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Association between Trivalent Inactivated Vaccination and Risk of Febrile Seizures among Children Aged 6-80 Months Old in the Influenza Season 2010-2011

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B.S., Beijing Forestry University, 2009

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Abstract:

Febrile seizures, also referred as febrile convulsions, are seizures occurring in children aged 6 months through 6 years old who do not have the intracranial infection, metabolic disturbance, or history of febrile seizures. Among several risk factors such as fever, prenatal and early childhood exposure, concurrent infection, and vaccination that were suggested to cause febrile seizure, the association between children-recommended vaccination and febrile convulsions has become one the most active research areas. Trivalent Inactivated Vaccine (TIV) was suspected to be associated with elevated risk of convulsion in several studies. Using a large cohort study dataset with an enrollment of over 790,000 children in the influenza season 2010-2011, we were able to thoroughly investigate the association between TIV and children convulsion. With the goal of assessing association between TIV and children convulsion, this cohort study first compared risk of at least one convulsion between TIV vaccinated and TIV unvaccinated children in the flu season of 2010-2011 by using logistic regression. Then we tested the association between the number of convulsion events and TIV vaccination from the 1st TIV vaccination date till the end of the season, by using Poisson regression and Negative Binomial Regression. Lastly, we investigated if non-linear effect of age on convulsion incidence exists after controlling for TIV vaccination. Results from different modeling method were consistent; TIV vaccination was positively associated with convulsion. Children aged between 12- 23 were the most vulnerable group to convulsion.

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Abbreviation

CDC	Centers for Disease Control and Prevention
DTaP	Diphteria, Tetanus, acellular Pertussis vaccine
HAV	Hepatitis A vaccine
HBV	Hepatitis B vaccine
Hib	Haemophillus influenza type b vaccine
Hib_HBV	Hib-HBV vaccine manufactured by Merck & Co.
IPV	Inactivated poliovirus vaccine
Kinrix	Dtap manufactured by GSK
LAIV	Live Attenuated Influenza Vaccine
LAIV-M	Monovalent 2009 H1N1 LAIV
MCO	Managed Care Organization
MIV	Monovalent 2009 H1N1 inactivated influenza vaccine
MMR	Measles, Mumps, Rubella vaccine
MMRV	Measles, Mumps, Rubella, Varicella vaccine
PCV7	Pneumococcal conjugate vaccine 7
PCV13	Pneumococcal conjugate vaccine 13
Pediarix	DTaP-HepB-IPV vaccine manufactured by SmilthKline Beecham
Pentacel	DTap-IPV-Hib vaccine manufactured by Sanofi Pasteur
RV1	Rotavirus vaccine 1
RV5	Rotavirus vaccine 5
TIV	Trivalent influenza vaccine
VAR	Varicella vaccine

Introduction

Definition, Incidence and Symptoms of Febrile Seizures

Febrile seizures, also known as febrile convulsions, are seizures occurring in febrile children aged 6 months through 6 years old who do not have any of the intracranial infection, metabolic disturbance, or history of febrile seizures, according to the definition by the American Academy of Pediatrics (2008). Febrile seizures are very common in children. The incidence was estimated to be about 240-480 incidences per 100,000 person-years in the United States (Freedman and Powell 2003). 2-5% of children under 5 years old have at least one febrile seizure event, and almost 30% of which have multiple febrile seizure events (Pavlidou and Panteliadis 2007). Children aged between 12 and 18 months are most vulnerable for febrile seizure, with a peak incidence at 18 months (1980). It is uncommon to see children over 6 years old to have febrile seizure (Waruiru and Appleton 2004).

Febrile seizures are usually categorized as either simple or complex (Waruiru and Appleton 2004). Simple febrile seizure is characterized as self-limiting, having short duration (< 15 minutes), tonic-clonic, having no recurrence within the next 24 hours, and no postictal pathology. It takes up the majority of febrile seizures that cause hospital admission. By comparison, complex febrile seizures is defined as those that have longer duration (> 15 minutes), having series of seizures within limited time intervals, may have recurrence within the next 24 hours, and focal seizures with one or several possible features, such as clonic and/or tonic movements, loss of muscle tone, beginning on one side of the body, with or without secondary generalization, head and/or eye deviation to one side, followed by transient unilateral,

and paralysis (lasting minutes to hours, occasionally days) (Karande 2007; Piperidou, Heliopoulos, Maltezos, Stathopoulos and Milonas 2002; Singhi and Srinivas 2001; Stenklyft and Carmona 1994; Wadhwa, Bharucha, Chablani and Contractor 1992). Complex febrile seizures only make up a minority of febrile seizures, but they are usually related to febrile first-time convulsive status epilepticus (Chin, Neville and Scott 2005; Fortnum and Davis 1993).

Risk Factors for Febrile Seizures

A number of studies have been conducted to investigate risk factors for febrile seizures. These proposed risk factors include genetics, fever, prenatal and early childhood exposure, concurrent infection, and even routine vaccination (Arne 2008). However, more than 50% of children who are diagnosed with febrile seizures do not have identified risk factors (Waruiru and Appleton 2004).

Evidence has been found that children with a positive family history (first degree relatives) of febrile seizures are more likely to develop febrile seizures (Van Esch A et al 1998). However, febrile seizures have a very complex genetic etiology. Although rare genes in large families have been identified to be related to febrile seizures where seizure disorders follow an autosomal dominant inheritance pattern (Baumann 1999; Baumann and Duffner 2000), genetic studies in this area are very complicated and that no studies so far was able to identify specific loci (Arne 2008).

Fever is believed to provoke febrile seizures, but to what extent of fever is required for developing febrile seizures remains unknown (Arne 2008). Prenatal and early childhood

exposure factors such as premature birth, developmental delay, and delayed discharge from neonatal intensive care unit were also reported to be associated with febrile seizures (Vestergaard, Basso, Henriksen, Ostergaard and Olsen 2002). Again, no causal relationship has been established, and the methodology used was criticized in some latter studies (Arne 2008).

Other studies suggest that febrile viral or bacterial illness may lead to febrile seizures (Vestergaard, Basso, Henriksen, Ostergaard and Olsen 2002). For example, 7% of children (n=309) diagnosed with febrile seizures in two pediatric emergency wards were reported to be infected by bacterial meningitis (Offringa, Beishuizen, Derksen-Lubsen, and Lubsen 1992). 18% of children diagnosed with complex febrile seizures were found to have bacterial meningitis in a prospective study (Chin, Neville, and Scott 2005).

Trivalent Inactivated Vaccine and Other Childhood Vaccination Related to Febrile Seizures

Recently, increasing attention has been given to some routine immunizations as risk factors of febrile seizures (Kelly, Carcione et al. 2010). For instance, Australian children experienced increased risk of febrile seizures after they received Southern Hemisphere Trivalent Inactivated Vaccine (TIV) manufactured by CSL Biotherapies in 2010 (Kelly, Carcione et al. 2010). An increased risk of febrile seizures was found on the day of receiving diphtheria and tetanus toxoids and whole-cell pertussis vaccine (DTP) (relative risk: 5.70, 95% CI (1.98-16.42)), 8-14 days after receipt of measles, mumps, and rubella vaccine (MMR) (relative risk: 2.83, 95% CI (1.44-5.55)) (Barlow et al 2001). Another study showed an elevated risk of febrile seizure after 3 days of DTP vaccination (relative risk: 3.70, 95% CI (1.4-10.0)) (Nelson 2011). Another post-licensure retrospective cohort study found that a combined measles, mumps,

rubella, varicella live vaccine (MMRV, Merck and Co., Inc., US) was also associated with an increased risk of febrile seizure after 5-12 days of vaccination, as compared to separate vaccination of MMR and Varicella on the same visit (Steven, 2009). While these vaccines are all childhood vaccines recommended for individuals aged between 0 and 59 months old by the Advisory Committee on Immunization Practices (ACIP), it becomes very important to monitor if other recommended childhood vaccines such as HepB, RV, DTaP, Hib, Pneumococcal, IPV, Varicella, and HepA are also associated with febrile seizures (Nelson 2011).

Different formulations of vaccines might be associated with different risk of febrile seizures. Other than TIV, influenza vaccines have 3 additional formulations, including live-attenuated influenza vaccine (LAIV), monovalent inactivated influenza A (H1N1) vaccine (MIV), and attenuated influenza A (H1N1) monovalent vaccine (LAIV-M). These various vaccine formulations could have different immunogenic properties and could be associated with different risks of seizure or fever (Tse et al. 2012). Although it was found to be associated with an increasing risk of febrile seizures in young children aged 6 months through 4 years old in Australia in 2010, CSL TIV was not used in the United States. TIV recommended in the United States were manufactured by different companies such as Sanofi Pasteur, GlaxoSmithKline, and Novartis. An increased risk of febrile seizures following TIV was not reported prior to the 2010-2011 influenza season in the United States either (Greene et al 2010; Glanz et al 2011; Lee et al 2011). Previous studies on the association between TIV and febrile seizure are lacking consistency in terms of risk interval: some used 0-7days, some used 0-3 days, and some used 0-1 days. Thus, it still remains unclear whether or not TIV and other vaccinations were associated with febrile seizures in the U.S.

Given the availability of a large national dataset from 10 different medical care organizations encompassing 9.2 million members annually across the United States, we are interested in examining the risk of febrile seizures in the young children after receipt of TIV vaccines in the United States, while controlling for demographic, health conditional, and other vaccination related covariates.

Statement of Research Questions

a) We are interested in comparing risks of having at least one convulsion among TIV vaccinated and TIV unvaccinated children after vaccination of 1st dose of TIV during the same season. Children may receive other vaccines regardless of receiving TIV.
b) We are interested in estimating association between the number of convulsion events and TIV vaccination from the date of the 1st TIV vaccination until the end of the season. For children who were not given TIV, Oct 3rd, 2010 was used to count the time between vaccination date to the end of the season, because it was the date when the majority of children received TIV.
c) While previous studies suggest that children aged 12-18 months old are most likely to develop convulsions (1980), we categorized age into 4 groups for model building in addressing the questions a) and b). We also considered non-linear effect of age on the number of convulsions in the entire season after controlling for TIV vaccination.

Data and Methods

Data Source and Study Design

This observational cohort study data were collected from 10 managed care organizations (MCO) with a total children population of about 790,000 enrolled between July 1st, 2010 and June 30th, 2011. These participating 10 MCOs included Group Health Cooperative (Washington State), Health Partners (Minnesota), Harvard Vanguard Medical Associates and Harvard Pilgrim Health Care (Massachusetts), Kaiser Permanente of Colorado, Kaiser Permanente of Southern California, Kaiser Permanente of Georgia, Kaiser Permanente of Hawaii, Kaiser Permanente of Northern California, Marshfield Clinic (Wisconsin), and Northwest Kaiser Permanente (Oregon and Washington). These MCOs provided computerized weekly aggregate data on demographics, immunizations, and medical encounters including inpatient and outpatient visits. Only inpatient and emergency department outpatient visits were utilized in this study . Institutional review boards (IRB) at CDC and each Vaccine Safety Datalink site have approved the study and agreed that informed consent was not required (Tse et al. 2012).

Study Population

The study population included all children from 6 months old through 80 months old who were enrolled in 10 MCOs during the influenza season 2010-2011 (July 1st, 2010 - June 30th, 2011). Vaccination history and medical visits during this season were used.

Outcome Definitions

Case-finding relies on International Classification Diseases ICD 9th Revision codes on the electronic medical records. Since there was not a single ICD 9 to represent febrile seizures, febrile seizures were identified as occurring on any visit with an ICD9 code as 780.3 (convulsion), 780.31 (simple febrile convulsion), 780.32 (complex febrile convulsion) and 780.39 (other convulsion) in either inpatient or outpatient emergency department settings. Convulsions occurred less than 42 days apart for the same child was considered as a single event.

Screening Explanatory Variables and Primary Analysis

For descriptive purposes, frequency statistics were summarized for every explanatory variable and outcome variable. Explanatory variables included: at least one TIV vaccination, age group , sex, MCO site, high risk, time to convulsion, exposed person-time, unexposed person-time, whether or not 2nd or more dose of TIV was present, and variables related to all other 18 common children vaccinations (Table 1).

After examining the frequencies of each variable of interest, univariate logistic regression models were fitted to filter potential important variables out of the 18 variables related to other vaccines and second or higher doses of TIV. The 7 variables (Hib-HBV, MMRV, LAIV, RV1, MLAIV, MIV, Kinrix) were filtered out (Table 2). The remaining 11 vaccines were then included as covariates in later modeling, together with other explanatory variables.

Logistic Regression Modeling

A multivariate logistic regression analysis with interaction terms (Model 1) was conducted to assess risk factors of convulsions. Model 1 is given as below.

Model (1)

$$\begin{aligned}&\text{logit}\ [\text{prob}(Y=1)]\\&=\alpha+\beta_1\text{TIV}+\beta_2\text{TIVA}+\beta_3\text{Gender}+\beta_4\text{Highrisk}+\sum_{i=2}^{4}\beta_{5i}\text{Agecat}_i+\sum_{i=1}^{9}\beta_{6i}\text{Site}_i+\sum_{i=1}^{11}\beta_{7i}\text{OthVac}_i\\&+\beta_8\text{Time}+\sum_{i=1}^{3}\beta_{9i}\text{Agecat}_i*\text{TIV}+\beta_{10}\text{Highrisk}*\text{TIV}\end{aligned}$$

Where **Y** indicates where or not at least one convulsion occurred from the 1st TIV vaccination date (Oct 3rd, 2010 was used for unvaccinated children) till the end of the season (June 30th, 2011). **TIV** denotes a binary exposure variable, i.e. whether or not at least one dose of TIV was given. **TIVA** denotes whether or not more than one dose of TIV was given. **Highrisk** denotes whether or not children have any kind of high risk illness in that season. **Agecat1 – Agecat3** are 3 dummy variables for 4 age groups (Group 1: 6~11 months, Group 2: 12~23 months, Group 3: 24~59 months, Group 4 (reference group): 60~80 months old), **Site1-Site9** are 9 dummy variables for 10 sites (Site W is the reference site), **OthVac1-OthVac11** denotes whether or not children were vaccinated with each of 11 other vaccines, namely, HBV, IPV, Hib, DTaP, VAR, HAV, PCV7, Pediarix, RV5, Pentacel, PCV13. **Time** denotes day length of

receiving 1st TIV (if not TIV vaccinated, replace it with Oct 3rd, 2013) till the end of the season). Interaction terms include those between **Agecat** with **TIV** and between **Highrisk** with **TIV**.

Stepwise selection was then performed on model 1. By using stepwise selection, variables were either entered or dropped out of the model (slentry=.05; slstay=.05). Indicator variable – presence of 1st TIV was forced to stay in the model. Variables were selected as reliable risk factors after the stepwise selection. Odds ratio statistics for the interaction terms were computed by using contrast statement in SAS (See Appendix). Model fitting was performed in SAS.

Hosmer and Lemeshow Goodness of Fit test was conducted to test how well the final logistic model fit the data.

Poisson Regression Modeling

Two multivariate Poisson regression models (Model 2, 3) with different outcome variables were used to assess associations between the number of convulsion following receipt of the first dose of the TIV vaccine, and receipt of TIV after controlling the other covariates. We assumed the number of convulsion follow a Poisson distribution. Model 2 used the number of convulsion event as outcome, Model 3 used the rate of convulsion as outcome. Model 2 and 3 were shown as below.

Model (2)

$$\log [E(Y)] = \alpha + \beta_1 \mathrm{TIV} + \beta_2 \mathrm{TIVA} + \beta_3 \mathrm{Gender} + \beta_4 \mathrm{Highrisk} + \sum_{i=2}^{4} \beta_{5i} \mathrm{Agecat}_i + \sum_{i=1}^{9} \beta_{6i} \mathrm{Site}_i + \sum_{i=1}^{11} \beta_{7i} \mathrm{OthVac}_i + \sum_{i=1}^{3} \beta_{8i} \mathrm{Agecat}_i * \mathrm{TIV} + \beta_9 \mathrm{Highrisk} * \mathrm{TIV}$$

Model (3)

$$\log [E(Y/t)] = \alpha + \beta_1 \text{TIV} + \beta_2 \text{TIVA} + \beta_3 \text{Gender} + \beta_4 \text{Highrisk} + \sum_{i=2}^{4} \beta_{5i} \text{Agecat}_i + \sum_{i=1}^{9} \beta_{6i} \text{Site}_i + \sum_{i=1}^{11} \beta_{7i} \text{OthVac}_i + \sum_{i=1}^{3} \beta_{8i} \text{Agecat}_i * \text{TIV} + \beta_9 \text{Highrisk} * \text{TIV}$$

Where **Y** is convulsion count from the 1st TIV vaccination date (for TIV unvaccinated children, use Oct 3rd, 2010) till the end of the season (June 30th, 2011). **t** denotes time at risk (day length from 1st TIV vaccination date till the end of the season), so that Y/t is convulsion rate. **-log t** is an adjustment term and each child may have a different value of person-time, it is referred as **offset** in the regression model. Explanatory variables are the same as those used in logistic model other than excluding covariate **Time**.

Adjusted Relative Risk estimate for interaction terms was computed by using ESTIMATE statement in SAS. Due to existence of under-dispersion, PSCALE option was added to correct estimate. The scale parameter was estimated by the square root of Pearson's Chi-square/degrees of freedom. Goodness of fit test was then conducted.

Negative Binomial Regression Modeling

Negative binomial regression is a discrete probability distribution of the number of successes (free of convulsions) in a sequence of Bernoulli trials before a specified (non-random) number of failures (convulsion event) occur. It is a robust alternative to the Poisson, which has larger variance than the Poisson when the number of event (convulsions) is small. Thus, in

addition to assumption of Poisson distribution for the number of convulsion, it is also reasonable to assume the number of convulsion follows a negative binomial distribution. Two negative binomial regression models with outcome variable to be either convulsion count or convulsion rate were fit into the data. Model formula are identical to Model 2 and Model 3.

Generalized Additive Modeling

Age is an important risk factor for children convulsion. While the above regression analyses only used age group as a categorical variable, the presence of non-linear effect of age on the risk of convulsions is still unknown. Thus, generalized additive model was applied to examine if age had non-linear effect on convulsion, by adjusting for TIV vaccination, gender, high risk conditions, and interaction term between age and TIV, and all the other vaccines listed in the model 2. The additive model is an extension of the class of generalized linear model by replacing the linear form $\alpha + \sum_j X_j\beta_j$ with the additive form $\alpha + \sum_j f_j(X_j)$. It is a linear model that can be represented as a sum of smooth functions, which is a function of producing estimates of a trend that is less variable than outcome itself. This process was performed by using gam package and smoothing function in R software. R code is attached as appendix**.**

Results

Descriptive Analysis

The total number of children in this study is 792,386. Very few data was missing (14 out of 792,386, < 0.002%). We can assume the data was missing randomly and missingness was not informative. Characteristics of children were summarized separately for TIV vaccinated and TIV unvaccinated children in this cohort study (Table 2). For categorical data, frequency and corresponding percentage were computed. Only 0.38% of children developed convulsion after receipt of 1st dose of TIV in this influenza season 2010-2011. 0.07% of the children had multiple convulsion events (Table 3a-b, Figure 1). 34.11% of children received at least one dose of TIV, while 9.22% of children received multiple doses of TIV (Table 4). The risk of getting convulsion during the same season is 2.197 as high among children who were TIV vaccinated compared to those that were not TIV vaccinated (Table 3c).

$$RR = \frac{\text{Risk among TIV vaccinated children}}{\text{Risk among TIV unvaccinated children}} = \frac{0.0059}{0.0027} = 2.197$$

Time from the receipt of TIV till 1st convulsion event was not normally distributed, but actually left skewed (Figure 2).

Logistic Regression (Model 1)

Stepwise selection approach was used to determine significant predictor variables in logistic regression model building. Main exposure variable include presence of TIV, and covariates gender, high risk, age group, site, time, presence of IPV, presence of DTap, presence

of HAV, presence of Pediarix, presence of PCV13, and the two interaction terms were reliable independent variables that predict children's risk of convulsions after the stepwise selection process (Table 5).

Results of the multivariate logistic regression analysis were summarized (Table 6 & Table 7). Higher odds of convulsions among children was associated with TIV vaccination, male, medical high risk conditions, age between 12-23 months old, geographic site, and vaccination of IPV, DTap, HAV, Pediarix, PCV13, and time to the convulsion event. The effect of TIV vaccination on children convulsion is modified by high risk conditions and age category. After adjusting gender, site, time, IPV, DTap, HAV, Pediarix, PCV13 vaccination, the odds of convulsion for TIV vaccinated children is greater than those without TIV vaccination. The odds ratio estimate and 95% CI were given for each combination of age category and high risk conditions (Table 7). Overall, children aged 12-23 months (agecat=2) has highest risk of convulsion (OR: 4.1434, 95% CI: 3.3292-5.1567), followed by children aged 24-59 months (agecat=3, OR: 2.7380, 95% CI: 2.2949-3.2665), and then children aged 6-11 months (agecat=1, OR: 1.6993), and finally the oldest children group aged 59-80 months (agecat=4, reference group).

However, Hosmer and Lemeshow Goodness-of-Fit test results showed a lack of fit for this final logistic regression ($p<0.0001$, Table 8). This might be because of the large dataset. Odds ratio estimate and 95% CI for the logistic model were given (Table 6 & Table 7).

Poisson Regression (Model 2 and 3)

Consistent with results from logistic regression, higher number of convulsions and higher rate of convulsions (convulsion number/person-time) were associated with TIV vaccination, gender, high risk, age group, site, several common children vaccination including IPV, DTaP, HAV, Pediarix, PCV13 (Table 9). VAR vaccination (p-value=0.0355) is only associated with the rate of convulsions when taking person time into account.

Poisson regression was first run with the outcome variable being convulsion count from the receipt of TIV till the end of the season, without taking person-time into account (Model 2). While person-time from vaccination until the convulsion event might be an important factor to consider, another Poisson model (Model 3) was run with the outcome variable being convulsion rate, by involving person time as offset factor.

Results of multivariate Poisson regression analysis were summarized (Table 10 & Table 11). Scale parameter was estimated by the square root of Pearson's Chi-square/DOF. The adjusted RR changes by adding person-time as offset. The effect of TIV vaccination on the number of convulsion was significantly modified by age and high risk conditions. Overall, children who were aged 12-23 months (agecat=2) and had high risk conditions had the highest risk of having more convulsion events (Table 11).

However, similar to goodness of fit test in logistic regression results, the goodness of fit test for Poisson regression regardless of controlling for person-time is not good either (scaled

deviance/df=0.0385 (Model 2) and 0.0343 (Model 3), $p<0.0001$, Table 12). Under-dispersion was detected in the dataset.

Negative Binomial Regression

To allow more flexibility, negative binomial regression was fit for the data. Results about significant association are the same as Poisson regression model (Model 2) did (Table 10 & Table 13). Similar estimate and confidence interval was obtained (Table 11 & Table 14). However, the negative binomial model with person-time as offset did not converge and thus did not have output. Goodness of fit test result also suggests a poor fit and under-dispersion (Table 15).

Non-linear Effect of Age

Non-linear effect of age on the risk of at least one convulsion events was examined for all children, TIV vaccinated children, and TIV unvaccinated children separately. Curves suggest obvious non-linear effect of age on risk of convulsion, after adjusting for gender, high risk conditions, presence of TIV vaccination, presence of other vaccines including IPV, DTaP, VAR, Pediarix, PCV13, respectively, and the interaction term TIV*AgeM (Figure 3). Apparent positive non-linear effect of age on occurrence of convulsion was detected for children aged roughly between 5 to 40 months old, while negative non-linear effect took place among children aged between 40 to 80 months old (Figure 3A), indicating positive association between the risk and age between 5 - 40 months old, and negative association between the risk and age 40 - 80 months old. Such effect of age on the risk of convulsion is modified by TIV vaccination (Figure

3B, 3C). The effect of age was strongest when children were at around 22 months old, suggesting children of 22 months old was most tangible to convulsion. This non-linear relationship agrees with the modeling result given by logistic regression in which age was categorized into 4 groups. Children aged 12-23 months (agecat=2) has the highest risk of getting at least one convulsion events.

Discussion

Validation

In this prospective cohort study, we used a total of 792,386 records collected on children 6-80 months old from 10 medical care organizations across the United States. Significant association were found between TIV vaccination and febrile seizures (specifically, convulsions) was present after controlling for children's characteristics and other vaccination variables. This study adds to the growing literature on the risk of developing adverse events after influenza vaccinations for children.

Logistic, Poisson, and Negative Binomial models were examined to address how the TIV vaccination was associated with convulsion. The estimated OR and adjusted RR were controlled for age group, gender, high risk, site, higher doses of TIV, and other common vaccines. We found that the OR and RR associated with TIV vaccination varied across age groups and was higher in high-risk children than in low-risk children. Logistic modeling compares risks of convulsion between TIV vaccinated/unvaccinated children. Poisson and Negative Binomial modeling examines association between TIV vaccination and convulsion count and convulsion rate by adding an adjustment term "-log (time)" as an offset because each child may have a different lengths of at- risk period (between receipt of TIV till convulsion event occurs).

Negative binomial regression is a discrete probability distribution for the number of successes (free of convulsions) in a sequence of Bernoulli trials before a specified (non-random) number of failures (convulsion event) occur. It is a robust alternative to the Poisson, which has

larger variance than the Poisson when the number of event (convulsions) is small. The estimated adjusted RR given is consistent with that given in Poisson regression.

Two interaction terms were considered in the modeling: TIV interacted with age, and with high risk conditions. Here we considered TIV as the main exposure variable of interest, while age and high risk were considered as the two most important confounders and effect-modifiers, as illustrated in previous studies. The interactions terms are significant. The effect of TIV vaccination on convulsion was modified by age and high risk condition. However, the estimate OR and RR of TIV on convulsion would be more robust if interaction between TIV and other vaccines was also tested.

Because we knew that children between 12-18 months old are most likely to develop convulsions (1980), we categorized age into 4 groups for model building. The modeling results about age group effect (children aged between 12-23 months have the highest risk of convulsion) were consistent with previous studies. Thus we further investigated how age affects the occurrence of convulsions when controlling for TIV vaccination. Generalized additive model was used to examine non-linear effect of age on convulsion, while controlling for TIV vaccination, sex, medical high risk conditions, medical care organization site, IPV, DTaP, VAR, Pediarix, PCV13 and product term of AgeM*TIV. The non-linear effect of age on the risk of convulsion was modified by TIV vaccination. The non-linear relationship agrees with the modeling result given by logistic regression. This result on the non-linear effect of age on convlusions adds more information to the results presented byPavlidou and Panteliadis in 2007.

Limitation and Future Work

By fitting logistic, Poisson, and negative binomial models, most variables included in the logistic and Poisson models were significantly associated with the outcome variable. However, 99.7% of children do not develop convulsion, meaning 99.7% of data has an outcome variable of zero. On the other hand, convulsion number was assumed to follow the Poisson distribution, that is, the variance is assumed to be equal to the mean. However, this assumption might not hold because we have more variability in the observed data. Under-dispersion or over-dispersion issue exist. Although Negative Binomial regression was tried as a robust alternative to Poisson regression, it might not fix the problem completely. More flexible models are needed to count data model variations. Zero-Inflation Poisson model might be a good option for future study.

In addition, during the screening procedure for the 18 other vaccine variables, each other vaccine was fit in a univariate logistic regression to test if they are associated with convulsion respectively. 11 out of 18 vaccines were significantly associated with convulsion and then used as covariate in later multivariate modeling regression. This is good for predictive modeling, but might not be as appropriate for an etiologic model. While our study focused on assessing effect of TIV on convulsion rather than testing all possible risk factors on convulsions, we were dealing with an etiologic model rather a predictive model. By this univariate regression screening method, it is possible that we excluded some vaccines that might not directly associate with convulsion, but are effect modifiers or confounders of TIV effect on convulsions. For future work, it might be good to test effect modification and confounding for each other vaccines before the final multivariate modeling.

Lastly, previous studies show that children who have one seizure are more likely to have a seizure again. History of convulsion prior to this influenza season for each child is a potentially important variable that we did not measure in this study. It would be better if we had data about convulsion history from birth till the influenza season that we were studying. Medical care organization sites were also considered as fixed effect here, and can alternatively be considered as random effect.

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Figures

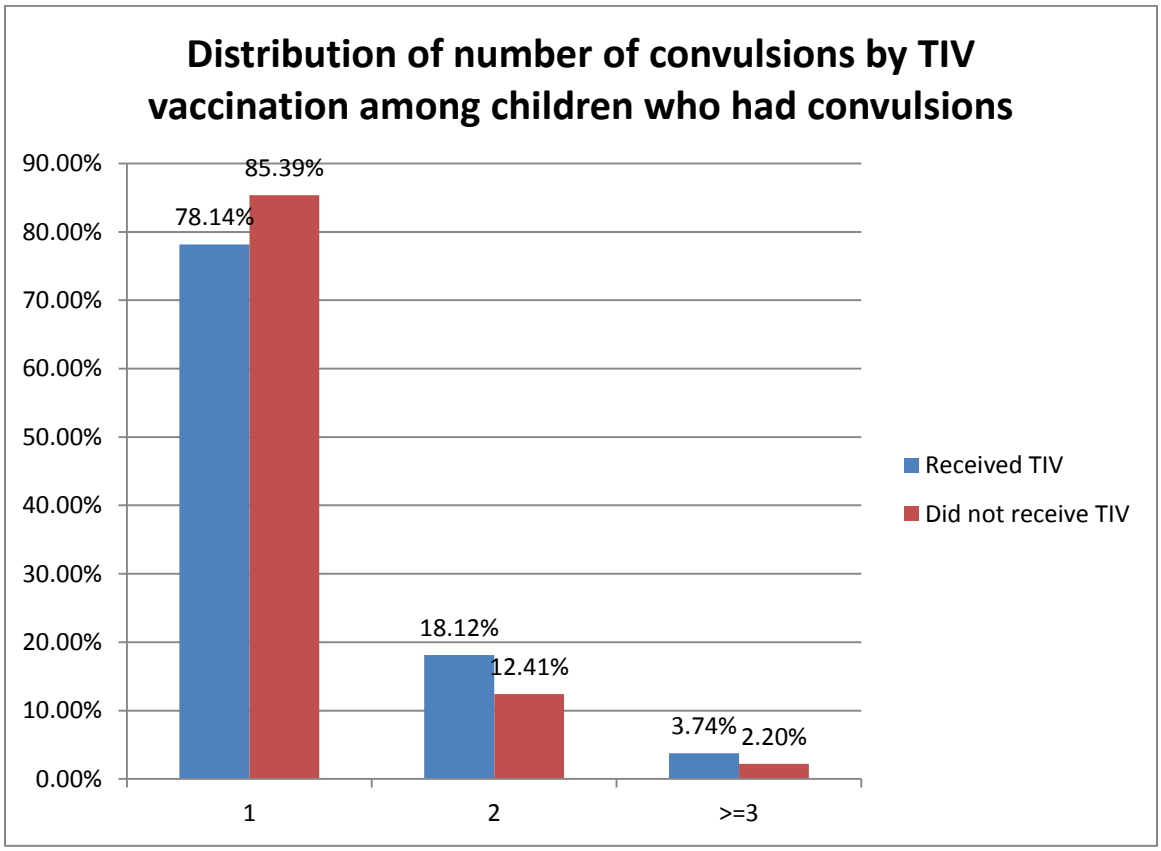


Figure 1 Distribution of number of convulsions by TIV vaccination among children who had convulsions

Among children who had TIV vaccination and later developed convulsions, 78.14% had only one convulsion, 18.12% had two convulsions, 3.74% had more than 2 convulsions in the season. By comparison, among children who did not have TIV but later developed convulsions, 85.39% of them had only one convulsion, 12.41% had two convulsions and 2.20% had more than 2 convulsions.

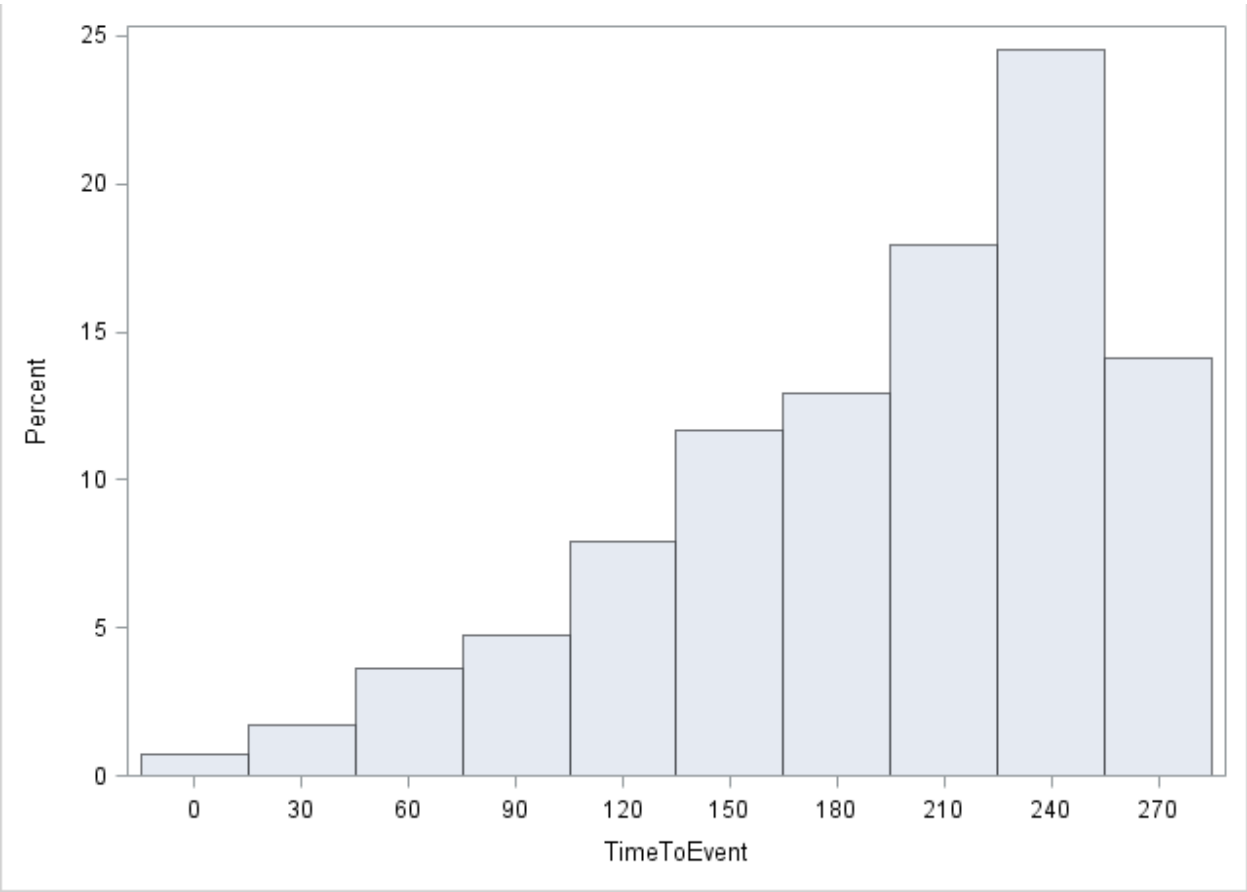
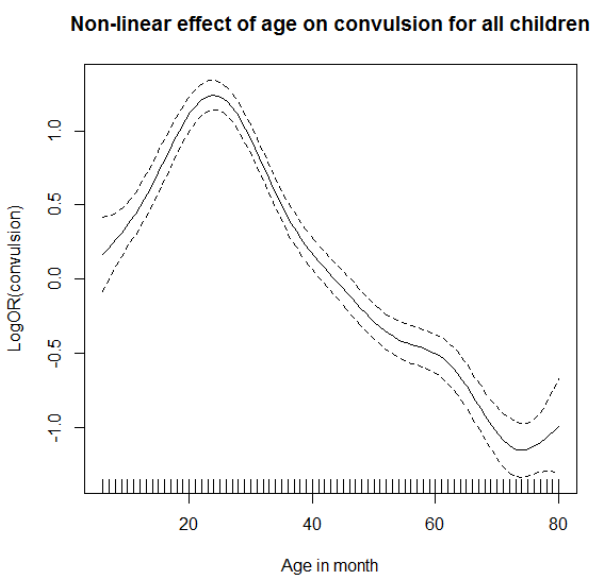
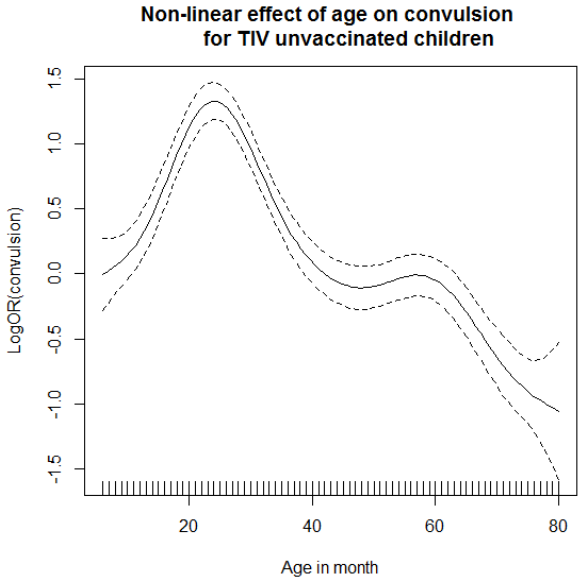


Figure 2 Distribution of time from 1st TIV vaccination to 1st convulsion event (unit: day)

People are tending to develop convulsion longer after receiving TIV vaccines. This is reasonable because other factors such as other vaccines are more likely to play roles in causing conclusions as time goes by.



A.



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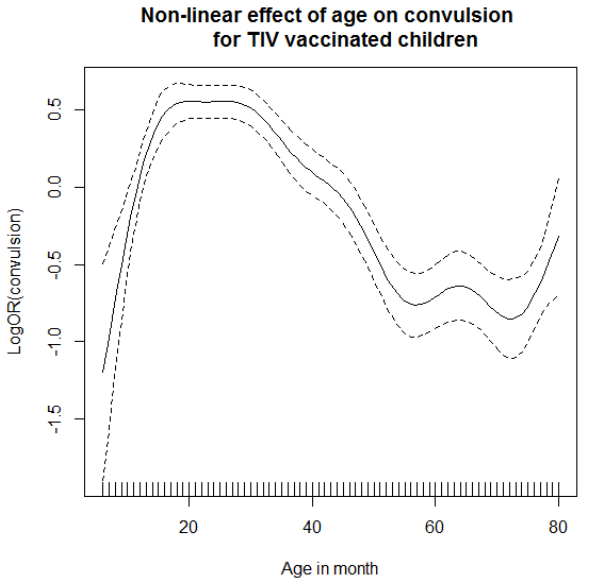

C.

Figure 3 Non-linear effect of age on the risk of at least one convulsion

A) shows the non-linear effect of age for all children. The trend shows apparent increased risk of convulsion and age between 5 - 40 months old, compared with decreased risk of convulsion and age 40 - 80 months old. The risk of convulsions peaks at around 22 months of age. Such effect of age on the risk of convulsion is modified by TIV vaccination; B) shows the non-linear effect of age for TIV unvaccinated children only; C) shows the non-linear effect of age for TIV vaccinated children only.

Tables

Table 1 List of explanatory variables

Explanatory Variables	Definition
TIV	Whether or not at least one dose of TIV was administered during the season(0=no, 1=yes)
gender	Gender (0=female, 1=male)
Highrisk	Whether or not child has a high risk medical condition in that season
agecat	Age group [1= (6~11 month), 2= (12~23 month), 3= (24~59 month), 4 = (60~80 month)]
Site	Managed Care Organization (Site=B, C, D, G, H, M, O, P, S, W)
Time	Days from the receipt day of 1st TIV till the day of the 1st convulsion following TIV vaccination; if no convulsion occurred in the same season, use the last day of the season (June 30th, 2011) as the stop date; if no TIV vaccination, use Oct 3rd, 2010 as the start day
TIVA	Whether or not multiple dose of TIV in the same season
HBV	Whether or not child was given HBV after receiving 1st TIV
IPV	Whether or not child was given IPV after receiving 1st TIV
Hib	Whether or not child was given Hib after receiving 1st TIV
DTaP	Whether or not child was given Dtap after receiving 1st TIV
VAR	Whether or not child was given VAR after receiving 1st TIV
HAV	Whether or not child was given HAV after receiving 1st TIV
Hib_HBV	Whether or not child was given Hib_HBV after receiving 1st TIV
MMRV	Whether or not child was given MMRV after receiving 1st TIV
PCV7	Whether or not child was given PCV7 after receiving 1st TIV
Pediarix	Whether or not child was given Pediarix after receiving 1st TIV
LAIV	Whether or not child was given LAIV after receiving 1st TIV
RV5	Whether or not child was given RV5 after receiving 1st TIV
RV1	Whether or not child was given RV1 after receiving 1st TIV
Pentacel	Whether or not child was given Pentacel after receiving 1st TIV
MLAIV	Whether or not child was given MLAIV after receiving 1st TIV
MIV	Whether or not child was given MIV after receiving 1st TIV
Kinrix	Whether or not child was given Kinrix after receiving 1st TIV
PCV13	Whether or not child was given PCV13 after receiving 1st TIV

Table 2 Characteristics of children by TIV exposure

	Received TIV (n= 270292)	**Did not receive TIV (n= 522094)**	***P* value**
Sex			
Male	139688 (34.42%)[a]	266121 (65.58%)	< .0001
Female	130603 (33.79%)	255960 (66.21%)	
Age in months			
6 to 11	11377 (19.34%)	47437 (80.66%)	
12 to 23	70855 (62.06%)	43311 (37.94%)	< .0001
24 to 59	129148 (34.77%)	242260 (65.23%)	
59 to 80	58912 (23.76%)	189086 (76.24%)	
High risk			
Yes	51767 (44.30%)	65080 (55.70%)	< .0001
No	218525 (32.35%)	457014 (67.65%)	
Convulsion			
Yes	1604 (53.25%)	1410 (46.75%)	< .0001
No	268688 (34.04%)	520684 (65.96%)	
Medical Care Organization (site)			
B	10069/18026 (55.86%)[b]	7957/18026 (44.14%)	
C	95674/275671 (34.71%)	179997/275671 (65.29%)	
D	13296/39328 (33.81%)	26032/39328 (66.19%)	
G	4821/22859 (21.09%)	18038/22859 (78.91%)	
H	9279/36290 (25.57%)	27011/36290 (74.43%)	<.0001
M	8171/21419 (38.15%)	13248/21419 (61.85%)	
O	11595/36172 (32.06%)	24577/36172 (67.94%)	
P	8974/19383 (46.30%)	10409/19383 (53.70%)	
S	98746/292940 (33.1%)	194194/292940 (66.29%)	
W	9667/30298 (31.91%)	20631/30298 (68.09%)	
Total	**270292/792386 (34.11%)**	**522094/792386 (65.89%)**	

a. Table entries are frequency (row percentage)

b. Table entries are frequency/ total number for each site (row percentage)

Table 3a Number of convulsions in the influenza season 2010-2011

Number of Convulsions	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	789370	99.62	789370	99.62
1	2459	0.31	791829	99.93
2	466	0.06	792295	99.99
3	82	0.01	792377	100
4	7	0	792384	100
5	2	0	792386	100

Table 3b. Number of convulsions by TIV exposure in the influenza season 2010-2011

Number of Convulsions	Received TIV	Did not receive TIV	Total
0	268686 (99.41%)	520684(99.73%)	789370
1	1255 (0.46%)	1204 (0.23%)	2459
2	291 (0.11%)	175 (0.03%)	466
3	60 (0.02%)	41 (0.01%)	91
Total	270292	522094	792386

*Frequency (column percent)

Table 3c. 2 X 2 Table

	Exposed (TIV+)	Unexposed (TIV-)
At least one Convulsion	1604	1410
No Convulsions	268688	520684
	13296	26032

Table 4 Number of TIV received in the influenza season 2010-2011

TIV Dosage	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	522094	65.89	522094	65.89
1	197205	24.89	719299	90.78
>=2	73087	9.22	792386	100

Table 5 Stepwise selection results in logistic regression modeling

Type 3 Analysis of Effects			
Effect	**DF**	**Wald Chi-Square**	**Pr > ChiSq**
TIVI	1	236.465	<.0001
gender	1	6.9613	0.0083
HighriskI	1	332.445	<.0001
agecat	3	228.567	<.0001
CDCSITE	9	62.456	<.0001
Time	1	443.006	<.0001
IPV	1	10.3856	0.0013
DTaP	1	19.4699	<.0001
HAV	1	162.518	<.0001
Pediarix	1	11.3608	0.0008
PCV13	1	102.132	<.0001
TIVI*HighriskI	1	6.3154	0.012
TIVI*agecat	3	47.6732	<.0001

Table 6 Odds ratio estimate and 95% confidence interval in Logistic regression

Odds Ratio Estimates and Wald Confidence Intervals						
Effect	**DF**	**Estimate**	**95% Confidence Limits**		**Wald Chi-Square**	**Pr > ChiSq**
TIVI	1	- [a]	-	-	236.4646	<.0001
gender	1	1.102	1.025	1.185	6.9613	0.0083
HighriskI	1	-	-	-	332.4448	<.0001
agecat	3	-	-	-	228.5673	<.0001
CDCSITE	9	-	-	-	62.456	<.0001
Time	1	1.009	1.008	1.01	443.0057	<.0001
IPV	1	1.404	1.142	1.727	10.3856	0.0013
DTaP	1	1.31	1.162	1.477	19.4699	<.0001
HAV	1	1.914	1.733	2.115	162.5178	<.0001
Pediarix	1	1.363	1.138	1.632	11.3608	0.0008
PCV13	1	1.622	1.477	1.782	102.1322	<.0001
TIVI*HighriskI	1	-	-	-	6.3154	0.012
TIVI*agecat	3	-	-	-	47.6732	<.0001

a. The odds ratio estimates for those used in interaction terms were shown in Table 7.

Table 7 Odds ratio estimate for TIV vaccination by contrast statement in logistic regression

Contrast OR Estimation and Testing Results					
Contrast	**Estimate**	**95% CI**		**Wald Chi-Square**	**Pr > ChiSq**
TIV vaccinated vs unvaccinated in agecat=1, highrisk=1	10.0784	6.568	15.464	111.866	<.0001
TIV vaccinated vs unvaccinated in agecat=2, highrisk=1	3.9998	3.423	4.6745	303.863	<.0001
TIV vaccinated vs unvaccinated in agecat=3, highrisk=1	4.7757	3.771	6.0489	168.126	<.0001
TIV vaccinated vs unvaccinated in agecat=4, highrisk=1	4.7757	3.771	6.0489	168.126	<.0001
TIV vaccinated vs unvaccinated in agecat=1, highrisk=0	12.3302	8.113	18.741	138.312	<.0001
TIV vaccinated vs unvaccinated in agecat=2, highrisk=0	4.8935	4.309	5.5578	597.714	<.0001
TIV vaccinated vs unvaccinated in agecat=3, highrisk=0	5.8427	4.666	7.3168	236.465	<.0001
TIV vaccinated vs unvaccinated in agecat=4, highrisk=0	5.8427	4.666	7.3168	236.465	<.0001
agecat=1 vs Agecat=4	1.6993	1.061	2.7225	4.8607	0.0275
agecat=2 vs Agecat=4	4.1434	3.329	5.1567	162.185	<.0001
agecat=3 vs Agecat=4	2.738	2.295	3.2665	125.096	<.0001
Highrisk vs not highrisk	2.4502	2.207	2.7203	282.019	<.0001

Table 8 Hosmer and Lemeshow Goodness-of- Fit test results for logistic regression

Chi-Square	DF	Pr > ChiSq
83.3643	8	<.0001

Table 9 Likelihood ratio test for Type 3 statistics for Poisson regression model

(a) when taking convulsion count as outcome

LR Statistics For Type 3 Analysis						
Source	**Num DF**	**Den DF**	**F Value**	**Pr > F**	**Chi-Square**	**Pr > ChiSq**
TIV	1	788855	121.04	<.0001	121.04	<.0001
Gender	1	788855	3.67	0.0555	3.67	0.0555
HighriskI	1	788855	305.92	<.0001	305.92	<.0001
agecat	3	788855	98.75	<.0001	296.25	<.0001
CDCSITE	9	788855	7.59	<.0001	68.28	<.0001
IPV	1	788855	5.02	0.0251	5.02	0.0251
DTaP	1	788855	16.94	<.0001	16.94	<.0001
VAR	1	788855	0.64	0.4243	0.64	0.4243
HAV	1	788855	84.18	<.0001	84.18	<.0001
Pediarix	1	788855	16.52	<.0001	16.52	<.0001
PCV13	1	788855	31.49	<.0001	31.49	<.0001
TIVI*agecat	3	788855	49.61	<.0001	148.84	<.0001
TIVI*HighriskI	1	788855	4.7	0.0302	4.7	0.0302

(b) when taking person-time into account, i.e., the outcome turns to convulsion rate, VAR (Varicella vaccine) becomes significant associated.

LR Statistics For Type 3 Analysis						
Source	**Num DF**	**Den DF**	**F Value**	**Pr > F**	**Chi-Square**	**Pr > ChiSq**
TIV	1	1.55E+06	29.4	<.0001	29.4	<.0001
gender	1	1.55E+06	12.22	0.0005	12.22	0.0005
HighriskI	1	1.55E+06	354.7	<.0001	354.7	<.0001
agecat	3	1.55E+06	87.43	<.0001	262.29	<.0001
CDCSITE	8	1.55E+06	11.49	<.0001	91.94	<.0001
IPV	1	1.55E+06	16.25	<.0001	16.25	<.0001
DTaP	1	1.55E+06	39.7	<.0001	39.7	<.0001
VAR	1	1.55E+06	4.42	0.0355	4.42	0.0355
HAV	1	1.55E+06	290.48	<.0001	290.48	<.0001
Pediarix	1	1.55E+06	38.66	<.0001	38.66	<.0001
PCV13	1	1.55E+06	113.94	<.0001	113.94	<.0001
TIVI*agecat	3	1.55E+06	6.32	0.0003	18.97	0.0003
TIVI*HighriskI	1	1.55E+06	6.81	0.0091	6.81	0.0091

Table 10 Adjusted relative risk estimate in Poisson regression model

(a) when taking convulsion count as outcome

Analysis Of Maximum Likelihood Parameter Estimates							
Parameter		**Estimate**	**Standard Error**	**Wald 95% Confidence Limits**		**Wald Chi-Square**	**Pr > ChiSq**
Intercept		-7.0116	0.1231	-7.2528	-6.7704	3245.66	<.0001
TIV		1.2814	0.1155	1.0551	1.5077	123.14	<.0001
gender	0	-0.0717	0.0375	-0.1452	0.0018	3.66	0.0558
HighriskI		1.1754	0.0612	1.0554	1.2954	368.46	<.0001
agecat	1	1.2765	0.1329	1.0159	1.537	92.2	<.0001
agecat	2	1.7478	0.1086	1.535	1.9606	259.22	<.0001
agecat	3	1.0704	0.0921	0.8898	1.2509	135.02	<.0001
IPV		0.2459	0.1071	0.036	0.4559	5.27	0.0217
DTaP		0.2583	0.0623	0.1362	0.3804	17.19	<.0001
VAR		0.0486	0.0607	-0.0704	0.1675	0.64	0.4237
HAV		0.482	0.0516	0.3809	0.583	87.4	<.0001
Pediarix		0.3881	0.0937	0.2045	0.5718	17.16	<.0001
PCV13		0.274	0.0483	0.1793	0.3686	32.19	<.0001
TIVI*agecat	1	-0.6528	0.2034	-1.0514	-0.2542	10.31	0.0013
TIVI*agecat	2	-1.3492	0.1329	-1.6097	-1.0888	103.07	<.0001
TIVI*agecat	3	-0.3569	0.1226	-0.5971	-0.1166	8.48	0.0036
TIVI*HighriskI		-0.175	0.0805	-0.3328	-0.0172	4.73	0.0297
Scale[a]		1.1251	0	1.1251	1.1251		

a. scale parameter was estimated by the square root of Pearson's Chi-Square/DOF.

(b) when taking convulsion rate as outcome

Analysis Of Maximum Likelihood Parameter Estimates							
Parameter		**Estimate**	**Standard Error**	**Wald 95% Confidence Limits**		**Wald Chi-Square**	**Pr > ChiSq**
Intercept		-7.0845	0.1013	-7.2829	-6.886	4894.26	<.0001
TIV		0.499	0.0935	0.3157	0.6824	28.46	<.0001
gender	0	-0.1003	0.0287	-0.1566	-0.044	12.18	0.0005
HighriskI		1.0044	0.0493	0.9077	1.1011	414.46	<.0001
agecat	1	1.1626	0.1103	0.9464	1.3789	111.02	<.0001
agecat	2	1.2576	0.0891	1.083	1.4323	199.24	<.0001

agecat	3	0.9946	0.0802	0.8374	1.1519	153.74	<.0001
IPV		0.3189	0.0767	0.1687	0.4692	17.31	<.0001
DTaP		0.2859	0.045	0.1976	0.3741	40.26	<.0001
VAR		0.0938	0.0445	0.0065	0.1811	4.44	0.0351
HAV		0.6736	0.0387	0.5977	0.7495	302.7	<.0001
Pediarix		0.4032	0.0634	0.2789	0.5274	40.44	<.0001
PCV13		0.388	0.036	0.3175	0.4585	116.38	<.0001
TIVI*agecat	1	-0.3635	0.1305	-0.6193	-0.1076	7.75	0.0054
TIVI*agecat	2	-0.3014	0.1042	-0.5057	-0.0971	8.36	0.0038
TIVI*agecat	3	-0.0787	0.0999	-0.2745	0.117	0.62	0.4305
TIVI*HighriskI		0.1639	0.063	0.0405	0.2874	6.77	0.0092
Scale		1.1033	0	1.1033	1.1033		

Table 11 Adjusted relative risk of TIV vaccinated children versus TIV unvaccinated children on the number of convulsion in Poisson regression model

(a) when taking convulsion count as outcome

Adjusted RR Estimate Results				
Label	**L'Beta Estimate**	**Standard Error**	**95% CI**	
Exp(TIV vaccinated vs unvaccinated in agecat=1, highrisk=1)	6.0669	1.314	3.9683	9.2752
Exp(TIV vaccinated vs unvaccinated in agecat=2, highrisk=1)	2.116	0.1572	1.8293	2.4478
Exp(TIV vaccinated vs unvaccinated in agecat=3, highrisk=1)	3.0235	0.3646	2.387	3.8297
Exp(TIV vaccinated vs unvaccinated in agecat=4, highrisk=1)	3.0235	0.3646	2.387	3.8297
Exp(TIV vaccinated vs unvaccinated in agecat=1, highrisk=0)	7.2271	1.5307	4.7718	10.9457
Exp(TIV vaccinated vs unvaccinated in agecat=2, highrisk=0)	2.5207	0.1521	2.2395	2.8372
Exp(TIV vaccinated vs unvaccinated in agecat=3, highrisk=0)	3.6016	0.4159	2.8722	4.5164
Exp(TIV vaccinated vs unvaccinated in agecat=4, highrisk=0)	3.6016	0.4159	2.8722	4.5164
Exp(agecat=1 vs Agecat=4)	0.4841	0.1119	0.3077	0.7616

Exp(agecat=2 vs Agecat=4)	4.0186	0.4629	3.2066	5.0364
Exp(agecat=3 vs Agecat=4)	2.9165	0.2687	2.4348	3.4936
Exp(Highrisk vs not highrisk)	2.7194	0.143	2.4531	3.0146

(b) when taking convulsion rate as outcome

Adjusted RR Estimate Results				
Label	**L'Beta Estimate**	**Standard Error**	**95% CI**	
Exp(TIV vaccinated vs unvaccinated in agecat=1, highrisk=1)	1.8238	0.2682	1.3671	2.433
Exp(TIV vaccinated vs unvaccinated in agecat=2, highrisk=1)	1.7936	0.106	1.5974	2.0138
Exp(TIV vaccinated vs unvaccinated in agecat=3, highrisk=1)	1.9405	0.192	1.5984	2.3558
Exp(TIV vaccinated vs unvaccinated in agecat=4, highrisk=1)	1.9405	0.192	1.5984	2.3558
Exp(TIV vaccinated vs unvaccinated in agecat=1, highrisk=0)	1.548	0.2181	1.1745	2.0403
Exp(TIV vaccinated vs unvaccinated in agecat=2, highrisk=0)	1.5224	0.0718	1.3881	1.6698
Exp(TIV vaccinated vs unvaccinated in agecat=3, highrisk=0)	1.6471	0.1541	1.3712	1.9785
Exp(TIV vaccinated vs unvaccinated in agecat=4, highrisk=0)	1.6471	0.1541	1.3712	1.9785
Exp(agecat=1 vs Agecat=4)	1.645	0.2656	1.1988	2.2573
Exp(agecat=2 vs Agecat=4)	3.2508	0.2806	2.7448	3.8501
Exp(agecat=3 vs Agecat=4)	2.7038	0.2169	2.3104	3.1641
Exp(Highrisk vs not highrisk)	3.2166	0.1268	2.9773	3.475

Table 12 Goodness-of-Fit test for Poisson regression model

Outcome Variable		Criteria For Assessing Goodness Of Fit Model 2 -Convulsion Count		Model 3 - Convulsion Rate	
Criterion	**DF**	**Value**	**Value/DF**	**Value**	**Value/DF**
Deviance	7.90E+05	38429.2626	0.0487	64621.0884	0.0417
Scaled Deviance	7.90E+05	30359.4994	0.0385	53082.35	0.0343
Pearson Chi-Square	7.90E+05	998538.0723	1.2658	1885969.651	1.2174
Scaled Pearson X2	7.90E+05	788855	1	1549211	1
Log Likelihood		-17306.3123		-30364.1979	
Full Log Likelihood		-22408.2011		-37664.0913	
AIC (smaller is better)		44868.4022		75378.1826	
AICC (smaller is better)		44868.404		75378.1835	
BIC (smaller is better)		45169.4399		75684.5145	

Deviance/DF is smaller than 1, suggesting of under-dispersion of the data. PSCALE option scale this standard errors of the parameter estimates by using the Persall residuals to account for the under-dispersion.

Table 13 Likelihood ratio statistics for Type 3 analysis for negative binomial regression

	LR Statistics For Type 3 Analysis					
Source	**Num DF**	**Den DF**	**F Value**	**Pr > F**	**Chi-Square**	**Pr > ChiSq**
TIVI	1	788855	127.68	<.0001	127.68	<.0001
gender	1	788855	4.9	0.0269	4.9	0.0269
HighriskI	1	788855	280.09	<.0001	280.09	<.0001
agecat	3	788855	1449.54	<.0001	4348.63	<.0001
CDCSITE	9	788855	6.68	<.0001	60.09	<.0001
IPV	1	788855	10.07	0.0015	10.07	0.0015
DTaP	1	788855	12.54	0.0004	12.54	0.0004
VAR	1	788855	0.69	0.4045	0.69	0.4045
HAV	1	788855	100.41	<.0001	100.41	<.0001
Pediarix	1	788855	14.95	0.0001	14.95	0.0001
PCV13	1	788855	44.25	<.0001	44.25	<.0001
TIVI*agecat	3	788855	40.78	<.0001	122.33	<.0001
TIVI*HighriskI	1	788855	2.47	0.1161	2.47	0.1161

Table 14 Adjusted relative risk estimate in negative binomial regression

Analysis Of Maximum Likelihood Parameter Estimates							
Parameter		**Estimate**	**Standard Error**	**Wald 95% Confidence Limits**		**Wald Chi-Square**	**Pr > ChiSq**
Intercept		-7.0193	0.1257	-7.2658	-6.7729	3116.69	<.0001
TIVI		1.2865	0.1133	1.0645	1.5085	129.03	<.0001
gender	0	-0.0893	0.0404	-0.1685	-0.0102	4.89	0.027
HighriskI		1.1803	0.068	1.0469	1.3137	300.89	<.0001
agecat	1	1.1467	0.1366	0.879	1.4144	70.47	<.0001
agecat	2	1.6917	0.1108	1.4745	1.9089	233.02	<.0001
agecat	3	1.0378	0.0878	0.8657	1.2099	139.68	<.0001
IPV		0.3877	0.1206	0.1513	0.6241	10.33	0.0013
DTaP		0.2509	0.0706	0.1125	0.3892	12.63	0.0004
VAR		0.0566	0.0678	-0.0763	0.1896	0.7	0.4039
HAV		0.5676	0.0562	0.4575	0.6777	102.06	<.0001
Pediarix		0.414	0.1071	0.2041	0.6239	14.94	0.0001
PCV13		0.3554	0.0532	0.2512	0.4596	44.7	<.0001
TIVI*agecat	1	-0.5321	0.2123	-0.9482	-0.116	6.28	0.0122
TIVI*agecat	2	-1.3059	0.1378	-1.5759	-1.0359	89.85	<.0001
TIVI*agecat	3	-0.2956	0.1214	-0.5335	-0.0576	5.93	0.0149
TIVI*HighriskI		-0.145	0.0922	-0.3256	0.0356	2.48	0.1157
Dispersion		58.2736	2.7125	53.1925	63.8401		

PSCALE option scale this standard errors of the parameter estimates by using the Persall residuals to account for the under-dispersion.

Table 15 Adjusted relative risk of TIV vaccinated children versus TIV unvaccinated children on the number of convulsion in negative binomial regression model

Contrast Estimate Results				
Label	**L'Beta Estimate**	**Standard Error**	**95% CI**	
Exp(TIV vaccinated vs unvaccinated in agecat=1, highrisk=1)	6.7892	1.5439	4.3476	10.602
Exp(TIV vaccinated vs unvaccinated in agecat=2, highrisk=1)	2.3302	0.2041	1.9626	2.7667
Exp(TIV vaccinated vs unvaccinated in agecat=3, highrisk=1)	3.1316	0.3796	2.4694	3.9713
Exp(TIV vaccinated vs unvaccinated in agecat=4, highrisk=1)	3.1316	0.3796	2.4694	3.9713
Exp(TIV vaccinated vs unvaccinated in agecat=1, highrisk=0)	7.8486	1.7676	5.0476	12.2038
Exp(TIV vaccinated vs unvaccinated in agecat=2, highrisk=0)	2.6938	0.168	2.384	3.044
Exp(TIV vaccinated vs unvaccinated in agecat=3, highrisk=0)	3.6202	0.41	2.8995	4.52
Exp(TIV vaccinated vs unvaccinated in agecat=4, highrisk=0)	3.6202	0.41	2.8995	4.52
Exp(agecat=1 vs Agecat=4)	0.5009	0.1205	0.3126	0.8027
Exp(agecat=2 vs Agecat=4)	4.0394	0.492	3.1816	5.1285
Exp(agecat=3 vs Agecat=4)	2.8229	0.2479	2.3766	3.3531
Exp(Highrisk vs not highrisk)	2.816	0.176	2.4913	3.183

Table 16 Goodness-of-Fit test for negative binomial regression model

Criteria For Assessing Goodness Of Fit			
Criterion	**DF**	**Value**	**Value/DF**
Deviance	7.90E+05	15020.101	0.019
Scaled Deviance	7.90E+05	14916.456	0.0189
Pearson Chi-Square	7.90E+05	794336.28	1.0069
Scaled Pearson X2	7.90E+05	788855	1
Log Likelihood		-19767.173	
Full Log Likelihood		-20406.275	
AIC (smaller is better)		40866.551	
AICC (smaller is better)		40866.553	
BIC (smaller is better)		41179.167	

Deviance/DF is much smaller than 1, suggesting of under-dispersion of the data.

APPENDIX A – SAS CODE

```
libname one xport "H:\000. CDC\1. Coding\sz cohort
data\d_seizdufv1_20120606ssh3m.xpt";

proc copy out=work in=one; run;

****Merge files;
data outpt_d1;
       set outpt;
       where DEPT='ER';
RUN;
data one;
set inpat outpt;
RUN;
***Now add two indicator variables for 2 big categories of outcome;
data caredate;
set one;
Convulsions=0;
Fever=0;

if (substr(DxCode,1,4) = '7803') and (DxCode ne '78033') then Convulsions=1;
if (substr(DxCode,1,4) = '7806') and (DxCode ne '78064') then Fever=1;
run;

***Now define season2010 (July2010-June2011) & season2009 (July2009-June2010);
data caredate_d;
set caredate;
if CareDate ge '01JUL2010'd and CareDate le '30JUN2011'd then careseason='2010';
else if CareDate ge '01JUL2009'd and CareDate le '30JUN2010'd then careseason='2009';
else if CareDate lt '01JUL2009'd then careseason='<2009';
else if CareDate ge '01JUL2011'd then careseason='>2010'; ********note >2010 does not
fully wrote to this var, it shows '>201';

if highrisk=. then highrisk=0;
if outcome=. then outcome=0;
run;


****Divide into 2 datasets;
data Conv_d;
set caredate_d;
if Convulsions=1;
run;
data Fever_d;
set caredate_d;
if Fever=1;
run;
****Define "new_conv" indicator variable;
proc sort data=Conv_d; by studyid caredate; run;
data Conv_d2010; set conv_d;if careseason='2010'; run;

*--------------------------------;
****For poisson regression model;

data conv_d2010; set conv_d2010; if caredate ge '03oct2010'd;run;
*--------------------------------;
```

```
******************;
data work.vaccine_d;
set work.vaccine;
run;
data vaccine_d1;
set vaccine_d;
if vac in ('111') then LAIV=1; else if LAIV=. then LAIV=0;
if vac in ('15' '16' '88' '140' '141') then TIV=1; else if TIV=. then TIV=0;
**monovalent pandemic 2009(H1N1) vaccines:;
if vac in ('125') then MLAIV=1; else if MLAIV=. then MLAIV=0;
if vac in ('126' '128' '801') then MIV=1; else if MIV=. then MIV=0;
run;

***Now define vaccine_d season2010 (July2010-June2011) & season2009 (July2009-
June2010);
data vaccine_d2;
set vaccine_d1;
if VacDate ge '01JUL2010'd and VacDate le '30JUN2011'd then fluseason='2010';
else if VacDate ge '01JUL2009'd and VacDate le '30JUN2010'd then fluseason='2009';
else if VacDate lt '01JUL2009'd then fluseason='<2009';
else if VacDate ge '01JUL2011'd then fluseason='>2010'; ********note >2010 does not
fully wrote to this var, it shows '>201';
run;

proc sort data=vaccine_d2 out=vaccine_dd3;
by fluseason studyid;
run;
data vaccine_dd3_2009;
set vaccine_dd3;
if fluseason='2009';
run;
data vaccine_dd3_2010;
set vaccine_dd3;
if fluseason='2010';
run;
data vaccine_dd3_2011;
set vaccine_dd3;
if fluseason='>201';
run;


**---------------------------------;
****For poisson regression model, to remove vacdate before 03oct2010;
data vaccine_dd3_2010;
set vaccine_dd3_2010; if vacdate ge '03oct2010'd;run;
*---------------------------------;
******************;


******************;
data ceall_d;
set ceall;
flag=0;
if stopdate lt '01JUL2010'd then flag=1; *'to be deleted' flag;
else if strtdate gt '30JUN2011'd then flag=1;
run;
data ceall_d2010 (drop=flag); *in the right season;
set ceall_d;
if flag=0;
```

```
run;
proc sort data=ceall_d2010 nodupkey out=ceall_d2010_1 ;
by studyid;
run;

data ceall_d2010_1;
set ceall_d2010_1;
AgeM= int(('30JUN2011'd-BrthDate)/30.5); *Add AgeM by the end of the season2010;
* get intergral part of the day;
if sex eq 'F' then gender = 0;
else if sex eq 'M' THEN gender=1;
run;
**********;



*1;
proc sort data=conv_d2010;
by studyid;
run;
*2;
data vaccine_dd3_2010;
set vaccine_dd3_2010;
othvac=0;
if sum(TIV,MIV,LAIV,MLAIV) eq 0 then othvac=1; *add othvac as indicator var;
run;
proc sort data=vaccine_dd3_2010;
by studyid vacdate;
run;
*3;
PROC SORT DATA=ceall_d2010_1;
BY studyid;
RUN;

*****;
data vaccine_dd3_2010_test ;
set vaccine_dd3_2010;
rename studyid=studyid_test;
run;

data conv_d2010_test ;
set conv_d2010;
rename studyid=studyid_1;
run;
proc sql;
create table BOTH_d2010 as
select a.*, b.*
from conv_d2010_test AS a full join vaccine_dd3_2010_test AS b
on a.studyid_1= b.studyid_test;
quit;
proc sql;
create table Four_conv2010 as
select c.*, d.*
from ceall_d2010_1 AS c left join BOTH_d2010 AS d
on c.studyid= d.studyid_test;
quit;

data Four_conv2010_1 (drop=studyid_1 studyid_test);
set Four_conv2010;
```

```
if convulsions=. then convulsions=0;
if highrisk=. then highrisk=0;
run;

proc sort; by studyid caredate; run;

data Four_conv2010_1 ;
set Four_conv2010_1;
by studyid;


retain conv_flag;
conv_flag+convulsions;
if first.studyid then conv_flag=convulsions;

if agem lt 6 then agecat=1;
else if agem lt 12 then agecat=2;
else if agem lt 24 then agecat=3;
else if agem lt 60 then agecat=4;
else agecat=5;

run;

***;

**TIVPLUS;
**find out all id that has at least 1 TIV record in the entire season
then merge back to original dataset to differentiate id with TIV versus id without
TIV;
data Four_conv2010_1TIV; set Four_conv2010_1; if TIV=1;RUN;
PROC SORT data=Four_conv2010_1TIV; BY studyid; run;
DATA Four_conv2010_1TIV1 (KEEP=studyid); SET Four_conv2010_1TIV; BY studyid; if
first.studyid=1;RUN;
DATA Four_conv2010_1TIV1; set Four_conv2010_1TIV1; rename studyid=studyid_test; run;
proc sql;
create table TIV_d2010 as
select a.*, b.*
from Four_conv2010_1 AS a RIGHT join Four_conv2010_1TIV1 AS b
on a.studyid= b.studyid_test;
quit;


proc sort data=tiv_d2010; by studyid caredate; run;


*(1.1)*** TIV+ CONV+;
DATA TIV_D2010_2 ; SET TIV_D2010; by studyid; if CONV_FLAG>0; RUN;

PROC SORT DATA=TIV_D2010_2; BY STUDYID CAREDATE; RUN;

data TIV_D2010_2;
set  TIV_D2010_2;
lagcaredate=lag(caredate);  *never use lag() in a conditional statement;
by studyid; *always put this by statement;

if first.studyid = 1 then new_conv=1; *the first visit for each id is counted as
newevent;
else if ((caredate-lagcaredate) ge 42) then new_conv=1; *if neither 1st visit nor 1st
outcome, the caredate interval >= 42 is also counted;
else new_conv=0;
```

```
run;

data TIV_D2010_3;
set TIV_D2010_2;
by studyid;


label firstTIVdate= "First TIV Date";
format firstTIVdate mmddyy10.;

retain count_conv;
count_conv + new_conv;
if first.studyid=1 then count_conv=new_conv;

retain firstTIVdate;
if first.studyid then firstTIVdate = vacdate;

run;


data TIV_D2010_4; SET TIV_D2010_3; BY STUDYID; IF LAST.STUDYID=1; RUN;
proc freq data=TIV_D2010_4; tables highrisk;run;
data TIV_d2010_4; set TIV_d2010_4; rename count_conv=count_conv_raw;run;

data TIV_d2010_4; set TIV_d2010_4;
      if caredate lt firsttivdate then conv_b4_tiv=count_conv_raw;
      else conv_b4_tiv=0;  *before 1st TIV;

      if caredate ge firsttivdate then count_conv=count_conv_raw;
      else count_conv=0; *count_conv after 1st TIV;
run;



*****************;
* (1.2)*** TIV+ CONV-;
/*data test; set tiv_d2010_5 (keep=caredate tiv); where tiv =1; run; */
DATA TIV_D2010_5; SET TIV_D2010; by studyid; if CONV_FLAG=0; RUN;
PROC SORT DATA=TIV_D2010_5; BY STUDYID CAREDATE; RUN;

data TIV_D2010_5; set TIV_D2010_5;
by studyid;
label firstTIVdate= "First TIV Date";
format firstTIVdate mmddyy10.;

retain firstTIVdate;
if first.studyid then firstTIVdate = vacdate;

run;
***;

DATA TIV_D2010_6; SET TIV_D2010_5; BY STUDYID; IF LAST.STUDYID=1;COUNT_CONV =0; RUN;

/*proc freq data=TIV_D2010_4; tables highrisk; run;*/
*****************;
* (1.1+1.2)**** TIV+ CONV+/1;
DATA TIVPLUS; SET TIV_D2010_4 TIV_D2010_6; BY STUDYID; RUN;
PROC SORT DATA=TIVPLUS NODUPKEY OUT=TIVPLUS; BY COUNT_CONV STUDYID; RUN;
```

```
DATA TIVPLUS
       (keep= highrisk outcome cdcsite studyid ageCAT gender caredate firstTIVdate
convulsions fever TIVI count_conv conv_b4_tiv);
       SET TIVPLUS;
       TIVI=1;
RUN;

**TIVNEG;
DATA Four_conv2010_1; set Four_conv2010_1; if TIV=. then TIV=0;RUN;
proc sort; by studyid caredate;run;
DATA Four_conv2010_1;
       set Four_conv2010_1;
       by studyid;

       label firstTIVdate= "First TIV Date";
       format firstTIVdate mmddyy10.;

       firstTIVdate = '03oct2010'd;

run;


DATA TIV_mm;
SET Four_conv2010_1;
by studyid;
retain count_TIV;
count_TIV+TIV;
if first.studyid then count_TIV=TIV;
run;
PROC SORT DATA=TIV_mm ; by studyid; RUN;
DATA TIV_Negative (KEEP=STUDYID); SET TIV_mm; by studyid; IF LAST.STUDYID=1 AND
COUNT_TIV=0; RUN;

DATA TIV_Negative; set TIV_Negative; rename studyid=studyid_test; run;

proc sql;
create table TIVNEG_1 as
select a.*, b.*
from Four_conv2010_1 AS a RIGHT JOIN TIV_Negative AS b
on a.studyid= b.studyid_test;
quit;


**********;
proc sort data=TIVNEG_1; by studyid caredate; run;
DATA TIVNEG_1;
SET TIVNEG_1;
by studyid;
IF caredate=. then caredate=0;
run;

**********;
*(2.1)*** TIV- CONV+;
DATA TIVNEG_2; SET TIVNEG_1; by studyid; if CONV_FLAG>0; RUN;
PROC SORT DATA=TIVNEG_2; BY STUDYID CAREDATE; RUN;
data TIVNEG_2;
       set TIVNEG_2;
       lagcaredate=lag(caredate);
```

```
      by studyid; *always put this by statement;
      if first.studyid = 1 then new_conv=1; *the first visit for each id is counted
as newevent;
      else if ((caredate-lagcaredate) ge 42) then new_conv=1; *if neither 1st visit
nor 1st outcome, the caredate interval >= 42 is also counted;
      else new_conv=0;
run;

data TIVNEG_3;
set TIVNEG_2;
by studyid;

retain count_conv;
count_conv + new_conv;
if first.studyid then count_conv=new_conv;
run;

data TIVNEG_4; SET TIVNEG_3; BY STUDYID; IF LAST.STUDYID=1; RUN;
/*proc freq; tables count_conv; run;*/
* (2.1)*** TIV- CONV-;
DATA TIVNEG_5; SET TIVNEG_1; by studyid; if CONV_FLAG=0; RUN;
PROC SORT; BY STUDYID; RUN;
DATA TIVNEG_6; SET TIVNEG_5; BY STUDYID; IF LAST.STUDYID=1;COUNT_CONV =0; RUN;

*****************;
* (2.1+2.2)**** TIV- CONV+/-;
DATA TIVNEG7; SET TIVNEG_4 TIVNEG_6; BY STUDYID; RUN;
PROC SORT DATA=TIVNEG7 NODUPKEY OUT=TIVNEG; BY COUNT_CONV STUDYID;RUN;
DATA TIVNEG
(keep=highrisk outcome  cdcsite studyid ageCAT gender firstTIVdate caredate
convulsions fever TIVI count_conv );
SET TIVNEG;
TIVI=0;
RUN;


*****************;
* (1+2)**** TIV+/- CONV+/-;
DATA FIVE; SET TIVPLUS TIVNEG; RUN;
DATA FIVE; set FIVE; if agecat>1; if count_conv ne 0 then
lnCount_conv=log(count_conv);run; * exlude children under 6 yrs bcz they do not
receive TIV;


***The final dataset was obtained;
***************************;




/*Adding highriskI */
data caredate_d; set caredate_d; if highrisk=. then highrisk=0; run;

proc sort data=caredate_d; by studyid caredate;run;

data caredate_d1;   set caredate_d;
      by studyid;
      retain count_highrisk;
      count_highrisk + highrisk;
```

```
      if first.studyid then count_highrisk = highrisk;
run;

data caredate_d2 (keep=studyid highrisk count_highrisk);  set caredate_d1; by studyid;
if last.studyid; run;

data caredate_d2 (keep=studyid HighriskI); set caredate_d2; if count_highrisk>0 then
HighriskI=1; else HighriskI=0;run;

proc sort; by highriskI; run;
/*proc freq; tables highriskI;run;*/

proc sort data=five; by studyid;run;
proc sort data=caredate_d2; by studyid;run;
data five_1; merge  five(in=a) caredate_d2(in=b); by studyid; if a;  run;
data five_1; set five_1; if HighriskI=. then HighriskI=0; run;




**********************;

data SIX;
      set Five_1;
      TimeExp=0; TimeUnx=0;
      if TIVI=1 then TimeExp='30JUN2011'd-firstTIVdate; *Time Exposed;
      if TIVI=1 then TimeUnx=firstTIVdate-'03Oct2010'd; *Time Unexposed;
      Else if TIVI=0 then TimeUnx=('30JUN2011'd -'03Oct2010'd);
run;

*TIV+, exposed person time after 1st TIV;
data Six_subset1
      (keep=cdcsite highriskI studyid ExpI firsttivdate AgeCat gender Count_Conv
PersonTime logPT);
      set SIX;
      ExpI=1;
      WHERE (TimeExp gt 0 and TIVI=1);
      LogPT=log(TimeExp);
      rename TimeExp=PersonTime;
run;


*TIV+, Unexposed person time before 1st TIV;
 data Six_subset2
      (keep= highriskI cdcsite studyid ExpI  firsttivdate AgeCat gender conv_b4_TIV
PersonTime logPT);
      set SIX;
      ExpI=0;
      where (TimeUnx gt 0 and TIVI=1);
      LogPT=log(TimeUnx);
      rename TimeUnx=PersonTime;
run;
data Six_subset2; SET Six_subset2; RENAME conv_b4_TIV=count_conv; run;



*TIV- & a few cases receivng TIV on June 30th, 2011;
data Six_subset3
            (keep= highriskI cdcsite studyid ExpI  firsttivdate AgeCat gender
Count_Conv PersonTime logPT);
```

```
       set SIX;
       ExpI=0;
       WHERE TimeExp =0;
       LogPT=log(TimeUnx);
       rename TimeUnx=PersonTime;
run;

data Six_subset4
             (keep=highriskI cdcsite studyid ExpI  firsttivdate AgeCat gender
Count_Conv PersonTime logPT);
       set SIX;
       ExpI=1;
       WHERE TimeExp =0;
       LogPT=0;
       rename TimeExp=PersonTime;
run;

proc sort data=six_subset1; by studyid; run;
proc sort data=six_subset2; by studyid; run;
proc sort data=six_subset3; by studyid; run;
proc sort data=six_subset4; by studyid; run;

data SIX_double_lines;  *2 lines for each id;
       set six_subset1 six_subset2 six_subset3 six_subset4;
       by studyid;
       if count_conv=. then count_conv=0;
run;



************************************************************;
************************************************************;

libname site_b "H:\000. CDC\1. Coding\FS 10 Sites\B";
libname site_c "H:\000. CDC\1. Coding\FS 10 Sites\c";
libname site_d "H:\000. CDC\1. Coding\FS 10 Sites\d";
libname site_g "H:\000. CDC\1. Coding\FS 10 Sites\g";
libname site_h "H:\000. CDC\1. Coding\FS 10 Sites\h";
libname site_o "H:\000. CDC\1. Coding\FS 10 Sites\o";
libname site_p "H:\000. CDC\1. Coding\FS 10 Sites\p";
libname site_m "H:\000. CDC\1. Coding\FS 10 Sites\m";
libname site_s "H:\000. CDC\1. Coding\FS 10 Sites\s";
libname site_w "H:\000. CDC\1. Coding\FS 10 Sites\w";
libname final "H:\000. CDC\1. Coding\FS 10 Sites\final";

proc sort data=site_b.seven; by studyid;run;
proc sort data=site_c.seven; by studyid;run;
proc sort data=site_d.seven; by studyid;run;
proc sort data=site_g.seven; by studyid;run;
proc sort data=site_h.seven; by studyid;run;
proc sort data=site_m.seven; by studyid;run;
proc sort data=site_o.seven; by studyid;run;
proc sort data=site_p.seven; by studyid;run;
proc sort data=site_s.seven; by studyid;run;
proc sort data=site_w.seven; by studyid;run;


data final.seven;
set site_b.seven  site_d.seven site_g.seven site_h.seven
```

```
            site_m.seven site_o.seven site_p.seven site_w.seven;
      by cdcsite studyid;
run;

data final.seven (drop=d2 d3 d4 d5 );
      set final.seven site_c.seven site_s.seven ;
      by cdcsite studyid;
run;

data final.seven (drop=age2 age3 age4 age5); set final.seven;run;

DATA FINAL.SEVEN (DROP=CONVULSIONS FEVER); SET FINAL.SEVEN;
      IF COUNT_CONV>0 THEN CONVI=1;
      ELSE IF COUNT_CONV=0 THEN CONVI=0;
      ELSE CONVI=.;
RUN;

data final.seven; set final.seven;
      TimeToEvent=0;
      if TIVI=1 then TimeToEvent='30JUN2011'd-firstTIVdate;
      else if TIVI=0 then TimeToEvent=('30JUN2011'd -'03Oct2010'd);
run;

data final.seven; set final.seven;
      if timetoevent gt 0 then logTime=log(timetoevent);
      else logtime=0;
run;


data final.timetoevent; set final.seven;
      where TIVI=1 and convI=1;

run;

proc univariate data=final.Timetoevent PLOT;
      var timetoevent;
      histogram
                  /midpoints=30 60 90 120 150 180 210 240 270;
run;

PROC FREQ DATA=FINAL.seven;
      TABLES
      HBVcount*TIVI
      IPVcount*TIVI
      Hibcount*TIVI
      DTaPcount*TIVI
      VARcount*TIVI
      HAVcount*TIVI
      Hib_HBVcount*TIVI
      MMRVcount*TIVI
      PCV7count*TIVI
      Pediarixcount*TIVI
      LAIVcount*TIVI
      RV5count*TIVI
      RV1count*TIVI
      Pentacelcount*TIVI
      MLAIVcount*TIVI
      MIVcount*TIVI
      Kinrixcount*TIVI
      PCV13count*TIVI
```

```
       TIVAcount*TIVI
       /nopercent norow chisq;
RUN;


PROC FREQ DATA=FINAL.SEVEN;
       TABLES
       HBV *CONVI
       IPV *CONVI
       Hib *CONVI
       DTaP *CONVI
       VAR *CONVI
       HAV *CONVI
       Hib_HBV *CONVI
       MMRV *CONVI
       PCV7 *CONVI
       Pediarix *CONVI
       LAIV *CONVI
       RV5 *CONVI
       RV1 *CONVI
       Pentacel *CONVI
       MLAIV *CONVI
       MIV *CONVI
       Kinrix *CONVI
       PCV13 *CONVI
       TIVA *CONVI

       /nopercent norow chisq;
run;



****************************************
*** Logistic regression modeling****;


ods rtf file= "H:\000. CDC\1. Coding\output2013\FINAL OUTPUT\LOGISTIC 0405 output-
8.rtf";
**add two interaction term;
proc logistic data=final.seven;
       title "Logistic Model";
       CLASS gender Agecat cdcsite/ param=ref;
       model ConvI(event='1')= TIVI
       gender highriskI Agecat cdcsite timetoevent
       TIVA HBV IPV Hib DTaP VAR HAV PCV7 Pediarix RV5 Pentacel PCV13
       HighriskI*TIVI Agecat*TIVI
       /selection=stepwise slentry=.05 slstay=.05  rl lackfit ;

       /***to only estimate OR for TIV************************************/
       contrast 'TIV vaccinated vs unvaccinated in agecat=2, highrisk=1' TIVI 1 -1
      HighriskI*TIVI 1 -1 0 0
     Agecat*TIVI  1 -1 0 0 0 0 0 0 / estimate=exp;

       contrast 'TIV vaccinated vs unvaccinated in agecat=3, highrisk=1' TIVI 1 -1
     HighriskI*TIVI 1 -1 0 0
     Agecat*TIVI  0 0 1 -1 0 0 0 0 / estimate=exp;

        contrast 'TIV vaccinated vs unvaccinated in agecat=4, highrisk=1' TIVI 1 -1
     HighriskI*TIVI 1 -1 0 0
```

```
      Agecat*TIVI  0 0 0 0 1 -1 0 0 / estimate=exp;

        contrast 'TIV vaccinated vs unvaccinated in agecat=5, highrisk=1' TIVI 1 -1
      HighriskI*TIVI 1 -1 0 0
      Agecat*TIVI  0 0 0 0 0 0 1 -1 / estimate=exp;

         contrast 'TIV vaccinated vs unvaccinated in agecat=2, highrisk=0' TIVI 1 -1
       HighriskI*TIVI 0 0 1 -1
      Agecat*TIVI  1 -1 0 0 0 0 0 0 / estimate=exp;

        contrast 'TIV vaccinated vs unvaccinated in agecat=3, highrisk=0' TIVI 1 -1
      HighriskI*TIVI 0 0 1 -1
      Agecat*TIVI  0 0 1 -1 0 0 0 0 / estimate=exp;

         contrast 'TIV vaccinated vs unvaccinated in agecat=4, highrisk=0' TIVI 1 -1
      HighriskI*TIVI 0 0 1 -1
      Agecat*TIVI  0 0 0 0 1 -1 0 0 / estimate=exp;

        contrast 'TIV vaccinated vs unvaccinated in agecat=5, highrisk=0' TIVI 1 -1
      HighriskI*TIVI 0 0 1 -1
      Agecat*TIVI  0 0 0 0 0 0 1 -1 / estimate=exp;

        ***to only estimate OR for agecat*************************************;
        contrast 'agecat=2 vs Agecat=5' agecat 1 0 0 -1
      Agecat*TIVI  1 1 0 0 0 0 -1 -1 / estimate=exp;

        contrast 'agecat=3 vs Agecat=5' agecat 0 1 0 -1
      Agecat*TIVI  0 0 1 1 0 0 -1 -1 / estimate=exp;

        contrast 'agecat=4 vs Agecat=5' agecat 0 0 1 -1
      Agecat*TIVI  0 0 0 0 1 1 -1 -1 / estimate=exp;

         ***to only estimate OR for highrisk************************************;
        contrast 'Highrisk vs not highrisk' highriskI 1 -1
      HighriskI*TIVI  1 1 -1 -1 / estimate=exp;


run;


ods rtf close;




*** Poisson regression modeling****;


ods rtf file= "H:\1. Coding\output2013\final output\0416 Poisson output1.rtf";

**Convulsion Count as Outcome;
proc genmod data=final.FIVE;
class gender agecat cdcsite/ param=ref;
model Count_Conv = TIVI gender highriskI AgeCat cdcsite
IPV DTaP  VAR  HAV Pediarix PCV13
agecat*TIVI highriskI*TIVI
/type3 dist=poisson link=log pscale;
*The scale parameter was estimated by the square root of Pearson's Chi-Square/DOF;
```

```
      /***to only estimate OR for TIV************************************/
       estimate 'TIV vaccinated vs unvaccinated in agecat=2, highrisk=1' TIVI 1 -1
      HighriskI*TIVI 1 -1 0 0
     Agecat*TIVI  1 -1 0 0 0 0 0 0/exp ;


       estimate 'TIV vaccinated vs unvaccinated in agecat=3, highrisk=1' TIVI 1 -1
     HighriskI*TIVI 1 -1 0 0
     Agecat*TIVI  0 0 1 -1 0 0 0 0 / exp;

        estimate 'TIV vaccinated vs unvaccinated in agecat=4, highrisk=1' TIVI 1 -1
     HighriskI*TIVI 1 -1 0 0
     Agecat*TIVI  0 0 0 0 1 -1 0 0 / exp;

       estimate 'TIV vaccinated vs unvaccinated in agecat=5, highrisk=1' TIVI 1 -1
     HighriskI*TIVI 1 -1 0 0
     Agecat*TIVI  0 0 0 0 0 0 1 -1 / exp;

       estimate 'TIV vaccinated vs unvaccinated in agecat=2, highrisk=0' TIVI 1 -1
      HighriskI*TIVI 0 0 1 -1
     Agecat*TIVI  1 -1 0 0 0 0 0 0 / exp;

       estimate 'TIV vaccinated vs unvaccinated in agecat=3, highrisk=0' TIVI 1 -1
     HighriskI*TIVI 0 0 1 -1
     Agecat*TIVI  0 0 1 -1 0 0 0 0 / exp;

       estimate 'TIV vaccinated vs unvaccinated in agecat=4, highrisk=0' TIVI 1 -1
     HighriskI*TIVI 0 0 1 -1
     Agecat*TIVI  0 0 0 0 1 -1 0 0 / exp;

       estimate 'TIV vaccinated vs unvaccinated in agecat=5, highrisk=0' TIVI 1 -1
     HighriskI*TIVI 0 0 1 -1
     Agecat*TIVI  0 0 0 0 0 0 1 -1 / exp;

       ***to only estimate OR for agecat************************************;
       estimate 'agecat=2 vs Agecat=5' agecat 1 0 0 -1
     Agecat*TIVI  1 1 0 0 0 0 -1 -1 / exp;

       estimate 'agecat=3 vs Agecat=5' agecat 0 1 0 -1
     Agecat*TIVI  0 0 1 1 0 0 -1 -1 / exp;

       estimate 'agecat=4 vs Agecat=5' agecat 0 0 1 -1
     Agecat*TIVI  0 0 0 0 1 1 -1 -1 /exp;

        ***to only estimate OR for highrisk************************************;
       estimate 'Highrisk vs not highrisk' highriskI 1 -1
     HighriskI*TIVI  1 1 -1 -1 / exp;

run;
ods rtf close;



/*********************************;
**Convulsion RATE as Outcome;*/

ods rtf file= "H:\1. Coding\output2013\final output\0416 Poisson output1 PT.rtf";

proc genmod data=final.SIX;
```

```
class gender agecat cdcsite/ param=ref;
model count_conv = TIVI gender highriskI AgeCat cdcsite
IPV DTaP  VAR  HAV Pediarix PCV13  agecat*TIVI highriskI*TIVI
      /type3 dist=poisson link=log pscale;
*The scale parameter was estimated by the square root of Pearson's Chi-Square/DOF;

      /***to only estimate OR for TIV************************************/
      estimate 'TIV vaccinated vs unvaccinated in agecat=2, highrisk=1' TIVI 1 -1
     HighriskI*TIVI 1 -1 0 0
    Agecat*TIVI  1 -1 0 0 0 0 0 0/exp ;


      estimate 'TIV vaccinated vs unvaccinated in agecat=3, highrisk=1' TIVI 1 -1
    HighriskI*TIVI 1 -1 0 0
    Agecat*TIVI  0 0 1 -1 0 0 0 0 / exp;

       estimate 'TIV vaccinated vs unvaccinated in agecat=4, highrisk=1' TIVI 1 -1
    HighriskI*TIVI 1 -1 0 0
    Agecat*TIVI  0 0 0 0 1 -1 0 0 / exp;

      estimate 'TIV vaccinated vs unvaccinated in agecat=5, highrisk=1' TIVI 1 -1
    HighriskI*TIVI 1 -1 0 0
    Agecat*TIVI  0 0 0 0 0 0 1 -1 / exp;

      estimate 'TIV vaccinated vs unvaccinated in agecat=2, highrisk=0' TIVI 1 -1
     HighriskI*TIVI 0 0 1 -1
    Agecat*TIVI  1 -1 0 0 0 0 0 0 / exp;

      estimate 'TIV vaccinated vs unvaccinated in agecat=3, highrisk=0' TIVI 1 -1
    HighriskI*TIVI 0 0 1 -1
    Agecat*TIVI  0 0 1 -1 0 0 0 0 / exp;

      estimate 'TIV vaccinated vs unvaccinated in agecat=4, highrisk=0' TIVI 1 -1
    HighriskI*TIVI 0 0 1 -1
    Agecat*TIVI  0 0 0 0 1 -1 0 0 / exp;

      estimate 'TIV vaccinated vs unvaccinated in agecat=5, highrisk=0' TIVI 1 -1
    HighriskI*TIVI 0 0 1 -1
    Agecat*TIVI  0 0 0 0 0 0 1 -1 / exp;

      ***to only estimate OR for agecat*************************************;
      estimate 'agecat=2 vs Agecat=5' agecat 1 0 0 -1
    Agecat*TIVI  1 1 0 0 0 0 -1 -1 / exp;

      estimate 'agecat=3 vs Agecat=5' agecat 0 1 0 -1
    Agecat*TIVI  0 0 1 1 0 0 -1 -1 / exp;

      estimate 'agecat=4 vs Agecat=5' agecat 0 0 1 -1
    Agecat*TIVI  0 0 0 0 1 1 -1 -1 /exp;

       ***to only estimate OR for highrisk******;
      estimate 'Highrisk vs not highrisk' highriskI 1 -1
    HighriskI*TIVI  1 1 -1 -1 / exp;

run;

ods rtf close;
```

```
*(3)NEGATIVE BINOMIAL*;

ods rtf file= "H:\000. CDC\1. Coding\output2013\final output\0417 NegBin output1.rtf";

**Convulsion Count as Outcome;
proc genmod data=final.FIVE;
class gender agecat cdcsite/ param=ref;
model Count_Conv = TIVI gender highriskI AgeCat cdcsite
IPV DTaP  VAR  HAV Pediarix PCV13
agecat*TIVI highriskI*TIVI
/type3 dist=negbin link=log pscale;

*The scale parameter was estimated by the square root of Pearson's Chi-Square/DOF;

       /***to only estimate OR for TIV*****/
       estimate 'TIV vaccinated vs unvaccinated in agecat=2, highrisk=1' TIVI 1 -1
      HighriskI*TIVI 1 -1 0 0
     Agecat*TIVI  1 -1 0 0 0 0 0 0/exp ;


       estimate 'TIV vaccinated vs unvaccinated in agecat=3, highrisk=1' TIVI 1 -1
     HighriskI*TIVI 1 -1 0 0
     Agecat*TIVI  0 0 1 -1 0 0 0 0 / exp;

        estimate 'TIV vaccinated vs unvaccinated in agecat=4, highrisk=1' TIVI 1 -1
     HighriskI*TIVI 1 -1 0 0
     Agecat*TIVI  0 0 0 0 1 -1 0 0 / exp;

       estimate 'TIV vaccinated vs unvaccinated in agecat=5, highrisk=1' TIVI 1 -1
     HighriskI*TIVI 1 -1 0 0
     Agecat*TIVI  0 0 0 0 0 0 1 -1 / exp;

       estimate 'TIV vaccinated vs unvaccinated in agecat=2, highrisk=0' TIVI 1 -1
      HighriskI*TIVI 0 0 1 -1
     Agecat*TIVI  1 -1 0 0 0 0 0 0 / exp;

       estimate 'TIV vaccinated vs unvaccinated in agecat=3, highrisk=0' TIVI 1 -1
     HighriskI*TIVI 0 0 1 -1
     Agecat*TIVI  0 0 1 -1 0 0 0 0 / exp;

       estimate 'TIV vaccinated vs unvaccinated in agecat=4, highrisk=0' TIVI 1 -1
     HighriskI*TIVI 0 0 1 -1
     Agecat*TIVI  0 0 0 0 1 -1 0 0 / exp;

       estimate 'TIV vaccinated vs unvaccinated in agecat=5, highrisk=0' TIVI 1 -1
     HighriskI*TIVI 0 0 1 -1
     Agecat*TIVI  0 0 0 0 0 0 1 -1 / exp;

       ***to only estimate OR for agecat**************;
       estimate 'agecat=2 vs Agecat=5' agecat 1 0 0 -1
     Agecat*TIVI  1 1 0 0 0 0 -1 -1 / exp;

       estimate 'agecat=3 vs Agecat=5' agecat 0 1 0 -1
     Agecat*TIVI  0 0 1 1 0 0 -1 -1 / exp;

       estimate 'agecat=4 vs Agecat=5' agecat 0 0 1 -1
     Agecat*TIVI  0 0 0 0 1 1 -1 -1 /exp;
```

```
        ***to only estimate OR for highrisk**********;
       estimate 'Highrisk vs not highrisk' highriskI 1 -1
      HighriskI*TIVI  1 1 -1 -1 / exp;

run;
ods rtf close;



**********************************;
**Convulsion RATE as Outcome;
ods rtf file= "H:\000. CDC\1. Coding\output2013\final output\0417 NegBin output1
PT.rtf";

proc genmod data=final.SIX;
class gender agecat cdcsite/ param=ref;
model count_conv = TIVI gender highriskI AgeCat cdcsite
IPV DTaP  VAR  HAV Pediarix PCV13  agecat*TIVI highriskI*TIVI
       / type3 dist=negbin link=log offset=logPT pscale;

*The scale parameter was estimated by the square root of Pearson's Chi-Square/DOF;

       /***to only estimate OR for TIV************************************/
       estimate 'TIV vaccinated vs unvaccinated in agecat=2, highrisk=1' TIVI 1 -1
      HighriskI*TIVI 1 -1 0 0
     Agecat*TIVI  1 -1 0 0 0 0 0 0/exp ;


       estimate 'TIV vaccinated vs unvaccinated in agecat=3, highrisk=1' TIVI 1 -1
     HighriskI*TIVI 1 -1 0 0
     Agecat*TIVI  0 0 1 -1 0 0 0 0 / exp;

        estimate 'TIV vaccinated vs unvaccinated in agecat=4, highrisk=1' TIVI 1 -1
     HighriskI*TIVI 1 -1 0 0
     Agecat*TIVI  0 0 0 0 1 -1 0 0 / exp;

       estimate 'TIV vaccinated vs unvaccinated in agecat=5, highrisk=1' TIVI 1 -1
     HighriskI*TIVI 1 -1 0 0
     Agecat*TIVI  0 0 0 0 0 0 1 -1 / exp;

       estimate 'TIV vaccinated vs unvaccinated in agecat=2, highrisk=0' TIVI 1 -1
      HighriskI*TIVI 0 0 1 -1
     Agecat*TIVI  1 -1 0 0 0 0 0 0 / exp;

       estimate 'TIV vaccinated vs unvaccinated in agecat=3, highrisk=0' TIVI 1 -1
     HighriskI*TIVI 0 0 1 -1
     Agecat*TIVI  0 0 1 -1 0 0 0 0 / exp;

       estimate 'TIV vaccinated vs unvaccinated in agecat=4, highrisk=0' TIVI 1 -1
     HighriskI*TIVI 0 0 1 -1
     Agecat*TIVI  0 0 0 0 1 -1 0 0 / exp;

       estimate 'TIV vaccinated vs unvaccinated in agecat=5, highrisk=0' TIVI 1 -1
     HighriskI*TIVI 0 0 1 -1
     Agecat*TIVI  0 0 0 0 0 0 1 -1 / exp;

       ***to only estimate OR for agecat************************************;
       estimate 'agecat=2 vs Agecat=5' agecat 1 0 0 -1
     Agecat*TIVI  1 1 0 0 0 0 -1 -1 / exp;
```

```
      estimate 'agecat=3 vs Agecat=5' agecat 0 1 0 -1
     Agecat*TIVI  0 0 1 1 0 0 -1 -1 / exp;

      estimate 'agecat=4 vs Agecat=5' agecat 0 0 1 -1
     Agecat*TIVI  0 0 0 0 1 1 -1 -1 /exp;

       ***to only estimate OR for highrisk************************************;
      estimate 'Highrisk vs not highrisk' highriskI 1 -1
     HighriskI*TIVI  1 1 -1 -1 / exp;

run;

ods rtf close;
```

APPENDIX B - R CODE

```
install.packages("lme4")
library(lme4)

install.packages("mgcv")
library(mgcv)


FIVE<-read.csv("H:\\000. CDC\\1. Coding\\Final code\\Final dataset\\FS_FIVE_Age.CSV")

summary(FIVE)
dim(FIVE)

attach(FIVE)

class(AgeM)

FIVE[1,]

## Generalized Additive Model

fit1 <- gam (ConvI~s(AgeM), family=binomial(link="logit"),data=FIVE)
plot(fit1)


fit2 <- gam (ConvI~s(AgeM)+factor(TIVI)+factor(gender)
+factor(HighriskI)+factor(HMO.Site)+AgeM:factor(TIVI),
family=binomial(link="logit"),data=FIVE)

summary(fit2)

plot(fit2)


fit3 <- gam (ConvI~s(AgeM)+factor(TIVI)+factor(gender)
+factor(HighriskI)+factor(HMO.Site)+AgeM:factor(TIVI)+factor(IPV)+factor(DTap)
+factor(VAR) +factor(Pediarix)+factor(PCV13), family=binomial(link="logit"),data=FIVE)

summary(fit3)

plot(fit3)


###Add interaction term

AgeM_TIVI<-AgeM*TIVI
attach(FIVE)

fit4 <- gam (ConvI~s(AgeM)+factor(TIVI)+factor(gender)
+factor(HighriskI)+factor(HMO.Site)+AgeM_TIVI+factor(IPV)+factor(DTaP)
+factor(VAR) +factor(Pediarix)+factor(PCV13), family=binomial(link="logit"),data=FIVE)

plot(fit4,xlab="Age in month", ylab= "LogOR(convulsion)",
 main="Non-linear effect of age on convulsion for all children")
```

```
###Subset FIVE dataset to TIV+ and TIV-

one <- subset(FIVE, TIVI > 0)
two <- subset(FIVE, TIVI < 1)

dim(one)
dim(two)



###When TIV=1
fit5 <- gam (ConvI~s(AgeM)+factor(gender)
+factor(HighriskI)+factor(HMO.Site)+factor(IPV)+factor(DTaP)
+factor(VAR) +factor(Pediarix)+factor(PCV13), family=binomial(link="logit"),data=one)

plot(fit5, xlab="Age in month", ylab= "LogOR(convulsion)",
 main="Non-linear effect of age on convulsion
      for TIV vaccinated children")



###When TIV=0
fit6 <- gam (ConvI~s(AgeM)+factor(gender)
+factor(HighriskI)+factor(HMO.Site)+factor(IPV)+factor(DTaP)
+factor(VAR) +factor(Pediarix)+factor(PCV13), family=binomial(link="logit"),data=two)

plot(fit6, xlab="Age in month", ylab="LogOR(convulsion)",
 main="Non-linear effect of age on convulsion
       for TIV unvaccinated children")
```