COMPLIANCE WITH GUIDELINES FOR H1N1 VACCINATION IN PEDIATRIC KAISER PERMANENTE MEMBERS

By

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CERTIFICATE OF APPROVAL

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Compliance with guidelines for H1N1 vaccination in pediatric Kaiser Permanente Members

Abstract:

This study investigated differences in compliance with dosing recommendations for the H1N1 influenza vaccine in pediatric patients. This study also examined the distribution of compliant and non-compliant individuals over several predictors of health behavior. The CDC recommendations for vaccination with H1N1 vaccine of children under the age of nine are to administer two doses at least 21 days apart. Due to many factors a large percentage of children did not receive the recommended dosage of vaccine. This cross-sectional study examined the distributions of patients receiving zero, one, and two doses of the vaccine and investigated differences in those groups. This study also developed a model to determine factors that affect compliance with vaccination recommendations. These factors may be useful for developing targeted health promotion materials for future influenza seasons.

Lay summary:

This study investigated differences in compliance with dosing recommendations for the H1N1 influenza vaccine in pediatric patients. This study also examined factors that affect compliance.

Research Question:

This is a cross-sectional study designed to evaluate differences in compliance with vaccination guidelines in pediatric patients by health status, patient demographics, and other potential risk factors.

Specific aims:

Current guidelines from the Center for Disease Control (CDC) are that all children older than 6 months and less than 17 years old receive two doses of H1N1 vaccine at least 21 days apart**.** Due to concerns about adverse events, difficulties in obtaining the vaccine, and other unknown factors, a large number of pediatric patients in the Portland area did not receive the second dose of the vaccine.

To address these concerns this study has the following specific aims:

1. Examine the distributions of patient characteristics in each vaccination compliance category of zero, one or two doses of H1N1 vaccine at the appropriate timing and by age, health status, Medicaid status, timing, or other potential factors.
2. Determine which factors are independently associated with compliance at either 0, 1, or 2 doses of vaccine.
    a. Determine which potential predictors including health status, timing of vaccine, demographic info, compliance with other vaccines, age, Medicaid status, and vaccination for seasonal influenza, are independently associated with compliance.
    b. Among the subset of patients who received at least 1 dose, determine whether there is an association between date of first vaccination and complete compliance (2 doses) after adjusting for confounders.

Background:

Burden of Disease

The recent outbreak of a novel strain of influenza (H1N1 or swine flu) has raised many questions about the burden of influenza and the efforts of public health agencies in prevention. Influenza is primarily a late fall and winter seasonal infection with cases starting in late October to early November, peaking in February, and dropping off in late March. Signs and symptoms of influenza include high fever, headache, tiredness, cough, sore throat, runny nose, body aches, and diarrhea and vomiting. Symptoms can range from very mild to very extreme (American Acadamy of Pediatrics, 2009). The age distribution of those infected usually take on a "U" shaped distribution with high numbers of very young and very old falling ill while those 18 to 64 are largely unaffected (Barr I., 2010) (Fisman D., 2009). Pandemic influenza such as the H1N1 seen in 1918 has a "W" shaped curve with a much higher infection rate of middle aged people. During an average flu season in the US seasonal influenza has accounted for over 36,000 deaths per year and at least 226,000 hospitalizations for influenza complications (CDC, 2010). Of those, a particular concern is the pediatric age group, which accounted for 285 deaths in the 2009-2010 season and averages 100 deaths per year (CDC, 2010). Pediatric age groups are more susceptible to influenza due to developing immune systems, poor knowledge of hygiene practices, and exposure to large numbers of individuals in school and daycare systems (Brownstein J., 2005). Kids are thought to become sick earlier and spread disease to other individuals within the family (Cauchemez S., 2009).

Pandemic Threat

Seasonal influenza strains vary slightly from year to year; so some immunity remains from previous infections (Greenbaum J., 2009). Gene swapping with avian, swine, or equestrian forms of the virus has the potential to create new viruses that have very low immunity in the human population (Labant A., 2009). Potential threats of Bird Flu and Swine Flu must be monitored very closely to prevent outbreaks on the scale seen in 1918 when millions of individuals became sick with influenza. Subsequent pandemics in 1957 and 1968 have resulted from the emergence of a new strain of influenza with limited human immunogenicity (Labant A., 2009). The 2009-2010 H1N1 strain of influenza is thought to be similar to the 1957 strain, with some immune response found in the elderly population exposed to the 1957 influenza (Jain S., 2009).

Pathogen

The influenza virus is from the family *orthomyxoviridae*, and types A and B are found to be most pathogenic in humans. Influenza viruses are named for the two main proteins on the surface of the virus: hemagglutinin and neuraminidase. Each protein subtype is numbered and is used to distinguish different strains of the virus. Pandemic influenza A in 2009 had protein subtypes H1 and N1 and was thus named H1N1 (Barr I., 2010). Recent strains circulating in the US also include H3N2, H2N2, and H5N1 (also known as bird flu). Influenza viruses are endemic in mammals and birds and can be transmitted across species. Gene mixing, also known as antigenic drift, can occur when two strains co-infect the same host. Antigenic drift allows the virus to avoid the immune response from year to year and re-infect the same population (Stephenson I, 2002). Most mutations are slight changes in the surface proteins of the virus and confer a minor advantage in avoiding the immune response. Occasionally a completely novel strain of

influenza arises in the population such as the case with the recent outbreak of H1N1 and H5N1 (avian flu) in 2004. When a novel strain emerges from an animal host there is no immunity in the human population and higher rates of infection are seen (Zhou L, 2009) (Mounts A, 1999). In addition, novel strains of influenza may be more virulent (Labant A., 2009).

Transmission

Influenza is spread by droplet transmission routes by either coughing or sneezing directly on another person, or by touching objects with respiratory droplets on them and then touching the mouth or face (CDC, 2010).

Treatment

Treatment of influenza depends on the severity of the case. Most cases are a mild form and no treatment is required (CDC, 2010). For more serious cases or for cases under 2 years of age oseltamivir (Tamiflu) and zanamivir (Relenza) are effective in treating influenza infection (American Acadamy of Pediatrics , 2009) (Labant A., 2009). Antivirals are usually recommended for five days; however, more serious cases may require additional treatment and hospitalization. Due to a much higher risk of severe complication, children under 2 years old are recommended to receive treatment for all confirmed or suspected cases of influenza (American Acadamy of Pediatrics, 2009). Older children are recommended to receive treatment only if a co-morbid condition, such as asthma, puts them at a higher risk of complications from influenza or if they are more seriously ill (Harper S., 2009). Antivirals can be used for chemoprophylaxis as well and are between 70 to 90% effective at preventing illness (American Acadamy of Pediatrics, 2009).

Prevention

The primary prevention most effective at reducing the burden of illness due to influenza is seasonal vaccination. Despite recommendations for universal vaccinations for children, rates remain lower than 15% in healthy children (Bekker, Chou, & Bernstein, 2009). Studies estimate that vaccines are 80% effective in preventing influenza in children over the age of 2 years old when the vaccine is matched to the current strains of influenza (Esposito S., 2009). Other prevention strategies such as hand washing, covering coughs, and social quarantine are helpful in preventing disease (Labant A., 2009) (CDC, 2010).

Vaccines work by exposing immune cells to the surface proteins on pathogens to create an immune response. When the immune cells are exposed to the same virus later, the immune response is much faster than in unvaccinated individuals. Vaccines consist of either weakened or killed forms of the influenza virus. Seasonal vaccines for influenza consist of the three most common strains of influenza currently circulating in the population (Barr I., 2010). New strains are chosen each February based on previous influenza activity. Since the H1N1 virus did not appear until late April in 2009, it was not included in the selection for strains in the 2009-2010 seasonal flu vaccine. The seasonal flu vaccine for 2009-2010 season included A/Brisbane/10/2007 H3N2 strain, A/Brisbane/59/2007 H1N1 strain (not swine flu H1N1), and B/Brisbane/60/2008 virus (Barr I., 2010). Vaccines are usually administered starting late in September or early October and are available until supplies run out or the early summer (CDC, 2010).

Herd Immunity

When vaccine coverage reaches a threshold level the virus cannot spread effectively to new people and infection rates drop (Loeb M., 2010). A study of vaccination in Canadian children found that 80% influenza vaccine coverage in children reduced the infection rate for those not vaccinated by 61% (Loeb M., 2010). For influenza, it is estimated that 83 to 94% vaccine coverage is needed to create herd immunity (Anikeeva O., 2009). As of 2009, estimates indicate approximately 29% of healthy children are vaccinated, indicating a substantial need for additional vaccinations (Allison M. D. M., 2009).

Vaccine Recommendations

The Center for Disease Control and Prevention (CDC), Advisory Committee on Influenza Practices (ACIP), and the American Academy of Pediatrics (AAP) recommend all children over 6 months old be vaccinated for influenza by either nasal or injectable forms of the vaccine (CDC, 2010) (American Acadamy of Pediatrics , 2009). For vaccine naïve children, two doses are recommended at least 21 days apart to reach an effective immune response. Nasal spray forms are not recommended for children with asthma or those on long term aspirin treatment (American Acadamy of Pediatrics , 2009). Most vaccinations have no side effects; however, a small percentage of those vaccinated experience local swelling or redness, low grade fever, and aches (CDC, 2010).

Vaccine Compliance

Much controversy over vaccination can be traced to the 1976 outbreak of influenza, when the vaccine was proven to be unsafe, while the influenza activity was substantially lower than expected by public health agencies (Vaughan E, 2009) (Goldrick

B, 2006). The 1957 vaccine was linked to Guillain-Barre syndrome with an additional 1 case per 100,000 people caused by the vaccination (CDC, 2010). No other influenza vaccines have been linked to any increase in Guillain-Barre syndrome (CDC, 2010). The combination of an unsafe vaccine and a much lower than predicted flu season may have led to a mistrust of influenza vaccines that continues to affect vaccine compliance today.

Compliance with vaccines is often explained by the health belief model. In the health belief model health, access is predicted by four factors: perception of risk of getting the disease, perception of severity of the disease, perception of benefit of vaccination, and perceived barriers to vaccination (Armstrong K., 2001). Surveys suggest factors of the health belief model vary with age and health conditions (Van Essen G., 1997) (Madjid M., 2009) (Mirza A., 2008). For healthy pediatric age groups, the severity of disease decreases as age increases and compliance is reduced (Center for Disease Control and Prevention, 2009). Additionally, surveys of high-risk groups indicate that many believe the vaccine is not effective in preventing influenza and can actually cause influenza (Mirza A., 2008).

The health belief model would predict that if people believe they are at risk of getting the disease and the disease is severe then prevention of the disease will become very important. Seventy four percent of people surveyed in Philadelphia believed they were at risk for influenza, and 93% believed it is a serious disease (Armstrong K., 2001). Unfortunately only 56% believed vaccination is effective at preventing influenza and 51% believe vaccination to have significant side effects (Armstrong K., 2001). Despite evidence of vaccine efficacy, significant percentages of the general public do not perceive the vaccine as effective (Van Essen G., 1997). Studies show influenza

vaccinations to be approximately 49% to 69% effective in preventing influenza depending on the match between the vaccine antigens and the circulating influenza strains (Table 1).

In addition to a lack of perceived benefit from vaccination, many have substantial perceived barriers to becoming vaccinated. Those with private insurance or not on Medicaid have higher rates of vaccine compliance compared to those who are on Medicaid (Van Essen G., 1997).

Factors Affecting Vaccine Compliance

Table 2 summarizes factors previously reported to be associated with vaccine compliance. Increasing age, lower socioeconomic status, and refusal of prior immunization were strongly associated with low influenza vaccination rates while chronic disease states, a previous immunization, and higher frequency of medical visits had a protective effect.

Overall Goal

This study attempts to determine health factors related to influenza vaccine compliance in pediatric members of Northwest Kaiser Permanente (KPNW) in the Portland area. Understanding health factors positively and negatively associated with vaccine compliance may identify potential at risk groups for non-compliance that can be targeted for health education. This study focused on KPNW members between the ages of 6 months and 9 years old as of 12/31/09. This population had 35,060 members with approximately even gender and age distributions.

Methods:

Overview of the Design: We identified all pediatric members of the KPNW by an electronic medical record search. We abstracted a number of variables for each pediatric health plan member including Medicaid status, date of birth, vaccines received, and ICD-9 data for health visits in the previous 18 months. This study looked the outcome of vaccine compliance among all KPNW Members (0, 1, or 2 doses). Predictor variables were evaluated on each outcome individually with chi-square tests and t-tests as appropriate. Logistic regression models were constructed to examine the independence and magnitude of effects and evaluate potential interactions between predictor variables.

Study Population:

KPNW is a federally qualified Health Maintenance Organization (HMO) serving more than 475,000 members in northwest Oregon and southwest Washington. KPNW's members are demographically representative of the coverage area and represent about 17% of the Portland Metro area's population. As of 2008 Oregon is 90.1% white, 2% black, 1.4% American Indian, and 3.6% Asian (US Census Bureau, 2010). Ninety percent of KPNW members receive benefits as part of a group membership, primarily through their employer, while the remaining members are individual subscribers. Twenty-five percent of KPNW's total membership works in public employment (e.g., state, county, and city agencies, school districts). Over 13% of KPNW's total membership works in the service or trade industries (department stores, banks, insurance providers, and utility companies). Eight percent of KPNW's total membership works in manufacturing. Medicare members represent about 12% of KPNW's total membership and 54% of non-group subscribers. Members over the age of 65 represent 11.5 % of total membership, and 2% are below 200% of the federal poverty level (CHR Census Data).

All data used in the study was obtained through the KPNW electronic medical records, the State of Oregon Immunization Registry, and the Vaccine Safety registry. Vaccine data was obtained from the vaccine safety database and included the type of H1N1 vaccine and date of administration.

Inclusion and Exclusion Criteria:

To be included in the study a patient must be a KPNW member as of 9/09. The patients must have a date of birth between 9/30/00 and 6/30/09 and have been a continuous KPNW member for at least one year prior to inclusion in the study or since time of birth. Gaps in coverage of less than 2 months were treated as continuous coverage. Patients with incomplete health information were excluded from the study. Missing health information included missing demographic information, such as date of birth or gender, or missing or conflicting vaccination information. No patient was excluded on the basis of race, ethnicity, health conditions, socioeconomic or Medicaid status.

Human Subjects Protection:

All analyses were done with existing health data and no human subjects were contacted. KPNW and OHSU IRB protocols were followed to prevent release and misuse of protected health information. Data was abstracted by a KPNW analyst and was provided to the researchers as a de-identified limited dataset. The data were stored on a password protected sever in the Kaiser Center for Health Research in Portland, Oregon. This study presented no more than minimal risk to participants and researchers. Participant identities and health information were protected in the manner described above and no physical interaction with participants occurred.

Statistical Analysis:

Aim 1: *Examine patient characteristics by vaccine compliance category*

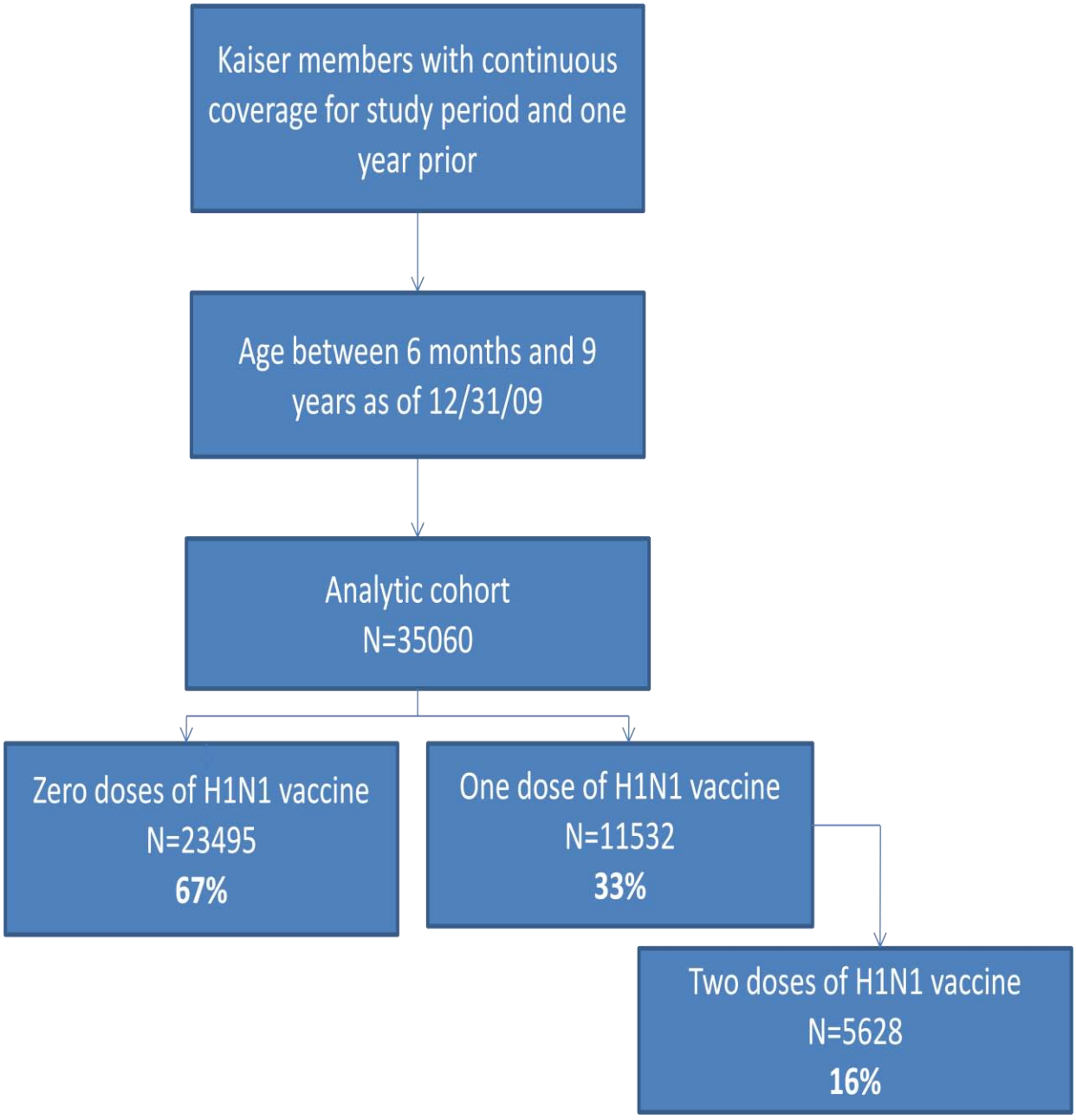
Chi square analyses were done to determine differences between groups.

Aim 2: *Determine factors independently associated with vaccine compliance*

Logistic regression models were used to identify factors independently associated with vaccine compliance. Risk factors with a p-value ≤ 0.1 in a univariate analysis were entered in the stepwise selection procedure to create a multivariable regression model. Entry into the selection procedure was set at $p \leq 0.1$, criteria to stay was a $p \leq 0.05$.

All outcomes were considered nominal, rather than ordinal, for the logistic regression analysis. Although gender, age group, and seasonal vaccine compliance had a proportional odds score test $p > .05$, the multivariable model and all other variables had a proportional odds score test p of $\leq .05$ indicating the odds ratios between groups were not equal. For ease of comparison all results were presented as nominal categories.

Figure 1. Selection of study sample. Percentages indicate proportion of analytic cohort at each level of vaccine compliance.



Variables:

Outcome variables:

Aim 1: *Examine patient characteristics by vaccine compliance category*

The outcome variable for specific aim #1 has three levels. A patient can have received zero, one, or two doses of H1N1 vaccine. Doses could be any combination of a nasal spray or an injectable form of the vaccine. Two doses of H1N1 vaccine had to be given at least 21 days apart with no maximum duration between doses. 33 individuals from aim 1 were excluded from this study due to incomplete or contradicting vaccination information in the database.

Aim 2: *Determine factors independently associated with vaccine compliance*

For aim 2 the outcome had three levels. A study subject could have received zero, one, or two doses of H1N1 vaccine. A subgroup of the population was also evaluated to determine the effect of timing of the first dose on compliance. This population included only those who had received a first dose and included 11,565 members. The outcome for this population was either fully compliant with CDC recommendations of two doses greater than 21 days apart compared to only one dose.

Predictor Variables: For both specific aims predictor variables are age, Medicaid status (as a proxy for SES), seasonal influenza vaccination, health care utilization, gender, chronic disease status, compliance with other vaccinations (non-influenza), and type of H1N1 vaccine (either nasal or injectable). The CDC recommends all infants receive vaccinations for polio, hib, hepatitis B, hepatitis A, PCV7, MMR, varicella, DTap, rotavirus and MMR. A schedule of dose timing from the CDC was used to create a dichotomous variable indicating if an individual was fully compliant with all

recommended vaccinations. Individuals were considered compliant if they were able to complete the recommended vaccines at the recommended intervals. For the analysis of timing of the first dose the week of first dose was also included as a predictor variable. An individual was categorized as having a chronic disease if they had an ICD-9 code for at least one of the following conditions during the 18 month study period: asthma, cancer, cardiac, renal, hepatic, immune deficiency, or diabetes. Obesity was not evaluated because BMI data was not available. ICD-9 codes used for chronic disease conditions are found in table 16.

Results:

Specific Aim 1: *Examine patient characteristics by vaccine compliance category*

A summary of the sample characteristics is found in table 4. The study population had an average age of 62 months (5 years old) and had an even gender distribution. 4.7% of children were enrolled in Medicaid for at least 1 month and 17% had at least one chronic disease during the study period. 5628 individuals (16.1%) were fully compliant while 29399 (83.9%) were considered non-compliant (table 11). 11563 individuals received at least one dose of H1N1 vaccine. Of those who received the first vaccination 5628 (49%) were fully compliant and 5904 (51%) only had one dose.

Table 5 summarizes each predictor variable by H1N1 vaccine dose level. Percents given in the table are column percentages and indicate the percent of individuals with each predictor in each outcome group.

Age: Individuals in the 6 month to 2.5 year age group had significantly higher proportions with two doses compared to older age groups.

Gender: There was a non-statistically significant difference in the genders in the population. Males composed 51.3% of the population. No significant differences were found in gender in compliance groups (p=.14).

Medicaid Status: 4.7% (1648 individuals) of the population was enrolled in Medicaid for at least one month during the study period. Of those enrolled in Medicaid 181 (3.2%) individuals had two doses, 238 (4%) had one dose, and 1229 (5%) individuals had zero doses (p<.001).

Vaccination with at least one dose of seasonal influenza vaccine: 19874 (57%) individuals had one dose of seasonal influenza during the 2009-2010 season. Of those, 4372 (78%) had 2 doses, 4337 (73%) had 1 dose, and 11165 (48%) had no doses of H1N1 vaccine (p<.001).

Vaccination with two doses of seasonal influenza vaccine: 877 individuals received a second dose of seasonal flu vaccine. Of those, 400 (7%) had 2 doses, 220 (4%) had 1 dose, and 254 (1%) had no doses of H1N1 vaccine. Two doses of seasonal influenza are only recommended for vaccine naïve individuals. No analysis was done to determine previous vaccine status to establish whether two doses were indicated.

Type of H1N1 vaccine received: 6926 people (18%) received at least one injectable form of the vaccine with 66% receiving two doses. 4998 people (12.5%) received at least one nasal form of the H1N1 vaccine with 44% of those receiving two doses. Table 6 shows the distribution of vaccine type by compliance status in the pediatric population.

Number of Health Visits: Those that had 2 doses of H1N1 vaccine had an average of 13.9 health visits per year compared to 12.2 in those with 1 dose and 9.6 in those with no doses of H1N1vaccine (p<.001).

Week of first H1N1 vaccination: Vaccines were first available starting September 28th, 2009. Date of first vaccination was categorized into approximate quartiles based on the number of individuals vaccinated. The distribution of groups is shown in figures 2 and 5, and table 7.

Interval between H1N1 vaccine doses: The average time to the second dose after the first dose of H1N1 was 46 days.

Chronic disease status: 5953 (17%) individuals were identified as having at least one chronic condition by ICD-9 codes. A breakdown of the chronic disease frequencies is shown in table 4. Statistically significant differences between compliant and non-compliant groups were found in those with asthma, cancer, immune-compromised, and hepatic conditions but not cardiac diabetes or renal conditions. Among those with at least one chronic disease 17.4% received two doses of H1N1 vaccine, 17% received one dose, and 12.2% received zero doses ($p<.001$).

Compliance with CDC recommendations for pediatric vaccines: Among those who were compliant 61% had 2 doses of H1N1 vaccine, 58% had one dose, and 49% had zero doses.

Summary of aim 1: *Examine patient characteristics by vaccine compliance category*

Variables with significant differences between compliance and non-compliance included age, Medicaid status, week of vaccination, seasonal flu vaccine, compliance with pediatric vaccine recommendations, having at least one chronic disease, having ILI symptoms, the number of health visits, having asthma, cancer, or hepatic conditions. No difference was found in gender, cardiac, renal, or diabetes conditions.

Specific Aim 2 - *Determine factors independently associated with vaccine compliance*

Two separate models were constructed for this aim; the first model is a multinomial logistic regression model with an outcome of zero, one, or two doses with each predictor variable. The second model is a binary logistic regression model with an outcome of either full compliance or only one dose received to determine the effect of week of first dose on compliance. The first model has a three level outcome of 0, 1, or 2 doses with 1 dose as the referent category. Each model was run twice; changing the reference group to obtain all possible combinations of outcome levels. Odds ratios were compared to evaluate differences in 0 compared to 2 doses, 1 dose compared to 0 doses, and 1 dose compared to 2 doses.

The first model fits predictor variables to the categorical outcome of zero, one or two doses of H1N1 vaccines. Of the 35060 individuals in the population 35027 were included in this model. The 33 missing individuals had two doses, but the doses were not >21 days apart and were excluded from the model. All predictors were modeled first as unadjusted logistic models and predictors with $p < 0.1$ were included in the multivariable analysis. The odds ratios and 95% confidence intervals are given in table 8.

Variables with $p < 0.1$ included age, infant vaccine compliance, chronic disease, Medicaid, at least one dose of seasonal flu vaccine, number of total healthcare visits, having an upper respiratory tract infection, and having two doses of seasonal flu vaccine. Inpatient and outpatient visits both had similar odds ratios and were consolidated to the variable healthcare visits. Similarly hepatitis A, hepatitis B, Polio, DTaP, Hib, MMR, PCV7, and varicella had similar OR and were consolidated into the variable infant compliance. Rotavirus was not included in this variable since recommendations changed in 2006 and compliance was very low in older age groups. Chronic diseases were also

consolidated for the same reasons. Zero doses compared to two doses seasonal flu vaccination was the strongest predictor with an OR of .045, indicating those with 2 doses of seasonal flu vaccine were .045 times as likely to have zero doses of H1N1 vaccine compared to those with zero doses of seasonal flu vaccine. Among those with one dose of seasonal flu vaccines the OR of 1 dose H1N1 compared to two doses was .63, and zero doses compared to one dose had an OR of 3.4.

Multivariable analysis: Variables with a $p < .1$ were included in a multivariable analysis. The outcome for this analysis was 0, 1, or 2 doses of H1N1 vaccine. A stepwise selection was done with entry set at $p \leq .1$ and $p \leq .05$ to stay in the model. 35027 individuals were included in this model.

Analysis of Week of First Vaccination:

To evaluate the effect of the timing of the first dose of vaccination a secondary analysis was conducted with a subset of the total study population. The subset included only those who had received at least one dose of either nasal or injectable H1N1 vaccine (n=11530). A multivariable model was built with those variables previously determined to be significant. A binary outcome was used with those receiving one dose as the referent group. After adjusting for other variables those vaccinated later in the year were 3.8 times less likely to complete the second dose of vaccination. Results of multivariable model are shown in table 10.

Summary of Aim 2. The strongest predictor in determining compliance with H1N1 vaccine recommendations is having a seasonal flu vaccination. Other significant factors increasing compliance were having a high healthcare utilization, a chronic disease, and complying with infant vaccine recommendations. Those eligible for Medicaid and older

age groups were found less likely to be compliant. Among those who received at least one dose, an earlier date of initial dose was found to be highly predictive of complying with a second dose. Having an ILI in 2009 was found to be a significant in unadjusted models but not significant after adjusting for other factors.

Discussion:

The factors found in aim 1 to be associated with vaccine compliance confirm previous studies' results. Age was found to be highly correlated with vaccine compliance in both the literature and in this study. School aged children were .722 times as likely to have the first dose of H1N1 vaccination and 1.6 times less likely to receive the second dose after having the first compared to younger children. This is may be due to a lower perception of the severity of influenza for older children. This is particularly concerning since school aged children have much higher exposures compared to younger children that stay home. School aged children have been linked to household spread of influenza and present serious transmission risks even if complications from influenza are less severe compared to younger children (Cauchemez S., 2009). Children with a higher frequency of health visits were found to be more likely to both start and complete the vaccination process. Higher frequency of healthcare interaction can be attributed to many factors related to compliance including a potentially sicker group of children with a higher perceived severity of disease, more knowledgeable use of the healthcare system, and a greater perceived benefit from vaccinations. Individuals with a high frequency of healthcare visits also have more opportunities for combining vaccination with other medical services reducing the barriers to accessing healthcare and increasing the likelihood of compliance with influenza vaccinations.

Medicaid was used as a proxy for socio-economic status in this study and was found to be inversely associated with compliance, similar to findings reported by Nelson et al (Nelson, 2009). Those enrolled in Medicaid were .722 times as likely to receive the first dose, and 1.8 times less likely to receive two doses of H1N1 vaccine indicating similar barriers related to both starting and completing the vaccine series.

Seasonal flu vaccination was the single highest predictor of compliance with H1N1 vaccination as would be expected from the health belief model. All four criteria from the health belief model are already met in seeking seasonal influenza vaccination and barriers are low when H1N1 vaccination is offered in the same health visit as a seasonal influenza vaccination. Compliance with other infant vaccines also meets the same health belief model criteria in predicting compliance with H1N1 vaccination and the results from this study indicate those who are compliant with childhood vaccines are 1.12 times as likely to receive the first dose and .72 times less likely to receive 2 doses compared to those who are not up to date on childhood vaccines.

No differences were found based on gender in either initiation or completion of the H1N1 influenza vaccine series. No biological mechanisms were postulated to expect a gender difference and most research has not found any (Armstrong K., 2001) (Van Essen G., 1997).

Children with at least one chronic disease state were 1.13 times more likely to receive one dose of H1N1 vaccine compared to healthy children, however they were no more likely to complete the series after the first dose. The health belief model would suggest that similar factors would be associated with both initiation and completion of the vaccination series and does not explain the lack of association in completing the second

dose. This predictor is largely based on asthma patients due to low numbers of other chronic conditions. This may bias the result toward the null if a high number of mild asthma cases were reported in the database.

The week of first dose of vaccination is highly predictive of completion of the series. Those vaccinated in the first month the vaccine was offered were 3.8 times as likely to have a second dose compared to those vaccinated after December 22nd. This could be related to the effects of the media in encouraging early vaccination. A less severe than predicted flu season may also explain why those vaccinated later in the year were less likely to complete the series.

Strengths and Limitations:

The main strength of this study is the very large number of individuals included in the analysis. A very small effect size was able to be seen due to the high number of individuals. Additionally adjustments could be made for a large number of health conditions and healthcare utilization practices due to the large data set available.

The study also had several limitations including being unable to analyze the effects of several potential predictors that may influence vaccine behavior, a homogenous ethnic profile that limits generalizability and the inability to account for differences in provider practices. Unmeasured confounding is most likely to be found in health factors such as obesity that are known to effect vaccination practices and susceptibility to influenza, however data were not available to determine effect sizes. Additionally, the use of ICD-9 codes provides information about a large number of health effects but is only as accurate as reporting and coding. Under-reporting of influenza like illness would also reduce the size of the effect seen. A difference in the reporting habits of those who

did not get a H1N1 vaccine compared to those that did is most likely to account for the small odds ratio found.

Differences in provider practices was also not evaluated but may have influenced the results of the study. Unmeasured confounding by provider practices may have influenced the results of the study since provider recommendations are a significant predictor of vaccination behavior (Dombkowski, Leung, & Clark, 2008).

The vaccine availability is another factor that was not accounted for in the analysis. Early in the season several restrictions were in place for obtaining H1N1 vaccine. None of the restrictions applied to young children in this study but media messages may have influenced vaccination behavior. Additionally shortages of vaccines led to a period of reduced availability which may have influenced individual's ability to find the vaccine. The shortages may have also influenced the decision to receive either the nasal or injectable form of the vaccine and the distribution in table 6 represents the doses available rather than individuals choice of dose type.

Race was not included in the analysis. Race is known to confound many healthcare relationships and may influence vaccination rates as well. Race is not well recorded in the Kaiser database and was not used in the analysis. The population KPNW covers is over 85% white and results will most likely reflect that population distribution and should be interpreted with caution when applied to other populations.

The relationships between members of a family unit might also effect compliance with vaccine uptake. Unfortunately data was not available to determine what types of family units were present and what effects different members may have on vaccine compliance. A high correlation is likely between siblings in a single family in

compliance that may also confound the relationships between age and chronic health status in vaccine compliance. Further study is needed to determine how family members and family structure effect compliance with vaccinations.

ILI was found to have a significant association in the unadjusted model however it was not significant in the multivariable model. This study was not able to examine the potential confounding of ILI. Future studies will hopefully examine this relationship and the role having an illness plays in seeking vaccines.

Conclusion:

This study supports the growing body of evidence of factors related to vaccination compliance in pediatrics. Perhaps the most interesting finding is that even with significant media hype about the severity of H1N1 and a vaccine shortage scare, the overall compliance among this population was only 16%. Approximately 33% received at least one dose indicating either a lack of understanding or ability to obtain a second dose. This highlights the need for additional education and efforts to increase compliance to achieve the 80% coverage required for herd immunity. Potential areas for improvement could be additional reminders and incentives to vaccinate early or providing influenza vaccines at schools or daycares to target older children. Influenza continues to be a burden on our healthcare system and increasing vaccination coverage among key transmission groups such as school aged children could significantly reduce the burden of influenza.

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Tables:

Table 1. Vaccine effectiveness in pediatric populations

Study	Study Design	Population	Outcome	N	Mag. Of Effect
Loeb et. al. Effect of influenza vaccination of children on infection rates in Hutterite Communities	Cohort	Canadian children 3-15 years old and families	Lab confirmed influenza cases	947	>61% reduction of infection rates p=.03
Allison et. al. Influenza Vaccine Effectiveness in Healthy 6 to 21 Month Old Children During the 2003-2004 Season	Retrospective Cohort	Infants from 5 Denver pediatric practices	Influenza like Illness (ILI) visits in medical records by ICD-9 codes	5193	69% reduction of ILI visits for 2 doses compared to no doses 95% CI (64%-74%)
Shuler et. al. Vaccine Effectiveness Against Medically Attended, Laboratory-confirmed Influenza Among Children Aged 6 to 59 Months, 2003-2004	Case Control	Children aged 6 to 59 months from one clinic in Atlanta	Lab confirmed cases of influenza	870	49% reduction of Confirmed cases of Influenza 95% CI (30%-60%)

(Allison M. D. M., 2006) (Loeb M., 2010) (Shuler C., 2007)

Table 2. Factors that affect vaccine compliance

Study	Design	Population	N	Outcome	Factors effecting compliance	OR
Van Essen et. al. Compliance with Influenza Vaccination	Cross sectional survey	High risk patients from 7 clinics in the Netherlands	2142	Compliance with Influenza Vaccine recommendations	Age (Less than 50 years old compared to greater than 50 years old)	2.0 (p<.01)
					SES(low vs high)	1.5 (p<.01)
					Light (ref) vs serious disease state	1.3 (p=.16)
					Single (ref) vs multiple disease states	2.7 (p<.01)
Nelson et. al. Compliance with multiple dose vaccine schedules Among older children, adolescents, and adults	Cohort	7 Medical Care organizations including Kaiser Permanente (5 regions) HealthPartners, and the Marshfield Clinic	Hepatitis A (n=594917)	Completion of Each Vaccine series	Age (years)	RR
					2-4	Ref
					5-8	.78 (95% CI=.77-.79)
					9-12	.93 (95% CI=.92-.94)
					Duration between doses	Adolescents less likely to complete series on time
					Medicaid (ref=no Medicaid)	.91 (95% CI=.90-.93)
					Any Chronic Disease Condition	1.0 (95% CI=.99-1.0)
					Number of medical visits in past year	1.15 (95% CI =1.13-1.16)
					Male	.98 (95% CI=.97-.99)
Armstrong et. al. Barriers to Influenza Immunization in a low income Urban Population	Cross sectional survey	Random Sample of West Philadelphia residents aged ≥65 years old	486	Influenza Vaccination	Prior Immunization	4.37 (95% CI =2.7-7.1)
					Prior immunization refusal	.41 (95% CI=.30-.56)
					Belief shot is painful	.53 (95% CI=.34-.82)
					Perceived Severity of flu	1.86 (95% CI =1.09-3.17)
					Perceived benefit	1.37 (95% CI =1.16-1.61)
					Perceived Susceptibility	1.29 (95% CI =1.06-1.57)
					MD Visit >2 times/year	1.34 (95% CI =1.06-1.68)

(Armstrong K., 2001) (Nelson, 2009) (Van Essen G., 1997)

Table 3. Description of Variables

Variable	Definition
Compliance with recommendations	Two doses of either nasal or injectable vaccine at least 21 days apart
Age	Measured in months from date of birth
Gender	Male or female
Medicaid status	Receiving Medicaid benefits for at least part of the study period
Week of vaccination	Date of receipt of vaccine, running Monday to Sunday starting 8/31/09
Vaccination for seasonal influenza	Compliance with seasonal vaccine recommendations (receipt of 2 doses of vaccine)
Health care utilization	Number of outpatient and inpatient visits in the past year
Chronic disease status	Diagnosis with a condition known to place individual at high risk for infection or complications from influenza (see table for ICD-9 codes and descriptions)
Compliance with non-influenza vaccines	Categorical variable as either compliant with all recommendations or non-compliant with at least one recommendation
Type of H1N1 vaccine	Nasal or injectable
Diagnosis of Influenza Like Illness (ILI) in 2009	At least one medical visit for an ILI

Table 4. Total Population Characteristics N=35027

Variable	Median (range)
Continuous Variables	
Age (months)	62.2 (7-114)
Health care visits (# visits over 18 month period)	8 (0-240)
Week of vaccination	8 (1-30)
Categorical variables	Frequency (%)
Male	17981 (51)
Female	17079 (48.9)
Enrolled in Medicaid	1649 (4.7)
At least 1 chronic disease	5953 (17.0)
Asthma	3068 (8.8)
Obese	1537 (4.4)
Cancer	917 (2.6)
	718 (2.1)
Immunocompromised	
Hepatic	238 (.68)
Cardiac	203 (.58)
Diabetes	84 (.24)
Renal	18 (.05)
Infant vaccine compliance	18420 (54.5)
Seasonal flu vaccine	
0 doses	14284 (41%)
1 dose	19899 (57%)
2 doses	877 (2%)
ILI during 2009-2010	12207 (34.8)

Table 5. Population Characteristics by Compliance Status

Variable	2 doses n=5628 Mean/frequency N (%)	1 dose n=5904 Mean/frequency N (%)	0 doses n=23528 Mean/frequency N (%)	p for χ^2
Age				
6 months to 2.5 years old	1154 (20.5)	931 (15.8)	3395 (14.5)	<.001
2.5 years to 5 years old	2235 (39.7)	2047 (34.7)	7090 (30.2)	<.001
5 years to 9 years old	2239 (39.8)	2926 (49.6)	13010 (55.4)	<.001
Male n=17981	2836 (50.4)	3029 (51.3)	12100 (51.5)	.1423
Medicaid n=1648	181 (3.2)	238 (4.0)	1229 (5.2)	<.001
Week of vaccination				
9/28/09-11/08/09	1704 (30.3)	1020 (17.3)	N/A	<.001
11/09/09-11/22/09	1739 (30.9)	1338 (22.7)	N/A	<.001
11/23/09-12/20/09	1476 (26.2)	1815 (30.7)	N/A	<.001
12/21/09-4/19/10	707 (12.8)	1731 (29.3)	N/A	<.001
# of health visits (0-240)	13.9	12.2	9.6	<.001
Seasonal Flu Vaccine				
0 doses	856 (15)	1347 (23)	12076 (51)	<.001
1 dose	4372 (78)	4337 (73)	11165 (48)	<.001
2 doses	400 (7)	220 (4)	254 (1)	<.001
Infant vaccine compliance	3420 (60.8)	3413 (57.8)	11566 (49.2)	<.001
ILI symptoms	1339 (23.8)	1213 (20.6)	3811 (16.2)	<.001
Chronic Disease				
>=1 chronic disease	978 (17.4)	1002 (17.0)	2859 (12.2)	<.001
Asthma n=3061	623 (11.1)	657 (11.1)	1781 (7.6)	<.001
Cancer n=917	209 (3.7)	164 (2.8)	544 (2.3)	<.001
Immune-compromised n=718	140 (2.5)	156 (2.6)	422 (1.8)	<.001
Hepatic n=236	58 (1.0)	44 (.75)	134 (.57)	.0001
Cardiac n=203	37 (.66)	46 (.78)	120 (.52)	.0557
Diabetes n=84	17 (.3)	29 (.49)	38 (.16)	.0016
Renal n=18	3 (.05)	2 (.03)	13 (.06)	.7985

Table 6. Distribution of H1N1 vaccine type by compliance status

Dose Type	Count	2 doses (n=5628)	1 dose (n=5904)	p for χ^2
Nasal	4998	43.9% (n=2473)	42.8% (n=2525)	p<.0001
Injectable	6926	65.7% (n=3700)	54.6% (n=3226)	p<.0001

Table 7. Week of first dose by vaccine level

Week of first dose	2 Doses	1 Dose	p for χ^2
9/28/09-11/08/09	1704 (30.3%)	1020 (18.1%)	<.001
11/09/09-11/22/09	1739 (30.9%)	1338 (23.8%)	<.001
11/23/09-12/20/09	1476 (26.2%)	1815 (32.3%)	<.001
12/22/09-4/19/10	707 (12.6%)	1731 (30.8%)	<.001

Table 8. Unadjusted logistic regression with 0, 1, or 2 doses as the outcome, n=35027

	Model 1*		Model 2*
Variable	0 Doses vs. 2 Doses	1 Dose vs. 2 Doses	1 Dose vs. 0 Dose
Male	1.05(.986-1.11) p=.135	1.04(.964-1.12) p=.327	.992 (.937-1.050) p=.788
Medicaid	1.66(1.42-1.94) p<.001	1.26(1.04-1.54) p=.0203	.761 (.660-.877) p=.0002
Age Group			
6 months – 2.5 years old	1.00	1.00	1.00
2.5 years old - 5 years old	1.08(.993-1.17) p=.072	1.14(1.02-1.26) p=.018	1.05 (.965-1.15) p=.249
5 years old – 9 years old	1.98(1.82-2.14) p<.001	1.62(1.46-1.79) p<.001	.820 (.755-.891) p<.001
Seasonal Flu Vaccine			
0 doses vaccine	1.00	1.00	1.00
1 dose vaccine	.181 (.167-.196) p<.001	.630 (.573-.694) p<.001	3.48 (3.26-3.72) p<.001
2 doses of vaccine	.045 (.038-.053) p<.001	.350 (.290-.421) p<.001	7.77 (6.43-9.38) p<.001
Number of Health Visits (Range 0-265)	.968(.966-.971) p<.001	.992(.989-.994) p<.001	1.02(1.021-1.027)p<.001
≥1 Medical visit for ILI in 2009	.620(.578-.665) p<.001	.828(.758-.904) p<.001	1.33 (1.24-1.74) p<.001
Up to date on all Infant Vaccines	.626(.590-.664) p<.001	.885(.821-.953) p<.001	1.48(1.39-1.56) p<.001
Chronic Health Impairment	.659(.608-.713) p<.001	.972(.882-1.07) p=.489	1.4 (1.3-1.5) p<.001
Asthma	.659(.598-.725) p<.001	1.01(.896-1.13) p=.920	1.53 (1.39-1.68) p<.001
Cancer	.614(.522-.722) p<.001	.740(.601-.911) p=.005	1.21 (1.01-1.44) p=.039
Cardiac	.776(.536-1.123) p=.179	1.19(.769-1.83) p=.439	1.53 (1.09-2.15) p=.015
Renal	1.04(.296-3.64) p=.954	.637(.106-3.81) p=.621	.613 (.139-2.72) p=.520
Hepatic	.550(.403-.749) p=.001	.720(.486-1.07) p=.101	1.31 (.930-1.84) p=.122
Immune	.717(.591-.870) p=.680	1.06(.844-1.34) p=.007	1.25 (1.12-1.4) p<.001
Diabetes	.535(.302-.948) p=.032	1.63(.894-2.97) p=.111	3.05(1.88-4.95) p<.001

* Each model contains the same variables but has a different reference group for the outcome. Model 1 used a reference group of two doses. Model 2 used a reference group of zero doses.

Table 9. Multivariable models with an outcome of 0, 1, or 2 doses. n=35027.

	Model 1*		Model 2*
Variable	0 Doses vs 2 Doses	1 Dose vs 2 Doses	0 Doses vs 1 Dose
Health Visits	.980 (.979-.985) p<.001	.996 (.993-1.00) p=.0164	1.016(1.013-1.019)p<.001
Medicaid Status	1.79 (1.52-2.12) p<.001	1.31 (1.08-1.60) p=.008	.722 (.624-.836) p<.001
Seasonal Flu Vaccine			
1 dose vs 0 doses	.186 (.172-.202) p<.001	.633 (.573-.700) p<.001	3.4 (3.17-3.64) p<.001
2 doses vs 0 doses	.068 (.057-.081) p<.001	.422 (.349-.510) p<.001	6.20 (5.11-7.51) p<.001
Chronic Disease	.952 (.881-1.04) p=.285	1.08 (.979-1.19) p=.125	1.13 (1.04-1.22) p=.003
Age Group			
6 months old to 2.5 years	1.00	1.00	1.00
2.5 years old to 5 years	1.38 (1.25-1.53) p<.001	1.20 (1.06-1.35) p<.004	.868 (.784-.962) p<.001
5 years old to 9 years old	2.05 (1.84-2.27) p<.001	1.63 (1.42-1.81) p<.001	.722 (.653-.868) p<.001
Infant Vaccine Compliance	.717 (.671-.768) p<.001	.814 (.750-.881) p<.001	1.13 (1.07-1.21) p<.001

* Each model contains the same variables but has a different reference group for the outcome. Model 1 used a reference group of two doses. Model 2 used a reference group of zero doses.

Table 10. Analysis of week of first dose. One dose is referent category n=11530

Variable	OR	
Week of first dose		
9/28/09-11/08/09	1.00	
11/09/09-11/22/09	1.294 (1.16-1.44)	p<.001
11/23/09-12/20/09	1.92 (1.73-2.14)	p<.001
12/21/09-4/19/10	3.82 (3.39-4.31)	p<.001

*Adjusted for age group, Infant vaccine compliance, Health Visits, at least one dose of seasonal flu vaccine, two doses of seasonal flu vaccine, chronic disease status, and Medicaid status

Table 11. Distribution of Compliance Groups for H1N1 vaccine

Vaccine compliance level	Frequency	%
No vaccine	23495	67.08
Only one dose H1N1	5904	16.86
2 doses >21 days apart	5628	16.07

Appendix:

Table 12. Variable Dictionary

Variable	Definition	Code	type/unit	Notes
Study ID	Unique identifier	studyid	number	
date of birth	Birthdate	brthdate	mmddyy	
Gender	gender	sex	m/f	
H1N1 vaccine	At least one dose of H1N1 vaccine(all types)	h1n1vac_1	0//1	
H1N1 vaccine	only received one dose of vaccine (all types)	h1n1vac_2	0/1	
H1N1 vaccine	Compliance with reccomendations	h1n1vac	0/1	
Interval between doses	Duration between each dose of vaccine	dose_interval	days	9999 for non-compliance
Medicaid status	At least one month of enrollment in medicaid from 9/1/2008 to 3/31/2010	any_medicaid	0/1	
Age	age in months	age		assumes month=30.4 days and is the difference between birthdate

				and 3/31/2010
Vaccination with seasonal flu vaccine	any flu vaccine in medical record	any_seasonal	0,1,2	any/all types of flu vaccine included, any point in past
Type of H1N1 vaccine	Injectable or nasal vaccine	h1n1_type	0-12	categorical variable with 13 levels
Week of vaccination	Week of first dose of vaccination with H1N1 vaccine	week	0-31	starting with week 1 as 9/28/09, first doses are 10/1/09. Two outliers 6/19/09 and 9/19/09. 99 codes for no recepit of vaccine
Health visits	Number of inpatient and outpatient visits from 9/1/08 to 3/31/10	health_visits	0-240	can have multiple visits per day
ILI symptoms during 2009 flu season	Any ILI codes in health record between 9/1/09 and 3/31/10	ILI	0/1	ILI defined as ICD code 460-466 and/or 480-488
Healthcomorbid states	at least 1 of health conditions	health_impaired	0/1	
	asthma	asthma	0/1	diagnosis codes 493.0-495, v17.5
	cancer	cancer	0/1	diagnosis codes 140-239
	heart	cardiac	0/1	diagnosis codes 390-459
	renal	renal	0/1	diagnosis codes 580-589
	hepatic	hepatic	0/1	diagnosis codes 570-579
	immune def.	immune	0/1	diagnosis codes 270-277, 042
	diabetes	diabetes	0/1	diagnosis codes 249-254, 775.1, 648, 588.1

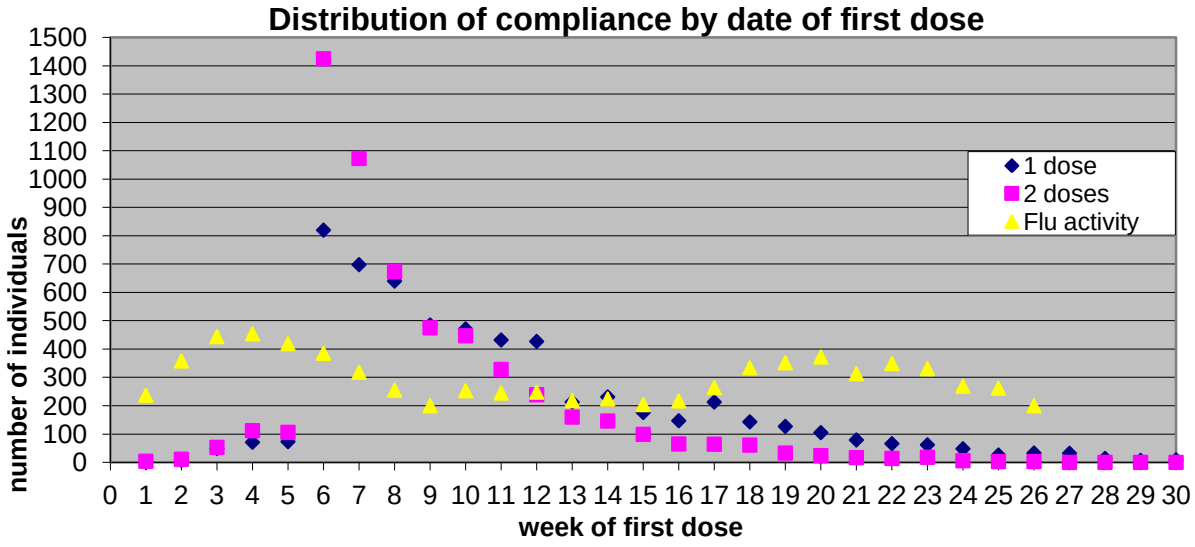
Table 13. ICD-9 Code Definition for ILI

ICD-9	Description
487	Influenza
4870	Influenza with Pneumonia
487.1	With other respiratory manifestations
487.8	Influenza with other respiratory manifestations
488	Influenza due to identified avian influenza virus
465.9	Acute Upper Respiratory site infection Unspecified site

Table 14. Frequency of Diagnosis in Health Database

dxcode	frequency	%	Description
V202	63814	17.2	Routine infant or child health check
4659	18705	5.04	Acute upper respiratory infections of multiple or unspecified sites, Excludes:upper respiratory infection due to:influenza(487.1)Streptococcus (034.0)
3829	14753	3.97	Suppurative and unspecified otitis media Unspecified otitis media
V053	6823	1.83	Need for prophylactic vaccination and inoculation against single diseases Viral Hepatitis
49390	5863	1.58	Asthma, unspecified
462	5596	1.50	Acute pharyngitis
V0481	5524	1.49	Need for prophylactic vaccination and inoculation against certain diseases Influenza
Missing	5365	1.44	Missing
6918	5340	1.43	Other atopic dermatitis and related conditions
4619	4888	1.31	Acute sinusitis, unspecified
7862	4471	1.28	Cough
78060	4336	1.16	Fever, unspecified
7999	3765	1.01	Other ill-defined and unknown causes of morbidity and mortality, Other unknown and unspecified cause
V0381	3742	1.00	Other specified vaccinations against single bacterial diseases Hemophilus influenza, type B [Hib]

Figure 2. Vaccine compliance by date of first vaccine.



*Flu activity from Kaiser ILI data

Figure 3. Compliance by Dose Level

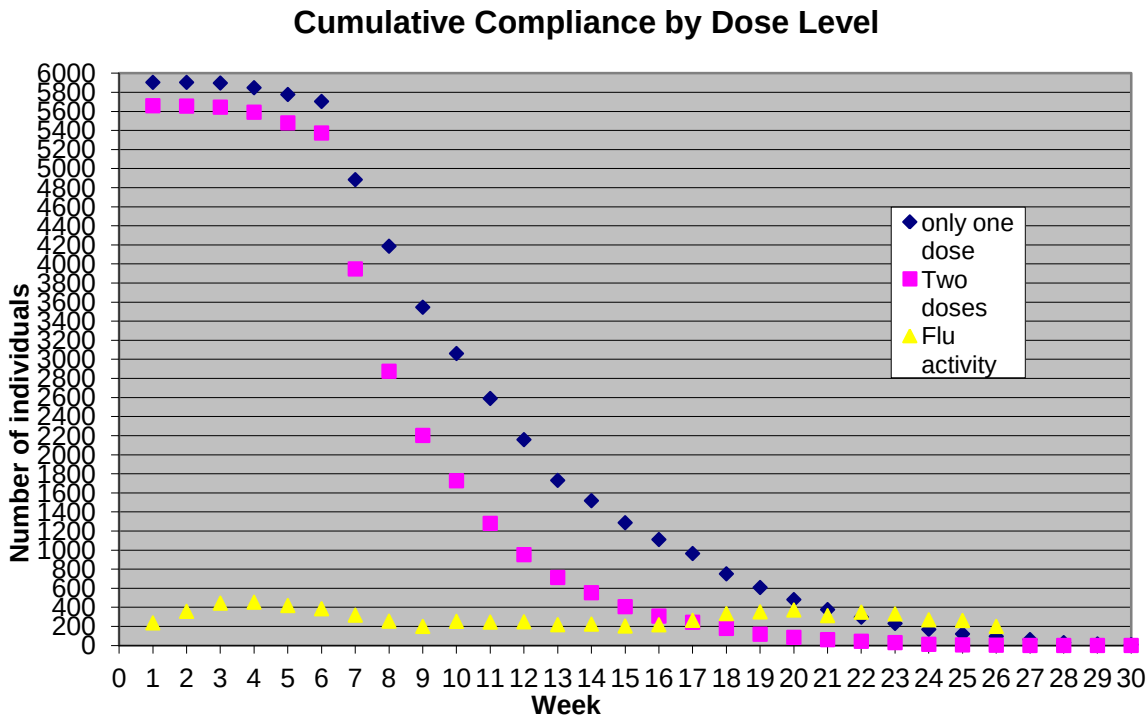


Figure 4. Distribution of Age

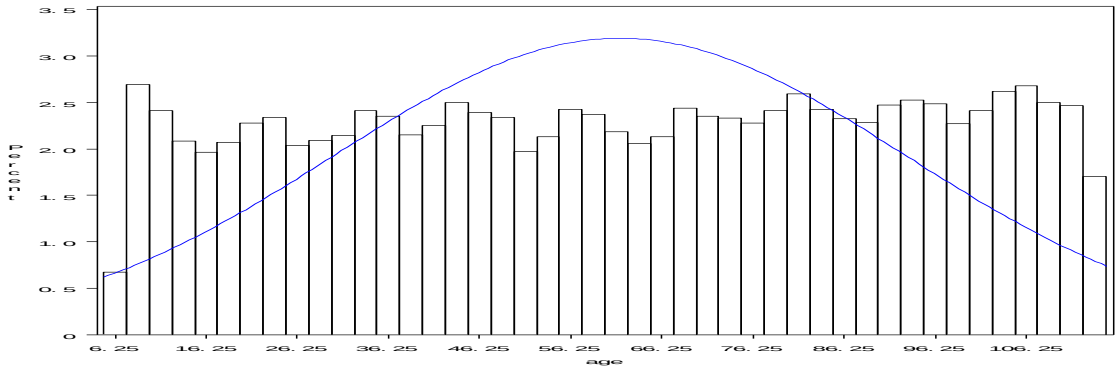


Figure 5. Week of Vaccination

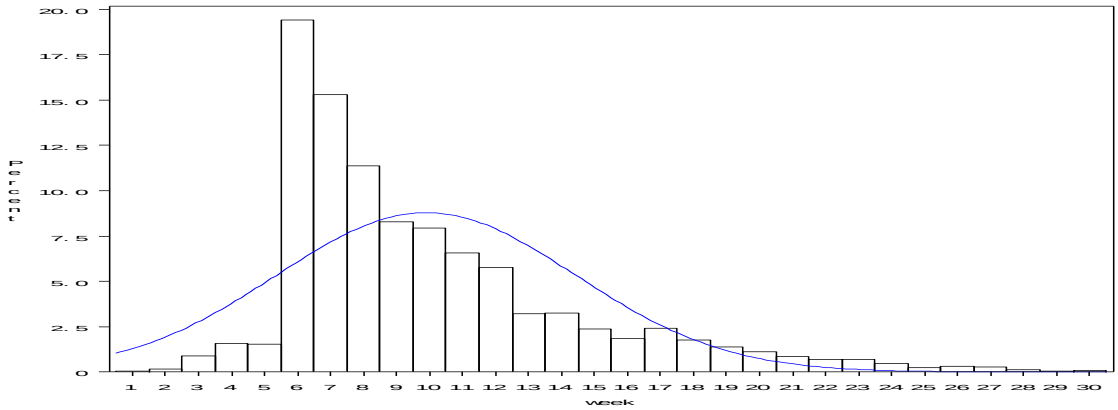


Table 15. ICD-9 codes used in defining Chronic Disease categories.

Possible risk factor	ICD-9 Codes	Description
Asthma	470-478, 490-496, V17.5	individuals with asthma and other chronic upper respiratory conditions, excluding acute conditions such as influenza or bronchitis
Cancer	140-239	all neoplasms including both benign and malignant
Cardiac Conditions	390-459	all diseases of the circulatory system including those of the heart, veins and lymphatics
Renal Conditions	580-589	nephritis, nephritic syndrome, and nephrosis and chronic kidney disease
Hepatic Conditions	570-579	disorders of the liver, gallbladder, and pancreas
Immune deficiency	270-277, 042	other metabolic and immunity disorders including diseases of ammnio-acid transport, carbohydrate transport and metabolism, lipid and protein metabolism, gout, and fluid or electrolyte imbalance and those with HIV/AIDS
Diabetes	249-250	secondary diabetes mellitus and diabetes mellitus