A Postmarketing Observational Evaluation of the Safety of FLUENZ in Children and Adolescents with High-risk Conditions

Sponsor Protocol Number:	MI-MA194
Application Number:	Not applicable
Product:	Influenza vaccine (trivalent, live attenuated, nasal)
Sponsor:	MedImmune, LLC, a member of the AstraZeneca Group of Companies One MedImmune Way Gaithersburg, Maryland, 20878, USA

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List of Abbreviations

Abbreviation or Specialized Term	Definition
att	attenuated
ca	cold-adapted
CI	confidence interval
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
GP	general practitioner
GPRD	General Practice Research Database
HES	Hospital Episode Statistics
MAE	medically attended event
MREC	Multi-center Research Ethics Committee
NHS	National Health Service
PSM	Propensity Score Matching
RMP	risk management plan
RR	relative risk
SAE	serious adverse event
SD	standard deviation
TIV	trivalent inactivated influenza vaccine
ts	temperature sensitive
UK	United Kingdom
US	United States
USA	United States of America
VAERS	United States Vaccine Adverse Event Reporting System
WHO	World Health Organization

Study Abstract

TITLE

A Postmarketing Observational Evaluation of the Safety of FLUENZ in Children and Adolescents with High-risk Conditions

OBJECTIVES

The primary objective of this study is to assess the safety of FLUENZ in regard to rates of serious adverse events (SAEs) relative to matched trivalent inactivated influenza vaccine (TIV) recipients, matched unvaccinated controls, and within cohort (a self-controlled analysis) among children 2 to 17 years of age who have high-risk underlying medical conditions.

Secondary objectives of this study are to describe the characteristics of FLUENZ recipients among children 2 to 17 years of age who have high-risk conditions and assess the safety of FLUENZ in this population in regard to rates of medically attended events (MAEs) relative to matched TIV recipients, matched unvaccinated controls, and within cohort (a self-controlled analysis).

STUDY DESIGN

This study will be a Phase 4, multiyear, observational prospective cohort study. The study will begin upon the first availability of FLUENZ in the United Kingdom (UK) and is expected to continue for multiple consecutive influenza seasons. Data will be collected for each subject for 18 months each season (12 months before and 6 months after FLUENZ or TIV receipt [or index date for unvaccinated controls]).

SUBJECT POPULATION

FLUENZ recipients, TIV recipients, and unvaccinated controls will be identified from the General Practice Research Database (GPRD), a large computerized database of anonymised longitudinal medical records from primary care in the UK. FLUENZ recipients will be selected based on receipt of FLUENZ, age 2 to 17 years (prior to 18th birthday) at the time of vaccination and the presence of a high-risk underlying medical condition. Unvaccinated controls will be selected from the pool of individuals during the same month that the reference FLUENZ recipient is vaccinated and include those who do not receive TIV or FLUENZ at any point during that season's vaccination period. Trivalent inactivated influenza vaccine -vaccinated controls will be selected from the pool of individuals who receive TIV during the same month that the reference FLUENZ recipient is vaccinated and do not receive FLUENZ at any point during that season's vaccination period.

TREATMENT REGIMEN

This is an observational study and no treatment will be assigned. Subjects will receive FLUENZ, TIV, or no influenza vaccine as a part of routine care.

ASSESSMENT OF ENDPOINTS

For each influenza season, the proportion of children and adolescents who received FLUENZ, TIV, or no influenza vaccine for each high-risk medical condition will be calculated.

The primary endpoints are the rates of SAEs (all-cause as well as respiratory-related) among FLUENZ recipients relative to controls. An SAE is defined as any event requiring hospitalisation, and will be monitored through both 42 days and 6 months following vaccination. Rates of SAEs will be calculated for analysis cohorts regardless of incidence during the pre-index period. Deaths will also be monitored.

Secondary endpoints are the rates of incident MAEs of interest among FLUENZ recipients relative to controls. An MAE is defined as a coded medical diagnosis made by a health care provider and associated with a medical encounter. Incident MAEs are defined as events in subjects without a record of the same event prior to the index date; hypersensitivity events will be monitored for the 3 days following vaccination, and other acute events of interest will be monitored up to 42 days following vaccination,

Serious adverse events, deaths, and incident MAEs following FLUENZ receipt will be compared to TIV recipients with similar high-risk underlying medical conditions, unvaccinated subjects with similar high-risk underlying medical conditions, and within-cohort. For the within-cohort analysis, FLUENZ recipients will serve as their own controls based on the observation time after vaccination. Risk intervals of 3 days (for hypersensitivity MAEs) and 42 days (for MAEs and SAEs) postvaccination will be compared with control intervals from 4 to 42 days postvaccination (for the 3-day risk interval) and 43 to 84 days postvaccination (for a 0 to 42-day risk interval).

PLANNED ANALYSES

The demographic and clinical characteristics of study patients by study cohort will be described using frequency and percentage distributions for categorical variables. The normally distributed continuous and count variables will be described using a mean (± standard deviation [SD]) and median; in the case of non-normal distribution, interquartile ranges will be used in place of SD. The statistical significance of differences in each group will be tested using Student's t-tests and Wilcoxon Rank-Sum tests for continuous variables that are found to be normally and non-normally distributed, respectively; chi-square tests and Fisher's exact tests will be used to test categorical variables, as appropriate. All statistical tests will be two-sided and performed at the significance level of 0.05, without adjustment of multiple comparisons.

For the primary analysis, a listing of primary diagnoses associated with SAEs by high-risk condition within 42 days and 6 months after the first vaccination will be enumerated and created. Event rates and relative risk (RR) for SAEs will be calculated along with 95% confidence intervals (CIs).

For the secondary analyses of MAEs, a listing of primary diagnoses associated with prespecified MAEs in all subjects within 3 days and 42 days after the first vaccination will be enumerated and created. Event rates and RR will be calculated with exact 95% CIs.

A statistically significant increased risk associated with FLUENZ vaccination will be declared if the lower bound of the exact 95% CI is > 1.00. Likewise, a statistically significant decreased risk associated with FLUENZ vaccination will be declared if the upper bound of the 95% CI was < 1.00. If the control group has zero events, statistical significance will be declared according to the p-value at the significance level of 0.05, if the p-value is available.

SAMPLE SIZE AND POWER CALCULATIONS

Statistical power calculations related to hospitalisations are based on the assumption of a conservative rate of 50 events per 1,000 person-seasons (5% per person-season) in the control groups, as substantiated by a preliminary analysis of GPRD data linked with the Hospital Episode Statistics (HES) database. Enrolment equivalent to 10,000 person-seasons in each arm of the study is planned. After linkage to HES, approximately 4,300 person-seasons should have data regarding hospitalisations available for analysis. As a result, the study has more than 80% statistical power to detect a RR of 1.7 in the SAE rate among FLUENZ recipients during the observation period of 42 days post vaccination, and more than 80% statistical power to detect a RR of 1.3 during the observation period of 6 months post vaccination. For the analysis of MAEs, the sample size of 10,000 person-seasons will be able to rule out with 95% probability the occurrence of an event with the incidence rate of 0.03% (1 in 3,333 person-seasons). The statistical power calculations are based on two-sided Fisher's exact test at the significance level of 0.05.

1 Introduction

1.1 Disease Background

Influenza is a highly contagious, acute febrile illness of global importance. It is the most common vaccine-preventable disease in the developed world. In humans, influenza illness is caused by 2 types of viruses: influenza A, with multiple subtypes categorized by hemagglutinin and neuraminidase surface antigens, and influenza B, which circulates as 2 major antigenic lineages. Subtypes A/H3N2 and A/H1N1 are the 2 influenza A subtypes that have circulated and caused human disease since 1977 (Kilbourne, 2006). Elderly persons, persons with compromised health (due to cardiovascular, respiratory, neurological, or metabolic diseases), persons with conditions or medical treatments resulting in suppressed immune function, and persons living in institutional settings are at increased risk for the development of serious influenza-associated complications (such as pneumonia and respiratory failure) and death. In the European Union (EU), national guidelines have emphasized annual influenza vaccination for persons in these "at-risk" groups as well as their close contacts and health care providers (Rennels and Meissner, 2002; Principi and Esposito, 2004).

Considerable health care system resources are consumed during a typical influenza season. In Europe, outpatient physician visits have been estimated to increase 35% to 100% during influenza seasons, with excess prescriptions for antibiotics in 30% to 40% of patients (Principi et al, 2003; Ploin et al, 2007; Meier et al, 2000). School-aged children, particularly, experience the highest influenza attack rates of any age group, with annual incidence rates reported to range from 23% to 48% (Monto and Sullivan, 1993; Sullivan, 1996; Szucs, 1999; Neuzil et al, 2002). A common influenza-associated complication and an important driver of health care-related costs, especially in children under 3 years of age, is acute otitis media (Heikkinen et al, 2004; Salo et al, 2006). High rates of secondary influenza cases among household members (also associated with excess outpatient physician visits and antibiotic prescriptions) and missed school and work days have been documented (Principi et al, 2003; Carrat et al, 2002; Ploin et al, 2007; ECDC, 2005-2009). These observations in the EU are consistent with those reported in the United States of America (USA) and worldwide (Neuzil et al, 2000; WHO, 2005; Poehling et al, 2006).

Current estimates of the number of excess deaths from seasonal influenza in the EU range up to 40,000 annually, with the combined mortality from influenza in seasonal (interpandemic) years considerably exceeding combined mortality due to pandemic influenza (ECDC, 2005-2009). Influenza-associated deaths in children, while rare, nevertheless represent a substantial proportion of vaccine-preventable deaths in childhood.

Vaccination is considered the most effective method for preventing seasonal influenza illness and its potentially severe complications (WHO 2009; Stephenson et al, 2008). Injectable, trivalent inactivated influenza vaccine (TIV) has been available for decades. In industrialized

countries, its efficacy in protecting healthy adults against clinical disease has been estimated to be ≥ 70%, particularly when there is a good match between strains in the vaccine and the predominant circulating wild-type virus (WHO, 2005). A recent meta-analysis by the Cochrane Collaboration reported that TIV efficacy in children was 59% (Jefferson et al, 2008). The lower efficacy of TIV among children has been attributed to a lack of previous influenza exposure in the youngest children, because immunologic "priming" appears to be required to produce a good response to TIV (Zangwill and Belshe, 2004).

1.2 Description of FLUENZ

FLUENZ™ (influenza vaccine [live attenuated, nasal]) is a live, attenuated trivalent nasally administered vaccine originally licensed in the USA in 2003 (trade name FluMist®) for the prevention of disease caused by influenza A and B viruses contained in the vaccine in eligible children and adolescents 5 to 17 years of age and healthy adults 18 to 49 years of age. In September 2007, the United States Food and Drug Administration (US FDA) approved an expansion of the indication to include children 24 to 59 months of age. In January 2011, FLUENZ was approved for use in the EU in eligible children and adolescents 24 months to less than 18 years of age.

1.2.1 Product Composition

FLUENZ is formulated to contain $10^{6.5\text{-}7.5}$ fluorescent focus units per dose of each of 3 strains (A/H1N1, A/H3N2, and B) of live, attenuated influenza virus reassortants that were propagated in specific pathogen-free hens' eggs. FLUENZ contains no preservatives (eg, thiomersal) and no adjuvants (eg, alum, squalene). The strains in the vaccine are selected annually to comply with the World Health Organization (WHO) recommendation (northern hemisphere) and EU decision for each influenza season. The reassortant influenza virus strains in FLUENZ are: cold-adapted (*ca*) (ie, they replicate efficiently at 25°C, a temperature that is restrictive for replication of many wild-type influenza viruses); temperature sensitive (*ts*) (ie, they are restricted in replication at 37°C [Type B strains] or 39°C [Type A strains], temperatures at which many wild-type influenza viruses grow efficiently); and attenuated (*att*) (ie, they do not produce classic influenza-like illness in the ferret model of human influenza infection). The cumulative effect of the *ca*, *ts*, and *att* phenotypes is that replication of the attenuated vaccine viruses is restricted to the upper respiratory tract, where the vaccine is thought to induce protective humoral, mucosal, and cellular immunity.

1.2.2 Summary of Clinical Experience

The safety and efficacy of FLUENZ have been extensively documented. From 1994 to 2008, a total of 73 clinical and postmarketing studies of the frozen or refrigerated formulations of FLUENZ were conducted. More than 140,000 subjects ranging in age from 7 weeks to 97 years

received FLUENZ in these studies, including individuals with underlying conditions such as chronic respiratory diseases or compromised immune status.

In the paediatric population, FLUENZ has demonstrated superior efficacy relative to TIV in 3 randomized, TIV-controlled studies (Belshe et al, 2007; Ashkenazi et al, 2006; Fleming et al, 2006), and FLUENZ has demonstrated an acceptable safety and tolerability profile among children 2 to 17 years of age. FLUENZ-attributable adverse reactions have generally consisted of transient upper respiratory and constitutional symptoms. In subset analyses in one TIV-controlled comparative study, rates of wheezing after vaccination were increased in FLUENZ recipients 6 to 23 months of age, and rates of hospitalisation for any cause were increased in FLUENZ recipients 6 to 11 months of age (Belshe et al, 2007). An increase in hospitalisations was not observed in children ≥ 12 months of age, and an increase in wheezing was not observed in children ≥ 24 months of age. In a large TIV-controlled comparative study in older children and adolescents with medically treated stable asthma, post vaccination rates of asthma exacerbation and hospitalisation for asthma were similar following either vaccine (Fleming et al, 2006).

More than 40 million doses of the seasonal vaccine and 27 million doses of pandemic live attenuated vaccine have been distributed commercially in the USA from initial licensure in 2003 to the end of the 2010-2011 influenza season, with use predominantly occurring among children. No unexpected safety risks have been identified upon review of data submitted to the US Vaccine Adverse Event Reporting System (VAERS) (Izurieta et al, 2005; Haber et al, 2009; Lee et al, 2011) or in completed and ongoing postmarketing studies conducted in individuals 2 to 49 years of age without high-risk underlying medical conditions (Studies FM025 and MA162).

1.3 Rationale for Study Conduct and Research Hypothesis

FLUENZ was approved for use in the EU in eligible children 2 through 17 years of age in 2011 and is expected to first be available for use in the EU during the 2012-2013 influenza season. FLUENZ was approved with contraindications against use in children and adolescents with hypersensitivity to vaccine components, those receiving salicylate therapy, and those who are clinically immunodeficient due to conditions or immunosuppressive therapy (eg, acute and chronic leukemias, lymphoma, symptomatic human immunodeficiency virus infection, cellular immune deficiencies, and high-dose corticosteroids). Additionally, FLUENZ was approved with warnings against use in children and adolescents with severe asthma or active wheezing and pregnant women. The Summary of Product Characteristics also notes that "Although safety in children and adolescents with mild-to-moderate asthma has been established, data in children with other pulmonary diseases or with chronic cardiovascular, metabolic, or renal diseases are limited. In studies of adults in which a high percentage of individuals had underlying chronic medical conditions, the safety profile of FLUENZ was comparable to the safety profile observed in individuals without these conditions."

As part of the FLUENZ risk management plan (RMP) agreed upon with the European Medicines Agency (EMA), MedImmune committed to conduct an observational study using a pre-existing database to characterize the safety of FLUENZ in regard to rates of specific events of interest in children and adolescents with high-risk conditions at the time of vaccination. It is expected that FLUENZ use will be minimal among children and adolescents for whom there is a contraindication or warning against use (clinical immunodeficiency, salicylate therapy, severe asthma). It is also expected that use of FLUENZ will be limited during the initial seasons of availability and will increase over time; as a result, this study will be conducted over multiple seasons.

Based on the safety profile of FLUENZ in older adults with underlying chronic medical conditions (De Villiers et al, 2010; Forrest et al, 2011), the research hypothesis is that FLUENZ will not be associated with increased rates of hospitalisation or medically attended events (MAEs) in children and adolescents with underlying chronic medical conditions.

1.4 Benefit-risk and Ethical Assessment

This study is observational and noninterventional. The study will not involve any risks to subjects.

2 Study Objectives

The primary objective is to assess the safety of FLUENZ in regard to rates of serious adverse events (SAEs) requiring hospitalisation, relative to matched TIV recipients, matched unvaccinated controls, and within cohort (a self-controlled analysis) among children 2 to 17 years of age who have high-risk underlying medical conditions.

Secondary objectives are to describe the characteristics of FLUENZ recipients among children 2 to 17 years of age who have high-risk conditions and assess the safety of FLUENZ in this population in regard to rates of MAEs relative to matched TIV recipients, matched unvaccinated controls, and within cohort (a self-controlled analysis).

3 Study Design

3.1 Overview of Study Design

Study MI-MA194 will be a Phase 4, multiyear, observational prospective cohort study to assess the use and safety of FLUENZ among children and adolescents 2 through 17 years of age (up until 18th birthday) with high-risk underlying medical conditions that predispose to complications of influenza. Children and adolescents who receive FLUENZ and their controls will be identified from the General Practice Research Database (GPRD) in the United Kingdom (UK).

To date, no unexpected safety risks have been identified from data submitted to the US VAERS (Izurieta et al, 2005; Haber et al, 2009) or in completed and ongoing postmarketing studies conducted in individuals 2 to 49 years of age without high-risk underlying medical conditions (Studies FM025 and MA162). The purpose of this study is to test the hypothesis that rates of hospitalisations, deaths, and MAEs will be similar in FLUENZ patients when compared to multiple control groups. A secondary purpose of this study is to collect information regarding the use of FLUENZ in the studied population. The study will be implemented in 2 stages. Stage 1, conducted using data from the first season of FLUENZ availability, will be a feasibility study that will allow optimization of the study design and analysis plan. Stage 2, the full study, will be conducted using data from multiple seasons of FLUENZ availability, including data from the first season.

3.2 General Practice Research Database Data

Data will be derived from the GPRD, one of the world's largest computerized databases of anonymised longitudinal medical records from primary care that is linked with other healthcare data. Currently, data are being collected on approximately 5 million active patients of research standard from approximately 625 primary care practices throughout the UK. Patients enrolled in participating practices are representative of the UK with regard to age, sex, geographic distribution, and annual turnover rate, and cover approximately 8% of the population. General practitioners (GPs) have been trained to record medical information including demographic data, medical diagnoses, hospitalisations, deaths, drug prescriptions, and vaccines using standard software and standard coding systems. The GPs generate prescriptions directly with the computer, and this information is automatically transcribed into the computer record. It contains the name of the preparation, instructions for use, route of administration, dose, and number of tablets for each prescription. Additionally, the GPRD holds information regarding lifestyle variables such as body mass index, smoking, and alcohol consumption. The GPRD has been used for multiple previous pharmacovigilance studies, including several that evaluated the safety of vaccines including TIV (Andrews et al, 2001; Smeeth et al, 2001; Stowe et al, 2006; Tata et al, 2003).

3.3 Study Setting

The GPRD contains detailed medical information on primary care patients in the UK, anonymised and collected directly from computerized GP records. Practices participating in the GPRD are remunerated for recording data on clinical diagnoses, test results, prescriptions, and referral data. Clinical data are captured using Read codes, which are widely used in British primary care. Each practice is issued a set of GPRD recording guidelines, describing how to record all significant morbidity events in each patient's medical history (Medicines and Healthcare products Regulatory Agency, 2004).

The raw data provided from each practice undergo extensive quality control and validity checks by a research team based at the Medicines and Healthcare products Regulatory Agency before release. These data are assessed by an 'up to standard' audit, confirming data recording in several key areas. Practices meeting this standard are included in the GPRD data warehouse. Patient-level data are also assessed, with patients considered 'acceptable' for inclusion in the GPRD if recorded details are internally consistent in 4 areas: age, sex, registration details, and event recording (Medicines and Healthcare products Regulatory Agency, 2007).

3.4 Estimated Duration of Subject Participation

The study will begin upon the first availability of FLUENZ in the UK and is expected to continue for multiple consecutive influenza seasons. Data will be collected for each subject for 12 months prior to and 6 months after FLUENZ or TIV receipt (or index date for unvaccinated controls).

3.5 Study-stopping Criteria

The study will be concluded with enrolment of at least 10,000 FLUENZ person-seasons.

3.6 Study Periods

The observational study will consist of 3 study periods.

1) Preindex period – The preindex period is defined as 12 months prior to (and not including) the index date. During this period, healthcare utilisation and comorbidities will be identified.
2) Index date – The index date for each subject is defined as the date with evidence of the first administration of FLUENZ, TIV, or the date of vaccination of the reference FLUENZ recipient for matched unvaccinated controls. Patient characteristics and demographics will be recorded on the index date. FLUENZ recipients and their controls will be identified between 01Sep and 30Apr of each season, which is the period during which the vast majority of influenza vaccinations are administered, as verified for the 2007-2008 and 2008-2009 seasons.
3) Follow-up period – The follow-up period will be defined as 6 months post index date (not including index date). Safety outcomes will be recorded and evaluated during this period.

3.7 Rationale for Study Design and Control Groups

Study MI-MA194 will utilise routinely collected data from a large sample of general practitioners to describe the real-world utilisation of FLUENZ in the UK among children and adolescents 2 to 17 years of age with high-risk underlying medical conditions. As of 10Jun2010, the GPRD was actively collecting information on 615,271 children and adolescents 2 to 17 years of age. Use of the GPRD ensures that FLUENZ utilisation and safety outcomes following vaccination reflect the real-world utilisation of FLUENZ. The size of the database also permits an assessment of rare events following vaccination as well as assessment of the safety of

FLUENZ in children and adolescents with multiple rare medical conditions, neither of which would be feasible in a prospective clinical study.

Consistent with current vaccine safety monitoring practices (Andrews, 2002; Yih et al, 2011), previous post-authorization safety studies of FLUENZ (Studies FM025 and MI-MA162) required by the US FDA have utilised a similar multiyear, observational prospective cohort design. In those studies, the incidence of MAEs following FLUENZ receipt was compared to 3 matched control groups: TIV recipients with similar high-risk underlying medical conditions, unvaccinated children and adolescents with similar high-risk underlying medical conditions, and a self-control based on the incidence of events in 2 time intervals following vaccination. Based on EU recommendations that children 2 to 17 years of age with high-risk medical conditions be vaccinated annually against influenza, it is anticipated that a significant number of TIV controls will be available for analysis. However, because influenza vaccination rates in this population are suboptimal (Blank et al, 2009), a significant number of unvaccinated controls will also be available for analysis.

FLUENZ recipients, TIV recipients, and unvaccinated children and adolescents will differ in multiple underlying characteristics, such as health-seeking behavior, health status, and various demographic and socioeconomic factors. The use of a within-cohort self-control helps to eliminate many of these differences (Farrington et al, 1996; Yih et al, 2011; Andrews, 2002). However, there are temporal differences inherent in the self-control comparison and an assessment of events many months following vaccination is not feasible with self-control comparisons (Andrews, 2002). As a result, comparisons of FLUENZ recipients to TIV recipients and unvaccinated individuals are also beneficial. To help reduce confounding due to differences between FLUENZ recipients, TIV recipients, and unvaccinated children, controls will be matched to FLUENZ recipients on the specific high-risk medical condition, age, calendar date, and healthcare utilisation in the past 12 months. However, even after matching for these factors, it is likely that differences between FLUENZ recipients and TIV and unvaccinated control groups will remain. The use of 3 control groups (TIV recipient controls, unvaccinated controls, and a within-cohort control) helps to ensure that events observed with increased frequency among FLUENZ recipients are not due to underlying population differences, as true large risk elevations resulting from FLUENZ receipt should be detectable in comparison with all 3 control groups.

4 Study Procedures

4.1 Subject Participation and Identification

FLUENZ recipients, TIV controls, and unvaccinated controls will be identified anonymously through the GPRD. As all information will be de-identified, no informed consent is required, in accordance with standard practice for GPRD analyses.

For the purposes of analysis, only the first vaccination of each influenza season will be evaluated and considered the index treatment, as the rate of receipt of 2 doses in a single season (which is recommended for previously unvaccinated children) is low. Use of data following the first vaccination avoids double-counting subjects in the same influenza season and eliminates any bias that could result from differential rates of second dose receipt between vaccine groups. Additionally, the 6-month observation interval will collect information on events occurring following any second vaccinations. Subjects revaccinated with either FLUENZ or TIV in subsequent influenza seasons will be included in the analysis for that corresponding season and counted as contributing an additional person-season; cohort assignment will be based on the current season's vaccination. As subjects will be enrolled on a per-season basis, the targeted enrolment for the study will be 10,000 FLUENZ person-seasons.

4.2 Subject Selection

FLUENZ recipients within a specific season will be selected based on receipt of FLUENZ, age 2 to 17 years (prior to 18th birthday) at the time of vaccination and the presence of a high-risk underlying medical condition (see inclusion criteria). Unvaccinated controls will be selected from the pool of individuals within the GPRD during the same month that the reference FLUENZ recipient is vaccinated and include those who do not receive TIV or FLUENZ at any point during that season's vaccination period. All TIV-vaccinated controls will be selected from the pool of individuals who receive TIV during the same month that the reference FLUENZ recipient is vaccinated and have no record of FLUENZ vaccination at any point during that season's vaccination period. To the extent possible, FLUENZ recipients will be matched 1:1 with each of TIV and unvaccinated controls based on the characteristics listed below.

- Specific high-risk underlying medical condition
    - For individuals with asthma, matching will also be based on asthma medication use in the prior 12 months as a surrogate for disease severity.
- Age
- Date (month) of vaccination (FLUENZ and TIV recipients)
- Healthcare utilisation in the previous 12 months (hospitalisations and outpatient visits)
- Geographic location

Due to the low prevalence of some high-risk conditions, matching on all parameters may not be possible; in those instances, the best available match will be utilised. FLUENZ recipients and controls with multiple high-risk medical conditions will be classified by the most severe condition. The matching process may be refined during Stage 1 of the study.

4.2.1 Inclusion Criteria

Subjects must meet all of the following criteria:

1) Age 2 through 17 years (prior to 18th birthday) of age at date of vaccination or index date

2) Evidence of a diagnosis of at least one of the following high-risk underlying medical conditions (Daley et al, 2004):
   - Asthma
   - Cystic fibrosis
   - Congenital lung abnormalities
   - Heart disease (significant congenital, valvular, and/or rheumatic heart disease)
   - Renal disease (glomerulonephritis, chronic or congenital kidney disease)
   - Sickle cell anemia
   - White blood cell disorders
   - Immunosuppressive disorders (excluding malignancy)
   - Malignancy
   - Diabetes mellitus
   - Lipid metabolism disorders
   - Cerebral palsy
   - Down syndrome
   - Any medical condition being treated with chronic aspirin therapy
   - Pregnancy
3) At least 18 months of continuous follow-up in the GPRD, with at least 12 months before and 6 months after vaccination (or index date for unvaccinated controls)

4.2.2 Exclusion Criteria

No exclusion criteria will be applied.

4.2.3 Replacement of Subjects

Not applicable

4.3 Treatment Assignment

This is an observational study and no treatment will be assigned. Subjects will receive FLUENZ, TIV, or no influenza vaccine as a part of routine care.

4.4 Blinding

Not applicable

4.5 Study Completion

Subjects will be observed for 6 months following each influenza vaccination (or index date for unvaccinated controls).

4.6 End of the Study

The study will conclude after enrolment of at least 10,000 FLUENZ person-seasons. Approximately 15,000 children 2 to 17 years of age with high-risk conditions identified in GPRD had evidence of receiving an influenza vaccination during the 2007-2008 and 2008-2009 seasons, for an estimated vaccination rate of approximately 13%. During 2009-2010, the number with evidence of receiving an influenza vaccination increased to approximately 28,000 (26%), likely as a result of the response to the 2009 H1N1 pandemic. As a result, there is uncertainty in projecting the number of high-risk children who will be vaccinated against influenza in future seasons. Based on a conservative estimate of 15,000 children and adolescents vaccinated against influenza each season, study enrolment would conclude after 3 influenza seasons if on average during those seasons 22% of vaccinated children and adolescents receive FLUENZ. It is expected that utilisation of FLUENZ will be low in the first seasons of availability and increase in subsequent seasons.

4.7 Schedule of Study Procedures

Cumulative data from the GPRD will be available for analysis each year approximately 6 months after the follow-up period for the last-identified subject of a particular season. The GPRD has an ongoing rolling collection process that is managed electronically. Incremental downloads are collected from practices approximately every 6 to 8 weeks. A static monthly snapshot of the data is then generated for research purposes. The length of the "fringe" or most recent period of calendar time for which the data may be changing due to the addition of new records or the GPs changing records is between 3 and 6 months. As a result, after QC and adjudication, final GPRD data is available 6 months following the time point of interest. Given that the vaccination period for each season concludes on 30Apr and subject follow-up is for 6 months following the index date, it is anticipated that data will be available for analysis 12 months following each influenza season.

5 Study Measures

5.1 Patient Demographics and Baseline Characteristics

Baseline patient demographic and clinical characteristics will be based on data collected at the time of the physician visit and reported for the FLUENZ, matched TIV, and matched unvaccinated cohorts. These data will include:

1) Demographic characteristics on index date
   - Age group (years): 2-4, 5–8, 9–17 years of age
   - Gender
   - Geographic location
2) Clinical characteristics leading up to index date
   - Number of office visits

- Number of hospitalisations
- Number of previous influenza vaccinations
- Tobacco status: Y (smoker); N (never smoked); D (ex-smoker)
- Alcohol status: Y (currently drinks); N (lifelong teetotaller); D (ex-drinker)
- High-risk medical conditions
- For subjects with a diagnosis of asthma, use of asthma medications in the last 12 months

5.2 Assessment of Safety Measures

An MAE is defined as a coded medical diagnosis made by a health care provider and associated with a medical encounter. One or more MAEs could be assigned for a single encounter. Consistent with previous studies (Lee et al, 2011), only incident MAEs will be evaluated, defined as events in subjects without a record of the same event prior to the index date. For patients who experience an MAE, narratives will be reported and will include to the extent feasible information from GP records that describe the subject's medical history. Serious adverse events, defined as any event requiring hospitalisation, will be identified for up to 6 months post vaccination. Hospitalisation for elective surgery related to a preexisting condition will not be considered an SAE. Rates of SAEs will be calculated for analysis cohorts regardless of incidence during the pre-index period.

MAEs of interest are identified in Table 5.2-1, consistent with the FLUENZ RMP, as agreed upon by the EMA as of 21Oct2010. Because of the low frequency of the specific MAEs and deaths and the low prevalence of many of the specific high-risk conditions, rate and relative risk (RR) comparisons will be conducted for the entire study population: all children and adolescents identified with high-risk medical conditions and their respective controls. Because all-cause and lower respiratory SAEs are more common, these events will be analyzed overall and for each high-risk condition separately. However, it is anticipated that the low prevalence of many high-risk conditions will permit descriptive analyses only. Subjects with more than one underlying condition will be analyzed in each cohort for this analysis.

Table 5.2-1 Serious Adverse Events and Medically Attended Events of Special Interest and Corresponding Risk Periods for Prespecified MAE Analysis

Event(s)	Period(s)	Analysis Population	Comparison Groups		
			Within-cohort	Matched Concurrent Controls	
				Unvaccinated	TIV
Any SAE Lower respiratory [a] SAEs	42 days	All subjects and each condition	Rates and RR	Rates and RR	Rates and RR
Any SAE Lower respiratory [a] SAEs	6 months	All subjects and each condition	NA	Rates and RR	Rates and RR
Hypersensitivity MAEs [b]	3 days	All subjects	Rates and RR	Rates and RR	Rates and RR
Guillain-Barre syndrome MAEs [b] Bell's palsy MAEs [b] Seizures/convulsions MAEs [b] Encephalitis MAEs [b] Neuritis MAEs [b] Vasculitis MAEs [b]	42 days	All subjects	Rates and RR	Rates and RR	Rates and RR
Deaths [b]	6 months	All subjects	NA	Rates and RR	Rates and RR

MAE = medically attended event; NA = not applicable; RR = relative risk; SAE = serious adverse event; TIV = trivalent inactivated vaccine

[a] Lower respiratory events are those associated with diagnoses of asthma, croup, wheezing, bronchiolitis, pneumonia, or acute respiratory failure.

[b] Narratives will be included in the final study report; to the extent feasible, narratives will describe patient characteristics and clinical history leading up to the adverse event such as date of adverse event, age, gender, medication history, and other characteristics where available.

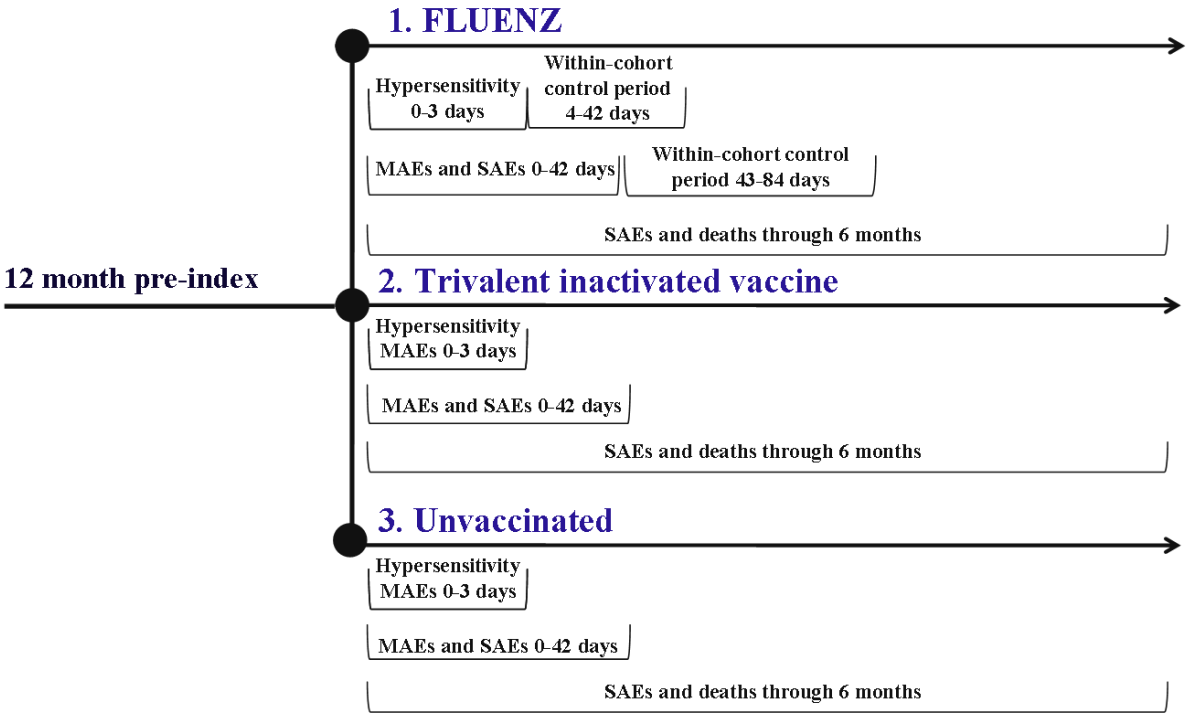

Figure 5.2-1 Study Flow Diagram and SAE/MAE Monitoring Intervals

MAE = medically attended event; SAE = serious adverse event

Events will be monitored during various intervals following vaccination, as indicated by the known pathogenesis of the event. Hypersensitivity events will be monitored for the 3 days following vaccination, other acute events of interest will be monitored up to 42 days following vaccination, serious events resulting in hospitalisation will be monitored through both 42 days and 6 months following vaccination, and deaths will be monitored through 6 months following vaccination. If a child has more than one medical claim with the same diagnosis code for a given hospitalisation, that diagnosis will be counted only once for that hospital stay.

For the within-cohort analysis, FLUENZ recipients will serve as their own controls based on the observation time after vaccination. Risk intervals of 3 and 42 days postvaccination will be compared with control intervals from 4 to 42 days postvaccination (for the 3-day risk interval) and 43 to 84 days postvaccination (for a 0–42-day risk interval). Use of a postvaccination reference interval avoids the introduction of bias due to the "healthy vaccinee effect" that can arise from use of a prevaccination reference interval. Specifically, individuals who are vaccinated are more likely to have recent good health because vaccination is not recommended in the presence of concurrent illness (eg, fever). As a result, prevaccination reference periods will have a lower incidence of adverse events and comparisons of postvaccination and prevaccination periods are biased toward demonstrating increased rates of adverse events post-vaccination (Virtanen et al, 2000; Jackson et al, 2006). For this reason, immediate prevaccination reference periods are generally avoided in within-cohort analyses of vaccine safety. The use of a postvaccination reference period in close temporal association with the postvaccination risk period (eg, 0-42 vs 43-84 days postvaccination) helps to minimize other potential confounders

that arise from temporal differences in the 2 periods (eg, subject age and seasonal circulation of respiratory viruses).

6 Statistical Considerations

6.1 General Considerations

Data will be provided in data listings sorted by treatment group and subject number. Tabular summaries will be presented by treatment group. Categorical data will be summarized by the number and percentage of subjects in each category. Continuous variables will be summarized by descriptive statistics, including mean, standard deviation, median, minimum, and maximum. Confidence intervals (CIs) will be two-sided, unless otherwise stated.

6.2 Endpoints

For each influenza season, the proportion of children and adolescents 2 to 17 years of age in the GPRD who received FLUENZ, TIV, or no influenza vaccine for each high-risk medical condition will be calculated. The primary endpoints are the rates of SAEs (all-cause as well as respiratory-related) among FLUENZ recipients relative to controls. Rates of SAEs will be calculated for analysis cohorts regardless of incidence during the pre-index period. Deaths will also be monitored. Secondary endpoints are the rates of incident MAEs of interest among FLUENZ recipients relative to controls. Incident MAEs are defined as events in subjects without a record of the same event prior to the index date.

6.3 Planned Analyses

Annual reports will be generated, consisting of listings and counts of the events of interest by cohort. A final study report, which will include RR calculations, will be generated once study enrolment is complete and cumulative analyses have been conducted.

The demographic and clinical characteristics of study patients, broken down by study cohort (FLUENZ, TIV, and unvaccinated), will be described using frequency and percentage distributions for categorical variables. The normally distributed continuous and count variables will be described using a mean (standard deviation [SD]) and median; in the case of non-normal distribution, following demonstration by the Shapiro-Wilk test, interquartile ranges will be used in place of SD. The statistical significance of differences in the characteristics of patients in each group will be tested using Student’s t-tests and Wilcoxon Rank-Sum tests for continuous variables that are found to be normally and non-normally distributed, respectively; chi-square tests and Fisher’s exact tests will be used to test categorical variables, as appropriate. All statistical tests will be two-sided and performed at the significance level of 0.05, without adjustment for multiple comparisons.

For evaluating the safety of FLUENZ during the influenza season, the following descriptive approach will be applied to summarize events potentially related to the medical conditions and known safety profile of FLUENZ among specific populations:

- For the primary endpoint analysis, a listing of primary diagnoses will be enumerated and associated with SAEs by high-risk conditions within 42 days and 6 months after the first vaccination. Hospitalisation rates will be defined as the number of unique subjects each season with at least one hospitalisation divided by the number of person-seasons.
- For the secondary endpoint analyses of MAEs, a listing of primary diagnoses will be enumerated and associated with prespecified MAEs in all subjects within 3 days and 42 days after the first vaccination as outlined in Table 5.2-1. The rate of MAEs will be defined by the number of unique subjects each season experiencing the MAE divided by the number of person-seasons.

Incidence rates will be reported as subjects with event per 100 person-seasons and exact 95% CIs will be calculated. If a subject has more than one event in the analysis window, the subject will be counted only once for the analysis. Relative risks and corresponding exact 95% CIs will be constructed for safety comparisons with control groups. The RR and 95% CI will be derived from the raw incidence rates without adjustment of any covariate. Multivariate analysis may be explored for the safety comparisons to control for potential confounders other than the matching factors.

A statistically significant increased risk associated with FLUENZ vaccination will be declared if the lower bound of the exact 95% CI is > 1.00. Likewise, a statistically significant decreased risk associated with FLUENZ vaccination will be declared if the upper bound of the 95% CI was < 1.00. Statistical significance will be determined before rounding. The corresponding p-values will be also provided. If any control group has zero events, corresponding RR will not be estimable due to a zero value of the denominator. If the p-value is available, statistical significance will be declared according to the p-value at the significance level of 0.05.

Within-cohort analyses will be performed within the FLUENZ recipient cohort. In the analyses using within-cohort controls, “risk” periods of Days 0 to 3 and Days 0 to 42 postvaccination will be compared to “reference” observation time occurring after the respective risk periods, ie, Days 4 to 42 for the risk period of Days 0 to 3 and Days 43 to 84 for the risk period of Days 0 to 42. Incidence rate ratios will be obtained for the 0-3 and 0-42 day periods.

All analyses will be conducted using SAS version 9.1 (SAS Institute Inc., Cary, North Carolina, USA).

6.4 Sample Size and Power Calculations

A preliminary analysis, linking the GPRD with the UK’s National Health Service (NHS) Hospital Episode Statistics (HES) database, estimated that the rate of all-cause hospitalisation 42 days and 6 months from 15Oct2009 among children 2 to 17 years with asthma ranged from 48 to 70 events per 1,000 person-seasons. Children and adolescents with asthma were considered

appropriate for estimating sample size as children with asthma account for approximately 85% of all children with high-risk conditions. Only a subset of GPRD subjects can be linked to the HES database because the HES database does not collect information on subjects in the UK outside of England and some subjects or practices may not consent to HES linkage. In the analysis described above, 43% of subjects in the GPRD could be linked to the HES database.

Statistical power calculations related to hospitalisations are based on the assumption of a conservative rate of 50 events per 1,000 person-seasons (5% per person-season) in the control groups. Enrolment equivalent to 10,000 person-seasons in each arm of the study is planned. After linkage to HES, approximately 4,300 person-seasons should have data regarding hospitalisations available for analysis. As a result, the study has more than 80% statistical power to detect a RR of 1.7 in the rate of hospitalisation among FLUENZ recipients during the observation period of 42 days post vaccination, and more than 80% statistical power to detect a RR of 1.3 during the observation period of 6 months post vaccination.

For the analysis of MAEs, the sample size of 10,000 person-seasons will be able to rule out with 95% probability the occurrence of an event with an incidence rate of 0.03% (1 in 3,333 person-seasons). The study will also provide more than 80% power to observe a statistically significant RR of 2.2 for events with an incidence rate of 0.2% (1 in 500 subjects) in the comparison group, respectively.

The statistical power calculations are based on two-sided Fisher's exact test at the significance level of 0.05.

6.5 Propensity Score

Dependent upon the direct matching success rate and available patients for analysis, an alternative matching methodology may be applied to better adjust for potential confounders. Prior related research has successfully used the Propensity Score Matching (PSM) approach, which can be defined as the conditional probability of receiving a particular treatment given the specified covariates of interest by balancing the covariates in the treatment and control groups (Rosenbaum and Rubin, 1983; Rosenbaum and Rubin, 1984; Rubin, 1980). The advantage of the PSM approach is that the outcome corresponds to a "quasi-randomized" experiment, as for each patient a propensity score is calculated by running a logistic regression incorporating multivariate information of all relevant covariates. This means that for each FLUENZ patient stratum, the best "twin" out of the control group is determined and used to to analyze the pure treatment effect of being treated with FLUENZ vs TIV.

If utilised, propensity scores will be estimated using 2 generalized linear mixed models with a logit link function and a binomial distribution. These scores will represent the propensity of initiating FLUENZ vs TIV (or FLUENZ vs no vaccination) on the index date given the set of select baseline variables (during the pre-index period and on the index date). Once the predictive model is developed, it can be used to generate a probability for each subject indicating the

likelihood of the subject being in his/her observed exposure group (in this case, receiving vaccination with FLUENZ), based on his/her observed baseline characteristics. For example, if a simple model can predict exposure assignment based on age only, then younger patients are more likely to get vaccination than healthy adult patients; this predicted probability is called the propensity score.

The propensity model will be stratified to require an exact match on the underlying medical condition. Within condition, the propensity model will initially be fit with the following predictors:

- Date (month and year) of vaccination (FLUENZ and TIV recipients)
- Age
- Gender
- Healthcare utilisation in the 12 months before index date
  - (a) Number of office visits (0-1, 2-4, 5 or more)
  - (b) Number of hospitalisations (0, 1 or more)
- Geographic location

Predictors will be removed from each model by backward elimination, using 2 successive thresholds. First, all predictors with a p-value < 0.15 will be removed from the model, and the reduced model will be fit iteratively, until all remaining predictors have $p < 0.15$. Second, the threshold will be lowered to $p < 0.05$, so that the final model includes only predictors with $p < 0.05$. Reduced models will be discarded, and a reduced form of exact matching will be implemented, if the final reduced model contains fewer than 3 significant predictors of propensity to receive FLUENZ.

There are many approaches by which propensity scores can be used to adjust for imbalances (Kurth et al, 2006). These approaches include propensity score matching, stratification, regression, and weighting. In the first approach, the score is used to match subjects from the groups of interest under the premise that 2 patients with the same score are likely to be interchangeable in terms of their exposure assignment (ie, the patient could have received either treatment). Matching will be attempted for both comparisons (FLUENZ vs TIV and FLUENZ vs unvaccinated) using "nearest neighbor" matching, with 0.05 as the maximum allowable difference in propensity scores (ie, a maximum propensity difference of 5 percent points). If the nearest-neighbor matching protocol finds matches for fewer than 85% of eligible FLUENZ patients, then the propensity score will instead be used to create strata for each propensity quintile (0-20%, > 20-40%, > 40-60%, > 60-80%, > 80%-100%), and RRs will be estimated using stratified log-binomial regressions, or log-Poisson regressions with Sandwich error estimation if the log-binomial regression fails to converge (Zou, 2004).

7 Study Limitations

As with any database study, there are limitations to be considered when interpreting data analyzed from the GPRD database. Findings from the study are fully generalisable only to office-based physicians and results may not be representative of all primary-care physicians in the country. The GPRD contains GP physician records; patients treated outside of the office-based setting will not be captured in this analysis and all data are subject to GP recording errors. However, as described in a systematic review (Khan et al, 2010), diagnoses coded in the GPRD electronic record were well recorded when compared against GP questionnaire responses, medical records held at the GP practice, or hospital letters. When the verification standard was GP confirmation, studies have estimated high positive predictive values for acute conditions coded in the GPRD. In a few studies, low positive predictive values have been demonstrated for select acute conditions, but these findings can be attributed to the strict diagnostic criteria required for case confirmation. Studies have shown that the GPRD captures 96% of all GP visits.

To the extent possible, confounders will be controlled for by means of matching; however, not all prescriber and patient bias can be eliminated from the analysis by this method. Due to selection criteria based on the criterion for 18 months of continuous enrolment, some patients who do not meet the postindex continuous enrolment criterion due to unavailable data will not be included in the analysis. The study will employ time periods to reflect the time interval in which the vast majority of high-risk patients are vaccinated, and patients who are vaccinated outside of the predefined window will not be captured for analysis.

8 Ethics

This study is an observational database study and will be conducted using records without any personal identifiers and without direct patient involvement. No treatment will be assigned; subjects will receive FLUENZ, TIV, or no influenza vaccine as a part of routine care.

The GPRD has gained ethics, scientific, and confidentiality approval to enable record linkage of GPRD data with other healthcare datasets via the patient's NHS number, sex, date of birth and Post Code. The linkage is done by an external NHS group in a way that the GPRD does not see the identifying details. The additional data are returned using the GPRD anonymised research level identifier.

The GPRD Group has obtained ethical approval from a Multi-center Research Ethics Committee for all purely observational research using GPRD data; namely studies which do not include patient involvement. The GPRD Independent Scientific Advisory Committee will review this protocol for scientific quality and may recommend that study-specific MREC approval be sought if ethical issues arise.

9 Dissemination of Results

Annual reports will be provided to the EMA. The final results of the study will be submitted for publication in a peer-reviewed scientific journal. Any publications by study investigators of any data from this study must be carried out in accordance with the clinical study agreement.

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