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Effects of Subject-level Characteristics on Influenza Illness and Vaccination

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2011

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## Abstract

Effects of Subject-level Characteristics on Influenza Illness and Vaccination
By Polina Elkind

A cohort study of 1,426 subjects utilized 2012-2013 influenza season data to carry out two objectives: firstly, to determine risk factors associated with influenza contraction, as well as the effect of vaccination against influenza infection, adjusting for various subject-level characteristics (race, sex, age, household size, and health risks); and, secondly, to evaluate the associations between these characteristics and vaccination status. A Cox proportional hazards regression model indicated that those who were both effectively vaccinated and from 4-member households (HR=0.45, p=0.006) were the least likely to contract influenza when compared to their respective reference group. Being 6 months-8 years of age (HR=1.55, p=0.047) was associated with a higher risk of contracting influenza. Adjusted vaccine effectiveness in the overall population was found to be 55% ($CI_{95\%}$ [20, 74]). Adults experienced significant protection, with a VE of 49% ($CI_{95\%}$ [2, 74]), but neither age category for children indicated significant protection from the flu due to effective vaccination. VE was also significant and protective for individuals from 4-member households (56%, $CI_{95\%}$ [23, 75]). Further, having been 6 months-8 years of age (OR=1.47, $CI_{95\%}$ [1.14, 1.90]) or 9-17 years of age (OR=1.60, $CI_{95\%}$ [1.22, 2.10]) were protective characteristics and yielded statistically significant associations with vaccination status. Having these characteristics increased the odds – in comparison to each characteristic's reference group – that an individual received a vaccination. Additionally, the interaction between health risks and sex indicated that females with health risks (OR=2.46, $CI_{95\%}$ [1.46, 4.12]), females without health risks (OR=1.43, $CI_{95\%}$ [1.14, 1.79]), and males with health risks (OR=4.42, $CI_{95\%}$ [2.24, 8.72]) all experienced significantly greater odds of vaccination when compared to males without health risks. Subjects who were of black (OR=0.65, $CI_{95\%}$ [0.43, 0.96]) or other/unknown race (OR=0.52, $CI_{95\%}$ [0.35, 0.79]), or lived in a household consisting of 5+ members (OR=0.78, $CI_{95\%}$ [0.63, 0.97]) were less likely to be vaccinated when compared to their respective reference groups.

# Effects of Subject-level Characteristics on Influenza Illness and Vaccination

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## 1. INTRODUCTION AND REVIEW OF THE LITERATURE

Randomized controlled trials are generally viewed as the gold standard for determining vaccine efficacy.[1] However, such studies are costly and the random assignment of subjects to vaccine or placebo intervention groups can be viewed as unethical. This is especially true in regards to the influenza vaccine, due to the increasing recommendation for universal influenza vaccination; vaccination has been known as an effective prevention measure against influenza contraction for some time now.[2] Since vaccine *efficacy* can only be determined using a clinical trial, the emphasis in research has shifted to the use of observational – case-control or cohort – studies for determining vaccine *effectiveness* (VE) for influenza vaccines.[2] Researchers who evaluate vaccine effectiveness are largely concerned with how it varies between both subjects and seasons.[2-6] Vaccine effectiveness, calculated as 100 x [1 - adjusted risk ratio], quantifies how well a vaccine works by calculating how many disease cases are prevented due to vaccination.[7,8] When vaccine effectiveness is calculated for a rare disease, an adjusted hazard ratio can be substituted for the adjusted risk ratio.[1]

Vaccine effectiveness is of special interest to public health authorities because the results are relevant for evaluating the success of large-scale vaccination programs. Because virus strains and vaccine compositions vary from year to year, the United States Influenza Vaccine Effectiveness (US Flu VE) Network has been established to monitor and estimate annual vaccine effectiveness in subjects seeking outpatient care for acute respiratory illnesses (ARI).[9] According to the CDC, vaccine effectiveness is determined, in part, by the strains of the virus present during a specific influenza season – or, more specifically, how well the developed vaccine matches the flu virus in circulation.[10]

However, the characteristics of the person being vaccinated are also believed to influence vaccine effectiveness.[10] Therefore, understanding these characteristics and the effects of variation among them is important.

Numerous associations between subject characteristics and flu outcome have already been evaluated and established in other studies. For example, it is generally recognized that the young, elderly, pregnant, and those who suffer from other health conditions are at a greater risk for experiencing complications from influenza.[11] If they contract the infection, these individuals can face hospitalization, and even death, as a result of pulmonary complications.[11] Since flu vaccination can reduce the risk of serious flu outcomes, immunization programs are generally targeted at these at-risk groups.[10]

The authors of a recently-published meta-analysis of the effectiveness of influenza vaccinations in different groups pointed out that by estimating vaccine effectiveness in high-risk populations, studies allow vaccination status to be linked to disease outcome.[11] However, they claim that not accounting for differences in baseline characteristics between vaccinated and unvaccinated subjects can lead to biased results.[11] This shortcoming suggests the need for a model, in which vaccination effect is adjusted for by subject-level baseline characteristics. Researchers have determined vaccine effectiveness estimates via models of this nature in the past, but these estimates change annually and reassessments are needed every season.[2-7] Additionally, while these studies considered the association of subject-level characteristics with influenza outcome, they did not evaluate the associations of these characteristics with vaccination status.

During the 2012-2013 influenza season, a study conducted by the Michigan School of Public Health utilized a Cox proportional hazards model, adjusted for age and

high-risk health status, to assess possible associations between vaccine effectiveness and repeated annual vaccination, virus strain, and age.[6] However, the model did not adjust for other subject-level characteristics, although this data was available. The ensuing analysis will utilize the 2012-2013 Michigan data set to carry out two main objectives. The first is to use a Cox proportional hazards regression model to evaluate possible associations between various subject-level factors and influenza contraction. This model will also be used to determine the effectiveness of vaccination on the prevention of influenza illness while adjusting for various factors. These factors are the subject's race, sex, age, household size, and health risks. The model will also include interactions between vaccination status and each of the factors mentioned above to explore possible heterogeneities in vaccine effectiveness across the levels of each factor (effect modification). The second objective of this analysis is to evaluate the associations of the aforementioned subject-specific characteristics with receiving the influenza vaccine via use of a logistic regression model. The results will indicate how vaccination status varies by different levels of these factors. Understanding this variation may help guide vaccination initiatives in targeting groups with low vaccination coverage.

## 2. METHODOLODY

### *2.1. Study Overview*

This analysis is based on a cohort study conducted by the University of Michigan School of Public Health (UM-SPH) during the 2012-2013 influenza season; this season was considered relatively long in duration. Households were selected based on records of subjects who had selected a primary healthcare provider within the University of

Michigan Health System, and were considered eligible if they consisted of at least four participating members and at least two children 18 years or younger.[12] Subjects were enrolled from June through September 2012, and surveillance was performed from October 2012 through May 2013.[6] Participants were expected to report instances of acute respiratory illness (ARI) to the study site at the UM-SPH; an ARI was determined by two or more of the following symptoms: cough, fever or feverishness, nasal congestion, chills, headache, body aches, and/or a sore throat.[6] In the case of an ARI, subjects had to receive throat and nasal swab specimens (nasal-only for children younger than three years old) within seven days of symptom-onset.[6] These specimens were tested for influenza using real-time reverse transcription polymerase chain reaction (RT-PCR); this test is designed to detect both influenza A and B viruses, subtypes of influenza A, and lineage determination of influenza B.[6]

### *2.2. Objectives*

This analysis considered two outcomes: whether a patient contracted influenza and whether the patient was vaccinated. Evaluations of each considered whether the outcomes were associated with certain subject-level characteristics.

#### *2.2.1. Objective 1: Evaluating Factors Associated with Contracting Influenza*

The first outcome of interest, whether a patient was diagnosed with influenza during the flu season, was determined at the time of an influenza-positive test. A patient was found to be influenza-positive if the RT-PCR indicated so. This variable was treated as a binary outcome where a patient was either flu positive or not. Only the first case of

influenza was considered in the case of multiple influenza outcomes for one individual.[4] The factors for which possible associations were evaluated were whether the person was effectively vaccinated, the number of people living in a household (4, 5+); age group (6 months-8 years, 9-17 years, and 18+ years); sex (male or female); race (white, black, Asian, unknown/other); and whether the person experienced a health risk (yes or no). A person who was diagnosed with influenza was considered effectively vaccinated if he/she received a vaccine at least 14 days prior to the onset of flu symptoms. In the absence of influenza contraction, effective vaccination simply began 14 days after receipt of vaccine. Children eight years or younger were required to have two doses of the vaccine to be considered effectively vaccinated. There was no "elderly" age group because, in the data set, this specific stratum was too small. Researchers were responsible for determining the presence of health conditions considered high-risk for complications of influenza; they did so by reviewing and evaluating participant medical records from the Michigan health-system.[6]

#### *2.2.2. Objective 2: Evaluating Factors Associated with Receiving an Influenza Vaccination*

The second outcome of interest, whether a patient was vaccinated, was determined at any time during the study (this was a time-varying outcome). Associations were evaluated between vaccination and the number of people living in a household (4, 5+); age group (6 months-8 years, 9-17 years, and 18+ years); sex (male or female); race (white, black, Asian, unknown/other); and whether the person experienced a health risk (yes or no).

### *2.3. Statistical Methods*

SAS 9.4 was used for all data analysis. Statistical test results were considered significant if the corresponding type I error rate was 0.05 or less. All model selection processes utilized backward elimination and a cut-off p-value of 0.10.

#### *2.3.1. Methods for Univariate Analysis*

Since the final dataset consisted of only categorical variables, contingency tables were used to evaluate the distribution of all of the previously-mentioned factors related to both flu and vaccination outcome categories. Further, a $\chi^2$ test of independence was used to establish whether a significant association existed between a risk factor and the outcome in question. Fisher's exact test was used in cases where any cell of a contingency table was less than five.

#### *2.3.2. Methods for Objective 1: Cox Proportional Hazards Regression Model*

A Cox proportional hazards regression model was used to evaluate the effects of receiving a flu vaccine, as well as other factors, on influenza outcome. The reason for using this model was that the main explanatory variable, namely vaccination status, was time-dependent. Many of the study participants were effectively vaccinated after the onset of the study. The model considered time, in days, from the start of flu season – July 1, 2012 – until a flu-positive test, or until the end of flu season (censoring) – June 30, 2013. In addition to vaccination status, the model included the baseline characteristics (age group, sex, race, household size, and health risks) as well as the interactions between vaccination status and all baseline characteristics. Reference coding was used for all covariates; the

reference groups were: not effectively vaccinated, 4-member households, 18+ years of age, male, white, and no health risks. Results from the model were also used to estimate the vaccine effectiveness, calculated as 100 x [1- hazard ratio].

### *2.3.3. Methods for Objective 2: Logistic Regression Model*

A logistic regression model was used to evaluate whether receiving the influenza vaccination was associated with various risk factors, such as, household size, age, sex, race, and health risks, as well as the interactions between health-risk status and the baseline characteristics. To quantify the effects of the risk factors under consideration on vaccination status, adjusted odds ratios and corresponding 95% Wald confidence intervals were calculated for each association. Since having been vaccinated was viewed as beneficial to a subject's health, a resulting OR less than 1.0 was considered harmful for a subgroup, as it indicated that these individuals were less likely to receive a vaccination as compared to their respective reference group. Meanwhile, an OR greater than 1.0 was viewed as protective to a subgroup's health. Reference coding was used for all covariates; the reference groups were: 4-member households, 18+ years of age, male, white, and no health risks.

# 3. RESULTS

## *3.1. Descriptive Statistics and Univariate Results*

There were a total of 1,426 subjects, from 321 households, whose records were utilized for this analysis. Table 1, on page 9, provides summary estimates that describe the group by its baseline characteristics, both by totals and broken down by vaccination and influenza status. Of the 1,426 subjects, 797 (55.89%) were effectively vaccinated, while 629 (44.11%) were not. The highest frequency of vaccination occurred during the fall of 2012. Further, 110 (7.71%) became influenza-positive at some point during the study, while 1,316 (92.29%) remained influenza-free. Among all subjects, 462 (32.40%) were 6 months-8 years of age, 371 (26.02%) were 9-17 years, and 593 (41.58%) were 18 years or older; 714 (50.05%) were male, while 712 (49.93%) were female; 1082 (75.88%) – the majority – were white, 117 (8.20%) were black, 121 (8.49%) were Asian, and 106 (7.43%) were of another or unknown race; 136 (9.54%) had experienced some form of a health risk, while 1,290 (90.46%) had not; 664 (46.56%) came from a household consisting of 4 members, while 762 (53.44%) from one of 5 members or more.

Age ($p=0.017$), sex, ($p=0.032$), race ($p=0.0035$), household size ($p=0.044$), and health risk presence ($p<0.0001$) were all found to have statistically significant associations with vaccination status (yes/no). Meanwhile, none of these variables had statistically significant associations with influenza outcome, although effective vaccination neared significance ($p=0.058$).

Table 1: Frequencies of Subject-Level Characteristics

| Subject Characteristic | ALL PATIENTS, # (col %) | VACCINATED, # (col %) (row %) | P-value for Association | INFLUENZA POSITIVE, # (col %) (row %) | P-value for Association |
|---|---|---|---|---|---|
| | | | | | |
| **Age** | | | | | |
| 6 mo-8 yrs | 462 (32.40) | 267 (33.50) (57.79) | 0.017* | 45 (40.91) (9.74) | 0.139 |
| 9-17 yrs | 371 (26.02) | 224 (28.11) (60.38) | | 25 (22.73) (6.74) | |
| ≥18 yrs | 593 (41.58) | 306 (38.39) (51.60) | | 40 (36.36) (6.75) | |
| **Sex** | | | | | |
| Male | 714 (50.07) | 379 (47.55) (53.08) | 0.032* | 58 (52.73) (8.12) | 0.5618 |
| Female | 712 (49.93) | 418 (52.45) (58.71) | | 52 (47.27) (7.30) | |
| **Race** | | | | | |
| White | 1082 (75.88) | 622 (78.04) (57.49) | 0.0035* | 81 (73.64) (7.49) | 0.772 |
| Black | 117 (8.20) | 59 (7.40) (50.43) | | 8 (7.27) (6.84) | |
| Asian | 121 (8.49) | 73 (9.16) (60.33) | | 12 (10.91) (9.92) | |
| Other/Unknown | 106 (7.43) | 43 (5.40) (40.57) | | 9 (8.18) (8.49) | |
| **Health Risk Present** | | | | | |
| Yes | 136 (9.54) | 100 (12.55) (73.53) | <.0001* | 6 (5.45) (4.41) | 0.129 |
| No | 1290 (90.46) | 697 (87.45) (54.03) | | 104 (94.55) | |
| **Household size** | | | | | |
| 4 | 664 (46.56) | 390 (48.93) (58.73) | 0.044* | 52 (47.27) (7.83) | 0.877 |
| 5+ | 762 (53.44) | 407 (51.07) (53.41) | | 58 (52.73) (7.61) | |
| **Month of Effective** Vaccination** | | | | | |
| September | 41 (2.88) | NA | NA | 1 (0.91) (2.44) | 0.058 |
| October | 344 (24.12) | NA | | 26 (23.64) (7.56) | |
| November | 246 (17.25) | NA | | 13 (11.82) (5.28) | |
| December | 90 (6.31) | NA | | 5 (4.55) (5.56) | |
| January | 43 (3.02) | NA | | 5 (4.55) (11.63) | |
| February | 30 (2.10) | NA | | 2 (1.82) (6.67) | |
| March | 2 (0.14) | NA | | 0 (0) (0) | |
| April | 1 (0.07) | NA | | 0 (0) (0) | |
| All Vaccinated | 797 (55.89) | NA | | 52 (47.27) (6.52) | |
| Not Vaccinated | 629 (44.11) | NA | | 58 (52.73) (9.22) | |
| | | | | | |
| **Overall** | 1426 | 797 (55.89) | NA | 110 (7.71) | NA |

* Significant at 0.05 Type I error

**An adult was considered effectively vaccinated 14 days after receiving the vaccine; a child 8 years or younger after two vaccine doses

### 3.2. *Results for Objective 1*

Backward model selection resulted in a Cox proportional hazards model containing effective vaccination status, age, household size, and the interaction between effective vaccination and household size as covariates. Results are shown in Table 2, below.

Table 2: Cox Proportional Hazards Model Results

| Parameter | Hazard Ratio (HR) | Adjusted HR P-value | Type III P-value |
|---|---|---|---|
| | | | |
| **Vaccination status (ref: not vaccinated)** | | | |
| Effectively vaccinated | 0.45 | 0.006 | 0.006 |
| **Age (ref: 18+ years)** | | | |
| 6 mo-8 yrs | 1.55 | 0.047 | 0.093 |
| 9-17 yrs | 1.03 | 0.905 | |
| **Household size (ref: 4 members)** | | | |
| 5+ members | 0.65 | 0.092 | 0.092 |
| **Interaction between vaccination status and household size (ref: not vaccinated, from home of 4)** | | | |
| Eff. Vacc. from 4 member home | 0.45 | 0.006 | 0.044 |
| Eff. Vacc. From 5+ member home | 0.65 | 0.100 | |
| Not Vacc. from 5+ member home | 0.65 | 0.092 | |

The hazard ratios calculated for those 6 months-8 years of age (HR=1.55, p=0.047) and 9-17 years of age (HR=1.03, p=0.905) suggested that children in these categories faced a higher risk of contracting influenza, although the hazard ratio comparing subjects 9-17 years to those 18+ years was not statistically significant. Additionally, the interaction between effective vaccination status and household size indicated that those who were effectively vaccinated saw protection from influenza contraction, but this protection decreased as household size increased. Subjects who were not vaccinated and from 5+ member homes still experienced protection from virus contraction in comparison to

those not vaccinated and from 4-member homes, but this interaction was not significant. Ultimately, being effectively vaccinated and from a 4-member household (in combination) caused a subject to progress towards infection more slowly when compared to individuals who were not vaccinated and from 4-member households.

Since the interaction term between effective vaccination and household size was significant above, the analysis further considered a Cox proportional hazards model, stratified by household size. Results are shown in Table 3 below.

Table 3: Cox Proportional Hazards Model Results, Stratified by Household Size

| Parameter | Hazard Ratio (HR) | Adjusted HR P-value | Type III P-value |
|---|---|---|---|
| **4-MEMBER HOUSEHOLDS** | | | |
| **Vaccination status (ref: not vaccinated)** | | | |
| Effectively vaccinated | 0.44 | 0.004 | 0.004 |
| **Age (ref: 18+ years)** | | | |
| 6 mo-8 yrs | 1.67 | 0.133 | 0.083 |
| 9-17 yrs | 2.06 | 0.031 | |
| **5+ MEMBER HOUSEHOLDS** | | | |
| **Vaccination status (ref: not vaccinated)** | | | |
| Effectively vaccinated | 0.61 | 0.208 | 0.208 |
| **Age (ref: 18+ years)** | | | |
| 6 mo-8 yrs | 1.35 | 0.297 | 0.019 |
| 9-17 yrs | 0.44 | 0.049 | |
| **Sex (ref: male)** | | | |
| Female | 0.41 | 0.027 | 0.027 |
| **Interaction of "vaccination status" and "sex" (ref: non-vaccinated male)** | | | |
| Non-vaccinated female | 0.41 | 0.027 | 0.028 |
| Vaccinated female | 0.88 | 0.687 | |
| Vaccinated male | 0.61 | 0.208 | |

The selected model for 4-member households indicated that being effectively vaccinated (HR= 0.44, p=0.004) protected against influenza contraction. Having been 6 months–8 years of age (HR=1.67, p=0.133) or 9-17 years of age (HR=2.06, p=0.031) were found to be harmful to the health of subjects living in 4-member households; however, only the comparison between 9-17 years and 18+ years was significant. The model for 5+ member households found that being 9-17 years of age (HR=0.44, p=0.049), and either a non-vaccinated female (HR=0.41, p=0.027), vaccinated female (HR=0.88, p=0.687), or a vaccinated male (HR=0.61, p=0.208) was associated with a decreased risk for influenza contraction; only being a non-vaccinated female or 9-17 years of age was significantly associated with influenza contraction, however. Although the variable was not significant, being 6 months-8 years of age (HR=1.35, p=0.297) was the only association yielding increased risk for influenza.

Table 4 on the following page shows results for VE, shown both for the overall sample, as well as by age group and household size. Adjusted vaccine effectiveness in the overall population was estimated to be 55% ($CI_{95\%}$ [20, 74]), which indicated significant protection in those who were effectively vaccinated as opposed to those who were not. Adults experienced a significant adjusted VE of 49% ($CI_{95\%}$ [2, 74]). However, neither age category for children indicated significant protection from the flu due to effective vaccination. Children aged 6 months-8 years of age saw an adjusted VE of 36% ($CI_{95\%}$ [-37, 70]), while those aged 9-17 years had an adjusted VE of 51% ($CI_{95\%}$ [-9, 78]). Adjusted VE for 4-member households was 56% and indicated high significant protection ($CI_{95\%}$ [23, 75]). The point estimate for adjusted VE of 39% ($CI_{95\%}$ [-31, 71]) for 5+ member households also suggested protection against influenza contraction; however, this result was not statistically significant.

Table 4: Overall and Stratified Vaccine Effectiveness

| Parameter | Influenza Positive, # (%) | | Unadjusted Vaccine Effectiveness | Unadjusted VE 95% Confidence Interval | Adjusted Vaccine Effectiveness | Adjusted VE 95% Confidence Interval |
|---|---|---|---|---|---|---|
| | Vaccinated | Unvaccinated | | | | |
| | | | | | | |
| **Overall** | | | | | | |
| | 58/792 (7.32) | 52/634 (8.20) | 30 | [-2, 52] | 55* | [20, 74] |
| **By Age Group** | | | | | | |
| 6 mo-8 yrs | 28/263 (10.65) | 17/199 (8.54) | -12 | [-102, 38] | 36 | [-37, 70] |
| 9-17 yrs | 10/224 (4.46) | 15/147 (10.20) | 51 | [-10, 78] | 51 | [-9, 78] |
| 18+ yrs | 14/305 (4.59) | 26/288 (9.03) | 49* | [2, 74] | 49* | [2, 74] |
| **By Household Size** | | | | | | |
| 4 members | 24/385 (6.23) | 28/279 (10.04) | 54* | [19, 74] | 56* | [23, 75] |
| 5+ members | 28/407 (6.88) | 30/355 (8.45) | -2 | [-71, 39] | 39 | [-31, 71] |
| * significant at the 0.05 Type I error level | | | | | | |

An interaction term, between effective vaccination and household size, was tested for statistical significance in order to determine whether VE varied by household size. Results indicated that there was a statistically significant interaction between these two factors, and therefore, vaccine effectiveness differed depending on the number of members in a household (p=0.047). Further, an interaction between effective vaccination and age indicated that vaccine effectiveness did not differ between those aged 8 years and younger and those aged 9 years and older (p=0.085). The tables for these results can be viewed in Tables 9 and 10 of the appendix.

Since, overall, the results indicated that effective vaccination carried a strong association with influenza outcome, and vaccination is generally known as an important preventive measure against influenza, it was important to explore which subject-level characteristics had an effect on whether an individual received a vaccination or not. These factors were explored in the following section.

### *3.3. Results for Objective 2*

The results of the logistic regression model are shown in Table 5 below. This model used vaccination status (yes/no) as the outcome in question. All described odds ratios refer to the adjusted measures.

Table 5: Logistic Regression Model Results

| Parameter | Unadjusted Odds Ratio | Unadjusted OR 95% Confidence Interval | Adjusted Odds Ratio | Adjusted OR 95% Confidence Interval | Adjusted OR P-value | Type III P-value |
|---|---|---|---|---|---|---|
| **Intercept (log-odds = -0.0579)** | | | | | | |
| | NA | NA | 0.94 | [0.75, 1.19] | 0.627 | NA |
| **Health Risk (ref: not present)** | | | | | | |
| Present | 2.36 | [1.59, 3.51] | 4.42 | [2.24, 8.72] | <.0001 | <.0001 |
| **Age (ref: 18+ years)** | | | | | | |
| 6 mo-8 yrs | 1.28 | [1.01, 1.64] | 1.47 | [1.14, 1.90] | 0.003 | 0.001 |
| 9-17 yrs | 1.43 | [1.10, 1.86] | 1.60 | [1.22, 2.10] | 0.001 | |
| **Sex (ref: male)** | | | | | | |
| Female | 1.26 | [1.02, 1.55] | 1.43 | [1.14, 1.79] | 0.002 | 0.002 |
| **Race (ref: white)** | | | | | | |
| Black | 0.75 | [0.51, 1.10] | 0.65 | [0.43, 0.96] | 0.031 | 0.003 |
| Asian | 1.13 | [0.77, 1.65] | 1.08 | [0.73, 1.59] | 0.708 | |
| Other/Unknown | 0.51 | [0.34, 0.76] | 0.52 | [0.35, 0.79] | 0.002 | |
| **Household size (ref: 4 members)** | | | | | | |
| 5+ members | 0.81 | [0.65, 0.99] | 0.78 | [0.63, 0.97] | 0.029 | 0.029 |
| **Interaction of "health risk" and "sex" (ref: male with no health risk)** | | | | | | |
| Female with health risk | 2.04 | [1.23, 3.36] | 2.46 | [1.46, 4.12] | 0.001 | 0.028 |
| Female without health risk | 1.33 | [1.07, 1.66] | 1.43 | [1.14, 1.79] | 0.002 | |
| Male with health risk | 4.27 | [2.18, 8.37] | 4.42 | [2.24, 8.72] | <.0001 | |

Results indicated that having been 6 months-8 years of age (OR=1.47, $CI_{95\%}$ [1.14, 1.90]), 9-17 years of age (OR=1.60, $CI_{95\%}$ [1.22, 2.10]), or Asian (OR=1.08, $CI_{95\%}$ [0.73, 1.59]) were all protective characteristics and yielded statistically significant associations with vaccination status. In other words, having these characteristics increased the odds – in comparison to each characteristic's reference group – that an individual received a

vaccination. However, the associations between vaccination status and being of Asian race was not statistically significant (p=0.633). Further, the interaction between health risks and sex indicated that females with health risks (OR=2.46, $CI_{95\%}$ [1.46, 4.12]), females without health risks (OR=1.43, $CI_{95\%}$ [1.14, 1.79]), and males with health risks (OR=4.42, $CI_{95\%}$ [2.24, 8.72]) all experienced significantly greater odds of vaccination when compared to males without health risks. Subjects who were black (OR=0.65, $CI_{95\%}$ [0.43, 0.96]) or of other/unknown race (OR=0.52, $CI_{95\%}$ [0.35, 0.79]), or lived in a household consisting of 5+ members (OR=0.78, $CI_{95\%}$ [0.63, 0.97]) were less likely to be vaccinated when compared to their respective reference groups. Lastly, the intercept estimate (-0.0579) represented the log-odds for a subject who had no health risks, was 18+ years old, male, white, and from a household of 4 members.

Since the interaction between health risks and sex was significant in the model, the analysis was further stratified by sex. Results are shown below in Table 6 on the following page.

Table 6: Logistic Regression Model Results, Stratified by Sex

| Parameter | Unadjusted Odds Ratio | Unadjusted OR 95% Confidence Interval | Adjusted Odds Ratio | Adjusted OR 95% Confidence Interval | Adjusted OR P-value | Type III P-value |
|---|---|---|---|---|---|---|
| **FEMALE** | | | | | | |
| **Intercept (log-odds = 0.3814)** | | | | | | |
| | NA | NA | 1.46 | [1.22, 1.75] | <.0001 | NA |
| **Health Risk (ref: not present)** | | | | | | |
| Present | 1.53 | [0.93, 2.53] | 1.59 | [0.95, 2.65] | 0.077 | 0.077 |
| **Race (ref: white)** | | | | | | |
| Black | 0.67 | [0.42, 1.10] | 0.63 | [0.38, 1.03] | 0.065 | 0.064 |
| Asian | 1.22 | [0.70, 2.13] | 1.19 | [0.68, 2.08] | 0.546 | |
| Other/Unknown | 0.56 | [0.32, 0.997] | 0.58 | [0.32, 1.02] | 0.059 | |
| **MALE** | | | | | | |
| **Intercept (log-odds = -0.1334)** | | | | | | |
| | NA | NA | 0.88 | [0.65, 1.17] | 0.371 | NA |
| **Health Risk (ref: not present)** | | | | | | |
| Present | 4.27 | [2.18, 8.37] | 4.47 | [2.26, 8.87] | <.0001 | <.0001 |
| **Age (ref: 18+ years)** | | | | | | |
| 6 mo-8 yrs | 1.61 | [1.13, 2.29] | 1.84 | [1.28, 2.66] | 0.001 | 0.001 |
| 9-17 yrs | 1.69 | [1.17, 2.45] | 1.84 | [1.25, 2.70] | 0.002 | |
| **Race (ref: white)** | | | | | | |
| Black | 0.83 | [0.44, 1.55] | 0.69 | [0.36, 1.33] | 0.268 | 0.080 |
| Asian | 1.04 | [0.61, 1.77] | 0.97 | [0.56, 1.68] | 0.921 | |
| Other/Unknown | 0.45 | [0.25, 0.80] | 0.48 | [0.26, 0.87] | 0.016 | |
| **Household size (ref: 4 members)** | | | | | | |
| 5+ members | 0.79 | [0.59, 1.05] | 0.74 | [0.54, 1.003] | 0.052 | 0.052 |

Among females, being of black (OR=0.63, $CI_{95\%}$ [0.38, 1.03]) or other/unknown race (OR=0.58, $CI_{95\%}$ [0.32, 1.02]) was associated with decreased vaccination odds; however, these associations only neared significance. Having health risks (OR=1.59, $CI_{95\%}$ [0.95, 2.65]) or being of Asian race (OR=1.19, $CI_{95\%}$ [0.68, 2.08]) was associated with increased vaccination odds; however, neither association was significant, with the health risk

covariate only nearing significance. Among males, the presence of health risks (OR=4.47, $CI_{95\%}$ [2.26, 8.87]), and being a child 6 month-8 years (OR=1.84, $CI_{95\%}$ [1.28, 2.66]) or 9-17 years (OR=1.84, $CI_{95\%}$ [1.25, 2.70]) of age were all factors significantly associated with increased odds of being vaccinated. Being of black (OR=0.69, $CI_{95\%}$ [0.36, 1.33]), Asian (OR=0.97, $CI_{95\%}$ [0.56, 1.68]), or other/unknown (OR=0.48, $CI_{95\%}$ [0.26, 0.87]) race, or from a 5+ member household (OR=0.74, $CI_{95\%}$ [0.54, 1.003]) were all factors that decreased the odds of vaccination. However, only being of other/unknown race or from a 5+ member household were significant factors.

## 4. DISCUSSION

Time-to-event analysis indicated that effective vaccination was very important in preventing influenza contraction. This was especially true in adults (18+ years) and those living in 4-member households, since significant vaccine effectiveness was found in these subgroups. This importance is generally known and the reason why influenza policy efforts are aimed at encouraging annual vaccination. The analysis also indicated that the interaction between vaccine effectiveness and household size had a significant association with influenza contraction and that the importance of vaccination became greater as the size of a household increased; individuals who were not vaccinated and from bigger families were more prone to infection than those who were not vaccinated and from 4-member families.

The importance of vaccination led the analysis to an evaluation of *who* actually received a vaccination during the 2012-2013 season. Statistically significant results

indicated that those who were 6 months-8 years or 9-17 years of age, females with health risks, females without health risks, or males with health risks were the most likely to be vaccinated (when compared to their reference groups). This is promising, as it indicates that already-known high-risk groups (the young and those with health risks) were actually seeking effective prevention against influenza. Women may have had higher odds of vaccination due to pregnancies, or the likelihood that women seek preventive medical care at higher rates than men do.[12] Interestingly, men were only more likely to be vaccinated when they had health risks (as compared to women with health risks). This finding suggests that men begin to seek preventive care more than women when they are faced with other health-risk complications. Further, the tendency for those with health risks to seek vaccination emphasizes the importance of adjusting for health status when estimating the effectiveness of the influenza vaccine.

## 5. LIMITATIONS AND FUTURE ANALYSES

This analysis encountered some limitations. For example, independence was assumed among study participants, however, all of them lived in the same household as at least three other participants and were, therefore, not likely to be independent of one another. Additionally, household information (other than the household size) was not accounted for in our analyses. Household characteristics are important factors to consider when evaluating influenza contraction. Further, only individuals who had symptoms and tested positive for influenza were considered to be cases. However, in reality, it is believed that about 50% of persons who are infected with the influenza virus do not develop any symptoms, even though they are still capable of infecting others.

Another important note is that VE was estimated as 100 x [1 – adjusted hazard ratio] rather than the common definition of 100 x [1 – adjusted risk ratio]. However, as mentioned previously, when vaccine effectiveness is calculated for a rare disease, an adjusted hazard ratio can be substituted for the adjusted risk ratio. The study could have also benefited from a larger sample size, since both the adjusted and unadjusted VE 95% confidence intervals were quite wide.

The analysis was also limited by the use of logistic regression to model vaccination status. This model provided odds ratio estimates, which were able to indicate which groups were more likely to be vaccinated; however, because the study utilized a cohort (rather than case-control) design, the odds ratios were not used to *quantify* the relationship. In a cohort study, risk ratios would have provided more precise estimates of the difference in these chances between groups. Future analysis could utilize a Poisson regression model to estimate these risk ratios.

Future research could also consider additional and more specific variables. For example, health risks could be broken down into specific conditions. Chronic disease is quite common among the U.S. population, so analyses of such covariates could aid with identifying new subpopulations that require annual vaccination. Other variables to consider would be pregnancy (although it could be difficult to obtain a large enough sample using this study design) and flu strain, since each season differs by varying prevalence rates of different strains. Data analysis would also benefit from an increased elderly stratum size. This is a subgroup typically known to be at a higher risk for complications resulting from influenza infection.

## 6. REFERENCES


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7. APPENDICES

## Table 7: Distribution of Subject-Level Characteristics by Age Group

Table 7a: Sex Distributed by Age Group

| SEX | | | |
|---|---|---|---|
| **AGE GROUP** | Male, # (col %) (row %) | Female, # (col %) (row %) | Total |
| 6 mo-8 yr | 249 (34.87) (53.90) | 213 (29.92) (46.10) | 462 |
| 9-17 yr | 206 (28.85) (55.53) | 165 (23.17) (44.47) | 371 |
| ≥18 yr | 259 (36.27) (43.68) | 334 (46.91) (56.32) | 593 |
| Total | 714 | 712 | 1426 |

Table 7b: Race, Distributed by Age Group

| RACE | | | | | |
|---|---|---|---|---|---|
| **AGE GROUP** | White, # (col %) (row %) | Black, # (col %) (row %) | Asian, # (col %) (row %) | Other/Unknown, # (col %) (row %) | Total |
| 6 mo-8 yr | 347 (32.07) (75.11) | 39 (33.33) (8.44) | 35 (28.93) (7.58) | 41 (38.68) (8.87) | 462 |
| 9-17 yr | 278 (25.69) (74.93) | 37 (31.62) (9.97) | 33 (27.27) (8.89) | 23 (21.70) (6.20) | 371 |
| ≥18 yr | 457 (42.24) (77.07) | 41 (35.04) (6.91) | 53 (43.80) (8.94) | 42 (39.62) (7.08) | 593 |
| Total | 1082 | 117 | 121 | 106 | 1426 |

Table 7c: Household Size, Distributed by Age Group

| HOUSEHOLD SIZE | | | |
|---|---|---|---|
| **AGE GROUP** | 4, # (col %) (row %) | 5+, # (col %) (row %) | Total |
| 6 mo-8 yr | 183 (27.56) (39.61) | 279 (36.61) (60.39) | 462 |
| 9-17 yr | 154 (23.19) (41.51) | 217 (28.48) (58.49) | 371 |
| ≥18 yr | 327 (49.25) (55.14) | 266 (34.91) (44.86) | 593 |
| Total | 664 | 762 | 1426 |

Table 7d: Health Risk Status, Distributed by Age Group

| HEALTH RISK PRESENT | | | |
|---|---|---|---|
| **AGE GROUP** | No, # (col %) (row %) | Yes, # (col %) (row %) | Total |
| 6 mo-8 yr | 429 (33.26) (92.86) | 33 (24.26) (7.14) | 462 |
| 9-17 yr | 341 (26.43) (91.91) | 30 (22.06) (8.09) | 371 |
| ≥18 yr | 520 (40.31) (87.69) | 73 (53.68) (12.31) | 593 |
| Total | 1290 | 136 | 1426 |

Table 7e: Flu-positive Status, Distributed by Age Group

| FLU-POSITIVE | | | |
|---|---|---|---|
| **AGE GROUP** | No, # (col %) (row %) | Yes, # (col %) (row %) | Total |
| 6 mo-8 yr | 417 (31.69) (90.26) | 45 (40.91) (9.74) | 462 |
| 9-17 yr | 346 (26.29) (93.26) | 25 (22.73) (6.74) | 371 |
| ≥18 yr | 553 (42.02) (93.25) | 40 (36.36) (6.75) | 593 |
| Total | 1316 | 110 | 1426 |

Table 7f: Month of Effective Vaccination, Distributed by Age Group

| MONTH OF EFFECTIVE VACCINATION | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **AGE GROUP** | Sept, # (col%) (row%) | Oct, # (col%) (row%) | Nov, # (col%) (row%) | Dec, # (col%) (row%) | Jan, # (col%) (row%) | Feb, # (col%) (row%) | Mar, # (col%) (row%) | Apr, # (col%) (row%) | Not Vaccinated, # (col%) (row%) | Total |
| 6 mo-8 yr | 10 (24.39) (3.75) | 94 (27.33) (35.21) | 95 (38.62) (35.58) | 37 (41.11) (13.86) | 20 (46.51) (7.49) | 11 (36.67) (4.12) | 0 (0.00) (0.00) | 0 (0.00) (0.00) | 195 (31.00) (42.21) | 462 |
| 9-17 yr | 13 (31.71) (5.80) | 102 (29.65) (45.54) | 70 (28.46) (31.25) | 19 (21.11) (8.48) | 11 (25.58) (4.91) | 8 (26.67) (3.57) | 1 (50.00) (0.45) | 0 (0.00) (0.00) | 147 (23.37) (39.62) | 371 |
| ≥18 yr | 18 (43.90) (5.88) | 148 (43.02) (48.37) | 81 (32.93) (26.47) | 34 (37.78) (11.11) | 12 (27.91) (3.92) | 11 (36.67) (3.59) | 1 (50.00) (0.33) | 1 (100.00) (0.33) | 287 (45.63) (48.40) | 593 |
| Total | 41 | 344 | 246 | 90 | 43 | 30 | 2 | 1 | 629 | 1426 |

## Table 8: Vaccination Status Distributed by Influenza Status

Table 8a: Vaccination (Yes/No) Status Distributed by Influenza Status

| | FLU PRESENT | | |
|---|---|---|---|
| **VACCINATED** | No, # (col %) (row %) | Yes, # (row %) (col %) | Total |
| No | 571 (43.39) (90.78) | 58 (52.73) (9.22) | 629 |
| Yes | 745 (56.61) (93.48) | 52 (47.27) (6.52) | 797 |
| Total | 1316 | 110 | 1426 |

Table 8b: Full Vaccination Status Distributed by Influenza Status

| | FLU PRESENT | | |
|---|---|---|---|
| **EFFFECTIVELY VACCINATED** | No, # (col %) (row %) | Yes, # (col %) (row %) | Total |
| Not Vaccinated | 571 (43.39) (90.78) | 58 (52.73) (9.22) | 629 |
| Vaccinated Effectively Before December | 591 (44.91) (93.66) | 40 (36.36) (6.34) | 631 |
| Vaccinated Effectively December or Later | 154 (11.70) (92.77) | 12 (10.91) (7.23) | 166 |
| Total | 1316 | 110 | 1426 |

## Table 9: Comparison of VE by Age

| **Parameter** | **Chi-square** | **P-value** |
|---|---|---|
| Effectively vaccinated | 1.19 | 0.276 |
| Age group* | 0.14 | 0.712 |
| Household size | 0.14 | 0.712 |
| Interaction between effective vaccination and age group | 2.97 | 0.085 |
| *dichotomous variable comparing those <=8 years and >=9 years | | |

## Table 10: Comparison of VE by Household Size

| **Parameter** | **Chi-square** | **P-value** |
|---|---|---|
| Effectively vaccinated | 7.46 | 0.006 |
| Age group | 3.91 | 0.048 |
| Household size | 2.89 | 0.089 |
| Interaction between effective vaccination and household size | 3.94 | 0.047 |

## Figure 1: SAS Code

```
libname a "h:\Thesis";

proc format;

value race_four
            1 = 'White'
            2 = 'Black'
            3 = 'Asian'
            4 = 'Other and Unknown';

value yes_no
        0 = 'No'
        1 = 'Yes';

value female
        0 = 'Male'
        1 = 'Female';

value house_size_two
        0 = "4"
        1 = "5+";

value health_two
        1 = "Below 90"
        2 = "Above 90 (inclusive)";

value health_four
        1 = "quartile 1 [0-80]"
        2 = "quartile 2 (80-89]"
            3 = "quartile 3 (89-95]"
            4 = "quartile 4 (95-100]";

value vax_status
        0 = "Not vaccinated"
        1 = "Vaccinated";

value flu_status
        0 = "Not flu pos"
        1 = "Flu pos";

value age_gr
        1 = "1 (<9)"
        2 = "2 (9-17)"
        3 = "3 (>=18)";

value vacc_and_flu_status
        0 = "UNVACC, NO FLU"
        1 = "UNVACC, FLU"
            2 = "VACC, NO FLU"
```

```
            3 = "VACC, FLU";

value vacc_before_dec
            0 = "NOT VACCINATED"
            1 = "VACCINATED EFF. BEFORE DEC"
            2 = "VACC EFF. DEC OR LATER";

value cal_month
            1 = "January"
            2 = "Febraury"
            3 = "March"
            4 = "April"
            5 = "May"
            6 = "June"
            7 = "July"
            8 = "August"
            9 = "September"
            10 = "October"
            11 = "November"
            12 = "December";

value month_adj
            7 = "January"
            8 = "Febraury"
            9 = "March"
            10 = "April"
            11 = "May"
            12 = "June"
            1 = "July"
            2 = "August"
            3 = "September"
            4 = "October"
            5 = "November"
            6 = "December";

run;

data a.new_flu_1213;
set a.All_data_1213_KA_092215;
drop FLU_POS_I FLU_POS;

*****CODING OF VARIABLES*****;


if ari=0; *ONLY SUMMARY RECORDS*;
if study_id ^= 330725; *REMOVE THIS ID BECAUSE IT IS MISSING DATA*;

*RECODE RACE INTO 4 CATS*;
if race=1 then race_4=1; *WHITE*;
else if race=2 then race_4=2; *BLACK*;
else if race=3 then race_4=3; *ASIAN*;
else if race in (4,5,6,8,9) then race_4=4; *OTHER AND UNKNOWN*;

*RECODE HOUSE SIZE INTO 2 CATS*;
if house_size=4 then house_size_2=0; *4 MEMBERS*;
else if house_size ge 5 then house_size_2=1; *5+ MEMBERS*;
```

```
*RECODE GENERAL_HLTH INTO 2 CATS*;
if general_hlth lt 90 then health_2=1; *LT 90*;
else if general_hlth ge 90 then health_2=2; *GE 90*;

*RECODE GENERAL HEALTH INTO QUARTILES*;
if 0<=general_hlth<=80 then health_4=1; *[0,80]*;
else if 80<general_hlth<=89 then health_4=2; *(80,89]*;
else if 89<general_hlth<=95 then health_4=3; *(89,95]*;
else if 95<general_hlth<=100 then health_4=4; *(95,100]*;

I_FLU_POS=0; *INDICATOR OF AT LEAST ONE FLU-POSITIVE RECORD*;
if n_flu_pos gt 0 then I_FLU_POS=1; *gt because n_flu_pos measures NUMBER of
flu occurences (not indicator variable)*;

*DIFFERENCE IN TIME BETWEEN VACCINATION AND FLU*;
FLU_VACC_DIFF_DAYS = d_flu_pos - d_vacc;
FLU_VACC_DIFF_WEEKS = flu_vacc_diff_days/7;
FLU_VACC_DIFF_WEEKS_ROUNDED = floor(flu_vacc_diff_weeks);

*MONTH OF VACCINATION*;
VACC_MONTH=month(d_vacc);

*DATE AND MONTH VACCINE EFFECTIVE*;
DATE_VACC_EFFECTIVE=d_vacc + 14;
format date_vacc_effective DATE9.;
MONTH_VACC_EFFECTIVE=month(date_vacc_effective);

*VACC AND FLU STATUS*;
if 14<=flu_vacc_diff_days<=9999 then VACC_AND_FLU_STATUS=3; *VACC, FLU*;
else if vax_status=1 and i_flu_pos=0 then vacc_and_flu_status=2; *VACC, NO
FLU*;
else if vax_status=0 and i_flu_pos=0 then vacc_and_flu_status=0; *UNVACC, NO
FLU*;
else if vax_status=0 or -9999<=flu_vacc_diff_days<14 then
vacc_and_flu_status=1; *UNVACC, FLU*;

*VACCINATED BEFORE DECEMBER?*;
if month_vacc_effective in (12,1,2,3,4,5,6) then VACC_BEFORE_DEC=2;
*VACCINATED EFF AFTER DEC*;
else if vacc_and_flu_status in (2,3) and month_vacc_effective in
(7,8,9,10,11) then VACC_BEFORE_DEC=1; *YES*;
else if vax_status=0 then VACC_BEFORE_DEC=0; *NOT VACCINATED*;

*CHANGE CALENDAR MONTH OF EFFECTIVENESS TO INFLUENZA-SEASON MONTH*;
if MONTH_VACC_EFFECTIVE=7 then MONTH_VACC_EFF_ADJ=1;
else if MONTH_VACC_EFFECTIVE=8 then MONTH_VACC_EFF_ADJ=2;
else if MONTH_VACC_EFFECTIVE=9 then MONTH_VACC_EFF_ADJ=3;
else if MONTH_VACC_EFFECTIVE=10 then MONTH_VACC_EFF_ADJ=4;
else if MONTH_VACC_EFFECTIVE=11 then MONTH_VACC_EFF_ADJ=5;
else if MONTH_VACC_EFFECTIVE=12 then MONTH_VACC_EFF_ADJ=6;
else if MONTH_VACC_EFFECTIVE=1 then MONTH_VACC_EFF_ADJ=7;
else if MONTH_VACC_EFFECTIVE=2 then MONTH_VACC_EFF_ADJ=8;
else if MONTH_VACC_EFFECTIVE=3 then MONTH_VACC_EFF_ADJ=9;
else if MONTH_VACC_EFFECTIVE=4 then MONTH_VACC_EFF_ADJ=10;
else if MONTH_VACC_EFFECTIVE=5 then MONTH_VACC_EFF_ADJ=11;
else if MONTH_VACC_EFFECTIVE=6 then MONTH_VACC_EFF_ADJ=12;
```

```
*CHANGE CALENDAR MONTH OF EFFECTIVENESS TO INFLUENZA-SEASON MONTH, MONTHS
BEFORE DEC ONLY*;
if MONTH_VACC_EFFECTIVE=7 then MONTH_VACC_EFF_ADJ_DEC=1;
else if MONTH_VACC_EFFECTIVE=8 then MONTH_VACC_EFF_ADJ_DEC=2;
else if MONTH_VACC_EFFECTIVE=9 then MONTH_VACC_EFF_ADJ_DEC=3;
else if MONTH_VACC_EFFECTIVE=10 then MONTH_VACC_EFF_ADJ_DEC=4;
else if MONTH_VACC_EFFECTIVE=11 then MONTH_VACC_EFF_ADJ_DEC=5;

*DISEASE-FREE TIME, TO BE USED FOR COX PH MODEL*;
if i_flu_pos=1 then TIME= d_flu_pos - '30-JUN-2012'd;
else time = '30-JUN-2013'd - '30-JUN-2012'd;

effvacc=0;
if time-(d_vacc-'30-JUN-2012'd) >= 14 then effvacc=1;

proc freq data=a.new_flu_1213;
tables effvacc effvacc*age_gr effvacc*house_size_2;
run;

label HOUSE_SIZE_2 = "4,5+"
            RACE_4 = "WHITE, BLACK, ASIAN, OTHER+UNKNOWN"
            HEALTH_2 = "BELOW/ABOVE 90 INDICATOR VARIABLE"
            HR_NEW = "WHETHER NEW HEALTH RISK"
            ARI = "ARI"
            N_FLU_POS = "# FLU POS DIAGNOSES"
            AGE_GR = "AGE GROUP"
            VAX_STATUS = "VAX_STATUS"
            GENERAL_HLTH = "NUMERICAL 0-100"
            VAX_STATUS = "WHETHER VACCINATED"
            FEMALE = "MALE OR FEMALE"
            FLU_VACC_DIFF_WEEKS_ROUNDED = "TIME DIFF (WEEKS, ROUNDED) BTW
VACC AND FLU"
            FLU_VACC_DIFF = "TIME DIFF BTW VACC AND FLU (KYLIE'S)"
            D_VACC = "DATE OF VACC"
            D_FLU_POS = "DATE OF FLU DIAGNOSIS"
            HEALTH_4 = "HEALTH QUARTILES"
            I_FLU_POS = "WHETHER FLU POSITIVE"
            FLU_VACC_DIFF_DAYS = "TIME DIFF (DAYS) BTW VACC AND FLU"
            FLU_VACC_DIFF_WEEKS = "TIME DIFF (WEEKS) BTW VACC AND FLU"
            VACC_AND_FLU_STATUS = "COMBO OF VACC AND FLU STATUS"
            TIME = "TIME TO FLU OR ON-STUDY TIME, DAYS"
            VACC_BEFORE_DEC = "VACC EFFECTIVELY IN/BEFORE NOV"
            VACC_MONTH = "MONTH OF VACCINATION, IF RECEIVED"
            MONTH_VACC_EFFECTIVE = "MONTH VACCINATION EFFECTIVE"
            MONTH_VACC_EFF_ADJ = "THE MONTH VACCINE IS EFFECTIVE, ADJUSTED
FOR INFLUENZA SEASON MONTH ORDER";

run;



*****ANALYSIS*****;


*FREQUENCY TABLES*;
proc freq data=a.new_flu_1213;
```

```
tables      house_size_2
            female
            race_4
            hr_new
            vax_status
            age_gr
            health_2
            health_4
            vacc_before_dec
            month_vacc_eff_adj;
format      house_size_2 house_size_two.
            female female.
            race_4 race_four.
            hr_new yes_no.
            vax_status vax_status.
            age_gr age_gr.
            health_2 health_two.
            health_4 health_four.
            vacc_before_dec vacc_before_dec.
            month_vacc_eff_adj month_adj.;
run;

*CHI-SQ TESTS: VARIABLES ASSOCIATED WITH I_FLU_POS*;
proc freq data=a.new_flu_1213;
tables      house_size_2*i_flu_pos
            hr_new*i_flu_pos
            race_4*i_flu_pos
            vax_status*i_flu_pos
            female*i_flu_pos
            age_gr*i_flu_pos
            health_2*i_flu_pos
            health_4*i_flu_pos
            vacc_and_flu_status*i_flu_pos
            vacc_before_dec*i_flu_pos
            vacc_month*i_flu_pos
            month_vacc_eff_adj*i_flu_pos / chisq nocol nopercent;
format      i_flu_pos flu_status.
            house_size_2 house_size_two.
            hr_new yes_no.
            race_4 race_four.
            vax_status vax_status.
            female female.
            age_gr age_gr.
            health_2 health_two.
            health_4 health_four.
            vacc_and_flu_status vacc_and_flu_status.
            vacc_before_dec vacc_before_dec.
            month_vacc_eff_adj month_adj.;
run;

*CHI-SQ TESTS: VARIABLES ASSOCIATED WITH VAX_STATUS*;
proc freq data=a.new_flu_1213;
tables      house_size_2*vax_status
            hr_new*vax_status
            race_4*vax_status
            female*vax_status
            age_gr*vax_status / chisq nocol nopercent;
```

```
format      vax_status vax_status.
            house_size_2 house_size_two.
            hr_new yes_no.
            race_4 race_four.
            female female.
            age_gr age_gr.;
run;

*NUMBER OF FLU DIAGNOSES AND VACCINATIONS, BY MONTH*;
proc freq data=a.new_flu_1213;
tables      d_flu_pos d_vacc;
format      d_flu_pos MONYY7.
            d_vacc MONYY7.;
run;

*ASSOCIATIONS BETWEEN AGE_GR/FLU DATE AND AGE_GR/VACC DATE*;
proc freq data=a.new_flu_1213;
tables      age_gr*d_flu_pos
            age_gr*d_vacc / chisq nocol nopercent;
format      d_flu_pos MONYY7.
            d_vacc MONYY7.
            age_gr age_gr.;
run;

proc freq data=a.new_flu_1213;
tables d_flu_pos*age_gr / chisq nocol nopercent;
tables d_vacc*age_gr / chisq nocol nopercent;
format d_flu_pos MONYY7.;
format d_vacc MONYY7.;
format age_gr age_gr.;
run;

*CHI-SQ TESTS: VAX_STATUS VS. I_FLU_POS, OVERALL AND STRATIFIED*;

*OVERALL*;
proc freq data=a.new_flu_1213;
tables vax_status*i_flu_pos / chisq nocol nopercent;
format      vax_status vax_status.
            i_flu_pos flu_status.;
run;

*BY HOUSE_SIZE_2*;
proc freq data=a.new_flu_1213;
tables i_flu_pos*house_size_2*vax_status / chisq nocol nopercent;
format      vax_status vax_status.
            i_flu_pos flu_status.
            house_size_2 house_size_two.;
run;

*BY RACE_4*;
proc freq data=a.new_flu_1213;
tables      race_4*vax_status*i_flu_pos / chisq nocol nopercent;
format      vax_status vax_status.
            i_flu_pos flu_status.
            race_4 race_four.;
run;
```

```
*BY AGE_GR*;
proc freq data=a.new_flu_1213;
tables age_gr*vax_status*i_flu_pos / chisq nocol nopercent;
format      vax_status vax_status.
            i_flu_pos flu_status.
            age_gr age_gr.;
run;

*BY HEALTH_2 AND HEALTH_4*;
proc freq data=a.new_flu_1213;
tables      health_2*vax_status*i_flu_pos
            health_4*vax_status*i_flu_pos / chisq nocol nopercent;
format      vax_status vax_status.
            i_flu_pos flu_status.
            health_2 health_two.
            health_4 health_four.;
run;

*BY HR_NEW*;
proc freq data=a.new_flu_1213;
tables hr_new*vax_status*i_flu_pos / chisq nocol nopercent;
format      vax_status vax_status.
            i_flu_pos flu_status.
            hr_new yes_no.;
run;

*VACC_BEFORE_DEC by FLU and VAX STATUS*;
proc freq data=a.new_flu_1213;
tables vax_status*i_flu_pos vacc_before_dec*i_flu_pos
vacc_before_dec*vax_status;
run;

*2x2 TABLES COMPARING VARIABLE CATEGORIES BY AGE GROUP*;
proc freq data=a.new_flu_1213;
tables      age_gr*house_size_2
            age_gr*female
            age_gr*race_4
            age_gr*hr_new
            age_gr*n_aris
            age_gr*n_flu_pos
            age_gr*n_nonflu_pos
            age_gr*vax_status
            age_gr*health_2
            age_gr*health_4
            age_gr*i_flu_pos
            age_gr*vacc_and_flu_status
            age_gr*vacc_month
            age_gr*vacc_before_dec
            age_gr*month_vacc_effective
            age_gr*month_vacc_eff_adj
            age_gr*month_vacc_eff_adj_dec / chisq nopercent;
format      race_4 race_four.
            age_gr age_gr.
            female female.
            hr_new yes_no.
            vax_status vax_status.
            house_size_2 house_size_two.
```

```
            health_2 health_two.
            health_4 health_four.
            vacc_month cal_month.
            i_flu_pos flu_status.
            vacc_before_dec vacc_before_dec.
            vacc_and_flu_status vacc_and_flu_status.
            month_vacc_effective cal_month.
            month_vacc_eff_adj month_adj.
            month_vacc_eff_adj_dec month_adj.;
run;

*COMPARING VACC AND FLU STATUS WITH HEALTH*;
proc freq data=a.new_flu_1213;
tables hr_new*vacc_and_flu_status health_2*vacc_and_flu_status
health_4*vacc_and_flu_status
            hr_new*vax_status health_2*vax_status health_4*vax_status
            hr_new*vacc_before_dec health_2*vacc_before_dec
health_4*vacc_before_dec / chisq nocol nopercent;
format vacc_and_flu_status vacc_and_flu_status.
          health_2 health_two.
            health_4 health_four.
            hr_new yes_no.
            vax_status vax_status.;
run;

proc sort data=a.new_flu_1213;
by age_gr;
run;

proc means data=a.new_flu_1213;
var n_aris;
by age_gr;
run;


*COX PH REGRESSION MODELS*;


*non-stratified adjusted*;
ods graphics on;
proc phreg data=a.new_flu_1213 plots(cl)=survival;
class age_gr(ref="3" param=ref) race_4(ref="1" param=ref);
model time*i_flu_pos(0) = effectively_vacc age_gr female race_4 house_size_2
hr_new effectively_vacc*age_gr effectively_vacc*female
effectively_vacc*race_4 effectively_vacc*house_size_2 effectively_vacc*hr_new
/ include=1 selection=backward slstay=.10;
effectively_vacc=0;
if time-(d_vacc-'30-JUN-2012'd) >= 14 then effectively_vacc=1;
estimate 'eff vacc house 4' effectively_vacc 1 house_size_2 0
effectively_vacc*house_size_2 0  / exp cl;
estimate 'eff vacc house 5+' effectively_vacc 1 house_size_2 1
effectively_vacc*house_size_2 1 / exp cl;
estimate 'noneff vacc house 5+' effectively_vacc 0 house_size_2 1
effectively_vacc*house_size_2 0 / exp cl;
run;
```

```
*non-stratified crude*;
ods graphics on;
proc phreg data=a.new_flu_1213 plots(cl)=survival;
model time*i_flu_pos(0) = effectively_vacc;
effectively_vacc=0;
if time-(d_vacc-'30-JUN-2012'd) >= 14 then effectively_vacc=1;
run;
ods graphics off;

*stratified by age_gr: 6mo-8yr adjusted*;
data age1;
set a.new_flu_1213;
where age_gr=1;
run;

ods graphics on;
proc phreg data=age1 plots(cl)=survival;
class race_4(ref="1" param=ref);
model time*i_flu_pos(0) = effectively_vacc female race_4 house_size_2 hr_new
effectively_vacc*female effectively_vacc*race_4 effectively_vacc*house_size_2
effectively_vacc*hr_new / include=1 selection=backward slstay=.10;
effectively_vacc=0;
if time-(d_vacc-'30-JUN-2012'd) >= 14 then effectively_vacc=1;
run;
ods graphics off;

*stratified by age_gr: 6mo-8yr crude*;
ods graphics on;
proc phreg data=age1 plots(cl)=survival;
model time*i_flu_pos(0) = effectively_vacc;
effectively_vacc=0;
if time-(d_vacc-'30-JUN-2012'd) >= 14 then effectively_vacc=1;
run;
ods graphics off;

*stratified by age_gr: 9-17yrs adjusted*;
data age2;
set a.new_flu_1213;
where age_gr=2;
run;

ods graphics on;
proc phreg data=age2 plots(cl)=survival;
class race_4(ref="1" param=ref);
model time*i_flu_pos(0) = effectively_vacc female race_4 house_size_2 hr_new
effectively_vacc*female effectively_vacc*race_4 effectively_vacc*house_size_2
effectively_vacc*hr_new / include=1 selection=backward slstay=.10;
effectively_vacc=0;
if time-(d_vacc-'30-JUN-2012'd) >= 14 then effectively_vacc=1;
run;
ods graphics off;

*stratified by age_gr: 9-17yrs crude*;
ods graphics on;
proc phreg data=age2 plots(cl)=survival;
model time*i_flu_pos(0) = effectively_vacc;
effectively_vacc=0;
```

```
if time-(d_vacc-'30-JUN-2012'd) >= 14 then effectively_vacc=1;
run;
ods graphics off;

*stratified by age_gr: 18+ yrs adjusted*;
data age3;
set a.new_flu_1213;
where age_gr=3;
run;

ods graphics on;
proc phreg data=age3 plots(cl)=survival;
class race_4(ref="1" param=ref);
model time*i_flu_pos(0) = effectively_vacc female race_4 house_size_2 hr_new
effectively_vacc*female effectively_vacc*race_4 effectively_vacc*house_size_2
effectively_vacc*hr_new / include=1 selection=backward slstay=.10;
effectively_vacc=0;
if time-(d_vacc-'30-JUN-2012'd) >= 14 then effectively_vacc=1;
run;
ods graphics off;

*stratified by age_gr: 18+ yrs crude*;
ods graphics on;
proc phreg data=age3 plots(cl)=survival;
model time*i_flu_pos(0) = effectively_vacc;
effectively_vacc=0;
if time-(d_vacc-'30-JUN-2012'd) >= 14 then effectively_vacc=1;
run;
ods graphics off;

*comparison of VE between <=8yrs and >=9yrs*;
data agedichot;
set a.new_flu_1213;
if age_gr=1 then age_di=1;
else if age_gr in (2,3) then age_di=2;
run;

ods graphics on;
proc phreg data=agedichot plots(cl)=survival;
model time*i_flu_pos(0) = effectively_vacc age_di house_size_2
effectively_vacc*age_di;
effectively_vacc=0;
if time-(d_vacc-'30-JUN-2012'd) >= 14 then effectively_vacc=1;
run;
ods graphics off;

*stratified by HH_size: 4 adjusted*;
data hh4;
set a.new_flu_1213;
where house_size_2=0;
run;

ods graphics on;
proc phreg data=hh4 plots(cl)=survival;
class age_gr(ref="3" param=ref) race_4(ref="1" param=ref);
```

```
model time*i_flu_pos(0) = effectively_vacc age_gr female race_4 hr_new
effectively_vacc*age_gr effectively_vacc*female effectively_vacc*race_4
effectively_vacc*hr_new / include=1 selection=backward slstay=.10;
effectively_vacc=0;
if time-(d_vacc-'30-JUN-2012'd) >= 14 then effectively_vacc=1;
run;
ods graphics off;

*stratified by HH_size: 4 crude*;
ods graphics on;
proc phreg data=hh4 plots(cl)=survival;
model time*i_flu_pos(0) = effectively_vacc;
effectively_vacc=0;
if time-(d_vacc-'30-JUN-2012'd) >= 14 then effectively_vacc=1;
run;
ods graphics off;

*stratified by HH_size: 5+ adjusted*;
data hh5plus;
set a.new_flu_1213;
where house_size_2=1;
run;

ods graphics on;
proc phreg data=hh5plus plots(cl)=survival;
class age_gr(ref="3" param=ref) race_4(ref="1" param=ref);
model time*i_flu_pos(0) = effectively_vacc age_gr female race_4 hr_new
effectively_vacc*age_gr effectively_vacc*female effectively_vacc*race_4
effectively_vacc*hr_new / include=1 selection=backward slstay=.10;
effectively_vacc=0;
if time-(d_vacc-'30-JUN-2012'd) >= 14 then effectively_vacc=1;
estimate 'nonvacc female' effectively_vacc 0 female 1 effectively_vacc*female
0  / exp cl;
estimate 'vacc female' effectively_vacc 1 female 1 effectively_vacc*female 1
/ exp cl;
estimate 'vacc male' effectively_vacc 1 female 0 effectively_vacc*female 0 /
exp cl;
run;
ods graphics off;

*stratified by HH_size: 5+ crude*;
ods graphics on;
proc phreg data=hh5plus plots(cl)=survival;
model time*i_flu_pos(0) = effectively_vacc;
effectively_vacc=0;
if time-(d_vacc-'30-JUN-2012'd) >= 14 then effectively_vacc=1;
run;
ods graphics off;


*comparison of VE between 4 and 5+ member households*;
ods graphics on;
proc phreg data=a.new_flu_1213 plots(cl)=survival;
model time*i_flu_pos(0) = effectively_vacc age_gr house_size_2
effectively_vacc*house_size_2;
effectively_vacc=0;
if time-(d_vacc-'30-JUN-2012'd) >= 14 then effectively_vacc=1;
```

```
run;
ods graphics off;

*LOGISTIC REGRESSION MODEL - ADJUSTED: VAX_STATUS*;

proc logistic data=a.new_flu_1213;
class age_gr(ref="3" param=ref) race_4(ref="1" param=ref);
model vax_status(event="1") = hr_new age_gr female race_4 house_size_2
hr_new*age_gr hr_new*female hr_new*race_4 hr_new*house_size_2 / expb
include=1 selection=backward slstay=.10;
estimate 'intercept' intercept 1 / exp cl;
estimate 'hr_new' hr_new 1 / exp cl;
estimate 'female' female 1 / exp cl;
estimate 'house_size_2' house_size_2 1 / exp cl;
estimate 'hr and female' female 1 hr_new 1 hr_new*female 1 / exp cl;
estimate 'no hr and female' female 1 hr_new 0 hr_new*female 0 / exp cl;
estimate 'hr and male' female 0 hr_new 1 hr_new*female 0 / exp cl;
run;

*LOGISTIC REGRESSION MODEL - CRUDE*;

proc logistic data=a.new_flu_1213;
model vax_status(event="1") = hr_new;
run;

proc logistic data=a.new_flu_1213;
class age_gr(ref="3" param=ref);
model vax_status(event="1") = age_gr;
run;

proc logistic data=a.new_flu_1213;
model vax_status(event="1") = female;
run;

proc logistic data=a.new_flu_1213;
class race_4(ref="1" param=ref);
model vax_status(event="1") = race_4;
run;

proc logistic data=a.new_flu_1213;
model vax_status(event="1") = house_size_2;
run;

proc logistic data=a.new_flu_1213;
model vax_status(event="1") = female hr_new female*hr_new / expb;
estimate 'hr and female' female 1 hr_new 1 hr_new*female 1 / exp cl;
estimate 'no hr and female' female 1 hr_new 0 hr_new*female 0 / exp cl;
estimate 'hr and male' female 0 hr_new 1 hr_new*female 0 / exp cl;
run;


*LOGISTIC REGRESSION MODEL - stratified by sex*;


*adjusted - female*;
data female;
set a.new_flu_1213;
```

```
where female=1;
run;

proc logistic data=female;
class age_gr(ref="3" param=ref) race_4(ref="1" param=ref);
model vax_status(event="1") = hr_new age_gr race_4 house_size_2 hr_new*age_gr
hr_new*race_4 hr_new*house_size_2 / expb include=1 selection=backward
slstay=.10;
estimate 'intercept' intercept 1 / exp cl;
run;

*crude ORs for significant variables in female adjusted*;

proc logistic data=female;
model vax_status(event="1") = hr_new / expb;
run;

proc logistic data=female;
class race_4(ref="1" param=ref);
model vax_status(event="1") = race_4 / expb;
run;

*adjusted - male*;
data male;
set a.new_flu_1213;
where female=0;
run;

proc logistic data=male;
class age_gr(ref="3" param=ref) race_4(ref="1" param=ref);
model vax_status(event="1") = hr_new age_gr race_4 house_size_2 hr_new*age_gr
hr_new*race_4 hr_new*house_size_2 / expb include=1 selection=backward
slstay=.10;
estimate 'intercept' intercept 1 / exp cl;
run;

*crude ORs for significant variables in male adjusted*;

proc logistic data=male;
model vax_status(event="1") = hr_new / expb;
run;

proc logistic data=male;
class age_gr(ref="3" param=ref);
model vax_status(event="1") = age_gr / expb;
run;

proc logistic data=male;
class race_4(ref="1" param=ref);
model vax_status(event="1") = race_4 / expb;
run;

proc logistic data=male;
model vax_status(event="1") = house_size_2 / expb;
run;
```