1. Number and rate of cases of ESRD by age, race and ethnicity in 2009[1]

	Incidence		Prevalence	
	Number	Rate* per million	Number	Rate* per million
Overall	113,908	355	571,414	1,738
Age				
20-44	13,894	131	100,031	924
45-64	43,646	610	256,803	3,433
65-74	26,459	1,407	116,607	6,066
75+	28,595	1,762	90,233	5,545
Race				
White	75,077	277	347,268	1,279
African American	32,116	976	180,685	5,284
Native American	1,404	522	7,682	2,735
Ethnicity				
Hispanic	14,766	501	87,866	2,538
Non-Hispanic	99,142	345	483,548	1,685

*Adjusted to 2005 population cohort.

Rates of ESRD vary substantially by geography. Generally, both incident and prevalent rates of ESRD are highest in the south and southwestern regions of the U.S. However, the oldest patients with incident ESRD are found in the upper Midwest, the Northeast and Florida. In addition, the highest rate for Whites and African Americans is in Pittsburg, Pennsylvania and for Hispanics is in Cincinnati, Ohio.[2]

Patients with ESRD are very ill and mortality is high among this population. In 2009, the mortality rate for all ESRD patients was 148.3 per 1,000 patient years and approximately 16% of prevalent cases of ESRD died. Mortality rates for patients on dialysis who are 65 years or older are ~6.5 times higher than the general population.[1] The five-year survival for patients on dialysis is 34%; however, elderly ESRD patients have lower survival–the five-year survival for

patients aged 65 to 74 years is 26% and 13% for those aged 75 and older.[1] Mortality is high during the first year of dialysis; specifically, months two and three after initiation of dialysis have the highest mortality rates.[3]

The cost of care of the ESRD patient population is substantial. In 2009, the cost of those covered through Medicare (~83% of all ESRD patients) was $29 billion, which was 6.7% of the total Medicare budget (not including Part D). This cost increased 3.1% from 2008. Hemodialysis accounted for ~86% of the cost of ESRD care. The per person per year cost of care for ESRD was $82,000.[1] Costs tend to be highest in the first year after initiating dialysis – due to high rates of hospitalization during initiation – and averaged $113,000 among older ESRD initiators.[4]

Causes of ESRD

The three most common causes of ESRD are diabetes, hypertension and glomerulonephritis. The mechanisms of kidney damage between these three causes frequently overlap, and often a patient will have both diabetes and hypertension, which can accelerate the process.

Diabetes is the most common cause of ESRD. Approximately 30% of people with Type 1 diabetes and 25 to 40% of Type 2 diabetics develop ESRD,[5] although the disease generally does not appear until decades after the initial diabetes diagnosis. It is thought that hyperfiltration and a simultaneous increase in the glomerular filtration rate causes the initial damage to kidney capillaries, which eventually leads to loss of nephrons.[5] In addition, complexes called advanced glycosylated end products (AGEs) may also contribute to kidney

damage. AGEs occur when excess glucose is bonded to red blood cells.[6] These complexes can be deposited within the capillaries in the kidney, contributing to increased pressure and subsequent increase in glomerular filtration rate.

Hypertension can also induce damage to the kidneys. High blood pressure is one of the leading predictors of development of ESRD.[7] Hypertension can lead to higher pressure in the kidneys, which results in changes to the structure of the kidney capillaries and an ultimate loss in nephrons in similar ways as described earlier. It is thought that the renin-angiotensin system is also disrupted, further causing changes to blood pressure.[8,9]

Glomerulonephritis is the third leading cause of ESRD, and is a term that encompasses many diseases that are characterized by inflammation of glomerular capillaries, and development of subsequent signs of nephritic syndrome including hematuria and proteinuria.[10] In some cases, infection is the causative agent that triggers an auto-immune response, leading to renal damage. Other diseases, such as lupus, are chronic autoimmune diseases, which can cause similar damage over time. These generally have an acute phase of glomerular damage, characterized by deposits of immune-complexes in the glomerular capillaries, leading to an eventual loss of nephrons.[10]

Diabetes has been increasing as the primary cause of ESRD. In 2007, 44% of new cases listed diabetes as the cause, whereas 28% were due to hypertension (Table 2). Incidence of ESRD due to diabetes has been increasing among younger minorities, although it seems to be stable among older populations and Whites.[2]

Table 2. Number and rate of ESRD cases by top causes in 2009[1]

	Incident ESRD		Prevalent ESRD	
Cause of ESRD	Number	Rate* per million	Number	Rate* per million
Diabetes	50,970	154	215,245	647
Hypertension	32,688	101	140,498	429
Glomerulonephritis	7,612	24	84,883	263

*Adjusted for age, gender, and race

Dialysis

Dialysis is the mechanical process by which the blood of an ESRD patient is cleaned of excess water, minerals and other products of metabolism. There are two types of dialysis: hemodialysis and peritoneal dialysis. Here we restrict our discussion to hemodialysis. The process of hemodialysis begins with a patient's blood flowing through tubes into a cylindrical structure called the dialyzer while a premixed solution called the dialysate flows into the dialyzer in the opposite or countercurrent direction. A semi-permeable membrane composed of synthetic material separates the blood and dialysate compartments, but allows for the diffusion of solutes and the movement of water. After the blood has passed through the dialyzer, it is returned to the patient through a separate tube. Patients undergoing hemodialysis generally must attend dialysis clinics three times a week. A small fraction of patients will attend only twice a week, if they have a higher level of kidney function. Hemodialysis sessions last approximately three to four hours.

There are several types of facilities that administer hemodialysis to ESRD patients. The facilities are generally divided into for-profit and non-profit categories. The two largest for-profit providers are Fresenius and DaVita, treating

more than 200,000 patients combined. In addition, there are a variety of smaller dialysis organizations and hospital-based dialysis units that are other options for patients; however these facilities generally operate on a regional basis.

Infectious complications

Infection is the third leading cause of death (behind cardiovascular and "other" causes) and the second leading cause of hospitalization among ESRD patients. Infection-related hospitalizations have increased 43% since 1993.[1] Infection-related hospitalization is especially high within the first year of starting dialysis, and has increased nearly 100% since 1993.[3] During 1996–2001, the one-year incidence proportion of infection-related hospitalization was 32% among adults initiating hemodialysis, and the three-year incidence was 53%.[11] The most common causes of infection-related hospitalization reported by the Hemodialysis Study – a randomized trial investigating the effects of dialysis dose - were infection from an unknown source including sepsis and bacteremia (35%), vascular access infection (23%) and respiratory infection (22%).[12]

Impaired immune response in ESRD patients

ESRD patients have impaired immune systems, which may complicate the response to vaccinations. It is thought that immune dysfunction is a result of two processes: (a) immune deficiency of both the adaptive and innate immune systems caused by uremic toxins and (b) immune activation resulting in chronic inflammation caused by the dialysis procedure.[13] Although many pathways of the innate immune system are affected, here we will concentrate on the adaptive immune system, as these are the components of immunity that are involved in

attaining an adequate response to vaccinations, particularly B-cell production of antibodies. The predominant cells of the adaptive immune system that are directly depressed in ESRD patients are T-cells, although B-cells and antigen-presenting cells (APCs) are also affected. T-cells control immunity by either directly attacking pathogens (killer T-cells) or by indirectly stimulating cells to produce antibodies (helper T-cells) and must be activated prior to differentiation. It is thought that overall T-cell activation is reduced in patients with ESRD.[13] In addition, uremic toxins in the blood causes the function of APCs to decline, which thus impairs the ability of T-cells to differentiate.[14] Patients with ESRD have fewer B-cells due to the indirect effect of having fewer helper T-cells and the direct effect of having a higher likelihood of B-cell apoptosis or cell-death.[15] Furthermore, the frequent, invasive process of hemodialysis has been shown to produce chronic inflammation. Inflammatory cytokines are upregulated and push differentiation toward the Th1 pathway (leading to more killer T-cells), which results in even fewer B-cells.[16] Finally, inflammation has been shown to be linked to atherosclerosis,[17] which can lead to development of cardiovascular events and further impaired renal function, leading to further uremia and immune system dysfunction.

Preventive Services

Patients with ESRD generally have multiple health problems, some of which can be addressed with preventive care. There are several preventive care services that are recommended for patients with ESRD, including erythropoietin and intravenous iron for anemia management, phosphate binders and

intravenous vitamin D for common bone mineral metabolism disorders, diabetes and blood pressure management, and vaccinations.

Anemia is a common problem in patients with ESRD. The National Kidney Foundation recommends that any person on dialysis achieve a hemoglobin level between 11.0-12.0 g/dl and no greater than 13.0 g/dl.[18] In 2009, only 40% of patients were within this target.[1] Anemia can be caused by iron deficiency, low levels of erythropoietin, or both.[19] In patients with severe anemia, using erythropoietin-stimulating agents and intravenous iron supplementation raises hemoglobin levels, which has shown beneficial effects for health outcomes.[20] However, controversy persists about optimal hemoglobin targets as RCTs have demonstrated that full correction of anemia may increase mortality risk.

Diabetes and hypertension are common causes of ESRD and management of these diseases can help to slow the progression of kidney failure. Patients with diabetes can slow kidney damage with glycemic control through insulin or oral hypoglycemic medications.[5] It is recommended that diabetic patients receive A1c tests, lipid tests, and eye exams periodically. However, only 17% of ESRD patients received all three tests in 2009.[1] In addition, it has been shown that treatment with blood pressure medications that affect glomerular pressure, such as angiotensin-converting enzyme inhibitors decrease the rate of renal failure among chronic kidney disease patients, although multiple medications may be needed.[7,9]

Vaccinations are another preventive service that can have significant impact on health and mortality, as infection is a common cause of illness in

patients with ESRD. Although this population has a weakened immune system, vaccinations generally produce an adequate immune response to protect against future infection[21] and have been found to be cost-effective, especially in older adults with chronic illness.[22,23]

The health status of patients with ESRD is complicated by multiple factors. These patients are usually taking many medications to manage their multiple disease conditions as well as undergoing dialysis. However; because these patients are in contact with the health care system several times per week, there are multiple opportunities to administer these additional preventive services. The combination of a high annual mortality rate and the nearly $24 billion in annual healthcare costs incurred by these patients represent a clinical and public health priority for the optimal management, including preventive care, of ESRD.

B. **Vaccinations and the ESRD population**

Vaccinations indicated for ESRD patients

The ACIP[24] recommends that all ESRD patients and patients with chronic kidney disease receive influenza, Hepatitis B, and pneumococcal vaccines. Other vaccines, such as Hepatitis A and tetanus/diphtheria/pertussis, can be administered on an as-needed basis.

Trivalent, inactivated influenza vaccine (TIV) is indicated for yearly administration among ESRD patients. TIV is made by growing the virus in chicken eggs. Subsequently, the virus is inactivated and purified into the vaccine form.[25] TIV contains three strains of influenza: Type A (H1N1), Type A (H3N2), and Type B. In nature, the influenza virus is constantly changing through a

process called antigenic drift. Therefore, the strains included in the vaccine are updated on a yearly basis to better match the strains that are circulating in the community. The vaccine is most effective when administered at least 2 weeks prior, but no more than 4 months before exposure to influenza in the community. Because influenza peaks between December and March, the optimal time for vaccination is October and November.[25] Vaccine is generally available as early as September. ESRD patients should not receive the live attenuated influenza vaccine due to their potential immunocompromised state.[24] Although patients on dialysis have lower response rates to influenza vaccine compared with healthy adults, it has been shown that 46–87% of dialysis patients developed protective antibody titers after vaccination.[21,26]

Hepatitis B vaccine is a recombinant vaccine, where the gene for Hepatitis B surface antigen is inserted into yeast cells. The surface antigen gene is expressed by the yeast cells, and the resulting protein is purified to form the vaccine.[25] It is recommended that all patients currently undergoing dialysis treatment receive a higher vaccine dose than is normally administered, as the immune response may not result in adequate antibody titers.[24] Thus, the recommended schedule is 3 doses of 40 micrograms each, given at 0, 1, and 6 months. In addition, antibody titers may wane faster among this population. Generally, patients with an initial immune response will lose adequate protection after one year following immunization.[27] Antibody titers can be checked periodically to monitor the level of protection and to assess the need for booster

doses. Booster doses should be provided when antibody levels drop below 10 mIU/mL.[25]

It is recommended that people who are at increased risk of pneumococcal infection, including patients with ESRD, receive the 23-valent pneumococcal polysaccharide vaccine. The vaccine contains 23 different strains of *Streptococcus pneumoniae*, including the six serotypes that cause the majority of invasive disease.[28] Capsular polysaccharide antigens from each bacterial serotype are purified to make the vaccine.[25] Pneumococcal vaccine is typically administered only once, but one booster dose can be given to ESRD patients after 5 years. People with chronic kidney disease generally produce an adequate response to immunization, however, the antibody level wanes faster than in healthy subjects. One study showed that 71% of hemodialysis patients produced a protective antibody level, but only 43% maintained that level at one year post-vaccination.[29] Generally, patients on dialysis have lower antibody titers than those with chronic kidney disease who are not on dialysis.[30]

Table 3. Recommended vaccinations for ESRD patients

Vaccine	Dosage schedule	Amount	Route
Influenza	Yearly	0.50 mL	Intramuscular
Hepatitis B	0, 1, 6 months + booster if needed	40 µg	Intramuscular
Pneumococcal	Once + 1 booster at >5 years	0.50 mL	Intramuscular

Utilization of vaccines among the ESRD population

The utilization of vaccines by patients with ESRD is low, even though Medicare covers the entire cost of the vaccines. Reported Medicare coverage rates are expected to be lower than the true utilization rate in the population because people who are covered with private insurance or who pay out of pocket (~17% of ESRD patients[1]) are not captured in coverage rates. However, estimation of relative trends over time should remain unbiased. Examination of these trends shows an increase in uptake for influenza, pneumococcal and Hepatitis B vaccines over the last ten years.[1]

Influenza vaccination rates remain much lower than the Healthy People 2010 goal of 90% coverage, even after increased educational campaigns. In 2009, only 64.3% of ESRD patients were reported to be vaccinated for influenza. Hemodialysis patients had a slightly higher vaccination rate of 69.3%[1], which is a 42% increase compared to the epidemic year of 1998–1999 where the immunization rate among hemodialysis patients was 48.8%.[31]

Overall pneumococcal vaccination rates remain low. Among patients with ESRD, revaccination is recommended once after 5 years.[28] Because patients could have been vaccinated prior to initiating dialysis, it is difficult to measure the absolute vaccination rate. However, trends over time suggest that rates of vaccination remained stable at approximately 13% until 2001, when the rates began increasing dramatically.[3] Although rates began to plateau in 2005, by 2009 the vaccination rate had doubled to 26%.[1] Hemodialysis patients have a slightly higher vaccination rate of 30%.

Hepatitis B vaccine has historically been an underused vaccine in the ESRD population and continues to be underutilized even though ESRD patients are at high risk of contracting Hepatitis B. In 2009, only 22.1% of patients received one Hepatitis B vaccine, meaning the percentage of patients receiving the required three doses was even lower.[1] Although the usage rate is low, not all prevalent ESRD patients may currently need a vaccine as evidenced by antibody testing. The rate among new dialysis initiators is unknown and may be a better indicator of coverage. Regardless of the method of calculation, the rates are lower than they should be. The low usage rates of Hepatitis B vaccine are most likely due to the sub-optimal antibody response rates that are achieved with this vaccine in this population. Investigations are currently ongoing into using different routes of administration of vaccine[32] and various adjuvants that may increase response rates and duration of protection.[33]

C. **Measuring influenza vaccine effectiveness**

Methodological considerations in measuring influenza vaccine effectiveness

Vaccine effectiveness (VE) is generally measured by comparing outcomes in people who are vaccinated versus those who are not vaccinated. Effectiveness is expressed as a percentage and is calculated as: VE = 1 - a measure of relative risk (i.e., risk ratio, odds ratio, hazard ratio).[34] Past studies of influenza vaccine effectiveness have focused on seniors older than 65 years, as this population is at higher risk of death from influenza, and the true effect of the vaccine is uncertain and likely lower than in healthy adults due to immune senescence. Influenza VE studies must rely on observational study designs, as randomized

control trials would be unethical to implement. Because vaccination is a preventive service, those that are vaccinated may constitute a much different population then those that are unvaccinated, leading to substantial confounding. Thus, there is significant controversy on the role of biases in influenza VE studies.

The bias that occurs when users of a preventive medication are a different population than nonusers is called the healthy-user bias. This bias is apparent when the users also undertake other healthy behaviors. This confounds the drug-disease relationship, making the drug or vaccine under study look better than it actually is.[35] The healthy-user bias has been illustrated in studies of hormone replacement therapy and cardiovascular disease[36] and with statin therapy and several disease outcomes.[37,38] Conversely, it has been suggested in studies of influenza vaccine effectiveness in the elderly–that patients who are not vaccinated have a lower functional status.[39] Often it is difficult to identify what these "healthy behaviors" are and even more difficult to measure them in administrative claims data. However, to obtain unbiased effect estimates it is critical to adjust for this bias in the analysis.

There are several other factors to consider when estimating influenza VE. First is the seasonality of influenza. Although influenza generally peaks between December and March, the virus can begin circulating as early as November and can last until May. Studies use different methods to delineate the start and end of the flu season, as well as the start of the "pre-flu" season – the period after vaccine has been distributed but before the start of circulating flu. Health

maintenance organization (HMO)-based studies often obtain a clearer picture of these dates by using laboratory results from testing isolates in their own patient population. Studies using national data sources, including administrative claims databases, usually use CDC estimates of national or regional estimates of influenza circulation. Although this method may induce some exposure misclassification, several studies have compared national estimates to local estimates and found little difference in dates.[40,41] Regional CDC estimates of start and end dates generally do not vary substantially from national estimates.

The degree to which the vaccine matches the circulating strain is another factor to consider. Each year, influenza vaccine includes three influenza strains (A/H1N1, A/H3N2, B), which are chosen months in advance of the beginning of the season and are based on the strains circulating in the southern hemisphere. Sometimes the virus that predominates in a season undergoes significant drift, and thus the vaccine does not provide immunity to that strain. Only seasons with a well-matched vaccine are expected to be effective in preventing influenza-related outcomes.

Some influenza seasons are more severe than others (i.e. there are more deaths/hospitalizations due to pneumonia/influenza). It has been shown that seasons that are predominated by A/H3N2 are generally more severe than seasons with circulating A/H1N1 or B strains (this excludes the recent situation of influenza shift, where an H1N1 strain re-assorted to produce a completely new strain).[42] Vaccine effectiveness would be expected to be greater in more severe

seasons because it is thought that the vaccine has the most effect on preventing severe disease.

Finally, the specificity of the outcome studied will have an impact on the estimate of VE. Studies vary in the outcome that is used: outcomes include all-cause mortality, influenza/pneumonia (I/P)-specific mortality, all-cause hospitalization, I/P hospitalization, cardiac hospitalization, and influenza-like illness. One would expect that as the specificity of the outcome decreases, the vaccine effectiveness would also decrease (for example, VE for all-cause mortality should be expected to be lower than VE for I/P hospitalization),[43] however this is not the case with traditional observational methods, due to suspected selection bias.

Traditional methods to measure influenza vaccine effectiveness produce biased results

Many studies have reported large vaccine effectiveness estimates for clinical health outcomes – some studies report up to a 50% reduction in all-cause mortality.[44-52] These estimates seem to be effected by substantial bias, as only ~5% of all wintertime, senior deaths are attributed to influenza.[53] Furthermore, traditional studies generally report a larger effect for all-cause mortality than more specific outcomes such as I/P hospitalization, which is difficult to logically interpret, as one would expect smaller estimates for less specific outcomes. Nichol et al. used propensity score methods with logistic regression models to adjust for several suspected confounders, but reported a 48% VE for all-cause death, and a 27% VE for I/P hospitalization.[54] Hak et al. used simple logistic regression, adjusting for comorbidities and reported a 50% VE for all-cause

death, and 48% for hospitalizations.[55] Nordin et al. used similar methods and reported a reduction in all-cause death of between 35–61% and a reduction in hospitalizations of 18–24% depending on the season.[49]

Methodological improvements in measuring influenza vaccine effectiveness

Using the pre-influenza period as a negative control

It is expected that VE during the "pre-influenza" period would be nearly zero, as influenza is rarely circulating (i.e., only sporadic cases may be seen), and thus the vaccine should not have any effect on health outcomes. Therefore, estimates during the pre-influenza period that are greater than zero, must be biased in some way. Several studies have used the pre-influenza period as a negative control, by implementing a model-building strategy using this time period to determine which variables adequately control the selection bias. These variables are subsequently included in their final VE model, which is calculated for the period during the influenza season.[41,56,57]

Including variables to account for confounding by frailty and the healthy-user bias

Jackson et al. have ascertained that functional status is a significant confounder in the relationship between influenza vaccine and all-cause mortality in seniors.[39] The ability of elderly people to travel to a place to receive a vaccine may be severely diminished if the person has limited mobility. Functional status is generally assessed using medical record review and may include variables such as presence of dementia, ability to walk without assistance (cane, walker, etc.), requiring assistance to bathe, and living in a non-home setting such as an assisted living facility. Patients with limited functional status were between 40–

50% less likely to receive influenza vaccine and 2 to 5 times more likely to die than those with adequate functional status.[39] Another cohort study using the General Practice Research Database used the number of repeat prescriptions in the preceding 12 months as a proxy for health status, which resulted in similar estimates of VE for respiratory disease hospitalization and death.[58] This study, however, did not compare the estimates to the pre-influenza period to determine the amount of residual bias.

It is uncertain whether functional status or frailty may act as a confounder in the ESRD population. Because ESRD patients come into contact with health care facilities 2 to 3 times per week, the issue of functionally being able to go out to receive the vaccine may not an issue. However, patients who are very near death (i.e., severely functionally limited) may be less likely to be vaccinated. Thus, the association between functional status and vaccination may be different in the ESRD population as compared with the general, elderly population.

Utilizing specific influenza seasons to determine effects of bias

Influenza seasons have varying levels of vaccine match. Using this external information can also function to provide a negative control for determining bias in estimating VE. To investigate the effects of bias on VE estimates, using a season with poor vaccine match to the circulating strain, should result in no effect, or at best a very small effect. Thus, if the estimate of VE is large, it is most likely biased in some way. The 1997–1998 and 2003–2004 seasons had very low levels of vaccine match. Therefore, utilizing these seasons would be best suited for investigating bias. Similarly, severity of the influenza

season is another issue to consider when pooling seasons to measure the effect of bias. One would expect more severe seasons to have higher levels of VE (i.e., if there is more virus circulating or a more virulent virus, the vaccine will have a higher likelihood of preventing serious illness). When trying to estimate the upper bound of VE, one should use severe seasons with high vaccine match.

Summary of vaccine effectiveness estimates using improved methods

Several studies have implemented the previously mentioned methodological improvements in elderly populations. Table 4 compares estimates of VE using traditional methods with studies that incorporated improvements to study design. Studies that use traditional adjustment methods result in larger estimates of VE than methods used to control selection bias. Thus, additional methods are needed to adequately control the healthy-user bias that is inherent in influenza VE studies.

Table 4. Comparison of VE estimates for traditional vs. improved analyses

	Traditional			Improved		
Population	**Methods Used**	**VE: All-cause death (95% CI)**	**VE: I/P hosp. (95% CI)**	**Methods Used**	**VE: All-cause death (95% CI)**	**VE: I/P hosp. (95% CI)**
Elderly >64 years	Cox model/ propensity score[54]	48% (45-50%)	27% (23-32%)	Conditional logistic/ functional status adjusted[39]	29% (-6, 53%)	
				Poisson/ adjusted for prescriptions[58]	21% (19-23%)	21% (17-26%)
	Adjusted logistic regression[55]	50% (23-68%)	48% (7-71%)	Case-centered logistic regression[59]	4.6% (1-8%)	8.5% (3-13%)
				Conditional logistic/Pre-flu period calibrated[41]		8%* (-10-23%)
	Matched, conditional logistic[60]	35-39%	27-30%			
	Meta-analysis[61]	50% (45-56%)	33% (19-47%)			
Elderly >64 years with chronic lung disease	Poisson/time-varying exposure[48]	70% (57-79%)	52% (18-72%)			

*VE estimate for community-acquired pneumonia

Using the ESRD population to measure vaccine effectiveness

There are many advantages to investigating methods for assessing influenza VE among ESRD patients. First, all patients with ESRD are eligible for Medicare and are captured in the USRDS. Although some patients do not have Medicare as a primary payer (and thus more detailed information is not captured), this proportion is small. Therefore, using the USRDS population represents the majority of the ESRD population. Second, patients with ESRD

come into contact with health care facilities often, up to 2 to 3 times per week. Thus, there are ample opportunities for vaccination. Although patients could receive influenza vaccine from outside facilities (and thus not be reported through Medicare), we think that this situation is most likely infrequent. Third, claims data are reported monthly, thus we have ample time points to assess vaccination status, hospitalizations, and other variables that may be useful in assessing proximity to death/functional status such as administration of preventive medications. Finally, there are many parallels between patients with ESRD and the general elderly population. Both have impaired immune systems and the true effectiveness of influenza vaccine is controversial in both populations. Methods developed using data on ESRD patients may be transferable to investigation of the general elderly population.

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III. STATEMENT OF SPECIFIC AIMS

Specific Aim One

Aim: Assessing influenza vaccine effectiveness among patients on hemodialysis by comparing vaccinated patients in a “high-match” year to vaccinated patients in a “low-match” year.

Hypothesis: Patients undergoing hemodialysis who receive the influenza vaccine in a high-match year will have a lower hazard of influenza-like illness and hospitalization due to influenza/pneumonia and a lower hazard of all-cause death than patients who receive the influenza vaccine in a low–match year, in seasons with comparable severity.

Rationale: We expect that there will be large differences in health status between patients who are vaccinated and those who are not. Therefore, comparing vaccinated with unvaccinated people may lead to a biased estimate of vaccine effectiveness. Thus, comparing only those who are vaccinated in different seasons with similar severity should reduce the healthy-user selection bias and allow for a better estimate of vaccine effectiveness.

Specific Aim Two

Aim: Assessing the relation of time-fixed and time-varying predictors, such as hospitalization and skilled nursing care, with the receipt of influenza vaccine to characterize the healthy-user bias in a population on hemodialysis.

Hypothesis: Patients undergoing hemodialysis and who have been recently hospitalized or received skilled nursing care are less likely to be vaccinated. Vaccinated patients are more likely to be healthier, younger, more adherent to their dialysis schedule, and more likely to take other preventive medications than those who are not vaccinated.

Rationale: Patients on hemodialysis who are hospitalized are likely to be sicker than those who have not been hospitalized, and physicians may be less likely to vaccinate if a patient has serious health problems. In the elderly population, it has been shown that those who are healthier are more likely to be vaccinated. It is not known whether this association will also be observed in the population undergoing hemodialysis. Because these patients have frequent contact (2–3 times per week) with health care facilities, it would be expected that they would have higher vaccination rates than the general elderly population. Knowledge of current vaccination patterns can also inform the development of healthcare quality improvement interventions designed to increase the utilization of preventive healthcare services.

Specific Aim Three

Aim: Assessing influenza vaccine effectiveness on mortality among patients on hemodialysis by developing a marginal-structural model to account for time-varying confounding by health status.

Hypothesis: It is anticipated that unadjusted analyses will attribute an exaggerated effect of vaccination on mortality risk. When important time-varying

measures of health status such as hospitalizations are adjusted for, we hypothesize that attenuated estimates of vaccine effectiveness will result.

Rationale: Vaccination status is a time-varying exposure, and any variable that vaccination affects and is also a confounder of subsequent vaccination and death cannot be modeled using traditional regression. This is because the time-varying confounders – such as hospitalization and skilled nursing care – are also intermediate variables, and adjustment for these variables using regression will produce a biased estimate. Marginal structural models use inverse-probability-of-treatment weights to create a pseudo-population where vaccination and death are unconfounded by time- varying confounders. Under certain assumptions, these methods can yield less biased estimates of vaccine effectiveness.

IV. METHODS

A. Subject Identification

Study Population

This study utilizes data on hemodialysis patients from the USRDS. The USRDS is a population-based, national system that collects information on all patients with ESRD in the United States. All persons that are diagnosed with ESRD and started on dialysis therapy are entered into the USRDS. The diagnosing physician is required to complete the End Stage Renal Disease Medical Evidence Report (CMS-2728), regardless of the insurance status of the patient. Basic information such as demographics, cause of kidney failure, and categories of comorbidity are included on this form. Although all patients with ESRD are eligible for Medicare coverage regardless of their age, some patients remain on private or HMO insurance or have a combination of insurance coverage. More detailed information such as physician services, hospitalizations, and cause of death is captured through administrative claims submitted through Medicare. Non-hospitalization-related claims, including routine dialysis care and medication use (including vaccinations) are generally submitted on a monthly basis. Vaccinations are identified using *Current Procedural Terminology* (CPT) and Health Care Financing Administration Common Procedural Coding System (HCPCS) codes (see the following). This information

is collected only for those patients who are enrolled in Medicare as a primary payer, and those that are not enrolled in Medicare can be considered as missing data. In 2009, approximately 83% of ESRD patients were covered by Medicare as a primary payer.[1] This study will be limited to Medicare patients who have been receiving dialysis for at least three months. This is the amount of time that is generally required to process the Medicare eligibility and enrollment forms.

Collection of data

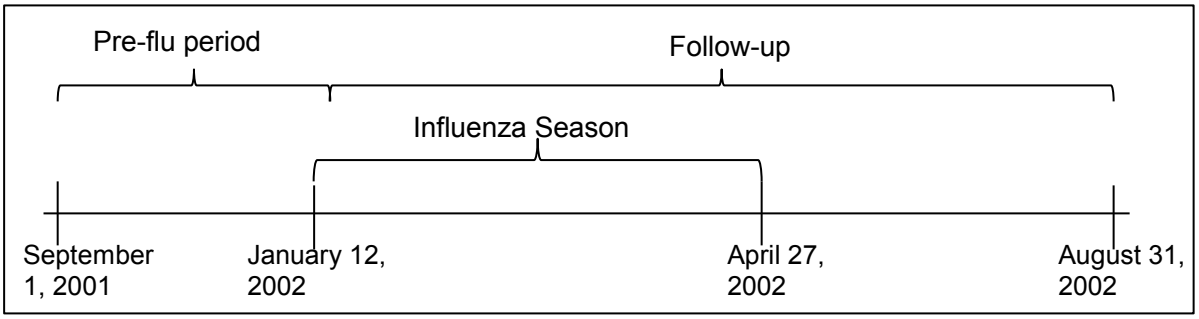
The USRDS collects data primarily from the Centers for Medicare and Medicaid Services (CMS) Renal Beneficiary and Utilization System, which is supplemented from the Renal Networks' Standard Information Management System.[1] Claims data are sent from each ESRD network to CMS on a monthly basis. Almost all patients diagnosed with ESRD are captured in the system, as all providers are required to submit a Medical Evidence Report, regardless of insurance status. Each patient is assigned a unique patient identification number upon receipt of the form. The first service date is generally considered to be complete for all patients, while other data fields (such as comorbidities) on the form may not be of similar quality.

Study Setting and Design

This study incorporates a cohort study design. Eligible patients were enrolled prior to the start of influenza season each year, and the outcome – ILI/hospitalization/mortality status for Aim 1, vaccination for Aim 2 and death for Aim 3 – was subsequently assessed. For Study Aims 1 and 3, each influenza season was divided into specific time periods: "a pre-influenza period" defined as

the time between the start of vaccine distribution (assumed to be September 1) and the start of the influenza season. The “influenza period” was defined using Centers for Disease Control and Prevention’s (CDC) national laboratory data on positive influenza isolates. The start date was defined as the midpoint of the first week with >10% of isolates submitted positive for influenza. We conducted a sensitivity analysis where the influenza season started when >5% of isolates were positive. The influenza season ends at distinct points, also characterized by CDC surveillance. However, we continued to follow patients for outcomes through August 31st of the following year. Figure 1 displays how the influenza season was broken into periods for analysis.

Figure 1. 2001-2002 influenza season periods



Identification of cohorts

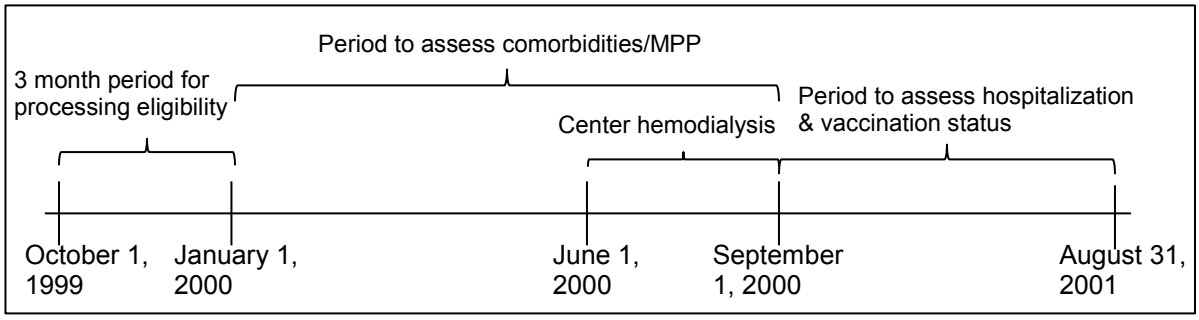
For each influenza season, a cohort of ESRD patients was identified. All adult patients (>17 years at first date of dialysis) on continuous hemodialysis with Medicare as their primary payer who initiated therapy prior to October 1 of the previous year and remained alive until September 1 of the current year (i.e., start of vaccine distribution) were eligible for that yearly cohort. Exposure was assessed starting on September 1 of each year and follow-up ended on the earliest date of outcome, death, transplant, or end of study (December 31 for Aim

2, August 31 for Aim 1 and 3). Claims from the USRDS that occurred between 1997 to 2005 were utilized. There were approximately 900,000 patient years available (~100,000 patient years per year). Figure 2 depicts the time periods used to construct the 2000–2001 influenza season annual cohort.

Table 5. Study eligibility requirements

Variable	Requirement
Age	18 years and older
Insurance status	Medicare as primary payer
Dialysis status	Continuous hemodialysis
Date of ESRD	Prior to October 1

Figure 2. Annual cohort for the 2000–2001 influenza season defined for Study Aim 3



B. **Exposure and Outcome Definitions**

Hospitalization and skilled nursing care exposures

Study Aim 2 investigates hospitalization due to any cause and skilled nursing care as the exposures of interest. Inpatient hospitalization and skilled nursing facility admission and discharge dates were assessed using the Part A – Hospitalization Medicare claims. Both variables were coded as a count of the number of hospital or skilled nursing days the patient had in the prior 30 days.

The data were structured into a person-week format, thus these variables were updated each week.

Vaccination (Aims 1 & 3 = exposure, Aim 2 = outcome)

Vaccinations were identified by searching billing codes from Medicare Part B (physician) and Part A (hospital outpatient) claims files. Vaccinations are coded using CPT or HCPCS codes. We also included the *International Classification of Diseases, 9th Revision, Clinical Modification* (*ICD-9-CM*) procedure code, so we could capture vaccinations administered in the hospital. Table 6 displays the *CPT*, HCPCS, and *ICD-9-CM* procedure codes that were searched to identify any vaccinations.

Table 6. CPT and HCPCS vaccination codes[2]

Vaccination	CPT	HCPCS	ICD-9 Procedure
Influenza	90724	G0008	99.52
	90656	G8482	
	90658		
	90659		
	90660		

Influenza-like illness

Inpatient and outpatient claims were examined and *ICD-9-CM* codes were searched for codes consistent with influenza-like illness (ILI), as in Lindsay, et al. (Table 7).[3]

Table 7. *ICD-9-CM* codes used to define influenza-like illness[3]

Description	*ICD-9-CM* code
Influenza	487, 487.0, 487.1, 487.8
Upper respiratory infections	465
Acute laryngitis and tracheitis	464
Acute bronchitis and bronchiolitis	466
Bronchitis not specified	490
Pulmonary collapse	518.0
Acute respiratory failure	518.81
Unspecified viral pneumonia	480.9
Bronchopneumonia organism unspecified	485
Pneumonia organism unspecified	486
Secondary bacterial pneumonias: *Klebsiella pneumonia, Haemophilus influenza, Streptococcus, Staphylococcus*	482.0, 482.2, 482.3, 482.4

Influenza/pneumonia hospitalization outcome

Discharge diagnoses for all hospitalizations were examined and *ICD-9-CM* codes were searched for influenza and pneumonia diagnoses. Codes 480.xx – 487.xx were used for this outcome. Pneumonia diagnoses were included because pneumonia is often a secondary complication to influenza infections. In general, diagnosis codes for pneumonia in administrative claims databases have modest sensitivity, but good specificity.[4,5] It has been shown that using outcome codes with high specificity will not bias the effect estimates of relative risk even when sensitivity is low.[6]

Death

Deaths are reported using CMS form 2746 – ESRD Death Notification. CMS requires all dialysis providers to submit this form within 30 days of a

patient's death. Reporting of deaths is nearly complete – CMS estimates 99% of deaths are captured using this form.[7] Data collected on this form include the date of death and the cause of death. Because cause of death may be difficult to ascertain, especially for deaths occurring in non-hospital settings, we used death from any cause as the outcome of interest in this analysis.

C. **Covariate Definitions**

All confounders were identified using the existing evidence base – including the investigative team's knowledge and the published literature. The model form of all covariates is given in Table 8. For all categorical variables, the reference category was coded with a "0." For the continuous variable age, more flexible functional forms (quadratic, restricted cubic spline) were investigated; however the simple linear form was deemed to be an adequate fit.

The Centers for Medicare and Medicaid Services form 2827, the Medical Evidence Form, was used to ascertain age, race, gender, first service date with ESRD, and cause of kidney failure. The eight month window from January 1 to August 31 was searched for use of oxygen and the following comorbidities in both Part A and Part B claims as identified in Liu et al.[8]–atherosclerotic heart disease, congestive heart failure, cerebrovascular accident/transient ischemic attack, peripheral vascular disease, other cardiac, chronic obstructive pulmonary disease, gastrointestinal bleeding, liver disease, dysrhythmia, cancer, and diabetes. Comorbidities were modeled as individual dichotomous variables in the final models. Adherence to dialysis was calculated using the sum of the number of dialysis sessions over the eight month baseline period: patients were

considered adherent if they had 95 sessions or more (assuming 12 dialysis sessions per month and allowing one less session due to the variable number of days per month). Patients with no dialysis sessions over the eight–month period were dropped from the analysis. We also included the total number of hospital days each patient accumulated over the eight–month period. Use of mobility aids were ascertained by searching Part A and Part B claims for HCPCS equipment codes for wheelchairs, walkers, canes, and assisted bathroom equipment during the baseline period (Table 9).

Table 8. Model form for all covariates

Variable	Coding
Age at September 1	Continuous, linear term
Race	0 = White 1 = African American 2 = Other
Sex	0 = Female 1 = Male
Cause of ESRD	0 = Diabetes 1 = Hypertension 2 = Glomerulonephritis 3 = Cystic Kidney 4 = Other
Dialysis vintage (years since dialysis initiation)	0 = 0 years 1 = 1–2 years 2 = 3–4 years 3 = 5–9 years 4 = 10+ years
Comorbidities	0 = Comorbidity absent 1 = Comorbidity present
Adherence to dialysis therapy	0 = Non-adherent 1 = Adherent
Use of mobility aids	0 = None 1= 1 mobility aid 2 = 2+ mobility aids
ESRD Network #1–18	Reference cell coding with Network 18 as the referent
Baseline hospital days	Continuous, linear term
Oxygen use	0 = No 1 = Yes

Table 9. Codes used to define the use of mobility aids & oxygen use

Mobility aid description	HCPCS code
Use of wheelchair	E0950 – E1228, E1230, E1240 – E1298
Use of walker/cane	E0130, E0135, E0140, E0141, E0143, E0144, E0147, E0148, E0149, E0105, E0100
Use of modified bathroom equipment	E0240 – E0248
Oxygen use	E0430-E0435, E0439-E0444

D. **Statistical Model**

The hazard of each outcome among exposed patients versus unexposed patients was modeled using the Cox proportional hazards model[9] with a time–varying exposure. The Cox model is specified as:

$$h(t|\boldsymbol{Z}) = h_0(t)\exp(\sum_{k=1}^{p}\beta_k Z_k),$$

where $h(t|\boldsymbol{Z})$ is the hazard rate at time *t* for an individual with covariate pattern Z, and $h_0(t)$ is the baseline hazard rate. To calculate the hazard ratio (HR) comparing vaccinated versus non-vaccinated patients for example, the ratio of the hazard rates in each group is computed as:

$$\frac{h(t|\boldsymbol{Z}) = h_0(t)\exp(\sum_{k=1}^{p}\beta_k Z_k)}{h(t|\boldsymbol{Z}^*) = h_0(t)\exp(\sum_{k=1}^{p}\beta_k Z_k^*)}$$

where Z_k includes all vaccinated and Z_k^* includes those that were unvaccinated. Patients were considered to be censored upon death (for non-death outcomes), transplant, loss to follow-up, or end of study. For some analyses, patients could be included in multiple cohorts and thus have multiple outcomes; thus, a robust variance estimator was inspected that would account for the non-independence of the data. For all Cox models, Efron's method for tied event times was used.[10]

E. **Methods pertaining to Specific Aim One**

Exposure Measure

The exposure measure was the degree that the vaccine matched the circulating strain during that influenza season. We chose to analyze specific years based on the characteristics of each influenza season – years with similar influenza severity and close temporally to the mismatched season. In addition, years before it was common to pay out of pocket at grocery stores or pharmacies were used to limit exposure misclassification. A "high -match" year was considered exposed. This means that the majority of isolates tested during the season were strains that were included in the vaccine. The following seasons were considered "high-match" years that had similar levels of severity (i.e., H3N2 strain predominated): 1998/99, 1999/00, and 2001/02. We excluded the 2000 season to limit differences between seasons due to influenza severity; the predominate strain in the community in 2000 was a less severe strain (A/H1N1).[11] A "low-match" year, 1997/98, was considered as unexposed. Most of the isolates in this season did not match the vaccine, and thus vaccine effectiveness would be anticipated to be low. It has been documented that the 1997–98 influenza vaccine (Wuhan variant) did not match the circulating strain (Sydney variant) [12] and outbreak investigations suggested that the vaccine provided limited protection.[13] A randomized controlled trial confirmed that the inactivated vaccine did not prevent clinical outcomes during the 1997–98 season among healthy, working adults younger than 65 years – vaccinated patients had more influenza-like illnesses and upper respiratory tract infections than placebo

patients.[14] Table 10 shows the characteristics of each season that was used in this analysis.

Table 10. Description of selected influenza seasons[12,15-18]

Season	% I/P hospitalization (Proxy for severity)	% Vaccine Match
1997–1998	9.8	19 (mismatch)
1998–1999	9.7	90
1999–2000	11.2	97
2001–2002	9.1	100

Statistical Model

A Cox proportional hazards model was developed that utilized interactions between vaccination and year. Influenza vaccination was coded as a time-varying variable. The model was specified as:

$$\lambda(t) = \exp(\beta_1(\text{vaccinated}) + \beta_2(\text{year98}) + \beta_3(\text{year99}) + \beta_4(\text{year01}) + \beta_5(\text{vaccinated} * \text{year98}) + \beta_6(\text{vaccinated} * \text{year99}) + \beta_7(\text{vaccinated} * \text{year01}) + \boldsymbol{\beta}_p' \boldsymbol{L})$$

where $\boldsymbol{\beta}_p'$ was the transpose of the vector of log hazard ratios for each of the remaining covariates $\boldsymbol{L}$. For some analyses, patients could be included in multiple cohorts and thus have multiple outcomes, thus a robust variance estimator was inspected that would account for the non-independence of the data. The variance did not change when using the robust variance; thus, the standard estimates were reported.

Additional Analyses

Several sensitivity analyses were conducted for Aim 1. First, the model was stratified by center. This was done because it was hypothesized that individual dialysis centers may have similar protocols for influenza vaccination, including the amount of encouragement given to patients to get vaccinated. Second, we ended follow-up at the approximate end of flu season. The survival

curves crossed at approximately the end of each flu season; therefore, the analysis was limited to the time prior to the crossing hazards. Because of the way the model was specified (i.e., includes all years in one model), we chose the year with the latest end of influenza season to be the end of follow-up for this sensitivity analysis.

In addition, the model was estimated stratified by age, vintage, and cause of ESRD. We hypothesized that the level of immune function and thus the vaccine effectiveness could vary within levels of these variables. We thought that immune function, and perhaps vaccine effectiveness would decrease with increasing age and with increasing time on dialysis. The cause of ESRD might also affect how well a person responds to the vaccine.

F. Methods pertaining to Specific Aim Two

Exposure Measure

The exposure measures were time-varying hospitalization and skilled nursing care status as defined in Section B. Only hospitalizations or skilled nursing care initiated prior to or on the same day as vaccination were counted. Patients could have multiple hospitalizations or admissions to skilled nursing facilities. Pooled logistic model coding was used to create the time-varying exposure.

Statistical Model

Two separate models were developed to assess hospitalization and skilled nursing care. Separate Cox proportional hazards models with time-varying exposure coding were developed to estimate hazard ratios of vaccination for

each exposure. Because the data was structured into a person-week format, the exposure variables were updated each week. Follow-up began on September 1 of each year and continued until the patient was vaccinated, died, was lost to follow-up or was administratively censored on December 31 of each year. For both exposures, we fit models that categorized hospitalization and skilled nursing days into temporary (1 day), short (2–3 days), medium (4–14 days), medium-long (15–25 days), and long stays (26–30 days), with zero days as the referent. This model was specified as:

$$\lambda(t) = \exp\big(\beta_1(\text{hosp1}) + \beta_2(\text{hosp2\_3}) + \beta_3(\text{hosp4\_14}) + \beta_4(\text{hosp15\_25}) + \beta_5(\text{hosp26\_30}) + \boldsymbol{\beta}_p'\boldsymbol{L}\big),$$

where $\boldsymbol{\beta}_p'$ was the transpose of the vector of log HRs for each of the remaining covariates $\boldsymbol{L}$. The model for skilled nursing care was specified in the same manner.

G. **Methods pertaining to Specific Aim Three**

Cox proportional hazards marginal structural model

This marginal structural model models potential outcomes of death as if vaccination were randomized within the population.[19] For this analysis, the origin was September 1 for each year and patients were followed until August 31 of the subsequent year. The analysis was also limited to the pre-influenza period to assess bias. The marginal structural model was estimated using inverse probability of treatment weights (IPTW). The IPTW create a "pseudo-population" where each subject is weighted by the inverse of the conditional probability of receiving the exposure that they actually did receive.[20] Thus, subjects with

infrequent covariate combinations are up-weighted and subjects with covariate patterns that are frequently represented in treatment assignment are down-weighted. Both time-fixed and time-varying confounders should be distributed equally across vaccination groups in the pseudo-population. Vaccine effectiveness is then estimated by comparing vaccinated to unvaccinated patients within this unconfounded pseudo-population.

The Cox proportional hazard marginal structural model is specified as:

$$\lambda_{T^{\bar{x}}}(t) = \lambda_0(t) \times \exp(\alpha_1 X_{it} + \boldsymbol{\alpha}_p' \boldsymbol{L}_{i0})$$

where $\lambda_{T^{\bar{x}}}(t)$ is the potential hazard of death at time *t* under treatment history $\bar{x}$, $\lambda_0(t)$ is the unspecified baseline hazard of death in the unvaccinated, X_{it} is a time-varying indicator variable for vaccination status prior to day *t* for subject *i*, α_1 is the log HR comparing vaccinated with unvaccinated, $\boldsymbol{L}_{i0}$ is a vector of measured baseline covariates, and $\boldsymbol{\alpha}_p'$ is the transpose of the vector of log HRs for each of the baseline covariates. The model specified earlier will be estimated using IPTW and is specified as:

$$\lambda_{T^{\bar{X}}}^{SW_{it}}(t) = \lambda_0(t) \times \exp(\beta_1 X_{it} + \boldsymbol{\beta}_p' \boldsymbol{L}_{i0})$$

where the hazard of death is weighted by the observed treatment $\bar{X}$. Here $\alpha_1 = \beta_1$ under the assumptions of consistency, positivity, correctly specifying the weight models, and no unmeasured confounding.[21]

To estimate the IPTW we fit a logistic model that treats each person-week as an observation (i.e., time-varying weights were estimated for each week of follow-up, from September 1 through August 31 of the following year). The weights were calculated from the predicted values outputted from the logistic

procedure using prior time–varying confounders, baseline confounders, and prior time-varying treatment as predictor variables. Patients were considered to be censored upon loss to follow-up or end of study (August 31 of following year).

The stabilized inverse probability of treatment weight is given as:

$$SW_{it}^{X} = \prod_{k=0}^{t} \frac{\Pr[X_{ik}|\bar{X}_{ik-1}, V_{i0}, \bar{C}_{ik-1} = 0]}{\Pr[X_{ik}|\bar{X}_{ik-1}, \bar{L}_{ik-1}, \bar{C}_{ik-1} = 0]}$$

Here the numerator is the probability of person *i* being vaccinated given their past exposure history ($\bar{X}_{ik-1}$), their baseline covariates (V_{i0}), and that they weren't censored in the preceding week ($\bar{C}_{ik-1} = 0$). This weight is stabilized because we are including the baseline covariates in the numerator. The denominator is the probability of person *i* being vaccinated given their past exposure history ($\bar{X}_{ik-1}$), their time–varying covariates (which include their baseline covariates) ($\bar{L}_{ik-1}$), and that they weren't censored in the preceding week ($\bar{C}_{ik-1} = 0$).

Exploring model assumptions

For marginal structural models to correctly estimate the causal effect of the exposure on the outcome, several assumptions must be made including: consistency, positivity, correctly specifying the weight models, and no unmeasured confounding. These assumptions were explored to determine if they were met in this analysis. First, the positivity assumption was checked for important confounders. For all levels of confounders there should be some subjects who are exposed. For example, there should be patients who were vaccinated with a range of hospital days in the past 30 days. Because very few patients were vaccinated in the hospital, recent hospitalization and skilled nursing

care were modeled both as functions of a linear term, as well as in quintiles to ameliorate any positivity issues. Next, the assumption of no unmeasured confounding was explored by specifying different functional forms for continuous variables and including a variety of confounders deemed important by subject-matter experts. Finally, the assumption of correctly specifying the weight model was explored by examining the distribution of the weights (i.e., mean, standard deviation, minimum and maximum). The stabilized weights should have a mean of one. Weights with extreme values or means that are not close to one, could indicate a miss-specification of the weight model or non-positivity.[21] Patients who received extreme weights (usually weights greater than 20 are considered extreme) are up-weighted heavily in the pseudo-population. These are often people who represent the extremes of the population and should not always be so influential to the final average estimate in the population. Therefore, weights with extreme values can be trimmed. However, in our analysis, we did not find extreme weights, therefore trimming was not necessary.

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V. RESULTS: "EVALUATING INFLUENZA VACCINE EFFECTIVENESS AMONG PATIENTS ON HEMODIALYSIS USING A NATURAL EXPERIMENT"

A. Introduction

Influenza causes substantial morbidity and mortality in the general population with approximately 39,000 people dying each year.[1] Patients with ESRD may be at higher risk of illness and death from influenza relative to healthy adults. For more than 40 years, trivalent inactivated influenza vaccine has been recommended by the Advisory Committee on Immunization Practices for patients with ESRD.[2] Seasonal influenza vaccination has become routine practice at most dialysis clinics during the past two decades. Although patients on hemodialysis have lower response rates to influenza vaccine compared with healthy adults, immunogenicity studies show that 50-93% of patients undergoing dialysis develop antibody titers after vaccination.[3,4] However, it is currently unclear how much morbidity and mortality is prevented by the influenza vaccine in patients with ESRD.[5] To date, one study among patients on hemodialysis has estimated a12% to 14% VE for influenza/pneumonia hospitalizations and 25% for all-cause mortality.[6] Recent studies in the elderly population who are not on dialysis have suggested that large VE effects (up to 50% reduction of all-cause mortality in some studies [7-9]) obtained from standard epidemiologic studies may be the result

of to confounding by unmeasured prognostic variables, and the true effect may be small to negligible.[10-14]

One potential way to avoid confounding by patient-level differences is to exploit the natural experiment that is caused by strong year-to-year variation in the match of the vaccine to the circulating strain. The influenza virus that predominates in a season can undergo antigenic drift after the vaccine strain has been chosen, resulting in a vaccine that provides reduced immunity. In seasons with a well-matched vaccine, vaccination is expected to be effective in preventing influenza related outcomes, whereas in mismatched seasons, vaccination is expected to have a minimal effect. It has been documented that the 1997–98 influenza vaccine strain (A/Wuhan/359/95) did not match the circulating strain (A/Sydney/5/97) [15] and outbreak investigations suggested that the vaccine provided limited protection.[16] A randomized controlled trial confirmed that the vaccine did not prevent clinically relevant outcomes during this season among healthy adults younger than 65 years: vaccinated patients had more influenza-like illnesses (ILI) and upper respiratory tract infections than patients receiving placebo.[17] In three of the following four years, the same strain of virus circulated in the community, and the vaccine was well matched.[18-20]

We evaluated the difference in VE between years in which the vaccine was well matched and the 1997–98 “placebo” year, in which the vaccine was poorly matched and was shown to have provided little benefit. By studying this natural experiment, we sought to reduce confounding bias due to frailty and unmeasured health behaviors to obtain a more accurate measure of VE.

B. **Methods**

Study Population

We used Medicare claims from the United States Renal Data System, a population-based national system that collects information on all patients with ESRD in the United States. Claims include information on physician services, codes from the International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM) assigned to hospitalizations and outpatient care; and information on dialysis care, medication, and immunization use. This information is captured for all patients with Medicare as a primary payer (no health maintenance organization insurance as a primary payer, or Medicare as a secondary payer).

Our cohorts consisted of all adult, patients with ESRD who had Medicare as a primary payer and underwent continuous hemodialysis use. Each yearly cohort consisted of patients who had initiated dialysis before October 1 of the preceding year. An eight month window from January 1 – August 31 of each year was used to identify insurance and comorbidities for the patients in that cohort. A three-month window from June 1 through August 31 was used to identify continuous hemodialysis status. For example, the cohort identified for the 1997-98 season would have initiated dialysis before October 1, 1996 and would have been receiving continuous hemodialysis from June 1 through August 31, 1997 and had Medicare as a primary payer from January 1 – August 31, 1997. Vaccination and outcome status were assessed beginning on September 1 of each year. Cohort members were followed each year until they experienced one

of the three study outcomes, death (for non-mortality outcomes), transplant, loss to follow–up, or administrative censoring on August 31 of the following year (e.g. August 31, 1998 for the 1997 influenza season).

Influenza Seasons

We chose to analyze specific years based on the characteristics of each influenza season: years with similar influenza severity and in temporal proximity to the mismatched season. We used years before paying out of pocket at grocery stores or pharmacies became common to limit exposure misclassification. Cohorts were created for the following influenza seasons: 1997, 1998, 1999, and 2001. Seasons were defined by the year in which vaccination began for that influenza season (e.g., the 1997–1998 season was defined as 1997). These four seasons were used because of their similar severity and strain of influenza, but various levels of vaccine match (i.e., how well the vaccine matched the strain circulating in the community).[15,18-20] We excluded the 2000 season to limit differences between seasons due to influenza severity; the predominate strain in the community in 2000 was a less severe strain (A/H1N1).[21] We estimated the start of each influenza season by using national influenza surveillance data from the CDC. We defined the start of the season as the midpoint of the first week during which more than 10% of the isolates were positive for influenza. A sensitivity analysis examined the effect of a less restrictive definition, with the start of the season defined as the week with 5% of isolates positive for influenza.

Vaccination Status

Medicare Part A hospital/outpatient files and Part B physician/supplier files were searched for *Current Procedural Terminology* codes 90724, 90656, and 90658-60, and Health Care Financing Administration Common Procedure Coding System codes G0008 and G8482. Because our study population is often hospitalized, we also searched for *ICD-9-CM* procedure code 99.52.

Outcomes

We examined the following three outcomes: all-cause mortality, influenza/pneumonia hospitalization and ILI. Mortality was identified by the Centers for Medicare and Medicaid Services form 2746, the ESRD Death Notification Form. We searched the principal discharge diagnoses in the Medicare Part A inpatient hospitalization files for the first instance of *ICD-9-CM* codes 480.xx – 487.xx to identify influenza/pneumonia hospitalizations. Inpatient and outpatient codes were searched to identify the first instance of ILI as classified by Lindsay, et al[22] (Table 7). In a sensitivity analysis, we limited ILI to more specific codes by removing *ICD-9-CM* codes 465, 466, and 490.

Covariates

All confounders were identified using the existing evidence base – including the investigative team's knowledge and the published literature. We used the Centers for Medicare and Medicaid Services form 2827, the Medical Evidence Form, to ascertain age, race, sex, first service date with ESRD, and cause of kidney failure. Parts A and B claims were searched during the eight–month window from January 1 to August 31 for oxygen use and the following comorbidities as identified by Liu et al.[23]: atherosclerotic heart disease,

congestive heart failure, cerebrovascular accident/transient ischemic attack, peripheral vascular disease, other cardiac disease, chronic obstructive pulmonary disease, gastrointestinal tract bleeding, liver disease, dysrhythmia, cancer, and diabetes mellitus (Appendix 1). Comorbidities were modeled as dichotomous variables in the final models. Adherence to dialysis was calculated by summing the number of dialysis sessions during the eight–month baseline period: patients were considered adherent if they had 95 sessions or more. Patients with no dialysis sessions during the baseline period were dropped from the analysis. We also included the number of hospital days during the baseline period. Use of mobility aids was ascertained by searching Parts A and B claims for Health Care Financing Administration Common Procedure Coding System equipment codes for wheelchairs, walkers, canes, and bathroom assistance equipment during the baseline period (Table 9).

Statistical Analysis

We used Cox proportional hazards models to estimate hazard ratios (HRs) comparing vaccinated with unvaccinated cohorts within each year.[24] Vaccination was modeled as a time-varying covariate, with all cohort members entering the analysis on September 1 as unvaccinated. Once vaccinated, patients remained in the vaccinated category until the end of that influenza year (August 31). To quantify bias in these estimates, we ran the same models during the pre-influenza period (September 1 through the day before the influenza season started). When limited to the period before the start of influenza season when vaccine effectiveness should be biologically negligible, we would expect

the HR estimate to be close to 1.0 if no confounding was present. This method identifies whether the conventional analysis remains biased even after adjustment.

To estimate effects between seasons, we ran proportional hazards models with an interaction between vaccination status and year, with vaccination status treated as described in the preceding paragraph. Kaplan-Meier survival curves are reported for the comparison of different years among vaccinated patients. We report the antilog of the beta coefficient for the interaction term, which represents the ratio of two HRs: comparing the vaccinated cohort in a matched year with the vaccinated cohort in the unmatched year divided by the comparison of the unvaccinated cohort in a matched year with the unvaccinated cohort in the unmatched year. We calculated VE as 1 – effect measure. Because patients could be in multiple cohorts, robust variance was used initially to account for the possibility of having multiple events in the analysis of events other than mortality. Using robust variance did not change the variance estimate; thus, we report standard variances.

Adjusted models in all analyses controlled for age, race, sex, cause of ESRD, length of time with ESRD (vintage), adherence to dialysis, number of mobility aids as a proxy for functional status, oxygen use, hospital days, ESRD network and comorbidities. The proportional hazard assumption was checked graphically. To examine the effect of non-proportional hazards, we limited our final model to run only through the end of the influenza season, which is approximately the time when the curves crossed. The analysis was conducted

using SAS 9.2 (Cary, NC) using Efron's method for tied event times.[25] This study was considered exempt from human subjects review by the institutional review board at the University of North Carolina.

C. **Results**

More than 100,000 patients met the inclusion criteria in each influenza season cohort, and vaccination rates were approximately 48% each year, similar to previously reported estimates (Table 11).[6,26] Patients who received the influenza vaccine were older, had fewer years with ESRD, were more likely to be White, and had better adherence to dialysis. These differences persisted during the study period. In addition, the mean age of the vaccinated cohorts increased, and the proportion who had diabetes mellitus as the cause of ESRD increased during the study period.

The A/H3N2 strain predominated in all the influenza seasons, and all were severe influenza seasons. The start of the influenza seasons ranged from late November to early January (Table 12).

Conventional analysis comparing vaccinated with unvaccinated patients resulted in average, adjusted VE estimates of 13%, 16%, and 30% for ILI, influenza/pneumonia hospitalization, and death, respectively (Table 13). Adjustment for measured confounders increased all VE estimates slightly. However, when limited to the period before the start of influenza season the estimates were similar or stronger, which strongly suggests that confounding bias was present. The adjusted HR for death in the pre-influenza period ranged from 0.36 to 0.51, indicating that there was severe bias in the comparison between

vaccinated and unvaccinated cohorts for the outcome of all-cause mortality. Defining the start of influenza season with an earlier date (with 5% of isolates positive) resulted in even more biased estimates (Table 13).

Vaccinated patients in all matched years had more events than did vaccinated patients in the unmatched year, and there was little difference in the survival curves for each outcome (Figure 3). The models for 1998 versus 1997 and 1999 versus 1997 produced similar results, showing no benefit for any of the three outcomes. The comparison between 2001 and 1997 produced a small beneficial effect. The pooled ratio of HRs comparing matched seasons with a placebo season resulted in a VE of 0% (95% CI: -3,2%) for ILI, 2% (-2,5%) for influenza/pneumonia hospitalization, and 0% (-3,3%) for death (Table 14). Neither limiting the model to run only through the end of the influenza season (data not shown) nor restricting the ILI definition (Table 15) appreciably changed the estimates. Starting follow-up on December 1 resulted in slightly stronger estimates, with the confidence intervals for ILI and hospitalization excluding the null (Table 15).

D. **Discussion**

In this population-based study, we analyzed the natural experiment created by year-to-year variation in the match of the influenza vaccine to the circulating virus. We used the vaccine during a mismatched year as a working "placebo" and compared its effectiveness to well-matched vaccines in subsequent years. We found little evidence that the well-matched vaccines were more effective than the mismatched vaccine for the prevention of ILI,

influenza/pneumonia hospitalization and all-cause mortality among patients on hemodialysis.

We also conducted traditional analyses comparing vaccinated and unvaccinated patients. These analyses revealed strong evidence of unobserved confounding. In all years, we found that the vaccinated patients were at decreased risk for all outcomes even before influenza began circulating in the community. Despite adjusting for many clinical factors, these analyses remained biased. Comparing patients who are vaccinated in one year with patients who are vaccinated in another year implicitly controlled for unmeasured aspects of health, functional status, and health behaviors that may differ between the vaccinated and unvaccinated cohorts.[27]

Patients with ESRD have some level of immune dysfunction that may limit their ability to respond adequately to the influenza vaccine. Specifically, these patients have fewer B-cells because of apoptosis and inflammatory cytokines pushing immune cell differentiation toward the T-cell pathway.[28,29] Although immunogenicity studies have shown that patients with ESRD can produce antibodies, antibody production may not be sufficient to provide protection from influenza infection.

Because patients with ESRD may have levels of immune deficiency similar to those of elderly individuals, our results are consistent with recent work in the elderly population. Fireman et al. reported an estimate of VE for all-cause mortality of 5% (1,8%),[30] whereas Baxter et al. reported estimates for influenza/pneumonia hospitalizations of 12% (2,22%) in persons aged 50–64,

and 9% (3,14%) in those 65 years or older.[14] Jackson et al. estimated VE for community-acquired pneumonia among elderly individuals as 8% (-10,23%).[12] Caution is needed, however, in comparing patients who have ESRD with the general elderly population. Patients with ESRD are seen at medical facilities 2-3 times per week for dialysis, therefore the reasons for being vaccinated may be different.

Our results comparing various influenza seasons differed from a previous observational study of influenza VE in ERSD patients. The previous study compared vaccinated with unvaccinated patients and reported VE estimates during the 1998–99 matched season of 14% (8%, 23%) for influenza/pneumonia hospitalizations and 23% (19%, 27%) for all-cause mortality.[6] These results were similar to our conventional adjusted estimates. By limiting our conventional analysis to the pre-influenza period, we showed that the traditional epidemiologic approach may exaggerate the benefits of vaccination.

There are limitations to this study. First, we assumed that the vaccine was ineffective in preventing clinical outcomes in the 1997 season. If the vaccine provided some benefit, the difference in effectiveness between the match and the mismatched years would be narrowed, and thus our estimate would be closer to the null than the true estimate. However, evidence from a randomized controlled trial showed that the vaccine did not protect against clinical outcomes among younger, healthier people.[17] Moreover, the vaccine is even less likely to have provided protection to an immune-compromised population. Second, because we used administrative claims data, we may have not adequately captured all the

important confounders, particularly variables that changed between years, such as quality of care, temperature variations, or other circulating viruses. We did, however, adjust for a variety of clinical characteristics, and this is the first study to our knowledge to account for adherence to dialysis, which may be an important predictor of exposure to preventive healthcare services. In addition, we limited the comparisons to a five year period to limit temporal changes. Third, it is likely that the ILI outcome was under-ascertained. Unless physicians were making their diagnosis in part on the basis of the patient's vaccination status during the visit, this misclassification would be non-differential. If a true effect did exist, we would expect the estimate to be stronger for a more specific influenza outcome, such as ILI, compared with a less specific outcome, such as mortality. Our estimates did not reflect this trend; therefore, it is possible that our estimate for ILI may be biased toward the null. Finally, we may have missed some vaccinations if patients received a vaccine that was paid out of pocket. Because influenza vaccine is covered by Medicare for our study population and because patients undergoing dialysis have healthcare encounters 2 to 3 times per week, we expect that the number of people who paid out of pocket would be low. These limitations cannot rule out a protective effect of the vaccine; however, we think our findings suggest that the effect may be smaller than previously believed.

The findings of this study should not be interpreted to mean that the practice of influenza vaccination be discouraged. Rather, they suggest that current strategies for vaccination, which rely on single dosing with a trivalent inactivated influenza virus, should be re-evaluated. Alternative vaccine

formulations exist and may be more suitable for the dialysis population. For example, adjuvants such as AS03 and MF59 can act as a delivery system for the virus and potentiate the immunogenic response. One recent study demonstrated a significantly higher antibody response in patients on hemodialysis who use the AS03a adjuvant vaccine compared with the standard vaccine.[31] A high-dose vaccine that contains three times the amount of virus compared with standard vaccine, also offers an alternative strategy. Future studies should examine the clinical effectiveness of these alternate vaccination strategies.

In summary, our analysis suggests that the potential health benefits of the current influenza vaccine may be small to negligible in the dialysis population. Conventional analyses comparing vaccinated with unvaccinated groups are prone to bias. Although it is premature to discontinue vaccinating high-risk patients, alternate vaccination strategies should be investigated in patients with ESRD to achieve better health outcomes.

Table 11. Description of study cohorts

Variable	1997		1998		1999		2001	
	Vaccinated N=52,287 N (%)	Unvaccinated N=55,178 N (%)	Vaccinated N=53,884 N (%)	Unvaccinated N=59,225 N (%)	Vaccinated N=56,796 N (%)	Unvaccinated N=60,248 N (%)	Vaccinated N=61,800 N (%)	Unvaccinated N=64,899 N (%)
Mean age (SD)	62.3 (14.2)	60.3 (15.0)	62.7 (14.1)	60.6 (15.0)	63.1 (14.2)	61.0 (14.9)	63.9 (14.0)	61.7 (14.8)
Male sex	27,310 (52.2)	27,827 (50.4)	28,363 (52.6)	30,213 (51.0)	29,963 (52.8)	30,621 (50.8)	32,727 (53.0)	33,476 (51.6)
Race								
White	29,625 (56.7)	25,975 (47.1)	30,744 (57.1)	27,857 (47.0)	32,100 (56.5)	28,606 (47.5)	35,571 (57.6)	31,631 (48.7)
Black	20,443 (39.1)	26,384 (47.8)	20,659 (38.3)	28,271 (47.7)	21,978 (38.7)	28,428 (47.2)	23,150 (37.5)	29,629 (45.7)
Other	2,219 (4.2)	2,819 (5.1)	2,481 (4.6)	3,097 (5.2)	2,718 (4.8)	3,214 (5.3)	3,079 (5.0)	3,639 (5.6)
Cause of ESRD								
Diabetes	19,988 (38.2)	20,277 (36.7)	21,453 (39.8)	22,550 (38.1)	23,336 (41.1)	23,614 (39.2)	26,457 (42.8)	27,044 (41.7)
Hypertension	16,503 (31.6)	18,055 (32.7)	16,650 (30.9)	18,947 (32.0)	17,207 (30.3)	18,988 (31.5)	18,365 (29.7)	19,923 (30.7)
Glomerulonephritis	6,998 (13.4)	7,595 (13.8)	6,931 (12.9)	8,002 (13.5)	7,114 (12.5)	7,842 (13.0)	7,300 (11.8)	7,784 (12.0)
Cystic Kidney	1,838 (3.5)	1,677 (3.0)	1,781 (3.3)	1,705 (2.9)	1,772 (3.1)	1,649 (2.7)	1,739 (2.8)	1,643 (2.5)
Other	6,960 (13.3)	7,574 (13.7)	7,069 (13.1)	8,021 (13.5)	7,367 (13.0)	8,155 (13.5)	7,939 (12.8)	8,505 (13.1)
1 or more mobility aid	4,096 (7.8)	4,767 (8.6)	3,840 (7.1)	4,563 (7.7)	3,910 (6.9)	4,141 (6.9)	4,080 (6.6)	4,411 (6.8)
Vintage (years)								
0	1,048 (2.0)	1,092 (2.0)	1,212 (2.2)	1,267 (2.1)	1,211 (2.1)	1,208 (2.0)	1,211 (2.0)	1,247 (1.9)
1-2	22,345 (42.7)	22, 313 (40.4)	22,715 (42.2)	23,473 (39.6)	23,750 (41.8)	23,667 (39.3)	25,283 (40.8)	25,279 (39.0)
3-4	13,588 (26.0)	13,867 (25.1)	13,944 (25.9)	14,976 (25.3)	14,644 (25.8)	14,868 (24.4)	16,214 (26.2)	16,244 (25.0)
5-9	11,154 (21.3)	12,521 (22.7)	11,783 (21.9)	13,766 (23.2)	12,981 (22.9)	14,247 (23.6)	14,042 (22.7)	15,725 (24.2)
10+	4,152 (7.9)	5,385 (9.8)	4,230 (7.9)	5,743 (9.7)	4,210 (7.4)	6,258 (10.4)	5,050 (8.2)	6,404 (9.9)
Adherent to dialysis	45,103 (86.3)	43,760 (79.3)	48,130 (89.3)	48,103 (81.2)	50,383 (88.7)	49,028 (81.4)	55,611 (90.0)	53,753 (82.8)
Mean hospital days (SD)	8.4 (14.8)	10.3 (18.1)	8.3 (14.6)	10.5 (18.3)	8.6 (15.2)	11.0 (19.0)	8.9 (15.8)	11.6 (19.6)
Oxygen Use	5,090 (9.7)	6,085 (11.0)	5,574 (10.3)	6,890 (11.6)	6,218 (10.9)	7,954 (13.2)	7,258 (11.7)	9,058 (14.0)
Atherosclerotic heart dis.	17,993 (34.4)	18,675 (33.8)	17,886 (33.2)	19,050 (32.2)	19,478 (34.3)	19,901 (33.0)	23,584 (38.2)	24,461 (37.7)
Congestive heart failure	18,572 (35.5)	20,585 (37.3)	17,885 (33.2)	20,961 (35.4)	19,174 (33.8)	21,444 (35.6)	22,408 (36.3)	25.428 (39.2)
TIA	7,197 (13.8)	8,602 (15.6)	6,725 (12.5)	8,540 (14.4)	7,102 (12.5)	8,389 (13.9)	8,675 (14.0)	10,430 (16.1)
Peripheral vascular dis.	16,028 (30.7)	17,680 (32.0)	15,315 (28.4)	17,794 (30.0)	16,423 (28.9)	17,938 (29.8)	19,759 (32.0)	21,761 (33.5)
Other cardiac disease	13,950 (26.7)	15,004 (27.2)	12,602 (23.4)	14,684 (24.8)	13,693 (24.1)	14,933 (24.8)	16,178 (26.2)	18,084 (27.9)
Liver disease	13,060 (25.0)	14,513 (26.3)	3,712 (6.9)	4,853 (8.2)	3,005 (5.3)	4,267 (7.1)	2,705 (4.4)	3,556 (5.5)
COPD	7,563 (14.5)	8,406 (15.2)	7,435 (13.8)	8,523 (14.4)	8,207 (14.4)	8,932 (14.8)	10,104 (16.3)	11,210 (17.3)
Gastrointestinal bleed	5,212 (10.0)	6,191 (11.2)	5,118 (9.5)	6,215 (10.5)	5,108 (9.0)	6,182 (10.3)	5,706 (9.2)	6,951 (10.7)
Dysrhythmia	13,354 (25.5)	13,883 (25.2)	11,443 (21.2)	12,745 (21.5)	12,129 (21.4)	13,123 (21.8)	14,158 (22.9)	15,547 (24.0)
Cancer	4,031 (7.7)	4,161 (7.5)	3,272 (6.1)	3,648 (6.2)	3,331 (5.9)	3,501 (5.8)	3,897 (6.3)	4,028 (6.2)
Diabetes	26,598 (50.9)	27,609 (50.0)	26,106 (48.4)	28,402 (48.0)	27,819 (49.0)	28,690 (47.6)	32,682 (52.9)	33,863 (52.2)

Table 12. Description of influenza seasons

	1997	1998	1999	2001
% Serologic Match	19%	90%	97%	100%
Predominate strain	A(H3N2)	A(H3N2), B	A(H3N2)	A(H3N2), B
Start of flu season (10%)	12/31/1997	1/13/1999	11/24/1999	1/9/2002
Start of flu season (5%)	12/24/1997	12/30/1998	11/10/1999	12/19/2001

Table 13. Estimates of vaccine effectiveness comparing vaccinated vs. unvaccinated by year

Year	No. Events	No. Lost/ Transplant	Crude HR 95% CI	Adjusted HR* 95% CI	Adjusted HR in pre-flu period† 95% CI	Adjusted HR in pre-flu period‡ 95% CI
1997						
ILI	30,107	2,807	0.95 (0.93, 0.97)	0.89 (0.87, 0.91)	0.90 (0.88, 0.92)	0.76 (0.73, 0.79)
Influenza/Pneumonia hosp.	16,081	3,035	0.92 (0.89, 0.95)	0.86 (0.83, 0.89)	0.87 (0.85, 0.90)	0.75 (0.70, 0.80)
Death	23,397	3,144	0.77 (0.75, 0.79)	0.70 (0.68, 0.72)	0.48 (0.46, 0.51)	0.47 (0.44, 0.49)
1998						
ILI	33,552	2,848	0.94 (0.92, 0.96)	0.88 (0.86, 0.90)	0.77 (0.74, 0.80)	0.74 (0.71, 0.77)
Influenza/Pneumonia hosp.	17,969	3,048	0.91 (0.88, 0.94)	0.84 (0.81, 0.87)	0.75 (0.71, 0.80)	0.73 (0.68, 0.78)
Death	25,768	3,159	0.79 (0.77, 0.81)	0.72 (0.70, 0.74)	0.51 (0.48, 0.53)	0.46 (0.44, 0.49)
1999						
ILI	34,837	2,783	0.94 (0.92, 0.96)	0.87 (0.85, 0.89)	0.67 (0.64, 0.71)	0.62 (0.58, 0.66)
Influenza/Pneumonia hosp.	18,893	3,020	0.90 (0.87, 0.93)	0.84 (0.81, 0.86)	0.63 (0.58, 0.68)	0.56 (0.51, 0.62)
Death	26,904	3,150	0.76 (0.74, 0.78)	0.70 (0.68, 0.72)	0.36 (0.33, 0.39)	0.28 (0.25, 0.31)
2001						
ILI	40,768	3,031	0.90 (0.88, 0.92)	0.86 (0.84, 0.88)	0.76 (0.73, 0.79)	0.69 (0.66, 0.72)
Influenza/Pneumonia hosp.	22,658	3,280	0.87 (0.85, 0.90)	0.82 (0.80, 0.85)	0.71 (0.68, 0.76)	0.64 (0.60, 0.69)
Death	30,221	3,417	0.76 (0.74, 0.78)	0.70 (0.68, 0.71)	0.46 (0.44, 0.49)	0.40 (0.37, 0.43)

* Adjusted for age, race, sex, cause of ESRD, vintage, adherence, hospital days, mobility aids, network, comorbidities, and oxygen use

† Pre-flu period as defined by 10% of isolates positive for influenza

‡ Pre-flu period as defined by 5% of isolates positive for influenza

Table 14. Ratio of hazard ratios (RHR) that estimate VE by comparing matched versus mismatched years among vaccinated versus unvaccinated

	1998 vs. 1997		1999 vs. 1997		2001 vs. 1997		Pooled vs. 1997
	Crude RHR 95% CI	Adjusted RHR* 95% CI	Crude RHR 95% CI	Adjusted RHR 95% CI	Crude RHR 95% CI	Adjusted RHR 95% CI	Adjusted RHR 95% CI
ILI	1.03 (1.00, 1.07)	1.03 (1.00, 1.07)	1.01 (0.98, 1.04)	1.00 (0.97, 1.03)	0.97 (0.94, 1.00)	0.98 (0.95, 1.01)	1.00 (0.98, 1.03)
I/P hosp.	1.02 (0.97, 1.06)	1.01 (0.97, 1.06)	1.00 (0.96, 1.05)	0.99 (0.95, 1.04)	0.95 (0.92, 0.99)	0.95 (0.91, 0.99)	0.98 (0.95, 1.02)
Death	1.03 (0.99, 1.06)	1.02 (0.99, 1.06)	0.99 (0.96, 1.03)	1.00 (0.96, 1.03)	0.99 (0.96, 1.03)	0.99 (0.96, 1.03)	1.00 (0.97, 1.03)

* Adjusted for age, race, sex, cause of ESRD, vintage, adherence, hospital days, mobility aids, network, comorbidities, and oxygen use
** Influenza/pneumonia

Table 15. Sensitivity analyses of ratio of hazard ratios (RHR) that estimate VE

	1998 vs. 1997		1999 vs. 1997		2001 vs. 1997		Pooled vs. 1997
	Crude RHR 95% CI	Adjusted RHR* 95% CI	Crude RHR 95% CI	Adjusted RHR 95% CI	Crude RHR 95% CI	Adjusted RHR 95% CI	Adjusted RHR 95% CI
Specific ILI codes	1.04 (1.00, 1.07)	1.03 (1.00, 1.06)	1.01 (0.98, 1.04)	1.00 (0.97, 1.03)	0.97 (0.94, 1.00)	0.98 (0.95, 1.02)	1.00 (0.98, 1.03)
Start follow-up on 12/1							
ILI	1.00 (0.97, 1.04)	0.99 (0.96, 1.03)	0.98 (0.95, 1.02)	0.97 (0.93, 1.00)	0.93 (0.90, 0.96)	0.94 (0.91, 0.97)	0.97 (0.94, 0.99)
I/P Hosp.	0.98 (0.94, 1.03)	0.98 (0.93, 1.02)	0.99 (0.94, 1.03)	0.97 (0.93, 1.02)	0.92 (0.88, 0.96)	0.93 (0.89, 0.97)	0.96 (0.92, 0.99)
Death	1.01 (0.97, 1.05)	1.01 (0.97, 1.06)	0.99 (0.95, 1.03)	1.00 (0.96, 1.04)	0.95 (0.91, 0.99)	0.95 (0.92, 0.99)	0.99 (0.95, 1.02)

* Adjusted for age, race, sex, cause of ESRD, vintage, adherence, hospital days, mobility aids, network, comorbidities, and oxygen use

Figure 3. Unadjusted, pooled survival curves among the vaccinated for A) ILI B) Influenza/pneumonia hospitalization C) Death

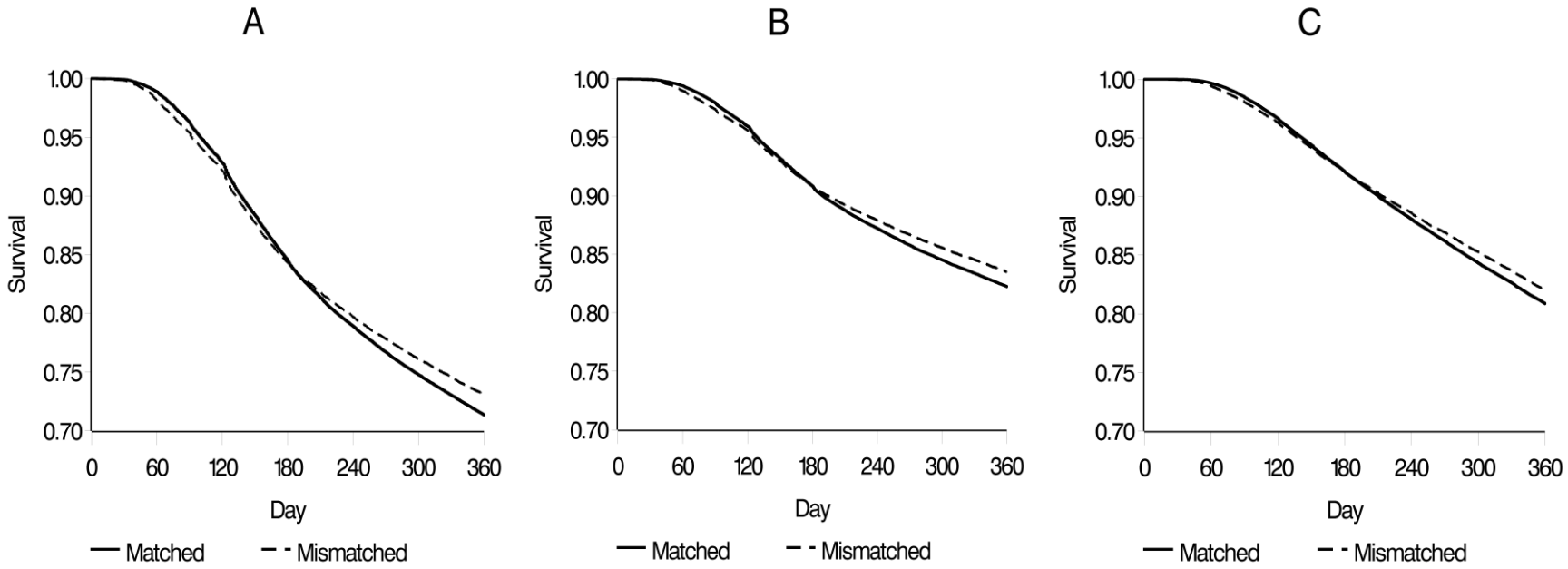

Table 16. Ratio of HRs by age.

	1998 vs. 1997 Crude RHR 95% CI	1998 vs. 1997 Adjusted RHR 95% CI	1999 vs. 1997 Crude RHR 95% CI	1999 vs. 1997 Adjusted RHR 95% CI	2001 vs. 1997 Crude RHR 95% CI	2001 vs. 1997 Adjusted RHR 95% CI	Pooled vs. 1997 Adjusted RHR 95% CI
65+ years							
ILI	1.09 (1.04, 1.14)	1.08 (1.03, 1.13)	1.02 (0.98, 1.06)	1.01 (0.96, 1.05)	0.98 (0.94, 1.02)	1.00 (0.96, 1.04)	1.03 (0.99, 1.06)
Flu/pneumo hosp	1.06 (1.00, 1.12)	1.05 (0.99, 1.11)	1.03 (0.97, 1.08)	1.02 (0.97, 1.07)	0.95 (0.91, 1.00)	0.97 (0.92, 1.02)	1.01 (0.96, 1.05)
Death	1.05 (1.00, 1.10)	1.04 (1.00, 1.09)	1.01 (0.97, 1.06)	1.01 (0.97, 1.06)	1.00 (0.95, 1.04)	1.01 (0.96, 1.05)	1.02 (0.98, 1.06)
<65 years							
ILI	0.98 (0.93, 1.02)	0.97 (0.93, 1.02)	1.00 (0.96, 1.05)	0.99 (0.95, 1.04)	0.96 (0.92, 1.00)	0.97 (0.92, 1.01)	0.98 (0.94, 1.02)
Flu/pneumo hosp	0.97 (0.91, 1.03)	0.96 (0.90, 1.02)	1.00 (0.94, 1.06)	0.98 (0.93, 1.05)	0.94 (0.89, 1.00)	0.94 (0.89, 1.00)	0.96 (0.91, 1.01)
Death	0.98 (0.92, 1.04)	0.98 (0.92, 1.04)	0.94 (0.89, 1.00)	0.94 (0.89, 1.00)	0.98 (0.92, 1.04)	0.97 (0.91, 1.03)	0.96 (0.92, 1.01)

Table 17. Ratio of HRs by cause of ESRD

	1998 vs. 1997 Adjusted RHR* 95% CI	1999 vs. 1997 Adjusted RHR 95% CI	2001 vs. 1997 Adjusted RHR 95% CI	Pooled vs 1997 Adjusted RHR 95% CI
Diabetes				
ILI	1.05 (1.00, 1.11)	1.01 (0.96, 1.06)	1.00 (0.95, 1.05)	1.02 (0.98, 1.06)
Flu/pnemo hosp	1.04 (0.98, 1.11)	1.04 (0.98, 1.11)	0.96 (0.91, 1.03)	1.01 (0.96, 1.07)
Death	1.04 (0.99, 1.10)	1.01 (0.95, 1.06)	1.01 (0.95, 1.06)	1.02 (0.97, 1.06)
Hypertension				
ILI	1.02 (0.96, 1.08)	0.99 (0.94, 1.05)	0.96 (0.91, 1.02)	0.99 (0.94, 1.04)
Flu/pnemo hosp	1.00 (0.93, 1,07)	0.97 (0.90, 1.04)	0.93 (0.87, 1.00)	0.96 (0.91, 1.02)
Death	0.97 (0.90, 1.03)	0.96 (0.90, 1.02)	0.96 (0.90, 1.02)	0.96 (0.91, 1.01)
Glomerulonep.				
ILI	1.03 (0.95, 1.13)	1.05 (0.96, 1.15)	1.02 (0.94, 1.12)	1.04 (0.96, 1.11)
Flu/pnemo hosp	0.95 (0.85, 1.06)	0.99 (0.88, 1.11)	0.99 (0.89, 1.11)	0.98 (0.89, 1.07)
Death	1.15 (1.03, 1.30)	1.06 (0.94, 1.19)	0.99 (0.88, 1.11)	1.06 (0.97, 1.17)
Cystic Kidney				
ILI	0.96 (0.80, 1.17)	0.99 (0.82, 1.20)	1.00 (0.83, 1.21)	0.99 (0.84, 1.16)
Flu/pnemo hosp	1.01 (0.78, 1.30)	1.00 (0.78, 1.29)	0.94 (0.73, 1.22)	0.98 (0.80, 1.22)
Death	1.13 (0.88, 1.43)	0.93 (0.73, 1.18)	1.01 (0.80, 1.29)	1.02 (0.84, 1.24)

Table 18. Ratio of HRs by vintage

	1998 vs. 1997 Adjusted RHR 95% CI	1999 vs. 1997 Adjusted RHR 95% CI	2001 vs. 1997 Adjusted RHR 95% CI	Pooled vs. 1997 Adjusted RHR 95% CI
0 years				
ILI	0.99 (0.80, 1.23)	1.13 (0.90, 1.40)	0.89 (0.72, 1.10)	0.99 (0.83, 1.19)
Flu/pnemo hosp	0.88 (0.66, 1.16)	0.98 (0.74, 1.30)	0.84 (0.64, 1.10)	0.89 (0.71, 1.13)
Death	0.96 (0.75, 1.24)	1.01 (0.79, 1.30)	0.87 (0.68, 1.12)	0.95 (0.77, 1.17)
1-2 years				
ILI	1.05 (1.00, 1.10)	0.98 (0.94, 1.03)	0.99 (0.94, 1.03)	1.00 (0.97, 1.05)
Flu/pnemo hosp	1.05 (0.98, 1.11)	1.01 (0.95, 1.07)	0.98 (0.93, 1.05)	1.01 (0.96, 1.06)
Death	0.98 (0.93, 1.04)	0.95 (0.90, 1.07)	0.97 (0.92, 1.02)	0.97 (0.92, 1.01)
3-4 years				
ILI	1.03 (0.96, 1.09)	1.03 (0.97, 1.09)	0.99 (0.93, 1.05)	1.01 (0.96, 1.07)
Flu/pnemo hosp	1.00 (0.92, 1.08)	1.05 (0.97, 1.14)	0.95 (0.88, 1.02)	1.00 (0.93, 1.06)
Death	1.07 (0.99, 1.14)	1.04 (0.97, 1.12)	1.01 (0.95, 1.09)	1.04 (0.98, 1.10)

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VI. RESULTS: "ASSESSING HOSPITALIZATION AND SKILLED NURSING CARE AS TIME-VARYING PREDICTORS OF INFLUENZA VACCINATION: AN EXAMPLE OF THE HEALTHY-USER EFFECT"

A. Introduction

Patients who receive prevention health care, such as preventive medications, screening tests, and vaccinations, have been shown to be in overall better health and more likely to engage in other healthy behaviors.[1,2] This situation has the potential to exaggerate the benefits of the intervention under study, resulting in what is called the healthy-user bias.[3] The healthy user bias has been suspected in studies of preventive medications such as hormone replacement therapy and cardiovascular disease,[4] and with statin therapy and several disease outcomes.[5-7] Alternatively, it has been suggested in studies of influenza vaccine effectiveness in the elderly, that patients who are not vaccinated have a lower functional status.[8] It appears to be difficult to adequately control for this bias using typical healthcare (e.g., claims) data.

Patients that are hospitalized or have skilled nursing care may represent the very extreme of the functional status continuum (i.e. they are very sick and more likely to die) and preventive medications and vaccinations are less likely to be administered to patients near death.[9,10] ESRD patients are at particularly high risk of hospitalization, due to an increased risk of infection and cardiovascular disease, as well as a high prevalence of comorbidities (e.g., diabetes). Yearly,

inactivated influenza vaccination is recommended for this high-risk population by the Advisory Committee on Immunization Practices; however few studies have described who gets the vaccine each year, or if the vaccinated population has underlying characteristics that predispose them to have better health outcomes. Understanding who is vaccinated can better elucidate characteristics that differ between the vaccinated and unvaccinated populations that must be taken into account in studies of vaccine effectiveness (i.e. confounding variables).

This study aimed to describe the vaccinated population within patients on hemodialysis and to assess if characteristics associated with vaccination changed over time. Specifically, we assessed how hospitalization and skilled nursing care were related to vaccination. We hypothesized that people with many hospital days or skilled nursing days each month would be less likely to be vaccinated, suggesting that time-varying measures of hospitalization and skilled nursing care may be a way of accounting for the healthy user bias in administrative claims data.

B. **Methods**

Study Population

We used Medicare claims obtained from the United States Renal Data System (USRDS). The USRDS is a population-based, national system that collects information on all patients with ESRD in the US. Detailed health claims are captured for all patients with Medicare as a primary payer status (no health maintenance organization or Medicare as a secondary payer). Information collected includes physician services, *ICD-9-CM* codes assigned to

hospitalizations and outpatient care, information on routine dialysis care and immunization use.

Yearly cohorts were created for each influenza season from 1999-2005. To limit outcome misclassification, we used years before it was common to obtain influenza vaccine in the community, such as grocery stores and pharmacies. Our cohorts consisted of all adult, ESRD patients with Medicare as a primary payer and continuous hemodialysis use when follow-up began on September 1 of each year. Each yearly cohort consisted of patients who had initiated dialysis prior to October 1 of the preceding year. An eight month window from January 1 – August 31 prior to the start of follow-up of each year was used to identify insurance status and comorbidities for the patients in that cohort. Patients were required to be on continuous hemodialysis for 3 months prior to the start of follow-up. For example, the cohort identified for the 1999 season would have initiated dialysis prior to October 1, 1998 and would have had Medicare as a primary payer from January 1 – August 31, 1999 and used continuous hemodialysis from June 1 – August 31. Hospital days, skilled nursing days and vaccination status were assessed beginning on September 1 of each year. We performed an analysis of time to vaccination where cohort members were followed each year until they experienced a vaccination event, death, kidney transplant, loss-to-follow up or administrative censoring on December 31 of that year, whichever came first.

Hospitalization, Skilled Nursing Care and Vaccination Status

Hospitalization and skilled nursing facility admission and discharge dates were assessed using the Part A – Hospitalization Medicare claims.

To identify influenza vaccinations, Medicare Part A hospital/outpatient files and Part B physician/supplier files were searched for Current Procedural Terminology codes 90724, 90656, 90658-60, HCPCS codes G0008 and G8482, and the *ICD-9-CM* procedure code 99.52.

Time-fixed Covariates

Time-fixed covariates were assessed to determine their effect on vaccination. The Centers for Medicare and Medicaid Services form 2827, the Medical Evidence Form, was used to ascertain age, race, gender, first service date with ESRD, and cause of kidney failure. The eight month window from January 1 to August 31 was searched for the following comorbidities in both Part A and Part B claims as identified in Liu et al.[11]: atherosclerotic heart disease, congestive heart failure, cerebrovascular accident/transient ischemic attack, peripheral vascular disease, other cardiac, chronic obstructive pulmonary disease, gastrointestinal bleeding, liver disease, dysrhythmia, cancer, and diabetes. Comorbidities were modeled as individual dichotomous variables in the final models. Adherence to dialysis was calculated using the sum of the number of dialysis sessions over the eight month baseline period: patients were considered adherent if they had 95 sessions or more. Patients with no recorded dialysis sessions over the eight month period were dropped from the analysis. We also included the number of hospital days over the baseline period and

controlled for an ad-hoc selection of potential frailty markers including oxygen use and use of mobility aids. Use of mobility aids were ascertained by searching Part A and Part B claims for HCPCS equipment codes for wheelchairs, walkers, canes, and assisted bathroom equipment during the baseline period (Table 9).

Statistical Analysis

For time-fixed covariates, we used Cox proportional hazards models to estimate hazard ratios[12] comparing baseline characteristics with vaccination status. For time-varying covariates including hospitalization and skilled nursing care, we used separate proportional hazards models to estimate hazard ratios of vaccination for each exposure. We counted the number of hospital or skilled nursing days the patient had in the prior 30 days. These time-varying variables were updated each week; however, vaccination status was measured on a continuous (daily) scale. We fit the time-varying models by categorizing hospitalization and skilled nursing days into temporary (1 day), short (2-3 days), medium (4-14 days), medium-long (15-25 days), and long stays (26-30 days).

We controlled for age at the start of follow-up, race, sex, cause of ESRD, length of time with ESRD (vintage), adherence to dialysis, number of mobility aids, ESRD network, baseline oxygen use, total baseline hospital days and comorbidities in all analyses. Continuous variables entered models assuming a log-linear association with vaccination. Analyses were conducted using SAS 9.2 (Cary, NC), using Efron's method for tied event times.[13] This study was determined to be exempt from full review by the Institutional Review Board at the University of North Carolina at Chapel Hill.

C. **Results**

There were more than 100,000 patients in the cohort for each year. Vaccination coverage increased from 47% to 60% over the study years. Whites had higher coverage than blacks and this difference increased throughout the study period (Table 19). In years when there was not a vaccine shortage, ~75% of vaccine doses were administered by the end of October. In the 2000, 2001, and 2004 seasons most doses were not given until November. (Figure 4).

In the multivariable Cox proportional hazard models adjusting for time-fixed covariates, blacks and other races were less likely to be vaccinated, as well as patients with greater than a 5-day hospital stay during the baseline period. Patients on dialysis for 10 years or more were generally less likely to be vaccinated, although this was a small group and thus the estimates were imprecise. Older patients and patients with a high level of dialysis adherence were more likely to be vaccinated (Table 20). Most comorbidities did not strongly predict vaccination status (Table 21). These differences persisted throughout the study period.

Patients with any length of hospital stay were less likely to be vaccinated, however the association was stronger in patients with longer stays (15-25 days: HR =0.64 (95% CI: 0.62, 0.65); 26-30 days: HR =0.40 (0.38, 0.42)), suggesting that recently hospitalized patients were much less likely to be vaccinated than those not in the hospital (Table 22 and Figure 5). The estimates were similar for patients with any length of skilled nursing care stay of more than 1 day; these patients were also less likely to be vaccinated (26-30 days HR = 0.66 (0.64,

0.69)). However, we found only a weak effect for patients with 1 day of skilled nursing care (HR = 0.95 (0.86, 1.04)) (Table 22 and Figure 6).

D. **Discussion**

In this population-based study of high-risk patients with ESRD, we found that patients with a recent, long-term hospital or skilled nursing facility stay were much less likely to receive an influenza vaccination. The strength of the association for long-term stays for both variables was similar each influenza season during the 7-year study period. Elective hospitalizations were most likely represented by short stays. Patients with stays of 2-3 hospital days were most similar to those with no hospitalizations, indicating that perhaps physicians were less likely to have time to provide vaccination for those with a stay of only 1 day, and less likely to vaccinate if the patient was sick enough to require a longer stay. A surprising finding was that patients with only 1 day of skilled nursing care were not less likely to be vaccinated than patients with no skilled nursing care. The reasons for requiring skilled nursing care for only 1 day are unclear, but it may indicate an additional encounter with the healthcare system.

In a study based on medical record review, Jackson et al. also found that patients with poor functional status are less likely to be vaccinated.[8] They found that adjusting for variables such as dementia, assistance bathing, assistance ambulating, and living in a non-home setting reduced the amount of bias present in estimates of vaccine effectiveness. These variables, however, are generally not present in administrative claims data and therefore vaccine effectiveness studies that adjust for frailty have been limited to small studies using chart

review. We found similar strengths of associations for vaccination status as Jackson's functional status variables, by using recent hospitalization or skilled nursing care in a time-varying manner.

It is possible that patients got vaccinated during their hospital stay without the hospital billing Medicare for the influenza vaccine, which provides an alternative explanation for the monotonic decline in vaccination rates with increasing number of hospital days above 1 day. However, data from the hospital discharge summaries from Healthcare Cost and Utilization Project indicate that hospitals rarely gave influenza vaccinations until 2004, when vaccinations began to increase.[14] This failure to offer influenza vaccine to hospitalized patients has recently been resolved – as of January 2012, the Centers for Medicare & Medicaid Services requires that all persons over the age of 6 months who are hospitalized be offered the influenza vaccine if discharged during the influenza season. While studies using recent data would need to take this into account, we do not think that the vaccination rate in the hospital was high enough during our study period to fully explain the results observed.

Often in studies using administrative claims, the presence of comorbidities are used to characterize the health status of each patient. We found most comorbidities were not strongly associated with vaccination status, indicating that using these variables may not adequately capture the healthy user effect. In fact, adjustment for comorbidities in a study estimating influenza vaccine effectiveness resulted in a more biased estimate in the presence of strong unmeasured confounding.[8] In addition, most comorbidities are assessed over a period at

baseline (8 months in our study). Therefore, having a claim for an illness at baseline would not capture acute illness, which may be a better proxy of severe frailty. Finally, it has been suggested that using *ICD-9-CM* comorbidity codes from administrative data may lack the sensitivity for identifying these illnesses, which can result in substantial residual confounding.[15,16]

We found persistent demographic disparities in who received the vaccine each year. African Americans and other races consistently were less likely to be vaccinated. This disparity has been documented in the dialysis population,[17] adults with high risk conditions[18], and the general Medicare population.[19] Explanations for this difference include varying rates of provider recommendations and fear of getting sick/side effects from the vaccine.[20]

There were two additional time-fixed variables that could potentially be variables to adjust for healthy-user bias in vaccine effectiveness studies. Patients who were more adherent to their dialysis regimens were more likely to be vaccinated, while patients with a long vintage, and who are presumably sicker were less likely to be vaccinated. If these variables were left unadjusted, both would make the vaccine look more protective in studies of vaccine effectiveness. In comparison, age is an indicator of confounding by indication. We found that the oldest age group was more likely to be vaccinated, which was the age indication for influenza vaccine during the years studied.

Our study may have been subject to some outcome misclassification. As with any study on influenza vaccination, it is possible that patients could have obtained the vaccine from a non-medical establishment and paid out-of-pocket.

In this case, there would not be a Medicare claim for vaccination and we could not have determined that they were vaccinated. We chose to examine years prior to the popularization of obtaining vaccine in groceries and pharmacies, although the later years in our study may have been affected by this trend. Additionally, because influenza vaccine is covered by Medicare for our study population and patients on dialysis usually have healthcare encounters 2-3 times per week, we expect that the number of people who paid out of pocket would be low.

In summary, this analysis suggests that patients with a recent, long-term hospitalization or skilled nursing facility stay were much less likely to undergo the preventive health measure of influenza vaccination. Further work on understanding how these variables could be used to control the healthy user bias in effectiveness studies of preventive medications is needed.

Table 19. Description of yearly cohorts

Year	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**
	N=118,659 %	N=123,241 %	N=127,954 %	N=131,179 %	N=133,154 %	N=128,847 %	N=122,671 %
Mean age (SD)	62.0 (14.6)	62.3 (14.5)	62.7 (14.5)	63.0 (14.4)	63.5 (14.4)	63.8 (14.3)	64.1 (14.3)
Male sex	51.9	52.2	52.4	52.8	52.9	53.0	53.2
Race							
White	51.6	52.0	52.8	53.3	53.9	54.0	54.4
Black	43.3	42.8	41.9	41.3	40.6	40.4	39.9
Other	5.1	5.2	5.3	5.4	5.5	5.6	5.7
Cause of ESRD							
Diabetes	40.3	41.2	42.3	43.6	44.3	45.4	46.3
Hypertension	30.9	30.5	30.2	29.9	29.9	29.9	29.8
Glomerulonephritis	12.8	12.4	11.9	11.3	10.7	10.1	9.7
Cystic Kidney	2.9	2.8	2.7	2.5	2.4	2.3	2.1
Other	13.2	13.0	12.9	12.7	12.7	12.3	12.1
Vintage							
0 years	2.1	2.0	2.0	1.9	1.9	2.0	1.9
1-2 years	40.8	40.5	40.1	39.7	39.2	38.6	38.0
3-4 years	25.2	25.2	25.6	26.0	25.9	26.0	26.0
5-9 years	23.1	23.4	23.4	23.4	24.0	24.3	24.6
10+	8.8	8.9	9.0	9.0	9.1	9.2	9.5
Mean hospital days (SD)	9.9 (17.3)	9.8 (17.3)	10.3 (17.9)	10.7 (18.3)	10.8 (18.4)	11.3 (18.8)	12.0 (19.4)

Table 20. Adjusted* hazard ratios for time fixed variables and vaccination status by year

Year	1999	2000	2001	2002	2003	2004	2005	Pooled
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
% Vaccinated	47.6	46.9	48.1	56.8	58.3	58.3	61.0	
Age								
18-44	1.00	1.00	1.00	1.00	1.00	1.00	1.00	
45-64	1.13 (1.10, 1.16)	1.16 (1.13,1.19)	1.18 (1.15, 1.22)	1.16 (1.13, 1.19)	1.17 (1.14, 1.20)	1.12 (1.10, 1.16)	1.10 (1.07, 1.13)	1.15 (1.13, 1.16)
65-74	1.25 (1.22, 1.29)	1.28 (1.24,1.32)	1.29 (1.25, 1.33)	1.24 (1.21, 1.28)	1.23 (1.19, 1.26)	1.17 (1.14, 1.20)	1.16 (1.13, 1.20)	1.23 (1.19, 1.27)
75+	1.25 (1.21, 1.29)	1.31 (1.27,1.35)	1.34 (1.30, 1.39)	1.26 (1.22, 1.29)	1.24 (1.20, 1.27)	1.22 (1.19, 1.26)	1.18 (1.15, 1.22)	1.25 (1.24, 1.28)
Male Sex	1.08 (1.06, 1.10)	1.06 (1.04,1.08)	1.06 (1.04, 1.08)	1.05 (1.04, 1.07)	1.06 (1.04, 1.07)	1.04 (1.02, 1.05)	1.04 (1.02, 1.05)	1.05 (1.05, 1.06)
Race								
White	1.00	1.00	1.00	1.00	1.00	1.00	1.00	
Black	0.75 (0.74, 0.77)	0.72 (0.71,0.74)	0.73 (0.72, 0.74)	0.77 (0.76, 0.79)	0.79 (0.78, 0.80)	0.78 (0.77, 0.79)	0.80 (0.79, 0.82)	0.77 (0.76, 0.77)
Other	0.88 (0.84, 0.91)	0.80 (0.77,0.83)	0.83 (0.80, 0.87)	0.87 (0.84, 0.90)	0.93 (0.90, 0.97)	0.81 (0.78, 0.84)	0.87 (0.84, 0.90)	0.86 (0.82, 0.89)
Cause								
Diabetes	1.00	1.00	1.00	1.00	1.00	1.00	1.00	
Hypertension	0.97 (0.94, 0.99)	1.00 (0.98, 1.03)	1.01 (0.98, 1.03)	0.99 (0.97, 1.01)	0.98 (0.96, 1.00)	0.99 (0.97, 1.01)	0.98 (0.96, 1.00)	0.99 (0.98, 1.00)
Glomeruloneph.	1.00 (0.97, 1.03)	1.00 (0.97, 1.04)	1.03 (1.00, 1.07)	1.01 (0.98, 1.04)	0.99 (0.97, 1.02)	0.99 (0.96, 1.02)	0.98 (0.95, 1.01)	1.00 (0.99, 1.01)
Cystic Kidney	1.05 (1.00, 1.10)	1.07 (1.02, 1.13)	1.04 (0.99, 1.10)	1.01 (0.97, 1.06)	0.99 (0.95, 1.04)	1.01 (0.96, 1.06)	0.99 (0.94, 1.05)	1.02 (1.00, 1.04)
Other	0.98 (0.95,1.01)	1.00 (0.97, 1.03)	1.01 (0.98, 1.04)	0.97 (0.95, 1.00)	0.96 (0.94, 0.99)	0.97 (0.95, 1.00)	0.97 (0.94, 0.99)	0.98 (0.97, 0.99)
Mobility aids								
None	1.00	1.00	1.00	1.00	1.00	1.00	1.00	
1 aid	1.06 (1.02, 1.10)	1.05 (1.02, 1.09)	1.04 (1.00, 1.07)	1.06 (1.03, 1.09)	1.06 (1.03, 1.09)	1.04 (1.02, 1.07)	1.02 (0.99, 1.05)	1.05 (1.04, 1.06)
2+ aids	1.33 (1.13, 1.55)	1.01 (0.84, 1.21)	1.27 (1.10, 1.47)	1.13 (0.98, 1.29)	1.14 (1.03, 1.26)	1.03 (0.94, 1.12)	1.02 (0.94, 1.10)	1.09 (1.05, 1.14)
Vintage								
0 years	1.00	1.00	1.00	1.00	1.00	1.00	1.00	
1-2 years	0.97 (0.92, 1.03)	1.03 (0.97, 1.09)	0.99 (0.93, 1.05)	0.98 (0.93, 1.03)	1.01 (0.96, 1.06)	1.07 (1.01, 1.12)	0.97 (0.92, 1.02)	1.00 (0.98, 1.02)
3-4 years	0.99 (0.93, 1.05)	1.03 (0.97, 1.10)	0.99 (0.94, 1.05)	0.98 (0.93, 1.03)	0.94 (0.90, 1.00)	1.09 (1.03, 1.15)	1.02 (0.97, 1.08)	1.00 (0.98, 1.02)
5-9 years	0.97 (0.91, 1.03)	0.99 (0.93, 1.05)	0.96 (0.90, 1.02)	0.97 (0.92, 1.02)	1.02 (0.97, 1.07)	0.95 (0.90, 1.01)	0.97 (0.91, 1.02)	0.98 (0.96, 1.00)
10+	0.80 (0.75, 0.86)	0.93 (0.87, 1.00)	0.94 (0.87, 1.01)	0.90 (0.84, 0.96)	0.93 (0.87, 0.99)	0.94 (0.88, 1.00)	0.90 (0.85, 0.96)	0.91 (0.88, 0.93)
Adherence	1.42 (1.38, 1.46)	1.29 (1.25, 1.32)	1.47 (1.43, 1.51)	1.57 (1.53, 1.61)	1.51 (1.47, 1.55)	1.56 (1.52, 1.60)	1.58 (1.54, 1.63)	1.48 (1.47, 1.50)
Oxygen use	1.02 (0.99, 1.06)	1.05 (1.01, 1.09)	0.98 (0.94, 1.03)	1.01 (0.98, 1.05)	1.06 (1.02, 1.09)	1.11 (1.08, 1.15)	1.05 (1.02, 1.08)	1.05 (1.03, 1.06)
No. hospital days								
None	1.00	1.00	1.00	1.00	1.00	1.00	1.00	
1-5 days	0.99 (0.96, 1.01)	0.97 (0.94, 0.99)	0.99 (0.96, 1.01)	0.98 (0.96, 1.00)	0.95 (0.93, 0.97)	1.00 (0.98, 1.02)	0.98 (0.96, 1.00)	0.98 (0.97, 0.99)
6-30 days	0.90 (0.88, 0.92)	0.89 (0.87, 0.91)	0.90 (0.88, 0.92)	0.89 (0.87, 0.90)	0.90 (0.88, 0.91)	0.93 (0.91, 0.94)	0.91 (0.89, 0.93)	0.90 (0.90, 0.91)
31+	0.77 (0.75, 0.80)	0.76 (0.74, 0.79)	0.78 (0.76, 0.81)	0.74 (0.72, 0.77)	0.78 (0.76, 0.81)	0.81 (0.79, 0.83)	0.80 (0.78, 0.82)	0.78 (0.77, 0.79)

* Adjusted for all other variables in the table, ESRD network, and baseline comorbidities

Table 21. Adjusted* association between comorbidities and vaccination status by year

	1999	2000	2001	2002	2003	2004	2005	Pooled
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
AHD	1.04 (1.02, 1.06)	1.06 (1.04, 1.08)	1.04 (1.02, 1.06)	1.04 (1.02, 1.06)	1.05 (1.03, 1.07)	1.03 (1.02, 1.05)	1.04 (1.03, 1.06)	1.04 (1.03, 1.05)
CHF	0.96 (0.94, 0.98)	0.98 (0.96, 1.00)	0.96 (0.94, 0.98)	0.94 (0.92, 0.96)	0.96 (0.94, 0.97)	0.95 (0.94, 0.97)	0.96 (0.94, 0.97)	0.96 (0.95, 0.97)
TIA	0.95 (0.92, 0.97)	0.94 (0.91, 0.96)	0.94 (0.92, 0.96)	0.94 (0.92, 0.96)	0.93 (0.91, 0.95)	0.95 (0.93, 0.97)	0.92 (0.90, 0.94)	0.94 (0.93, 0.95)
PVD	1.00 (0.98, 1.02)	0.99 (0.97, 1.01)	0.99 (0.97, 1.01)	0.97 (0.96, 0.99)	0.97 (0.96, 0.99)	0.97 (0.96, 0.99)	0.96 (0.94, 0.97)	0.98 (0.97, 0.98)
Other CD	1.02 (0.99, 1.04)	1.00 (0.98, 1.02)	1.01 (0.99, 1.03)	0.99 (0.97, 1.00)	1.02 (1.01, 1.04)	1.02 (1.00, 1.04)	1.00 (0.98, 1.01)	1.01 (1.00, 1.01)
Liver disease	0.88 (0.85, 0.91)	0.95 (0.91, 0.99)	0.93 (0.89, 0.97)	0.95 (0.92, 0.98)	1.00 (0.97, 1.03)	1.04 (1.00, 1.07)	1.03 (1.00, 1.06)	0.97 (0.96, 0.99)
COPD	1.00 (0.97, 1.02)	1.00 (0.98, 1.03)	1.00 (0.98, 1.02)	1.01 (0.99, 1.03)	1.00 (0.98, 1.02)	1.00 (0.98, 1.02)	0.99 (0.97, 1.01)	1.00 (0.99, 1.01)
GI bleed	0.99 (0.96, 1.02)	1.03 (1.00, 1.06)	0.98 (0.95, 1.01)	0.98 (0.95, 1.00)	0.94 (0.91, 0.96)	1.00 (0.97, 1.02)	0.95 (0.93, 0.98)	0.98 (0.97, 0.99)
Dysrhythmia	0.99 (0.97, 1.02)	1.00 (0.98, 1.03)	1.00 (0.98, 1.02)	1.00 (0.98, 1.02)	0.98 (0.96, 1.00)	1.01 (0.99, 1.03)	0.99 (0.97, 1.01)	1.00 (0.99, 1.00)
Cancer	1.03 (0.99, 1.06)	1.04 (1.00, 1.07)	1.05 (1.02, 1.08)	1.02 (0.99, 1.05)	1.02 (0.99, 1.05)	1.02 (0.99, 1.05)	1.02 (1.00, 1.05)	1.03 (1.02, 1.04)
Diabetes	1.02 (1.00, 1.05)	1.04 (1.01, 1.06)	1.04 (1.02, 1.07)	1.02 (1.00, 1.04)	1.01 (0.99, 1.03)	0.99 (0.97, 1.03)	0.98 (0.96, 1.00)	1.01 (1.00, 1.02)

* Adjusted for all other comorbidities in the table, ESRD network, and all other time-fixed covariates. AHD = Atherosclerotic heart disease, CHF = Congestive heart failure, PVD = Peripheral vascular disease, CD = cardiac disease, COPD = Chronic obstructive pulmonary disease, GI = Gastrointestinal

Table 22. Adjusted* assessment of hospitalization and skilled nursing care as time-varying predictors of vaccination

Year	1999	2000	2001	2002	2003	2004	2005	Pooled
	Adjusted	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Hospital days								
None	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
1 day	0.91 (0.83, 1.01)	0.80 (0.73, 0.87)	0.83 (0.76, 0.91)	0.82 (0.75, 0.89)	0.84 (0.77, 0.91)	0.79 (0.72, 0.86)	0.85 (0.79, 0.93)	0.83 (0.81, 0.86)
2-3 days	0.95 (0.91, 1.00)	0.96 (0.92, 1.00)	0.95 (0.91, 0.99)	0.93 (0.89, 0.97)	0.91 (0.88, 0.95)	0.90 (0.87, 0.94)	0.95 (0.91, 0.98)	0.93 (0.92, 0.95)
4-14 days	0.84 (0.81, 0.87)	0.84 (0.81, 0.87)	0.79 (0.77, 0.82)	0.87 (0.84, 0.89)	0.86 (0.84, 0.88)	0.85 (0.83, 0.88)	0.83 (0.81, 0.85)	0.84 (0.83, 0.85)
15-25 days	0.59 (0.54, 0.64)	0.61 (0.56, 0.66)	0.62 (0.58, 0.67)	0.68 (0.64, 0.73)	0.64 (0.60, 0.68)	0.66 (0.62, 0.70)	0.62 (0.58, 0.66)	0.64 (0.62, 0.65)
26-30 days	0.35 (0.30, 0.41)	0.31 (0.26, 0.37)	0.30 (0.26, 0.35)	0.41 (0.36, 0.46)	0.42 (0.37, 0.47)	0.47 (0.42, 0.53)	0.42 (0.38, 0.47)	0.40 (0.38, 0.42)
SNF days								
None	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
1 day	0.62 (0.40, 0.96)	0.87 (0.67, 1.13)	0.52 (0.38, 0.72)	0.96 (0.78, 1.19)	1.07 (0.83, 1.38)	1.23 (1.00, 1.52)	0.98 (0.80, 1.19)	0.95 (0.86, 1.04)
2-3 days	0.58 (0.42, 0.80)	0.67 (0.53, 0.83)	0.67 (0.55, 0.82)	0.58 (0.48, 0.70)	0.62 (0.52, 0.73)	0.72 (0.59, 0.88)	0.67 (0.56, 0.80)	0.65 (0.60, 0.70)
4-14 days	0.64 (0.58, 0.71)	0.61 (0.55, 0.67)	0.64 (0.58, 0.70)	0.66 (0.60, 0.71)	0.67 (0.62, 0.72)	0.71 (0.66, 0.76)	0.65 (0.61, 0.70)	0.66 (0.64, 0.68)
15-25 days	0.63 (0.56, 0.72)	0.55 (0.48, 0.62)	0.61 (0.54, 0.67)	0.66 (0.60, 0.72)	0.63 (0.58, 0.69)	0.68 (0.63, 0.74)	0.65 (0.60, 0.70)	0.64 (0.62, 0.66)
26-30 days	0.68 (0.59, 0.78)	0.59 (0.52, 0.67)	0.55 (0.49, 0.62)	0.67 (0.61, 0.74)	0.61 (0.56, 0.67)	0.72 (0.66, 0.78)	0.72 (0.67, 0.78)	0.66 (0.64, 0.69)

*Adjusted for age, race, sex, cause of ESRD, vintage, adherence, mobility aids, ESRD network, oxygen use, baseline hospital days and comorbidities

Figure 4. Distribution of vaccination administration by month and year

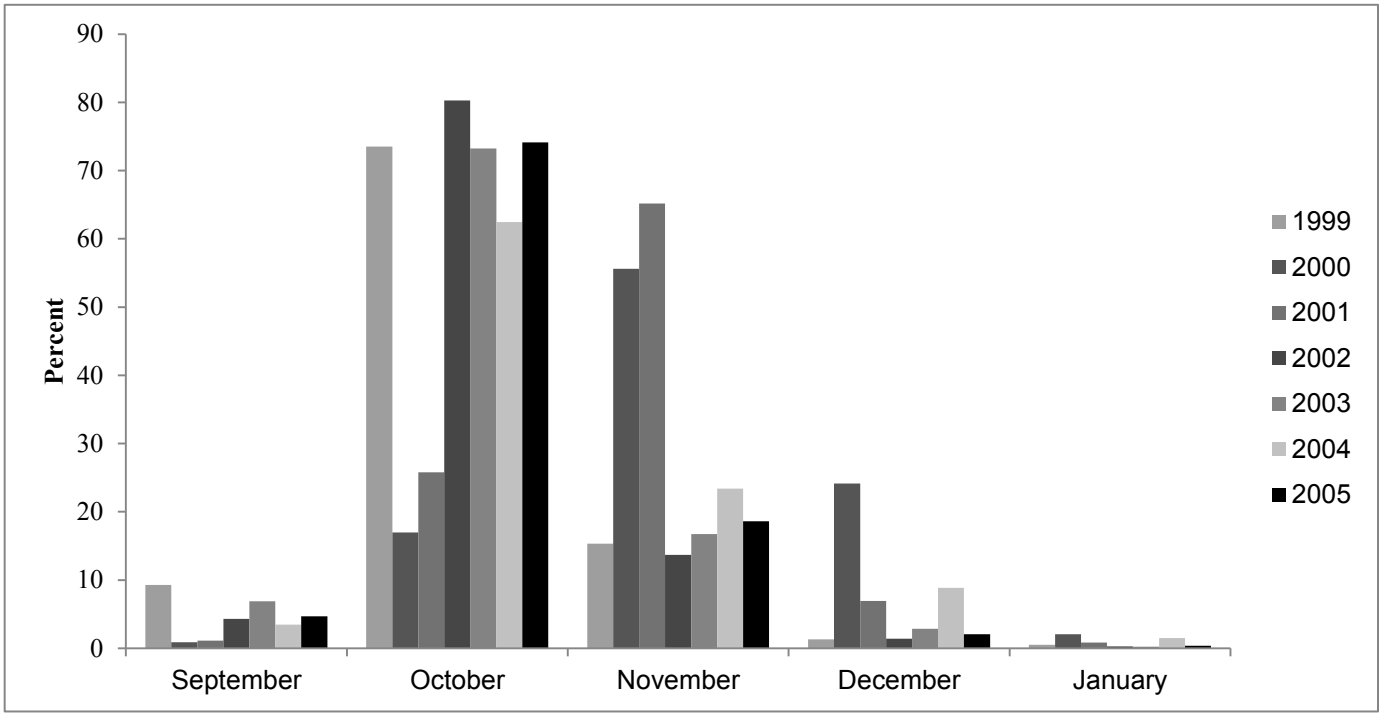


Figure 5. Cumulative incidence of vaccination by hospital days and year

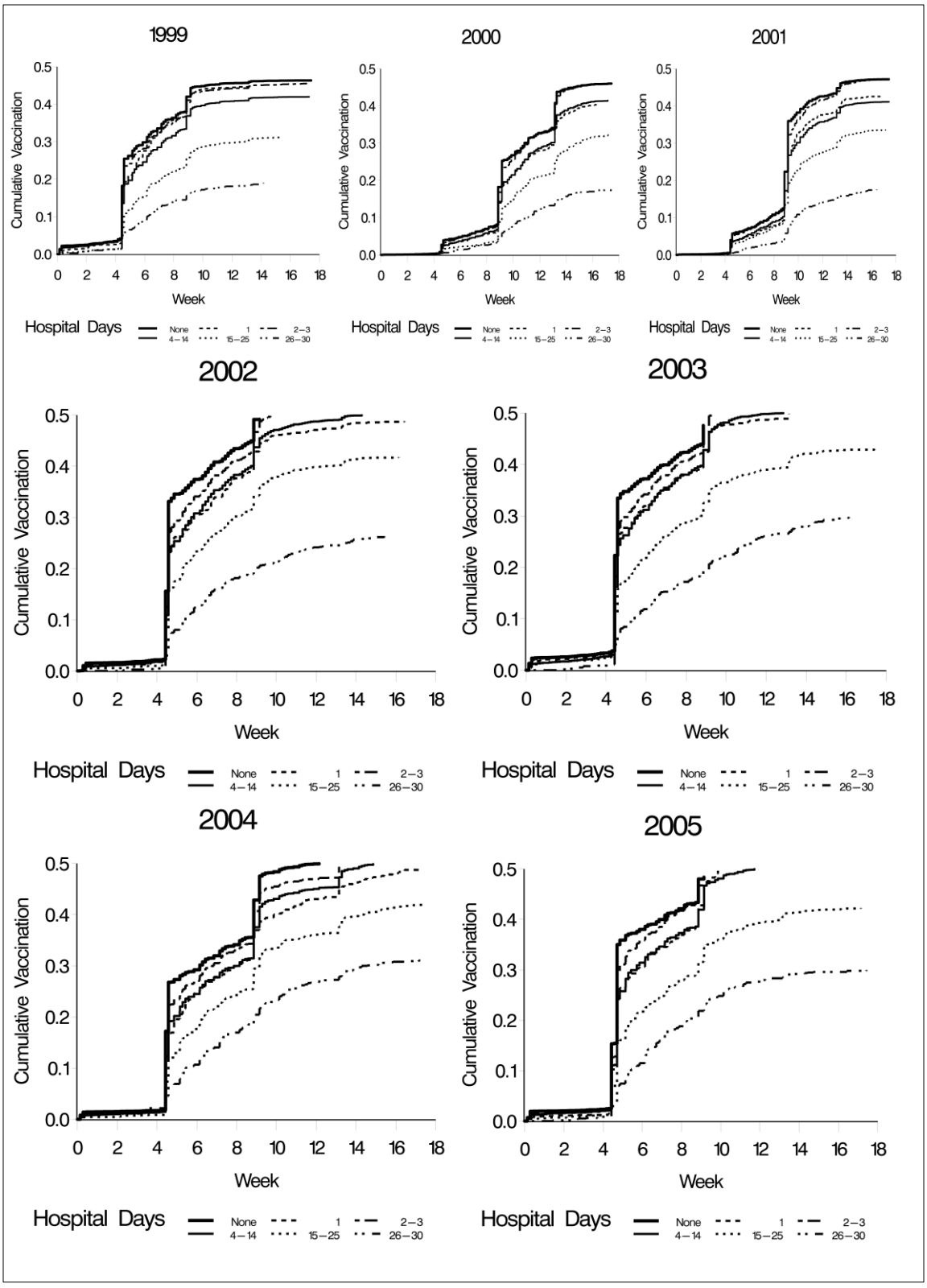
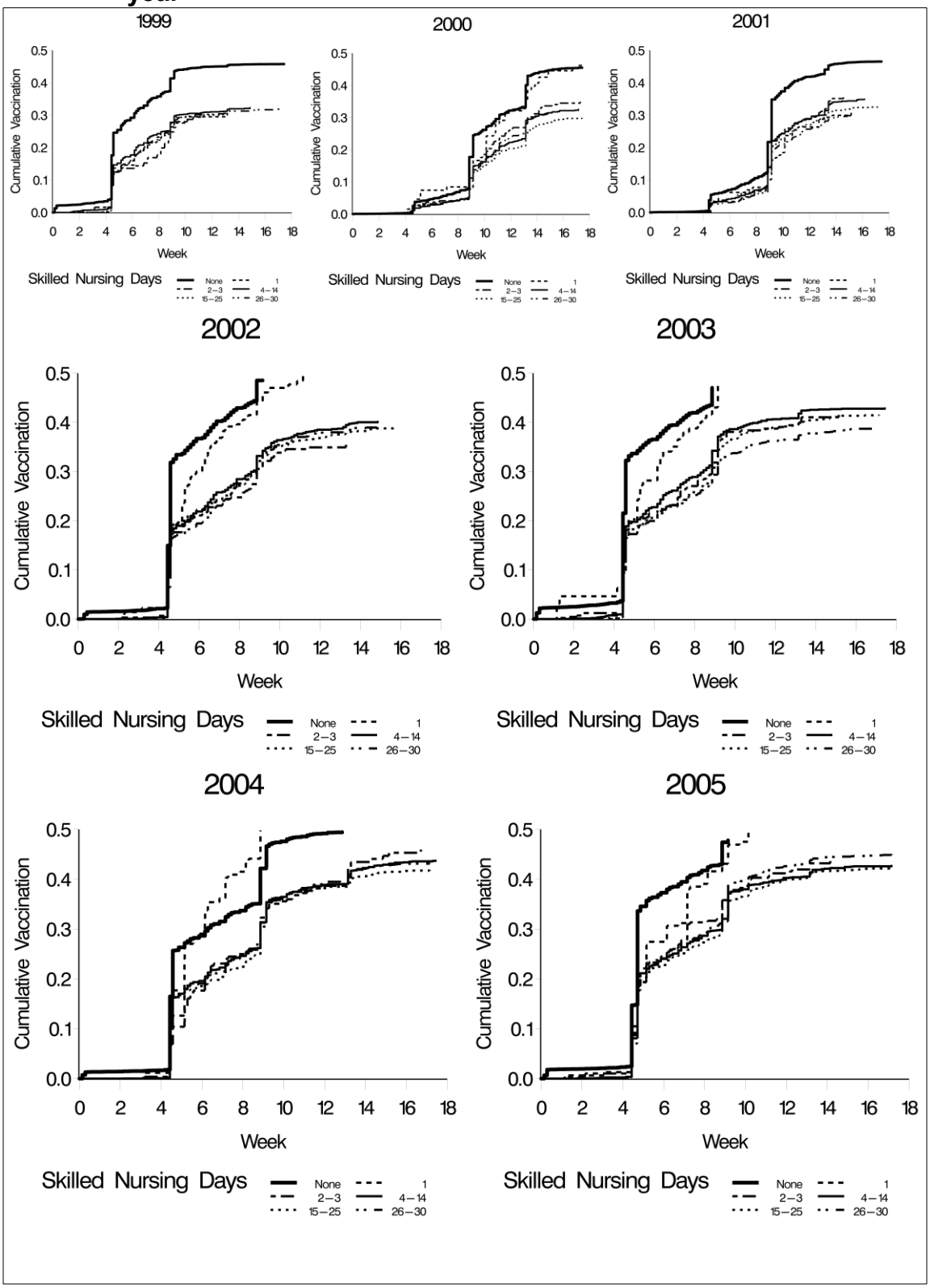


Figure 6. Cumulative incidence of vaccination by skilled nursing days and year



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VII. RESULTS: "ESTIMATING INFLUENZA VACCINE EFFECTIVENESS USING A MARGINAL STRUCTURAL MODEL TO CONTROL FOR THE HEALTHY USER BIAS"

A. Introduction

Administration of trivalent, inactivated seasonal influenza vaccine to patients on hemodialysis has become routine practice at most dialysis clinics over the past two decades. Although influenza vaccine has been recommended by the Advisory Committee on Immunization Practices for all ESRD patients for over 40 years,[1] it is currently unclear if the vaccine has an effect on clinical health outcomes such as mortality.[2] To date, there have been only two studies in this population that estimated vaccine effectiveness (VE) that produced conflicting results: one study reported VE for influenza/pneumonia hospitalizations to be 12-14% and 25% for all-cause mortality,[3] while a more recent study reported no effect.[4] Recent studies in the non-dialysis, elderly population have suggested that large VE effects (up to 50% reduction of all-cause mortality in some studies[5-7]) obtained from standard epidemiologic studies may be due to confounding by uncontrolled variables leading to the healthy user bias, and the true vaccine effect may be smaller than previously thought.[8-12] It has been suggested that functional status/frailty is the primary cause of this confounding.[8] Patients who are currently hospitalized or are receiving skilled nursing care are likely at a greater risk of death. Because preventive medications are less likely to be

administered to patients near death,[13] hospitalization and skilled nursing care may also represent strong predictors of vaccination. Changes in frailty occur over time and likely have acute effects on death, and should therefore be accounted for in a time-varying manner. It is also likely that frailty, marked by hospitalization or skilled nursing care is affected by prior vaccination during the influenza season.[14] Therefore, frailty is likely a time-varying confounder since it predicts vaccination status, is affected by prior vaccination status, and is clearly an independent risk factor for mortality. In the situation of time-varying confounding that is affected by prior exposure, marginal structural models have been proposed to provide an unbiased, causal estimate.[15] We aimed to estimate the causal effect of influenza vaccination on mortality among patients on hemodialysis using a marginal structural model estimated with inverse probability of treatment weights.

B. **Methods**

Study Population

Cohorts were constructed using Medicare claims obtained from the USRDS. The USRDS is a population-based, national system that collects information on all patients with ESRD in the US. While mortality information is collected on all patients, detailed health claims are captured only for patients who have Medicare as their primary payer. Health information that is collected includes physician services, *ICD-9-CM* codes assigned to hospitalizations and outpatient care, information on routine dialysis care and immunization use.

We created cohorts in two different influenza seasons that were dominated by the same influenza strain and matched the vaccine strain: 1999-2000 and 2001-2002.[16,17] For comparison, we also created a cohort for the 2003-2004 season where the vaccine strain did not match the circulating virus.[18] To limit exposure misclassification, we used years before it was common to obtain influenza vaccine in the community, such as grocery stores and pharmacies. Our cohorts consisted of all adult, ESRD patients with Medicare as a primary payer and continuous hemodialysis use. Each yearly cohort consisted of patients who had initiated dialysis prior to October 1 of the preceding year. An eight month window from January 1 through August 31 of each year was used to identify insurance status and comorbidities for the patients in that cohort. Patients were required to be on continuous hemodialysis for 3 months prior to the start of follow-up. For example, the cohort identified for the 1999 season would have initiated dialysis prior to October 1, 1998 and would have had Medicare as a primary payer from January 1 – August 31, 1999 and used continuous hemodialysis from June 1 – August 31. Hospital days, skilled nursing days and vaccination status were assessed beginning on September 1 of each year. Cohort members were followed each year until they experienced death, loss-to-follow up or administrative censoring on August 31 of the following year.

Exposure and outcome assessment

To identify influenza vaccinations, Medicare Part A hospital/outpatient files and Part B physician/supplier files were searched for CPT codes 90724, 90656,

90658-60, HCPCS codes G0008 and G8482, and the *ICD-9-CM* procedure code 99.52.

Deaths are reported using CMS form 2746: ESRD Death Notification. Dialysis providers are required to submit this form within 30 days of a patient's death. Reporting of deaths is nearly complete – CMS estimates 99% of patient deaths are captured using this form.[19]

Covariates

Hospitalization and skilled nursing facility admission and discharge dates were assessed using the Medicare institutional claims. We counted the number of hospital and skilled nursing days in the prior 7 days and updated these variables at the beginning of each week.

We also adjusted for time-fixed baseline covariates. The Centers for Medicare and Medicaid Services form 2827, the Medical Evidence Form, was used to ascertain age, race, gender, first service date with ESRD, and cause of kidney failure. The eight month window from January 1 to August 31 was searched for oxygen use and pneumococcal vaccination (CPT code=90732, HCPCS code=G0009), and the total number of hospital days. Adherence to dialysis was calculated using the sum of the number of dialysis sessions over the eight month baseline period: patients were considered adherent if they had 95 sessions or more. Patients with no recorded dialysis sessions over the eight month period were dropped from the analysis. Use of mobility aids were ascertained by searching Part A and Part B claims for HCPCS equipment codes

for wheelchairs, walkers, canes, and assisted bathroom equipment during the baseline period (Table 9).

Statistical Analysis

A separate model was fit for each influenza season, where the origin was September 1 for each year and patients were followed until August 31 of the subsequent year. For the conventional analysis, we used pooled logistic models using week as the timescale to estimate discrete-time approximations[20] of hazard ratios[21] comparing vaccinated to unvaccinated within each year. The largest per week proportion of deaths was 3%, which satisfies the rare event requirement for the discrete-time approximation.[20] Vaccination was modeled as a time-varying covariate, with all cohort members entering the analysis in September 1 as unvaccinated. Once vaccinated, patients remained in the vaccinated category until they experienced death, were lost to follow-up, or were censored at the end of that influenza year (August 31).

The marginal structural model was estimated using inverse probability of treatment weights. These weights create a "pseudo-population" where each subject is weighted by the inverse of the probability of receiving the exposure that they actually did receive conditional on covariates.[22] Confounders should be distributed equally across vaccination groups in the pseudo-population. Vaccine effectiveness was estimated by comparing vaccinated to unvaccinated patients within this unconfounded pseudo-population.

To estimate the weights we fit a logistic model that treats each person-week as an observation (i.e. time-varying weights were estimated for each week

of follow-up, from September 1 through August 31st of the following year). The weights were calculated from the predicted values from the pooled logistic model using prior time-varying confounders, baseline confounders, and prior time-varying vaccination status as predictor variables. To ensure correct ordering of covariate and exposure data, we used covariate information up through the previous week, to predict the current week's vaccination status.[23] The denominator of the weights was estimated using a pooled logistic model for the probability of being vaccinated each week. We used all time-fixed covariates including number of baseline hospital days modeled using categories (0, 1-8, 9-15, 16+ days), age modeled with a quadratic term, and indicator variables for the time-varying number of hospitalization and skilled nursing facility days that a patient had in the past 7 days. The weights were stabilized by using a pooled logistic model to estimate the marginal probability of being vaccinated. We used robust variance estimates equivalent to generalized estimated equations with an independent working covariance matrix.[24]

To quantify bias in both the conventional and MSM estimates, we ran the same models during the pre-influenza period (September 1 through the day before the influenza season started each year). When limited to the period prior to the start of influenza season when vaccine effectiveness should be biologically negligible, we would expect the HR estimate to be close to 1 if no confounding were present. This method identifies if analyses remain biased even after adjustment or weighting.[9,25] We estimated the start of each influenza season by using national influenza surveillance data from the Centers for Disease Control

and Prevention. We defined the start of the season as the midpoint of the first week where more than 10% of the isolates were positive for influenza. Analyses were conducted using SAS 9.2 (Cary, NC). This study was determined to be exempt from full review by the Institutional Review Board at the University of North Carolina.

C. **Results**

There were more than 100,000 patients in each yearly cohort, from which we sampled 10% to run the models. Overall, 48% of patients were vaccinated in 1999 and 2001, and 58% were vaccinated in 2003. In all years, patients who received the vaccine were older, more likely to be white, had fewer baseline hospital days, higher adherence to dialysis, and more likely to have had the pneumococcal vaccine than unvaccinated patients (Table 23). These relationships were also observed in the 10% sampled data.

Standard Cox regression comparing vaccinated to unvaccinated patients produced naive estimates of VE on mortality between 20% (14%, 25%) in 2003 and 27% (21%, 32%) in 2001 (Table 24). Adjustment for time-fixed baseline covariates moved the estimate away from the null; however, including time-varying hospitalization and skilled nursing care moved the estimate toward the null. The fully adjusted models produced estimates of VE ranging from 13% (6%, 19%) in 2003 to 20% (13%, 27%) in 2001. For all years, the model estimates were much farther from the null in the pre-influenza period. The fully adjusted models produced estimates closest to the null, however these were still more

exaggerated than the estimates from the full season, indicating residual confounding.

The stabilized weights for both the complete follow-up and the pre-influenza season analyses were well behaved with means of near 1 for all years (Table 25). There was less variation between years using the marginal structural model, with estimates of VE ranging from 34% (24%, 43%) in 2003 to 40% (31%, 48%) in 2001 (Table 26). Estimates from the pre-influenza period analysis suggested that these results were also subject to residual confounding. There was a suggestion of modification by baseline health status (measured by hospitalization during the baseline period) in 1999, with a less biased effect in the non-hospitalized patients; however, this difference did not persist in later years (Table 26).

D. **Discussion**

We attempted to control the healthy user bias by using measurements of time-varying hospitalization and skilled nursing care, analyzed with standard and marginal structural models to account for time-varying confounding. This method did not appear to capture all of the differences in health status between the vaccinated and unvaccinated populations, and using the marginal structural model resulted in estimates with greater bias than conventional Cox proportional hazards models. The VE estimates of 34%-40% from the marginal structural model in all years most likely exaggerated the protective effect of the vaccine on mortality, as less than 10% of wintertime deaths are attributed to influenza each year.[26,27]

The standard Cox regression model that was adjusted for time-varying hospitalization and skilled nursing care produced estimates of 13% – 20%, which is closer to what has been seen in the general elderly population. However, even these estimates were likely biased as evidenced by high VE effects in the pre-influenza period. Estimates of VE on all-cause mortality in previous studies in the general elderly population have ranged from 5% (1%, 8%) from a case-centered logistic regression model,[28] to 21% (19%, 23%) from a Poisson model adjusted for number of prescriptions.[29] Although the population on hemodialysis most likely has similar levels of immune-compromise as elderly individuals, caution is needed in directly comparing the two groups. Patients on hemodialysis are seen at medical facilities 2-3 times per week for dialysis treatments, therefore the reasons for being vaccinated may be different.

There are several assumptions that have to be made to interpret the estimate from a marginal structural model causally, namely positivity, correct model specification, uninformative censoring, and exchangeability.[15] We believe that we adequately satisfied the first three assumptions. Patients were vaccinated within all levels of the covariates and the weights had distributions with mean of 1.0, suggesting that there were no positivity violations.[23] Our results were robust to model specification and choice of the functional form of the model. Also, we had little loss-to-follow-up in each cohort and thus even if the censoring were informative it would not have strongly affected the estimates. It is doubtful, however, that the assumption of exchangeability was satisfied, and using IPTW may have amplified this bias due to unmeasured confounding.

This is the first study of influenza VE to our knowledge that has attempted to use time-varying measures of health status. While patients that are hospitalized or have skilled nursing care are clearly at increased risk for mortality, these two variables did not capture all of the differences in health status between vaccinated and unvaccinated patients. It is possible that there may be other indicators of health status in this population that may be measurable in claims data that could help address the residual confounding bias. For example, recent use of other preventive health care services could represent proxies for important time-varying confounders.[30] Previous research in the USRDS database has found that doses of erythropoiesis stimulating agents tend to be reduced in patients nearing death.[31] This may also be true with other preventive medications used in this population such as intravenous vitamin D and iron administration. Recent missed outpatient dialysis sessions could also be used to identify patients in failing health.

Perhaps because of the potential for unmeasured confounding, there have been only a few studies that have fit marginal structural models using administrative claims data.[32-36] None to our knowledge have used a negative control to verify the assumption of no unmeasured confounding. Two studies used the USRDS data: one investigated low hemoglobin levels and risk of hospitalization and death,[37] and the other examined the effect of intravenous levocarnitine therapy on hospitalization.[38] Either one or both of these studies used hospitalization, comorbid conditions, anemia treatment (intravenous iron, erythropoietin) vitamin D, and blood transfusions as time-dependent covariates to

estimate the weights. These variables could potentially be used in our models; however, it is questionable how prior vaccination could be related to some of these measures.

Our study may also have been subject to some exposure misclassification. Vaccinations that were paid for out of pocket by a patient would not be captured in our data. Because the influenza vaccine is covered by Medicare for our study population and dialysis patients have healthcare encounters 2-3 times per week, we expect that the number of people who paid out of pocket would be low. In addition, we used years before it was common to receive the influenza vaccine at grocery stores or pharmacies.

In summary, both the conventional and marginal structural models appeared to remain biased even after accounting for time-varying confounding, which likely resulted in exaggeration of the protective effect of the vaccine. Using the pre-influenza period as a negative control allowed us to determine if residual confounding was affecting our estimates. Further research is needed to identify time-varying, claims-based predictors of preventive health care use in the dialysis population. Identification of such predictors could reduce bias in studies of preventive health services in patients on hemodialysis.

Table 23. Description of study cohorts

Season	1999				2001				2003			
Vaccine match	Match				Match				Mismatch			
Start of season	11/24/1999				1/9/2002				10/22/2003			
	Full cohort		Sample		Full cohort		Sample		Full Cohort		Sample	
Variable	V* N=56,504 %	Not V N=62,155 %	V N=5,533 %	Not V N=6,260 %	V N=61,482 N (%)	Not V N=66,472 N (%)	V N=6,121 %	Not V N=6,595 %	V N=77,606 N (%)	Not V N=55,548 N (%)	V N=7,751 %	Not V N=5,519 %
Mean age (SD)	63.0 (14)	61.0 (15)	62.8 (14)	61.1 (15)	63.8 (14)	61.7 (15)	63.6 (14)	61.8 (15)	64.2 (14)	62.7 (15)	64.0 (14)	62.5 (15)
Male sex	52.8	51.0	54.2	50.6	53.0	51.8	51.5	51.9	53.3	52.3	53.8	53.1
Race												
White (3)	56.3	47.3	57.1	48.2	57.3	48.5	57.6	47.9	57.0	49.6	57.0	49.7
Black (2)	38.9	47.2	38.1	46.4	37.7	45.8	37.2	46.3	37.5	44.9	37.5	45.1
Other (1)	4.8	5.4	4.7	5.4	5.0	5.7	5.2	5.7	5.5	5.5	5.4	5.3
Cause of ESRD												
Diabetes	41.2	39.4	41.1	39.2	42.9	41.8	43.5	42.4	45.3	42.9	45.8	41.9
Hypertension	30.2	31.4	30.1	30.7	29.7	30.7	30.2	30.6	29.3	30.7	28.5	32.1
Glomerulonephritis	12.5	13.0	13.5	13.2	11.8	12.0	11.4	11.4	10.6	10.9	11.0	10.5
Cystic Kidney	3.1	2.7	2.9	2.7	2.8	2.5	2.4	2.5	2.5	2.3	2.5	2.2
Other	12.8	13.5	12.4	14.2	12.7	13.1	12.5	13.1	12.2	13.3	12.3	13.4
1 or more mobility aid	6.9	6.6	7.1	6.8	6.6	6.6	6.4	6.8	7.2	6.8	6.9	6.7
Vintage (years)												
0	2.1	2.0	2.5	2.2	2.0	2.0	2.0	1.9	1.9	1.8	1.8	2.0
1-2	41.9	39.9	41.5	40.1	41.0	39.3	41.7	39.0	40.6	37.1	40.3	37.7
3-4	25.8	24.6	25.5	23.1	26.3	25.0	25.6	25.0	25.1	26.9	25.5	25.7
5-9	22.8	23.3	22.9	24.9	22.7	24.0	22.8	25.1	23.9	24.0	24.2	24.6
10+	7.3	10.2	7.6	9.8	8.1	9.8	8.0	9.0	8.4	10.1	8.2	10.0
Adherent to dialysis	89.3	78.8	89.0	78.9	90.6	80.8	90.4	80.9	92.1	82.4	92.1	81.6
Mean hosp. days (SD)	7.5 (14)	9.9 (18)	7.7 (14)	9.7 (18)	7.6 (14)	10.4(19)	7.5(14)	10.7(19)	8.0 (15)	11.3(20)	8.1 (15)	10.4(19)
Oxygen Use	4.7	4.5	5.1	4.4	5.7	5.0	5.5	5.0	5.9	5.5	6.2	5.5
Pneumococcal vaccination	2.3	1.5	2.6	1.2	3.4	2.0	3.3	2.0	3.2	1.9	3.1	2.0

* V = vaccinated

Table 24. Estimates of effect of vaccination on mortality using standard Cox regression

	1999		2001		2003	
Model	Mortality HR (95% CI)	Mortality HR (95% CI)	Mortality HR (95% CI)	Mortality HR (95% CI)	Mortality HR (95% CI)	Mortality HR (95% CI)
	Full follow-up	Pre-flu period	Full follow-up	Pre-flu period	Full follow-up	Pre-flu period
Crude Cox model	0.79 (0.73, 0.85)	0.50 (0.42, 0.60)	0.73 (0.68, 0.79)	0.48 (0.41, 0.57)	0.80 (0.75, 0.86)	0.18 (0.12, 0.27)
Baseline adjusted* Cox model	0.73 (0.67, 0.79)	0.48 (0.40, 0.57)	0.69 (0.64, 0.75)	0.46 (0.39, 0.55)	0.74 (0.69, 0.80)	0.18 (0.12, 0.28)
Baseline + time-varying adjusted** Cox model	0.84 (0.77, 0.91)	0.63 (0.52, 0.76)	0.80 (0.73, 0.87)	0.62 (0.52, 0.73)	0.87 (0.81, 0.94)	0.29 (0.19, 0.44)

*Adjusted for age, race, cause of ESRD, vintage, adherence, mobility aids, oxygen use, pneumococcal vaccine, baseline hospital days
**Adjusted for all baseline variables and time-varying hospitalization and skilled nursing care

Table 25. Distribution of weights

Year	Mean (SD)	Minimum	Maximum
Full Season			
1999	0.99 (0.40)	0.48	14.31
2001	0.99 (0.39)	0.46	15.65
2003	1.00 (0.64)	0.36	30.82
Pre-flu period			
1999	1.00 (0.32)	0.47	15.17
2001	1.00 (0.28)	0.46	15.58
2003	1.00 (0.36)	0.46	39.86

Table 26. Estimates of effect of vaccination on mortality using marginal structural model* to account for time-varying confounding affected by prior exposure

	1999		2001		2003	
Model	Mortality HR (95% CI)	Mortality HR (95% CI)	Mortality HR (95% CI)	Mortality HR (95% CI)	Mortality HR (95% CI)	Mortality HR (95% CI)
	Full follow-up	Pre-flu period	Full follow-up	Pre-flu period	Full follow-up	Pre-flu period
Weighted, MSM model	0.65 (0.56, 0.75)	0.56 (0.44, 0.72)	0.60 (0.52, 0.69)	0.53 (0.44, 0.63)	0.66 (0.57, 0.76)	0.20 (0.13, 0.30)
Weighted, MSM model by baseline hospitalization						
No hospitalization	0.84 (0.61, 1.15)	0.80 (0.47, 1.35)	0.63 (0.49, 0.81)	0.58 (0.42, 0.80)	0.69 (0.56, 0.84)	0.25 (0.12, 0.55)
Hospitalized	0.57 (0.48, 0.67)	0.47 (0.38, 0.58)	0.58 (0.49, 0.69)	0.51 (0.42, 0.63)	0.64 (0.53, 0.78)	0.18 (0.11, 0.29)

*Covariates used in denominator of weight: race, age, cause, vintage, adherence, mobility aids, oxygen use, pneumococcal vaccine, categorized baseline hospitalization, hospitalization and skilled nursing care in the past 7 days

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VIII. CONCLUSIONS

The results of this dissertation suggest that the healthy user bias is present and likely very strong in a population of patients with end-stage renal disease. Therefore, conventional analyses of influenza vaccine effectiveness that compare vaccinated patients with unvaccinated patients are likely to be biased. Using the period prior to influenza circulation or the “pre-influenza” period when the vaccine should have no effect, is a negative control that allows the investigator to check the amount of residual bias.

In Specific Aim 1, we used a natural experiment to control for the healthy user bias among patients on hemodialysis. We used the vaccine during a mismatched year as a working “placebo” and compared its effectiveness to well-matched vaccines in subsequent years. The pooled ratio of hazard ratios comparing matched seasons with a placebo season resulted in a VE of 0% (95% CI: -3,2%) for ILI, 2% (-2,5%) for hospitalization, and 0% (-3,3%) for death. Using this novel study design, we found little evidence that the well-matched vaccines were more effective than the mismatched vaccine for the prevention of ILI, influenza/pneumonia hospitalization and all-cause mortality.

In Specific Aim 2, we assessed two time-varying covariates – hospitalization and skilled nursing care in the past 30 days, as predictors of vaccine use. Patients with any length of hospital stay were less likely to be vaccinated, and this association was stronger in patients with longer stays (15-25

days: HR = 0.64 (95% CI: 0.62, 0.65); 26-30 days: HR = 0.40 (95% CI: 0.38, 0.42). Patients were equally likely to be vaccinated if they received skilled nursing care for 1 day (HR = 0.95 (95% CI: 0.86, 1.04)), but less likely to be vaccinated if they had longer periods of skilled nursing care (26-30 days HR = 0.66 (95% CI: 0.64, 0.69)). This finding supports the hypothesis that patients who are very sick are less likely to receive preventive care, including vaccinations. Because hospitalization and skilled nursing care are both associated with mortality, these variables could be used to adjust for confounding due to the healthy user bias in studies of influenza vaccine effectiveness on mortality.

Specific Aim 3 assessed VE for all-cause mortality by using a marginal structural model. This approach accounted for time-varying confounding by hospitalization and skilled nursing care that was affected by prior vaccination status. The marginal structural model remained biased even after accounting for these time-varying confounders, which likely resulted in exaggeration of the protective effect of the vaccine. It is possible that by using this method the bias was amplified. Additional variables that characterize health status are needed to obtain a more accurate estimate of VE.

In general, controlling for the healthy user bias using a natural experiment that implicitly controlled for all underlying health status and healthy behaviors resulted in estimates of VE for all outcomes that were close to the null. This suggests that the current influenza vaccine strategy may have a smaller effect on morbidity and mortality in the ESRD population than previously thought. While this work is not meant to suggest that vaccination should be discouraged, we

hope to spark the discussion of re-evaluating the current vaccine strategy for high-risk patients with end-stage renal disease.

There are alternate strategies that are already approved and recommended for other populations or vaccines currently being developed or used in other countries. For example, adjuvants such as AS03 and MF59 can act as a delivery system for the vaccine virus and potentiate the immunogenic response. One recent study demonstrated a significantly higher antibody response in patients on hemodialysis who use the AS03a adjuvant vaccine compared with the standard vaccine.[1] A high-dose vaccine that contains three times the amount of virus compared with standard vaccine, also offers an alternative strategy.[2] This vaccine is currently approved for the general elderly population, with no specific recommendation for high-risk patients. Finally, an intradermal vaccine was just licensed by the Food and Drug Administration. Currently this vaccine uses 40% less antigen than TIV to obtain the same immune response. There is potential for this route of administration to deliver higher doses of antigen for immunocompromised patients.

A. **Strengths**

There has been considerable debate in the literature regarding the effectiveness of influenza vaccines in the general elderly population. Various attempts have been made to control for the healthy user bias. This dissertation adds to the literature by using two novel methods to assess influenza VE in a high-risk population. The first method was a natural experiment. By comparing vaccinated patients in years when there was good vaccine match with vaccinated

patients in a year when there was a mismatch, we were able to inherently control all unmeasured health behaviors that could never be captured in an administrative claims dataset. The second method was a marginal structural model. This approach accounts for time-varying confounders affected by prior exposure, and allows for an estimate of VE that is unconfounded by time-varying health status. Neither method has been used in VE studies, and only a few examples of marginal structural models using administrative claims data can be found in the literature.[3-6]

Other strengths of this work included elements of the design and analysis. We used a variety of years in each analysis, as VE can vary from year to year. We selected certain years based on criteria of each influenza season to minimize variation between seasons. For example, we used only seasons that were severe and had the same type of influenza strain predominate. Furthermore, we specifically used the level of vaccine match in each season to make further comparisons. Strengths of our analysis included using covariates that had never been used before to control confounding. Adherence to dialysis was an important predictor of influenza vaccination, and could indicate exposure to other preventive health care services. We also attempted to capture functional status by using claims for mobility assistance devices; however the relationship of this variable with vaccination status was unclear. Using additional variables to explain a patient's underlying health status could decrease the amount of residual bias in the final estimate of VE.

The final strength of this study was using the USRDS database. This database captures information on all patients with ESRD in the US, thus this study can be considered population-based. Therefore, our sample size was very large – we had more than 100,000 patients for each influenza season. Although we selected patients based on eligibility requirements, our estimates estimated the population effect among all those selected (i.e. hemodialysis and Medicare as a primary payer). Furthermore, because we are restricting our analysis to patients with Medicare as a primary payer, we should capture all vaccinations, regardless of where they were administered (i.e. hospital, dialysis clinic, pharmacy). Vaccinations would only be missed if patients paid out of pocket – and this scenario is expected to be only a small proportion of all influenza vaccinations as we limited our analysis to years before it became common practice to offer the vaccine in settings where paying out of pocket was necessary, such as grocery stores.

B. **Limitations**

One of the major limitations of using administrative claims databases is the lack of information on potential confounding variables. Therefore, the assumption of no unmeasured confounding may not be valid. While this assumption is inherent in all models of observational data, it is particularly important when using models for causal inference, as in the case of the marginal structural model. Although we cannot test this assumption, using a variety of baseline variables, as well as time-varying confounders may be adequate for this population. An important variable that we may not have captured fully was

frailty/functional status. We attempted to capture mobility by using claims for wheelchairs, walkers, canes and bathroom equipment. However, we would not have captured long-term mobility impairments, which could likely influence a person's functional status. Additionally, restricting the population to patients with end-stage renal disease reduces the variability in health status, as all patients are relatively sick because they are on dialysis. Finally, we did not have drug information, which could have further helped to elucidate healthy user behaviors by identifying those patients who were taking preventive medications, such as statins.

Another important limitation is ascertainment of outcomes used in this analysis. The best outcome to use for vaccine effectiveness studies would be lab-confirmed influenza. This information is rarely collected however; thus we had to use less specific outcomes, which could dilute the effect of the vaccine because some of the outcomes may have been caused by infections other than influenza. Additionally, there may have been error in collecting and coding of outcomes. Particularly in Study Aim 1, the outcomes of ILI and influenza/pneumonia hospitalization may have been misclassified. The specificity for the influenza/pneumonia outcome was likely high (i.e. if the patient did not have a claim, they did not have the outcome), which would not bias effect estimates even in the presence of modest sensitivity.[7] Additionally, it is likely that the ILI outcome was under-ascertained. Unless physicians were making their diagnosis in part on the basis of the patient's vaccination status during the visit, this misclassification would be non-differential and the bias would be toward the

null. Because this outcome has only been used in one other study, further validation of this outcome would strengthen the results. Additionally, using a dataset with drug information would likely find more cases of ILI if prescription drug claims for antiviral prescriptions (i.e. amantadine, rimantadine, oseltamivir, Zanamivir) could be ascertained.

C. **Future directions**

This research has attempted to resolve the methodological issues surrounding the healthy user bias using observational data. Our results from the natural experiment suggest that the vaccine does not work as well as previously thought. Because there are several other options on the market (either recommended for other populations or vaccine formulations used in other countries) a randomized controlled trial among patients on hemodialysis may be warranted. Due to ethical limitations this study could not be a placebo-controlled trial, however, patients could be randomized to either the “newer” vaccines or the standard TIV dose given currently. Vaccines that could be tested include the high-dose vaccine, intradermal vaccine, adjuvanted vaccines (used in Europe) or the TIV vaccine given in multiple doses. Both serological and clinical endpoints would be of interest.

Further analysis of comorbidity data and development of a method of ascertaining the severity of comorbidities in claims data is also needed. For example, it may be the case that a comordibity claim for a patient that has been vaccinated may indicate less severe disease and routine use of health care services, while the same comordibity claim in an unvaccinated patient could

represent severe disease, as patients who are unvaccinated are generally less healthy and less likely to receive routine services. Identifying patterns in codes or validation studies with linked databases could help to understand what certain comorbidity claims actually represent. This could not only assist with confounding control in studies of influenza vaccine effectiveness, but could also be used to obtain improved estimates in any health outcomes study that adjusts for comorbidities.

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