# Federal Plans to Monitor Immunization Safety for the Pandemic 2009 H1N1 Influenza Vaccination Program

Federal Immunization Safety Task Force

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Agency for Healthcare Research and Quality
Centers for Disease Control and Prevention
Food and Drug Administration
Health Resources and Services Administration
Indian Health Service
National Institutes of Health
Department of Defense
Department of Veterans Affairs

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**Frequently Used Acronyms:**

ACIP—Advisory Committee on Immunization Practices
AAAAI—American Academy of Allergy, Asthma, and Immunology
AAN—American Academy of Neurology
AEFI—Adverse Event Following Immunization
BARDA—Biomedical Advanced Research and Development Authority
CDC—Centers for Disease Control and Prevention
CISA—Clinical Immunization Safety Assessment
CMS—Centers for Medicare and Medicaid Services
CPT—Current Procedural Terminology
DMSS—Defense Medical Surveillance System
DoD—Department of Defense
EIS—Epidemic Intelligence Service
FDA—Food and Drug Administration
GBS—Guillain-Barré Syndrome
H1N1 VSRAWG—Vaccine Safety Risk Assessment Working Group
HHS—United States Department of Health and Human Services
HRSA—Health Resources and Services Administration
IHS—Indian Health Service
IIS—Immunization Information Systems
ILI—Influenza-Like Illness
IOM—Institute of Medicine
MCOs—Managed Care Organizations
NIH—National Institutes of Health
NIIP—National Influenza Immunization Program
NVAC—National Vaccine Advisory Committee
NVPO—National Vaccine Program Office
OTIS—Organization of Teratology Information Specialists
PRISM—Post-Licensure Rapid Immunization Safety Monitoring
RCA—Rapid Cycle Analysis
RMEs—Reportable Medical Event systems
RTIMS—Real Time Immunization Monitoring System
SEC—Slone Epidemiology Center
SME—Subject Matter Expert
VA—Department of Veterans Affairs
VAERS—Vaccine Adverse Event Reporting System
VAMPSS—Vaccines and Medications in Pregnancy Surveillance System
VSD—Vaccine Safety Datalink

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I. Executive Summary

Since the 2009 H1N1 influenza first was identified in the spring, the U.S. Department of Health and Human Services has worked in close partnership with virtually every part of the federal government under a national preparedness and response framework. With unprecedented speed, federal health officials collaborated with industry partners to produce, test, and license 2009 H1N1 influenza vaccines that ultimately will be made available to everyone who wants to get vaccinated. As with seasonal influenza, young children, persons with some chronic health disorders, and pregnant women have a higher risk of severe disease. Clinical trials and safety testing of H1N1 flu vaccines are a critical part of the federal government's H1N1 influenza response plans, and careful stewardship of vaccine safety is integral to maintaining public health and trust in the 2009 H1N1 influenza immunization program

The 2009 H1N1 influenza outbreak poses unprecedented opportunities for collaboration and coordination of activities to monitor vaccine safety. A robust plan for monitoring adverse events following immunization during mass vaccination for 2009 H1N1 influenza is a critical component to ensure the safety of these vaccines. While the safety of 2009 H1N1 flu vaccines are anticipated to be similar to seasonal influenza vaccines, which have an excellent record, extensive efforts have been made to enhance safety systems for 2009 H1N1 influenza monitoring. The primary intent of these efforts is to accelerate the availability of safety data to inform the immunization program, health care providers, and the public.

Departments and agencies across the government are involved in 2009 H1N1 influenza vaccine research, surveillance, or programmatic activities to determine if vaccine safety 'signals,' or adverse events following immunization, are related to the vaccine by chance or are truly adverse reactions. These efforts are being coordinated at the federal level within the U.S. Department of Health and Human Services through the Centers for Disease Control and Prevention, Food and Drug Administration, National Institutes of Health, Health Resources and Services Administration, and the Indian Health Service. Vaccine safety monitoring efforts also are being coordinated with the Department of Veterans Affairs and the Department of Defense. The National Vaccine Program Office within HHS is responsible for coordinating federal vaccine activities, including vaccine safety.

Existing vaccine safety monitoring efforts, which have been in place for many years, are being expanded to respond to the 2009 H1N1 influenza. New systems also have been developed to support the vaccine safety monitoring efforts. This system strengthening includes increased staffing, database improvements, and efforts to enhance reporting to systems such as the Vaccine Adverse Events Reporting System (VAERS). VAERS is operated by the CDC and FDA to take reports from health care providers and the public on possible adverse events following immunization. Improvements for the 2009-2010 influenza season allow VAERS to handle up to 1000 reports per day and follow-up 400 serious adverse events per day, compared to current capacity of 150 reports and 20 follow-ups per day. Other projects include bolstering the Vaccine Safety Datalink, a large-linked database of managed care organizations administered by the CDC

that covers about 9 million people, to determine if adverse events for pre-specified conditions are related to immunization in near real-time.

New systems include the linking of exposure and outcome data following 2009 H1N1 influenza vaccination from large health plans and state registries, covering more than 10 percent of the U.S population or roughly 20 million people, to facilitate safety monitoring of 2009 H1N1 influenza vaccine in near real-time. Another project will explore the safety of 2009 H1N1 vaccine in pregnant women through a collaboration of health care providers, academic medical centers, and vaccine researchers to conducts studies of vaccine, influenza antiviral, and natural influenza exposure and maternal and fetal outcomes. In addition, the CDC is working with the American Academy of Neurology and through additional surveillance sites to identify possible cases of Guillan-Barré syndrome, a rare neurological disorder, following vaccination.

Independent review of the 2009 H1N1 influenza vaccines safety profile is also integral to providing transparent information to health providers, policy makers, and the public. To facilitate this, the National Vaccine Advisory Committee (NVAC) created the H1N1 Vaccine Safety Risk Assessment Working Group to review 2009 H1N1 vaccine safety data as it accumulates. This working group of outside experts will conduct regular, rapid reviews of available data from the federal safety monitoring systems and present them to NVAC and federal leadership for appropriate policy action and follow-up.

Ultimately, the safety profile of the 2009 H1N1 influenza vaccines needs to be considered in the context of the benefits of vaccination, which includes the disease epidemiology and the vaccine effectiveness. A rapid, transparent process for scientific exploration of the vaccines' safety and effectiveness and ongoing communications are important for ensuring optimal policy decisions and public confidence in the immunization program.

II. Introduction

Ensuring that vaccines are as safe as possible is a public health priority and national expectations for vaccine safety are high. A robust plan for monitoring adverse events following immunization (AEFI) during mass vaccination for 2009 H1N1 influenza is an important component to ensure the safety of this novel vaccine. At the federal level, within the United States Department of Health and Human Services (HHS), the Centers for Disease Control and Prevention (CDC), Food and Drug Administration (FDA), National Institutes of Health (NIH), Health Resources and Services Administration (HRSA), and Indian Health Service (IHS) are involved in vaccine safety research, surveillance, or programmatic activities as well as Department of Veterans Affairs (VA), and the Department of Defense (DoD). The HHS National Vaccine Program Office (NVPO) is responsible for coordinating federal vaccine activities, including vaccine safety.

If the 2009 H1N1 monovalent vaccine is widely used as expected, the immunization program requires and the public expects that the federal government has the ability to quickly and effectively ascertain the safety profile of the vaccine to inform vaccine benefit---risk decision making. Proactively communicating this information to the federal government leadership and to the American people is critical to maintaining confidence in vaccine programs. Safety is carefully assessed during pre-licensure, yet some rare adverse events cannot be detected in clinical trials. Therefore, on-going monitoring allows for the detection of rare adverse events.

Additionally, we need to be prepared for the reality that AEFI will occur by chance alone. Every day in the United States people suffer from heart attacks, miscarriages, strokes, and other health-related events. Some result in serious illness, even death. During the pandemic 2009 H1N1 influenza vaccination program, these events will continue to occur. It is important to understand these events will not necessarily be caused by vaccination. For example, there are approximately 6 million pregnancies in the United States each year. Unfortunately, approximately 15% of pregnancies will end in miscarriage. This translates into about 2,500 miscarriages each day in the United States. This is a statistical average; the actual number of miscarriages can vary greatly from day to day and also may be clustered geographically and within clinical practices by chance. A major challenge for this fall's pandemic 2009 H1N1 influenza vaccination program is to be able to quickly identify and characterize any adverse reactions to the vaccine that may occur, and distinguish events that are related to the vaccine from background events that happen to occur simultaneously.

There is heightened public and media interest in vaccine safety, in part because of the 1976 National Influenza Immunization Program (NIIP). The NIIP was intended to curtail what was viewed as an imminent flu pandemic. In less than three months, over 40 million doses of influenza vaccine were administered. However, the NIIP was suspended as cases of Guillain-Barré syndrome (GBS), a rare neurological disorder, were associated with the vaccine. Within four months of the start of the program more than 500 cases of GBS (including 25 deaths) had been reported. Some commentators have speculated that the purported associations between the influenza vaccine and GBS would have had a much smaller impact had the pandemic occurred. The flu pandemic did not materialize and the NIIP was characterized by the New York Times as the "Swine Flu Fiasco." The Institute of Medicine (IOM) recently issued a report concluding

that the evidence favors acceptance of a causal relationship between the 1976 swine influenza vaccine and GBS. While there is mixed evidence that influenza vaccines post-1976 caused GBS, the IOM report concluded that the evidence is inadequate to accept or reject a causal relationship between GBS and influenza vaccines after 1976.

As exemplified by the 1976 swine flu vaccine experience, the federal government needs the capacity to quickly respond to vaccine safety 'signals,' evaluate if they are adverse events temporally related to the vaccine by chance or are truly vaccine adverse reactions, and effectively communicate real benefits and risks. There are three primary areas for vaccine safety monitoring for AEFI that need to be considered: (1) signal detection (hypothesis generation); (2) signal strengthening and verification (hypothesis refinement); and (3) signal confirmation (hypothesis confirmation). Causality assessment is also very important however it may be difficult or impossible within the timeframe needed in the case of a mass vaccination program.

While there are multiple definitions of signals, in this document a signal refers to a concern that an AEFI could be temporally occurring more often than anticipated based on chance alone (i.e., that the AEFI could be related to the receipt of the vaccine). Signals may arise from a variety of sources, including from pre-licensure clinical trials, case reports, passive surveillance, clinical experience, the literature, expert committee reviews, the media, and/or the public. A signal also may arise from a single individual with a convincing clinical pattern such as a challenge/rechallenge case in a person with a disease that is not expected to recur (identical reaction occurs after each vaccination in a series) or in instances where the vaccine strain organism (e.g. attenuated virus) is isolated and associated with a pathological process. Usually, the number of hypotheses raised from these data exceeds the number that is subjected to rigorous hypothesis testing studies due to a dearth of adequate data sources and resources needed for the latter.

Signal strengthening and verification (hypothesis refinement) is a possible intermediate step between hypothesis generation and hypothesis testing to better assess if the AEFI is associated with the use of the vaccine and if the vaccine is a possible cause. Signal strengthening and verification may include a variety of types of studies, including clinical studies and database studies. Many of the databases to be described include a broad sample of the United States population, including young children, adolescents, adults and the elderly. In recent years, large healthcare databases have been used for signal strengthening. Database studies might include exploratory analyses to assess whether claims data reinforce a signal identified using another data source such as the Vaccine Adverse Event Reporting System (VAERS), a national passive surveillance system. This capability may be especially useful internally to help assess which signal(s) to invest resources in a rigorous hypothesis testing study. However, any consideration of results from exploratory analyses would especially need to take into account possible bias (and whether the bias is toward or away from the null hypothesis), confounding, and chance associations (e.g., due to variability in the data or multiple testing). Without further rigorous study to minimize these factors, such analyses generally will not be adequate for signal evaluation.

A rigorous hypothesis confirmation study (signal confirmation) can be performed either within the same database used for signal strengthening and verification or another database system, or

using alternative data sources altogether. Methods typically employed for these sorts of studies are retrospective cohort, self-controlled case series, and case control studies. Typically these studies include investigating cases through medical record review using a standardized case definition. Multiple studies using different study designs in different populations are often conducted. Confirmation studies will determine if there is an association between the AEFI and the exposure (vaccine) and if such as association exists, it is important to quantify the potential magnitude of the risk and identify any subpopulations that may be at increased risk for the AEFI.

An additional phase is causality assessment, which considers all available evidence (e.g., biological plausibility, elimination of confounding factors, etc.) to see if the AEFI is not only associated with use of the vaccine but also the most likely explanation for the AEFI. The establishment of true causality is likely to be difficult or impossible within the timeframe needed to take initial public health action after a signal is verified. As causality assessments draw upon existing research, they typically occur after a number of studies have been done. The Institute of Medicine has reviewed a multitude of vaccine-adverse event causality questions.

More information regarding the vaccine safety system can be found here: *A Comprehensive Review of Federal Vaccine Safety Programs and Public Health Activities*. http://www.hhs.gov/nvpo/nvac/documents/vaccine-safety-review.pdf

III. Vaccine Licensure and Recommendations

On September 15, 2009, four influenza vaccine manufacturers received approval from the FDA for use of 2009 H1N1 monovalent influenza vaccines in the prevention of influenza caused by the 2009 H1N1 influenza virus[1]. The vaccines will be distributed nationally through manufacturers CSL Limited, MedImmune LLC, Novartis Vaccines and Diagnostics Limited, and Sanofi Pasteur Inc. Both live, attenuated and inactivated 2009 H1N1 monovalent vaccine formulations are available; each contains the strain A/California/7/2009(H1N1)pdm. None of the approved 2009 H1N1 monovalent influenza vaccines or seasonal influenza vaccines contain adjuvants, substances to enhance immune response to a vaccine. Children aged 6 months--9 years receiving 2009 H1N1 monovalent vaccines should receive 2 doses, with doses separated by approximately 4 weeks; persons aged 10 years or older should receive 1 dose.

The Advisory Committee on Immunization Practices (ACIP) recommends that programs and providers administer vaccine to persons in the following five target groups (order of target groups does not indicate priority)[2]:

- Pregnant women
- Persons who live with or provide care for infants aged <6 months (e.g., parents, siblings, and daycare providers)
- Health-care and emergency medical services personnel
- Persons aged 6 months--24 years
- Persons aged 25--64 years who have medical conditions that put them at higher risk for influenza-related complications

These five target groups comprise an estimated 159 million persons in the United States. This estimate does not accurately account for persons who might be included in more than one category (e.g., a health-care worker with a high-risk condition).

Decisions about expanding vaccination to include additional populations beyond the five initial target groups should be made at the local level because vaccine availability and demand might vary considerably by area. Once vaccination programs and providers are meeting the demand for vaccine among the persons in the five initial target groups, vaccination should be expanded to all persons aged 25--64 years. Current studies indicate the risk for infection among persons aged ≥65 years is less than the risk for persons in younger age groups. Expanding vaccination recommendations to include adults aged ≥65 years is recommended only after assessment of vaccine availability and demand at the local level. Once demand for vaccine among younger age groups is being met, vaccination should be expanded to all persons aged ≥65 years. This recommendation may need to be reassessed as new epidemiologic, immunologic, or clinical trial data warrant and in the context of global need for vaccine.

[1] Centers for Disease Control and Prevention (CDC). Update on influenza A (H1N1) 2009 monovalent vaccines. MMWR Morb Mortal Wkly Rep. Oct 9;58(39):1100-1.

[2] Centers for Disease Control and Prevention (CDC). Use of Influenza A (H1N1) 2009 Monovalent Vaccine: Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2009. MMWR Morb Mortal Wkly Rep. Aug 21;58(Early Release):1-8

IV. Current Federal Plans to Monitor 2009 H1N1 Monovalent Vaccine Safety

Federal plans for safety monitoring of a 2009 H1N1 monovalent influenza vaccine must be flexible enough to account for the aforementioned uncertainties and changes in the vaccination program. Tables 1 and 2 outline activities and data sources that will be used divided into categories based on their primary role as either "Signal Detection" or "Signal Strengthening and Hypothesis Testing." The Tables provide a summary of strengths and limitations for 2009 H1N1 monovalent vaccine in signal detection, signal verification and hypothesis testing activities.

**1. Signal Detection**

i. The Vaccine Adverse Event Reporting System (VAERS)

The primary method the government will employ to detect vaccine safety signals is VAERS, a national passive surveillance system that accepts reports from physicians, other healthcare providers, and the public. FDA and CDC co-manage VAERS, which was established in 1990. VAERS is an important tool for signal detection of clinically significant AEFIs, such as with intussusception following RotaShield vaccine[3]. The strengths of VAERS are that it is national, it can include any sub-population that receives the vaccine, it can detect signals of rare events, and it can monitor adverse events on a lot-specific basis. However, there are a number of limitations to what VAERS can accomplish in isolation. VAERS is affected by potential reporting biases, including under-reporting (not all events that occur are reported) and media-stimulated reporting leading to over-reporting. Further, VAERS submissions may be incomplete (reports with missing data or insufficient information to validate diagnoses). VAERS can only collect events without the context of the number of doses given (denominator). Distributed doses may act as a crude surrogate denominator, but there is no *true* denominator available for vaccine administration. Consequently, the data do not allow true incidence or prevalence data to be generated. In addition, VAERS data do not include a control (unvaccinated) group, thus not providing a comparison of the risk of adverse events among persons vaccinated to those who were not vaccinated. Given its limitations, VAERS can provide an early signal that a possible vaccine safety problem requires further investigation (signal detection), VAERS data alone are not suitable to evaluate associations between vaccines and adverse events or to establish causality.

For the pandemic 2009 H1N1 influenza vaccination program, VAERS will be utilized for monitoring adverse events and identification of potential unanticipated AEFIs. The CDC is conducting outreach to promote VAERS reporting during the pandemic 2009 H1N1 influenza vaccination program. To enhance the completeness of reporting, an influenza vaccine record card will be delivered together with vaccine to providers. The providers will be asked to complete these cards by filling in information for vaccine type, dose, date, lot number, and VAERS reporting information and give these cards to the vaccinee (or caregiver) to keep with them for one year following the last influenza vaccine received.

[3] Centers for Disease Control and Prevention (CDC). Intussusception among recipients of rotavirus vaccine--United States, 1998-1999. MMWR Morb Mortal Wkly Rep. 1999 Jul 16;48(27):577-81.

CDC and FDA are working to increase capacity for processing, coding, and follow-up of adverse event reports. Database improvements and increased staffing will allow VAERS to handle up to 1000 reports per day and follow-up 400 serious AEFI per day, compared to current capacity of 150 reports and 20 serious AEFI follow-ups per day. Serious AEFI can be defined as those that involve life-threatening conditions, hospitalization, permanent disability, or death. The FDA and CDC have assigned medical officers to work in concert with VAERS case-review and follow-up. In addition, CDC will work with vaccine safety experts in the Clinical Immunization Safety Assessment (CISA) Network to review more closely selected adverse events of clinical interest (e.g., GBS). Other methods of signal detection will be considered, such as signals that may arise during clinical trials or concerns discussed through the media and Internet.

The CDC and FDA will monitor VAERS for pre-specified prioritized outcomes of interest for vaccine monitoring based on potential epidemiological association with current or past vaccines or on biological plausibility regardless of whether the association is a causal relationship. CDC and FDA will also monitor VAERS for unanticipated adverse events and all serious reports will be reviewed. The CDC medical officers will review all pre-specified and serious reports received by VAERS, including medical records when available.

**Table 1: 2009 H1N1 Government Toolbox: Signal Detection**

| Data Source | Strengths | Limitations |
|---|---|---|
| **VAERS** | • Nationwide<br>• Near real-time<br>• Detection of rare or unexpected events<br>• Lot specific surveillance<br>• Data mining | • Underreporting<br>• Consistency<br>• Variable quality of reported information<br>• Specifics on vaccines used<br>• Variable reporting biases<br>• Poorly defined denominators<br>• No controls |

## 2. Signal Strengthening and Verification, and Hypothesis Confirmation

i. Background Rates

Background rates or the rates of health events that typically occur without the use of a 2009 H1N1 monovalent vaccine for common and rare events are needed to assess if the number of AEFIs observed during the pandemic 2009 H1N1 influenza vaccination program are above expected rates. The following groups, in close coordination, have been calculating background rates for pre-specified prioritized outcomes: VSD, VA, DoD, CMS, and PRISM.

ii. Vaccine Safety Datalink (VSD)

The VSD is a large-linked database of managed care organizations (MCOs) administered by the CDC since 1990. The VSD includes eight MCOs that together cover about 9 million people or about 3 percent of the United States population. MCO records that are typically available through the VSD include vaccination history such as date and type (exposure data), outpatient, emergency department, hospital, and laboratory data (outcome data), and demographic information. Rapid cycle analysis is a key methodology that allows for near real-time surveillance for AEFI. Limitations to VSD include the size of the populations under study (which is fairly large, but still not large enough for some rare AEFI), the VSD population is not entirely representative of the U.S. population, and there is limited variability in practice patterns (types of vaccines used). The VSD has provided the infrastructure for a large number of vaccine safety studies and is widely considered the "backbone" of the U.S. vaccine safety system as it is readily able to test hypotheses.

Existing VSD infrastructure can be used for determination of whether or not the vaccine is associated with the AEFI. The VSD has developed a protocol to monitor the safety of 2009 H1N1 monovalent vaccine in near real time, using sequential probability methods (i.e., the Rapid Cycle Analysis [RCA][4]). The protocol will assess risk for 18 pre-specified prioritized outcomes in persons receiving 2009 H1N1 monovalent inactivated and live vaccine products. One method of analysis will compare the risk in time periods for which occurrence of a vaccine adverse event is biologically plausible (risk window) with risk before or after vaccination during other time periods (time frames outside the risk window). Another analytical method will examine whether 2009 H1N1 monovalent vaccine administered in this 2009-10 season is riskier than seasonal influenza vaccines administered in cumulative previous seasons. The 2009 H1N1 monovalent vaccine RCA could be amended if new adverse events of concern were detected in VAERS or through other systems.

iii. Centers for Medicare and Medicaid Services Database

The CMS National Claims History File and Enrollment Database could potentially be used for retrospective and prospective studies. This CMS Medicare database has the potential to be used for vaccine safety studies of the elderly (over 65 years old), as Medicare insures about 35 million elderly persons. However, since the ACIP did not recommend the 2009 H1N1 monovalent vaccine for most Medicare-eligible populations, the use of the vaccine in the CMS population may be minimal, and the utility of the database may be therefore be limited. FDA and CMS have done initial studies using seasonal influenza and pneumococcal vaccines and near real-time surveillance using Medicare raw weekly data. The primary limitation to CMS for vaccine safety monitoring is the use of this dataset for these purposes is fairly new and does not have the historic

[4] Real-Time Vaccine Safety Surveillance for the Early Detection of Adverse Events. Lieu TA, Kulldorff M, Davis RL, Lewis EM, Weintraub E, Yih K, Yin R, Brown JS, Platt R; for the Vaccine Safety Datalink Rapid Cycle Analysis Team. Med Care. 2007 Oct;45(10 Supl 2):S89-95.

experience of systems like the VSD. The Medicare database is important for monitoring adverse events in the elderly, which are often underrepresented in other active surveillance databases.

CMS and FDA developed unique billing codes for 2009 H1N1 monovalent vaccine products to distinguish them from each other and from seasonal influenza vaccine. Current activities include validation of the systems and early testing with 2009 seasonal influenza vaccine. If used, the CMS database would only be helpful if vaccination sites bill CMS for vaccine administration or vaccination data are collected and are able to be linked to the CMS database. Furthermore, data may be available later in the season given the prioritization for who receives the 2009 H1N1 monovalent vaccine does not currently include those 65 and over among the first group of vaccine recipients. The CMS database may be able to provide near-real time claims data, currently available at FDA, to study AEFIs, including the performance of rapid cycle analysis and the potential of case verification through medical records access when appropriate.

iv. Post-Licensure Rapid Immunization Safety Monitoring (PRISM)

The PRISM project entails a system for monitoring the safety of 2009 H1N1 monovalent influenza vaccine in near real-time. PRISM will use vaccine exposure and outcome data from large health plans covering approximately 10% of the United States population, together with vaccine exposure data from Immunization Information Systems (IIS) in eight states. Of the population covered, registry-enhanced data will include about 20 million of these persons. The program will have these components: (1) active surveillance for increased risk of key pre-specified conditions, including Guillain-Barré syndrome, and (2) a system to investigate unanticipated specific concerns when HHS makes requests based on signals from VAERS or other sources. To address the latter need, a Rapid Response System will quickly evaluate the rates of specific outcomes after 2009 H1N1 monovalent vaccine via facilitated access to (a) vaccine exposures, via health plan claims and state IIS data; and (b) outcomes of interest, via health plan data on outpatient and inpatient diagnoses.

Strengths of PRISM are that it uses many components of the well-tested VSD system and will potentially be able to capture a much larger population than VSD. PRISM will be able to link state registry exposure data to health plan data. The novel state registry component of the project will be dependent on states being able to capture the majority of public setting vaccinees in a timely and complete fashion. The primary limitation of PRISM is that the use of the datasets for these purposes is relatively new and does not have the historic experience of systems such as the VSD. Another limitation of this study is that in many instances vaccine type/manufacturer will not be recorded with the exposure data. Current Procedural Terminology (CPT) codes will not be able to capture this specific information and consequently PRISM data that are not supplemented by state registry data will not be able to distinguish between 2009 H1N1 monovalent vaccine manufacturers. The size of PRISM facilitates rapid assessment of rare outcomes.

v. Defense Medical Surveillance System (DMSS)

The DMSS will be used as an active medical surveillance system for the United States military. The DMSS can query personnel (about 1.4 million person-years each year from 1998 to the present), and relational medical databases that contain information on demographics, inpatient and outpatient visits, vaccination, and deployment. For each individual, the DMSS can connect temporal relationships between vaccination and interactions with the Military Health System. The DMSS can be used to search for specific diagnosis codes, calculate rates for adverse events, create concurrent or historical comparison groups, and create a vaccine specific 'severity index' to identify unusual potential events or events not normally identified as impacting safety. As with the VSD, the DMSS has the ability to test vaccine safety hypotheses.

DoD is collaborating with FDA and CDC to use the Defense Medical Surveillance System and the DoD's electronic health record (AHLTA) to implement a three-phase enhanced surveillance system and epidemiologic safety study. The DMSS contains longitudinal health care information covering approximately 2.6 million persons. This project is seeking to coordinate and synchronize the data structure and analysis with the VSD network. Potential signals detected through Rapid Cycle Analysis techniques will be verified using nested case-control and cohort studies. Potential cases will be verified using validated abstraction tools utilizing the DoD's electronic health record system. The DoD will also include passive surveillance through spontaneous reporting to its Reportable Medical Event systems (RMEs) as well as VAERS.

Only active duty military personnel have near-complete capture in the DMSS system and active military personnel are not representative of the U.S. population in terms of age and health status. There is a short delay from when health care services are provided (outcomes are captured) and when they are cleaned and available in the surveillance system. The DMSS also has limited experience with conducting real-time surveillance. Active duty DoD personnel will be among the first to receive the vaccine under current vaccine allocation plans, and consequently this infrastructure will add valuable data on adults aged 17-50 years for assessing vaccine safety early in the use of the 2009 H1N1 monovalent vaccine.

The DoD also has a registry to evaluate the reproductive health outcomes of women who have experienced potential exposures of concern including military occupations, 2009 H1N1 monovalent influenza vaccination, and other military-unique exposures. The DoD Birth and Infant Health Registry captures all birth and health outcomes up to an infant's first birthday to evaluate epidemiologic associations between these outcomes and these specific exposures.

vi. Department of Veterans Affairs Databases

Veterans Affairs has two databases it can use to monitor vaccine safety: (1) Veteran patients and (2) VA employees and volunteers. Veterans Affairs is conducting an evaluation in a pilot cohort of approximately 1.1 million Veteran patients in collaboration

with the FDA that can be used for active surveillance and signal strengthening. The pilot project focuses on evaluation of pre-specified prioritized outcomes of interest. Outcomes associated with seasonal influenza vaccinations in the identified patient cohort (historic cohort Fiscal year 2008). The pilot cohort represents the same facilities where patients will be vaccinated and will be used for tracking H1N1 vaccine administration and seasonal flu vaccination in the fall. Data from VA's linked automated national databases (vaccine administration, ICD-9 codes, laboratory, demographics, geographic regions) are merged at the unique patient level and the rate of events will be assessed. Veterans Affairs databases have been used extensively for signal strengthening and hypothesis testing for medication adverse events and will also be available for signal strengthening or hypothesis testing with chart validation for certain AEFIs. Presently there is a two-week lag between vaccination and follow-up in the pilot integrated database. Veterans Affairs is working to shorten the timeframe for follow-up to 1 week or less. Veterans Affairs database has limitations in terms of the diversity of populations covered and use of the system for vaccine surveillance is fairly new and does not have the historic experience of systems like the VSD. However, VA database offers the opportunity to study populations that might otherwise be difficult to capture.

Veterans Affairs will also have a database which houses information on approximately 377,000 VA employees and volunteers. In addition another estimated 180,000 non-VA federal employees are expected to be vaccinated by designated VA personnel and will have pertinent information regarding vaccine administration in the database. This database will house all reported AEFIs and these will all be reported to VAERS

vii. Population-Based Guillain Barré syndrome Active Case Finding

CDC, through the Emerging Infections Program (EIP), has planned population-based surveillance at ten sites to perform enhanced active neurologic case finding through hospitals and neurologists in multiple geographic areas and assess if there is a risk of developing Guillain-Barré syndrome following vaccination. Assessing for an increased risk will include observed versus expected analysis and self-controlled case series. CDC has developed the protocol and distributed it to principal investigators at selected sites. The budget and funding for this program has been completed and the database and management structure are finalized. CDC is also collaborating with the American Academy of Neurology (AAN) to educate and promote VAERS reporting; the AAN is also providing additional outreach activities targeting neurologists particularly in the EIP catchment areas to enhance GBS case reporting. This collaboration has been funded and several educational activities have begun..

viii. Real Time Immunization Monitoring System (RTIMS)

Post-licensure safety monitoring will be supplemented with an automated internet based system for active post-licensure monitoring of adverse events associated with pandemic 2009 H1N1 immunization. However, VAERS has been and will continue to be the primary mechanism for AEFI reporting from the public. Investigators at Johns Hopkins in collaboration with the CDC have developed an active surveillance system called Real

Time Immunization Monitoring System that will monitor school children (K-12), health care workers, and possibly pregnant women. This system was pilot tested in the 2008-09 influenza season and required vaccinees to answer a series of questions 1 day, 1 week, and 6 weeks post vaccination to monitor late onset serious adverse events. Answers are analyzed using a rule-based algorithm in real-time. The system is programmed to identify adverse events and is set up to send an alert that is displayed at central or satellite facilities allowing for prompt identification of individuals reporting serious symptoms. Challenges include gaining support from vaccination site personnel to provide contact information for vaccinees. All adverse events identified through this system will be reported to VAERS.

ix. Indian Health Service Resource and Patient Management Database (IHS)

The Indian Health Service (IHS) is planning to use electronic health records to conduct surveillance for influenza-like illness (ILI) throughout participating centers. This system has the potential to capture up to 1.6 million persons depending on site participation rates. The IHS has added on ICD-9 codes for AEFI using FDA's list of pre-specified outcomes. IHS will have the data uploaded with approximately a two-week delay. potential limitation of the IHS study is that they have limited experience with vaccine safety studies and the collaboration with FDA is untested. The IHS will be an important population to monitor as it has a large population of pregnant women and children.

x. Clinical Immunization Safety Assessment (CISA)

The Clinical Immunization Safety Assessment (CISA) Network is a network of six academic centers that provides the following: (1) development of research protocols for clinical evaluation (2) case classification and management of AEFI (3) improvement of the understanding of AEFI at the individual level, including possible genetic and other risk factors that might predispose individuals and/or high-risk sub-populations (4) development of evidence-based guidelines for vaccination of individuals at risk for serious AEFIs (5) expert opinion for clinical vaccine safety inquiries. The CISA network has a repository for collection and storage of biological specimens to be used for future studies designed for the in-depth investigation of selected AEFI. The CDC and CISA have developed standard operating procedures for the coordination of CISA Subject Matter Expert (SME) support, particularly recruiting neurologists at each site, during the pandemic 2009 H1N1 influenza vaccination program. CDC will continue to support CISA in the ongoing collection of biological specimens from persons that were reported to VAERS with GBS to test serum for antiganglioside antibodies, and genetic material by whole genome analysis. The DoD's Vaccine Health Care Network can initiate a registry within DoD to ensure long-term follow-up of potential cases of AEFIs, similar to the CISA network repository.

xi. The Vaccines and Medications in Pregnancy Surveillance System (VAMPSS)

The Vaccines and Medications in Pregnancy Surveillance System (VAMPSS) is a collaboration of the Organization of Teratology Information Specialists (OTIS), and

Slone Epidemiology Center (SEC) at Boston University, and the American Academy of Allergy, Asthma, and Immunology (AAAAI). VAMPSS will conduct prospective cohort studies and retrospective case-control studies of vaccine, influenza antiviral, and natural influenza exposure and maternal and fetal outcomes. OTIS receives calls from pregnant women who have been exposed to a variety of medical and environmental substances, including vaccines, and seek information on their safety during pregnancy. Callers may then be enrolled in a cohort study, during which interviews are conducted three times during pregnancy and once post-partum. Outcomes, which are confirmed by chart review, may be compared between participants who were exposed and not exposed to the vaccine, medication, or influenza infection.

The sample size available for study will depend on the vaccination rates of pregnant women; using seasonal influenza vaccine as a model, with a 20% vaccination rate in pregnant women, a conservative estimate of sample size at the end of five years would be 2900 pregnant women/2320 live births (2400 vaccinated, 500 unvaccinated). The SEC Birth Defects Study enrolls mothers with infants with a broad range of birth defects. Mothers are interviewed within six months of delivery about all vaccines and medications received immediately before and during pregnancy. Over a five year period, the SEC Birth Defects Study expects to enroll 8000 subjects with birth defects and 2000 subjects without birth defects. The VAMPSS investigators will initiate a study of the 2009 H1N1 vaccine, antiviral medications, influenza infections and the following outcomes: spontaneous miscarriages, preeclampsia, fetal deaths, preterm births, intrauterine growth restriction, total major congenital malformations, and specific major malformations (e.g., cardiovascular defects and subgroups, oral clefts, limb reduction defects). Because the approach uses direct interview of study participants, vaccinees from a variety of traditional and non-traditional vaccine administration sites may be captured. To gather product information, study subjects will be asked to report the approximate date of administration and the name and location of the administration site. The facility will be contacted to obtain the product information used at that time. Results from a pilot study with seasonal influenza vaccine suggest exposure and product details may be obtained for the large majority of study participants using this approach.

One limitation of this study is its inability to provide timely results. Because a typical pregnancy lasts 9 months, if the length of the pandemic influenza season is similar to seasonal epidemics results will be available only after the influenza season is completed. Small or moderate risks of very rare adverse events may go undetected as the sample size is small. Further, the generalizability of the study may be limited in that women who call the VAMPSS hotline are not likely to be representative of the general pregnant population. Finally, there is the potential for recall bias when they ask parents for previous exposure data once their child has a disability/deformity. The study will commence once the contract and funding have been finalized. AAAAI serves as the coordinating center for both of the studies.

**Table 2: Government 2009 H1N1 Toolbox: Signal Verification and Hypothesis Testing**

| Data Source | Strengths | Limitations |
|---|---|---|
| **VSD** | • Representative ages<br>• Rapid<br>• Proven experience (since 1990)<br>• Large sample (millions)<br>• Chart review possible | • Does not capture vaccinations received outside the MCOs<br>• Delays in receiving data on hospitalizations outside of MCO hospitals |
| **CMS** | • Elderly<br>• Rapid<br>• Very large (>38 million elderly) | • Not certain will be able to identify who received vaccine if States do not bill Medicare<br>• Ability for chart reviews may be limited<br>• Database developed for administrative claims data |
| **PRISM** | • Can capture vaccinations not in medical record<br>• Rapid<br>• Very large (>35 million)<br>• Chart review possible | • Publicly delivered vaccine will be limited to states using IIS<br>• Limited experience in real time surveillance<br>• Registry data sharing for vaccine safety untested<br>• Database developed for administrative claims data |
| **DMSS** | • First respondents<br>• Data on vaccinees<br>• Large (>1 million) | • Healthy population<br>• Limited experience in real time surveillance<br>• Database developed for administrative claims data |
| **VA** | • Includes elderly and federal employees (other than DoD)<br>• ID for those Vaccinated<br>• Rapid<br>• Large sample<br>• Chart reviews possible<br>• Signal Strengthening efforts are a standard operation | • Vaccine database not well tested<br>• Limited experience in signal detection methodology |
| **GBS active case finding** | • Large sample size<br>• Timely<br>• Chart reviews possible | • Challenges in making comparisons to background rates developed from other sources |
| **RTIMS** | • Includes pregnant women, children and healthcare workers | • May be difficult to obtain contact information for vaccinees |
| **IHS** | • Includes minority population<br>• Vaccinee ID may be possible<br>• Large sample (millions)<br>• Chart reviews possible | • Limited experience with vaccine safety studies<br>• Collaboration untested |
| **CISA** | • Provide expert clinical consultation on complex adverse events | • Limited capacity |

| Data Source | Strengths | Limitations |
|---|---|---|
| | • Repository to store specimens<br>• Can look at genetic markers<br>• Develop algorithms and guidelines for assessing AEFIs<br>• Causality assessment | |
| **VAMPSS** | • Capture exposure in a variety of settings<br>• Captures outcomes of exposures both prospectively and retrospectively | • Long lag time until most outcomes of interest may occur<br>• Selection & recall bias<br>• Moderate sample size may cause small or moderate risks of very rare adverse events to go undetected |

xii. Special Studies

Depending on the outcome of interest, ad hoc studies are often conducted to investigate vaccine safety issues. Typically, these studies investigate fairly uncommon events and consequently case-control studies are frequently conducted. There are a variety of approaches that can be used to identify cases for a case-control study. During the 1955 investigation of an outbreak of polio associated with vaccine manufactured by Cutter Laboratories, Polio Reporting Officers were designated by each state, and personnel of local health departments informed the Reporting Officers of vaccine-associated cases; CDC Epidemic Intelligence Service (EIS) officers assisted as well. Similarly, during the last experience with a mass vaccination for a novel influenza virus (1976 swine flu), vaccine safety studies were conducted through a collaborative effort between CDC and state and local health authorities, who reached out to practicing neurologists to identify cases of GBS and reported cases to CDC daily. In 1999, hospitals in 19 states were identified with significant cases of intussusception and CDC coordinated a field investigation to identify cases of intussusception following RotaShield vaccination. A recently published study used the VAERS database to identify cases to examine whether receipt of the Lyme disease vaccine antigen was associated with arthritis in individuals with treatment-resistant Lyme arthritis-associated HLA alleles. The primary advantage of special studies is that they can be tailored to address the specific issue of concern and be done relatively quickly. However, special studies require considerable effort and resources and need time to plan, execute and analyze. Utilization of existing infrastructure for special studies (e.g., identifying cases) can reduce the time needed to conduct such studies. The CDC will be ready to support state/local health departments to conduct field investigations as required during vaccination with 2009 H1N1 monovalent vaccines. Efforts are being made to prepare for rapid investigations to help in signal verification, if signals are identified.

V. Assessing the Safety Profile of the Vaccine

The National Vaccine Advisory Committee (NVAC) recommended in July 2009 that an independent group of outside experts be formed to transparently review 2009 H1N1 monovalent vaccine safety data as it accumulates. In direct response to this NVAC recommendation the "H1N1 Vaccine Safety Risk Assessment Working Group (H1N1 VSRAWG)" was created to aid in review of the safety data. The VSRAWG is a working group of NVAC. The H1N1 VSRAWG will independently synthesize the available information and conduct ongoing safety risk assessments that are transparent and based on the best available surveillance knowledge. The H1N1 VSRAWG will conduct regular, rapid reviews of available data from the federal safety monitoring systems. Findings from the H1N1 VSRAWG will be presented to the NVAC for its deliberation and NVAC's advice will be formally communicated to the Assistant Secretary for Health and will be shared with other relevant Agencies, Departments, and HHS Advisory Committees for appropriate policy action and follow-up.

While the safety profile of 2009 H1N1 monovalent vaccines are anticipated to be similar to seasonal influenza vaccines, which have been used extensively with an excellent safety profile, efforts have been made to enhance safety systems for H1N1 monitoring. The primary intent of these safety enhancements is to accelerate the availability of safety data to inform the immunization program, health care providers, and the public. Despite these efforts, there will inevitably be a time delay between when safety signals arise and when science is available to inform assessments of whether such signals are due to the vaccine or temporally related coincidental events that are anticipated. The time that is required for such determinations is primarily dependent on the incidence of the health event under investigation, how the health event is diagnosed and reported to large-linked databases, and the magnitude of the risk that is being explored. Ultimately, the safety profile of the vaccine needs to be considered in the context of the benefits of vaccination, which includes the disease epidemiology and the vaccine effectiveness. Rapid scientific exploration of the safety and effectiveness of the vaccine, a transparent process for such evaluations, and rapid and ongoing communications are important for ensuring optimal policy decisions and public confidence in the immunization program.