# SENTINEL METHODS WHITE PAPER

# EXPLORING THE FEASIBILITY OF CONDUCTING VACCINE EFFECTIVENESS STUDIES IN SENTINEL'S PRISM PROGRAM

**Prepared by:** Catherine A. Panozzo, MPH, PhD,[1] Maria Said, MD, MHS,[2] Deepa Arya, MD, MPH, MBA[2] Roger Baxter, MD,[3] Elizabeth C. Dee, MPH,[1] Kevin Fahey,MA,[4] Sandra Feibelmann, MPH,[1] Bruce Fireman, MA,[3] Richard A. Forshee, PhD,[2] Hector Izurieta, MD,MPH,[2] Lisa Jackson, MD, MPH,[5] Nicola Klein, MD, PhD,[3] Yun Lu, PhD,[2] David Menschik, MD,MPH,[2] James Nordin, MD, MPH,[6] Douglas Pratt, MD,[2] Carla Rodriguez, MPH, PhD,[7] Nandini Selvam, MPH, PhD,[8] Azadeh Shoaibi, MS, MHS,[2] Meghan Baker, MD, ScD[1]

**Author Affiliations:** 1.Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA 2.Center for Biologics Evaluation and Research, US Food and Drug Administration, Silver Spring, MD 3.Kaiser Permanente Northern California Division of Research, Oakland, CA 4.America's Health Insurance Plans, Inc., Washington, D.C. 5.Kaiser Permanente Washington, Seattle, WA 6.Health Partners Institute for Education and Research, Minneapolis, MN 7.Mid-Atlantic Kaiser Permanente Research Institute, Rockville, MD 8.HealthCore, Inc., Alexandria, VA

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The Sentinel System is sponsored by the U.S. Food and Drug Administration (FDA) to proactively monitor the safety of FDA-regulated medical products and complements other existing FDA safety surveillance capabilities. The Sentinel System is one piece of FDA's Sentinel Initiative, a long-term, multi-faceted effort to develop a national electronic system. Sentinel Collaborators include Data and Academic Partners that provide access to healthcare data and ongoing scientific, technical, methodological, and organizational expertise. The Sentinel Coordinating Center is funded by the FDA through the Department of Health and Human Services (HHS) Contract number HHSF223201400030I.

# Sentinel White Paper

# Exploring the Feasibility of Conducting Vaccine Effectiveness Studies in Sentinel's PRISM Program

## Table of Contents

# I. EXECUTIVE SUMMARY

The Post-licensure Rapid Immunization Safety Monitoring (PRISM) program, a component of the Food and Drug Administration's Sentinel System, was developed to monitor vaccine safety, but has never been used to assess vaccine effectiveness. This work evaluates the feasibility of using available data elements, existing programming tools, and major study designs to conduct vaccine effectiveness assessments in PRISM. While PRISM cannot address all questions of potential interest (e.g., questions requiring lengthy follow-up time), it has several features, including the ability to conduct analyses in a large, geographically diverse population and the possibility of chart validation, that could make the examination of certain questions about vaccine effectiveness possible.

# II. INTRODUCTION

The Post-licensure Rapid Immunization Safety Monitoring (PRISM) program, initiated in 2009 by the Department of Health and Human Services in response to the need to monitor the safety of the H1N1 influenza vaccine, has developed into the immunization safety monitoring component of the Food and Drug Administration's (FDA) Sentinel System ("Sentinel"). The Sentinel System uses a large distributed data infrastructure created to actively monitor the safety of medical products using electronic health information [1,2]. The PRISM database, which is comprised of health information from a subset of Sentinel Data Partners, has been used to evaluate vaccine safety using administrative claims data captured as part of health system encounters. An evaluation of the risk of intussusception after rotavirus vaccine in PRISM led to a change in the prescribing information and safety communications [3,4]. Two other assessments in PRISM contributed to public safety risk communications: an evaluation of the risk of febrile seizures after the influenza vaccine [5,6] and an assessment of venous thromboembolism after the quadrivalent human papillomavirus vaccine [7,8]. The purpose of this report is to evaluate the suitability of using PRISM to estimate vaccine effectiveness.

Vaccine effectiveness may be defined as a measure of how well a vaccine reduces incidence of disease in a population under ordinary real-world conditions. Thus, vaccine effectiveness is usually evaluated after a vaccine is licensed and marketed, using observational study designs. In contrast, vaccine efficacy usually refers to a measure of how well a vaccine reduces disease incidence under ideal conditions (e.g., double-blind, randomized, well-controlled, well-monitored clinical trials) [9,10]. However, vaccine effectiveness estimates in observational studies may be influenced by factors such as vaccination coverage in the population of interest and exposure to the infectious disease of interest. Such factors would be well-balanced across treatment arms in large randomized studies and unlikely to affect efficacy estimates.

Regulatory approval (licensure) of a vaccine in the U.S. requires demonstration of substantial evidence of effectiveness [11]. There is an expectation that effectiveness data supporting licensure be obtained from adequate and well-controlled clinical trials, as described below. Regulations provide for expedited clinical development pathways for certain products intended to treat or prevent serious and life-threatening conditions and that provide meaningful therapeutic benefit over existing treatments: 1) Under accelerated approval, effectiveness is established in adequate and well-controlled clinical trials by establishing the product's effect on a surrogate endpoint or intermediate endpoint that is reasonably likely to predict clinical benefit [12]. 2) Under the "animal rule", evidence of effectiveness is based on adequate and well-controlled animal studies when the results of those animal studies establish that the

biological product is reasonably likely to produce clinical benefit in humans [13]. The animal rule applies to certain biologic products when human efficacy studies cannot be conducted because it would be unethical or not feasible. Vaccines approved under either accelerated approval or animal rule regulations are subject to a requirement to conduct additional confirmatory studies post-licensure to verify and describe the predicted clinical benefit. For products approved under the animal rule, confirmatory studies would be conducted when they become feasible and ethical.

The period from accelerated approval, or approval under the "animal rule", to completion, submission, and FDA evaluation of the confirmatory clinical trials creates a potential role for observational studies conducted in PRISM to provide an independent and complementary real-world assessment of a vaccine's effectiveness. Even for vaccines undergoing traditional approval, including a randomized Phase III efficacy study, uncertainties may remain about their performance in select sub-populations for which sample sizes were too small in clinical trials to fully characterize their effectiveness (e.g., the elderly population), or that were excluded from clinical trials (e.g., pregnant women, immunocompromised individuals), or for rare outcomes, including severe disease. There may be other situations, such as when a randomized controlled trial (RCT) is neither ethical nor feasible, or for rapid evaluation of an approved vaccine during an epidemic or pandemic, that observational studies may play a role in providing substantial evidence of effectiveness. For all vaccines, real-world effectiveness may vary from efficacy estimates derived from clinical trials for many reasons, including differences in underlying characteristics in the populations who receive them and the potential for waning immunity over extended observation periods.

Although vaccine safety studies conducted within PRISM have contributed to FDA's regulatory decision making, it cannot be assumed that vaccine effectiveness studies would result in any regulatory action. First, the Sentinel System was developed to obtain information specific to safety, as required by the 2007 Food and Drug Administration Amendments Act (FDAAA). Second, regulations specify that clinical investigations supporting claims of effectiveness be adequate and well-controlled, and that characteristics of such investigations include a method of assigning patients to treatment and control groups that minimize bias, such as randomization, and that adequate measures are taken to minimize bias on the part of the subjects, observers, and analysts of the data, such as through blinding [11]. Because PRISM can be used for observational studies, but not for RCTs that meet these regulatory expectations, it cannot provide the same level of evidence needed to support vaccine approval. Nevertheless, evidence provided by PRISM vaccine effectiveness studies could supplement clinical trial data, and might be of value in certain situations, where RCTs are neither ethical nor feasible, and when the observational studies are well-designed to the extent possible to minimize bias.

Use of PRISM for vaccine effectiveness studies highlights a number of other important considerations. Signal detection, a key focus in vaccine safety work and an activity conducted in PRISM, is not as relevant to vaccine effectiveness since most effectiveness studies evaluate predefined health outcomes. The availability of laboratory data and results from other diagnostic testing, may be more important in vaccine effectiveness compared to vaccine safety studies. For example, a diagnostic test for influenza is potentially important for assessment of influenza vaccine effectiveness [14]. Another consideration is that vaccine effectiveness studies may require longer follow-up than vaccine safety evaluations [15,16] that often focus on well-defined acute onset outcomes [3,6,8]. A rotavirus vaccine safety evaluation might focus on intussusception within a week or three weeks of vaccination, whereas an effectiveness evaluation might focus on gastroenteritis up to 12 or 24 months after vaccination[3, 14].

The main objective of this white paper is to assess the potential of using PRISM for vaccine effectiveness studies. The question of feasibility was approached by: (a) exploring available data elements, including vaccine exposures, outcomes, and covariates; (b) developing an overview and comparison of designs

and methods that have been used to estimate vaccine effectiveness in administrative claims data [9,10,17-19]; and, (c) providing a description of relevant reusable and customizable analytic tools available in Sentinel. We then use some of these tools to illustrate an example use case in which we identify high-dose and standard-dose inactivated influenza vaccine exposures, influenza and pneumonia outcomes, and potentially associated covariates. Finally, we address the most important strengths and limitations of PRISM in assessing vaccine effectiveness.

# III. DATA ELEMENTS

## A. SENTINEL SYSTEM POPULATION

Sentinel has one of the largest cohorts in the US general population for active medical product safety surveillance [1,20,21]. Sentinel comprises primarily administrative health plan claims data held by 16 health plan partner organizations and includes approximately 223 million individuals (178 million members with both medical and prescription coverage) and 425 million person-years of observation time [2]. The subset PRISM database, which contains data from 2006, includes over 150 million individuals. Thirty-two million individuals within PRISM are currently enrolled in participating health plans and accumulating new data, and 33 million individuals, including both those who are currently or were previously enrolled, have at least one laboratory test result.

The population in the Sentinel distributed database is also notable for its geographic diversity, which enables evaluations in subgroups, or of rare outcomes in a population that is likely representative of the privately insured US population [1,2,22]. All age groups are included in the distributed database; however, the population ≥65 years, approximately 15% of the population in the Sentinel Distributed Database [2], is not as well represented in Sentinel compared to other data sources such as the Centers for Medicare and Medicaid Services (CMS). The population is limited to an insured population, and although geographic coverage is wide, data partners may be regionally focused.

## B. EXPOSURE DATA

Vaccines given in the outpatient primary care setting are well-captured within the Sentinel System [23], and therefore, information about administration of early childhood vaccines tends to be complete. Identification of individual vaccines may be possible for some, but not all vaccines; for example, standard-dose trivalent inactivated influenza vaccines may be grouped together and cannot be analyzed separately (i.e., by trade name). Vaccines from different manufacturers that share the same Current Procedural Terminology (CPT) code and the same dosage schedule and administration route cannot be analyzed separately. Information on the dose number within a vaccine series is not readily captured but could be approximated using coding algorithms. PRISM has the ability to link with the immunization registries, enabling identification of some vaccines given in locations other than the primary health care setting where claims-based data may be missing; however, this approach may increase the timeline and cost of an assessment, and the data available in immunization registries vary by state [23-25].

Identifying comparison groups for vaccine effectiveness assessments poses challenges. Determining a group to be truly unvaccinated is difficult, as exposure data may be missing among individuals in the inpatient setting or among those who receive vaccines outside of the traditional medical home (and are therefore not reimbursed via routine insurance company claims system), such as in employee influenza vaccine clinics. Additionally, children who do not receive vaccines on a regular schedule may not be comparable to the majority of children who do, thus introducing selection bias if only certain groups of children are selected to participate in studies. To address such bias, other approaches, such as

comparisons with individuals who received another unrelated vaccine which has no effect on the outcome of interest, could be performed.

## C. OUTCOME DATA

Outcomes can be identified using diagnosis codes (e.g., International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM)), procedure codes (e.g., CPT), or dispensing codes (i.e., National Drug Codes (NDCs)) [26]. Examples of vaccine effectiveness outcomes may include acute gastroenteritis or rotavirus gastroenteritis for rotavirus vaccines, or influenza or pneumonia for influenza vaccines. Certain important limitations related to defining outcomes in PRISM need to be considered. First, data on mortality and cause of mortality are not systematically populated across data partners. Certain health plans perform routine or ad hoc linkages with local or state death registries, but the process is not standardized, which leads to variability in data quality and completeness. Second, only some of the PRISM data partners contribute selected standardized laboratory test results. For these data partners, the test results come from large laboratory vendors, but because not all vendors send results, capture is incomplete and this results in decreased specificity of certain outcomes. In the case of influenza diagnosis codes, specificity can be improved by adding laboratory procedure or anti-viral dispensing codes. Third, although many vaccine effectiveness outcome algorithms that use administrative claims data have been validated in other settings [27,28], most algorithms are not yet validated in the Sentinel distributed database, potentially leading to misclassification of important study outcomes and potentially biased vaccine effectiveness estimates. Finally, questions related to long-term vaccine effectiveness or waning immunity may be difficult to explore using the Sentinel System because the median follow-up time for health plan members is approximately 17 months, and Sentinel cannot track individuals who switch insurance partners [29]. Although it may not be possible to assess long-term effectiveness under most circumstances, questions about waning protection that involve a more limited time frame, or that can be restricted to certain data partners or populations who tend to have longer follow-up, could be explored in PRISM.

## D. COVARIATE DATA

Potential confounders defined with a single or combination of diagnosis, procedure, or dispensing codes can be incorporated into analyses. In addition, pre-existing programs developed within Sentinel to determine the combined comorbidity index (CCI), a summary score that predicts short- and long-term mortality [21], and health care utilization metrics can be used to help define complex factors, such as frailty within the elderly. Both the CCI and health care utilization measures have been used as adjustment measures in propensity score-matched cohort studies [30] and can also be included in descriptive analyses highlighting baseline characteristics of the study and comparator groups, as was done in our data and descriptive tool exploration (**Section IV**, **Table 4** and **Table 5**). The PRISM program is currently evaluating the use of three-digit zip codes of members' primary place of residence. These data can be aggregated to geographic units of interest, including metropolitan statistical areas and regions using standard files available from the U.S. Census Bureau [31,32]. Such data could allow vaccine effectiveness studies to focus on differences in vaccine impact among geographic areas (e.g., regions with high versus low influenza circulation), or include geographic units as a potential confounder.

### E. GENERAL LIMITATIONS OF CLAIMS-BASED DATA

Aside from Sentinel and PRISM-specific limitations, there are general limitations of using administrative claims-based data to examine vaccine effectiveness. First, claims data are generated by insurance companies for billing purposes, not public health surveillance. Diagnosis codes that appear in the claims data may not be the main (e.g., due to reimbursement considerations) or final (e.g., due to latent key signs/symptoms) diagnosis of the patient. In addition, exposure, outcome, and covariate definitions are limited to how they are defined by Healthcare Common Procedure Coding System (HCPCS), NDC, or ICD-9-CM codes and may be affected by coding changes, such as the ICD-9-CM to ICD-10-CM transition that occurred on October 1, 2015. However, use or development of validated algorithms and medical record review have the potential to circumvent some of these well-known limitations in certain circumstances.

Second, although data can generally be accessed more rapidly from claims than from most prospective data collection methods, Sentinel data are not available in real-time. The data are refreshed quarterly, semi-annually, or annually, depending on the data partner, and then undergo a rigorous quality assurance process by the Sentinel Operations Center, before the data are available for querying. Thus, by the time the data are available for analysis, they are typically at least 9 months old [33].

Finally, vaccine effectiveness estimates based on claims data such as PRISM cannot account for the probability of disease exposure or transmission; these must be assumed to be equal between vaccinated and control groups [23].

## IV. METHODS: STUDY DESIGNS AND STATISTICAL ADJUSTMENT METHODS

Study designs and statistical methods relevant to the study of vaccine effectiveness using administrative claims data were identified and reviewed. Identification of methods primarily involved expert discussion; however, to ensure that no approaches were overlooked, the work group also conducted a literature scan in PubMed. The sections that follow briefly define and summarize the strengths and limitations of six study designs and one data sharing technique in relation to the study of vaccine effectiveness, highlighting a few examples from the literature, and describing their potential applicability to PRISM.

### A. BETWEEN-PERSON COMPARISONS

#### 1. Cohort

In a cohort study, a group of people are identified and followed for a certain period to ascertain the occurrence of health-related events. The goal is usually to determine whether an exposure is related to the incidence of an event [34]. In vaccine effectiveness cohort studies that use administrative claims data, a cohort is often formed naturally via membership to a particular health plan (e.g., Aetna) from which an "exposed," vaccinated group and "unexposed," unvaccinated (or other comparator group) are drawn (**Table 1)**. Strengths of the cohort study design for vaccine effectiveness using administrative claims data include longitudinal data capture of most medical encounters, standardized medical coding systems, low cost for data access, and a large sample size that enables subgroup analyses. An important limitation is the difficulty in identifying an unvaccinated, comparator group either because the vaccine has high coverage (e.g., measles, mumps, and rubella vaccine (MMR), diphtheria, tetanus, and acellular pertussis vaccine (DTaP)), or because the vaccine may be received outside the medical setting (e.g., influenza vaccines received at the workplace will not generate an insurance claim). Thus, in some instances, it may be best to focus on comparative vaccine effectiveness or investigate within-cohort

differences. The cohort design is applicable to the study of vaccine effectiveness in PRISM, and there are currently analytic tools available to assist with such analyses.

### 2. Natural Experiment

One variation of a cohort study is the natural experiment, a situation in which a naturally occurring circumstance subsets the population to different levels of exposure in a situation resembling a randomized study [35]. A natural experiment can potentially control for both measured and unmeasured confounders, offering a major advantage over other observational study designs. Natural experiments have been used to assess bias and ultimately produce more valid comparative effectiveness estimates of the influenza vaccine in the elderly [15,36]. For example, Jackson *et al.* and McGrath *et al.* took advantage of vaccine effectiveness demonstrated during periods with little to no seasonal influenza activity or with a known vaccine mismatch to demonstrate likely bias [15,36]. Estimates from these groups can ultimately be used as the control in an influenza vaccine effectiveness study. The studies that are applicable to studying vaccine effectiveness in PRISM are the ones where the natural conditions create the "right" condition for a particular research question. For example, the situation in which a PRISM data partner exclusively uses (via reimbursement policy) the pentavalent rotavirus vaccine and a second PRISM data partner exclusively uses the monovalent rotavirus vaccine could lend itself to a comparative effectiveness study of the two rotavirus vaccines. However, the low frequency of these types of situations limit the usefulness of this design in PRISM.

### 3. Case-control

A case-control study can be thought of as an efficient cohort study, whereby all of the cases are used, but rather than including the entire source population that gave rise to the cases, only a sample of controls is selected [37]. Any case-control study designed in PRISM would be considered a "nested" case-control study because the population available is already part of the health plan cohort. As such, like other pharmacoepidemiologic studies that rely on secondary data sources, there would generally be no cost or time advantage to conducting a case-control as opposed to a cohort study in PRISM unless chart review is planned or additional laboratory values need to be collected from the data partners. Similar to cohort studies, identifying a sufficient number of true, unexposed controls may be difficult for vaccines with high coverage and limit study power. An additional challenge of case-control studies is the uncertainty of whether the selected controls accurately represent the source population.

### 4. Test-negative Designs

In a traditional, prospective test-negative design, people seeking health care for symptoms related to a non-specific infectious condition (e.g., acute respiratory illness) are recruited into a study and tested for a specific, vaccine-preventable disease (e.g., influenza) [18]. The vaccine effectiveness measurement is estimated as one minus the ratio of odds of vaccination in subjects testing positive to the odds of vaccination in those testing negative to the specific, vaccine-preventable disease (e.g., influenza). The test-negative design offers the advantage of mitigating confounding by health care-seeking behavior which is often a major source of bias in influenza vaccine effectiveness studies, as persons who are more likely to seek vaccination may also be more likely to seek health care for an acute respiratory illness [18].

At this time, test-negative influenza vaccine effectiveness studies cannot be performed in PRISM. First, while influenza laboratory outpatient test results (e.g., enzyme immunoassay, nucleic acid test) are available from 10 Sentinel data partners, over 80% of the influenza A and influenza B test results contributed from 2006 through mid-2015 were from a single data partner and the results have not been characterized nor standardized within the Sentinel Common Data Model [38]. Even if additional resources

were devoted to standardizing the test results across the data partners, influenza laboratory tests performed in the outpatient setting are often performed at the provider's discretion, which makes their availability prone to bias.

Second, to date, the test-negative design has been largely used in a prospective manner [39], where acute respiratory symptoms and other eligibility criteria (e.g., duration of illness, not immunocompromised) are verified and lead to study enrollment, and then standardized specimen collection and influenza testing occurs. To obtain and verify information on symptoms and eligibility criteria using PRISM, retrospective chart review would need to be conducted on patients who already have influenza laboratory result information; however, not all of the necessary information is likely to be documented in medical health records. Furthermore, a highly specific test is usually needed for test-negative studies and the retrospective nature of the PRISM data would not be able to control for the sensitivity and specificity of the laboratory test results. Thus, developing a case definition that can be consistently and fairly applied to all study subjects could be difficult.

### 5. Screening Methods

The screening method is useful for estimating vaccine effectiveness when denominator data are unavailable (e.g., fieldwork, other settings where resources are low) [40]. The validity of the method depends on the accuracy of the external vaccine coverage estimates, and challenges concerning confounding adjustment and confidence intervals estimates using the method persist [41,42]. Since PRISM data are comprised primarily of administrative claims that allow longitudinal follow-up of health plan members via enrollment data, a denominator is available. Thus, the main advantage of the screening method is not relevant to PRISM, and the disadvantages outweigh the advantages. However, this method could be useful when non-comparative, vaccine effectiveness estimates are desired and vaccine capture is suboptimal.

## B. WITHIN-PERSON COMPARISONS

### 1. Case-only Designs (Self-controlled)

Case-only designs, such as the self-controlled risk interval and self-controlled case series, compare the risk of a health outcome of interest in a risk interval with that of a control interval within a single individual and thereby eliminate the bias from both measured and unmeasured time-invariant confounders between vaccinated and unvaccinated individuals that can plague cohort studies [43]. While self-controlled risk interval designs are widely used and often the preferred design in vaccine safety studies that utilize large health care databases [3,6,8], these designs are difficult to use in vaccine effectiveness in PRISM because, in most cases, there is no clear period of transient, heightened risk of contracting an effectiveness outcome shortly following vaccination. This limitation may be mitigated somewhat during an epidemic or pandemic when information on disease circulation is available; however, defining a precise and appropriate time interval of risk for a particular outcome may remain a challenge.

**Table 1. Summary of study designs**

| Study design | Brief description | Strengths and limitations | Recommended for use in PRISM | Literature examples |
|---|---|---|---|---|
| ***Between-person comparisons*** | | | | |
| Cohort | Group of vaccinated and unvaccinated health plan members (or other comparator) identified and followed up to ascertain vaccine-preventable disease events | Strengths: Takes advantage of large, captive population with longitudinal information<br>Limitations: May be difficult to accurately ascertain or obtain sufficient numbers of unvaccinated members so comparative effectiveness studies may be more viable | Yes | 16,44,45 |
| Natural experiment | Variation of a cohort study where exposure is determined by conditions not associated with the outcome (thus, in a way, resembling a random assignment) | Strengths: Can control for measured and unmeasured confounders<br>Limitations: Proper conditions must exist on their own so may not be suitable for every question | Yes | 15,36,46 |
| Case-control | Efficient study whereby all available cases are used, but only a selection of members from the source population (controls) are used for the comparison group | Strengths: May be possible to conduct chart review on entire study population (cases and controls)<br>Limitations: May be difficult to accurately ascertain or obtain sufficient numbers of unvaccinated members among cases and controls; controls may not accurately represent source population | Yes | 47,48 |
| Test-negative | Type of case-control study where health plan members seeking health care for symptoms related to a non-specific infectious condition are tested for a vaccine-preventable disease outcome; those testing positive are compared to those testing negative with regards to vaccine exposure | Strengths: Mitigates confounding by health care-seeking behavior<br>Limitations: Lab test result availability, bias in selection of patients for testing, characterization of symptom onset, specificity of case definition, accurately identifying vaccine exposure | No | 48-51 |

| Study design | Brief description | Strengths and limitations | Recommended for use in PRISM | Literature examples |
|---|---|---|---|---|
| Screening method | Estimates the odds of vaccination in cases compared with the odds of vaccination estimated from sources external to the study (e.g. vaccine coverage in the general population) | Strengths: Requires data on individuals for cases only. Useful in low resource settings where comparator/control group data are unavailable (usually not the case in PRISM) Limitations: Validity depends on external vaccine coverage estimates, controlling for confounding a challenge | No | 40-42 |
| ***Within-person comparisons*** | | | | |
| Case only (self-controlled) | Compares the risk of a health outcome of interest in a risk interval with that in a control interval within a single individual | Strengths: implicitly controls for time-invariant measured and unmeasured confounders; time varying covariates can usually be included in the analysis Limitations: Requires well-defined intervals of heightened, transient risk of contracting outcomes after vaccination | No | 22,52 |

## C. DATA SHARING TECHNIQUE

### 1. Case-centered Approach

The case-centered approach is a data sharing technique that outputs only aggregate data and thus maximizes patient privacy across data networks. It compares the observed odds of prior vaccination among the cases with the expected odds (under the null hypothesis) within a stratum of similar individuals based on the proportion in the entire stratum who were vaccinated. This approach can be especially useful in examining differences-in-differences: differences between the vaccine's effects during different periods, on different sub-types of outcome events, or in different subgroups of vaccinees. A complete description of the approach is detailed in Fireman *et al* and Baxter *et al* [17,53].

The case-centered approach has several features that make it relevant for conducting vaccine effectiveness studies in PRISM. First, since only risk set level data are required for analysis, data partners can maximize patient privacy when returning data to the Sentinel Operations Center while allowing the study to produce the same results that would normally require patient-level data (e.g., time-to-event analysis using Cox regression). Second, the approach is particularly useful when the exposure-outcome association varies markedly over time, as in the case of influenza vaccination and influenza disease or waning vaccine effectiveness. Third, computational time can be reduced compared with other methods. Fourth, the approach can flexibly handle change over time in vaccine effectiveness. Although it has mostly been used to examine vaccine safety during transient risk intervals, it can also be used to

examine the waning of vaccine effectiveness over long periods of time. This approach permits a unique way of implementing a cohort design while preserving patient-privacy. Given the strengths of this data sharing technique, vaccine effectiveness studies in PRISM should consider the approach in the study design phase.

# V. ASSESSMENTS: ROUTINE QUERY TOOLS AND PROTOCOL-BASED ASSESSMENTS

Sentinel has a suite of tools that can be leveraged to quickly query data transformed into the Sentinel Common Data Model. This querying system allows FDA to rapidly identify cohorts of interest and perform analyses. The routine query tools vary in complexity and can perform simple descriptive analyses, as well as adjusted analyses, with confounding control. Analyses using these tools can be performed much faster than traditional pharmacoepidemiology studies because the time required for both programming and quality control is reduced significantly.

The simplest of Sentinel's routine querying tools are referred to as Summary Table queries. With this tool, investigators can quickly identify counts, prevalence, and incidence of medical product dispensings, diagnosis codes, and procedure codes. Output can be stratified by pre-determined age group, sex, year, and care setting. The bulk of the routine querying tools include modular programs, defined as reusable statistical software programs that are customized by adjusting various parameters, such as enrollment requirements, inclusion and exclusion criteria, and exposure and outcome definitions. Modular programs are grouped into three levels.

Level 1 modular programs can be used to identify cohorts of interest and perform unadjusted descriptive analyses. Level 1 modular programs have the capability to answer many common questions about the Sentinel population. These programs can describe: (a) background rates, (b) uptake, use, and persistence of new medical products, (c) exposures and follow-up time, (d) health outcomes following medical product exposure, (e) concomitant medical product use, (f) health outcomes during concomitant use, (g) most frequently observed diagnoses, procedures, or drug dispensing, (h) medical product use during pregnancies that result in live births or (i) baseline distributions of potential confounders. These analyses can be stratified by age group, sex, year, month, comorbidity score, or healthcare utilization metrics.

Level 2 modular programs can be used to identify cohorts and perform adjusted analyses with confounding control, generating effect estimates and confidence intervals. There are currently two types of Level 2 modular programs. The first can be used to identify exposures, follow-up time, outcomes, and covariates, estimate propensity scores, and match or stratify patients in an exposure cohort to those in a comparison cohort based on propensity scores. The second type of Level 2 program uses a self-controlled risk interval design, allowing investigators to identify exposures, define risk and control windows relative to the exposure date, and evaluate the occurrence of outcomes during the risk and control windows.

Level 3 modular programs can be used to identify cohorts and continually perform adjusted analyses with confounding control as part of prospective sequential analysis. Currently, prospective sequential analysis can be done with either propensity score matching or a self-controlled risk interval design, described above.

The major advantage to using the Sentinel routine querying tools is the speed at which results can be generated. The time required to generate query results depends on several factors, including the

complexity of the query specifications, the number of other queries undergoing processing, and the priorities of the FDA. Once the Level 1 query parameters for a modular program have been finalized, results are typically available within 3 to 8 weeks.

There are also limitations to these tools. Because tools are pre-defined, specific areas of interest may not have been built into the capabilities. For example, the tools are currently unable to describe the length of hospitalization for a cohort of interest. However, limitations are tracked and new enhancements or programs are prioritized and developed in consultation with FDA. In addition, as a privacy protecting measure, results from data partners are returned in aggregate to the Sentinel Operations Center so investigators cannot easily parse data after it is returned to troubleshoot or examine alternative, non-pre-specified subgroups.

When existing tools do not meet the demands of a particular project, protocol-based assessments can be used, as has been done in previous PRISM vaccine safety investigations [3,6,8]. This kind of study generally has a longer timeline and costs more than a study that uses tools because it involves writing a detailed protocol and original analytic programming code, as well as enacting specific quality control and testing measures. These types of studies may also involve medical health record review, significantly increasing the timeline and cost of the study.

Beyond tools and protocol-based assessments, there are additional features available to the Sentinel System, and thus PRISM, that may strengthen the study of vaccine effectiveness. First, medical record review can assist in verifying exposures and outcomes and validating their timing [3,8]. Second, PRISM data can be linked to vaccine registries to help verify vaccine exposure or obtain additional information about the vaccination (e.g., lot number); however, these linkages are not actively maintained so they must be performed on a study-by-study basis. To date, PRISM studies have linked once to vaccination registries in Florida, Michigan, Minnesota, New York City, New York State, Pennsylvania, Wisconsin, and Virginia [23]. The main trade-offs of medical record review and vaccine registry linkage relate to the potentially high costs and lengthy processes.

Current work essential to the ability of assessing the effectiveness of maternal vaccination (e.g., with Tdap or influenza vaccine) in preventing disease in newborns includes: 1) estimating the percentage of mothers that can be linked to their newborns and characterizing variation by data partner and 2) linking claims data to birth certificates and understanding whether this effort results in improved estimates of gestational age [54,55]. Future work may also include using PRISM to evaluate indirect effectiveness or population impact, as other studies utilizing administrative claims data have done [16,56]. Such work may be useful to more fully evaluate the benefits of vaccines that may have medium-to-low direct effectiveness estimates but potentially large "herd immunity" effects.

# VI. DATA AND DESCRIPTIVE TOOL EXPLORATION (USE CASE)

We conducted a descriptive, exploratory exercise for the purpose of better understanding the strengths and limitations of using PRISM to address questions about vaccine effectiveness. For our example, we examined some of the elements necessary to conduct a vaccine effectiveness study comparing high-dose, inactivated influenza vaccine ("high-dose") to standard-dose, inactivated influenza vaccine ("standard dose") using a Level 1 modular program designed to evaluate background rates. Since the goal was not to determine an estimate for vaccine effectiveness, all exposures and outcomes were evaluated separately. In addition, baseline covariate distribution was evaluated for members receiving high-dose versus standard-dose influenza vaccines. The specifications and results are described in the sections below.

## A. ENROLLMENT CRITERIA

To be considered in the exposure, outcome, and covariate cohorts, health plan members ≥65 years of age were required to be continuously enrolled with both drug and medical coverage at one of six Sentinel data partners for a minimum of 183 days, allowing gaps in coverage of up to 45 days. The cohort was limited to members ≥65 years of age to match the FDA-approved indication and usage for the high-dose, inactivated influenza vaccine. The covariate cohort included an additional cohort that required members to have 548 days (1.5 years) of enrollment to better capture whether administration of an influenza or pneumonia vaccine or hospitalization had occurred during the previous influenza season. The query examination period spanned from August 1, 2010 – July 31, 2015. *Exposures.* All vaccine exposures were defined using HCPCS codes. They were grouped according to whether they were the 1) standard dose, inactivated influenza vaccine formulations (all manufacturers), or 2) the high-dose, inactivated influenza vaccine formulation (Sanofi Pasteur). Within the standard dose group, information was also gathered on the trivalent versus quadrivalent formulations for the 2013–2014 and 2014–2015 seasons. The vaccines could be provided in any care setting (e.g., outpatient, inpatient, emergency department).

## B. OUTCOMES

Five outcomes were considered: 1) influenza diagnosis; 2) pneumonia diagnosis; 3) influenza laboratory test procedure performed in any care setting; 4) influenza rapid test performed followed by an oseltamivir dispensing within a two-day period in the outpatient setting; and 5) influenza laboratory test performed followed by an influenza diagnosis within a three-day period in any care setting. Influenza and pneumonia diagnoses were defined using ICD-9-CM codes and the care setting type varied between inpatient or emergency department; inpatient only (primary position); emergency department only; outpatient only; and any care setting. Laboratory tests were defined using CPT codes, and oseltamivir dispensings were defined by NDCs.

## C. COVARIATES

Covariates examined included patient characteristics (e.g., sex, age), pre-existing conditions or medications (e.g., asthma, heart disease, statin use, combined comorbidity score), and health service utilization intensity metrics (e.g., number of filled prescriptions, number of emergency room encounters). For high-risk disorders, including asthma, blood disorder, chronic lung disease, diabetes, heart disease, kidney disorders, liver disorders, neurological conditions, and weakened immune system, we utilized the codes employed in Izurieta *et al* [44].

## D. DESCRIPTIVE ANALYSIS

Prevalent use of vaccines and the occurrence of outcomes were assessed separately and were reported for each group by season (August 1– July 31, 2010–2015), age (65–74 years, 75–84 years, and ≥85 years), sex, and month. In the covariate analysis, we compared frequencies or means of the selected variables between those ≥65 years of age receiving the high-dose versus the standard dose, inactivated influenza vaccine for each season. Baseline characteristics were assessed during 183 and 548 day periods prior to the influenza vaccination.

## E. RESULTS

Due to the volume of data generated, we present select tables and data elements from only the most recent and complete season (August 2013- July 2014) available at the time the analysis was distributed on April 6, 2016. Results for the other seasons, and for trivalent versus quadrivalent vaccine use can be viewed in Appendices A-E. Sample output from the Level 1 modular program highlighting the prevalence of use of standard-dose and high-dose, inactivated influenza vaccines in the 65–74, 75–84, and ≥85 year-old age groups during the 2013–2014 season are shown in **Table 2**. The number of patients 65–74 years old who received standard-dose versus high-dose, inactivated influenza vaccine was 581,423 and 120,829 out of approximately three million eligible health plan members 65–74 years old in 2013–2014, respectively. The proportion of patients 65-74 years of age receiving high-dose increased each season while the proportion of patients receiving standard-dose remained steady across the seasons examined. Similarly, sample output highlighting the prevalence of the five selected outcomes (irrespective of influenza vaccine exposure) during the 2013–2014 season is shown in **Table 3.** The number of patients 65-74 years with an influenza diagnosis in the inpatient or emergency department settings was 3,058, and the number of patients 65-74 years with a pneumonia diagnosis in either of these settings was 47,577among >3 million eligible members in 2013-2014; these figures were within the range of the estimates produced for the other seasons. Results for the 2013–2014 covariate analysis with the 183 day and 548 day lookback periods are shown in **Table 4** and **Table 5**, respectively. In general, the prevalence of the pre-existing conditions increased as the lookback period increased from 183 to 548 days, and the prevalence of pre-existing conditions was higher in the standard-dose compared with the high-dose, inactivated influenza vaccine group for all seasons, including 2013- 2014. The most prevalent pre-existing conditions were heart disease and diabetes, and statin use during the baseline period was approximately 50%.

## F. COMMENT

This use case demonstrated the ability of PRISM data and tools to identify a specific vaccine product (Sanofi Pasteur's Fluzone High-Dose) and markers of outcomes (i.e., utilization of oseltamivir and influenza rapid test) that have been used to examine influenza vaccine effectiveness in other studies. Although power calculations were beyond the scope of this feasibility exercise, the large number of health plan members with documentation of influenza vaccination in the data and the large number of outcomes identified make a comparative vaccine effectiveness study of standard-dose, inactivated influenza vaccine and high-dose influenza vaccine likely feasible, although the overall prevalence of influenza vaccine use was lower than expected, perhaps as a result of missing exposures. Important strengths and some limitations relevant to this and other vaccine effectiveness questions are reviewed in the section that follows.

**Table 2. Summary of Prevalent Influenza Vaccine Use† in PRISM between August 1, 2013 and July 31, 2014, by Vaccine Type, and Age Group**

| | Vaccinated Patients | Eligible Members | Prevalence of Vaccination per 1000 Members |
|---|---|---|---|
| **High-dose** | | | |
| 65-74 Years | 120,829 | 3,037,491 | 39.78 |
| 75-84 Years | 70,962 | 1,465,343 | 48.43 |
| 85+ Years | 24,794 | 550,100 | 45.07 |
| **Standard-dose, inactivated** | | | |
| 65-74 Years | 581,423 | 3,037,491 | 191.42 |
| 75-84 Years | 354,466 | 1,465,343 | 241.90 |
| 85+ Years | 129,237 | 550,100 | 234.93 |

†Includes all vaccination episodes

**Table 3. Summary of Prevalent Influenza Outcomes† in PRISM between August 1, 2013 and July 31, 2014, by Outcome Definition and Age Group**

| | Patients with an Outcome | Eligible Members | Prevalence of Outcome per 1000 Members |
|---|---|---|---|
| **Influenza diagnosis** | | | |
| Inpatient or Emergency Department | | | |
| 65- 74 years | 3,058 | 3,037,491 | 1.01 |
| 75- 84 years | 1,931 | 1,465,343 | 1.32 |
| 85+ years | 996 | 550,100 | 1.81 |
| Inpatient/Principal Diagnosis | | | |
| 65- 74 years | 477 | 3,037,491 | 0.16 |
| 75- 84 years | 383 | 1,465,343 | 0.26 |
| 85+ years | 188 | 550,100 | 0.34 |
| Emergency Department | | | |
| 65- 74 years | 1,273 | 3,037,491 | 0.42 |
| 75- 84 years | 494 | 1,465,343 | 0.34 |
| 85+ years | 180 | 550,100 | 0.33 |
| Outpatient | | | |
| 65- 74 years | 11,046 | 3,037,491 | 3.64 |
| 75- 84 years | 3,951 | 1,465,343 | 2.70 |
| 85+ years | 1,368 | 550,100 | 2.49 |
| Any Care Setting | | | |
| 65- 74 years | 12,922 | 3,037,491 | 4.25 |
| 75- 84 years | 5,274 | 1,465,343 | 3.60 |
| 85+ years | 2,078 | 550,100 | 3.78 |

| | | | |
|---|---|---|---|
| **Pneumonia diagnosis** | | | |
| Inpatient or Emergency Department | | | |
| 65- 74 years | 47,577 | 3,037,491 | 15.66 |
| 75- 84 years | 48,647 | 1,465,343 | 33.20 |
| 85+ years | 33,817 | 550,100 | 61.47 |
| Inpatient/Principal Diagnosis | | | |
| 65- 74 years | 10,577 | 3,037,491 | 3.48 |
| 75- 84 years | 11,478 | 1,465,343 | 7.83 |
| 85+ years | 8,414 | 550,100 | 15.30 |
| Emergency Department | | | |
| 65- 74 years | 7,391 | 3,037,491 | 2.43 |
| 75- 84 years | 6,290 | 1,465,343 | 4.29 |
| 85+ years | 4,172 | 550,100 | 7.58 |
| Outpatient | | | |
| 65- 74 years | 54,711 | 3,037,491 | 18.01 |
| 75- 84 years | 46,944 | 1,465,343 | 32.04 |
| 85+ years | 30,836 | 550,100 | 56.06 |
| Any Care Setting | | | |
| 65- 74 years | 80,035 | 3,037,491 | 26.35 |
| 75- 84 years | 72,754 | 1,465,343 | 49.65 |
| 85+ years | 48,726 | 550,100 | 88.58 |
| **Influenza laboratory test performed** | | | |
| 65- 74 years | 29,337 | 3,037,491 | 9.66 |
| 75- 84 years | 11,909 | 1,465,343 | 8.13 |
| 85+ years | 3,863 | 550,100 | 7.02 |
| **Influenza rapid test performed and an oseltamivir dispensing** | | | |
| 65- 74 years | 3,221 | 3,037,491 | 1.06 |
| 75- 84 years | 770 | 1,465,343 | 0.53 |
| 85+ years | 153 | 550,100 | 0.28 |
| **Influenza laboratory test performed and an influenza diagnosis** | | | |
| 65- 74 years | 5,564 | 3,037,491 | 1.83 |
| 75- 84 years | 1,639 | 1,465,343 | 1.12 |
| 85+ years | 393 | 550,100 | 0.71 |

†Includes all outcome episodes

**Table 4. Characteristics of Patients Receiving High-Dose and Standard-Dose Influenza Vaccine during the 2013-2014 Influenza Season (183-day Covariate Window)[†]**

**Primary Analysis**

| Characteristic | High-Dose | | Standard-Dose | |
|---|---|---|---|---|
| | N | % | N | % |
| Patients | 216,580 | 100.0% | 1,065,046 | 100.0% |
| **Patient Characteristics** | | | | |
| Mean age | 75.2 | 7.1 (std)[‡] | 75.4 | 7.2 (std) |
| Age: 65–74 years | 120,829 | 55.8% | 581,423 | 54.6% |
| Age: 75–84 years | 70,958 | 32.8% | 354,422 | 33.3% |
| Age: 85+ years | 24,793 | 11.4% | 129,201 | 12.1% |
| Gender (Female) | 121,824 | 56.2% | 599,109 | 56.3% |
| Gender (Male) | 94,747 | 43.7% | 465,908 | 43.7% |
| Gender (Unknown) | 9 | <0.1% | 29 | <0.1% |
| **Recorded History of:** | | | | |
| Asthma | 9,533 | 4.4% | 48,661 | 4.6% |
| Blood Disorders | 32,460 | 15.0% | 181,745 | 17.1% |
| Chronic Lung Disease | 37,439 | 17.3% | 207,917 | 19.5% |
| Diabetes | 61,048 | 28.2% | 324,593 | 30.5% |
| Heart Disease | 76,509 | 35.3% | 410,686 | 38.6% |
| Influenza Hospitalization | 39 | <0.1% | 285 | <0.1% |
| Influenza Vaccination | 360 | 0.2% | 581 | 0.1% |
| Kidney Disorders | 22,256 | 10.3% | 154,861 | 14.5% |
| Liver Disorders | 4,879 | 2.3% | 27,760 | 2.6% |
| Neurological Conditions | 25,771 | 11.9% | 135,702 | 12.7% |
| Pneumococcal Vaccine | 5,421 | 2.5% | 23,066 | 2.2% |
| Pneumonia Hospitalization | 2,676 | 1.2% | 14,881 | 1.4% |
| Statin Use | 104,042 | 48.0% | 519,869 | 48.8% |
| Weakened Immune System | 24,123 | 11.1% | 122,677 | 11.5% |
| Mean Combined Comorbidity Score | 0.7 | 1.8 (std) | 0.9 | 2.0 (std) |
| **Health Service Utilization Intensity:** | | | | |
| Mean number of generic drugs | 5.9 | 4.5 (std) | 6.1 | 4.6 (std) |
| Mean number of unique drug classes | 5.6 | 4.2 (std) | 5.8 | 4.2 (std) |
| Mean number of filled prescriptions | 14.5 | 13.6 (std) | 15.2 | 14.1 (std) |
| Mean number of inpatient hospital encounters | 0.1 | 0.4 (std) | 0.1 | 0.4 (std) |
| Mean number of non-acute institutional encounters | 0.1 | 0.8 (std) | 0.1 | 0.8 (std) |
| Mean number of emergency room encounters | 0.2 | 0.6 (std) | 0.2 | 0.6 (std) |
| Mean number of ambulatory encounters | 8.1 | 8.2 (std) | 8.7 | 9.6 (std) |
| Mean number of other ambulatory encounters | 1.8 | 4.5 (std) | 2.1 | 4.8 (std) |

[†]Includes first vaccination episode; [‡]std: standard deviation

**Table 5. Characteristics of Patients Receiving High-Dose and Standard-Dose Influenza Vaccine during the 2013-2014 Influenza Season (548-day Covariate Window)[†]**

**Primary Analysis**

| Characteristic | High-Dose | | Standard-Dose | |
|---|---|---|---|---|
| | N | % | N | % |
| Patients | 181,082 | 100.0% | 889,355 | 100.0% |
| **Patient Characteristics** | | | | |
| Mean age | 75.7 | 7.0 (std)[‡] | 75.9 | 7.2 (std) |
| Age: 65-74 years | 96,516 | 53.3% | 462,230 | 52.0% |
| Age: 75-84 years | 62,211 | 34.4% | 310,842 | 35.0% |
| Age: 85+ years | 22,355 | 12.3% | 116,283 | 13.1% |
| Gender (Female) | 101,696 | 56.2% | 499,798 | 56.2% |
| Gender (Male) | 79,377 | 43.8% | 389,529 | 43.8% |
| Gender (Unknown) | 9 | <0.1% | 28 | <0.1% |
| **Recorded History of:** | | | | |
| Asthma | 14,713 | 8.1% | 73,823 | 8.3% |
| Blood Disorders | 48,676 | 26.9% | 263,316 | 29.6% |
| Chronic Lung Disease | 58,971 | 32.6% | 311,539 | 35.0% |
| Diabetes | 59,823 | 33.0% | 317,925 | 35.7% |
| Heart Disease | 89,728 | 49.6% | 472,005 | 53.1% |
| Influenza Hospitalization | 317 | 0.2% | 1,893 | 0.2% |
| Influenza Vaccination | 122,994 | 67.9% | 583,140 | 65.6% |
| Kidney Disorders | 28,845 | 15.9% | 190,794 | 21.5% |
| Liver Disorders | 8,831 | 4.9% | 49,203 | 5.5% |
| Neurological Conditions | 39,230 | 21.7% | 204,959 | 23.0% |
| Pneumococcal Vaccine | 20,997 | 11.6% | 92,335 | 10.4% |
| Pneumonia Hospitalization | 6,241 | 3.4% | 32,691 | 3.7% |
| Statin Use | 95,913 | 53.0% | 479,813 | 54.0% |
| Weakened Immune System | 30,205 | 16.7% | 151,825 | 17.1% |
| Mean Combined Comorbidity Score | 1.4 | 2.5 (std) | 1.7 | 2.6 |
| **Health Service Utilization Intensity:** | | | | |
| Mean number of generic drugs | 9.2 | 6.7 (std) | 9.6 | 6.8 (std) |
| Mean number of unique drug classes | 8.4 | 5.9 (std) | 8.7 | 5.9 (std) |
| Mean number of filled prescriptions | 43.1 | 38.8 (std) | 45.3 | 40.1 (std) |
| Mean number of inpatient hospital encounters | 0.3 | 0.8 (std) | 0.3 | 0.9 (std) |
| Mean number of non-acute institutional encounters | 0.4 | 1.7 (std) | 0.4 | 1.8 (std) |
| Mean number of emergency room encounters | 0.5 | 1.2 (std) | 0.5 | 1.2 (std) |
| Mean number of ambulatory encounters | 24.5 | 20.1 (std) | 26.1 | 24.5 (std) |
| Mean number of other ambulatory encounters | 5.3 | 10.7 (std) | 6.1 | 11.9 (std) |

# VII. STRENGTHS AND LIMITATIONS

## A. STRENGTHS

The PRISM distributed database includes a large, geographically diverse population. The large size supports robust evaluations that may include subgroup analyses. Childhood vaccines and other vaccines commonly administered in the primary care setting are well-captured in Sentinel and PRISM [23]. Finally, chart validation of exposures, outcomes and covariates is possible, although it adds to the cost and timeline of an evaluation.

Use of a quality checked common data model coupled with customizable analytic tools enables PRISM to address standard queries efficiently. Immunization rates and background rates of health outcomes for power calculations and feasibility evaluations may be obtained rapidly using existing tools. Additional reusable and customizable analytic tools continue to be developed to support Sentinel analyses. Formal assessment of a vaccine's effectiveness, however, may require a protocol tailored to the specific question.

## B. LIMITATIONS

Overall, as with other claims-based systems, PRISM data are captured primarily for administrative purposes rather than research or public health surveillance. Misclassification of exposures and outcomes can occur, possibly introducing bias. Additionally, the data are not available in real-time. With the addition of quality checks, the data lag for most partners is at least 9 months. Identification of specific vaccines by tradename is generally not possible if shared codes are used to identify immunizations. Availability of laboratory test results and other diagnostic testing results are limited in PRISM [57]. Many outcomes, as defined by codes, have not been validated using administrative claims data. Waning vaccine effectiveness may not be feasibly assessed considering the relatively short median follow-up time in PRISM and because distinct vaccination histories are not available.

# VIII. CONCLUSION

In certain circumstances, PRISM may be a potentially valuable resource for vaccine effectiveness studies. Existing Sentinel tools provide important groundwork for future effectiveness work. However, there are important factors specific to vaccine effectiveness evaluations that must be considered. First, the level of evidence required to make regulatory decisions regarding vaccine effectiveness is high; studies conducted within PRISM would have to be considered within the limitations of observational data and study designs, but could be considered, in some situations, as a complement to evidence provided in randomized clinical trials. Second, limitations in the availability of certain data elements, particularly laboratory and other diagnostic test results, as well as timeliness, affect the ability to fully and rapidly assess vaccine effectiveness. Still, the PRISM system, for some specific effectiveness questions, may be able to provide important information that can supplement existing knowledge. Furthermore, the Sentinel System, and thus PRISM, is dynamic, with ongoing work to improve the availability of data, refine methods, and create more rapid and accessible querying tools. The work conducted by this group into the feasibility of using PRISM to conduct vaccine effectiveness studies should be regarded as an initial exploration that can be further evaluated and expanded as regulatory questions that might be answered within PRISM arise.

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## X. ACKNOWLEDGMENTS

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# XI. APPENDICES

## A. APPENDIX A

### 1. Appendix A: Summary of Prevalent Influenza Vaccine Use† in the Sentinel Distributed Database between August 1, 2010 and July 31, 2013 and August 1, 2014 and July 31, 2015, High-dose versus Standard-dose, by Influenza Season and Age Group

| | Vaccinated Patients | Eligible Members | Prevalence of Vaccination per 1000 Members |
|---|---|---|---|
| **2010-2011 Influenza Season** | | | |
| **High-dose** | | | |
| 65-74 Years | 25,811 | 2,378,898 | 10.85 |
| 75-84 Years | 16,755 | 1,206,554 | 13.89 |
| 85+ Years | 5,336 | 442,202 | 12.07 |
| **Standard-dose, inactivated** | | | |
| 65-74 Years | 503,140 | 2,378,898 | 211.50 |
| 75-84 Years | 314,603 | 1,206,554 | 260.75 |
| 85+ Years | 104,286 | 442,202 | 235.83 |
| **2011-2012 Influenza Season** | | | |
| **High-dose** | | | |
| 65-74 Years | 56,247 | 2,640,734 | 21.30 |
| 75-84 Years | 36,120 | 1,318,291 | 27.40 |
| 85+ Years | 11,954 | 491,609 | 24.32 |
| **Standard-dose, inactivated** | | | |
| 65-74 Years | 527,905 | 2,640,734 | 199.91 |
| 75-84 Years | 327,720 | 1,318,291 | 248.59 |
| 85+ Years | 111,828 | 491,609 | 227.47 |
| **2012-2013 Influenza Season** | | | |
| **High-dose** | | | |
| 65-74 Years | 93,790 | 2,806,684 | 33.42 |
| 75-84 Years | 58,160 | 1,379,848 | 42.15 |
| 85+ Years | 19,989 | 521,812 | 38.31 |
| **Standard-dose, inactivated** | | | |
| 65-74 Years | 598,670 | 2,806,684 | 213.30 |
| 75-84 Years | 364,591 | 1,379,848 | 264.23 |
| 85+ Years | 128,864 | 521,812 | 246.95 |
| **2014-2015 Influenza Season** | | | |
| **High-dose** | | | |
| 65-74 Years | 190,648 | 3,159,277 | 60.35 |
| 75-84 Years | 108,908 | 1,526,993 | 71.32 |
| 85+ Years | 37,739 | 567,331 | 66.52 |
| **Standard-dose, inactivated** | | | |

| | Vaccinated Patients | Eligible Members | Prevalence of Vaccination per 1000 Members |
|---|---|---|---|
| 65-74 Years | 636,397 | 3,159,277 | 201.44 |
| 75-84 Years | 384,083 | 1,526,993 | 251.53 |
| 85+ Years | 139,111 | 567,331 | 245.20 |

†Includes all vaccination episodes

## B. APPENDIX B

### 1. Appendix B: Summary of Prevalent Influenza Vaccine Use† in the Sentinel Distributed Database between August 1, 2013 and July 31, 2015, Trivalent versus Quadrivalent Vaccine, by Influenza Season and Age Group

| | Vaccinated Patients | Eligible Members | Prevalence of Vaccination per 1000 Members |
|---|---|---|---|
| **2013-2014 Influenza Season** | | | |
| **Standard dose, inactivated (trivalent)** | | | |
| 65-74 Years | 175,313 | 3,037,491 | 57.72 |
| 75-84 Years | 80,133 | 1,465,343 | 54.69 |
| 85+ Years | 27,896 | 550,100 | 50.71 |
| **Standard dose, inactivated (quadrivalent)** | | | |
| 65-74 Years | 23,649 | 3,037,491 | 7.79 |
| 75-84 Years | 11,734 | 1,465,343 | 8.01 |
| 85+ Years | 4,003 | 550,100 | 7.28 |
| **2014-2015 Influenza Season** | | | |
| **Standard dose, inactivated (trivalent)** | | | |
| 65-74 Years | 129,724 | 3,159,277 | 41.06 |
| 75-84 Years | 57,436 | 1,526,993 | 37.61 |
| 85+ Years | 20,146 | 567,331 | 35.51 |
| **Standard dose, inactivated (quadrivalent)** | | | |
| 65-74 Years | 93,704 | 3,159,277 | 29.66 |
| 75-84 Years | 50,320 | 1,526,993 | 32.95 |
| 85+ Years | 17,522 | 567,331 | 30.88 |

†Includes all vaccination episodes

## C. APPENDICES C1-C4

### 1. Appendix C1: Summary of Prevalent Influenza Outcomes† in the Sentinel Distributed Database between August 1, 2010 and July 31, 2011, by Outcome Definitions and Age Group

| | Patients with an Outcome | Eligible Members | Prevalence of Outcome per 1000 Members |
|---|---|---|---|
| **Influenza diagnosis** | | | |
| Inpatient or Emergency Department | | | |
| 65- 74 years | 1,570 | 2,378,898 | 0.66 |
| 75- 84 years | 1,315 | 1,206,554 | 1.09 |
| 85+ years | 884 | 442,202 | 2.00 |
| Inpatient/Principal Diagnosis | | | |
| 65- 74 years | 228 | 2,378,898 | 0.10 |
| 75- 84 years | 245 | 1,206,554 | 0.20 |
| 85+ years | 167 | 442,202 | 0.38 |
| Emergency Department | | | |
| 65- 74 years | 565 | 2,378,898 | 0.24 |
| 75- 84 years | 299 | 1,206,554 | 0.25 |
| 85+ years | 122 | 442,202 | 0.28 |
| Outpatient | | | |
| 65- 74 years | 7,288 | 2,378,898 | 3.06 |
| 75- 84 years | 3,085 | 1,206,554 | 2.56 |
| 85+ years | 1,209 | 442,202 | 2.73 |
| Any Care Setting | | | |
| 65- 74 years | 8,324 | 2,378,898 | 3.50 |
| 75- 84 years | 4,061 | 1,206,554 | 3.37 |
| 85+ years | 1,901 | 442,202 | 4.30 |
| **Pneumonia diagnosis** | | | |
| Inpatient or Emergency Department | | | |
| 65- 74 years | 39,069 | 2,378,898 | 16.42 |
| 75- 84 years | 42,448 | 1,206,554 | 35.18 |
| 85+ years | 29,589 | 442,202 | 66.91 |
| Inpatient/Principal Diagnosis | | | |
| 65- 74 years | 9,648 | 2,378,898 | 4.06 |
| 75- 84 years | 11,102 | 1,206,554 | 9.20 |
| 85+ years | 7,864 | 442,202 | 17.78 |
| Emergency Department | | | |
| 65- 74 years | 5,449 | 2,378,898 | 2.29 |
| 75- 84 years | 4,914 | 1,206,554 | 4.07 |
| 85+ years | 3,215 | 442,202 | 7.27 |
| Outpatient | | | |
| 65- 74 years | 46,222 | 2,378,898 | 19.43 |
| 75- 84 years | 40,689 | 1,206,554 | 33.72 |

| | Patients with an Outcome | Eligible Members | Prevalence of Outcome per 1000 Members |
|---|---|---|---|
| 85+ years | 25,796 | 442,202 | 58.34 |
| Any Care Setting | | | |
| 65- 74 years | 67,388 | 2,378,898 | 28.33 |
| 75- 84 years | 63,860 | 1,206,554 | 52.93 |
| 85+ years | 41,969 | 442,202 | 94.91 |
| **Influenza laboratory test performed** | | | |
| 65- 74 years | 13,617 | 2,378,898 | 5.72 |
| 75- 84 years | 5,391 | 1,206,554 | 4.47 |
| 85+ years | 1,655 | 442,202 | 3.74 |
| **Influenza rapid test performed and an oseltamivir dispensing** | | | |
| 65- 74 years | 1,408 | 2,378,898 | 0.59 |
| 75- 84 years | 369 | 1,206,554 | 0.31 |
| 85+ years | 98 | 442,202 | 0.22 |
| **Influenza laboratory test performed and an influenza diagnosis** | | | |
| 65- 74 years | 2,505 | 2,378,898 | 1.05 |
| 75- 84 years | 792 | 1,206,554 | 0.66 |
| 85+ years | 238 | 442,202 | 0.54 |

†Includes all outcome episodes

**2. Appendix C2: Summary of Prevalent Influenza Outcomes† in the Sentinel Distributed Database between August 1, 2011 and July 31, 2012, by Outcome Definitions and Age Group**

| | Patients with an Outcome | Eligible Members | Prevalence of Outcome per 1000 Members |
|---|---|---|---|
| **Influenza diagnosis** | | | |
| Inpatient or Emergency Department | | | |
| 65- 74 years | 888 | 2,640,734 | 0.34 |
| 75- 84 years | 899 | 1,318,291 | 0.68 |
| 85+ years | 604 | 491,609 | 1.23 |
| Inpatient/Principal Diagnosis | | | |
| 65- 74 years | 103 | 2,640,734 | 0.04 |
| 75- 84 years | 112 | 1,318,291 | 0.08 |
| 85+ years | 86 | 491,609 | 0.17 |
| Emergency Department | | | |
| 65- 74 years | 293 | 2,640,734 | 0.11 |
| 75- 84 years | 159 | 1,318,291 | 0.12 |
| 85+ years | 70 | 491,609 | 0.14 |
| Outpatient | | | |
| 65- 74 years | 4,388 | 2,640,734 | 1.66 |
| 75- 84 years | 2,308 | 1,318,291 | 1.75 |
| 85+ years | 946 | 491,609 | 1.92 |
| Any Care Setting | | | |
| 65- 74 years | 5,037 | 2,640,734 | 1.91 |
| 75- 84 years | 3,024 | 1,318,291 | 2.29 |
| 85+ years | 1,439 | 491,609 | 2.93 |
| **Pneumonia diagnosis** | | | |
| Inpatient or Emergency Department | | | |
| 65- 74 years | 41,418 | 2,640,734 | 15.68 |
| 75- 84 years | 43,910 | 1,318,291 | 33.31 |
| 85+ years | 31,076 | 491,609 | 63.21 |
| Inpatient/Principal Diagnosis | | | |
| 65- 74 years | 10,186 | 2,640,734 | 3.86 |
| 75- 84 years | 11,234 | 1,318,291 | 8.52 |
| 85+ years | 8,142 | 491,609 | 16.56 |
| Emergency Department | | | |
| 65- 74 years | 5,812 | 2,640,734 | 2.20 |
| 75- 84 years | 5,020 | 1,318,291 | 3.81 |
| 85+ years | 3,354 | 491,609 | 6.82 |
| Outpatient | | | |
| 65- 74 years | 48,475 | 2,640,734 | 18.36 |
| 75- 84 years | 42,507 | 1,318,291 | 32.24 |
| 85+ years | 27,367 | 491,609 | 55.67 |
| Any Care Setting | | | |

| | Patients with an Outcome | Eligible Members | Prevalence of Outcome per 1000 Members |
|---|---|---|---|
| 65- 74 years | 70,863 | 2,640,734 | 26.83 |
| 75- 84 years | 66,308 | 1,318,291 | 50.30 |
| 85+ years | 44,199 | 491,609 | 89.91 |
| **Influenza laboratory test performed** | | | |
| 65- 74 years | 10,519 | 2,640,734 | 3.98 |
| 75- 84 years | 4,428 | 1,318,291 | 3.36 |
| 85+ years | 1,445 | 491,609 | 2.94 |
| **Influenza rapid test performed and an oseltamivir dispensing** | | | |
| 65- 74 years | 534 | 2,640,734 | 0.20 |
| 75- 84 years | 198 | 1,318,291 | 0.15 |
| 85+ years | 57 | 491,609 | 0.12 |
| **Influenza laboratory test performed and an influenza diagnosis** | | | |
| 65- 74 years | 1,107 | 2,640,734 | 0.42 |
| 75- 84 years | 482 | 1,318,291 | 0.37 |
| 85+ years | 151 | 491,609 | 0.31 |

†Includes all outcome episodes

**3. Appendix C3: Summary of Prevalent Influenza Outcomes† in the Sentinel Distributed Database between August 1, 2012 and July 31, 2013, by Outcome Definitions and Age Group**

| | Patients with an Outcome | Eligible Members | Prevalence of Outcome per 1000 Members |
|---|---|---|---|
| **Influenza diagnosis** | | | |
| Inpatient or Emergency Department | | | |
| 65- 74 years | 3,946 | 2,806,684 | 1.41 |
| 75- 84 years | 3,752 | 1,379,848 | 2.72 |
| 85+ years | 2,508 | 521,812 | 4.81 |
| Inpatient/Principal Diagnosis | | | |
| 65- 74 years | 619 | 2,806,684 | 0.22 |
| 75- 84 years | 877 | 1,379,848 | 0.64 |
| 85+ years | 719 | 521,812 | 1.38 |
| Emergency Department | | | |
| 65- 74 years | 1,863 | 2,806,684 | 0.66 |
| 75- 84 years | 1,302 | 1,379,848 | 0.94 |
| 85+ years | 542 | 521,812 | 1.04 |
| Outpatient | | | |
| 65- 74 years | 16,031 | 2,806,684 | 5.71 |
| 75- 84 years | 7,605 | 1,379,848 | 5.51 |
| 85+ years | 3,096 | 521,812 | 5.93 |
| Any Care Setting | | | |
| 65- 74 years | 18,386 | 2,806,684 | 6.55 |
| 75- 84 years | 9,918 | 1,379,848 | 7.19 |
| 85+ years | 4,652 | 521,812 | 8.92 |
| **Pneumonia diagnosis** | | | |
| Inpatient or Emergency Department | | | |
| 65- 74 years | 47,958 | 2,806,684 | 17.09 |
| 75- 84 years | 51,122 | 1,379,848 | 37.05 |
| 85+ years | 36,411 | 521,812 | 69.78 |
| Inpatient/Principal Diagnosis | | | |
| 65- 74 years | 11,428 | 2,806,684 | 4.07 |
| 75- 84 years | 13,032 | 1,379,848 | 9.44 |
| 85+ years | 9,581 | 521,812 | 18.36 |
| Emergency Department | | | |
| 65- 74 years | 7,294 | 2,806,684 | 2.60 |
| 75- 84 years | 6,657 | 1,379,848 | 4.82 |
| 85+ years | 4,404 | 521,812 | 8.44 |
| Outpatient | | | |
| 65- 74 years | 56,160 | 2,806,684 | 20.01 |
| 75- 84 years | 49,393 | 1,379,848 | 35.80 |
| 85 + years | 32,990 | 521,812 | 63.22 |
| Any Care Setting | | | |

| | Patients with an Outcome | Eligible Members | Prevalence of Outcome per 1000 Members |
|---|---|---|---|
| 65- 74 years | 81,732 | 2,806,684 | 29.12 |
| 75- 84 years | 76,172 | 1,379,848 | 55.20 |
| 85+ years | 51,907 | 521,812 | 99.47 |
| **Influenza laboratory test performed** | | | |
| 65- 74 years | 33,454 | 2,806,684 | 11.92 |
| 75- 84 years | 15,246 | 1,379,848 | 11.05 |
| 85+ years | 5,519 | 521,812 | 10.58 |
| **Influenza rapid test performed and an oseltamivir dispensing** | | | |
| 65- 74 years | 4,154 | 2,806,684 | 1.48 |
| 75- 84 years | 1,440 | 1,379,848 | 1.04 |
| 85+ years | 433 | 521,812 | 0.83 |
| **Influenza laboratory test performed and an influenza diagnosis** | | | |
| 65- 74 years | 7,499 | 2,806,684 | 2.67 |
| 75- 84 years | 3,344 | 1,379,848 | 2.42 |
| 85+ years | 1,109 | 521,812 | 2.13 |

†Includes all outcome episodes

**4. Appendix C4: Summary of Prevalent Influenza Outcomes† in the Sentinel Distributed Database between August 1, 2014 and July 31, 2015, by Outcome Definitions and Age Group**

| | Patients with an Outcome | Eligible Members | Prevalence of Outcome per 1000 Members |
|---|---|---|---|
| **Influenza diagnosis** | | | |
| Inpatient or Emergency Department | | | |
| 65- 74 years | 6,981 | 3,159,277 | 2.21 |
| 75- 84 years | 6,831 | 1,526,993 | 4.47 |
| 85+ years | 4,750 | 567,331 | 8.37 |
| Inpatient/Principal Diagnosis | | | |
| 65- 74 years | 1,029 | 3,159,277 | 0.33 |
| 75- 84 years | 1,601 | 1,526,993 | 1.05 |
| 85+ years | 1,503 | 567,331 | 2.65 |
| Emergency Department | | | |
| 65- 74 years | 3,752 | 3,159,277 | 1.19 |
| 75- 84 years | 2,754 | 1,526,993 | 1.80 |
| 85+ years | 1,308 | 567,331 | 2.31 |
| Outpatient | | | |
| 65- 74 years | 25,296 | 3,159,277 | 8.01 |
| 75- 84 years | 12,736 | 1,526,993 | 8.34 |
| 85+ years | 5,374 | 567,331 | 9.47 |
| Any Care Setting | | | |
| 65- 74 years | 28,887 | 3,159,277 | 9.14 |
| 75- 84 years | 16,383 | 1,526,993 | 10.73 |
| 85+ years | 8,061 | 567,331 | 14.21 |
| **Pneumonia diagnosis** | | | |
| Inpatient or Emergency Department | | | |
| 65- 74 years | 50,399 | 3,159,277 | 15.95 |
| 75- 84 years | 51,278 | 1,526,993 | 33.58 |
| 85+ years | 35,724 | 567,331 | 62.97 |
| Inpatient/Principal Diagnosis | | | |
| 65- 74 years | 10,788 | 3,159,277 | 3.41 |
| 75- 84 years | 11,753 | 1,526,993 | 7.70 |
| 85+ years | 8,639 | 567,331 | 15.23 |
| Emergency Department | | | |
| 65- 74 years | 8,446 | 3,159,277 | 2.67 |
| 75- 84 years | 7,318 | 1,526,993 | 4.79 |
| 85+ years | 4,571 | 567,331 | 8.06 |
| Outpatient | | | |
| 65- 74 years | 58,630 | 3,159,277 | 18.56 |
| 75- 84 years | 50,329 | 1,526,993 | 32.96 |
| 85+ years | 32,645 | 567,331 | 57.54 |
| Any Care Setting | | | |

| | Patients with an Outcome | Eligible Members | Prevalence of Outcome per 1000 Members |
|---|---|---|---|
| 65- 74 years | 85,287 | 3,159,277 | 27.00 |
| 75- 84 years | 77,391 | 1,526,993 | 50.68 |
| 85+ years | 51,636 | 567,331 | 91.02 |
| **Influenza laboratory test performed** | | | |
| 65- 74 years | 59,239 | 3,159,277 | 18.75 |
| 75- 84 years | 28,489 | 1,526,993 | 18.66 |
| 85+ years | 10,500 | 567,331 | 18.51 |
| **Influenza rapid test performed and an oseltamivir dispensing** | | | |
| 65- 74 years | 9,639 | 3,159,277 | 3.05 |
| 75- 84 years | 3,813 | 1,526,993 | 2.50 |
| 85+ years | 1,179 | 567,331 | 2.08 |
| **Influenza laboratory test performed and an influenza diagnosis** | | | |
| 65- 74 years | 14,975 | 3,159,277 | 4.74 |
| 75- 84 years | 7,207 | 1,526,993 | 4.72 |
| 85+ years | 2,581 | 567,331 | 4.55 |

*Includes all outcome episodes

## D. APPENDICES D1-D4

### 1. Appendix D1: Characteristics of Patients Receiving High-Dose and Standard-Dose Influenza Vaccine during the 2010-2011 Influenza Season (183-day Covariate Window)

| Characteristic | Primary Analysis | | | |
|---|---|---|---|---|
| | High-Dose | | Standard-Dose | |
| | N | % | N | % |
| Patients | 47,901 | 100.0% | 921,966 | 100.0% |
| **Patient Characteristics** | | | | |
| Mean age | 75.4 | 7.1 (std)‡ | 75.3 | 7.1 (std) |
| Age: 65–74 years | 25,811 | 53.9% | 503,140 | 54.6% |
| Age: 75–84 years | 16,754 | 35.0% | 314,560 | 34.1% |
| Age: 85+ years | 5,336 | 11.1% | 104,266 | 11.3% |
| Gender (Female) | 26,837 | 56.0% | 515,504 | 55.9% |
| Gender (Male) | 21,062 | 44.0% | 406,435 | 44.1% |
| Gender (Unknown) | 2 | <0.1% | 27 | <0.1% |
| **Recorded History of:** | | | | |
| Asthma | 1,983 | 4.1% | 39,463 | 4.3% |
| Blood Disorders | 7,029 | 14.7% | 152,645 | 16.6% |
| Chronic Lung Disease | 8,487 | 17.7% | 180,518 | 19.6% |
| Diabetes | 13,019 | 27.2% | 262,780 | 28.5% |
| Heart Disease | 16,736 | 34.9% | 344,748 | 37.4% |
| Influenza Hospitalization | 7 | 0.0% | 176 | 0.0% |
| Influenza Vaccination | 183 | 0.4% | 1,819 | 0.2% |
| Kidney Disorders | 3,764 | 7.9% | 107,962 | 11.7% |
| Liver Disorders | 921 | 1.9% | 21,506 | 2.3% |
| Neurological Conditions | 5,866 | 12.2% | 115,770 | 12.6% |
| Pneumococcal Vaccine | 783 | 1.6% | 14,142 | 1.5% |
| Pneumonia Hospitalization | 575 | 1.2% | 11,979 | 1.3% |
| Statin Use | 22,605 | 47.2% | 438,000 | 47.5% |
| Weakened Immune System | 5,598 | 11.7% | 108,101 | 11.7% |
| Mean Combined Comorbidity Score | 0.6 | 1.8 (std) | 0.8 | 1.9 (std) |
| **Health Service Utilization Intensity:** | | | | |
| Mean number of generic drugs | 5.9 | 4.4 (std) | 6.0 | 4.4 (std) |
| Mean number of unique drug classes | 5.5 | 4.1 (std) | 5.7 | 4.1 (std) |
| Mean number of filled prescriptions | 15.6 | 14.3 (std) | 16.2 | 14.6 (std) |
| Mean number of inpatient hospital encounters | 0.1 | 0.4 (std) | 0.1 | 0.4 (std) |
| Mean number of non-acute institutional encounters | 0.1 | 0.5 (std) | 0.1 | 0.7 (std) |
| Mean number of emergency room encounters | 0.2 | 0.5 (std) | 0.2 | 0.5 (std) |
| Mean number of ambulatory encounters | 8.4 | 8.4 (std) | 8.5 | 9.2 (std) |
| Mean number of other ambulatory encounters | 1.6 | 4.1 (std) | 2.0 | 4.5 (std) |

†Includes first vaccination episode; ‡std: standard deviation

## 2. Appendix D2: Characteristics of Patients Receiving High-Dose and Standard-Dose Influenza Vaccine during the 2011-2012 Influenza Season (183-day Covariate Window)

| Characteristic | Primary Analysis | | | |
|---|---|---|---|---|
| | High-Dose | | Standard-Dose | |
| | N | % | N | % |
| Patients | 104,320 | 100.0% | 967,388 | 100.0% |
| **Patient Characteristics** | | | | |
| Mean age | 75.5 | 7.1 (std)‡ | 75.4 | 7.1 (std) |
| Age: 65–74 years | 56,247 | 53.9% | 527,905 | 54.6% |
| Age: 75–84 years | 36,119 | 34.6% | 327,679 | 33.9% |
| Age: 85+ years | 11,954 | 11.5% | 111,804 | 11.6% |
| Gender (Female) | 58,645 | 56.2% | 541,373 | 56.0% |
| Gender (Male) | 45,672 | 43.8% | 425,991 | 44.0% |
| Gender (Unknown) | 3 | <0.1% | 24 | <0.1% |
| **Recorded History of:** | | | | |
| Asthma | 4,376 | 4.2% | 41,854 | 4.3% |
| Blood Disorders | 15,513 | 14.9% | 160,773 | 16.6% |
| Chronic Lung Disease | 18,634 | 17.9% | 189,643 | 19.6% |
| Diabetes | 29,320 | 28.1% | 283,053 | 29.3% |
| Heart Disease | 36,628 | 35.1% | 363,587 | 37.6% |
| Influenza Hospitalization | 13 | 0.0% | 156 | 0.0% |
| Influenza Vaccination | 216 | 0.2% | 806 | 0.1% |
| Kidney Disorders | 8,921 | 8.6% | 121,632 | 12.6% |
| Liver Disorders | 2,102 | 2.0% | 23,461 | 2.4% |
| Neurological Conditions | 12,813 | 12.3% | 121,559 | 12.6% |
| Pneumococcal Vaccine | 1,901 | 1.8% | 17,310 | 1.8% |
| Pneumonia Hospitalization | 1,365 | 1.3% | 12,889 | 1.3% |
| Statin Use | 50,559 | 48.5% | 473,275 | 48.9% |
| Weakened Immune System | 11,713 | 11.2% | 111,901 | 11.6% |
| Mean Combined Comorbidity Score | 0.7 | 1.8 (std) | 0.8 | 2.0 (std) |
| **Health Service Utilization Intensity:** | | | | |
| Mean number of generic drugs | 6.0 | 4.4 (std) | 6.1 | 4.4 (std) |
| Mean number of unique drug classes | 5.7 | 4.1 (std) | 5.8 | 4.1 (std) |
| Mean number of filled prescriptions | 15.4 | 13.9 (std) | 16.0 | 14.3 (std) |
| Mean number of inpatient hospital encounters | 0.1 | 0.4 (std) | 0.1 | 0.4 (std) |
| Mean number of non-acute institutional encounters | 0.1 | 0.5 (std) | 0.1 | 0.6 (std) |
| Mean number of emergency room encounters | 0.2 | 0.5 (std) | 0.2 | 0.5 (std) |
| Mean number of ambulatory encounters | 8.2 | 8.4 (std) | 8.4 | 9.1 (std) |
| Mean number of other ambulatory encounters | 1.8 | 4.3 (std) | 2.0 | 4.5 (std) |

†Includes first vaccination episode; ‡std: standard deviation

### 3. Appendix D3: Characteristics of Patients Receiving High-Dose and Standard-Dose Influenza Vaccine during the 2012-2013 Influenza Season (183-day Covariate Window)

| Characteristic | Primary Analysis | | | |
|---|---|---|---|---|
| | High-Dose | | Standard-Dose | |
| | N | % | N | % |
| Patients | 171,939 | 100.0% | 1,092,037 | 100.0% |
| **Patient Characteristics** | | | | |
| Mean age | 75.4 | 7.1 (std)‡ | 75.3 | 7.2 (std) |
| Age: 65–74 years | 93,790 | 54.5% | 598,670 | 54.8% |
| Age: 75–84 years | 58,160 | 33.8% | 364,544 | 33.4% |
| Age: 85+ years | 19,989 | 11.6% | 128,823 | 11.8% |
| Gender (Female) | 96,646 | 56.2% | 611,006 | 56.0% |
| Gender (Male) | 75,285 | 43.8% | 481,003 | 44.0% |
| Gender (Unknown) | 8 | <0.1% | 28 | <0.1% |
| **Recorded History of:** | | | | |
| Asthma | 7,201 | 4.2% | 47,842 | 4.4% |
| Blood Disorders | 25,142 | 14.6% | 180,100 | 16.5% |
| Chronic Lung Disease | 29,432 | 17.1% | 207,747 | 19.0% |
| Diabetes | 48,127 | 28.0% | 323,485 | 29.6% |
| Heart Disease | 59,856 | 34.8% | 410,155 | 37.6% |
| Influenza Hospitalization | 40 | 0.0% | 282 | 0.0% |
| Influenza Vaccination | 400 | 0.2% | 816 | 0.1% |
| Kidney Disorders | 15,829 | 9.2% | 144,931 | 13.3% |
| Liver Disorders | 3,652 | 2.1% | 27,369 | 2.5% |
| Neurological Conditions | 20,422 | 11.9% | 135,606 | 12.4% |
| Pneumococcal Vaccine | 3,619 | 2.1% | 22,581 | 2.1% |
| Pneumonia Hospitalization | 2,192 | 1.3% | 14,516 | 1.3% |
| Statin Use | 81,047 | 47.1% | 519,782 | 47.6% |
| Weakened Immune System | 19,065 | 11.1% | 125,291 | 11.5% |
| Mean Combined Comorbidity Score | 0.7 | 1.8 (std) | 0.9 | 2.0 (std) |
| **Health Service Utilization Intensity:** | | | | |
| Mean number of generic drugs | 5.7 | 4.4 (std) | 5.9 | 4.5 (std) |
| Mean number of unique drug classes | 5.4 | 4.1 (std) | 5.6 | 4.1 (std) |
| Mean number of filled prescriptions | 14.5 | 13.7 (std) | 15.0 | 14.0 (std) |
| Mean number of inpatient hospital encounters | 0.1 | 0.4 (std) | 0.1 | 0.4 (std) |
| Mean number of non-acute institutional encounters | 0.1 | 0.7 (std) | 0.1 | 0.7 (std) |
| Mean number of emergency room encounters | 0.2 | 0.6 (std) | 0.2 | 0.6 (std) |
| Mean number of ambulatory encounters | 8.0 | 8.1 (std) | 8.4 | 9.4 (std) |
| Mean number of other ambulatory encounters | 1.8 | 4.3 (std) | 2.0 | 4.6 (std) |

†Includes first vaccination episode; ‡std: standard deviation

## 4. Appendix D4: Characteristics of Patients Receiving High-Dose and Standard-Dose Influenza Vaccine during the 2014-2015 Influenza Season (183-day Covariate Window)

| | Primary Analysis | | | |
|---|---|---|---|---|
| **Characteristic** | **High-Dose** | | **Standard-Dose** | |
| | **N** | **%** | **N** | **%** |
| Patients | 337,292 | 100.0% | 1,159,541 | 100.0% |
| **Patient Characteristics** | | | | |
| Mean age | 75.1 | 7.1 (std)‡ | 75.4 | 7.2 (std) |
| Age: 65–74 years | 190,648 | 56.5% | 636,397 | 54.9% |
| Age: 75–84 years | 108,905 | 32.3% | 384,049 | 33.1% |
| Age: 85+ years | 37,739 | 11.2% | 139,095 | 12.0% |
| Gender (Female) | 189,222 | 56.1% | 655,636 | 56.5% |
| Gender (Male) | 148,059 | 43.9% | 503,888 | 43.5% |
| Gender (Unknown) | 11 | <0.1% | 17 | <0.1% |
| **Recorded History of:** | | | | |
| Asthma | 15,331 | 4.5% | 53,537 | 4.6% |
| Blood Disorders | 50,824 | 15.1% | 202,673 | 17.5% |
| Chronic Lung Disease | 57,136 | 16.9% | 223,004 | 19.2% |
| Diabetes | 95,073 | 28.2% | 357,641 | 30.8% |
| Heart Disease | 119,632 | 35.5% | 449,545 | 38.8% |
| Influenza Hospitalization | 69 | 0.0% | 378 | 0.0% |
| Influenza Vaccination | 569 | 0.2% | 716 | 0.1% |
| Kidney Disorders | 37,723 | 11.2% | 178,032 | 15.4% |
| Liver Disorders | 8,082 | 2.4% | 31,680 | 2.7% |
| Neurological Conditions | 40,064 | 11.9% | 148,594 | 12.8% |
| Pneumococcal Vaccine | 8,487 | 2.5% | 25,772 | 2.2% |
| Pneumonia Hospitalization | 3,856 | 1.1% | 15,218 | 1.3% |
| Statin Use | 168,579 | 50.0% | 582,174 | 50.2% |
| Weakened Immune System | 37,849 | 11.2% | 132,637 | 11.4% |
| Mean Combined Comorbidity Score | 0.7 | 1.9 (std) | 1.0 | 2.1 (std) |
| **Health Service Utilization Intensity:** | | | | |
| Mean number of generic drugs | 6.0 | 4.5 (std) | 6.2 | 4.6 (std) |
| Mean number of unique drug classes | 5.7 | 4.2 (std) | 5.9 | 4.2 (std) |
| Mean number of filled prescriptions | 14.8 | 13.6 (std) | 15.3 | 14.1 (std) |
| Mean number of inpatient hospital encounters | 0.1 | 0.4 (std) | 0.1 | 0.5 (std) |
| Mean number of non-acute institutional encounters | 0.1 | 0.7 (std) | 0.1 | 0.8 (std) |
| Mean number of emergency room encounters | 0.2 | 0.6 (std) | 0.2 | 0.6 (std) |
| Mean number of ambulatory encounters | 8.2 | 8.3 (std) | 8.7 | 9.8 (std) |
| Mean number of other ambulatory encounters | 1.8 | 4.4 (std) | 2.1 | 4.8 (std) |

†Includes first vaccination episode; ‡std: standard deviation

## E. APPENDICES E1-E4

### 1. Appendix E1: Characteristics of Patients Receiving High-Dose and Standard-Dose Influenza Vaccine during the 2010-2011 Influenza Season (548-day Covariate Window)

| Characteristic | Primary Analysis | | | |
|---|---|---|---|---|
| | High-Dose | | Standard-Dose | |
| | N | % | N | % |
| Patients | 38,141 | 100.0% | 734,965 | 100.0% |
| **Patient Characteristics** | | | | |
| Mean age | 75.8 | 7.1 (std)‡ | 75.7 | 7.1 (std) |
| Age: 65-74 years | 19,797 | 51.9% | 382,703 | 52.1% |
| Age: 75-84 years | 13,785 | 36.1% | 262,363 | 35.7% |
| Age: 85+ years | 4,559 | 12.0% | 89,899 | 12.2% |
| Gender (Female) | 21,407 | 56.1% | 411,748 | 56.0% |
| Gender (Male) | 16,732 | 43.9% | 323,192 | 44.0% |
| Gender (Unknown) | 2 | <0.1% | 25 | <0.1% |
| **Recorded History of:** | | | | |
| Asthma | 2,894 | 7.6% | 58,167 | 7.9% |
| Blood Disorders | 9,901 | 26.0% | 210,978 | 28.7% |
| Chronic Lung Disease | 12,309 | 32.3% | 254,962 | 34.7% |
| Diabetes | 12,143 | 31.8% | 247,623 | 33.7% |
| Heart Disease | 18,823 | 49.4% | 384,327 | 52.3% |
| Influenza Hospitalization | 30 | 0.1% | 786 | 0.1% |
| Influenza Vaccination | 25,180 | 66.0% | 439,325 | 59.8% |
| Kidney Disorders | 4,735 | 12.4% | 127,668 | 17.4% |
| Liver Disorders | 1,680 | 4.4% | 36,925 | 5.0% |
| Neurological Conditions | 8,454 | 22.2% | 168,486 | 22.9% |
| Pneumococcal Vaccine | 3,279 | 8.6% | 59,675 | 8.1% |
| Pneumonia Hospitalization | 1,279 | 3.4% | 24,922 | 3.4% |
| Statin Use | 20,197 | 53.0% | 393,457 | 53.5% |
| Weakened Immune System | 6,632 | 17.4% | 128,716 | 17.5% |
| Mean Combined Comorbidity Score | 1.3 | 2.4 (std) | 1.6 | 2.6 |
| **Health Service Utilization Intensity:** | | | | |
| Mean number of generic drugs | 9.4 | 6.6 (std) | 9.7 | 6.6 (std) |
| Mean number of unique drug classes | 8.4 | 5.6 (std) | 8.7 | 5.7 (std) |
| Mean number of filled prescriptions | 47.1 | 41.0 (std) | 49.3 | 41.7 (std) |
| Mean number of inpatient hospital encounters | 0.4 | 0.8 (std) | 0.4 | 0.9 (std) |
| Mean number of non-acute institutional encounters | 0.3 | 1.1 (std) | 0.3 | 1.9 (std) |
| Mean number of emergency room encounters | 0.5 | 1.0 (std) | 0.4 | 1.0 (std) |
| Mean number of ambulatory encounters | 25.4 | 20.5 (std) | 25.7 | 23.2 (std) |
| Mean number of other ambulatory encounters | 4.6 | 10.3 (std) | 5.7 | 11.1 (std) |

†Includes first vaccination episode; ‡std: standard deviation

## 2. Appendix E2: Characteristics of Patients Receiving High-Dose and Standard-Dose Influenza Vaccine during the 2011-2012 Influenza Season (548-day Covariate Window)

| Characteristic | Primary Analysis | | | |
|---|---|---|---|---|
| | High-Dose | | Standard-Dose | |
| | N | % | N | % |
| Patients | 85,067 | 100.0% | 794,299 | 100.0% |
| **Patient Characteristics** | | | | |
| Mean age | 75.8 | 7.0 (std)‡ | 75.8 | 7.1 (std) |
| Age: 65-74 years | 44,193 | 52.0% | 415,170 | 52.3% |
| Age: 75-84 years | 30,475 | 35.8% | 280,727 | 35.3% |
| Age: 85+ years | 10,399 | 12.2% | 98,402 | 12.4% |
| Gender (Female) | 47,990 | 56.4% | 445,513 | 56.1% |
| Gender (Male) | 37,074 | 43.6% | 348,763 | 43.9% |
| Gender (Unknown) | 3 | <0.1% | 23 | <0.1% |
| **Recorded History of:** | | | | |
| Asthma | 6,603 | 7.8% | 62,946 | 7.9% |
| Blood Disorders | 23,032 | 27.1% | 231,443 | 29.1% |
| Chronic Lung Disease | 28,089 | 33.0% | 277,714 | 35.0% |
| Diabetes | 27,944 | 32.8% | 275,225 | 34.7% |
| Heart Disease | 42,342 | 49.8% | 417,614 | 52.6% |
| Influenza Hospitalization | 73 | 0.1% | 807 | 0.1% |
| Influenza Vaccination | 56,631 | 66.6% | 511,739 | 64.4% |
| Kidney Disorders | 11,464 | 13.5% | 148,959 | 18.8% |
| Liver Disorders | 3,829 | 4.5% | 40,972 | 5.2% |
| Neurological Conditions | 19,142 | 22.5% | 182,187 | 22.9% |
| Pneumococcal Vaccine | 7,984 | 9.4% | 71,405 | 9.0% |
| Pneumonia Hospitalization | 2,925 | 3.4% | 27,260 | 3.4% |
| Statin Use | 45,800 | 53.8% | 434,646 | 54.7% |
| Weakened Immune System | 14,291 | 16.8% | 137,133 | 17.3% |
| Mean Combined Comorbidity Score | 1.3 | 2.4 (std) | 1.6 | 2.6 |
| **Health Service Utilization Intensity:** | | | | |
| Mean number of generic drugs | 9.6 | 6.7 (std) | 9.9 | 6.7 (std) |
| Mean number of unique drug classes | 8.6 | 5.7 (std) | 8.8 | 5.7 (std) |
| Mean number of filled prescriptions | 46.7 | 40.3 (std) | 48.5 | 41.2 (std) |
| Mean number of inpatient hospital encounters | 0.3 | 0.8 (std) | 0.4 | 0.9 (std) |
| Mean number of non-acute institutional encounters | 0.3 | 1.2 (std) | 0.3 | 1.5 (std) |
| Mean number of emergency room encounters | 0.5 | 1.1 (std) | 0.5 | 1.1 (std) |
| Mean number of ambulatory encounters | 25.1 | 20.7 (std) | 25.6 | 23.2 (std) |
| Mean number of other ambulatory encounters | 5.0 | 10.9 (std) | 5.8 | 11.3 (std) |

†Includes first vaccination episode; ‡std: standard deviation

### 3. Appendix E3: Characteristics of Patients Receiving High-Dose and Standard-Dose Influenza Vaccine during the 2012-2013 Influenza Season (548-day Covariate Window)

| Characteristic | Primary Analysis | | | |
|---|---|---|---|---|
| | High-Dose | | Standard-Dose | |
| | N | % | N | % |
| Patients | 138,692 | 100.0% | 875,753 | 100.0% |
| **Patient Characteristics** | | | | |
| Mean age | 75.8 | 7.0 (std)‡ | 75.8 | 7.1 (std) |
| Age: 65-74 years | 72,448 | 52.2% | 460,042 | 52.5% |
| Age: 75-84 years | 49,144 | 35.4% | 305,749 | 34.9% |
| Age: 85+ years | 17,100 | 12.3% | 109,962 | 12.6% |
| Gender (Female) | 78,044 | 56.3% | 490,473 | 56.0% |
| Gender (Male) | 60,640 | 43.7% | 385,255 | 44.0% |
| Gender (Unknown) | 8 | <0.1% | 25 | <0.1% |
| **Recorded History of:** | | | | |
| Asthma | 10,806 | 7.8% | 69,989 | 8.0% |
| Blood Disorders | 37,145 | 26.8% | 255,825 | 29.2% |
| Chronic Lung Disease | 44,698 | 32.2% | 300,834 | 34.4% |
| Diabetes | 45,765 | 33.0% | 306,787 | 35.0% |
| Heart Disease | 68,552 | 49.4% | 459,690 | 52.5% |
| Influenza Hospitalization | 91 | 0.1% | 604 | 0.1% |
| Influenza Vaccination | 91,081 | 65.7% | 559,621 | 63.9% |
| Kidney Disorders | 20,025 | 14.4% | 173,795 | 19.8% |
| Liver Disorders | 6,461 | 4.7% | 47,144 | 5.4% |
| Neurological Conditions | 30,729 | 22.2% | 199,595 | 22.8% |
| Pneumococcal Vaccine | 14,184 | 10.2% | 86,196 | 9.8% |
| Pneumonia Hospitalization | 4,696 | 3.4% | 30,286 | 3.5% |
| Statin Use | 75,522 | 54.5% | 485,009 | 55.4% |
| Weakened Immune System | 23,117 | 16.7% | 149,898 | 17.1% |
| Mean Combined Comorbidity Score | 1.3 | 2.5 (std) | 1.6 | 2.6 |
| **Health Service Utilization Intensity:** | | | | |
| Mean number of generic drugs | 9.5 | 6.6 (std) | 9.8 | 6.7 (std) |
| Mean number of unique drug classes | 8.6 | 5.7 (std) | 8.9 | 5.7 (std) |
| Mean number of filled prescriptions | 45.4 | 39.6 (std) | 47.4 | 40.4 (std) |
| Mean number of inpatient hospital encounters | 0.3 | 0.8 (std) | 0.3 | 0.9 (std) |
| Mean number of non-acute institutional encounters | 0.3 | 1.3 (std) | 0.3 | 1.5 (std) |
| Mean number of emergency room encounters | 0.5 | 1.1 (std) | 0.5 | 1.1 (std) |
| Mean number of ambulatory encounters | 24.4 | 20.2 (std) | 25.5 | 23.2 (std) |
| Mean number of other ambulatory encounters | 5.2 | 10.4 (std) | 6.0 | 11.5 (std) |

†Includes first vaccination episode; ‡std: standard deviation

## 4. Appendix E4: Characteristics of Patients Receiving High-Dose and Standard-Dose Influenza Vaccine during the 2014-2015 Influenza Season (548-day Covariate Window)

| Characteristic | Primary Analysis | | | |
|---|---|---|---|---|
| | High-Dose | | Standard-Dose | |
| | N | % | N | % |
| Patients | 261,552 | 100.0% | 910,249 | 100.0% |
| **Patient Characteristics** | | | | |
| Mean age | 75.6 | 7.0 (std)‡ | 76.0 | 7.2 (std) |
| Age: 65-74 years | 140,344 | 53.7% | 470,873 | 51.7% |
| Age: 75-84 years | 88,879 | 34.0% | 318,533 | 35.0% |
| Age: 85+ years | 32,329 | 12.4% | 120,843 | 13.3% |
| Gender (Female) | 145,981 | 55.8% | 512,882 | 56.3% |
| Gender (Male) | 115,560 | 44.2% | 397,350 | 43.7% |
| Gender (Unknown) | 11 | <0.1% | 17 | <0.1% |
| **Recorded History of:** | | | | |
| Asthma | 21,676 | 8.3% | 75,626 | 8.3% |
| Blood Disorders | 70,295 | 26.9% | 274,057 | 30.1% |
| Chronic Lung Disease | 81,535 | 31.2% | 308,797 | 33.9% |
| Diabetes | 86,189 | 33.0% | 329,786 | 36.2% |
| Heart Disease | 130,419 | 49.9% | 487,503 | 53.6% |
| Influenza Hospitalization | 295 | 0.1% | 1,256 | 0.1% |
| Influenza Vaccination | 172,295 | 65.9% | 578,329 | 63.5% |
| Kidney Disorders | 44,707 | 17.1% | 206,064 | 22.6% |
| Liver Disorders | 13,306 | 5.1% | 52,001 | 5.7% |
| Neurological Conditions | 57,114 | 21.8% | 211,318 | 23.2% |
| Pneumococcal Vaccine | 29,516 | 11.3% | 91,109 | 10.0% |
| Pneumonia Hospitalization | 8,257 | 3.2% | 31,942 | 3.5% |
| Statin Use | 142,138 | 54.3% | 501,069 | 55.0% |
| Weakened Immune System | 43,638 | 16.7% | 153,354 | 16.8% |
| Mean Combined Comorbidity Score | 1.5 | 2.5 (std) | 1.8 | 2.7 |
| **Health Service Utilization Intensity:** | | | | |
| Mean number of generic drugs | 9.3 | 6.7 (std) | 9.7 | 6.8 (std) |
| Mean number of unique drug classes | 8.5 | 5.8 (std) | 8.8 | 5.9 (std) |
| Mean number of filled prescriptions | 43.3 | 38.5 (std) | 45.2 | 40.0 (std) |
| Mean number of inpatient hospital encounters | 0.3 | 0.8 (std) | 0.3 | 0.9 (std) |
| Mean number of non-acute institutional encounters | 0.4 | 1.7 (std) | 0.4 | 1.9 (std) |
| Mean number of emergency room encounters | 0.5 | 1.2 (std) | 0.5 | 1.3 (std) |
| Mean number of ambulatory encounters | 24.7 | 20.3 (std) | 26.1 | 24.6 (std) |
| Mean number of other ambulatory encounters | 5.1 | 10.7 (std) | 6.1 | 11.9 (std) |

†Includes first vaccination episode; ‡std: standard deviation