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Immunization-Safety Monitoring Systems for the 2009 H1N1 Monovalent Influenza Vaccination Program

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The effort to vaccinate the US population against the 2009 H1N1 influenza virus hinged, in part, on public confidence in vaccine safety. Early in the vaccine program, 20% of parents reported that they would not vaccinate their children. Concerns about the safety of the vaccines were reported by many parents as a factor that contributed to their intention to forgo vaccination (see www.hsph.harvard.edu/news/press-releases/2009-releases/survey-40-adults-absolutely-certain-h1n1- vaccine.html and www.med.umich.edu/mott/npch/reports/h1n1.htm). The safety profiles of 2009 H1N1 monovalent influenza vaccines were anticipated to be (and have been) similar to those of seasonal influenza vaccines, for which an excellent safety profile has been demonstrated. Here we describe steps taken by the US government to (1) assess the key federal systems in place before 2009 for monitoring the safety of vaccines and (2) integrate and upgrade those systems for optimal vaccine-safety monitoring during the 2009 H1N1 monovalent influenza vaccination program. These efforts improved monitoring of 2009 H1N1 vaccine safety, hold promise for enhancing future national monitoring of vaccine safety, and may ultimately help improve public confidence in vaccines.

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abstract

The effort to vaccinate the US population against the 2009 H1N1 influenza virus hinged, in part, on public confidence in vaccine safety. Early in the vaccine program, >20% of parents reported that they would not vaccinate their children. Concerns about the safety of the vaccines were reported by many parents as a factor that contributed to their intention to forgo vaccination (see www.hsph.harvard.edu/news/press-releases/2009-releases/survey-40-adults-absolutely-certain-h1n1-vaccine.html and www.med.umich.edu/mott/npch/reports/h1n1.htm). The safety profiles of 2009 H1N1 monovalent influenza vaccines were anticipated to be (and have been) similar to those of seasonal influenza vaccines, for which an excellent safety profile has been demonstrated. Here we describe steps taken by the US government to (1) assess the key federal systems in place before 2009 for monitoring the safety of vaccines and (2) integrate and upgrade those systems for optimal vaccine-safety monitoring during the 2009 H1N1 monovalent influenza vaccination program. These efforts improved monitoring of 2009 H1N1 vaccine safety, hold promise for enhancing future national monitoring of vaccine safety, and may ultimately help improve public confidence in vaccines. *Pediatrics* 2011;127:S78–S86

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KEY WORDS

vaccine safety, H1N1 influenza

ABBREVIATIONS

FDA—Food and Drug Administration
HHS—Department of Health and Human Services
GBS—Guillain-Barré syndrome
VA—Department of Veterans Affairs
DoD—Department of Defense
VAERS—Vaccine Adverse Event Reporting System
CDC—Centers for Disease Control and Prevention
VSD—Vaccine Safety Datalink
RCA—rapid cycle analysis
MCO—managed care organization
CISA—Clinical Immunization Safety Assessment
NVAC—National Vaccine Advisory Committee
RTIMS—Real Time Immunization Monitoring System
PRISM—Post-licensure Rapid Immunization Safety Monitoring
VAMPSS—Vaccines and Medications in Pregnancy Surveillance System
VSRAWG—Vaccine Safety Risk Assessment Working Group

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Central to the federal response to the 2009 H1N1 influenza pandemic was a vaccination program unprecedented in its size and scope in the United States. The 2009 H1N1 monovalent influenza vaccines were approved by the US Food and Drug Administration (FDA) of the US Department of Health and Human Services (HHS) as a strain change to each manufacturer's seasonal influenza vaccine. There is considerable experience with seasonal influenza vaccine development and production. Influenza vaccines have a long track record of safety and effectiveness in the United States. The 2009 H1N1 monovalent influenza vaccines underwent the same testing and lot-release procedures that are in place for seasonal influenza vaccines. Consequently, the safety profiles of 2009 H1N1 monovalent influenza vaccines were anticipated to be similar to the excellent safety profile of seasonal influenza vaccines. In addition, the safety of the 2009 H1N1 monovalent influenza vaccines was carefully assessed in multiple clinical trials. The sample sizes of these trials limited the ability to detect rare adverse events. Populations at high risk, such as those with chronic diseases, are sometimes not well represented in clinical studies; however, additional efforts were made for 2009 H1N1 monovalent influenza vaccines to include in clinical trials pregnant women and people with underlying illness such as asthma and HIV infection.

A key component of any immunization program is postlicensure safety monitoring.[1] Such a monitoring system must have the ability to quickly identify and characterize adverse events after vaccination. A vaccine-safety monitoring system should have the capacity to distinguish a potential increased risk of an adverse event caused by the vaccine from events that occur as part of the background incidence of these diseases in temporal association with vaccination.[1] Broad and integrated efforts that monitor vaccine safety after licensure are important for rapidly and effectively defining the safety profile of a vaccine.

The vaccine-safety monitoring process includes 3 primary activities:

1. Signal detection, strengthening, and verification involve detection of medical events after vaccination and an evaluation of whether these adverse events could be occurring more frequently after vaccination than expected by chance alone. For this activity, potential signals are evaluated to assess whether they warrant further investigation. This evaluation includes examining if the reported events were well defined and properly coded, if the events were reported from multiple reporting sources or only by a few, or if there was a pattern of association between vaccination and adverse events (eg, temporal or demographic relationships or subpopulations affected). Efforts are also made to look for unexpected clinical clusters and positive rechallenges (symptoms that reoccur after readministration of vaccine).
2. Assessment of association involves evaluating whether there is an association between vaccination and an adverse event. If an association between the vaccine and the outcome is found, it is important to determine the magnitude of the association and whether potential subpopulations are at increased risk.
3. Assessment of the evidence and causality involves evaluating whether the available science favors acceptance or rejection of a relationship between the vaccine and the adverse event, which often requires population-based active surveillance and formal epidemiologic studies. Causality assessments typically include consideration of the strength or magnitude of the association, consistency, specificity, temporality, biological gradient, biological mechanism, coherence, experimental evidence, and analogy.[2]

Before the initiation of the 2009 H1N1 monovalent influenza vaccination program, a number of existing systems addressed these 3 activities of the safety monitoring system. The HHS led an effort to enhance existing systems and integrate new vaccine-safety monitoring systems. These efforts were deemed to be integral to the immunization program given its size and prominence and residual concerns about the 1976 pandemic influenza vaccination program in which the vaccine was associated with Guillain-Barré syndrome (GBS). In this article, we discuss the existing systems for monitoring vaccine safety and enhancements that were made to support the 2009 H1N1 influenza vaccination program.

FEDERAL SYSTEMS FOR MONITORING VACCINE SAFETY BEFORE THE 2009 H1N1 MONOVALENT INFLUENZA VACCINES

The US vaccine-safety system is composed of a number of programs managed by federal agencies within the HHS, the Department of Veterans Affairs (VA), and the Department of Defense (DoD). A brief description of the vaccine-safety system before the 2009 H1N1 monovalent influenza vaccines follows. A more comprehensive review of federal vaccine-safety monitoring systems is available elsewhere.[3]

Signal Detection, Strengthening, and Verification

The Vaccine Adverse Event Reporting System (VAERS), established in 1990, is co-managed by the FDA and the Cen-

ters for Disease Control and Prevention (CDC). The VAERS is a national passive surveillance system that receives reports of potential adverse events from many sources including health care providers and the public. The VAERS can assess early indicators of a possible vaccine-safety problem that may present as new or unusual adverse events or patterns of reports. For example, in 1999, the VAERS was the first postlicensure source to signal an increased risk of intussusception after the first dose of the rotavirus vaccine RotaShield (Wyeth Laboratories, Marietta, PA). This signal was later confirmed to be a true association.[4] Because the VAERS is a passive reporting system for those who have been vaccinated, it is not able to determine how many people have been vaccinated or the rates of events among persons not vaccinated. In addition, as a passive reporting system, the VAERS suffers from underreporting and incomplete reporting. Consequently, it is useful for signal detection, whereas other systems are used to determine associations between vaccination and adverse events.[5]

Four related systems take advantage of administrative and clinical data available in health care systems. The Vaccine Safety Datalink (VSD), administered by the CDC, uses rapid cycle analysis (RCA) to strengthen and verify signals of prespecified outcomes and to assess associations (discussed more later). The VSD consists of a large linked database of 8 managed care organizations (MCOs) that cover ~9 million people, or 3% of the US population. MCOs contribute demographic and vaccination data linked to diagnoses from medical encounters. The VSD can be used for a broad range of studies, because it has fairly complete data on vaccine exposures and health outcomes coupled with chart review as needed.

The DoD uses the Defense Medical Surveillance System (DMSS) as a central repository of medical surveillance data for the US armed forces (~1 million persons). Military health records in this system can be used to examine medical outcomes after vaccination.[6–8] The DMSS can be used for signal detection through data-mining as well as signal strengthening and verification.

The VA has collaborated with the FDA since 2008 to use data from the VA national databases to detect potential vaccine-safety signals among the veteran and VA employee populations. Early evaluations have assessed the safety of influenza and pneumococcal vaccines.

The FDA and the Centers for Medicare and Medicaid Services initiated a pilot project in 2006 to assess the feasibility of using Medicare data for prospective rapid safety assessment of vaccines administered in the Medicare population. Medicare insures persons who are 65 years old or older and younger persons with disabilities or end-stage renal disease. More than 45 million persons (including 38 million people aged ≥65 years) are enrolled in Medicare. Claims data are available for ~35 million persons with fee-for-service Medicare. Although largely limited to older populations, the size of the enrolled population provides opportunities to evaluate rare adverse events that other systems may not be able to address.

Assessment of Association

The VSD is the primary system for assessing associations between vaccines and adverse events, because it links vaccination status and health outcomes, which provides the infrastructure to rapidly test hypotheses. The VSD is used for a large number of vaccine-safety studies and is widely considered to be the backbone of the US vaccine-safety system. A broad range of study designs are used by the VSD, including cohort, case-control, and self-controlled case-series studies.

The Defense Medical Surveillance System has capabilities similar to those of the VSD and is widely used within the DoD to investigate a broad array of exposures and outcomes that are often unique to the military population.

Additional studies may be conducted, in coordination with state health departments and/or epidemic intelligence service officers, as part of outbreak investigations to evaluate potential vaccine-safety concerns. Because these studies typically investigate rare events, case-control studies can be conducted, such as those examining intussusception after the rotavirus vaccine. A variety of approaches can be used to identify cases for case-control studies, including active surveillance systems.[4,9]

Assessment of the Evidence and Causality

In 2001, the CDC established the Clinical Immunization Safety Assessment (CISA) Network. Centers in the CISA Network investigate the pathophysiologic mechanisms and biological risks of vaccine adverse events, which are important considerations for causality assessment. These centers conduct in-depth immunologic, pathologic, and genetic assessments to elucidate underlying mechanisms of vaccine adverse events. In addition to contributing to the body of evidence needed for causality assessments, the CISA Network assists clinicians in evaluating and managing the conditions of people with possible vaccine adverse reactions.

For independent expert review of the evidence for causality of particular vaccines and adverse events, the US government has periodically relied on independent, nongovernmental review through the Institute of Medicine (IOM) of the National Academies. The IOM

conducted its first report on vaccine safety in 1977 and has subsequently published 6 adverse-event reviews. These reviews cover a range of adverse events such as encephalopathy, GBS, and sudden infant death syndrome. Reviewers consider potential biological mechanisms, epidemiologic and clinical data, the burden of the adverse event, the burden of the vaccine-preventable disease, and salience to the public. The IOM is currently conducting a comprehensive review of the epidemiologic, clinical, and biological evidence regarding adverse health events associated with specific vaccines covered by the National Vaccine Injury Compensation Program.

ENHANCING THE VACCINE-SAFETY MONITORING SYSTEM TO SUPPORT THE 2009 H1N1 MONOVALENT INFLUENZA VACCINE PROGRAM

The 2009 H1N1 monovalent influenza vaccine program prompted the federal government and the National Vaccine Advisory Committee (NVAC), a federal advisory committee that provides recommendations to the Assistant Secretary for Health, to assess the capacity of the existing safety-monitoring systems. The NVAC made 5 recommendations[10,11] regarding 2009 H1N1 vaccine-safety monitoring: (1) enhance active surveillance for signal confirmation and evaluation of possible associations between vaccines and adverse events; (2) establish a transparent and independent review of vaccine-safety data as it accumulates; (3) develop and disseminate a federal plan to monitor 2009 H1N1 monovalent influenza vaccine safety; (4) assemble background rates of adverse events that occur in the general population; and (5) develop and, when possible, test in advance a strong and organized response to scientific and public concerns about vaccine safety. Actions taken to respond to these recommendations are described below.

Signal Detection, Strengthening, and Verification

A number of efforts were made to facilitate adverse-event reporting. The CDC developed an influenza vaccination record card for immunization providers to give to the vaccine recipient with the vaccine. The card included information on how to report an adverse event to the VAERS. Providers were asked to record vaccine type, dose, date, and lot number on the card. At the time of vaccination, cards were given to the vaccine recipient (or caregiver) to keep for 1 year after the last 2009 H1N1 influenza vaccine received. All reports of serious events to the VAERS were reviewed daily, and the frequency of events after 2009 H1N1 monovalent influenza vaccines was compared with the frequency of events after seasonal influenza vaccines. Medical records from people who experienced serious adverse events were quickly obtained and reviewed. In addition, the CDC actively monitored newspaper articles and blogs to quickly identify public concerns that might indicate a vaccine-safety signal.

The HHS Indian Health Service developed and deployed in May 2009 the Influenza Awareness System. This system covered seasonal and 2009 H1N1 vaccination and potential vaccine adverse events.

The Real Time Immunization Monitoring System (RTIMS), developed at Johns Hopkins University and sponsored by the CDC, used an automated Web-based active surveillance system to track adverse events among vaccines. Previously, the DoD piloted a similar electronic monitoring system to assess patient experiences after smallpox and seasonal influenza vaccination.[12,13] The RTIMS was pilot-tested by Johns Hopkins in the 2008–2009 influenza season. During the 2009–2010 influenza season, vaccine recipients either gave permission to be contacted for follow-up at the time of their immunization or chose to log onto a Web site and answer an electronic questionnaire. Follow-up e-mail reminders provided a link to questionnaires to provide answers to a series of health-related questions at various time points after vaccination. Answers were analyzed by using a rule-based algorithm in real time. Like the VAERS, this system only collected data on vaccine recipients and lacked data from a nonvaccinated comparison group. Comparisons between types of vaccines (eg, seasonal versus 2009 H1N1 monovalent influenza vaccines and live versus inactivated) were made. RTIMS investigators collected supplemental information by follow-up telephone and e-mail contact with vaccine recipients and their health care providers. Reporting rates for adverse events among those who received 2009 H1N1 monovalent influenza and seasonal influenza vaccines were assessed. Strengths and limitations of the VAERS and RTIMS are summarized in Table 1.

A prioritized list of potential adverse events, along with plausible time windows for their occurrence to be related to the vaccine, was developed on the basis of epidemiologic associations with current or past vaccines or on biological plausibility (see Appendix). These prespecified outcomes were investigated by using rapid surveillance methodologies (RCA) in the VSD, Defense Medical Surveillance System, and other systems described below. For example, background rates were calculated for GBS and other potential neurologic illnesses of the central nervous system (such as acute disseminated encephalomyelitis, encephalitis, myelitis, and optic neuritis) for comparison to rates after vaccination.[14–24] Additional health outcomes could have been added for RCA had po-

TABLE 1 Signal Detection Programs Strengths and Limitations

Data Source	Strengths	Limitations
VAERS	Nationwide	Passive system prone to underreporting, lack of consistency in reporting, and variable quality of reported information
	Near real-time	
	Can detect rare or unexpected events	Not well-defined denominators only available from other sources
	Lot-specific surveillance	No comparison group
	Data-mining	
RTIMS	Actively soliciting symptoms after vaccination by enrolling participants the same day or shortly after receipt of vaccine (14 000 2009 H1N1 monovalent influenza vaccine doses captured)	Recruiting large numbers of persons is challenging
		Sample size inadequate for rare events
	Can target subpopulations	Surveys completed after vaccination

tential signals arisen during the course of the vaccine program, which to date has not been the case. RCA compares the rates of prespecified events that occurred after 2009 H1N1 monovalent influenza vaccination with the number of events that would be expected. Expected rates were initially calculated on the basis of persons who received seasonal influenza vaccine in previous years, which allowed comparisons to be made on an ongoing and regular basis. Final (end-of-season) analyses will calculate expected rates among persons who received the 2009 H1N1 monovalent influenza vaccine during different time periods (self-controlled analysis). The self-controlled analysis has advantages over making comparisons to historic controls (those who received seasonal influenza vaccines in previous years), because it does not suffer from potential bias that may be caused by differences in the underlying populations (those who receive seasonal influenza vaccines may be different from those who receive 2009 H1N1 vaccines). However, self-controlled analysis is less timely, because it requires additional time windows used for comparison purposes to elapse. For both of these analyses, power is primarily driven by the number of persons who receive 2009 H1N1 monovalent influenza vaccines captured in the surveillance systems.

The VSD, DoD, VA, and Centers for Medicare and Medicaid Services systems can use data on who was vaccinated and assess their health outcomes. Although the primary purpose of these systems during 2009 H1N1 vaccine-safety monitoring was signal detection, strengthening, and verification, they have the ability to assess associations if needed.

Assessment of Association

Several systems were used to assess an association in addition to the VSD, which historically met this need. The VSD has been a critical element of the vaccine-safety system, especially in assessing associations between vaccines and adverse events. However, the NVAC noted that the capacity of the VSD to meet the needs for monitoring safety during the 2009 H1N1 monovalent influenza vaccine program may be limited for 2 primary reasons. First, despite its large size, the ability of the VSD to rapidly assess emerging issues might not be timely enough, particularly for extremely rare adverse events and events that occur among subpopulations. Second, MCOs that participate in the VSD may not necessarily capture significant portions of 2009 H1N1 monovalent influenza vaccine administered at sites outside of the MCOs such as health departments, schools, and mass-vaccination clinics. To address these limitations, several approaches (described below) were used to enhance assessment of associations.

The Post-licensure Rapid Immunization Safety Monitoring (PRISM) Network, a collaborative effort between multiple health plans, federal and state health agencies, for-profit and nonprofit organizations, and academic institutions, was established to address these potential limitations. The PRISM Network linked health plan and Immunization Information Systems (IIS) data, conducted continuous active surveillance for prespecified outcomes, and could provide timely information on unanticipated potential risks if needed. PRISM was built on a distributed research network in which data were physically held and managed by each data owner. Development of PRISM benefited from previous experiences with the VSD and a recent study in which GBS among adolescents who received the meningococcal conjugate vaccine was examined.[25] PRISM used vaccine exposure and claims-based outcomes from 5 large health plans that covered ~26 million people, together with vaccine-exposure data from IIS in 8 states. Registry-enhanced data from ~14 million persons captured publicly delivered vaccine. Data from the PRISM network started to be available in January 2010.

The Indian Health Service, VA, and DoD adapted their data systems to conduct RCA in as harmonized a manner as feasible with the VSD and PRISM Network to facilitate data-sharing and interpretation.

Through the collaborative efforts of the FDA and Centers for Medicare and Medicaid Services, the development of methods to use Medicare data for near–real-time active safety surveillance of 2009 H1N1 monovalent influenza vaccines was accelerated. This

work focused on monitoring GBS. Availability of vaccinations in the Medicare data depends on providers billing Medicare. The Centers for Medicare and Medicaid Services created new billing codes for use by vaccine providers to distinguish administration of 2009 H1N1 monovalent influenza vaccines from seasonal influenza vaccines.[26,27]

The CDC implemented population-based active surveillance at 10 sites around the country that participate in its Emerging Infections Program (EIP) to identify cases of GBS. The catchment population was ~45 million people. The primary method for case ascertainment was through a network of neurologists and hospitals. GBS cases captured through this system were reviewed by using standardized case definitions. GBS cases identified and verified through this system were compared with the expected number of GBS cases determined through estimates of vaccine coverage and background rates of GBS available through the literature. The CDC also collaborated with the American Academy of Neurology to educate neurologists about reporting to the VAERS and to enhance GBS case-finding.

The Vaccines and Medications in Pregnancy Surveillance System (VAMPSS) is a collaboration of the Organization of Teratology Information Specialists (OTIS), Slone Epidemiology Center, and the American Academy of Allergy, Asthma and Immunology. The VAMPSS received funding from the HHS Office of the Assistant Secretary for Preparedness and Response and its Biomedical Advanced Research and Development Authority. The VAMPSS conducts prospective cohort and retrospective case-control studies of influenza vaccines, influenza antiviral drugs, and natural influenza exposure and maternal and fetal outcomes. The OTIS receives calls from pregnant women who have been exposed to a variety of medical and environmental substances including vaccines. The OTIS collects information on vaccine exposure during pregnancy and enrolls subjects in cohort and case-control studies. As of May 2010, the VAMPSS was still in the process of study initiation for 2009 H1N1 monovalent influenza vaccines.

The DoD's Naval Health Research Center, through its Center for Deployment Health Research and Birth and Infant Health Registry, initiated both a prospective and retrospective analysis among pregnant women who received 2009 H1N1 monovalent influenza vaccines. The study objective is to describe the incidence and prevalence of adverse reproductive health outcomes among female military service members who received the vaccine during pregnancy. As of May 2010, data were not yet available. Final results are expected within 1 year of the infants reaching their first birthday.

The CISA Network supported 2009 H1N1 monovalent influenza vaccine-safety monitoring by collecting medical histories and biological samples for prespecified events (including many listed in the Appendix) reported to the VAERS. For example, some vaccine recipients who reported GBS to the VAERS were contacted by CISA Network investigators who requested serum and mucosal swab specimens that could be used for host risk-factor assessment if and when the need arises.

Table 2 provides the status of the systems described above in relation to 2009 H1N1 monovalent influenza vaccine-safety monitoring as well as their strengths and limitations for signal strengthening and verification and assessment of association.

Assessing the Evidence

The NVAC H1N1 Vaccine Safety Risk Assessment Working Group (VSRAWG) was created to independently assess the safety profile of 2009 H1N1 monovalent influenza vaccines and to develop, on a timely basis, appropriate information for presentation to, and deliberation by, the NVAC. The VSRAWG included a broad range of expertise important for assessing vaccine safety and included representatives from 5 federal vaccine advisory committees (Vaccines and Related Biological Products Advisory Committee, Advisory Committee on Immunization Practices, NVAC, National Biodefense Science Board, and Defense Health Board) and a consumer representative. The VSRAWG was responsible for reviewing data generated by the systems described above on a biweekly basis and more frequently as necessary. If potential signals were identified, the VSRAWG was charged with examining possible associations between 2009 H1N1 monovalent influenza vaccines and the adverse event of interest. The NVAC deliberated on the information presented to it by the VSRAWG, forwarded the reports of the VSRAWG (as it deemed appropriate) to the HHS, and made recommendations to the Assistant Secretary for Health on the basis of the NVAC deliberations. If associations were found, the VSRAWG would advise whether the association between the vaccine and the adverse event was likely caused by the vaccine. The VSRAWG provided monthly reports that summarized its findings to the NVAC.[28] NVAC reports from the VSRAWG were rapidly shared with international health authorities and made publicly available.

CONCLUSIONS

The US government made a number of enhancements to existing vaccine-safety monitoring systems in preparation for the 2009 H1N1 monovalent influenza vaccine program. Analyses of data are ongoing and will be published once complete. Thus far, these systems have demonstrated that the 2009 H1N1 monovalent influenza vaccines have a similar safety profile to that of seasonal influenza vaccines, which

TABLE 2 Signal Strengthening and Verification and Assessment of Association Programs Strengths and Limitations

Data Source and Status in Relation to 2009 H1N1 Monovalent Influenza Vaccination Program	Strengths	Limitations
VSD: existing	Includes people from all life phases (eg, children, adults, pregnant women, etc)	Does not capture all vaccinations received outside the MCOs
	Rapid	Delays in receiving data on health encounters and hospitalizations outside of MCO hospitals
	Experienced (since 1991)	
	Large sample (1.5 million 2009 H1N1 monovalent influenza vaccine doses captured)	
	Can link with vaccine registries when needed	
	Chart-review capability	
CMS Medicare data: accelerated development for 2009 H1N1	Predominately aged ≥65 y	Database developed for administrative claims data
	Rapid	Elderly not initially part of 2009 H1N1 vaccine priority group
	Very large (3 million 2009 H1N1 monovalent influenza vaccine doses captured, primarily for the elderly)	Capturing vaccination data depends on providers billing Medicare
PRISM: newly developed for 2009 H1N1	Includes people from all life phases (eg, children, adults, pregnant women, etc)	Incomplete capture of vaccinations
	Can capture vaccinations not in medical record	Limited ability to distinguish between specific 2009 H1N1 vaccine types (ie, live vs inactivated)
	Ascertainment of publicly delivered vaccine	Publicly delivered vaccine will be limited to states that use the Immunization Information System
	Rapid once system fully functional	Data-sharing for vaccine safety untested
	Very large (2.5 million 2009 H1N1 monovalent influenza vaccine doses captured)	Database developed for administrative claims data
	Chart review possible	Data started to become available in January 2010
DMSS: existing	Captures the DoD's mandatory vaccination program	Healthy population
	Clinical data from the electronic health record on exposure and outcomes	Limited ages represented
	Large (1.3 million 2009 H1N1 monovalent influenza vaccine doses captured)	Limited experience in real-time surveillance
	Rapid	Database developed for traditional epidemiologic studies
	Experienced	Focused on military-unique exposures
	Chart reviews possible	
VA: accelerated development for 2009 H1N1	Includes elderly and federal employees (other than those of the DoD)	Focused primarily on veteran-unique exposures
	Rapid	Vaccine database not well tested
	Large (1.2 million 2009 H1N1 monovalent influenza vaccine doses captured)	Limited experience in vaccine-safety studies
	Chart reviews possible	
GBS, active case-finding: newly developed for 2009 H1N1	Large sample size (catchment population of 45 million people)	Imprecision in making comparisons to background rates developed from other sources
	Timely	Imprecision in vaccinated population estimated from survey data
	Chart reviews	
Indian Health Service: newly developed for 2009 H1N1	Includes people from all life phases (eg, children, adults, pregnant women, etc)	Limited experience with vaccine-safety studies
	Includes minority population	
	Moderate-sized population (321 000 2009 H1N1 monovalent influenza vaccine doses captured)	
	Vaccination and adverse events collected via unified system	
	Chart reviews possible	
VAMPSS: newly developed for 2009 H1N1	Captures exposures in a variety of settings	Long lag time until most outcomes of interest may occur
	Captures outcomes of exposures both prospectively and retrospectively	Potential for selection and recall bias
		Moderate sample size may cause small or moderate risks of very rare adverse events to go undetected

have an excellent safety profile. An evaluation is planned for all programs and systems developed to monitor 2009 H1N1 monovalent influenza vaccine safety. These programs may prove useful for future mass and routine vaccination programs. In addition, these programs may lead to a sustainable, more robust vaccine-safety monitoring system for the nation.

FEDERAL IMMUNIZATION SAFETY TASK FORCE H1N1 WORKING GROUP MEMBERS

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APPENDIX Prespecified Outcomes and Definitions Used for RCA

Influenza Vaccine Type	Outcome	ICD-9 CM Code	Primary Postvaccination Follow-up Window (Secondary Window), d
All	GBS	357.0	1–42
All	Myelitis, acute disseminated encephalomyelitis, and other encephalitis	323.5, 323.51, 323.52, 323.6, 323.61, 323.62, 323.63, 323.8, 323.81, 323.82, 323.9, and 341.2	1–42 (1–21)
All	Bell's palsy	351.0	1–60 (1–42)
All	Anaphylaxis	995.0 and 999.4	0–2
All	Other demyelinating disease (multiple sclerosis, demyelinating disease of central nervous system, optic neuritis, chronic inflammatory demyelinating polyneuropathy)	340, 341.0, 341.8, 341.9, 377.30, 377.31, 377.32, 377.34, 377.39, and 357.81	1–42
All	Disorders of the peripheral nervous system and neuropathies (peripheral autonomic neuropathy, mononeuritis, peripheral neuropathy, polyneuropathy due to drugs or other toxic agents, critical illness polyneuropathy, other inflammatory and toxic neuropathy)	337.0, 337.9, 354.1–354.9, 355.0–355.9, 356.4, 356.8, 357.6, 357.7, 357.82, 357.89, and 357.9	1–42
All	Seizures (epilepsy, convulsions)	345.00–345.91, 780.3, 780.31, and 780.39	0–7 (0–14)
All	Other cranial nerve disorders	350.1–350.9, 351.1, 351.8, 351.9, and 352.0–352.9	1–42
All	Ataxia	334.3	1–42
All	Angioneurotic edema, allergic reaction, urticaria	995.1, 995.3, 708.0, 708.1, and 708.9	1–2
All	Spontaneous abortion, missed abortion	632 and 634.0–634.9	1–14
All	Stillborn	V27.1, V27.3, V27.4, V27.7, V32, V35, and V36	1–14
All	Preeclampsia, eclampsia	642.4, 642.5, 642.6, and 642.7	1–14
All	Hemorrhagic stroke	430, 431, and 432.0–432.9	1–42
All	Ischemic stroke	433.01, 433.11, 433.21, 433.31, 433.81, 433.91, and 434.0–434.9	1–42
All	Immune thrombocytopenia	287.31, 287.4, and 287.5	1–42 (7–28)
Live, attenuated	Myocarditis, pericarditis	420.90, 420.91, 422.0, 422.90, 422.91, and 422.99	1–42
Live, attenuated	Asthma/wheezing	493.0, 493.1, 493.9, 786.07, and 519.11	1–14
Live, attenuated	Asthma/wheezing /bronchiolitis	466.1, 466.11, 466.19, 493.0–493.9, 786.07, 786.09, and 519.1	1–14 days (1–42)

ICD-9 indicates *International Classification of Diseases, Ninth Revision.*

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