Seasonal Influenza Vaccination: Understanding Vaccine Effectiveness in Immunocompromised Adults

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Influenza vaccine effectiveness (VE) among immunocompromised (IC) adults is severely under-researched despite the large and increasing magnitude of this demographic group. Current IC adult influenza vaccine research is limited to vaccine immunogenicity and efficacy studies with small sample sizes, leaving substantial gaps in our understanding of influenza VE among IC adults. Our long-term objective is to understand the VE of influenza vaccines among IC adults to guide clinical decision making, decrease influenza-related hospitalizations, and improve influenza outcomes.

Using the Centers for Disease Control and Prevention datasets- Hospitalized Adult Influenza Vaccine Effectiveness Network (HAIVEN) and the U.S. Flu Vaccine Effectiveness Network (US FluVE)- from the 2017-2018 influenza season, we calculated and compared VE for inpatient and outpatient adults ≥18 years with and without immunocompromising conditions. The HAIVEN 2018-2019 dataset was used to determine the VE of the recombinant seasonal influenza vaccine compared to non-recombinant seasonal influenza vaccines in IC adults.

Of the 3524 adults enrolled in HAIVEN 2017-2018, 1210 (34.3%) had an IC condition. VE was 5% (95% CI, –29% to 31%) vs. 41% (95% CI, 27–52) among IC and non-IC adults, respectively. Of the 8900 individuals enrolled in US FluVE 2017-2018, 455 (8%) of the 5671 adults had an IC condition. VE was -5 (95% CI: -68, 34) among IC adults and 29 (95% CI: 20, 37) among non-IC adults. Finally, of the 3975 individuals enrolled in the HAIVEN 2018-2019 study,

952 (24%) individuals were classified as IC. VE for the recombinant and non-recombinant seasonal influenza vaccine was 39% (95% CI: -23, 70) and 10% (95% CI: -37, 41), respectively.

The results of our studies offer insight into the protection provided by influenza vaccines to IC adults. Understanding the effectiveness of the influenza vaccines will allow providers to suggest additional infection prevention measures such as increased masking during the influenza season, delayed vaccination, or potentially booster shots. By standardizing the definition of immunocompromised using ICD-10 and CPT codes, our research can be replicated in future influenza seasons and influenza vaccine studies. Preventing influenza infections in immunocompromised adults is critical for protecting this vulnerable population.

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Preface

Completing a PhD is never an easy task. This task was made monumentally more difficult by doing a PhD while working full-time in infectious disease research during a global pandemic. My committee deserves more thanks than I could ever express for the support they provided during these *unprecedented times* all while working as infectious disease and family medicine physicians and researchers. I am so grateful for opportunity the provided to grow as an epidemiologist and researcher.

Thank you to the study participants who graciously participated in the HAIVEN and U.S. FluVE studies which allowed us to have a robust and large study population. Large, multi-center, prospective studies are challenging, resource intensive, and require adaptability. The HAIVEN and U.S. FluVE studies were so fortunate to have PIs and study personnel that worked tirelessly to ensure successful completion of the studies. Thank you to all the site and CDC PIs who provided feedback and support on our initial paper (aim 1). Thank you to Caroline Cheng (University of Michigan) for providing the beautifully written and detailed exclusion SAS code for aim 3, saving me hours of frustration and stress. Thank you to Kathleen Sheridan for the SAS assistance at the beginning of the project and for helping me to troubleshoot a key component of my code.

Finally, thank you to my friends, coworkers, and family for being there for this entire graduate school journey. Thank you for checking in, cheering me on, and listening to me excitedly talk about flu vaccines. Thank you to my mom for her endless support, daily phones calls, and for making bad days better as only a mom can. Lastly, but most importantly, thank you to my wonderful husband, Adam, who has been on this adventure with me since day one. He had no idea when he dropped me off at Nancy Glynn's office in Fall 2015 to talk about potential graduate

programs that I would spend the next six years at the School of Public Health. From a pandemic wedding during the second semester of my PhD program to late nights writing papers, he has been a constant source of support and encouragement. After an MHA (Adam), an MPH (me), and a PhD (me) all at the University of Pittsburgh School of Public Health, we are very excited to no longer be making tuition payments for the first time since Fall 2014.

1.0 Background

During the 2018-2019 influenza season, there were an estimated 29 million cases of influenza, including 380,000 hospitalizations and 28,000 deaths from influenza in the United States.[1] These hospitalizations disproportionately affect adults 65 years and older and individuals with high-risk conditions.[2] The economic burden of influenza is also significant at approximately $2.5 billion in direct medical costs associated with influenza.[3] With the current COVID-19 pandemic straining healthcare systems and resources, preventing influenza infections is paramount. A study using data from the 2015-2016 influenza season found influenza vaccinations halved the risk of hospitalizations, reinforcing the need for improved vaccination rates, especially among immunocompromised patients.[4] Furthermore, immunocompromised individuals had a 5-8 fold higher risk of hospitalizations from acute respiratory illnesses compared to non-immunocompromised individuals.[5]

1.1 Defining Immunocompromised Adults

Due to advances and expanded uses of biologics, medications, and chemotherapy, the number of immunocompromised adults continues to increase annually. The level of immunosuppression varies between the immunocompromising conditions primarily based on the immunosuppressing medications involved. For this reason, the groups are hierarchically listed below based on level of immunosuppression. Our work will focus on adults with the following immunocompromising conditions, described in detail below: solid organ transplants, stem cell

transplants, underlying immunodeficiencies, connective tissue disorders, chemotherapy and radiation therapy, hematologic conditions, chronic steroids, and HIV.

In 2018, 36,527 transplants were performed in the United States, a number expected to grow as advancements, such as HIV+ donor to HIV+ recipient transplants, increase.[6] Solid organ transplant recipients require a regimen of immunosuppressive drugs to prevent the recipient's immune system from attacking and rejecting the donated organ. Without the immunosuppressive drugs, transplant recipients face acute and chronic rejection which can damage their transplanted organs.

Approximately 22,000 stem cell transplants are performed each year, occurring predominantly in white individuals.[7] Prior to undergoing a stem cell transplant, recipients receive a myeloablative regimen to destroy hematopoietic cells in the bone marrow followed by either total body radiation therapy or chemotherapy to reduce or eradicate tumor cells.[8–10] After a stem cell transplant, the patient is at risk for viral, bacteria, and fungal infections due to the ablation of their immune system prior to transplant. The length of time they remain immunosuppressed varies based on the intensity of their conditioning regimen.

Underlying immunodeficiencies consist of over 200 different types of primary immunodeficiency diseases which range extensively in severity. Some types, such as severe combined immunodeficiency, are typically diagnosed in infancy, require intense isolation, and can cause premature death if not properly managed. While other forms, such as common variable immunodeficiency, may not be diagnosed until adulthood.

Connective tissue disorders broadly groups various diseases such as rheumatoid arthritis and lupus. The number of individuals affected has not been well documented due in part to underdiagnosis. Management of connective tissues disorders is patient specific and differs based

on type of connective tissue disorder, disease progression, severity, and comorbidities. Immunosuppressive medications like biologics, chemotherapy, and steroids are increasingly being used to treat and control these disorders.

Chemotherapy, immunotherapy, and radiation therapy are commonly used to treat cancer and function by preventing cell division, including division of healthy cells. While chemotherapy and radiation therapy have historically been limited to cancer treatment and stem cell transplants, their role as novel treatment options to treat non-cancer diseases, including relapsing multiple sclerosis, has been expanding.

The prevalence of the hematologic conditions, including leukemia and myeloma, is estimated at over 1.5 million in the United States.[11] Whereas chemotherapy and radiation therapy impact the body's blood cells, hematologic conditions alter the function of the body's T cells and B lymphocytes, crucial components of the immune system. Without a fully operational immune system, individuals are at higher risk for infections, including influenza.

Chronic steroids are used to treat a multitude of inflammatory conditions including irritable bowel syndrome, rheumatoid arthritis, and asthma. Estimating the impact of chronic steroid use is challenge given the lack of a standardized definition of what constitutes chronic steroid use. While chronic steroids can drastically improve the quality of life of individuals living with inflammatory conditions, they, like many other medications, suppress the immune system.

Approximately 1.8 million people are living with HIV in the United States.[12] Without treatment, HIV infections usually progress to AIDS (CD4 cell count <200 cells/microL or the presence of any AIDS-defining condition) and eventually death. However, advances in treatment options have made HIV a chronic condition. Since a sequela of HIV is a decreased CD4+ count,

even well managed individuals living with HIV can be more susceptible to infections than individuals not living with HIV.[13]

While the conditions above impact the immune system in different ways and at variable levels, the ability to compare immunocompromised to non-immunocompromised individuals is valuable in the medical community, especially in the context of vaccines. Currently, a standardized definition for the immunocompromising conditions listed above does not exist, causing issues when comparing multiple studies. Our research defined the ICD-10 codes and CPT codes used for each of the immunocompromising conditions, allowing similar vaccine effectiveness research to be replicated with subsequent influenza seasons and additional vaccine preventable infectious diseases.

1.2 Current Vaccine Immunogenicity

Currently, the CDC recommends all individuals six months and older without contraindications be vaccinated against influenza, including immunocompromised individuals.[14] The Infectious Diseases Society of America (IDSA) recommends the annual influenza vaccination for all immunocompromised adults and suggests immunocompromised adults avoid the live-attenuated influenza vaccines.[15]

Information on influenza vaccine immunogenicity, efficacy, and vaccine effectiveness among immunocompromised adults is extremely limited and primarily focuses on vaccine immunogenicity. Vaccine immunogenicity is measured by an individual's seroconversion (minimal fourfold increase in hemagglutination inhibition) and seroprotection (hemagglutination inhibition $\geq$ 1:40). Whereas vaccine effectiveness is how well a vaccine performs in the "real

world" outside of controlled clinical trials. As shown in Figure 1, current literature suggests vaccine efficacy fluctuates widely both between studies and between immunocompromising conditions.[16–32,33(p1)]

The large variations in vaccine efficacy between immunocompromised groups are a result of differing levels of immunosuppression both within and between groups, the small sample sizes of vaccine efficacy studies (often less than 100 participants), and the various influenza seasons represented. Additionally, influenza vaccine efficacy and effectiveness change each influenza season based on how well the strains included in the vaccine matched the circulating strains. Aims 1 and 2 addressed the gap in knowledge regarding vaccine effectiveness in immunocompromised adults by estimated inpatient and outpatient influenza vaccine effectiveness.

1.3 Influenza Strains

While there are four types of influenza- A, B, C, and D- only types A and B tend to cause substantive seasonal influenza in humans. Influenza A and influenza B strains are more variable than other circulating virus given their ability to mutate due to antigenic drift and antigenic shift. Antigenic drift causes small genetic mutations to the surface proteins. Usually, these changes are minor, but overtime, these changes accumulate and cause our bodies to not recognize the virus leading to influenza infection. Antigenic shift is the abrupt change in influenza A to which humans lack immunity and can create a new subtype. The emergence of these new subtypes is what leads to pandemics.[34]

The subtypes (influenza A) and lineages (influenza B) that circulate may change annually and are pressured by both antigenic drift and antigenic shift. For influenza A, changes to the viral

surface proteins hemagglutinin and neuraminidase cause the variations. There are 18 subtypes of hemagglutinin and 11 subtypes of neuraminidase leading to a potential 198 subtype combinations. Some subtypes, such as H1N1 and H3N2, have been circulating for decades if not longer, while others, such as H5N7, have very few human cases documented. The subtypes can further be broken down into clade and subclades which add additional challenges to strain selection.[35] Influenza B strains are divided into lineages- Victoria and Yamagata- that have some cross-protection. The B lineages are further divided into clades and subclades.[35] Unlike influenza A, variations occur less often in B lineages. The multitude of strains creates challenges when studying vaccine effectiveness as there are often numerous strains circulating in a given influenza season. However, the difference in vaccine effectiveness between immunocompromised and non-compromised individuals remain constant.

1.4 Vaccine Strain Selection

One of the most challenging aspects of manufacturing the annual influenza vaccine is choosing the strains to include. Selecting the strains to include in the North American influenza vaccine is based on year-round global surveillance. Based on strains selected by participating countries and surveillance data, the World Health Organization (WHO) recommends which strains should be included in the upcoming influenza vaccine. In the United States, an FDA advisory panel reviews the WHO recommendation along with additional country-specific data to determine which strains should be included in the influenza vaccines available in the United States.[36] Since the strains included in the influenza vaccine change annual, creating a multi-year influenza vaccine

cohort is not possible. *This can be problematic when attempting to study the effectiveness of influenza vaccines across multiple countries.*

1.5 Influenza Vaccine Availability in the United States

Outside of the influenza H1N1 monovalent influenza vaccines made available during the 2009 H1N1 pandemic, annual influenza vaccines are trivalent or quadrivalent vaccines and are available as live attenuated, high-dose, adjuvanted, and recombinant vaccines.[37] Due to the large number of influenza vaccines available, the emergence of pandemic strains, and the variability of the influenza virus, estimating the vaccine effectiveness for annual influenza vaccines can be challenging. Estimates of influenza vaccine effectiveness range from 19-52% for the overall population, including both adults and children, and 41-51% among hospitalized adults.[38–41]

While both trivalent and quadrivalent influenza vaccines are available worldwide, studies have shown the quadrivalent influenza vaccine provides better immunogenicity against influenza than the trivalent vaccine.[42–45] In the United States, for the 2021 influenza season, only quadrivalent vaccines are available and include inactivated, live-attenuated, adjuvanted, cell-based, and recombinant vaccines (FluBlok).

The live-attenuated quadrivalent influenza vaccine contains live-attenuate (weakened, not killed) influenza virus, is administered intranasally, and is only recommended for individuals 2-49 years old. Since it contains live-attenuated virus and is produced using eggs, it is not recommended for individuals who are pregnant, immunocompromised, children <4 years old with asthma, children 2-17 years old taking aspirin, and individuals with egg allergies.[46] The high-dose inactivated vaccine contains four times the antigen compared to standard dose vaccines and was

found to be more effective than the standard dose in individuals 65 years and older due to an aging-associate lower immune response.[4,15,47–49] The adjuvanted influenza vaccine contains an adjuvant (an ingredient) which elicits a stronger immune response. Like the high-dose vaccine, the adjuvanted vaccine is only recommended for adults 65 years and older.[50] The cell-based vaccine reflects how the vaccine is manufactured. Since cell-based vaccines are grown in cell-cultures instead of eggs, they are safe for individuals with egg allergies.[51] A 2020 study found that among US Medicare recipients, the recombinant, adjuvanted, and high-dose influenza vaccines worked better than the standard dose influenza vaccine.[52]

The recombinant vaccine is produced using the baculovirus-insect cell system instead of the traditional embryonated chicken egg and is therefore, egg-free. The recombinant vaccine is recommended for individuals 18 years and older, especially those 65 years and older, and is currently available as FluBlok. As individuals age, they develop more comorbidities and their immune systems naturally become less responsive, and they become at higher risk of serious complications should they develop influenza. A CDC study found that individuals 65 years and older had a stronger antibody response after vaccination with a recombinant influenza vaccine.[53] As with many efficacy studies, the sample size was small (n=200) and immunocompromised individuals were not specifically studied. Aim 3 estimated the vaccine effectiveness of the recombinant seasonal influenza vaccine in immunocompromised adults to ascertain if the increased immune response seen in adults 65 years and older is replicated in a population of immunocompromised adults.

1.6 Gaps in Knowledge

While vaccine efficacy can provide investigators insight to an individual's protection, it does not reflect how the vaccine will work in the "real-world". Vaccine effectiveness captures how well a vaccine protects against the disease in sub-optimal conditions. Compounding the issue of influenza vaccine effectiveness among immunocompromised adults is the large number of conditions that can cause an individual's immune system to become compromised. Aside from studies focusing on chemotherapy and radiation therapy, most influenza vaccine immunogenicity, efficacy, and effectiveness studies on immunocompromised individuals are small (less than 100 participants) and lack the statistical power needed to confirm the results or be clinically relevant.

Only individuals with cancer had vaccine effectiveness results with reported an overall vaccine effectiveness against laboratory-confirmed influenza of 21% (95% CI, 15% to 26%) and 8% (95% CI, –5% to 19%) among patients with hematologic malignancies; the type of vaccine received was not reported.[54] Since the definition of chemotherapy and radiation therapy can differ between studies, the reported vaccine effectiveness fluctuates widely. While additional influenza vaccine effectiveness studies for hematological conditions are available, they are predominantly pediatric studies which reflects the high rate of blood cancers in pediatric populations. The dearth of immunocompromised influenza vaccine effectiveness data leads to a lack evidence on which to base clinical guidance.

2.0 Effectiveness of Influenza Vaccine for Preventing Laboratory-Confirmed Influenza Hospitalizations in Immunocompromised Adults

2.1 Introduction

The number of immunocompromised (IC) individuals has increased due to greater longevity of the population, increasing numbers of solid organ and stem cell transplants, advances in the treatment of hematologic and solid malignancies, increase in the number of individuals living with human immunodeficiency virus (HIV), and the use of steroids, immune-modulating agents, and other immunosuppressive drugs to treat autoimmune and inflammatory conditions.[15,55] Immunosuppressive conditions are heterogeneous and the degree and type of immune deficiency caused by each one of these conditions vary, but a unifying consequence is an increased risk of many infectious diseases including influenza.[56] Influenza is a common cause of illness and death, with an estimated 140,000-810,000 influenza-associated hospitalizations and 12,000-61,000 influenza-associated deaths annually in the United States.[57]

IC individuals are at higher risk for influenza-related complications, including increased frequency of hospitalization, ICU admission, longer duration of hospitalization, and death.[58–63] Influenza vaccination is the best available intervention for preventing these complications and annual influenza vaccination is recommended for IC individuals.[64] However, the data on protection afforded by influenza vaccines in IC adults are scarce. A recent study on cancer patients demonstrated a vaccine effectiveness (VE) of 20% against influenza hospitalization, as compared to 42% in the general population.[54,65] Most studies of IC adults are small and evaluate immunogenicity as a surrogate of effectiveness.[66] These immunogenicity studies among various

IC groups have demonstrated that antibody responses to inactivated influenza vaccines are suboptimal compared to those without immunosuppression.[66,67] However, immune response to vaccine does not necessarily directly relate to vaccine effectiveness.[68,69] Since the 2015-2016 influenza season, the Centers for Disease Control and Prevention (CDC)-funded U.S. Hospitalized Adult Influenza Vaccine Effectiveness Network (HAIVEN) has estimated influenza VE among adults hospitalized for acute respiratory infections.

Understanding influenza VE in IC individuals is crucial to the development of appropriate vaccination and public health policies. The purpose of this study was to evaluate influenza VE among hospitalized immunocompromised adults enrolled in the HAIVEN study during the 2017-2018 influenza season, when specific efforts were made to identify immunocompromised patients using case-definitions for immunocompromising conditions.

2.2 Methods

2.2.1 Study Design and Enrollment

The HAIVEN study is a multi-center, prospective, test-negative case-control study to determine an annual estimate of VE against influenza-associated hospitalizations among adults in the United States. Methods for the HAIVEN study have been described previously.[4] Briefly, adults ≥ 18 years of age with new or worsening cough or sputum production of ≤10 days' duration and a respiratory specimen collected ≤ 10 days from illness onset and ≤ 72 hours after hospital admission at one of ten hospitals in Pennsylvania, Michigan, Tennessee, and Texas were eligible. Inclusion criteria included age ≥18 years, admission for an acute respiratory illness, or worsening

of a chronic respiratory illness with a new or worsening cough. During the 2017-2018 influenza season, details on demographics, symptoms, influenza vaccination status, number of recent hospitalizations, and history of organ or stem cell transplant and, chemotherapy or radiation therapy in the preceding year were collected through the enrollment interview. Information about the clinical course and disease severity was obtained from electronic medical records (EMR). All international classification of diseases-10 diagnosis clinical modification (ICD-10-CM) codes and current procedural terminology (CPT) codes from all encounters in the 12 months before enrollment were obtained from the EMR and utilized to identify the high-risk conditions associated with an increased risk of serious influenza complications.[64]

2.2.2 Influenza Case Classification

Enrolled patients provided respiratory specimens for influenza testing by polymerase chain reaction (PCR). Specimens were either nasal and oropharyngeal swabs that were tested in research laboratories with CDC PCR protocols or clinical nasopharyngeal specimens tested by PCR in hospital laboratories provided they were collected within 10 days of illness onset and 72 hours of admission. Enrolled patients who tested positive for influenza were classified as cases and those who tested negative for all influenza types were controls.

2.2.3 Influenza Vaccination Status

Self-reported current season influenza vaccination status was confirmed by medical record review, state immunization registry records, occupational health records, health insurance billing claims, and records from patients' primary care providers. Information collected included date

and route of administration and product name, manufacturer, and lot number. Self-reported vaccination was accepted if the patient provided a date and location for the vaccination. A participant was considered vaccinated if s/he received the 2017-18 influenza vaccine ≥ 14 days before illness onset. Because up to 14 days is required to mount an immune response to vaccination, those vaccinated 0 to 13 days before illness onset were excluded due to indeterminate vaccination status.

2.2.4 Identification of Immunocompromising Conditions

All ICD-10-CM codes for all encounters and receipt of the biologic chemotherapeutic agents bortezomib, carfilzomib, daratumumab, dasatinib, gemtuzumab, and imatinib in the year before study enrollment were collected from EMR data. In the 2017-2018 influenza season the enrollment questionnaire asked if the participant received chemotherapy or radiation therapy for cancer in the 12 months before enrollment. Eight groups of immunocompromising conditions were defined: organ transplantation, stem cell transplantation, underlying immunodeficiency, connective tissue disorder, receipt of chemotherapy or radiation therapy, hematologic conditions, chronic steroid use, and HIV. The basis for the groups was a previously described algorithm for identifying patients with active immunosuppression utilizing ICD and CPT codes in a large database of patients with severe sepsis.[70] We slightly modified this algorithm in two aspects. For solid malignancies, we only included patients actively treated with chemotherapy or radiation to improve specificity of immunosuppression. We also included patients with chronic use of steroids. We considered the enrollment question on receipt of chemotherapy or radiation therapy as the gold standard and our data found that ICD-10-CM and CPT codes have low sensitivity to identify patients receiving chemotherapy or radiation therapy (Appendix Table 1). Therefore, we identified

patients with immunocompromising conditions based on ICD-10-CM codes listed (Table 1 and Appendix Table 2), except for the receipt of chemotherapy or radiation therapy, which were determined from ICD-10-CM codes, or receipt of one of the biologic chemotherapeutic agents listed, or a positive answer to the enrollment question about the receipt of chemotherapy or radiation therapy.

The IC groups were mutually exclusive; therefore, if a participant had more than one IC condition, they were grouped hierarchically following the group order listed above. The hierarchical order of groups is shown in Appendix Figure 1 and was based on the authors' expert opinion, to better identify active immunosuppressive conditions because we did not have data on the use of immunosuppressants other than steroids and biologicals in the dataset. For example, to identify patients with malignancies on active therapy, chemotherapy or radiation therapy preceded hematologic condition.

2.2.5 Statistical Analysis

Demographic and other characteristics of the IC and non-IC groups were compared using Pearson X^2 test or Fisher exact test for categorical variables and two-sample t-test for continuous variables.

VE was calculated by estimating the odds of influenza positivity among vaccinated patients compared to unvaccinated patients for the IC and non-IC groups using multivariate logistic regression using influenza positivity as the outcome and vaccination status as the exposure variable, with VE = (1 – adjusted odds ratio) × 100%.[71]

In the primary analysis, we stratified the sample by immunocompromised status and estimated VE in each stratum:

$$For\ i = 1\ to\ 2\ strata\ of\ overall\ (any)\ immunocompromising\ status,$$

$$logit\ (flu = 1) = \beta_0 + \beta_1(vacc) \ldots + \beta_Z Z$$

where

flu = 1 if PCR-confirmed flu case (of specific type/subtype); 0 otherwise

vacc = 1 if received vaccine ≥14 d prior to symptom onset; 0 otherwise

Z = vector of adjustment variables including age (continuous), enrollment site, race, days from illness onset to specimen collection, date of illness onset (categorized as pre-peak, peak, or post-peak influenza periods[4]), self-reported health status (poor/fair and good/very good/excellent) and self-reported number of hospitalizations

and with VE defined as

$$\widehat{VE} = [1 - \exp(\beta_1)] * 100\% .$$

To test if VE differed by immunocompromised status, we regressed flu status on vaccination status, immunocompromised status, and the pairwise multiplicative interaction between vaccination status and immunocompromised status:

$$logit\ (flu = 1) = \beta_0 + \beta_1(vacc) + \beta_2(IC) + \beta_3(vacc * IC)\ \ldots + \beta_Z Z$$

where variables are defined as above and

IC =1 if immunocompromised (any immunocompromising condition); 0 otherwise

Effect modification of VE by immunocompromised status was assumed to be statistically significant if the test statistic for assessing if the coefficient for the interaction term, β_3, differed from zero had a p value <0.05.

In secondary analyses, we stratified subjects by type-specific immunocompromised status and estimated VE within each stratum using a main effects model:

$$For\ i = 1\ to\ 9\ strata\ of\ type - specific\ immunocompromising\ status,$$

$$logit\,(flu = 1) = \beta_0 + \beta_1(vacc) \ldots + \beta_Z Z$$

where variables are defined as above except for models for immunodeficiency and HIV subgroups in which

Z = vector of adjustment variables including age (continuous), enrollment site, race, days from illness onset to specimen collection, date of illness onset (categorized as pre-peak, peak, or post-peak influenza periods[4]), self-reported health status (poor/fair and good/very good/excellent) and self-reported number of hospitalizations

Because we did not specifically calculate sample sizes for this study, we did a post hoc power analysis based on the observed number of cases (n=900) and controls (2600), vaccination rate among controls (67%), power of 80%, and a significance level of 0.05. We determined a minimum detectable vaccine effectiveness of 20% in our overall study population during the 2017-2018 influenza season based on these assumptions.

Analyses were conducted with SAS version 9.4 software. Statistical significance was defined as a p-value < 0.05 or a 95% confidence interval (CI) excluding the null value. We interpreted differences in VE estimates by IC vs non-IC subgroups, considering p-value <0.15 as statistically significant which is in line with guidance for interpreting interaction between two dichotomous variables when effect size is expected to be moderate to high.[72,73] The study protocol was approved by the research ethics boards at the participating institutions.

2.3 Results

A total of 4,108 hospitalized adults were enrolled in HAIVEN in the 2017-2018 influenza season. Of these, 584 were excluded because of enrollment earlier or later than the period of

influenza circulation in the community (n=259), missing vaccination status (n=201), missing number of self-reported past year hospitalizations (n=59), and other reasons (n=65) (Figure 1). In the resulting dataset (n=3,524), 1,210 (34.3%) adults were identified as having an immunocompromising condition: organ transplant (n=144, 11.9%); stem cell transplant (n=28, 2.3%); underlying immunodeficiency (n=49, 4.0%); connective tissue and rheumatologic disease (n=130, 10.7%); chemotherapy and radiation therapy (n=242, 20%); hematologic condition (n=175, 14.5%); chronic steroid use (n=397, 32.8%) and HIV (n=45, 3.7%).

Overall, participants were more likely to be female (56.9%) and white (62.2%). Mean age was 61 (SD 17.1) years, 66.7% were vaccinated, 25.8% had influenza, and 84.2% had ≥ 3 high-risk conditions (Table 2). The IC and non-IC groups differed for several characteristics. IC participants were significantly more likely than non-IC to be of white race (67.9% vs 59.3%, $p<0.001$), have a lower BMI (30.1 vs 31.2, $p=0.003$), be vaccinated (60.2% vs 54.6%, $p=0.002$), have a longer length of stay (4 vs 3 days, $p<0.001$), have ≥ 3 high-risk conditions (94.2% vs 79%, $p<0.001$), have had ≥ 4 hospitalizations in the previous year (25.5% vs 19.1%, $p<0.001$), and present earlier in the pre-peak period (42.1% vs 37.4%, $p=0.02$). IC participants were significantly less likely than non-IC participants to test positive for influenza (22% vs 27.8%, $p<0.001$) and to self-report their health as fair or poor (45% vs 53.6%, $p<0.001$) (Table 2).

There were 266 influenza cases in the IC adults and 644 influenza cases in non-IC adults. Most influenza infections were caused by influenza A, and 530 (78.8%) were A(H3N2) viruses. Of 238 influenza B infections, 200 (84%) were due to B Yamagata lineage viruses (Figure 2).

The patients in the 8 immunocompromised groups differed in sex, enrollment site, age/age group, race, BMI, influenza status, documented influenza vaccination, number of high-risk conditions, and self-reported health status, but not in the number of hospitalizations in the previous

year, interval from illness onset to specimen collection, and date of illness onset (Supplementary Table S3).

Overall, vaccination was 33% (95% CI, 21% to 44%) effective in preventing hospitalization. Among IC adults, VE was 5% and not significant (95% CI, -29% to 31%). VE in non-IC adults was 41% (95% CI, 27% to 52%) ($p<0.05$ for interaction term) (Table 3). VE for the different immunocompromised conditions varied widely, from -73% for individuals with underlying immunodeficiency to 84% for stem cell transplant; however, this study was not powered to look at these subgroups and the confidence intervals varied widely (Supplementary figure S2).

2.4 Discussion

During the high-severity 2017-2018 US influenza season, we found that influenza vaccination reduced the risk of influenza-associated hospitalization among adults by 33%. Overall, VE during the 2017-2018 season was lower than that estimated in previous seasons in this network (42-54%).[4,41] The fact that influenza A(H3N2) viruses circulating in 2017-2018 were antigenically different from the vaccine H3N2 strain because of suspected egg-adapted glycosylation in the antigenic epitopes of the vaccines may be responsible for the lower VE.[74] As compared with VE in non-IC adults (41%), VE in IC adults was significantly lower (5%) during this season. This lower VE among IC adults is unlikely to be an artifact, because the findings are consistent with the immunogenicity studies of inactivated influenza vaccines (IIVs) that have demonstrated significantly reduced humoral immune responses to standard IIVs in immunosuppressed patients with HIV, organ transplants, cancer, and those receiving immunosuppressants.[66] In this network,

influenza vaccination rate among controls was greater in the IC (60%) than in the non-IC group (54%), which is consistent with national US data in the insured population.[5] The higher vaccination rate among IC may be due to more frequent healthcare encounters and closer monitoring among IC patients offering more opportunities to vaccinate, or a heightened perception of risk for influenza complications by providers, leading to increased willingness to recommend influenza vaccine, and by patients, leading to greater willingness to receive vaccination.

Limited data exist on the prevention of influenza infection on immunocompromised adults by vaccination. Most studies have focused on the measurement of humoral antibody response among patients with particular immunocompromising conditions and have reported significantly reduced humoral immune responses.[67,75,76] However, this approach disregards the relationship between clinical outcomes and immune response, the levels of antibody titers from previous immunizations that may cause overestimations of response, nor does it consider the role of cell-mediated immune response to vaccination in the prevention of influenza infection. While studies of high dose influenza vaccine have demonstrated improved antibody responses in adult organ transplant recipients and improved antibody responses and outcomes in adults older than 65 years of age as compared to standard dose vaccine, it is unknown if enhanced vaccine options, such as high dose and adjuvanted vaccines, could improve VE in immunocompromised groups.[49,76–78] Increasing the evidence base for informing the use of enhanced influenza vaccines in immunosuppressed populations is necessary for determining if these interventions might offer added value to standard influenza vaccines and potentially contribute to improving efficacy of these vaccines.

A primary challenge in the study of influenza VE in IC individuals is the definition of immunocompromise. Immunocompromising conditions are heterogenous and the degree of

immunosuppression among groups is challenging to quantify. Additionally, within a defined IC group, differences in the degree of immunosuppression are difficult to assess, based on clinical records. We considered ~34% of the adults hospitalized with an acute respiratory illness during the influenza season as being immunocompromised by pre-defining groups of immunocompromising conditions that were identified by ICD-10-CM codes for all medical encounters in the preceding year. To complement our case definition, we also analyzed the addition of CPT codes for chemotherapy administration, chemotherapeutic drugs recorded in the EMR, and a question at the time of enrollment about the receipt of chemotherapy or radiation therapy in the preceding 12 months. Although we did not collect other immunosuppressant and biological data, we identified a similar proportion of IC adults among those hospitalized with acute respiratory illness as identified in the study by Patel et al. that utilized MarketScan data to estimate the prevalence of immunosuppressive conditions and risk for acute respiratory illnesses.[5]

Findings of this study should be interpreted in the context of several limitations. Although we used an objective and systematic mechanism to identify the different IC groups, our identification of the immunocompromising groups accounts for only a rough measure of immunosuppression. We did not consider the presence of more than one immunocompromising condition, and we were unable to evaluate the effect of timing of vaccination in relation to the immunosuppression. We were unable to evaluate VE among different IC because of inadequate sample sizes. A study with a greater number of IC adults that allows for analyses of subgroups, virus subtypes, and different vaccine formulations is needed for definitive conclusions. Our study is also limited to a single season when vaccine was mismatched to the circulating A/H3N2 viruses and thus may not be applicable to other influenza viruses. Data are also from 4 U.S. sites and may not be generalizable.

Our study's strengths include the use of a standardized protocol with symptom-based eligibility and comprehensive PCR testing to identify influenza cases and controls, a test-negative case control design and, recruitment in geographically diverse areas. Furthermore, our study shows that immunocompromising conditions can be identified based on EMR data, without the need for cumbersome medication reviews.

Proper identification of IC groups in future VE studies will have implications for public policy development, such as a recommendation for a different vaccine formulation for IC groups, or a consideration for chemoprophylaxis for those with immunocompromise.

Vaccine effectiveness against influenza was not significant among hospitalized immunocompromised patients. In light of our findings, decreasing the burden of influenza in IC individuals may be less dependent on improving their vaccine coverage than on improving vaccination rates of close contacts of the immunocompromised individual, thereby creating a circle of protection around an IC individual. Mathematical modeling has shown that even small improvements in VE and vaccine coverage are associated with substantial reductions in influenza burden.[79]

2.5 Subsection

Table 1: ICD-10 and CPT Codes Used to Classify the Immunocompromised Group

Immunocompromised Group	ICD-10 Codes
Organ Transplant	T86.1, T86.2, T86.3, T86.4, T86.81, T86.85, Z48.2, Z94.0, Z94.1, Z94.2, Z94.3, Z94.4, Z94.82, Z94.83
Stem Cell Transplant	Z94.84, T86.0, T86.5
Underlying Immunodeficiency	D80, D81.0, D81.1, D81.9, D82, D83, D84, D84.1, D84.8, D84.9, D89.8, D89.9

Connective Tissue Disorder	M05, M06, M 08.0, M 08.2, M08.3, M08.4, L40.54, L40.59, M32, M30.0, M30.1, M30.2, M31.3, M33, M34, M34.0, M34.1, M34.9, M35.0, M35.9
Chemotherapy/Radiation Therapy	Z51.0, Z51.1
Hematologic Conditions	C95.00, C95.10, D61.0, D61.2, D61.9, D70, D71, D72, D73.0, C81, C82, C83, C84, C85, C86, C88, C90, C91, C92, C93, C94, C96, D46
Steroids	Z79.5, Z79.52
HIV	B20, B97.35, O98.7, Z21
	CPT Codes
Chemotherapy	96401-96417, 96420-96425, 96440-96450, G0498
Radiation therapy	77402-77412, G6003-G6014, 77385-77386, 77418, G6015-G6016, 77387, G6001-G6002, G6017, 77371-77372, 77373, 77778, 77770-77772, 77761-77763

CPT codes for chemotherapy and radiation therapy were collected at the Pennsylvania sites only

Table 2: Patient Characteristics overall by immunocompromising condition, US Hospitalized Adult Influenza Vaccine Effectiveness (HAIVEN) study, 2017-2018 (n=3,524)

	Total (n= 3,524)	Non-Immunocompromised (n=2,314)	Immunocompromised (n=1,210)	p-value
Enrollment site, n (%)				
Michigan	943 (26.8)	714 (30.9)	229 (18.9)	**<0.001**
Pennsylvania	834 (23.7)	571 (24.7)	263 (21.7)	
Tennessee	589 (16.7)	369 (16.0)	220 (18.2)	
Texas	1158 (32.9)	660 (28.5)	498 (41.2)	
Female, n (%)	2004 (56.9)	1317 (56.9)	687 (56.8)	0.94
Age group, n (%)				
18-49	790 (22.4)	534 (23.1)	256 (21.2)	0.37
50-64	1173 (33.3)	753 (32.5)	420 (34.7)	
65-74	798 (22.6)	517 (22.3)	281 (23.2)	
75+	763 (21.7)	510 (22.0)	253 (20.9)	
Age, mean ± SD	61.0 ± 17.1	60.8 ± 17.7	61.4 ± 15.9	0.29
Race, n (%)				
White, non-Hispanic	2193 (62.2)	1371 (59.3)	822 (67.9)	**<0.001**
Non-white	1331 (37.8)	943 (40.8)	388 (32.1)	
BMI, mean ± SD	30.8 ± 9.5	31.2 ± 9.8	30.1 ± 8.9	**0.001**
Any flu, n (%)				
Negative	2614 (74.2)	1670 (72.2)	944 (78.0)	**<0.001**
Positive	910 (25.8)	644 (27.8)	266 (22.0)	
Documented vaccination, n (%)				
No	1174 (33.3)	805 (34.8)	369 (30.5)	**0.01**
Yes	2350 (66.7)	1509 (65.2)	841 (69.5)	
Length of stay, median (IQR)	3.0 (4.0)	3.0 (3.0)	4.0 (4.0)	**<0.001**
Influenza-like illness (ILI) symptoms, n (%)				
No	1208 (34.3)	797 (34.4)	411 (34.0)	0.78
Yes	2316 (65.7)	1517 (65.6)	799 (66.0)	
Number of high-risk conditions, n (%)				
No high-risk conditions	162 (4.6)	141 (6.1)	21 (1.7)	**<0.001**
1-2 high-risk conditions	394 (11.2)	345 (14.9)	49 (4.1)	
≥3 high-risk conditions	2968 (84.2)	1828 (79.0)	1140 (94.2)	

Self-reported hospitalizations in the prior year, n (%)				
0-3 hospitalizations	2773 (78.7)	1871 (80.9)	902 (74.6)	**<0.001**
≥4 hospitalizations	751 (21.3)	443 (19.1)	308 (25.5)	
Interval from illness onset and specimen collection, n (%)				
0-1 days	693 (19.7)	435 (18.8)	258 (21.3)	0.14
2-4 days	1621 (46.0)	1065 (46.0)	556 (46.0)	
5-10 days	1210 (34.3)	814 (35.2)	396 (32.7)	
Onset date				
Pre-peak	1374 (39.0)	865 (37.4)	509 (42.1)	**0.02**
Peak	844 (24.0)	559 (24.2)	285 (23.6)	
Post-peak	1306 (37.1)	890 (38.5)	416 (34.4)	
Self-reported health status, n (%)				
Excellent/ very good/ good	1739 (49.4)	1074 (46.4)	665 (55.0)	**<0.001**
Fair/ poor	1785 (50.7)	1240 (53.6)	545 (45.0)	

Table 3: Influenza Vaccine Effectiveness for Prevention of Influenza A or B-Associated Hospitalizations in Immunocompromised and Non-Immunocompromised Adults, US Hospitalized Adult Influenza Vaccine Effectiveness (HAIVEN) Study, 2017-2018

	N Influenza Cases (% vaccinated)	Unadjusted VE, % (95% CI)	Adjusted VE, % (95% CI)*
All, n=3524	910 (67)	28 (16, 38)	33 (21, 44)
Non-immunocompromised, n=2314	644 (65)	36 (23,47)	41 (27, 52)
Immunocompromised, n=1210	266 (70)	-0.3 (-35, 25)	5 (-29, 31)
Non-immunocompromised, influenza A	471 (65)	31 (15, 44)	31 (14, 46)
Immunocompromised, influenza A	202 (70)	1 (-37, 29)	4 (-36, 32)
Non-immunocompromised, H1N1	71 (65)	57 (32, 74)	52 (19, 71)
Immunocompromised, H1N1	33 (70)	60 (17, 80)	51 (-2, 77)
Non-immunocompromised, H3N2	369 (65)	21 (0, 37)	23 (0, 40)
Immunocompromised, H3N2	161 (70)	-28 (-87, 12)	-18 (-75, 20)
Non-immunocompromised, influenza B	173 (65)	34 (10, 52)	45 (22, 61)
Immunocompromised, influenza B	65 (70)	1 (-70, 43)	13 (-52, 51)

*Adjusted for enrolling site, onset date (pre-peak, peak, post-peak), age, race, days from illness onset to specimen collection (0-1, 2-4, 5-10 days), self-reported health (poor/fair, good/very good/excellent), and self-reported hospitalizations

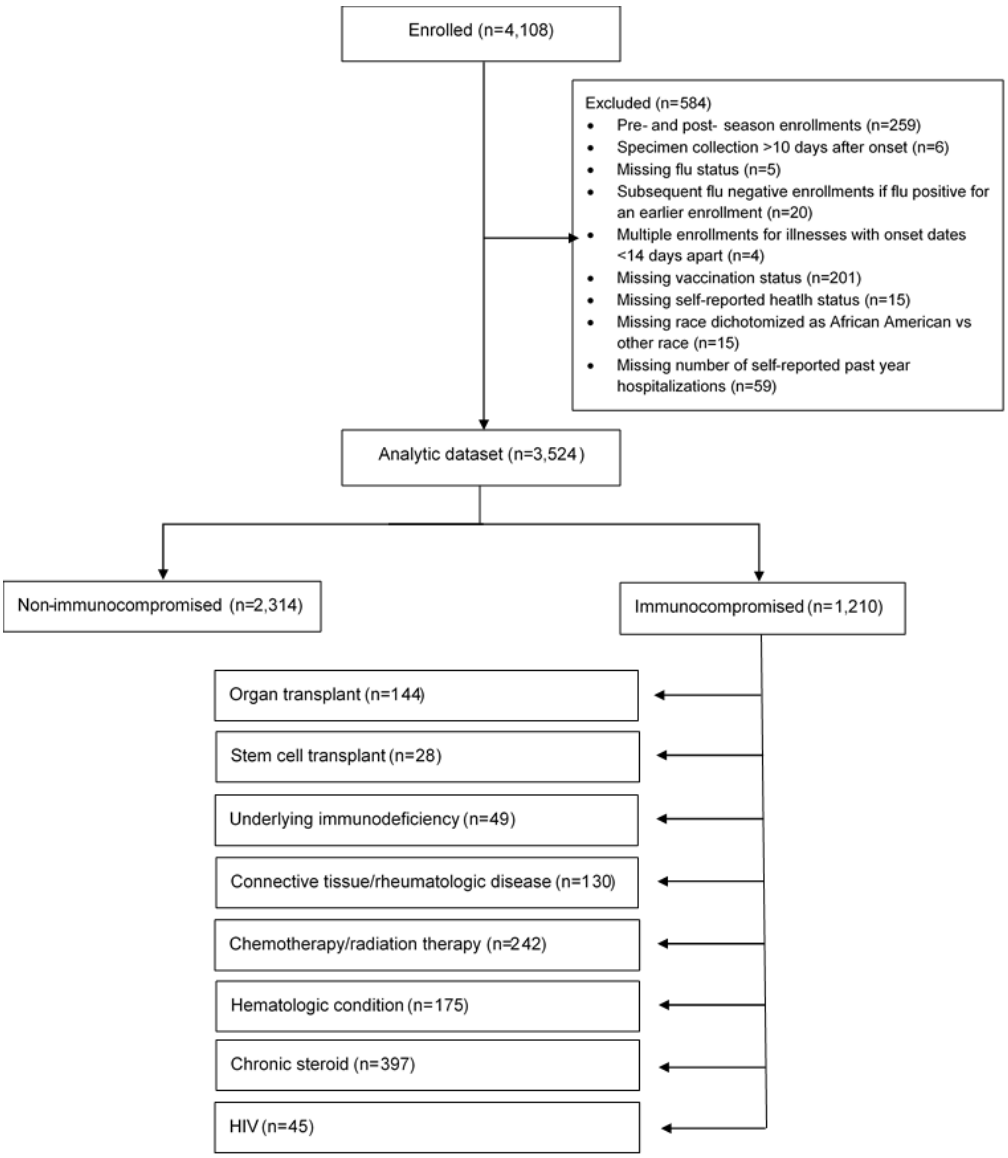


Figure 1: US Hospitalized Adult Influenza Vaccine Effectiveness Network (HAIVEN) Study Population, 2017–2018

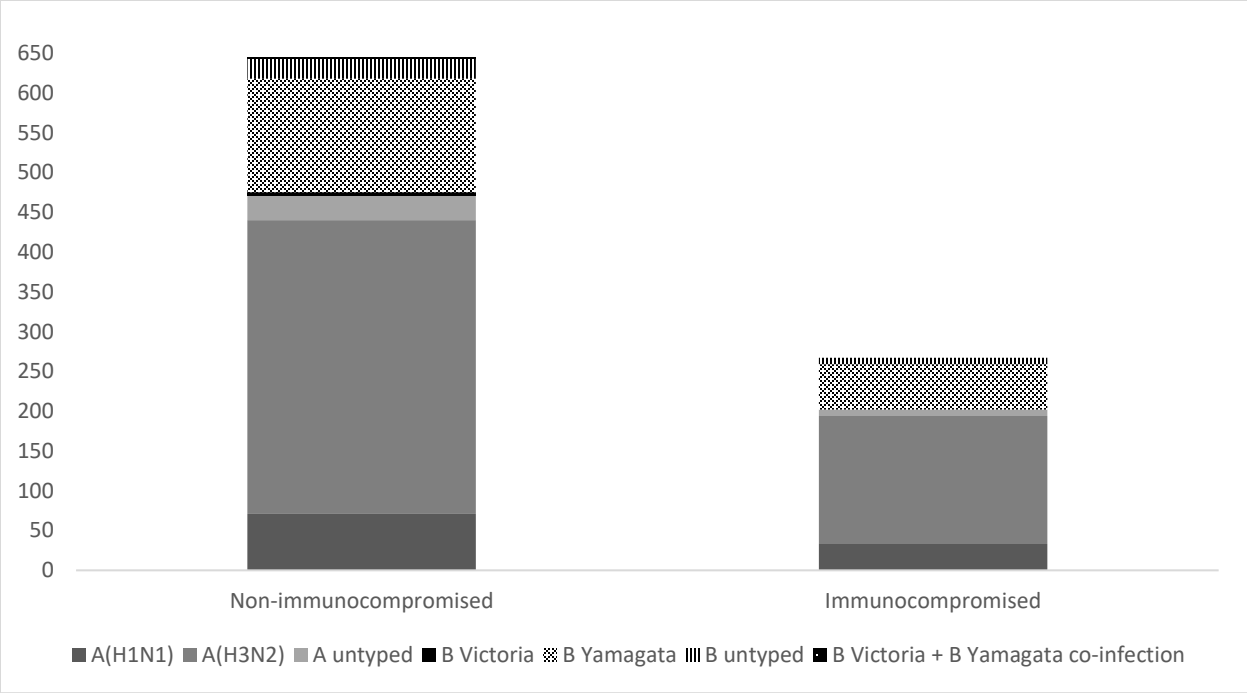


Figure 2: Influenza Virus Type/Subtype and Lineage in the Non-Immunocompromised and Immunocompromised Groups

3.0 Effectiveness of Influenza Vaccine for Preventing Laboratory-Confirmed Influenza Infections in Outpatient Immunocompromised Adults

3.1 Introduction

During the 2017-2018 influenza season, there were an estimated 41 million cases of influenza, including approximately 710,000 hospitalizations and 52,000 deaths from influenza in the United States.[1] Influenza hospitalizations disproportionately affect adults 65 years and older and individuals with high-risk conditions with immunocompromised (IC) individuals having a 5-8 fold higher risk of hospitalizations from acute respiratory illnesses compared to non-immunocompromised (non-IC) individuals.[2,5] The economic burden of influenza is also significant, with an estimated $2.5 billion in direct medical costs annually.[3] With the current COVID-19 pandemic straining healthcare systems and resources, preventing influenza infections among IC individuals is paramount. Although the annual influenza vaccination continues to be recommended to prevent influenza infections and influenza-related hospitalizations among IC adults, influenza vaccine effectiveness (VE) among IC adults remains severely under researched.[80]

Existing IC adult influenza vaccine research is limited to vaccine immunogenicity and efficacy studies leaving major gaps in our understanding of the influenza vaccine effectiveness among IC adults.[16–23,25–28,30–33,81,82] While vaccine efficacy can provide investigators insight to an individual's protection, it does not reflect how the vaccine will work in the "real-world". Additionally, aside from studies focusing on chemotherapy and radiation therapy, most influenza vaccine immunogenicity, efficacy, and effectiveness studies on IC individuals are small and lack the statistical power needed to confirm the results or be clinically relevant.[16–23,25–28,30–33,81,82]

As IC individuals represent 2.7% of the US adult population, the role of influenza vaccination in the prevention of influenza and subsequent influenza-associated hospitalizations is of increasing importance. Understanding the level of protection afforded by influenza vaccinations can lead to improved quality of life, decreased influenza hospitalizations, and better management for IC individuals.[83] This study investigated the role of the seasonal influenza vaccine in preventing influenza and hospitalizations among IC adults.

3.2 Methods

3.2.1 Study Design and Enrollment

The US Flu VE study is a multicenter, prospective, test-negative, case-control study to estimate the vaccine effectiveness (VE) of the annual influenza vaccine among children and adults seen in outpatient settings. Methods for the US Flu VE study have been previously described.[38,84,85] Briefly, adults and children >6 months of age presenting to one of the enrolling outpatient centers in Michigan, Pennsylvania, Texas, Washington, or Wisconsin with an acute respiratory illness with cough within 7 days of symptom onset were eligible for the study. Demographics, symptoms related to influenza-like illness (ILI), vaccination status, symptom onset, self-reported health status, smoking status, oxygen use, and functional status questions, were obtained through patient interviews and confirmed through electronic medical records (EMR). Number of high-risk conditions and prior year hospitalizations and outpatient visits were collected from the EMR. High-risk conditions were defined as having one or more of the following conditions: chronic pulmonary or cardiovascular conditions, renal, hepatic, neurologic, hematologic, or metabolic

disorders, and immunosuppression caused by medications, HIV infections, and primary immunodeficiency. To allow for comparison to other adult influenza VE studies, this analysis focused solely on adult participants aged ≥18 years.

3.2.2 Influenza Case Classification

All enrolled participants provided a respiratory specimen (nasal and oropharyngeal swabs) for influenza testing by polymerase chain reaction (PCR).[86] Testing was performed at study site research laboratories using a Centers for Disease Control and Prevention (CDC) PCR protocol. Participants with a positive PCR were considered cases.

3.2.3 Influenza Vaccination Status

Current season influenza vaccination status was confirmed by medical record review, state immunization registry records, occupational health records, health insurance billing claims, and records from patients' primary care providers. Self-reported vaccination was accepted if the patient provided a date and location for the vaccination or a vaccine card. Due to the high potential for bias in self-report, multiple efforts were made to confirm self-reported vaccination with the vaccination administration location information provided by the patient. A participant was considered vaccinated if he or she received the influenza vaccine ≥ 14 days before illness onset. Participants vaccinated 0–13 days before illness onset were excluded from the analysis because up to 14 days is required to mount an immune response to vaccination.

3.2.4 Identification of Immunocompromising Conditions

All ICD-10-CM codes for all encounters were collected from EMR data. Eight groups of immunocompromising conditions were defined: organ transplantation, stem cell transplantation, underlying immunodeficiency (primary immunodeficiencies), connective tissue disorder, receipt of chemotherapy or radiation therapy, hematologic conditions, chronic steroid use, and HIV (Appendix Table 1). The basis for the groups was a previously described algorithm for identifying patients with active immunosuppression using ICD and CPT codes in a large database of patients with severe sepsis and mirrored the ICD-10 codes utilized in prior influenza vaccine effectiveness studies.[5,70,87] For this study, the algorithm was modified to only utilize ICD-10 codes, to only include patients treated with chemotherapy or radiation at study enrollment to improve specificity of immunosuppression.

3.2.5 Statistical Analysis

Demographic and other characteristics of the IC and non-IC groups were compared using the Pearson χ 2 test or Fisher exact test for categorical variables and the two-sample *t* test for continuous variables.

VE was calculated by estimating the odds of influenza positivity among vaccinated patients compared with unvaccinated patients for the IC and non-IC groups using multivariable logistic regression using influenza positivity as the outcome and vaccination status as the exposure variable, with VE = (1 – adjusted odds ratio) × 100%.[88] Model building and prior literature was used to determine which variables to include in the final model.[88,89] To determine if VE differed by immunocompromised status, we stratified the sample to IC and non-IC and adjusted for

enrollment site, race, self-report health status, age, and onset date of symptoms. Unlike previous vaccine effectiveness studies, we did not adjust for enrollment site or self-reported health status.[41,87] Enrollment site was excluded because the majority of FluBlok recipients were enrolled from the Pennsylvania sites. Model building exercises showed a negligible difference in AIC and BIC when self-reported health status was added. Given the smaller sample size, especially in the FluBlok group, we elected to leave out self-reported health status to prevent non-convergence.

A post hoc power analysis was completed with Power Analysis and Sample Size Software (PASS) 2022 using the observed number of cases (n = 455) and controls (n=5215), the vaccination rate among controls (51%), and a significance level of 0.05. The resulting power was 100%.

Analyses were completed using SAS, version 9.4. Statistical significance was defined as $p< .05$ or a 95% confidence interval (CI) excluding the null value. This protocol was approved by each institutions' Institutional Review Board and completed following good clinical practices and funded by the Centers for Disease Control.

3.3 Results

From November 2017 through February 2018, 8900 individuals were enrolled in the US Flu VE Network. After excluding pediatric cases, 5671 participants were included in the adult analytic dataset, and among those there were 455 IC individuals (Figure 3). Among the US FluVE Network adults, there were 1969 (34.7%) confirmed influenza infections and 2974 (52.4%) had their influenza vaccination verified. The majority of the overall, non-IC and IC participants received the inactivated influenza vaccine (79.0% vs 79.0% vs. 80%), and the vaccine product breakdown was not significant when comparing non-IC and IC (p=0.760). Most of the participants

rated their health as fair/poor (62.1%) and had high-risk conditions in the prior year (59.3%). However, this did not translate to high health care utilization with only 29.2% reporting >3 healthcare visits in the last year and only 0.4% reporting >3 hospitalizations in the last year (Table 4).

Compared to the non-IC group, the IC group was more likely to be female (71.9% vs 63.9%, p=0.003), older (56.5 years vs 47.3 years, p<.001), white (81.8% vs 77.1%, p<.001), vaccinated (71.4% vs 50.8%, p<.001), have high-risk conditions in the prior year (98.9% vs 55.8%, p<.001), have >3 outpatient visits (78.7% vs 24.8%, p<.001), and have >3 hospitalizations in the last year (3.1% vs 0.2%, p<.001). IC participants were less likely than non-IC participants to report their health as fair/poor (38.2% vs 64.2%, p<.001). There were no significant differences in BMI, date of symptom onset, or influenza positivity between IC and non-IC participants (Table 4).

The unadjusted overall VE was 25% (95% CI: 17, 33), 27% (95% CI: 18, 35) among non-IC participants, and -7% (95% CI: -65, 31) among IC participants. After adjusting for enrollment site, presence of high-risk conditions, age in years, and onset date of symptoms, the overall VE increased to 29% (95% CI: 21, 37), 31% (95% CI: 22, 39) among non-IC participants, and -4 % (95% CI: -66, 35) among IC participants.

3.4 Discussion

In this large, multicenter, test-negative cases control study, conducted during the 2017-2018 influenza season in the United States, we observed significantly lower VE among IC individuals compared with those without IC conditions. Overall, the majority of the study population was vaccinated, reported their health to be fair/poor, and had high-risk conditions in

the year prior to study enrollment. There were significant demographic differences between IC and non-IC participants with IC participants more likely to be female, older, identify as Caucasian, and receive an influenza vaccine. As evident by the significant differences in high-risk conditions and healthcare utilization, the immunocompromised group was also at higher risk for influenza-related complications and hospitalizations. Notably, IC participants were more likely than non-IC participants to describe their health as good/very good/excellent. As participants were recruited from primary care or urgent offices, it is possible that non-IC participants were reflecting on their health in the setting of the illness that caused them to seek care. Finally, the overall adjusted VE was 29%; non-IC and IC participants had an adjusted VE of 31% and -4%, respectively.

Negative VEs have been discussed in prior papers and do not necessarily indicate an increased risk of infection among vaccinated individuals. Possible reasons for a lack of precision of the estimate include increased contact among vaccinated individuals, increased provider-directed testing in IC individuals, and increased test-seeking behaviors among IC individuals.[90–92] Increased provider-directed testing and test-seek behaviors in the IC population could increase the number of cases. While the test-negative case-control design reduces bias from healthcare seeking behaviors, as we were unable to adjust for potential selection bias from provider-directed testing and test-seeking behavior, residual confounding may be present.

This study had two major limitations. First, while significantly larger than most prior influenza VE papers, the number of IC participants relative to the overall sample size was small. Work on a previous study demonstrated that compared to ICD-10 codes, interview questions better captured chemotherapy and radiation therapy; unfortunately, participants were not asked about their chemotherapy and radiation therapy during the interview.[87] Additionally, groups such as solid organ transplants and individuals living with HIV may seek their routine care at specialized clinics

and thus be underrepresented in the study cohort. Second, because of the small sample size, we were unable to examine if vaccine effectiveness differed by vaccine type (recombinant vs. high dose vs. standard dose). Future outpatient influenza VE studies can address limitations highlighted in this study by including specialized providers, such as transplant and cancer centers, in their enrollment populations and ascertaining chemotherapy and radiation therapy use directly from the participants.

Influenza vaccination for IC individuals continues to be recommended by the CDC's Advisory Committee on Immunization Practices.[80] However, influenza vaccination campaigns are resource intensive, requiring advertisement, patient education, and time spent battling misinformation and disinformation on social media. Given tightening budgets and dwindling healthcare staff, it remains crucial that interventions have positive outcomes for patients and healthcare systems. Continuing to expand the literature in this topic has the potential to improve patient outcomes and decrease healthcare costs.

This study was an important step in establishing literature to support large, comprehensive VE studies in IC populations. By demonstrating the ability to enroll a substantial IC population in a study where the primary focus was not IC individuals, we have shown the feasibility of enrolling IC populations in future studies. These future IC-specific VE studies may lead to greater knowledge about specific protections afforded by the influenza such as decreased influenza-related hospitalizations and severity of disease. The study also demonstrated a stark difference in influenza VE in IC individuals compared to non-IC individuals and the need to consider additional confounding variables when analyzing the IC population. Finally, future studies should examine whether vaccine effectiveness among IC individuals varies by vaccine type. which should be considered when selecting which influenza vaccine product to administer to IC individuals.

3.5 Subsection

Table 4: Patient Characteristics Overall and by Immunocompromising Conditions, US FluVE Network Study Adults, 2017-2018 (n=5671)

	Whole (n= 5671)	Non-Immunocompromised (n=5216)	Immunocompromised (n=455)	p-value
Enrollment site, n (%)				
Michigan	848 (15.0)	785 (15.1)	63 (13.9)	**<.001**
Pennsylvania	978 (17.3)	919 (17.6)	59 (13.0)	
Texas	1208 (21.3)	1099 (21.1)	109 (24.0)	
Washington	1386 (24.4)	1300 (24.9)	86 (18.9)	
Wisconsin	1251 (22.1)	1113 (21.3)	139 (30.3)	
Female, n (%)	3659 (64.5)	3332 (63.9)	327 (71.9)	**0.003**
Age group, n (%)				
18-49	2938 (51.8)	2784 (53.4)	154 (33.9)	**<.001**
50-64	1547 (27.3)	1399 (26.8)	148 (32.5)	
65-74	760 (13.4)	679 (13.0)	81 (17.8)	
75+	426 (7.5)	354 (6.8)	72 (15.8)	
Age (years), mean ± SD	48.1 + 18.1	47.3 + 17.9	56.5 + 17.2	**<.001**
Race, n (%)				
White, non-Hispanic	4394 (77.5)	4022 (77.1)	372 (81.8)	**0.023**
Other	1277 (22.5)	1194 (22.9)	83 (18.2)	
BMI, mean ± SD	32.1 + 11.6	32.1 + 11.9	32.2 + 8.2	0.891
Any flu, n (%)				
Negative	3702 (65.3)	3395 (65.1)	307 (67.5)	0.306
Positive	1969 (34.7)	1821 (34.9)	148 (32.5)	
Verified influenza vaccine, n (%)				
No	2697 (47.6)	2567 (49.2)	130 (28.6)	**<.001**
Yes	2974 (52.4)	2649 (50.8)	325 (71.4)	
Onset date				
Influenza vaccine type, n (%)				
Inactivated trivalent	91 (3.3)	84 (3.5)	7 (2.3)	0.760
Recombinant trivalent	3 (0.1)	3 (0.1)	0 (0.0)	
Inactivated quadrivalent	2160 (79.1)	1919 (79.0)	241 (79.5)	
High-dose quadrivalent	465 (17.0)	412 (17.0)	53 (17.5)	
Recombinant quadrivalent	13 (0.5)	11 (0.5)	2 (0.7)	
Pre-peak	2067 (36.5)	1912 (36.7)	155 (34.1)	0.176
Peak	1588 (28.0)	1468 (28.1)	120 (26.4)	
Post-peak	2016 (35.6)	1836 (35.2)	180 (39.6)	
Self-reported health status, n (%)				
Excellent/ very good/ good	2151 (37.9)	1870 (35.9)	281 (61.8)	**<.001**
Fair/ poor	3520 (62.1)	3346 (64.2)	147 (38.2)	
High-risk conditions in the prior year[a], n (%)				
No	2310 (40.7)	2305 (44.2)	5 (1.1)	**<.001**
Yes	3361 (59.3)	2911 (55.8)	450 (98.9)	
Number of outpatient visits in the prior year, n (%)				

0-3	4018 (70.9)	3921 (75.2)	97 (21.3)	**<.001**
>3	1653 (29.2)	1295 (24.8)	358 (78.7)	
Number of inpatient visits in the prior year, n (%)				
0-3	5646 (99.6)	5205 (99.8)	441 (96.9)	<.001
>3	25 (0.4)	11 (0.2)	14 (3.1)	

a: chronic pulmonary or cardiovascular conditions, renal, hepatic, neurologic, hematologic, or metabolic disorders, and immunosuppression caused by medications, HIV infections, and primary immunodeficiency
bold indicates $p<0.05$

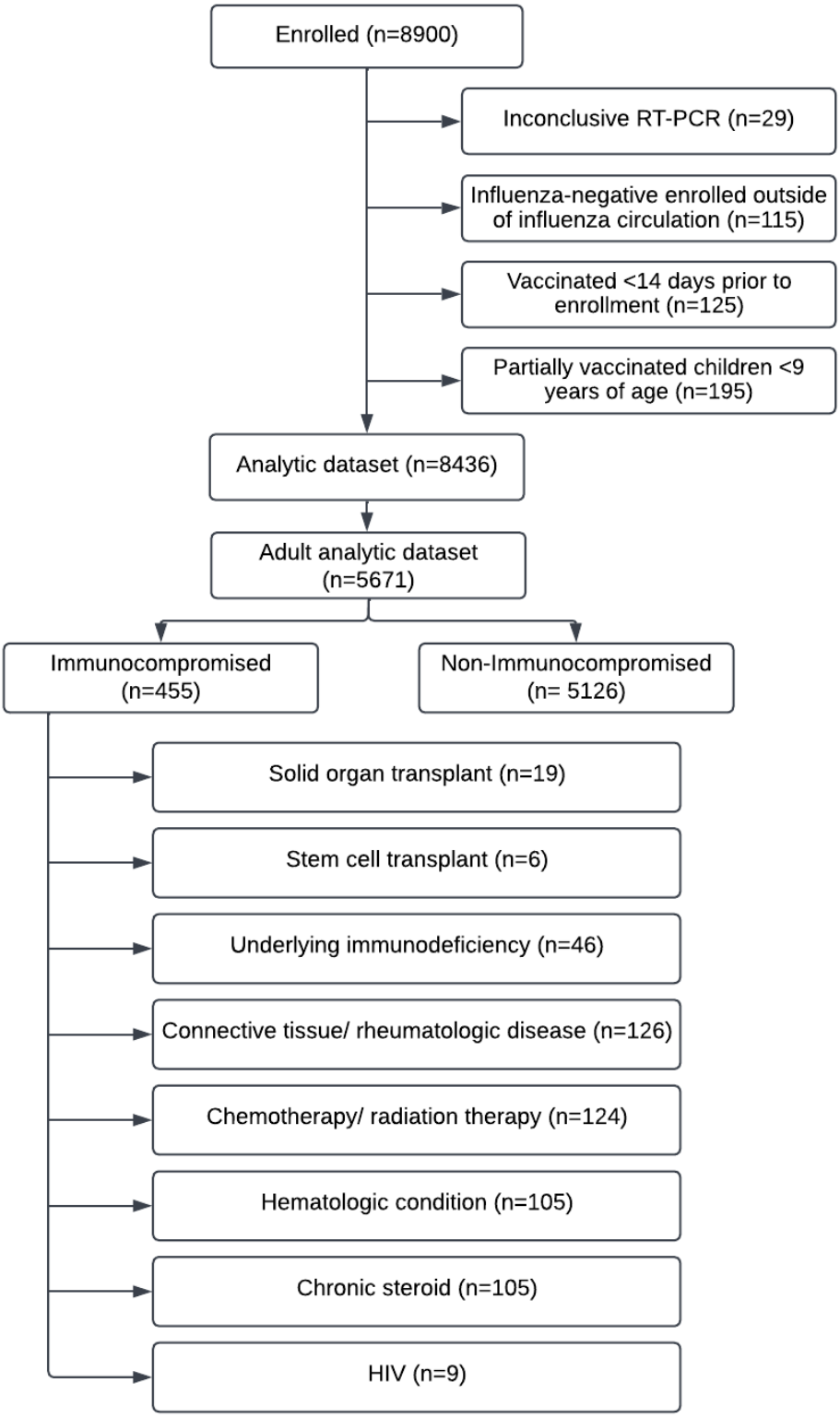


Figure 3: US FluVE Network Study Population, 2017-2018; Immunocompromised groups were mutually exclusive and hierarchical following the order listed here.

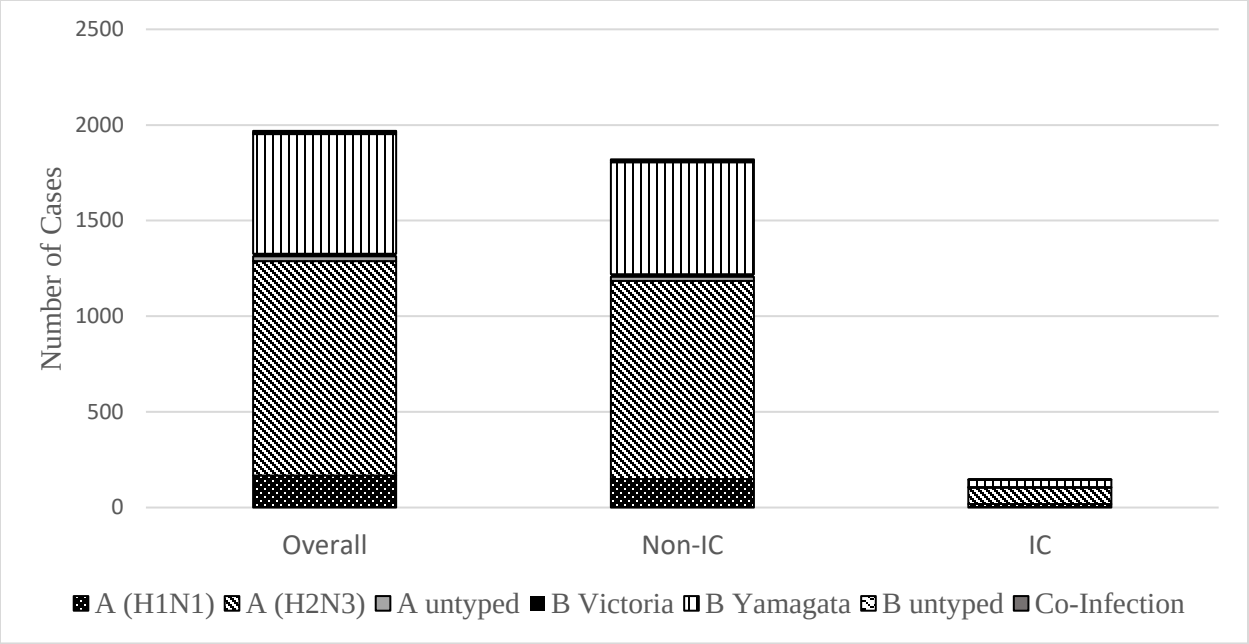


Figure 4: Influenza Virus Type/Subtype and Lineage, 2017-2018

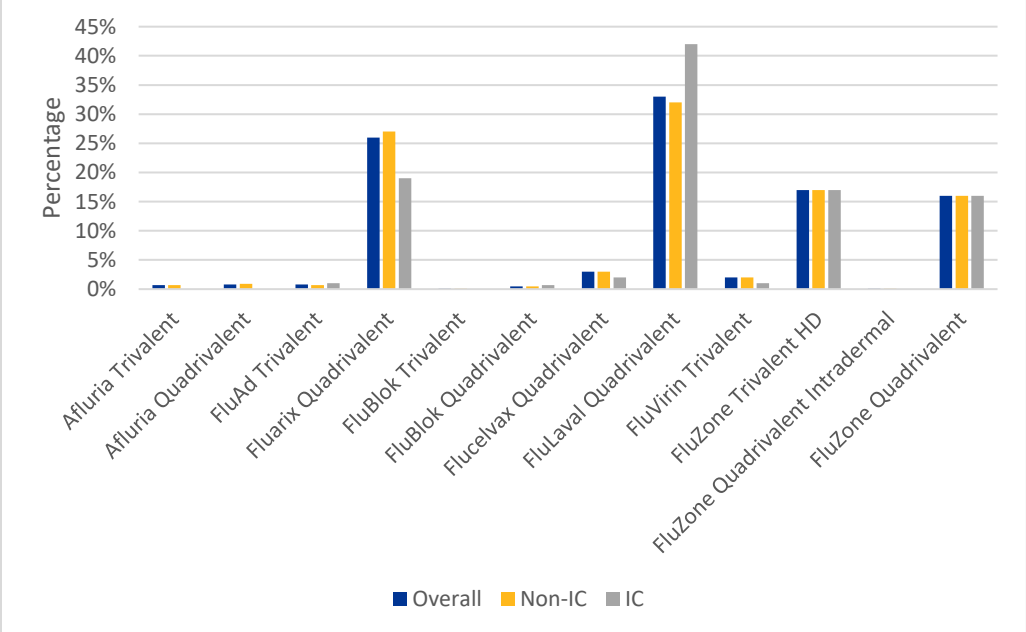


Figure 5: Influenza Vaccine Type, 2017-2018

4.0 Vaccine Effectiveness of the Recombinant Influenza Vaccine in Immunocompromised Adults During the 2018-2019 Influenza Season

4.1 Introduction

During the 2018-2019 influenza season, ten influenza vaccine products were available for adults in the United States, including trivalent and quadrivalent standard dose, trivalent high dose (FluZone High-Dose), recombinant (FluBlok), and live attenuated (FluMist).[93] While the Advisory Committee on Immunization Practices (ACIP) releases influenza vaccine guidance annually, until the 2022-2023 season, they had no preferential recommendation on the brand or type of influenza vaccine; the 2022-2023 guidance introduced the recommendation of high-dose, adjuvanted (Afluria), or recombinant influenza vaccines for individuals $\geq$ 65 years.[80] The type of influenza vaccine individuals receive is often determined by the entity administering the vaccine, and, under the Affordable Care Act (ACA), are administered free of cost with insurance.[94] While the ACA covers the cost of the influenza vaccine, it does not require companies to offer all types of influenza vaccines. Since recombinant, high-dose, and adjuvanted influenza vaccines are more expensive than standard dose, it is important that the companies purchasing the vaccines receive a return on their investment in the form of decreased healthcare utilization.[95]

In five superiority trials, FluBlok, a recombinant hemagglutinin vaccine, was shown to elicit a superior immune response compared to placebo, FluZone, and Afluria in healthy adults aged 18-49, 50-64, and 65-92, and ambulatory and medically stable adults $\geq$ 50; however, none of these studies included IC adults.[96–100] Given previous research demonstrating a decreased influenza vaccine effectiveness (VE) among IC adults, it is important to identify whether VE

differs by vaccine product in the general population and also among vulnerable subsets including IC adults who are at a higher risk for complications and hospitalization.[87] This study aims to investigate how the protection afforded by the recombinant seasonal influenza vaccine compares to the protection provided by the non- recombinant seasonal influenza vaccines by comparing the recombinant VE to the non-recombinant VE in IC adults.

4.2 Methods

4.2.1 Study Design and Enrollment

Data from the 2018-2019 Hospitalized Adult Influenza Vaccine Effectiveness Network (HAIVEN) study was used for this analysis. The methods for HAIVEN have been previously described.[4,39,101] Briefly, HAIVEN utilized a test-negative case-control study design and enrolled adults admitted to study hospitals with new or worsening respiratory symptoms in the ten days prior to hospital admission. Study hospitals were located in Michigan, Pennsylvania, Tennessee, and Texas and represented diverse socioeconomic and geographic populations.

Demographics, vaccine information, healthcare utilization, transplant status, and biologic, and chemotherapy and radiation therapy use were ascertained during in-person interviews and verified through electronic medical records (EMRs). Illness-related symptom(s), smoking status, oxygen use, self-perception of health status, socioeconomic status, and quality of life variables were also collected during the interview. Race was dichotomized into non-Hispanic White and not non-Hispanic White. Symptom onset date was categorized into pre-peak, peak, and post-peak based on the tertiles of the onset date.

While HAIVEN enrollment was open to all hospitalized adults meeting inclusion criteria, this analysis was restricted to IC participants. IC individuals were identified using ICD-10 codes (all IC conditions) and interview responses (chemotherapy and radiation therapy only) following guidance from previous publications studying influenza VE in IC individuals (Appendix Figure 1) and included organ transplants, stem cell transplants, underlying immunodeficiencies, connective tissue disorders, chemotherapy or radiation therapy, hematologic conditions, chronic use of steroids, and HIV.[87] The IC groups were mutually exclusive and hierarchical based on the order listed.

4.2.2 Influenza Case Definition

Nasal and oropharyngeal swabs were collected from all participants at either study enrollment or from remnant clinical samples. Remnant clinical samples were used if collected up to 72 hours prior to study enrollment. Polymerase chain reaction (PCR) testing was completed on all swabs by local research laboratories using a Centers for Disease Control and Prevention (CDC) PCR protocol.[86] PCR tests positive for influenza were considered cases. Negative tests and tests positive for other respiratory viruses were classified as controls.

4.2.3 Influenza Vaccination

Vaccination status was ascertained during participant interviews and was verified through EMRs, state vaccine registries, and health insurance claim reviews. When possible, the vaccine product was documented. Individuals vaccinated $\geq$ 14 days prior to symptom onset were considered vaccinated. Participants with FluBlok and 'recombinant vaccine' were classified as

'recombinant', and all other influenza vaccines, including unknown, were classified as 'non-recombinant'.

4.2.4 Statistical Analysis

Analyses were completed using SAS, version 9.4. Statistical significance was defined as $p < .05$ or a 95% confidence interval (CI) excluding the null value. Demographic and other characteristics of the unvaccinated, recombinant, and non-recombinant groups were compared using the Pearson $\chi 2$ and Fisher's Exact tests for categorical variables and ANOVA for continuous variables. VE was calculated by estimating the odds of influenza positivity among vaccinated patients compared with unvaccinated patients for the recombinant and non-recombinant groups using multivariable logistic regression using influenza positivity as the outcome and vaccination status as the exposure variable, with VE = (1 – adjusted odds ratio) × 100%.[88]

VE was first calculated for the overall study population. To determine if VE differed between the recombinant recipients and non-recombinant influenza vaccine recipients, vaccination status was categorized into three groups: unvaccinated, recombinant, and non-recombinant influenza vaccine. To determine the final model, we reviewed prior literature on influenza vaccine effectiveness utilizing a test-negative design.[4,39,41,71,89,101,102] Combining the literature review and results from model building, the model adjusting for age (continuous), symptom onset date, race, and sex was determined to be the best model.

A post hoc power analysis was completed with Power Analysis and Sample Size Software (PASS) 2022 using the observed number of cases (n = 146) and controls (n=806), the percent who received the recombinant influenza vaccine (24%), and a significance level of 0.05. The resulting power was 96%.

This protocol was approved by each institutions' Institutional Review Board and completed following good clinical practices and funded by the Centers for Disease Control and Prevention.

4.3 Results

During the 2018-2019 influenza season, 3975 individuals were enrolled in the HAIVEN study, of which, 1185 were excluded (Figure 5). In the resulting dataset of 2860 participants, 952 individuals were classified as immunocompromised. The breakdown of IC conditions was as follows: organ transplant (n=76), stem cell transplant (n=7), underlying immunodeficiency (n=26), connective tissues/rheumatologic disease (n=95), chemotherapy/radiation therapy (n=229), hematologic condition (n=113), chronic steroid use (n=371), and HIV (n=35). The average age of participants was 62.2 years $\pm$ 15.0, and the majority of the participants were female (55.4%), white (72.8%), influenza negative (84.7%), and vaccinated (75.6%). Fifty-two percent of participants reported fair/poor health (52.1%) and 23.5% were hospitalized four or more times in the previous 12 months. The median length of stay (LOS) was 3.0 days (IQR: 4.0). Two-hundred thirty-two (24%) participants were unvaccinated, 609 (64%) received a non-recombinant seasonal influenza vaccine, and 111 (12%) received the recombinant seasonal influenza vaccine (Table 5).

Between the unvaccinated, non-recombinant, and recombinant groups, there were statistically significant differences in enrollment site (p=<.001), age groups (p=<.001), and race (p=.001). The recombinant group was predominantly enrolled at Pennsylvania sites (97.3%); the recombinant vaccine was the only influenza vaccine offered at the largest medical center in western PA. While not statistically significant, the non- recombinant group was older and least likely to be hospitalized four or more times in the last year, the highest percentage of individuals identifying

as White, non-Hispanic compared to the unvaccinated and recombinant groups (Table 5). There were significant differences in influenza virus type/subtype and lineage between the unvaccinated, non- recombinant, and recombinant groups (p=.04) (Figure 6).

The overall adjusted VE was 15% (95% CI: -29, 44), while adjusted VE for recombinant and non- recombinant was 39% (95% CI: -23, 70) and 10% (95% CI: -37, 41), respectively (Table 6).

4.4 Discussion

The vaccination rate (76%) for the study population was higher than the reported 2018-2019 vaccine coverage estimates of 35%, 47%, and 68% for 18–49 years, 50–64 years, and ≥65 years, respectively.[15,102,103] This elevated vaccination rate among IC is likely reflective of the continuous recommendations for seasonal influenza vaccines from the American Society for Transplantation (AST), Infectious Disease Society of America (IDSA), and ACIP for over 20 years.[15,93,103] The increased recombinant VE (39%) compared to the non- recombinant VE (10%) is consistent with the previously published vaccine efficacy and immunogenicity studies on recombinant influenza vaccines.[104]

The difference in VE between recombinant and non- recombinant influenza vaccines in IC individuals is an important finding as the number of individuals considered to be IC continues to rise. In recent years, the indications for biologics and chemotherapy medications have expanded outside of the traditional uses.[105,106] As IC individuals are at higher risk for hospitalizations and severe outcomes related to influenza, it remains critical to provide the highest level of protection.

By decreasing the risk of severe influenza and hospitalizations among IC individuals, we can increase quality of life (QoL) and decrease healthcare spending and utilization.

Produced using insect cell cultures, the recombinant vaccine is an egg-free alternative to traditional influenza vaccines, and since the recombinant vaccine contains hemagglutinin proteins instead of live virus, it is safe for use in pregnant persons and immunocompromised individuals. The average wholesale price (AWP) of the recombinant vaccine is approximately three times higher than most other influenza vaccines; however the the recombinant vaccine AWP is in line with other specialty influenza vaccines such as the Fluzone High Dose and Fluad (adjuvanted).[95] With the increased AWP associated with the recombinant vaccine, it is important that the vaccine effectiveness supports the elevated costs on healthcare networks and purchasers.

Since the majority of the recombinant vaccine recipients were enrolled at the Pennsylvanian sites, this could limit generalizability to other parts of the country. The Pennsylvania sites were all urban hospitals and a mixture of tertiary, secondary, and primary care centers. Additionally, this limitation could introduce bias due to site level differences in hospitalization thresholds and vaccination practices. Another limitation of this study was that given the small sample size of IC patients, we were unable to evaluate the effectiveness of the high-dose or adjuvanted influenza vaccines.

The results of this study can be used to assist hospitals, insurance companies, and other healthcare entities in determining the type of influenza vaccines offered to their IC patients. Furthermore, providing this information can be helpful to patients who are given the option of choosing which vaccine they receive. Future studies should build upon these results to examine the recombinant influenza vaccine VE in larger populations and subsequent influenza seasons to determine if the increased recombinant influenza vaccine VE holds. Recombinant influenza

vaccines produced by other manufactures might have similar results but those vaccines are not yet available in the USA.

Despite early studies highlighting the benefits of recombinant influenza vaccines, there is a dearth of recombinant influenza vaccine efficacy and effectiveness studies, especially in IC populations. [38,107] This study has demonstrated the importance of recombinant influenza vaccine effectiveness studies in the vulnerable, immunocompromised population.

4.5 Subsection

Table 5: Patient Characteristics by Type of Vaccine, 2018-2019 (n=952)

	Total (n= 952)	Unvaccinated (n=232)	Non-recombinant (n=609)	Recombinant (n=111)	p-value
Enrollment site, n (%)					
Michigan	63 (6.6)	14 (6.0)	49 (8.1)	0 (0.0)	**<0.001**
Pennsylvania	315 (33.1)	81 (34.9)	126 (20.7)	108 (97.3)	
Tennessee	207 (21.7)	52 (22.4)	155 (25.5)	0 (0.0)	
Texas	367 (38.6)	85 (36.6)	279 (45.8)	3 (2.7)	
Female, n (%)	527 (55.4)	143 (61.6)	322 (52.9)	62 (55.9)	0.073
Age group, n (%)					
18-49	168 (17.7)	54 (23.3)	92 (15.1)	22 (19.8)	**<0.001**
50-64	340 (35.7)	95 (41.0)	195 (32.0)	50 (45.1)	
65-74	241 (25.3)	56 (24.1)	159 (26.1)	26 (23.4)	
75+	203 (21.3)	27 (11.6)	163 (26.8)	13 (11.7)	
Age, mean ± SD	62.2 ± 15.0	58.3 ± 14.6	64.2 ± 14.8	59.5 ± 14.4	**<0.001**
Length of stay, median (IQR)	4.0 (3.0)	4.0 (3.5)	3.0 (4.0)	3.0 (3.0)	0.364
Race, n (%)					
White, non-Hispanic	693 (72.8)	151 (65.1)	468 (76.9)	74 (66.7)	**0.001**
Non-white	259 (27.2)	81 (34.9)	141 (23.2)	37 (33.3)	
Any flu, n (%)					
Negative	806 (84.7)	194 (83.6)	513 (84.2)	99 (89.2)	0.362
Positive	146 (15.3)	38 (16.4)	96 (15.8)	12 (10.8)	
Verified vaccine, n (%)					
No	232 (24.4)				
Yes	720 (75.6)				
Onset date					
Pre-peak	477 (50.1)	123 (53.0)	303 (49.8)	51 (46.0)	0.097
Peak	197 (20.7)	52 (22.4)	128 (21.0)	17 (15.3)	
Post-peak	278 (29.2)	57 (24.6)	178 (29.2)	43 (38.7)	

Self-reported health status, n (%)					
Excellent/ very good/ good	456 (47.9)	111 (47.8)	296 (48.6)	49 (44.1)	0.688
Fair/ poor	496 (52.1)	121 (52.2)	313 (51.4)	62 (55.9)	
Number of hospitalizations over the past 12 months, n (%)					
0	296 (31.1)	64 (27.6)	199 (32.7)	33 (29.7)	0.139
1	191 (20.1)	55 (23.7)	118 (19.4)	18 (16.2)	
2	151 (15.9)	31 (13.4)	106 (17.4)	14 (12.6)	
3	90 (9.5)	20 (8.6)	54 (8/9)	16 (14.4)	
4 or greater	224 (23.5)	62 (26.7)	132 (21.7)	30 (27.0)	

bold indicates $p<0.05$

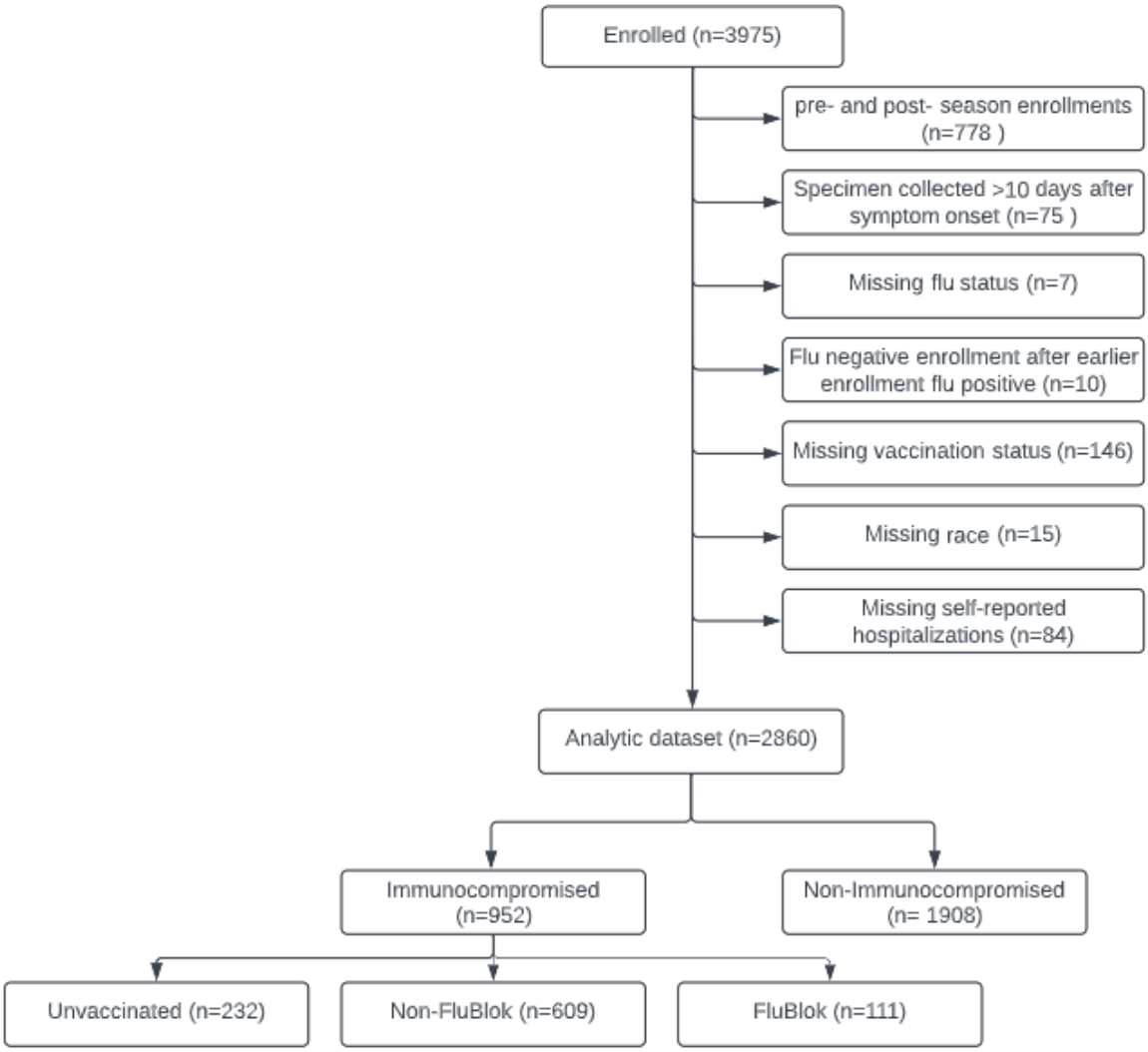


Figure 6: HAIVEN Study Population, 2018-2019

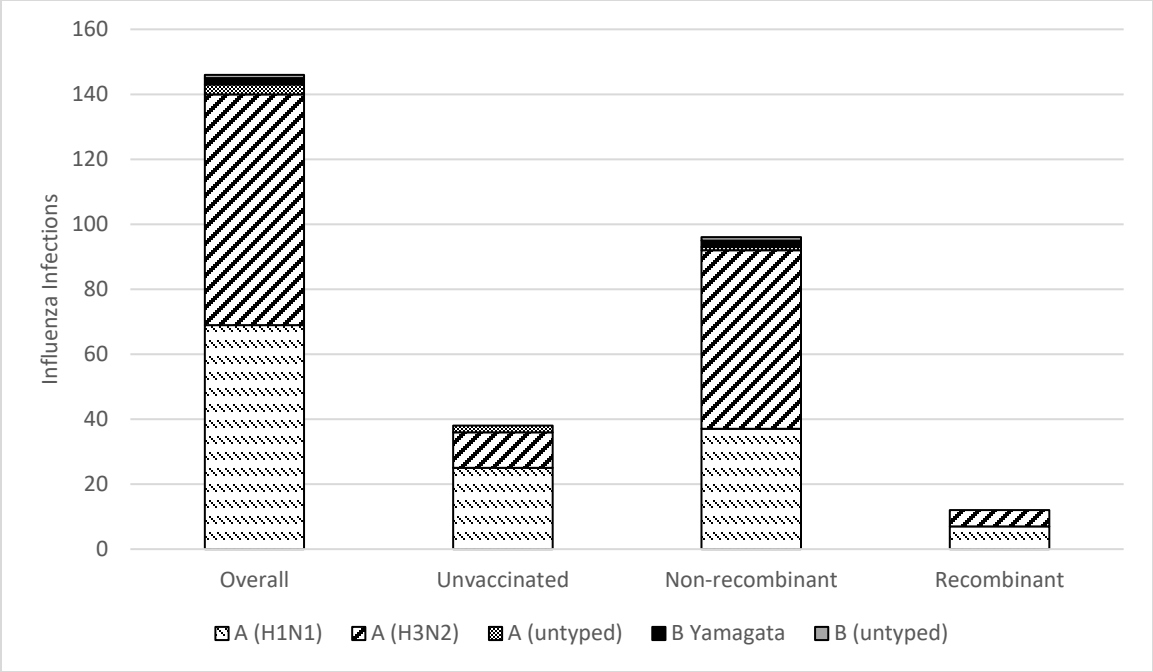


Figure 7: Influenza Virus Type/Subtype and Lineage in the Overall Study Population and by Vaccination Status

Table 6: Immunocompromised VE, HAIVEN 2018-2019

	VE (95% CI)	
	Unadjusted	**Adjusted[a]**
Overall, n= 952	10 (-35, 40)	15 (-29, 44)
Non-recombinant, n= 609	5 (-44, 37)	10 (-37, 41)
Recombinant, n=111	38 (-24, 70)	39 (-23, 70)

a: adjusted for onset date, age, sex, race

5.0 Conclusion

In conclusion, when compared to the outpatient immunocompromised vaccine effectiveness, the inpatient immunocompromised vaccine effectiveness was higher. When comparing non-immunocompromised individuals to immunocompromised individuals, the non-immunocompromised vaccine effectiveness was higher. Among immunocompromised individuals, the recombinant vaccine effectiveness was higher than vaccine effectiveness for the non-recombinant influenza vaccines, and there was no influenza B among the recombinant influenza vaccine recipients.

Through our studies, we demonstrated that ICD-10 codes were sufficient to accurately capture many immunocompromising conditions. Finally, our studies made significant contributions to the number of immunocompromised influenza vaccine effectiveness studies. We demonstrated the ability to use existing dataset to study an under researched population and created a standardized immunocompromised definition that has already been used in other influenza studies. The public health significance of these studies is the addition of immunocompromised influenza vaccine effectiveness data to base clinical guidance. Future studies will expand on these studies to increase sample size and target specific immunocompromised populations.

Appendix A Supplemental Tables and Figures

Appendix Table 1: ICD-10 and CPT Codes Used to Classify the Immunocompromised Groups

Immunocompromising Condition	**ICD-10 code**
Organ transplant	
Complications of kidney transplant	T86.1
Complications of heart transplant	T86.2
Complications of heart-lung transplant	T86.3
Complications of liver transplant	T86.4
Complications of lung transplant	T86.81
Complications of intestine transplant	T86.85
Encounter for aftercare following organ transplant	Z48.2
Kidney transplant status	Z94.0
Heart transplant status	Z94.1
Lung transplant status	Z94.2
Heart and lung transplant status	Z94.3
Liver transplant status	Z94.4
Intestine transplant status	Z94.82
Pancreas transplant status	Z94.83
Stem cell transplant	
Stem cells transplant status	Z94.84
Complications of bone marrow transplant	T86.0
Complications of stem cell transplant	T86.5
Underlying immunodeficiency	
Immunodeficiency with predominantly antibody defects	D80
Severe combined immunodeficiency [SCID] with reticular dysgenesis	D81.0
Severe combined immunodeficiency [SCID] with low T- and B-cell numbers	D81.1
Severe combined immunodeficiency [SCID] with low or normal B-cell numbers	D81.2

Combined immunodeficiency, unspecified	D81.9
Immunodeficiency associated with other major defects	D82
Common variable immunodeficiency	D83
Other immunodeficiencies	D84
Defects in the complement system	D84.1
Other specified immunodeficiencies	D84.8
Immunodeficiency, unspecified	D84.9
Other specified disorders involving the immune mechanism, not elsewhere classified	D89.8
Disorder involving the immune mechanism, unspecified	D89.9
Connective tissue disorder	
Rheumatoid arthritis with rheumatoid factor	M05
Other rheumatoid arthritis	M06
Unspecified juvenile rheumatoid arthritis	M08.0
Juvenile rheumatoid arthritis with systemic onset	M08.2
Juvenile rheumatoid polyarthritis (seronegative)	M08.3
Pauciarticular juvenile rheumatoid arthritis	M08.4
Psoriatic juvenile arthropathy	L40.54
Other psoriatic arthropathy	L40.59
Systemic lupus erythematosus	M32
Polyarteritis nodosa	M30.0
Polyarteritis with lung involvement [Churg-Strauss]	M30.1
Juvenile polyarteritis	M30.2
Wegener's granulomatosis	M31.3
Dermatopolymyositis	M33
Systemic sclerosis [scleroderma]	M34
Progressive systemic sclerosis	M34.0
CR(E)ST syndrome	M34.1
Systemic sclerosis, unspecified	M34.9
Sicca syndrome [Sjogren]	M35.0
Systemic involvement of connective tissue, unspecified	M35.9

Chemotherapy or radiation therapy	
Encounter for antineoplastic radiation therapy	Z51.0
Encounter for antineoplastic chemotherapy and immunotherapy	Z51.1
Hematologic conditions	
Acute leukemia of unspecified cell type not having achieved remission	C95.00
Chronic leukemia of unspecified cell type not having achieved remission	C95.10
Constitutional aplastic anemia	D61.0
Idiopathic aplastic anemia	D61.2
Aplastic anemia, unspecified	D61.9
Neutropenia	D70
Functional disorders of polymorphonuclear neutrophils	D71
Other disorders of white blood cells	D72
Hyposplenism	D73.0
Hodgkin lymphoma	C81
Follicular lymphoma	C82
Non-follicular lymphoma	C83
Mature T/NK-cell lymphoma	C84
Other specified and unspecified types of non-Hodgkin lymphoma	C85
Other specified types of T/NK-cell lymphoma	C86
Malignant immunoproliferative diseases and certain other B-cell lymphomas	C88
Multiple myeloma and malignant plasma cell neoplasms	C90
Lymphoid leukemia	C91
Myeloid leukemia	C92
Monocytic leukemia	C93
Other leukemias of specified cell type	C94
Other and unspecified malignant neoplasms of lymphoid, hematopoietic and related tissue	C96
Myelodysplastic syndromes	D46
Chronic use of steroids	
Long term (current) use of steroids	Z79.5

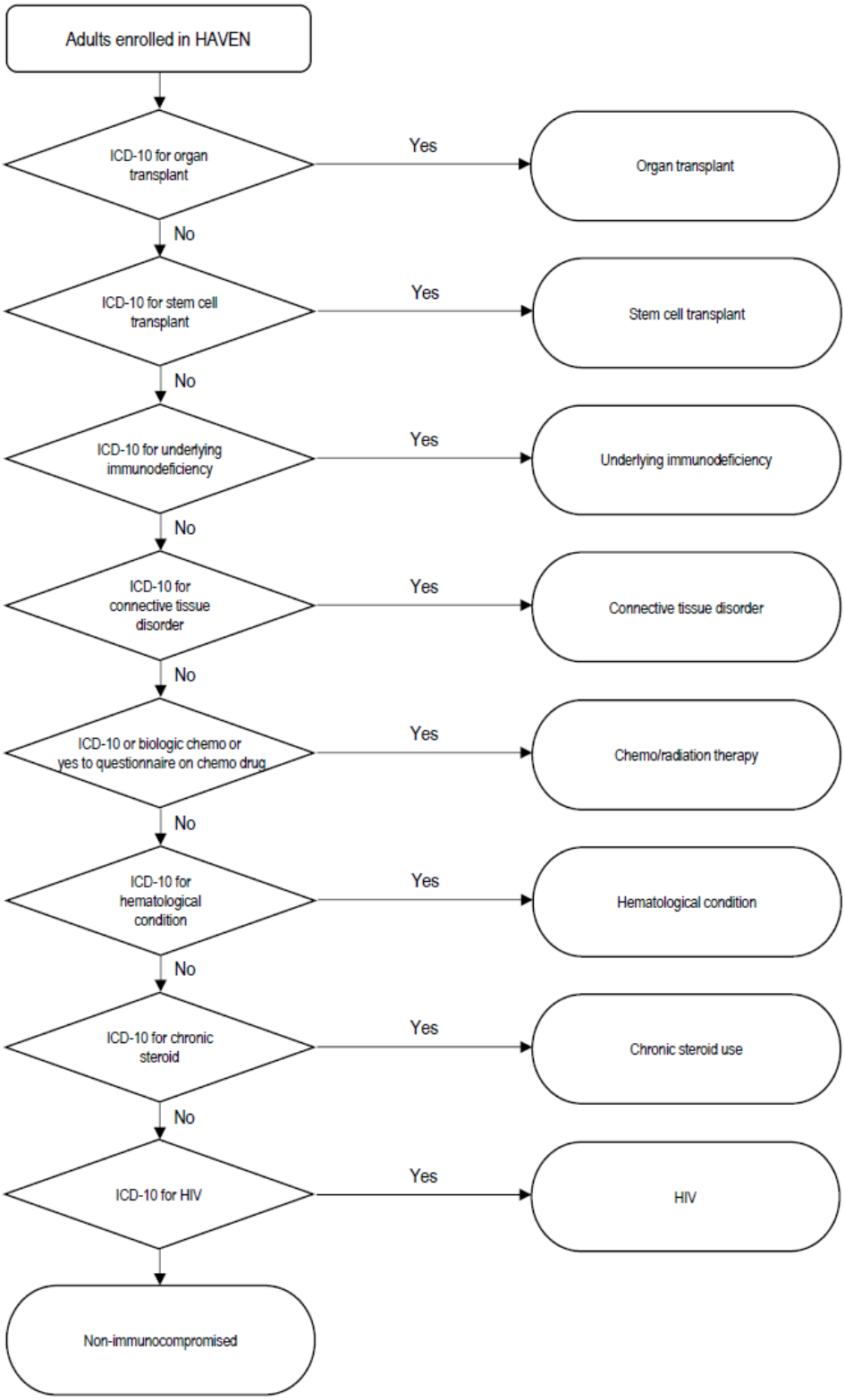
Long term (current) use of systemic steroids	Z79.52
HIV	
Human immunodeficiency virus [HIV] disease	B20
Human immunodeficiency virus, type 2 [HIV 2] as the cause of diseases classified elsewhere	B97.35
Human immunodeficiency virus [HIV] disease complicating pregnancy, childbirth and the puerperium	O98.7
Asymptomatic human immunodeficiency virus [HIV] infection status	Z21
	CPT code
Chemotherapy	96401-96417
	96420-96425
	96440-96450
	G0498
Radiation therapy	
External Beam Radiation Therapy	77402-77412 G6003-G6014
Intensity Modulated Radiation Therapy	77385-77386 77418 G6015-G6016
Image-guided Radiation Therapy	77387 G6001-G6002 G6017
Stereotactic Radiosurgery	77371-77372
Stereotactic Body Radiation Therapy	77373
Brachytherapy	77778 77770-77772
Intracavitary Radiation Therapy	77761-77763

CPT codes for chemotherapy and radiation therapy were collected at the Pennsylvania sites only

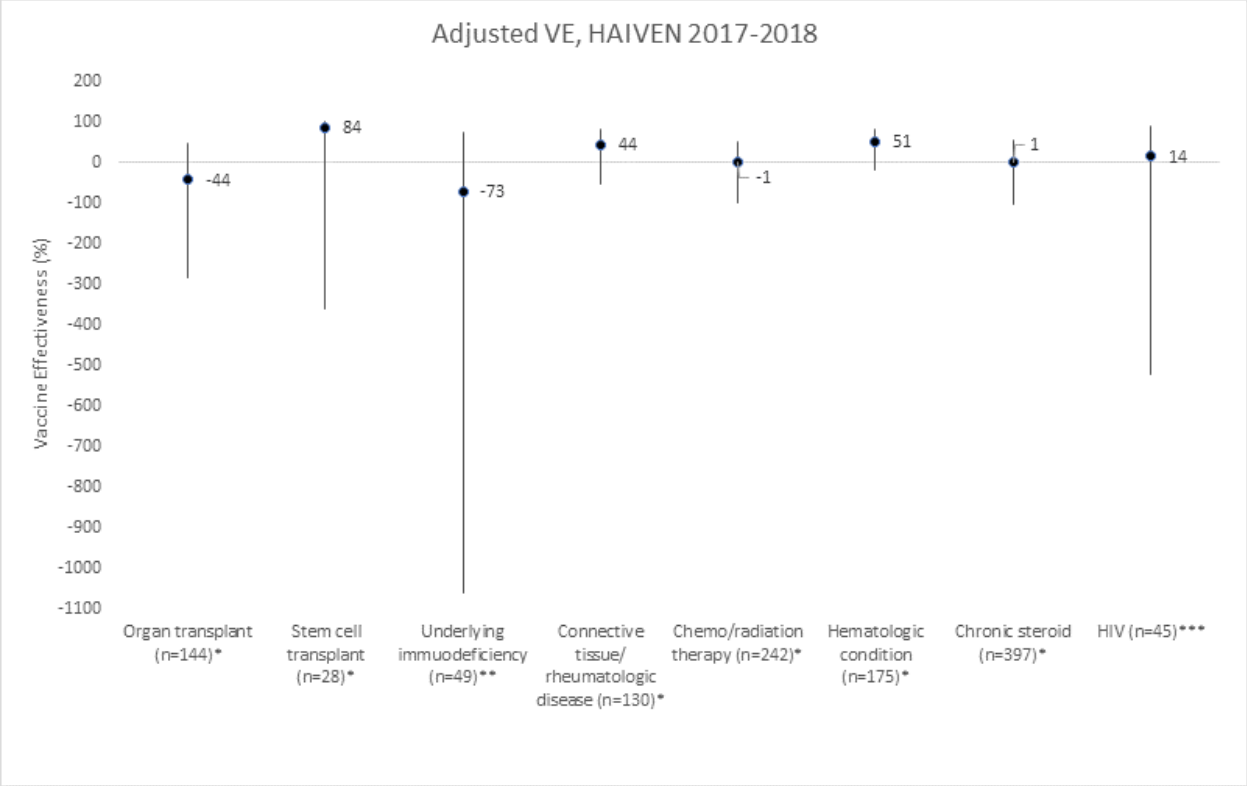
Appendix Table 2: Patient Characteristics Overall by Type of Immunocompromising Conditions, US Hospitalized Adult Influenza Vaccine Effectiveness (HAIVEN) Study, 2017-2018 (n=1,210)

	Organ Transplant (n=144)	Stem Cell Transplant (n=28)	Underlying Immunodeficiency (n=49)	Connective Tissue/ Rheumatologic Disease (n=130)	Chemo/ Radiation Therapy (n=242)	Hematologic Condition (n=175)	Chronic Steroid Use (n=397)	HIV (n=45)	p-value
Female, n (%)	55 (38.2)	11 (39.3)	22 (44.9)	104 (80.0)	117 (48.4)	105 (60.0)	259 (65.2)	14 (31.1)	**<0.001**
Enrollment site, n (%)									
Michigan	43 (29.9)	12 (42.9)	14 (28.6)	29 (22.3)	55 (22.7)	31 (17.7)	31 (7.8)	14 (31.1)	**<0.001**
Pennsylvania	45 (31.3)	6 (21.4)	8 (16.3)	31 (23.9)	68 (28.1)	35 (20.0)	66 (16.6)	4 (8.9)	
Tennessee	33 (22.9)	8 (28.6)	11 (22.5)	29 (22.3)	40 (16.5)	59 (33.7)	31 (7.8)	9 (20.0)	
Texas	23 (16.0)	2 (7.1)	16 (32.7)	41 (31.5)	79 (32.6)	50 (28.6)	269 (67.8)	18 (40.0)	
Age Group, n (%)									
18-49	37 (25.7)	5 (17.9)	13 (26.5)	31 (23.9)	42 (17.4)	43 (24.6)	65 (16.4)	20 (44.4)	**<0.001**
50-64	58 (40.3)	12 (42.9)	13 (26.5)	46 (35.4)	75 (31.0)	69 (39.4)	126 (31.7)	21 (46.7)	
64-74	40 (27.8)	9 (32.1)	14 (28.6)	29 (22.3)	71 (29.3)	25 (14.3)	89 (22.4)	4 (8.9)	
75+	9 (6.3)	2 (7.1)	9 (18.4)	24 (18.5)	54 (22.3)	38 (21.7)	117 (29.5)	0 (0.0)	
Age, mean ± SD	57.5 ± 13.5	60.1 ± 13.3	60.8 ± 17.9	60.4 ± 15.8	63.2 ± 14.7	59.5 ± 18.1	64.4 ± 15.7	49.8 ± 10.8	**<0.001**
Race, n (%)									
White, non-Hispanic	98 (68.1)	24 (85.7)	41 (83.7)	78 (60.0)	179 (74.0)	113 (64.6)	268 (67.5)	21 (46.7)	**<0.001**
Non-White	46 (31.9)	4 (14.3)	8 (16.3)	52 (40.0)	63 (26.0)	62 (35.4)	129 (32.5)	24 (53.3)	
BMI, mean ± SD	28.2 ± 6.3	27.1 ± 6.2	29.4 ± 8.3	29.9 ± 8.3	28.4 ± 7.3	30.8 ± 8.9	31.9 ± 10.3	29.7 ± 12.2	**<0.001**
Any Flu, n (%)	37 (25.7)	13 (46.4)	12 (24.5)	31 (23.9)	50 (20.7)	35 (20.0)	75 (18.9)	13 (28.9)	**0.03**
Documented vaccination, n (%)	109 (75.7)	20 (71.4)	33 (67.4)	87 (66.9)	145 (59.9)	107 (61.1)	306 (77.1)	34 (75.6)	**<0.001**
Length of Stay, median (IQR)	4.0 (3.5)	4.0 (4.0)	4.0 (4.0)	4.0 (5.0)	3.0 (4.0)	4.0 (5.0)	4.0 (3.0)	3.0 (3.0)	0.08
Number of high-risk conditions, n (%)									
None	2 (1.4)	0 (0.0)	0 (0.0)	3 (2.3)	6 (2.5)	4 (2.3)	5 (1.3)	1 (2.2)	**0.03**
1-2	1 (0.7)	0 (0.0)	1 (2.0)	5 (3.9)	10 (4.1)	17 (9.7)	12 (3.0)	3 (6.7)	
≥3	141 (97.9)	28 (100.0)	48 (98.0)	122 (93.9)	226 (93.4)	154 (88.0)	380 (95.7)	41 (91.1)	
Self-reported hospitalizations in the prior year, n (%)									
0-3 hospitalizations	105 (72.9)	17 (60.7)	38 (77.6)	101 (77.7)	171 (70.7)	137 (78.3)	297 (74.8)	36 (80.0)	0.34

≥4 hospitalizations	39 (27.1)	11 (39.3)	11 (22.5)	29 (22.3)	71 (29.3)	38 (21.7)	100 (25.2)	9 (20.0)	
Interval from illness onset and specimen collection, n (%)									
0-1 days	29 (20.1)	2 (7.1)	10 (20.4)	25 (19.2)	57 (23.6)	32 (18.3)	95 (23.9)	8 (17.8)	0.29
2-4 days	57 (39.6)	19 (67.9)	23 (46.9)	64 (49.2)	106 (43.8)	79 (45.1)	184 (46.4)	24 (53.3)	
5-10 days	58 (40.3)	7 (25.0)	16 (32.7)	41 (31.5)	79 (32.6)	64 (36.6)	118 (29.7)	13 (28.9)	
Onset date									
Pre-peak	53 (36.8)	12 (42.9)	18 (36.7)	48 (36.9)	100 (41.3)	80 (45.7)	180 (45.3)	18 (40.0)	0.13
Peak	46 (31.9)	6 (21.4)	9 (18.4)	27 (20.8)	58 (24.0)	30 (17.1)	99 (24.9)	10 (22.2)	
Post-peak	45 (31.3)	10 (35.7)	22 (44.9)	55 (42.3)	84 (34.7)	65 (37.1)	118 (29.7)	17 (37.8)	
Self-reported health status, n (%)									
Excellent/ very good/ good	63 (43.8)	13 (46.4)	29 (59.2)	83 (63.9)	121 (50.0)	89 (50.9)	239 (60.2)	28 (62.2)	**0.003**
Fair/ poor	81 (56.3)	15 (53.6)	20 (40.8)	47 (36.2)	121 (50.0)	86 (49.1)	158 (39.8)	17 (37.8)	



Appendix Figure 1: Algorithm for Identification of Immunocompromised Groups



Appendix Figure 2: Adjusted Vaccine Effectiveness Against Influenza A and B Among Patients with Specific Immunocompromising Conditions, HAIVEN study, 2017-2018

*Adjusted for enrolling site, onset date (pre-peak, peak, post-peak), age, race, days from illness onset to specimen collection (0-1, 2-4, 5-10 days), self-reported health (poor/fair, good/very good/excellent), self-reported hospitalizations
**Adjusted for enrolling site, onset date (pre-peak, peak, post-peak), age, days from illness onset to specimen collection (0-1, 2-4, 5-10 days), self-reported health (poor/fair, good/very good/excellent), self-reported hospitalizations because the full model did not converge
***Adjusted for enrolling site, age because the full model did not converge

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