

National Vaccine Advisory Committee
(NVAC)

H1N1 Vaccine Safety Risk Assessment
Working Group (VSRAWG)

January 31, 2012

H1N1 Vaccine Safety Risk Assessment Working Group (VSRAWG) Membership

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Executive Summary

The emergence of the 2009 pandemic influenza A (H1N1) influenza virus in the spring of 2009 led to the development and licensing of five influenza A (H1N1) 2009 monovalent vaccines. Commensurate with the size and scope of the vaccination program, a comprehensive safety monitoring system was implemented. The National Vaccine Advisory Committee (NVAC) H1N1 Vaccine Safety Risk Assessment Working Group (VSRAWG) was established to conduct independent, rapid reviews of available data from the Federal H1N1 immunization safety monitoring program. During the 2009 influenza A (H1N1) pandemic, CDC estimated that approximately 60 million cases of 2009 H1N1 influenza disease occurred in the United States, including approximately 270,000 H1N1-related hospitalizations and about 12,270 deaths. An estimated 70-80 million persons were vaccinated with coverage levels highest in children. While the focus of the VSRAWG was on assessing vaccine safety, it is important to recognize the benefits of vaccination as ultimately policy makers, providers and the public must consider the risks of the vaccine within the context of vaccine benefits.

The VSRAWG was created on October 30, 2009. After an initial in person meeting, conference call meetings were held bi-weekly until May when the vaccination program scaled down and the amount of new safety data available decreased. The VSRAWG continued to meet to review final, end of season analysis. The VSRAWG met a total of 20 times.

Clinical trials were conducted which included more than 3,000 individuals. Passive surveillance was conducted by the Vaccine Adverse Event Reporting Systems (VAERS). Along with VAERS, the Real Time Immunization Monitoring System (RTIMS) looked for possible safety signals that might warrant further investigation. Rapid Cycle Analysis was conducted for a comprehensive list of pre-specified outcomes in multiple databases, including the Vaccine Safety Datalink (VSD), the Post-licensure Rapid Immunization Safety Monitoring (PRISM) Network, and databases from the Indian Health Services, Department of Defense, and Department of Veterans Affairs. Guillain-Barré syndrome (GBS) was also monitored in the Centers for Medicare and Medicaid Services and the Emerging Infections Program (EIP). The Vaccine and Medicine Pregnancy Surveillance System (VAMPSS) examined the safety of the vaccine among pregnant women and their births (neonates). Clinical review was conducted by the Clinical Immunization Safety Assessment Centers. A meta-analysis was conducted across systems for GBS.

The VSRAWG drafted monthly reports starting in December, 2009, and drafted a total of six interim reports that were deliberated upon and ultimately voted on by the NVAC. The first four reports concluded that there were no signals between influenza A (H1N1) 2009 monovalent vaccines and adverse events which were monitored. The fifth report showed that preliminary results indicated weak signals (statistically significant but not yet rigorously evaluated by chart review and other methods) for an association between the vaccines and two adverse events, thrombocytopenia/idiopathic thrombocytopenic purpura (TP/ITP) and Bell's palsy (BP). It also reported a potential weak signal with GBS. The sixth report indicated that the two signals remained and the GBS potential signal had changed to a weak signal. The seventh report concluded that EIP detected a weak signal for GBS, with an estimated attributable risk of 1 excess case per 1 million persons vaccinated, and no other systems crossed the weak signal threshold. NVAC unanimously approved each of the reports, which were then transmitted to the

Assistant Secretary for Health (ASH) who then transmitted them to the relevant agencies. All reports were rapidly posted on the National Vaccine Program Office (NVPO) website.

This final report includes careful review of all final analyses from all systems with the exception of VAMPPS where the children of vaccinated mothers are still being followed. All data are still considered preliminary until they have gone through peer review. The VSRAWG concluded after careful medical record review and analysis to identify true incident TP/ITP, that no significant association with TP/ITP was detected. The signal for BP appeared to be due to seasonal differences between the timing of the H1N1 immunization initiative and the timing of the vaccine administration for the controls. Consequently the VSRAWG concluded that the vaccine is not associated with BP. The EIP and VSD found statistically significant increased risks for GBS and non-statistically significant trends were seen in other systems. The GBS meta-analysis revealed an increased risk for GBS following H1N1 monovalent vaccines, such that there were 1-3 excess cases of GBS per 1 million doses of vaccine. In addition, the VSRAWG noted that hypersensitivity reactions might be more common with H1N1 vaccine compared with seasonal influenza vaccines.

The VRSWAG also noted several issues not related to any specific adverse events. Methods of surveillance of pregnant women are not optimal and should be enhanced. Continued methodological development of data mining approaches for signal detection is warranted. Finally, reports of vaccination administration errors (not associated with adverse events) suggest the need to explore opportunities to reduce such errors.

This report was provided to the NVAC for their deliberation and vote on February 7, 2012.

I. Establishment of H1N1 Vaccine Safety Risk Assessment Working Group

The emergence of the 2009 pandemic influenza A (H1N1) influenza virus in the spring of 2009 led to the development and licensing of five influenza A (H1N1) 2009 monovalent vaccines. The Government adapted existing safety surveillance programs, accelerated the development of additional safety monitoring systems that were being pilot tested, and developed new safety monitoring systems specifically for the H1N1 vaccine program (Table 1). The National Vaccine Advisory Committee (NVAC) reviewed Federal plans for vaccine safety monitoring in the summer of 2009 and made several recommendations to the U.S. Department of Health and Human Services (HHS) to enhance its safety monitoring systems in preparation for the H1N1 vaccine program. These recommendations included:

Consideration should be given to a transparent and independent review of vaccine safety data as it accumulates. This Vaccine Safety Assessment Committee (VSAC) would be an independent group of outside experts with a charge to advise the Assistant Secretary for Health (ASH) and/or Assistant Secretary for Preparedness and Response (ASPR) on the presence, investigation, interpretation, and implications of possible side effects of H1N1 vaccines. The committee should be reviewing pre- and post-licensure vaccine safety data accumulated in a timely way and not await activation when a specific signal is declared. The VSAC should advise on distinguishing spurious from genuine side effects; anticipating and responding to coincident (non-causal) events; evaluating the occurrence, frequency, and seriousness of possible side effects associated with vaccine; programmatic and policy steps to take in response to purported or demonstrated safety concerns; strategies and content of communication about vaccine safety; and such other matters related to vaccine safety that the ASH/ASPR would find useful. Such an external review would involve an independent group of experts with no professional or commercial stake in the vaccines or conduct of an immunization program, to speed and improve response to possible vaccine side effects, to enhance public confidence, and to provide focused advice on what can become a scientifically and politically contentious issue. The VSAC may be made up of members of an existing Federal advisory committee, such as NVAC, and supplemented by other vaccine safety experts. The committee would only assess risks (not consider vaccine benefits) and the committee would be only advisory and not decision making. The ASH/ASPR would be responsible for assuring programmatic response to the assessment of risk.

The NVAC H1N1 Vaccine Safety Risk Assessment Working Group (VSRAWG) was established on October 30, 2009 in response to this recommendation with a minor name revision to reflect its status as a Working Group as opposed to a subcommittee. The charge to the VSRAWG was to conduct independent, rapid reviews of available data from the Federal H1N1 immunization safety monitoring systems.

While the focus of the VSRAWG is on assessing vaccine safety, it is important to recognize the benefits of vaccination as ultimately policy makers, providers and the public must consider the risks of the vaccine within the context of vaccine benefits. During the 2009 influenza A (H1N1) pandemic, CDC estimated that approximately 60 million cases of 2009 H1N1 influenza disease occurred in the United States, including approximately 270,000 H1N1-related hospitalizations and about 12,270 deaths.¹ Approximately 90% of estimated hospitalizations and 87% of

estimated deaths occurred in people younger than 65 years old. In contrast, with seasonal influenza, about 60% of seasonal flu-related hospitalizations and 90% of flu-related deaths occur in people 65 years and older.² These data confirms that the 2009 H1N1 impacted younger adults and children more than older adults compared to seasonal flu. Working with state, local and private sector partners, HHS was able to rapidly distribute an effective licensed monovalent 2009 H1N1 influenza vaccine to the US public to mitigate morbidity and mortality from influenza disease.^{3,4,5} An estimated 70-80 million persons were vaccinated with coverage levels highest in children.⁶ This report focuses on the charge of the VSRAWG and includes no further discussion of vaccine benefit as the VSRAWG did not examine data on disease burden or vaccine effectiveness however ultimately any consideration of vaccine risks must consider vaccine benefits.

Table 1: H1N1 Safety Monitoring Systems by Data Source, Managing Federal Agency, Population Covered, Attributes and Stage of Development

Data Source	Agency/ Dept.	H1N1 Doses Captured	Attributes	Development	Outcomes Monitored
Clinical Trials	NIAID	3,313	Optimal study design, limited size	Enhanced for H1N1	All health events
Rapid Signal Detection Systems					
Vaccine Adverse Event Reporting System	CDC/FDA	305,000,000a	Stimulated Passive	Adapted for H1N1	All health events
Real Time Immunization Monitoring System	CDC	14,149	Active surveillance	Accelerated Development for H1N1	All health events
Hypothesis Testing Systems					
Vaccine Safety Datalink	CDC	1,314,827	Active surveillance	Adapted for H1N1	Pre-specified outcomes for RCA (Appendix 3)
Veteran Patients & VA Employee and Volunteers	VA	342,698	Active surveillance	Accelerated Development for H1N1	Pre-specified outcomes for RCA (Appendix 6)
Defense Medical Surveillance System	DoD/FDA/ CDC	1,288,353	Active surveillance	Accelerated Development for H1N1	Pre-specified outcomes for RCA (Appendix 7)
National Claims History File & Enrollment Database	CMS/ FDA	3,300,000	Active surveillance	Accelerated Development for H1N1	Guillain-Barré syndrome
Post-licensure Rapid Immunization Safety Monitoring (PRISM)	NVPO/ FDA/CDC	2,620,995	Active surveillance	Newly Developed for H1N1	Pre-specified outcomes (Appendix 5)
Emerging Infections Program GBS Surveillance	CDC	45,000,000 ^a	Active surveillance	Newly Developed for H1N1	Guillain-Barré syndrome

^a Persons under surveillance – system does not specifically capture number of H1N1 doses uses coverage data by county to estimate denominator data

Indian Health Service Resource & Patient Management Database	IHS/FDA	321,305	Active surveillance	Newly Developed for H1N1	Pre-specified outcomes (Appendix 4)
Long-Term Studies					
Clinical Immunization Safety Assessment	CDC	NA	Understanding adverse events at the individual level	Adapted for H1N1	
Vaccines and Medicine Pregnancy Surveillance System	BARDA	<549 (data pending)	Special studies (Distal Outcomes)	Newly Developed for H1N1	

II. Membership

Qualification Criteria

Qualification criteria were developed to ensure that a broad and comprehensive range of important scientific expertise was included. Membership included expertise in vaccinology, biostatistics, epidemiology, maternal and child health, pediatrics, internal medicine, family medicine, and infectious diseases. The VSRAWG was chaired by Dr. Marie McCormick. One member from each of the five Federal advisory committees that potentially had a role in the H1N1 vaccine program (NVAC, Centers for Disease Control and Prevention’s (CDC) Advisory Committee on Immunization Practices (ACIP), the Food and Drug Administration’s (FDA) Vaccines and Related Biological Products Advisory Committee (VRBPAC), the Department of Defense’s (DoD) Defense Health Board (DHB), and the National Biodefense Science Board (NBSB) and the public representative from VRBPAC) was selected as a member based on expertise in the aforementioned areas. In order to ensure appropriate expertise after selection of these seven members, two members with the aforementioned expertise who had served on one of these advisory committees or an Institute of Medicine committee were included as members of the VSRAWG. Stringent conflict of interest criteria (Appendix 1) were developed by HHS and potential candidates for membership were screened by HHS ethics officers to ensure they met these criteria before becoming members of the VSRAWG. VSRAWG members are listed in the beginning of this report.

III. Process of Review

Background Preparation

The VSRAWG was created on October 30, 2009. A systematic and comprehensive literature review was conducted on articles published on influenza vaccine safety in PubMed from 1967 to 2009. Search terms included influenza, vaccines, vaccination, adverse events and a list of specified outcomes of interest (adapted from the “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 relationship is a causal relationship). A binder including paper and electronic copies was distributed to each member in advance of its first meeting in early November 2009. Members were also given the protocols from each of the vaccine safety monitoring systems to review analytic plans.

At the first full-day meeting on November 2, 2009, presentations included clinical trials safety data to date as well as design and analysis plans from each of the H1N1 vaccine safety monitoring systems summarized in Table 1.

Meeting Schedule

VSRAWG meetings were held bi-weekly via conference call. By May 2010, the vaccination program scaled down and the amount of new information the members were reviewing decreased, therefore the group reduced the frequency of meetings to approximately once per month as they awaited the final end-of-season analyses. At the time of the writing of this report, the VSRAWG met a total of 20 times.

Federal Immunization Safety Task Force H1N1 Data Coordination Working Group

The Federal Immunization Safety Task Force (ISTF) established the H1N1 Data Coordination Working Group, composed of Federal staff from each of the agencies or departments supporting and contributing to the H1N1 vaccine safety monitoring system, to share data internally and to support the VSRAWG. The ISTF Data Coordination Working Group included the HHS as well as DoD and the Department of Veterans Affairs. The ISTF H1N1 Data Coordination Working Group met bi-weekly in advance of each of the VSRAWG meetings in order to compile H1N1 vaccine safety data from each of the systems, review the results internally, and prepare the presentations for the VSRAWG.

Procedural Guidelines

Following the first meeting of the VSRAWG on November 2, 2009, the members felt that additional guidelines would be helpful for issues surrounding press communications, terminology, data presented, timelines, and reports to NVAC. The VSRAWG developed procedural guidelines to ensure optimal data review and processes for the VSRAWG (Appendix 2).

Meeting Process

VSRAWG meetings were scheduled for 2 hours; the first part was devoted to presentations of data from each of the monitoring systems. VSRAWG members were provided these presentations in advance of their meeting for review, generally three days prior to the meeting. During this first portion of the meeting members asked questions from each of the presenters about his or her presentation and interpretation of data. There was also discussion among the larger group. To preserve the independence of the VSRAWG and in accordance with the procedural guidelines, the discussion in the second part of the call focused on interpretation of the data, and was conducted only among the VSRAWG members. Federal Advisory Committee Act regulations required that a designated federal official be present at working group meetings. Therefore, representatives from the National Vaccine Program Office were present to ascertain and convey requests of VSRAWG members for further information and to make a record of the discussion. NVPO representatives did not take part in the discussions and conclusions of the VSRAWG.

Reports to NVAC

The H1N1 VSRAWG drafted monthly reports starting in December 2009 (after approximately every 2 VSRAWG meetings) that were presented to, deliberated, and ultimately voted upon by the NVAC. Six reports were issued in total on the following dates: December 16, January 20, February 26, March 23, April 23, and June 2. The reports provided by the VSRAWG to NVAC included the following sections:

1. Data summary
2. VSRAWG assessment, including an assessment of the strength and magnitude of any signals or associations using predetermined criteria
3. Considerations for follow-up studies
4. Statement that VSRAWG is not and will not make recommendations for vaccine usage
5. Request NVAC vote on accepting report

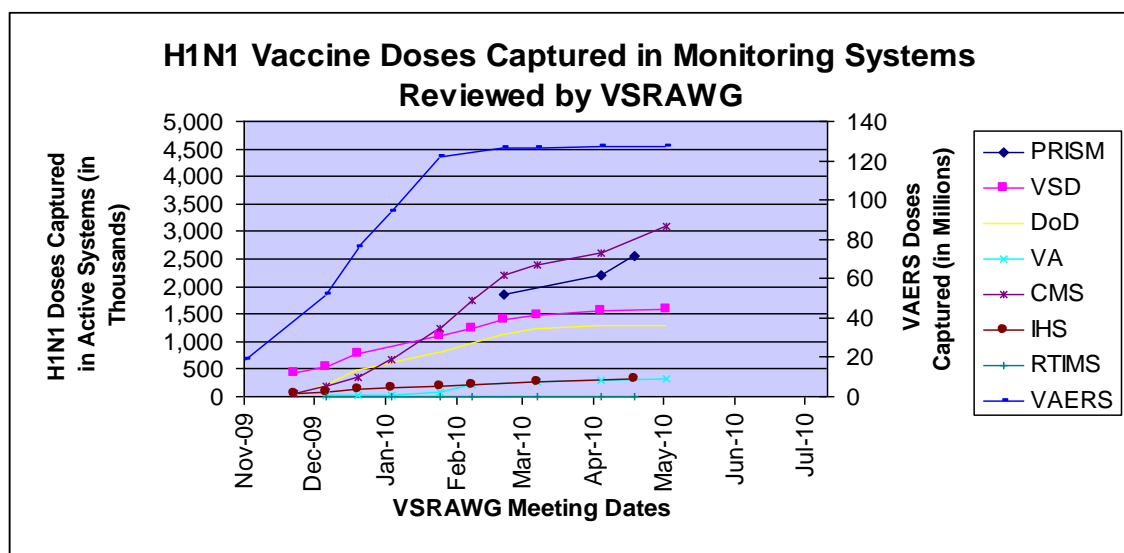
The final report was presented to the NVAC on February 7, 2012.

In summary, the first four reports issued concluded that there was no signal between influenza A (H1N1) 2009 monovalent vaccines and adverse events which were monitored. The fifth report showed that preliminary results indicated weak signals (statistically significant but not yet rigorously evaluated by chart review and other methods) for an association between two adverse events, thrombocytopenia/idiopathic thrombocytopenic purpura (TP/ITP) and Bell's palsy (BP), and influenza A (H1N1) 2009 monovalent vaccines. It also reported a potential weak signal with Guillain-Barre Syndrome (GBS). The sixth report indicated that the two signals remained and the GBS potential signal had changed to a weak signal. This report concluded that this weak signal from EIP for GBS translates into an estimated attributable risk of 1 excess case per 1 million persons vaccinated. No other systems crossed the weak signal threshold. NVAC unanimously approved each of the reports, which were then transmitted to the Assistant Secretary for Health (ASH) who then transmitted them to the relevant agencies. All reports were rapidly posted on the NVPO website. Reports 1 through 6 are shown in appendices 9 through 14, respectively.

IV. End-of-Season Analyses

Each monitoring system developed its own protocol for monitoring potential adverse events from influenza A (H1N1) 2009 monovalent vaccines. Many of the systems used an analytic method called Rapid Cycle Analysis (RCA) for investigating pre-specified health-outcomes.⁷ These outcomes were chosen based on biological plausibility and epidemiological associations with current or past vaccines. The RCA pre-specified outcomes for relevant systems may be found in Appendices 4-7.

Initially the VSRAWG reviewed data on an approximately bi-weekly basis. The graph below displays the doses captured by each monitoring system with each point representing a meeting where VSRAWG reviewed data from the corresponding system.



Note: VAERS doses are doses distributed whereas all other systems are doses administered

V. Methodology of each Vaccine Safety System

The Vaccine Adverse Event Reporting System (VAERS)^{8,9,10,11,12}

VAERS is a national passive vaccine adverse event reporting system that was established in 1990 and is jointly managed by CDC and FDA. It receives reports online, via fax, or via mail from healthcare providers, manufacturers, and the general public. The primary role of VAERS is signal detection it is intended to identify early warning signs of vaccine safety concerns. The primary objectives of VAERS include 1. detecting rare vaccine adverse events, or emerging patterns of adverse events; 2. monitoring for increases in known adverse events; 3. Identifying potential patient risk factors for particular types of adverse events; 4. identifying vaccine lots with potentially increased numbers or types of reported adverse events; and 5. monitoring the safety of newly licensed vaccines.

In response to the 2009-2010 H1N1 influenza season, VAERS increased staffing to process and review reports. VAERS also enhanced its communication and education efforts. For example,

CDC provided information about VAERS to relevant professional societies (such as the American Academy of Neurology to enhance GBS reporting), facilitated reporting of manufacturer lot and number information by providing influenza vaccination cards to individuals at the time of vaccination that included VAERS reporting information, established a mechanism to electronically and securely transmit state-specific VAERS reports to states, and trained state public health officials involved with vaccine safety. CDC also participated in media outreach and disseminated vaccine safety messaging through the CDC and VAERS websites and through partners, and provided weekly summaries of the VAERS data.

For the summary analyses of VAERS data, influenza vaccination adverse event reports were captured through automated reporting if the vaccination occurred between 07/01/2009 and 01/31/2010 and the report was received by 03/15/2010. This totaled 10,085 H1N1 influenza vaccine adverse event reports, and 6,469 seasonal influenza vaccine reports. The Medical Dictionary for Regulatory Activities (MedDRA) coding system was used for identifying and calculating frequency of symptoms, signs, and syndromes. As defined by the Code of Federal Regulations, Title 21 (21 CFR 314.80), reports were coded as serious in the automated system if they were reported as death, life-threatening illness, hospitalization, prolongation of hospitalization, persistent or significant disability, or congenital anomaly. Trend analysis compared the proportion of VAERS reports coded as serious or as GBS after 2009 H1N1 vaccination to the proportions of reports coded as serious or as GBS in the 2009-2010 seasonal influenza vaccine and four earlier influenza seasons. For calculating reporting rates, denominator data was estimated by using doses administered for four age groups of the 2009-10 seasonal influenza vaccine (08/2009 through 01/2010), and 2009-H1N1 (10/2009 through 01/2010) from the National 2009-H1N1 Flu Survey (NHFS), conducted in March, 2010.

Clinicians from the CDC and FDA reviewed all VAERS reports after H1N1 vaccination in persons vaccinated during 09/01/2010 to 01/31/2010 with reports received by March 15, 2010. All reports coded serious (as above), possible GBS, and anaphylaxis (received through 1/21/2010) underwent clinical review, in which medical records were requested and reviewed. Possible GBS and anaphylaxis diagnoses were verified using physician diagnoses and Brighton collaboration criteria. Reports of death were verified by autopsy, death certificate, or medical record. Clinicians further classified serious, non-fatal adverse event reports into one of 12 diagnostic categories: (1) neurologic, including GBS; (2) musculoskeletal; (3) cardiovascular, including cerebrovascular accident; (4) gastrointestinal; (5) ear, nose, and throat, excluding upper respiratory tract infections; (6) allergic, including anaphylaxis; (7) local reaction (inactivated vaccine only); (8) pregnancy-specific outcomes (e.g. spontaneous abortion); (9) psychological conditions (e.g. conversion disorder); (10) respiratory, influenza, and influenza-like-illness, pneumonia (including upper respiratory infections); (11) other non-infectious conditions (e.g. thrombocytopenia, syncope, diabetes); and (12) other infectious conditions (e.g. sepsis).¹³

FDA conducted Empirical Bayesian data-mining to complement the automated and clinical methods of data review. As a general overview, data-mining is a statistical technique that compares observed frequencies of adverse events per vaccine to expected frequencies of adverse events per vaccine. The expected frequencies are calculated based on the overall frequency of each adverse event for all vaccines, and the total number of reports of the vaccine of interest. If for a particular vaccine adverse event pair the observed frequencies is larger than the expected

frequencies, the finding is considered disproportionate. Because these adverse events are often rare and because and multiple comparisons are being performed, Empirical Bayesian methods are used to account for the instability of small numbers by “shrinking” observed-to-expected ratios. The Empirical Bayesian Geometric Mean (EBGM) is the point estimate of disproportionality. A cutoff value of 2 at the lower bound (5%) of the confidence interval surrounding the EBGM is termed the EB05 and is used to identify vaccine adverse event pairs that should receive additional evaluation. An EBGM of 2 does not necessarily demonstrate that a particular vaccine caused a particular adverse event, but that further evaluation is warranted. All analyses excluded reports from outside of the United States, and were adjusted for gender, year received, and age group (0-1, 2-17, 18-64, 65+). Additional stratified analyses were conducted with eleven different age groups. The H1N1 live, attenuated monovalent vaccine (LAMV) reports were compared with US live viral vaccines (seasonal live, attenuated influenza, measles, mumps, rubella, varicella, oral polio, rotavirus, smallpox, zoster, and yellow fever vaccines). The H1N1 monovalent inactivated vaccine (MIV) reports were compared with reports for US inactivated vaccines (all except the aforementioned live viral vaccines, oral typhoid vaccine, and BCG vaccine).

The Real Time Immunization Monitoring System (RTIMS)

(Source documents cited throughout but not specifically within)^{14,15,16}

RTIMS is a joint collaboration between CDC and Johns Hopkins University. It has the capacity to monitor large numbers of persons from healthcare sites across the US, with the ability to focus on certain subpopulations, such as healthcare workers, children, and pregnant women. The objectives of RTIMS are (1) to have early signal detection of possible vaccine adverse event problems; (2) to identify host factors associated with vaccine adverse events; (3) to compare rates of vaccine adverse events associated with different influenza vaccine products; and (4) to expedite reporting and investigation of serious adverse events to VAERS.

RTIMS distinguishes between receiving “active capture” and “passive capture” information. RTIMS receives post-vaccination active capture information by directly soliciting permission from vaccine recipients at the time of vaccination and then sends follow-up emails with links to surveys to capture health information and adverse events. RTIMS receives post-vaccination passive capture information when persons sign up after vaccination by accessing the surveys via websites maintained by CDC, health departments or Johns Hopkins University. Volunteers report information via sequential online questionnaires shortly after immunization and 7 and 42 days later. RTIMS uses an automated, web-based algorithm to analyze these results in near real-time and can thus rapidly detect potential signals. However, the limitations of RTIMS include that it lacks comparison data to a non-vaccinated group (though for influenza, comparisons are made between seasonal and H1N1 vaccines, both for live and inactivated vaccines).

For the 2009-2010 influenza season, RTIMS captured 14,149 influenza individuals who had been vaccinated. The baseline survey usually occurred within a few days after vaccination. Follow-up emails were sent to obtain information at days 7 and 42. If the baseline survey was not completed within before the fifth day post-vaccination, the 7-day follow-up was not performed.

Responses for influenza vaccination safety monitoring data included information about the vaccines, the vaccine recipients, and adverse events. Information about the vaccines included the type of vaccine received (only the seasonal vaccine, the H1N1 vaccine, both vaccines, and intranasal vs. injectable vaccines), date of vaccination, and site of vaccine administration (health department clinic, doctor's office, pharmacy, school, workplace, or hospital). Information collected about the vaccine recipients included gender (male, female, or unknown), age, underlying medical conditions, and risk group (children 0-19 years of age, pregnant women, health care workers, or other adults). Health care worker and pregnant women information included the presence of care-seeking and/or hospitalization.

In the automated RTIMS system, adverse events that were programmed to trigger an alert were grouped as follows: (1) general (fever, malaise, etc.); (2) respiratory (wheezing, difficulty breathing, or shortness of breath); (3) heart or blood vessels (chest pain, or fainting); (4) nervous system (numbness or tingling in limbs, difficulty walking, difficulty talking, difficulty moving arms or legs, slurred speech, neck stiffness, or seizures); (5) skin (hives, urticaria, rash, other); and (6) injection site (large local swelling reaction, or moderate to severe pain). Reported symptoms were scored for severity on a scale of 0-10.

Alerts were reviewed by RTIMS staff and prioritized if they indicated possible hypersensitivity or neurological problems. If indicated, health care providers were contacted after obtaining consent and HIPAA releases. Alerts were adjudicated with the RTIMS PI and clinical expert review, including consultations with Clinical Immunization Safety Assessment (CISA) working group experts. Adjudicated diagnoses were grouped into 12 categories: (1) immediate hypersensitivity; (2) delayed hypersensitivity; (3) respiratory illness; (4) cardiovascular illness; (5) neurological; (6) gastrointestinal problem; (7) genito-urinary problem; (8) fainting; (9) large local swelling; (10) persistent pain (>3 days); (11) non-specific symptoms; and (12) other. From all of these data, several multivariate rate analyses and cumulative incidence analyses were performed, with particular attention on sub-analyzing adjudicated respiratory illness adverse events, adjudicated neurologic events, and pregnancy complications.

The Vaccine Safety Datalink (VSD)^{17,18,10,11,42, 43}

VSD is a collaborative effort between the CDC and eight managed care organizations (MCOs) that cover approximately 9.5 million people annually. This is over three percent of the US population, containing persons from all phases of life (children, adults, pregnant women, among others). It was established in 1990 and provides active surveillance for vaccine adverse events and addresses gaps in the scientific knowledge about rare and serious adverse events following vaccination. The VSD does this by linking immunization records, enrollment and demographic data, hospital discharge diagnosis codes, Emergency Department discharge diagnosis codes, outpatient visit diagnosis codes, and birth and death certificate data to individual study identification numbers without personal identifiers. Furthermore, some VSD sites incorporate data from state immunization registries, and electronic medical records are available for review at all VSD sites.

The VSD has 5 strategic priorities: (1) to evaluate the safety of newly licensed vaccines;

(2) to evaluate the safety of new vaccine recommendations for existing vaccines; (3) to evaluate clinical disorders after immunizations; (4) to assess vaccine safety in special populations at high risk; and (5) to develop and evaluate methodologies for vaccine safety assessment.

In 2005, VSD launched Rapid Cycle Analysis (RCA) – a methodology for conducting near real-time surveillance for potential AEs following the introduction of new vaccines or schedules. VSD RCA has typically used 2 types of comparison groups to evaluate whether the risk of pre-specified AEs is higher for the vaccine of interest: (1) historical comparison groups, or (2) concurrent controls. Recently, VSD RCA has also used the self-controlled case series (SCCS) method as a third approach to monitoring risk. As doses of new vaccines are captured in VSD, observed rates are compared to expected rates using the historical comparison, or events in the risk window are compared to a control window using either the concurrent control or SCCS method. Statistical methods are used to adjust for sequential and multiple looks at the data. If a critical threshold is reached, than a statistical “signal” is found. Signals based on electronic data can be investigated rapidly using pre-determined methods to check for data quality, proper ICD-9 coding, appropriate comparison groups, and other issues that might result in a spurious finding. Chart review can be performed to further evaluate statistical signals based on automated data. From past experience, approximately 90% of signals identified from RCA turn out to be false signals after careful evaluation.¹⁹

For H1N1 vaccine safety surveillance, adverse events were specified *a priori* including GBS , demyelinating disease, disorders of the peripheral nervous system and neuropathies, seizures (epilepsy and convulsions), encephalitis/myelitis/encephalomyelitis, Bell’s Palsy, other cranial nerve disorders (e.g. facial nerve disorders, trigeminal nerve disorders), ataxia, anaphylaxis, other allergic reactions (e.g. angioneurotic edema, allergic reaction, urticaria), hemorrhagic stroke (e.g. subarachnoid hemorrhage, intracerebral hemorrhage, other and unspecified intracranial hemorrhage), ischemic stroke (excluding transient ischemic attack), myocarditis/pericarditis (LAMV only), wheezing (LAMV only), pregnancy outcomes (spontaneous abortions, stillbirth, pre-eclampsia/eclampsia), and outcomes that might be of concern with adjuvanted vaccines (autoimmune hepatitis and thrombocytopenia).

Risk windows for each adverse event were specified *a priori* and depended on the timing of the adverse event relative to vaccination as observed in the literature and according to biologic plausibility. The day of vaccination was only included in the risk period for adverse events for which a same-day diagnosis was deemed biologically plausible (such as anaphylaxis). Certain adverse event definitions were limited to those occurring in inpatient or emergency department settings only in order to improve specificity. Analyses were done either by the historical comparison method (comparing rates after 2009 H1N1 vaccine with rates after seasonal influenza vaccines given in previous seasons, for very rare events in order to improve timeliness of signal detection) or by the self-controlled case series (SCCS) methodology (for more common events). Historical rate comparisons are limited by the assumption that persons receiving previous seasonal flu vaccine are similar to persons receiving H1N1 vaccine. This assumption is not made for the SCCS methodology, which inherently adjusts for fixed confounders that do not vary over time, such as underlying co-morbidities.

In addition to H1N1 RCA analyses, end of season analyses were also performed using either historical comparison or SCCS methods. These end of season analyses allow for more detailed analyses (i.e., controlling for potential confounders, assessing risk of AEs following first vs, second vaccine dose, assessing risk of AEs among those who received both H1N1 and seasonal vaccines within a short time period), permit the data to “settle” so that data lag issues are not a factor, and allow for the additional analyses that use a comparison period that extends months beyond the vaccination date.

For the 2009-2010 influenza season, the VSD captured 1,314,827 doses of the H1N1 monovalent inactivated vaccine (MIV), and used a historical comparison of 12,640,159 captured doses of trivalent inactivated vaccine (TIV).

The Emerging Infections Program (EIP)

The Emerging Infections Program (EIP) is an established collaboration among CDC, state health departments, and academic centers in 10 states. Using the EIP, a population-based, active surveillance program designed to provide rapid case identification and assessment of risk for GBS following 2009 H1N1 vaccination was implemented as part of H1N1 vaccine safety surveillance efforts. EIP includes approximately 45 million residents in 10 specifically defined catchment areas of the United States (the states of Connecticut, Maryland, Minnesota, New Mexico, and Tennessee, the state of New York excluding Manhattan, and selected metropolitan counties in California, Colorado, Georgia, and Oregon). Cases of GBS with hospital admission after September 30, 2009 were actively sought through newly established, predominantly neurologist networks and review of hospital administrative discharge data (ICD-9 code 357.0) for all catchment hospitals. Trained surveillance officers reviewed medical charts to confirm the diagnosis and obtain data on antecedent illnesses, vaccinations, and clinical outcomes; additional vaccination data was obtained from primary care physicians and state immunization registries when possible. Potential cases were classified by surveillance officers according to the Brighton Collaboration criteria for GBS; difficult to classify cases were reviewed in consultation with a panel of neurologists. Cases meeting Brighton Levels 1 and 2 were considered confirmed GBS cases, and cases that met Brighton Level 3 were considered probable. Each patient meeting Brighton Levels 1, 2, or 3 was contacted for a telephone interview to gather further information about medical and vaccination history.

Analysis 1

GBS incidence was calculated and compared for the vaccinated and unvaccinated populations, which were estimated by age group, using data from CDC’s Behavioral Risk Factor Surveillance System (BRFSS) and National 2009 H1N1 Flu Survey (NHFS) telephone survey data for the counties in the EIP catchment areas, using methods published previously.²⁰ The total person-time of follow-up was calculated by multiplying the population under surveillance by the number of days since the start of surveillance, October 1, 2009. Person-time at risk for GBS in the vaccinated population was calculated by multiplying the number of vaccines by 42 days (or the number of days from vaccination to the end of the surveillance period if <42 days). Children aged 6 months–9 years who received a second dose of 2009 H1N1 vaccine were presumed to

have received it 28 days after the first dose, as recommended by the Advisory Committee on Immunization Practices, giving them an additional 28 days of person-time at risk. To calculate the corresponding person-time in the unvaccinated population, the person time at risk for GBS was summed among the vaccinated population and then subtracted from the total person-time of follow-up under surveillance.

Incidence among the vaccinated population was calculated by dividing the number of GBS cases who were vaccinated within the 42-day risk window preceding onset by the total amount of person-time at risk following vaccination. Incidence among the unvaccinated population was calculated by dividing the number of GBS cases unexposed to vaccine or exposed to vaccine outside the risk window by the total amount of person-time unexposed to 2009 H1N1 vaccine. Bootstrapping methods were used to estimate 95% confidence intervals (CIs) for the rate ratios that incorporated the variance of vaccine coverage estimates.²¹ A Poisson distribution was assumed for the occurrence of cases and a normal distribution for the vaccine coverage estimates; the Mantel-Haenszel method was used for age-adjusted CIs. A temporal scan statistic was used to assess for any significant clustering in the interval between vaccination and illness onset in vaccinated cases.²²

Analysis 2 (Self-controlled analysis)

The self-controlled analyses are case-only methods in which each subject's follow-up period is partitioned into risk and control intervals.²³ Self-controlled designs have the advantage of avoiding confounding that may arise from person-level risk factors for vaccine receipt and disease when comparing vaccinated with unvaccinated groups. The relative risk was calculated using both open variable-window and fixed window analyses; for both approaches, the risk interval included days 1-42 after vaccination, during which vaccine-associated GBS was considered to be biologically plausible. For the variable-window analysis, the control interval extended from day 43 after vaccination to the end of the study period (April 30, 2010). For the fixed-window analysis, the control interval was days 43-84 after vaccination; for this analysis, we included only cases that had at least 84 days of follow-up from vaccination to the end of the study period to ensure an equal chance of identifying cases in both the risk and control intervals. For both the variable and fixed window analyses, we calculated the relative risk and confidence interval using conditional Poisson regression.

For the variable-window analysis, we first constructed a primary model to estimate the effect of vaccine on risk of GBS. Second, we added interaction terms to the primary model to assess whether the vaccine relative risk varied among the following subgroups: age group, sex, vaccine type (injected, intra-nasal, or unknown), whether seasonal influenza vaccine had been received in the 42 days prior to H1N1 vaccine receipt, and the EIP site reporting the data. We calculated the attributable risk of vaccine receipt by applying measures of vaccine relative risk to an estimated baseline incidence of GBS (1.2 per 100,000 person-years) based on 13 studies for age-specific rates from North America and Europe.

The Post-Licensure Rapid Immunizations Safety Monitoring (PRISM) Network

Methods

Establishment of PRISM

The Post-Licensure Rapid Immunization Safety Monitoring (PRISM) Network is a cohort-based active surveillance network initiated by HHS in 2009 to evaluate the safety of 2009 H1N1 vaccines in a large representative population, incorporating immunizations delivered in non-traditional settings.²⁴ PRISM was funded by the FDA through a CDC cooperative agreement with America's Health Insurance Plans (AHIP), which was responsible for the project's administration. The Harvard Medical School Department of Population Medicine (DPM) at the Harvard Pilgrim Health Care Institute led the implementation of the scientific components, working with the Computer Science Corporation (CSC) for technical support. Five health care organizations or consortia and nine state or city immunization registries supplied the data. The Public Health Informatics Institute (PHII) assisted with the organizational linkages between state immunization registries and health plans.

Study population

The participating health plans were grouped into five "sites" for purposes of data-processing and analysis: Aetna; Blue Care Network of Michigan and Blue Cross Blue Shield of Michigan; CIGNA; Humana; and Wellpoint California, Wellpoint Colorado, and Wellpoint New York (total membership 38 million). The study population consisted of members of participating health plans whose records indicated receipt of at least one dose of H1N1 or seasonal influenza vaccine between August 1, 2009 and April 30, 2010 (7 million) or receipt of at least one dose of inactivated or not otherwise specified (NOS) seasonal influenza vaccine between August 1 and April 30 of either the 2007-2008 or the 2008-2009 influenza seasons (8 million first doses, not necessarily unique patients). Doses of inactivated vaccine received at less than six months of age were excluded, as were doses of live vaccine received outside of the recommended age range of 2-49 years. To simplify the identification of the study population, enrollment data were not used other than to provide a snapshot of membership at one point in the fall of 2009.

Data sources

Health plan claims data were used to identify pre-specified outcomes after H1N1 and seasonal influenza vaccination during the 2009-2010 influenza season and after inactivated or NOS seasonal influenza vaccination during the 2007-2008 and 2008-2009 influenza seasons. This source was also used to collect all diagnoses in the one year prior to vaccination in each of the three seasons, for identification of high- vs. low-risk patients.

Two sources were used to obtain vaccination data: claims data and, for the 2009-2010 season only, state immunization registries also. Immunization registries were selected for participation based on the size of the population expected to belong to the participating health plans, the anticipated completeness and timeliness of H1N1 vaccine data, the expected amount of detail available about influenza vaccine, and experience in exchanging data with health plans. Registries in Arizona, Florida, Georgia, Michigan, Minnesota, New York, New York City, Pennsylvania, and Wisconsin participated. Because of membership geography and contractual issues, not all health plans were expected to exchange data with all nine registries. In the case of

two health plan-registry pairs, data-exchange agreements could not be finalized. Ultimately, 26 of an attempted 28 health plan-registry pairings succeeded in exchanging data.

Exposures

Claims data reflected H1N1 and seasonal influenza vaccination predominantly via CPT4 codes and to a lesser extent HCPCS codes and an ICD9 procedure code. The H1N1 codes available in claims data during the surveillance period did not distinguish between inactivated and live, attenuated vaccine.

Some IISs provided H1N1 and seasonal influenza vaccination data as CPT4 codes, others as CVX codes. The use of CVX codes did not guarantee that inactivated and live H1N1 vaccines would be distinguished from each other, as an H1N1 NOS CVX code was frequently used by some registries.

Baseline risk estimates were obtained from historical claims data on outcomes occurring during outcome-specific risk windows after inactivated/NOS seasonal influenza vaccine in the prior two influenza seasons, 2007-2008 and 2008-2009. Live attenuated seasonal influenza vaccine was not used in baseline risk estimates, due to low numbers of events and expected instability of the estimates.

To recover some H1N1 live vaccine from the H1N1 NOS category, prior to analysis the coordinating center converted all H1N1 NOS vaccine manufactured by Medimmune to live, since the only kind of H1N1 vaccine made by that manufacturer was live.

Outcomes

Pre-specified health outcomes were very similar to the set monitored by the Vaccine Safety Datalink²⁵ and were selected in consultation with the CDC and the FDA based on seriousness and their potential association with influenza vaccine. The following 12 outcomes were studied for both inactivated/NOS and live H1N1 vaccines: Guillain-Barre syndrome (GBS), demyelinating disease, peripheral nervous system disorders, seizures, encephalitis/myelitis/encephalomyelitis, Bell's palsy, other cranial nerve disorders, ataxia, anaphylaxis, allergic reactions, hemorrhagic stroke, and ischemic stroke. For live vaccine, myocarditis/pericarditis and wheezing were also monitored. Risk window durations were based on the literature^{26,27} and considerations of biological plausibility. Three pregnancy outcomes were also monitored and will be reported on separately.

Pre-analysis data processing

PRISM employed a distributed data-processing model, by which the health plans maintained control over patient-level data, sending only aggregate data to the coordinating center for analysis (except for purposes of GBS chart review, which is ongoing and will be described elsewhere). Health plans extracted data from their systems, organizing it into four files of standard format specified by the coordinating center: Demography, including birth-date, sex, and zip code information; Vaccine Claims, including vaccination date and vaccine code; and

Inpatient and Outpatient, each including care-date and diagnostic codes, with Outpatient additionally specifying the setting of the encounter as emergency department or outpatient clinic.

When data quality was considered adequate, programs to aggregate the event-level data written at the coordinating center were run by health plan analysts on the event-level data files.

Aggregate data were returned to the coordinating center, consisting of counts of vaccine doses and of outcomes in strata defined by a number of covariates, including week of vaccination, age, sex, vaccine type (H1N1 or seasonal; inactivated, live, NOS), dose number, whether a patient had gotten both H1N1 and seasonal vaccine during the 2009-2010 influenza season or rather only one or the other, and intervals among doses of H1N1 and seasonal influenza vaccines. Further quality-checking of the aggregate data was done prior to analysis.

Data transmission

Health plans uploaded data-quality reports and aggregate data to a secure, password-protected website, from which coordinating center analysts downloaded them. Initial historical data were provided in December 2009–January 2010. Data for the 2009-2010 season were provided on approximately a biweekly basis thereafter. Final data on vaccinations through April 30, 2010 and on outcomes through July 24–August 7, 2010 (exact date depending on site) were provided in August 2010.

Registries sent immunization data for health plan members to the health plans at several points during the season, using a variety of secure file transport methods. The final matches of health plan members with registry data and transmissions of registry data occurred in May 2010.

Data lags and truncations

To guard against bias due to delays in the arrival of vaccination or diagnosis codes in the claims data, the degree of delay in each site's data were first characterized and then the date beyond which the site's data would be excluded from analysis was established. To characterize the delay, programs were run on Vaccine Claims, Inpatient, and Outpatient files to ascertain the cumulative proportion of vaccination, inpatient, and outpatient data existing in the system as of Week 1, 2, 3, and so on, up to at least 24 weeks after specific care dates at least 6 months in the past. For two sites, such reports were not possible due to the lack of data arrival date, so lag estimates from the site with the greatest data lag of the other three sites were substituted.

The aggregate data, organized by week of vaccination, were truncated to ensure that counts of outcomes in neither the risk or, for the self-controlled analysis, comparison period would be artificially low due data lag. For end-of-surveillance analysis, for each site, the last week for which any inpatient or outpatient data were present (the week of August 1, 2010 for most sites) were subtracted by the time required for at least 95% of both the inpatient and outpatient data to arrive in the claims data (11-15 weeks), and further subtracted by 12 weeks to allow the maximum risk window (6 weeks) plus maximum post-risk-window comparison window (6 weeks) to elapse. This led to inclusion of H1N1 vaccinations through weeks in January or February 2010, amounting to approximately 90% of H1N1 vaccinations through April 30, 2010.

Analysis

Sequential analysis

Sequential analysis using the Poisson maxSPRT or the conditional maxSPRT for current vs. historical comparisons or the binomial maxSPRT for self-controlled comparisons^{28,29} was conducted on approximately a biweekly basis to monitor for increased risk of 11 outcomes during the 2009-2010 season (per the protocol, three outcomes—hemorrhagic stroke, ischemic stroke, and wheezing—were statistically analyzed only at the end of surveillance). These methods were essentially the same as those used for influenza vaccine safety surveillance by the Vaccine Safety Datalink in 2009-2010 and previous seasons.^{25,30,31} The results reported here are not from sequential analysis but rather from end-of-surveillance analysis, of which the methods are described below.

Designation of primary analysis

For the 14 outcomes, the number of cases appearing in the immediate post-vaccination risk window were compared with the number of cases in either (i) unexposed windows either before vaccination or after the risk window had elapsed for the same group of current season vaccines or (ii) the same-length post-vaccination window for a historical comparison group who received inactivated/NOS seasonal influenza vaccination in prior years. The first of these, a self-controlled approach, was the preferred analysis method, since the population vaccinated for H1N1 may have differed significantly from historical influenza vaccines in characteristics for which full adjustment would not be possible. With the self-controlled approach, the main limitation was potential bias due to the presence of time-varying confounders, such as seasonality.

For certain outcomes, especially rare ones, the current-vs.-historical comparison was designated as primary due to its greater statistical power. The main limitation of this approach is that the historical comparison group may not be comparable to current vaccines, particularly if population characteristics change over time. This was of concern within the PRISM system since current vaccines included those identified from both health plan claims data and immunization registry data, whereas historical vaccines were identified from health plan data only. For example, individuals who seek vaccination outside the usual health care system, such as in community settings, may be different than individuals who seek vaccination from health care providers. Also, with a current vs. historical comparison, secular trends in adverse events or coding for adverse events, independent of vaccination, may potentially bias our findings.

For some outcomes, separate analyses were conducted for those ≤ 24 and > 24 years of age, considering the possibility that the two groups might differ in risk and mechanism of certain neurological conditions and that a high frequency in one age group might mask an effect in the other. A cutoff of 24 rather than 17 years was used, to match ACIP recommendations for H1N1 vaccination.

The null hypothesis for all analyses was that the risk of adverse events in a pre-specified risk window following vaccination was no different when compared to the risk in either a historical cohort of seasonal influenza vaccine recipients or in the same current-season individuals during an unexposed period.

Type 1 error rates and confidence intervals

Prior to analysis, a decision was made to reject the null hypothesis with a type 1 error of $\alpha=0.05$ for the analyses of GBS and anaphylaxis, the two outcomes of greatest concern, and $\alpha=0.01$ for all other outcomes. The purpose of using a 0.01 type 1 error for most outcomes was to informally guard against too many false positives, in view of the multiple testing inherent in the many outcomes looked at.

Patient groups analyzed

The primary vaccination group for analysis was *all* recipients of first doses of inactivated/NOS H1N1 vaccine, regardless of whether seasonal influenza vaccination was also received, hereafter referred to as Patient Group 1.

Given the unusual situation in the 2009-10 season where both H1N1 and seasonal influenza vaccines were administered separately, two additional vaccination groups were studied: those people who had received inactivated/NOS H1N1 vaccine without any overlapping exposure to seasonal influenza vaccines (Patient Group 2, defined as those *who had not received seasonal influenza vaccine* at all in the 2009-2010 season (for both self-controlled and current vs. historical analyses) or *who had received seasonal influenza vaccine > 42 days prior to H1N1* (only for the current vs. historical analyses)) and those individuals who had received both H1N1 and seasonal influenza vaccines *concomitantly* (Patient Group 3). Patient Groups 2 and 3 are subsets of Patient Group 1, as shown in schematic form in Figure 1.

In addition, for comparative purposes, analyses were done for inactivated/NOS seasonal influenza vaccines who had not received H1N1 vaccine. However, as seasonal influenza vaccine safety was not the subject of this study, these results are not reported except in relation to the three instances of statistically significantly elevated risk after inactivated/NOS H1N1 vaccine.

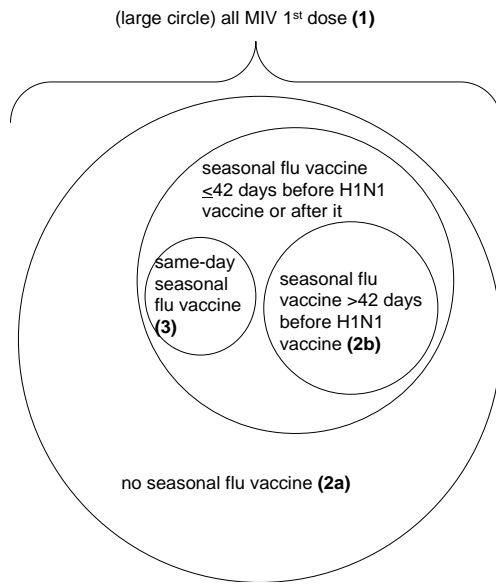


Figure 1. Vaccination groups analyzed. Numbers in parentheses indicate the patient groups discussed in the text. “MIV” (monovalent inactivated vaccine) refers to inactivated/NOS H1N1 vaccine. Patient Group 2, unexposed to seasonal influenza vaccine, consists of Set 2a for the self-controlled analyses and Set 2a + Set 2b for the current vs. historical analyses.

Current vs. historical analysis

People who received inactivated/NOS seasonal influenza vaccine during the 2007-2008 and 2008-2009 influenza seasons were used as the comparison group. Logistic regression analysis was performed, in which the dependent variable was whether the person had the adverse event of interest within the risk window after vaccination. The independent variable of interest was binary, whether the person received the vaccination of interest (inactivated/NOS H1N1; live, attenuated H1N1; or inactivated/NOS seasonal influenza vaccine) in the 2009-2010 season or was part of the historical comparison group. The analyses were adjusted for health plan, sex, and age group (6m-17y, 18-49y, 50-64y, ≥65y).

Self-controlled analysis

With the self-controlled analysis,³¹ the risk of the outcome in a predefined risk window following immunization was compared with an unexposed comparison window, the null hypothesis assuming that the risk was equal during the two periods. By comparing numbers of events in risk and comparison periods within vaccines, this method controls for confounders that do not vary over the observation period, including sex, health plan, genetics, socio-economic factors and most underlying chronic diseases. The relative risk was determined by dividing the number of events observed in the risk vs. comparison periods, adjusting for their unequal length when needed. Confidence intervals were constructed by first calculating the approximate confidence intervals for binomial proportions,³² and then transforming the results to relative risks, using the formula that relative risk = binomial proportion / (1-binomial proportion).

The Centers for Medicare & Medicaid Services (CMS)

Active surveillance for vaccine safety among the Medicare population is a collaborative project between the Food and Drug Administration (FDA) and Centers for Medicare & Medicaid Services (CMS). Medicare insures approximately 46.5 million persons, including 38.8 million elderly (age ≥ 65 years) and 7.8 million others with disability or end stage renal disease (2009 data).³³ Most (approximately 76%) are enrolled in fee-for-service Medicare and their healthcare utilization is represented in the Medicare claims data used for analysis. This project provides a key resource for active safety surveillance among the elderly who may be underrepresented in some other healthcare databases. Also, the large size of the Medicare population makes it feasible to monitor relatively rare conditions for which smaller databases may lack sufficient statistical power.

Starting in 2006, the FDA and CMS initiated a pilot project to develop a rapid system to actively monitor vaccine safety among the elderly, especially as related to seasonal and pandemic influenza vaccines. Part of the motivation for this project was to prepare for an influenza pandemic and the potential rapid development and widespread use of vaccines against pandemic strains. The project aimed to develop the capacity to use incoming Medicare claims data for vaccine safety monitoring as soon as they accrued each week. The pilot phase over the next years included both technical and methodological development work. FDA, CMS, and a CMS contractor, Acumen, LLC, collaborated in this effort. The capacity developed through this project provided the foundation for safety monitoring of influenza vaccines and potentially other medical products received by the Medicare population.

For the 2009-2010 influenza season, active safety surveillance of influenza vaccines was implemented. Safety monitoring focused on Guillain-Barré Syndrome (GBS). Some studies of the 1976 swine influenza vaccine found an elevated risk of 5-10 excess GBS cases per million persons vaccinated.^{34,35,36} Detection of such infrequent events requires evaluation among very large populations. Thus, during 2009-2010, the large Medicare databases contributed an important resource for monitoring GBS. Data through July 30, 2010 monitored 3,295,435 H1N1 vaccinations.

Influenza vaccinations and hospitalizations for possible GBS (defined by principal diagnosis code) were ascertained from the Medicare claims data. The observed GBS rate within 42 (also 21) days after vaccination was monitored and compared to an expected rate based on 5 prior years. Because there is a lag in the observed data between the date of service (i.e., date of vaccination, date of hospital admission) and date the claim appears in the data, methods were implemented to adjust for this factor. A signal was defined as an observed GBS rate that exceeds a threshold (critical limit) that indicates the observed rate is statistically higher than the expected rate. A signal, if it occurs, would not indicate a conclusive association and additional evaluation would be needed (e.g., checks for data quality, potential confounders, robustness to alternate design choices).

In addition to the weekly surveillance during the 2009-2010 influenza season, end of season analyses, including self-controlled case series (SCCS), self-controlled risk interval (SCRI) and traditional risk interval methods, were conducted on cases confirmed via medical record review using the standardized case definition established by the Brighton Collaboration GBS Working

Group. The end of season analyses were able to better control for potential data lags and confounders. The population of incident GBS cases that underwent medical chart review consisted of Medicare beneficiaries enrolled in Part A or B fee-for-service (and not Part C) with no prior GBS hospitalization in the 12 preceding months who were vaccinated with monovalent 2009 H1N1 influenza vaccine between October 1, 2009 and March 26, 2010 and admitted to the hospital for GBS within 126 days post-vaccination or through May 28, 2010, regardless of duration between vaccination and admission date.

Each analysis required the application of different inclusionary and exclusionary criteria to the population of chart-confirmed GBS cases to comprise analysis-specific cohorts. These cohorts were created by excluding any cases that did not occur within the selected risk or comparator period(s) for each respective analytic method. We included all cases meeting Brighton level 1–3 GBS or Fisher syndrome cases among H1N1-vaccinated individuals with symptom onset during an observation period of November 1, 2009 through April 30, 2010 for the SCCS and symptom onset between October 1, 2009 and March 26, 2010 and having chart-confirmed GBS symptom onset within 119 days post-vaccination for the SCRI and Risk Interval methods.

The risk immediately after H1N1 vaccination (1–42 days post-vaccination) was compared to a later post-vaccination period (43 days post-vaccination through April 30, 2010 for SCCS, days 50-119 for SCRI and Risk Interval). Sensitivity analyses included the use of alternate risk periods (8-21 days post-vaccination), alternate comparator periods (50–91 and 57-98 days post-vaccination), and alternate case definitions (Brighton levels 1–2 instead of Brighton levels 1–3).

The Indian Health Service (IHS) Influenza Awareness System (IIAS)

In response to the 2009-2010 H1N1 influenza pandemic, the Indian Health Service (IHS), Division of Epidemiology and Disease Prevention (DEDP) and IHS Office of Information Technology created an electronic surveillance system, the IHS Influenza Awareness System (IIAS). The IIAS serves as a sentinel indicator of the disease burden of influenza-like illness (ILI) and as a nexus of data collection on ILI hospitalizations, influenza vaccine administration, potential adverse events following immunization and risk factor surveillance in the American Indian/Alaska Native (AI/AN) population served by IHS.

In an effort to monitor the safety of the novel H1N1 vaccine and expand surveillance of adverse event monitoring following immunization, a collaboration between the IHS/DEDP and the Food and Drug Administration (FDA) was formalized in November, 2009 to provide a robust capacity for (1) near real-time, nationwide electronic surveillance, (2) clinical validation and (3) timely risk analysis of potential adverse events following immunization (pAEFI) in IHS beneficiaries.

Electronic Surveillance

Utilizing the IIAS, enhanced passive surveillance is achieved through a near real-time data extraction from the clinical databases of the IHS Resource and Patient Management System (RPMS); a health information technology platform representing 1.5 million AI/AN beneficiaries including prenatal, infant and geriatric populations.

Prespecified diseases selected for adverse event safety monitoring were coded under the *International Classification of Disease*, version 9 (ICD9) nomenclatures for algorithm-based extraction from the IIAS. Extracted records along with pertinent clinical data, demographics, health risk factors and vaccine administration information were then compiled daily for review of completeness and queued for clinical validation.

Clinical Validation

Through a clinician network representing facilities participating in the IIAS and DEDP staff, extracted records were validated by their pAEFI extraction ICD9 code. Records with a validated pAEFI code were adjudicated by provider narrative or under standard FDA case definitions (thrombocytopenic conditions) with categorization as incident or prevalent.

Statistical Risk Analysis

The age-, and gender-specific risks of the specified potential adverse events following H1N1 vaccine administration were assessed by standardized incidence ratio (SIR)^{37,38} analysis. Potential adverse event incidence data for IHS from October 1, 2008 to April 15, 2009 were used as the reference rates to calculate the expected number of adverse events according to the total number of H1N1 vaccine doses administered in the IHS facilities participating in the IIAS, from October 1, 2009 to April 30, 2010. The SIR for each adverse event outcome was computed as the quotient of the observed number of cases and the expected number of cases. Assuming the observed number of pAEFI follow a Poisson distribution, the exact 95% confidence intervals for SIR were calculated using methods described in Sahai and Khurshid^{39,40} using STATA 11.0 (StataCorp, College Station, TX).

The Department of Defense (DoD) Military Vaccine (MILVAX) Agency

The Military Vaccine Agency oversees the Department of Defense (DoD) Immunization Program. During the 2009-2010 H1N1 influenza season the Military Vaccine (MILVAX) Agency, in collaboration with the Armed Forces Health Surveillance Center (AFHSC); the Food and Drug Administration, Center for Biologics Evaluation and Research (CBER) and the Centers for Disease Control and Prevention (CDC), used the Defense Medical Surveillance System (DMSS), to monitor the novel H1N1 influenza vaccines for pre-specified high priority outcomes of interest. The outcomes of interest were: Guillain-Barré Syndrome (GBS), optic neuritis (ON), Bell's palsy, other demyelinating neurological conditions, including acute disseminated encephalomyelitis (ADEM) and acute transverse myelitis (ATM), anaphylaxis, and thrombocytopenia (TP).

The Defense Medical Surveillance System (DMSS), administered by the AFHSC, is a centralized electronic database, which contains both current and historical data on diseases, medical events, vaccination history, demographics, Service (Army, Air Force, Navy, Marine Corps, and Coast Guard), and deployment status for the U.S. military active duty personnel since 1990. DMSS includes both inpatient and outpatient (including emergency room) data. Case diagnoses identified in the DMSS during the H1N1 surveillance were verified in the electronic health record, the Armed Forces Health Longitudinal Tracking Application, or AHLTA.

To evaluate the safety of the H1N1 vaccines among the active duty military population, two methods were used: (1) an indirect adjustment method, and (2) a self-controlled case series. Selection of the method for a specific outcome of interest was based on the sample size requirement. However, the self-controlled cases series was used to evaluate the association between H1N1 vaccine and thrombocytopenia, Guillain-Barre Syndrome, and Bell's Palsy.

Indirect Adjustment Method

The Indirect Adjustment analysis included the H1N1 cohort and a historical cohort. The H1N1 cohort was comprised of active duty Service members who received H1N1 vaccine during the 2009-2010 H1N1 vaccination season (November 1, 2009, – April 30, 2010). The historical cohort was comprised of active duty Service members who received seasonal influenza vaccine during November 1, 2008, – April 30, 2009. Because influenza vaccines (seasonal and H1N1) are mandatory for all military personnel, Service members who did not receive a seasonal influenza vaccine in the previous season or who did not receive H1N1 influenza vaccine during the H1N1 vaccination season were excluded to avoid potential selection bias due to vaccine contraindication.

Cases were identified through ICD-9-CM diagnosis codes in DMSS among eligible Service members of the H1N1 cohort and the historical cohort. For eligible cases identified in DMSS, healthcare records were reviewed using the military's electronic health record to verify the diagnosis.

Using the historical cohort as the source of reference rates, the ratio of the total number of observed events to the number of expected events following H1N1 vaccination provides an estimate of the factor-adjusted rate ratio, referred to as standardized incidence ratio (SIR). The SIR was estimated adjusting for three factors, one at a time, including age, gender, and seasonal influenza vaccine exposure. The data was also adjusted for the differences in the composition of the study populations by the confounding factor(s).

Crude incidence rates of outcome of interest was first calculated and compared between the H1N1 cohort and the historical cohort. For both cohorts, person time was then stratified by seasonal influenza vaccine exposure into three categories: exposed to seasonal LAIV, exposed to seasonal TIV, and unexposed to seasonal influenza vaccine. Incidence rates were calculated for each stratum of the historical cohort. The expected number of cases in each stratum of the H1N1 cohort was calculated by multiplying the corresponding stratum-specific rates observed in the historical cohort times the person time in the H1N1 cohort stratum. The ratio of the total number of observed cases to the overall sum of expected cases in the H1N1 cohort is an estimate of incidence rate ratio comparing the H1N1 cohort with the historical cohort (which served as a source of reference rates), adjusting for seasonal influenza vaccine exposure. Confidence limits were calculated at alpha level =0.05, two sided. The same procedures were used for age and gender.

Self-Controlled Case Series

The self-controlled case series study was nested within the population of the Service members who are in the 'active component' (versus National Guard or Reserve Forces) of their respective Military Services between November 1, 2009, and April 30, 2010. As a condition of military service, those individuals are between 17 and 64 years of age. Because the primary interest is incident cases, except for anaphylaxis, individuals ever having a diagnosis of the outcome of interest prior to November 1, 2009, were excluded from this study. For anaphylaxis, a 1 year incidence rule was applied. The study was comprised of cases only.

Identified cases with continuous recording in DMSS between November 1, 2009, and April 30, 2010, were eligible for the proposed self-controlled case series study. Except for anaphylaxis, cases having the outcome of interest prior to November 1, 2009, were excluded. For anaphylaxis, cases having a diagnosis of anaphylaxis in one year prior to November 1, 2009 were excluded. Cases with incomplete recording between November 1, 2009, and April 30, 2010, were excluded.

The DMSS database was searched to identify H1N1 vaccine exposure, seasonal vaccine exposure, and date(s) of vaccination for each eligible confirmed case between November 1, 2009, and April 30, 2010. Administered influenza doses in the Immunization Tracking Systems (ITS) are recorded by vaccine name, vaccine type (live versus inactivated), vaccination date, dose number, manufacturer, and lot number.

The major advantage of the case series method is that the analysis adjusts for individual level fixed covariates including gender, genetic factors, etc. Three time-varying variables were used for this study, including H1N1 vaccine exposure, seasonal vaccine exposure, and seasonality (to account for the possible fluctuation of disease occurrence over the calendar time). Because the study population is comprised of adults and will be observed for less than 1 year, the effect of age change in each Service member on his/her disease occurrence during the observation period is deemed low and thus, age was not used as a time-varying variable in this study.

A 14-day time period prior to vaccination was excluded from baseline to account for the healthy vaccine effect (i.e. people who have acute illness may have vaccine deferred; diseases are unlikely to occur immediately prior to vaccination). Exposed period is the risk window pre-defined for each outcome of interest following H1N1 vaccination. The pre-defined risk windows were evaluated and possibly refined by Scan Statistics (SaTScan Software, developed by Dr. Martin Kulldorff, <http://www.satscan.org>). Sensitivity analyses were conducted using different risk windows.

To assess the associations between H1N1 vaccination and Thrombocytopenia and Bell's Palsy occurring among active duty military personnel, each individual's observation time was split up into successive intervals determined by the time-varying exposure(s) and time-varying covariate(s) within the observation period, regardless of the time of disease occurrence. In analysis, two time-varying exposures (H1N1 and seasonal vaccine exposures) and successive 30-day cut points for seasonality were included.

The Department of Veterans Affairs (VA)

The Department of Veterans Affairs (VA) H1N1 vaccine safety monitoring program initiated for the 2009-2010 influenza season consisted of both a Passive Surveillance program and a pilot Active Surveillance initiative. Passive surveillance consisted of provider reported or provider confirmed adverse events across the entire VA health care system through the national web-based VA Adverse Event Reporting System (VA ADERS). VA ADERS is the VA's passive surveillance database for drugs and vaccines. Influenza vaccine adverse events (AEs) reported in VA ADERS were sent to the Food and Drug Administration (FDA) and Centers for Disease Control (CDC) Vaccine Adverse Event Reporting System (VAERS). Manual tracking of the vaccine AE reports transferred from VA to CDC/FDA was conducted for the 2009-2010 season. All H1N1 AE VA ADERS reports were successfully transferred to VAERS by the end of the H1N1 vaccine safety monitoring season.

The VA's immunization package and linked automated databases were used in the vaccine safety monitoring program to track AEs through the pilot Active Surveillance initiative. Immunization package data from two VA Regions (Regions 1-Northeastern States and 4-Western States) were available at the national level during the 2009-2010 influenza season. The pilot Rapid Cycle Analysis (RCA) and subsequent end of season analysis (EOS) was conducted using data from these regions. The two regions cover approximately 2 million Veterans. Patients in these two regions were also used to determine the historical outcomes of interest for 2007, 2008 and 2009. The end of season analysis was conducted using data from November 1, 2009 through April 30, 2010 to be consistent with the time frame recommended by the FDA.

The VA immunization package was used to identify H1N1 exposed patients for the identified regions and the linked automated databases located in Austin, TX were used to determine outcome diagnoses and demographics and to confirm the VA sites. A total of 342,030 Veterans were exposed to the H1N1 vaccine in the VA pilot dataset. The outcomes of interest evaluated in the VA included Guillan Barre Syndrome (GBS), Idiopathic Thrombocytopenia (ITP) and Bell's palsy. The initial analysis was conducted using ICD-9 codes to identify the conditions, 357.0 (GBS), 287.31(ITP), and 351.0/781.94 (Bell's palsy). The final analysis was conducted using chart confirmed cases. Two separate methodologies were used to analyze the data; Self Controlled Case Series (SCCS) and Indirect Adjustment (IA) analyses. Both methods are described.

SCCS

All Veteran patients ≥ 17 years who received a diagnosis of outcome of interest following H1N1 vaccine with no prior history of the outcomes of interest were included in the analysis. Veteran patients entered the study following exposure to H1N1 vaccination. Patients were evaluated using different risk windows, all of which were determined *a priori*. The observation time period for each patient was partitioned into successive intervals based on the following dates: (A) Index date-date of H1N1 vaccination; (B) Risk period end, the last day of the exposure period; (C) Diagnosis, the day of diagnosis; (D) Season 1 end, the last day of season 1; (E) Season 2 end – the last day of season 2/ End day, the last day of the observation period. Seasonal influenza vaccine exposure and seasonality were included in the model as time-varying variables. Data were analyzed via Poisson regression model. The risk of outcome period of 1-42 days for GBS, Bell's palsy, and ITP were compared with 43 or more days after H1N1 vaccination.

Additionally, the risk outcome period of 1-60 days was compared with 61 or more days for Bell's palsy. The relative risk (RR) and 95% confidence intervals were reported for each of the outcomes.

Indirect Adjustment

The goal of the IA analysis was to assess the incidence ratio of the specific adverse outcomes following the H1N1 vaccination relative to background rates. The H1N1 cohort was identified between 11/1/2009 and 4/30/2010. Patients were followed using a pre-defined risk window of 42 days after exposure or until the date of event, date of death or the end of the study period. The historical cohort consisted of patients who received seasonal influenza vaccination between 11/1/2008 and 4/30/2009. Follow-up for the historical cohort was similar to that of the H1N1 cohort. All patients ≥ 17 years and with no prior history of the outcomes of interest were evaluated.

Total person time was calculated for both cohorts and then stratified by seasonal influenza vaccine exposure. Each individual contributed an exposed person time and an unexposed person time depending on whether they received the seasonal influenza vaccination. Person times for exposed and unexposed stratum were calculated by summing each individual's person-time within each stratum. An incidence rate was calculated for each historical cohort stratum. The expected number of cases for the H1N1 cohort was calculated by multiplying incidence rates of the historical cohort by person-time of the corresponding H1N1 cohort. The standardized incidence ratio (SIR) was calculated by dividing observed by expected cases (SIR=observed/expected). The SIR and corresponding 95% confidence intervals were reported for each outcome.

Chart Validation

All identified GBS, ITP and Bell's palsy cases were reviewed through chart validation, using validation criteria developed by the FDA. The final end of season analysis was conducted using the confirmed cases.

Meta-Analysis for GBS

GBS data were combined across systems to determine if monovalent inactivated vaccine was associated with an increased risk of GBS. A SCCS was conducted using chart reviewed Brighton level 1 and 2 cases. Days 1-42 post vaccination were compared with days 50-91, with days 43-49 serving as a washout period. There was visual examination of the distribution of cases days post-vaccination. Incident Rate Ratios and Absolute or Attributable Risk were calculated. Homogeneity of results across studies was examined. Secondary analysis included analysis of more narrow time windows within 42 days, inclusion of Brighton Level 3 cases, and stratification by receipt of seasonal flu vaccine, influenza-like-illness, and age categories.

VI. Conclusions Regarding Adverse Events Associated with H1N1 Vaccine

As reported previously, signals for three conditions and H1N1 vaccine emerged in the surveillance systems. These were: Thrombocytopenia/idiopathic thrombocytopenic purpura, Bells's Palsy, and Guillan-Barre Syndrome.

Thrombocytopenia/idiopathic thrombocytopenic purpura (TP/ITP)

Three systems detected a weak signal of an increased risk of TP/ITP associated with H1N1 vaccine using diagnostic codes in administrative data. All three systems were either newly developed or had undergone accelerated development for H1N1 surveillance, and were still exploring the processes for surveillance. After careful medical record review and analyses to identify true incident TP/ITP, no significant association of incidence thrombocytopenia was detected. The VSRAWG does not believe, based upon available data, that the H1N1 vaccine is associated with TP/ITP.

Bell's Palsy

A weak signal for Bell's Palsy was noted in two systems. More refined end-of-season analysis in one system (VSD) led to the conclusion that the observed signal was due to seasonal differences between the timing of H1N1 administration and the timing of administration of other vaccines used as controls. H1N1 vaccine was administered in early winter when other infections associated with Bell's Palsy are more prevalent than the comparison vaccines usually administered in the fall. The relationship between Bell's Palsy and H1N1 vaccine was not consistent across analyses suggesting that this was not a real association with the vaccine. The VSRAWG does not believe, based upon available data, that the H1N1 vaccine is associated with Bell's Palsy.

Guillain-Barré Syndrome (GBS)

Data from the Emerging Infections Program suggested an association between H1N1 vaccines and GBS.⁴¹ While not seen in early RCA analyses, RCA analyses of chart confirmed cases of GBS in the VSD system also detected an elevated risk of GBS with H1N1 vaccines when compared to historical data; this risk was also demonstrated in self-controlled case series and case-centered analyses (case-centered analysis showed a non-significant trend). Non-statistically significant trends suggesting increased risks were noted in the primary analyses in other systems.

Results from the meta-analysis across systems revealed an increased risk of GBS following H1N1 monovalent vaccine, such that there were 1-3 excess cases of GBS per 1 million doses of vaccine. It should be noted that risk-benefit analysis considering overall influenza morbidity averted and specifically cases of GBS due to influenza was not part of the charge to the group. The VSRAWG concluded that there was an increased risk of GBS following H1N1 vaccine but that the risk was very small.

In addition to these main findings, the VSRAWG also wishes to make note of four other issues.

Hypersensitivity Reactions

Final reports from the RTIMS system suggested that reports of hypersensitivity reactions may be more common with H1N1 vaccine compared with seasonal influenza vaccine. In

PRISM, but not VSD, analyses also suggested an increased risk of allergic reactions with inactivated H1N1 vaccine and concomitant seasonal influenza vaccine, and of wheezing with live attenuated H1N1 vaccine. The VSRAWG concluded that there was a possible signal that should be investigated further.

Pregnancy Outcomes

Because of the importance of H1N1 immunization for pregnant women and the effort to increase uptake of the vaccine in this group, surveillance of pregnancy outcomes was conducted in systems where that was possible. Under different assumptions and with different data sets, there were weak statistical signals for an increased risk of pre-eclampsia and still birth following vaccine administration in some systems. However, the results were not consistent across data sets. There were also several important methodological limitations to these analyses. In addition, a new surveillance effort, VAMPPS was initiated and only preliminary results have been reported at this time. The VSRAWG concluded that surveillance was adequate to detect large effect size of serious pregnancy complications associated with vaccine, and these were not seen. However, additional methodological efforts are needed to enhance the surveillance for this population.

FDA-Data Mining Analyses with VAERS Data

The FDA analyses compared the proportions of adverse events with H1N1 vaccine with similar vaccines, e.g. live-attenuated H1N1 vaccine compared with other live virus vaccines, and inactivated H1N1 vaccine with other inactivated vaccines. The VSRAWG found these results difficult to interpret for several reasons. The first is the instability of the results with an adverse event being seen in one round of analysis but not necessarily in other rounds. Second, the comparisons may reflect differences in the vaccine administration not specific to H1N1 vaccine. For example, increased risks of respiratory symptoms were seen with live-attenuated H1N1 vaccine compared to other live attenuated vaccines, but H1N1 vaccine was delivered intranasally in contrast to the other live vaccines delivered by injection. If this analytic approach is to be used again for surveillance of this type, some refinement may be needed, such as using comparable modes of administration where possible.

Vaccine Administration Errors

A stable result seen recurrently in the FDA analyses was indication of errors in vaccine administration, either the incorrect vaccine or incorrect dose. While none of these errors were associated with severe adverse events, epidemiologic studies of vaccine administration errors may be helpful in identifying ways to minimize or eliminate them.

Appendix 1: Conflict of Interest Criteria

All members of H1N1 VSRAWG were subject to stringent conflict of interest standards, including:

- a. Person will be not be considered for participation if they, their spouse, or children are directly employed by a vaccine manufacturer or its parent company.
- b. Persons who hold stock in any vaccine manufacturer or its parent company will not be considered for participation unless they agree to divest themselves of such stock before their tenure on the VSRAWG begins and all nominees must agree that they, their spouse and minor children will not purchase such stock during their tenure on the H1N1 VSRAWG .
- c. A person will be not be considered for participation if that person is a holder of, or otherwise is entitled to royalties or other compensation for, a patent on a vaccine product or process, immunologic agent, adjuvant or preservative that may be used for a 2009 H1N1 vaccine.
- d. To participate in the H1N1 VSRAWG , a potential participant must agree to resign any advisory or consulting roles, whether paid or unpaid, to a vaccine manufacturer (except participation in clinical trials or service on data monitoring boards unrelated to H1N1 influenza vaccine or other flu vaccines) and to forego such consultation or membership on any vaccine manufacturer advisory committees (except participation in clinical trials or service on data monitoring boards unrelated to H1N1 influenza vaccine or other flu vaccines), during his/her tenure on the H1N1 VSRAWG .
- e. Except as allowed under d., potential participants must agree that during their tenure on the H1N1 VSRAWG they will forego solicitation or acceptance of funds from vaccine manufacturers on behalf of themselves or others (e.g., to support educational activities of their Department or an organization of which they are a member, officer or employee).
- f. Potential participants must agree that during their tenure on the H1N1 VSRAWG they will not serve as a paid litigation consultant or expert witness in litigation involving a vaccine manufacturer.
- g. Potential participants must agree that during their tenure on the H1N1 VSRAWG they will not accept honoraria or travel reimbursement with a funding source from a vaccine manufacturer for attendance at scientific meetings, with the exception that they may receive travel reimbursement for Continuing Medical Education (CME) presentations where the source of funding is an unrestricted grant to the CME provider by a vaccine manufacturer.

H1N1 VSRAWG members must have on file an Office of Government Ethics (OGE) Confidential Financial Disclosure Report, Form 450, as required by OGE regulations. Waivers for conflicts of interest may be granted pursuant to statutory requirements. See 18 U.S.C. 208(b)(3). (Note: no waivers were granted).

Appendix 2
Procedural Guidelines for the NVAC H1N1
Vaccine Safety Risk Assessment Working Group

Consistent with the H1N1 NVAC Vaccine Safety Risk Assessment Working Group (VSRAWG) guidelines provided to Working Group members by HHS, the VSRAWG has developed the following procedural guidelines to ensure optimal data review and processes for the Working Group. Following the first meeting of the VSRAWG on November 2, 2009, the members felt that additional guidelines were required for issues surrounding press communications, terminology, data presented, timelines, and reports to NVAC.

Communications

HHS will communicate with the press regarding the VSRAWG. HHS will not refer the press to any VSRAWG members without first gaining approval from the member. However, once the list of VSRAWG members becomes public the press will likely go directly to VSRAWG members without going through HHS.

To be certain that all members are speaking with one voice, requests for information will generally be forwarded to NVPO. Should the reporter wish to speak to a member of the committee, these requests will be forwarded to the Chair of the Working Group.

Standard Terminology

The VSRAWG understands that the terminology for serious adverse events used by NIH is protocol-specific and thus not an appropriate general definition for other data presented to the VSRAWG. For data from all other sources (excluding clinical trials), the VSRAWG requests the definition of serious adverse experience follow the FDA definition “Any adverse experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition”. Rapid Cycle Analysis (RCA) and clinical trial data should be stratified by this definition of serious and all other (non-serious). (CFR Title 21, Volume 7).

Data Requested

The VSRAWG would like to see summary data from all data sources regardless of the direction of the findings (positive or negative). Summary data should be given to the VSRAWG stratified by serious/non-serious (using the definition provided above). Unless specifically requested, the VSRAWG does not wish to see detailed analysis plans for data. However, if during the course of analysis certain signals/associations are detected and dismissed (due to miscoding, confounding, etc), the VSRAWG should be made aware of all of the signals/associations detected and the reason for their dismissal. For data involving deaths or serious adverse events (by FDA definition), the VSRAWG expects greater detail. VSRAWG will not comment on individual cases (including serious adverse events and deaths) but rather will comment on

whether or not there are signals, associations, or causally related events (see Predetermined Assessment Outcomes below). It may be necessary for the VSRAWG to gain detailed individual information if such information is warranted, however the VSRAWG will not be conducting individual-level causality assessment (as is done by CISA). Only in very rare cases will the reports from the VSWRAWG reflect data on individual cases.

Timeline for Materials

The VSRAWG requests 2 weeks between VSRAWG meetings and NVAC meetings to ensure the Working Group has proper time to deliberate on the findings, draft a report, and provide the report to NVAC in advance of a vote. The VSRAWG requests a 72-hour turnaround from NVPO for meeting minutes and related documents following a VSRAWG meeting. The VSRAWG will provide a report to the NVAC for its review no less than 2 business days before an NVAC meeting during which a vote is planned.

Proposed Timeline for VSRAWG and NVAC Meetings		
VSRAWG Meetings	Tentative NVAC Meeting where reports presented	Number of Full Working Days between VSRAWG and NVAC Meetings
November 2, 2009	December 16	6
November 23		
December 7		
December 21	January 20	10
January 4, 2010		
January 25	February 26	12
February 8		
February 22	March 23	10
March 8		
March 22	April 21	11
April 5		
April 19	May 19	11
May 3		
May 17	TBD	TBD

Deliberations

To preserve the independence of the VSRAWG, the discussion of the findings and conclusions will be conducted only among the VSRAWG members without participation of the federal members of the Immunization Safety Task Force. FACA regulations require that a federal representative must be present at working group meetings. Therefore, representatives from the NVPO will be present to ascertain and convey requests of VSRAWG members for further information and to make a record of the discussion. These representatives will not take part in the discussions and conclusions of the VSRAWG.

Report Format

The report provided by the VSRAWG to NVAC will likely include the following sections:

- 6. Data summary

7. Working Group assessment, including an assessment of the strength and magnitude of any signals or associations using predetermined criteria
8. Considerations for follow up studies
9. Statement that VSRAWG is not and will not make recommendations for vaccine usage
10. Request NVAC vote on accepting statement

This report template may be modified based on the data presented to the Working Group at its meetings. With the possible exception regarding individual cases noted above, the reports will be based on grouped data, and may not be reflect experiences of individuals.

Predetermined Assessment Outcomes

To communicate the VSRAWG’s assessment of H1N1 vaccine safety profiles, the VSRAWG will attempt to summarize its findings using the framework listed below for consistency and clarity in their assessments.

Outcome	Data Availability	Assessment Options	Recommendation
Signal: An event that could be temporally occurring more often after vaccination than anticipated based on chance alone (i.e., that the event could be related to the receipt of the vaccine).	The data are inadequate to assess the presence or absence of a signal	No assessment possible	Continue to monitor
	The data are adequate to assess the presence/absence of a signal	The data do not likely favor a signal between the outcome and the vaccine	Continue to monitor
		The data may favor a signal between the outcome and vaccine	Explore issue through other monitoring activities
Association: the incidence of an event varies in relation to an exposure (i.e. vaccine). The strength of association is quantified by the ratio of occurrence of an event in the exposed and non exposed population; the greater the association, the more evidence exists for a causal relationship.	The data are inadequate to assess the presence or absence of an association	No assessment possible	Continue to monitor
	The data are adequate to assess the presence/absence of an association	The data do not likely favor an association between the outcome and vaccine	Continue to monitor
		The data may favor an association between the outcome and vaccine	Request more/different information/analyses
Causality: An event is the direct consequence of an exposure. To evaluate causality, the Bradford Hill Criteria will be used, which are guidelines for	The data are inadequate to assess the causal relationship between outcome and vaccine	No assessment possible	Continue to monitor
	The data are adequate	Evidence favors a	Continue to monitor if

Outcome	Data Availability	Assessment Options	Recommendation
determining whether a causal relationship exists: 1) Strength 2) Consistency 3) Specificity 4) Temporality 5) Biological gradient 6) Biological Mechanism (Plausibility) 7) Coherence 8) Experiment 9) Analogy	to assess the causal relationship between outcome and vaccine	rejection of a causal relationship	warranted
		Evidence favors acceptance of a causal relationship	Request more/different information/analyses.
		Evidence establishes a causal relationship	Request more/different information/analyses if warranted.

Data Requests by the NVAC

The status of all data presented to the VSRAWG should be clearly identified with regard to 1) publicly availability, and 2) ability to be obtained by a FOIA request. If data is already publicly available, the VSRAWG is free to share the data with the NVAC. If data is not publicly available but would be released in response to a FOIA request, the VSRAWG may share the data with the NVAC if requested to do so. If the data would be withheld in response to a FOIA request, the VSRAWG may not share the data with the NVAC; however, a justification for why the data would be withheld under the FOIA must be provided by HHS.

Appendix 3: Pre-specified Outcomes and Definitions used for Rapid Cycle Analysis in VSD

Flu vaccine type	Outcome	ICD-9 CM Codes
All	Guillain-Barré syndrome (GBS)	357.0
All	Encephalitis/myelitis/encephalomyelitis	323.5 323.51 323.52 323.6 323.61 323.62 323.63 323.8 323.81 323.82 323.9 341.2
All	Bell's Palsy (BP)	351.0
All	Anaphylaxis	995.0 999.4
All	Demyelinating disease (multiple sclerosis, demyelinating disease of CNS, optic neuritis, CIDP)	340 341.0 341.8 341.9 377.30 377.31 377.32 377.34 377.39 357.81
All	Disorders of the peripheral nervous system and neuropathies (peripheral autonomic neuropathy, mononeuritis, peripheral neuropathy, polyneuropathy due to drugs of toxic agents, critical illness polyneuropathy, other inflammatory and toxic neuropathy)	337.0 337.9 354.1-354.9 355.0-355.9 356.4 356.8 357.6 357.7 357.82 357.89 357.9
All	Seizures (epilepsy, convulsions)	345.00-345.91 780.3 780.31 780.39
All	Other cranial nerve disorders	350.1-350.9 351.1 351.8 351.9 352.0-352.9
All	Ataxia	334.3
All	Angioneurotic edema, allergic reaction, urticaria	995.1 995.3 708.0 708.1 708.9
All	Spontaneous abortion, missed abortion	631 632

Flu vaccine type	Outcome	ICD-9 CM Codes
		634.0-634.9 656.4 761.8
All	Stillborn	V27.1 V27.4 V27.7
All	Pre-eclampsia, eclampsia	642.4 642.5 642.6 642.7
All	Hemorrhagic stroke	430 431 432.0-432.9
All	Ischemic stroke	433.01 433.11 433.21 433.31 433.81 433.91 434.0-434.9 435
Live, attenuated	Myocarditis, pericarditis	420.90 420.91 422.0 422.90 422.91 422.99
Live, attenuated	Asthma/wheezing/bronchiolitis	493.0 786.07 786.09 519.1 466.1 493.1 493.9 786.07 519.11

Appendix 4: Pre-specified Outcomes and Definitions used for Rapid Cycle Analysis in IHS

Flu vaccine type	Outcome	ICD-9 CM Codes
All	Guillain-Barré Syndrome (GBS)	357.0
All	Optic neuritis	
All	Optic neuritis, unspecified	377.30
All	Optic papillitis	377.31
All	Retrobulbar neuritis	377.32
All	Optic neuritis, other	377.39
All	Encephalomyelitis and myelitis	
All	Encephalitis, myelitis, and encephalomyelitis following immunization procedures	323.5
All	• Encephalitis and encephalomyelitis following immunization procedures	323.51
All	• Myelitis following immunization procedures	323.52
All	Postinfectious encephalitis, myelitis, and encephalomyelitis	323.6
All	• Infectious acute disseminated encephalomyelitis (ADEM) (includes acute necrotizing hemorrhagic encephalopathy)	323.61
All	• Other postinfectious encephalitis and encephalomyelitis	323.62
All	• Postinfectious myelitis	323.63
All	Other causes of encephalitis, myelitis, and encephalomyelitis (includes noninfectious ADEM)	323.8
All	• Other causes of encephalitis and encephalomyelitis (includes noninfectious ADEM)	323.81
All	• Other causes of myelitis (includes transverse myelitis NOS)	323.82
All	Unspecified cause of encephalitis, myelitis, and encephalomyelitis	323.9
All	Acute transverse myelitis	341.2
All	Bell's palsy	351.0
All	Anaphylaxis	
All	Other anaphylactic shock	995.0

Flu vaccine type	Outcome	ICD-9 CM Codes
All	Anaphylactic reaction to serum	999.4
All	Idiopathic thrombocytopenic purpura	
All	Idiopathic thrombocytopenic purpura	287.31
All	Secondary thrombocytopenia	287.4
All	Thrombocytopenia, unspecified	287.5
Live, attenuated	Asthma / Wheezing	
Live, attenuated	• Intrinsic asthma (includes late-onset asthma)	493.1
Live, attenuated	• Asthma, unspecified	493.9
Live, attenuated	• Wheezing	786.07
Live, attenuated	Influenza (when 2009 pandemic H1N1 vaccine virus is isolated)	488.1
Live, attenuated	• In vaccinee	488.1
Live, attenuated	• In vaccinee contact	488.1

Appendix 5: Pre-specified Outcomes and Definitions used for Rapid Cycle Analysis in PRISM

Flu vaccine type	Outcome	ICD-9 CM Codes
All	Guillain Barre Syndrome	357.0
All	Demyelinating disease (multiple sclerosis, demyelinating disease of CNS, optic neuritis, CIDP)	340* 341.0 341.8 341.9 377.30 377.31 377.32 377.34 377.39 357.81
All	Disorders of the peripheral nervous system and neuropathies (peripheral autonomic neuropathy, mononeuritis, peripheral neuropathy, polyneuropathy due to drugs of toxic agents, critical illness polyneuropathy, other inflammatory and toxic neuropathy)	337.0 337.9 354.1-354.9 355* 356.4 356.8 357.6 357.7 357.82 357.89 357.9
All	Seizures (epilepsy, convulsions)	345.0*-345.9* 780.3 780.31 780.39
All	Encephalitis/myelitis/encephalomyelitis (following immunization, postinfectious, other causes, unspecified cause, transverse myelitis)	323.5*323.6* 323.8* 323.9 341.2
All	Bell's palsy	351.0
All	Other cranial nerve disorders	350* 351.1 351.8 351.9 352*
All	Ataxia (other cerebellar ataxia, ataxia)	334.3
All	Anaphylaxis	995.0 999.4
All	Spontaneous abortion, missed abortion, other abnormal product of conception (for monitoring counts only)	631 632 634* 656.4* 761.8
All	Stillborn, papraceous fetus (for monitoring counts only)	V27.1 V27.4

Flu vaccine type	Outcome	ICD-9 CM Codes
		V27.7 646.0*
All	Pre-eclampsia, eclampsia (for monitoring counts only)	642.4* 642.5* 642.6* 642.7*
Live, attenuated	Myocarditis, pericarditis	420.90 420.91 422.0 422.90 422.91 422.99

Appendix 6: Pre-specified Outcomes and Definitions used for Rapid Cycle Analysis in VA

Flu vaccine type	Outcome	ICD 9
All	Guillain Barre Syndrome	357.0
All	Optic neuritis, optic papilitis, retrobulbar neuritis, toxic optic neuropathy	377.30, 377.31 , 377.32, 377.39
All	Encephalitis/myelitis/encephalomyelitis	323.5, 323.6, 323.8 , 323.9, 341.2
All	Bell's palsy	351.0, 781.94
All	Anaphylaxis	995.0, 999.4
All	Thrombocytopenia	287.31, 287.5


Appendix 7: Pre-specified Outcomes and Definitions used for Rapid Cycle Analysis in DMSS

Outcome	ICD-9 CM Codes
Guillain-Barré Syndrome (GBS)	
Guillain-Barré Syndrome (GBS)	357.0
Optic neuritis	
Optic neuritis, unspecified	377.30
Optic papillitis	377.31
Retrobulbar neuritis	377.32
Toxic optic neuropathy	377.34
Optic neuritis, other	377.39
Neurologic Outcomes	
Encephalitis, myelitis, and encephalomyelitis following immunization procedures	323.5
• Encephalitis and encephalomyelitis following immunization procedures	323.51
• Myelitis following immunization procedures	323.52
Postinfectious encephalitis, myelitis, and encephalomyelitis	323.6
• Infectious acute disseminated encephalomyelitis (ADEM) (includes acute necrotizing hemorrhagic encephalopathy)	323.61
• Other postinfectious encephalitis and encephalomyelitis	323.62
• Postinfectious myelitis	323.63
Other causes of encephalitis, myelitis, and encephalomyelitis (includes noninfectious ADEM)	323.8
• Other causes of encephalitis and encephalomyelitis (includes noninfectious ADEM)	323.81
• Other causes of myelitis (includes transverse myelitis NOS)	323.82
Unspecified cause of encephalitis, myelitis, and encephalomyelitis	323.9
Acute transverse myelitis	341.2
Bell's palsy	
Bell's palsy	351.0
Facial weakness/facial droop	781.94
Anaphylaxis	
Other anaphylactic shock	995.0
Anaphylactic reaction to serum	999.4
Idiopathic thrombocytopenic purpura	
Idiopathic thrombocytopenic purpura	287.31
Secondary thrombocytopenia	287.4
Thrombocytopenia, unspecified	287.5

Appendix 8: VSRAWG Report to the NVAC 1 – December 2009

National Vaccine Advisory Committee

<http://www.hhs.gov/nvpo/nvac/reports/2009vaccinesafetyreport.html>



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National Vaccine Advisory Committee

Report on 2009 H1N1 Vaccine Safety Risk Assessment

Approved by the National Vaccine Advisory Committee on December 16, 2009
Approved by the Assistant Secretary for Health on December 23, 2009

Background

The National Vaccine Advisory Committee (NVAC) established the H1N1 Vaccine Safety Risk Assessment Working Group (the Working Group) with the charge to conduct independent, rapid reviews of available safety monitoring data for the 2009 H1N1 influenza vaccines. Since the Working Group was created it has met twice to review available data from the Federal vaccine safety monitoring systems listed in Table 1. Based on the discussions of H1N1 safety data reviewed available as of its meeting on December 7, 2009, it provided the following assessment for NVAC's consideration on December 16, 2009, via telephone conference call.

Report

Based on the data summarized in Table 1, the Working Group concluded that the data are adequate to assess the presence or absence of a signal. Additionally, the Working Group concluded that the data do not favor a signal between the outcomes examined and the H1N1 vaccines. A signal is defined as an event that could be temporally occurring more often after vaccine receipt than anticipated by chance alone. The evidence for this includes:

1. No serious adverse events (SAE) have been attributed to the H1N1 vaccines in the clinical trials to date.
2. Comparison of reporting in the Vaccine Adverse Event Reporting System (VAERS) of SAE after seasonal and other similar vaccines and H1N1 influenza vaccines generally show similar levels of SAE.
3. For those systems conducting rapid cycle analysis¹, the rates of adverse events for pre-specified outcomes are within expected values.

It is still early in the H1N1 vaccination program and data on H1N1 vaccines' safety are limited; as more H1N1 vaccine doses are administered these conclusions will be based on a larger accumulation of data. Several of these analyses are based on small numbers of adverse events. Larger samples may be needed to detect rare adverse events. Finally, adverse events already reported are still being validated. Thus, the Working Group recommends that the Federal government continue to monitor H1N1 vaccine safety as more doses are administered and the body of evidence accumulates on the safety profile of H1N1 vaccines.

All recommendations of the NVAC are made to the Department's Assistant Secretary for Health. Thus, the recommendation on vaccine safety monitoring listed above will be formally transmitted to the Assistant Secretary for Health, who will review and consider it for potential implementation options to include communications with various components of the Department.

H1N1 Vaccine Safety Risk Assessment Working Group Membership:

Stephen Cantrell, Associate Professor of Emergency Medicine, University of Colorado
 Vicky Debold, Director of Research and Patient Safety, National Vaccine Information Center
 Kathryn Edwards, Professor of Pediatrics, Vanderbilt University
 Susan Ellenberg, Professor of Biostatistics, University of Pennsylvania
 Marie McCormick*, NVAC member, Professor of Maternal and Child Health, Harvard School of Public Health, former Chair of the IDU Immunization Safety Review Committee
 Laura Riley, Assistant Professor of Obstetrics, Gynecology and Reproductive Biology, Massachusetts General Hospital
 *Chair of the NVAC H1N1 Vaccine Safety Risk Assessment Working Group

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Table 1: Number of Persons Exposed to H1N1 Vaccine in Monitoring Systems Reviewed by the H1N1 VSRAWG

Vaccine Safety Program	Outcomes Monitored	Population Monitored	H1N1 MEV ¹ Exposures Captured in System	H1N1 LAMV ² Exposures Captured in System	Total H1N1 Vaccine Exposures Captured in System	Current as of	Analyses	Results
H1N1 Vaccine Trials	All health events	10,852	10,352 ^a	500 ^a	10,852 ^a	12/4/09	Adjudication and analysis of SAE	No SAE related to vaccine
Vaccine Adverse Event Reporting System (VAERS)	All health events	US Population	39,628,820 ^b	12,243,700 ^b	51,872,520 ^b	11/27/09	Comparison of reports for H1N1 versus seasonal influenza vaccines	SAE reporting after H1N1 are comparable to seasonal influenza immunization; GBS reporting is lower for H1N1 compared to seasonal

Appendix 9: VSRAWG Report to the NVAC 2 – January 2010

National Vaccine Advisory Committee

<http://www.hhs.gov/nvpo/nvac/reports/2010vaccinesafetyreport.html>



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Working Groups

Reports, Recommendations, & Resolutions

Historical Information

National Vaccine Plan

Partners

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National Vaccine Advisory Committee

Report on 2009 H1N1 Vaccine Safety Risk Assessment

Approved by the National Vaccine Advisory Committee on January 20, 2010
Approved by the Assistant Secretary for Health on January 22, 2010

Background

The National Vaccine Advisory Committee (NVAC) established the H1N1 Vaccine Safety Risk Assessment Working Group (H1N1 VSRAWG) with the charge to conduct independent, rapid reviews of available safety monitoring data for the 2009 H1N1 influenza vaccines. Since the Working Group was created it has met five times to review available data from the Federal vaccine safety monitoring systems listed in Table 1. Based on the discussions of H1N1 safety data reviewed available as of its meeting on January 4, 2010, it has provided the following assessment for NVAC's consideration on January 20, 2009, via telephone conference call.

Report

Since our last report, an additional 35,085,900 doses of inactivated H1N1 and 7,191,600 doses of live attenuated H1N1 vaccine have been distributed. A total of 74,714,720 doses of inactivated H1N1 and 19,435,300 doses of live attenuated H1N1 vaccine have been distributed as of 12/25/2009. Based on the data summarized in Table 1, the Working Group concluded that the data are adequate to assess the presence or absence of a signal. Additionally, the Working Group concluded that the data do not favor a signal between the outcomes examined and the H1N1 vaccines. A signal is defined as an event that could be temporally occurring more often after vaccine receipt than anticipated by chance alone. The evidence for this includes:

1. No serious adverse events (SAE) have been attributed to the H1N1 vaccines in the clinical trials to date.
2. Comparison of reporting in the Vaccine Adverse Event Reporting System (VAERS) of SAE after seasonal and other similar vaccines and H1N1 influenza vaccines generally show similar levels of SAE.
3. For those systems conducting rapid cycle analysis¹, the rates of adverse events for pre-specified outcomes are within expected values.

The size of the population captured under active surveillance for vaccine safety is still limited and some analysis are based on small number of events. As more data are available through active surveillance, conclusions will be based on a larger accumulation of data. Larger samples may be needed to detect rare adverse events. Finally, the data collected and analyses conducted across systems are not uniform, making a consistent interpretation difficult. Thus, the Working Group recommends that the Federal government continue to monitor H1N1 vaccine safety as more doses are administered and captured under active surveillance and thus the body of evidence accumulates on the safety profile of H1N1 vaccines.

All recommendations of the NVAC are made to the Department's Assistant Secretary for Health. Thus, the recommendation on vaccine safety monitoring listed above will be formally transmitted to the Assistant Secretary for Health, who will review and consider it for potential implementation options to include communications with various components of the Department.

H1N1 Vaccine Safety Risk Assessment Working Group Membership:

Stephen Cantrell, Associate Professor of Emergency Medicine, University of Colorado
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Kathryn Edwards, Professor of Pediatrics, Vanderbilt University
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Marie McCormick*, NVAC member, Professor of Maternal and Child Health, Harvard School of Public Health, former Chair of the IOM Immunization Safety Review Committee
Laura Riley, Assistant Professor of Obstetrics, Gynecology and Reproductive Biology, Massachusetts General Hospital
Mark Sawyer, Professor of Clinical Pediatrics, University of California, San Diego

*Chair of the NVAC H1N1 Vaccine Safety Risk Assessment Working Group

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Table 1: Number of Persons Exposed to H1N1 Vaccine in Monitoring Systems Reviewed by the H1N1 VSRAWG

Vaccine Safety Program	Outcomes Monitored	Population Monitored	H1N1 H1V ¹ Exposures Captured in System	H1N1 LAMY ² Exposures Captured in System	Total H1N1 Vaccine Exposures Captured in System	Current as of	Analyses	Results
H1N1 Vaccine Trials	All health events	10,852	10,352*	500*	10,852*	12/4/09	Adjudication and analysis of SAE	No SAE related to vaccine
Vaccine Adverse Event Reporting System (VAERS)	All health events	US Population	74,714,720 ^b	19,435,300 ^b	94,150,020 ^b	12/25/09	Comparison of reports for H1N1 versus seasonal influenza vaccines	SAE reporting after H1N1 are comparable to seasonal influenza immunization; GBS reporting is lower for

Appendix 10: VSRAWG Report to the NVAC 3 – February 2010

National Vaccine Advisory Committee

http://www.hhs.gov/nvpo/nvac/reports/vsrawg_report_feb2010.html



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National Vaccine Advisory Committee

Report on 2009 H1N1 Vaccine Safety Risk Assessment

Approved by the National Vaccine Advisory Committee on February 26, 2010
Approved by the Assistant Secretary for Health on March 1, 2010

Background

The National Vaccine Advisory Committee (NVAC) established the H1N1 Vaccine Safety Risk Assessment Working Group (H1N1 VSRAWG) with the charge to conduct independent, rapid reviews of available safety monitoring data for the 2009 H1N1 influenza vaccines. Since the Working Group was created it has met seven times to review available data from the Federal vaccine safety monitoring systems listed in Table 1. Based on the review and discussion of H1N1 safety data available as of its meeting on February 8, 2010, it has provided the following assessment for NVAC's consideration on February 26, 2010, via telephone conference call.

Report

Since our last report, an additional 25,641,000 doses of inactivated H1N1 and 1,983,200 doses of live attenuated H1N1 vaccine have been distributed. A total of 100,355,720 doses of inactivated H1N1 and 21,418,500 doses of live attenuated H1N1 vaccine have been distributed as of January 22, 2011. Based on the data summarized in Table 1, the Working Group concluded that the data are adequate to assess the presence or absence of a signal. Additionally, the Working Group concluded that the data do not favor a signal between the outcomes examined and the H1N1 vaccines. A signal is defined as an event that could be temporally occurring more often after vaccine receipt than anticipated by chance alone. The evidence for this includes:

1. No serious adverse events (SAE) have been attributed to the H1N1 vaccines in the clinical trials to date.
2. Comparison of reporting in the Vaccine Adverse Event Reporting System (VAERS) of SAE after seasonal and other similar vaccines and H1N1 influenza vaccines generally show similar levels of SAE.
3. For those systems conducting rapid cycle analysis¹, the rates of adverse events for pre-specified outcomes are within expected values.

As more data are available through active surveillance, conclusions will be based on a larger accumulation of data. Larger samples may be needed to detect rare adverse events. Finally, although the data collected and analyses conducted across systems are not uniform, making a consistent interpretation difficult, there has been some progress in implementing more uniform definitions that should reduce these difficulties in the future. Thus, the Working Group recommends that the Federal government continue to monitor H1N1 vaccine safety as more doses are administered and captured under active surveillance and the body of evidence accumulates on the safety profile of H1N1 vaccines and to continue work towards harmonizing surveillance approaches. The VSRAWG has been pleased with the thoughtfulness and thoroughness with which the Federal agencies have examined their data, and with their responsiveness to additional requests for data and analyses from VSRAWG members.

All recommendations of the NVAC are made to the Department's Assistant Secretary for Health. Thus, the recommendation on vaccine safety monitoring listed above will be formally transmitted to the Assistant Secretary for Health, who will review and consider it for potential implementation options to include communications with various components of the Department.

H1N1 Vaccine Safety Risk Assessment Working Group Membership:

Stephen Cantrill, Associate Professor of Emergency Medicine, University of Colorado

Vicky Debold, Director of Research and Patient Safety, National Vaccine Information Center

Kathryn Edwards, Professor of Pediatrics, Vanderbilt University

Theodore Eickhoff, Professor Emeritus, University of Colorado School of Medicine

Susan Ellenberg, Professor of Biostatistics, University of Pennsylvania

Marie McCormick*, NVAC member, Professor of Maternal and Child Health, Harvard School of Public Health, former Chair of the IOM Immunization Safety Review Committee

Laura Riley, Assistant Professor of Obstetrics, Gynecology and Reproductive Biology, Massachusetts General Hospital

Mark Sawyer, Professor of Clinical Pediatrics, University of California, San Diego

*Chair of the NVAC H1N1 Vaccine Safety Risk Assessment Working Group

References

1. Lieu TA, et al. Real-time vaccine safety surveillance for the early detection of adverse events. *Med Care* 2007; 45 (suppl2): S89-S95


Table 1: Number of Persons Exposed to H1N1 Vaccine in Monitoring Systems Reviewed by the H1N1 VSRAWG

Vaccine Safety Program	Outcomes Monitored	Population Monitored	H1N1 MIV ¹ Exposures Captured in System	H1N1 LAMV ² Exposures Captured in System	Total H1N1 Vaccine Exposures Captured in System	Current as of	Analyses	Results

Appendix 11: VSRAWG Report to the NVAC 4 – March 2010

National Vaccine Advisory Committee

http://www.hhs.gov/nvpo/nvac/reports/vsrawg_report_mar2010.html



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National Vaccine Advisory Committee

Report on 2009 H1N1 Vaccine Safety Risk Assessment

Approved by the National Vaccine Advisory Committee on March 23, 2010
Approved by the Assistant Secretary for Health on March 25, 2010

Background

The National Vaccine Advisory Committee (NVAC) established the H1N1 Vaccine Safety Risk Assessment Working Group (H1N1 VSRAWG) with the charge to conduct independent, rapid reviews of available safety monitoring data for the 2009 H1N1 influenza vaccines. Since the Working Group was created, it has met nine times to review available data from the Federal vaccine safety monitoring systems listed in Table 1. Based on the review and discussion of H1N1 safety data available as of its meeting on March 8, 2010, it has provided the following assessment for NVAC's consideration on March 23, 2010, via telephone conference call.

Report

Since our last report, an additional 4,604,900 doses of inactivated H1N1 and 318,900 doses of live attenuated H1N1 vaccine have been distributed through the immunization program. A total of 104,960,620 doses of inactivated H1N1 and 21,737,400 doses of live attenuated H1N1 vaccine have been distributed as of March 3, 2010. Most H1N1 vaccine safety monitoring systems report a substantial slowing of distribution and administration of H1N1 vaccine. However, since the last report, new data includes results from the PRISM system and data on pregnancy outcomes.

Based on the data summarized in Table 1, the Working Group concluded that the data are adequate to assess the presence or absence of a signal. Additionally, the Working Group concluded that the data do not favor a signal between the outcomes examined and the H1N1 vaccines. A signal is defined as an event that could be temporally occurring more often after vaccine receipt than anticipated by chance alone. The evidence for this includes:

1. No serious adverse events (SAE) have been attributed to the H1N1 vaccines in the clinical trials to date.
2. Comparison of reporting in the Vaccine Adverse Event Reporting System (VAERS) of SAE after seasonal and other similar vaccines and H1N1 influenza vaccines generally show similar levels of SAE.
3. For those systems conducting rapid cycle analysis¹, the rates of adverse events for pre-specified outcomes are within expected values.
4. Preliminary analyses on pregnancy outcomes have not detected a signal.

Since our last report, more H1N1 vaccine safety data has become available, and early results from the planned "end of season" analyses are emerging. As the pace of H1N1 vaccination in the population declines, the amount of new information being captured in each of the monitoring systems is decreasing. As a result, the Working Group will focus its efforts on reviewing new information and summarizing its experience for its final report. As a result, moving forward, the VSRAWG plans to meet on a monthly rather than bi-weekly basis. If a signal were to occur warranting the VSRAWG's attention, the VSRAWG would resume its bi-weekly meeting schedule. The VSRAWG will continue to provide monthly reports to the NVAC and will provide a final report once sufficient data have accumulated.

Thus, the Working Group recommends that the Federal government continue to monitor H1N1 vaccine safety as the body of evidence accumulates on the safety profile of H1N1 vaccines.

All recommendations of the NVAC are made to the Department's Assistant Secretary for Health. The recommendation on vaccine safety monitoring listed above will be formally transmitted to the Assistant Secretary for Health, who will review and consider it for potential implementation options to include communications with various components of the Department.

H1N1 Vaccine Safety Risk Assessment Working Group Membership:

Stephen Cantrill, Associate Professor of Emergency Medicine, University of Colorado
 Vicky Debold, Director of Research and Patient Safety, National Vaccine Information Center
 Kathryn Edwards, Professor of Pediatrics, Vanderbilt University
 Theodore Eickhoff, Professor Emeritus, University of Colorado School of Medicine
 Susan Ellenberg, Professor of Biostatistics, University of Pennsylvania
 Marie McCormick*, NVAC member, Professor of Maternal and Child Health, Harvard School of Public Health, former Chair of the IOM Immunization Safety Review Committee
 Laura Riley, Assistant Professor of Obstetrics, Gynecology and Reproductive Biology, Massachusetts General Hospital
 Mark Sawyer, Professor of Clinical Pediatrics, University of California, San Diego

*Chair of the NVAC H1N1 Vaccine Safety Risk Assessment Working Group

References

1. Lieu TA, et al. Real-time vaccine safety surveillance for the early detection of adverse events. *Med Care* 2007; 45 (suppl2): S89-S95

Table 1: Number of Persons Exposed to H1N1 Vaccine in Monitoring Systems Reviewed by the H1N1 VSRAWG

Vaccine Safety Program	Outcomes Monitored	Population Monitored	H1N1 MIV ¹ Exposures Captured in System	H1N1 LANV ² Exposures Captured in System	Total H1N1 Vaccine Exposures Captured in System	Current as of	Analyses	Results

Appendix 12: VSRAWG Report to the NVAC 5 – April 2010

National Vaccine Advisory Committee

http://www.hhs.gov/nvpo/nvac/reports/vsrawg_report_apr2010.html

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National Vaccine Advisory Committee
Report on 2009 H1N1 Vaccine Safety Risk Assessment
Approved by the National Vaccine Advisory Committee on April 23, 2010
Approved by the Assistant Secretary for Health on April 27, 2010

Background
The National Vaccine Advisory Committee (NVAC) established the H1N1 Vaccine Safety Risk Assessment Working Group (H1N1 VSRAWG) with the charge to conduct independent, rapid reviews of available safety monitoring data for the 2009 H1N1 influenza vaccines. Since the Working Group was created, it has met eleven times to review available data from the federal vaccine safety monitoring systems listed in Table 1. Based on the review and discussion of H1N1 safety data available as of its meeting on April 19, 2010, the Working Group has provided the following assessment for NVAC's consideration on April 23, 2010, via telephone conference call.

Report
Since our last report, an additional 136,800 doses of inactivated H1N1 and 17,800 doses of live attenuated H1N1 vaccine have been distributed through the immunization program. A total of 105,097,420 doses of inactivated H1N1 and 21,755,200 doses of live attenuated H1N1 vaccine have been distributed as of March 31, 2010. Most H1N1 vaccine safety monitoring systems report a substantial slowing of distribution and administration of H1N1 vaccine.

To place this report in context, a review of the guidelines for the Working Group is provided. Under the guidelines, summary data are presented to the members at the Working Group's regularly scheduled meetings, including evidence of any potential link between the receipt of an H1N1 vaccine and an adverse event. The Working Group then can make an assessment as to whether there is evidence of:

- ◆ A signal, defined as adverse event occurrence following receipt of vaccine at a rate greater than anticipated based on chance alone;
- ◆ An association, defined as a stronger linkage between vaccination and the event, varying with exposure to vaccine, as well as greater strength of association;
- ◆ Causality, defined as the assessment that the adverse event is a direct consequence of an exposure to vaccine using Bradford-Hill criteria.

In most of the surveillance systems reviewed by the Working Group, screening for a signal is conducted by comparing the rate of a number of pre-specified diagnoses, as coded from inpatient and outpatient medical encounters, with the rates seen in comparison situations. The potential of a signal is indicated by the rate in the H1N1-exposed group crossing a pre-specified statistical threshold. It should be noted that the detection of a signal does not necessarily indicate an association, and that, per protocol, several steps must be taken to validate the signal. To be assured that the signal is valid, individual cases must be reviewed to check for coding errors and for other supporting evidence of the diagnosis. In addition, it should be noted that the Working Group does not conduct its own analyses, but critically reviews the analyses conducted by the various federal agencies and departments, questions aspects of the results and suggests additional considerations.

At the Working Group's meeting on April 5, preliminary results were seen from five reporting systems for three adverse events for H1N1 monovalent inactivated vaccine: Guillain-Barré syndrome (GBS), thrombocytopenia/idiopathic thrombocytopenic purpura (TP/ITP) and Bell's palsy (BP). The Working Group requested further investigation and follow-up of these findings, which were reviewed during its meeting on April 19.

Based on the data presented in Table 1, the Working Group concluded that the data are adequate to assess the presence or absence of a signal. With regard to the specific adverse events above, the Working Group concluded the following:

1. Guillain-Barré syndrome
A potential weak signal between H1N1 vaccine exposure and GBS was initially detected in the Emerging Infections Program (EIP) data. Additional analyses with updated information on estimates of vaccine coverage and accounting for variation in the estimation of vaccination coverage rates further weakened the signal. GBS surveillance is also being conducted in five other systems. Although some systems are reporting elevated relative risks, none have crossed the threshold for a signal. The Working Group will continue to monitor these data including an updated analysis from the EIP with data from March (current data is through February). Of importance is the fact that, even if an association between H1N1 vaccine exposure and GBS were substantiated, the estimate is that the vaccine would account for only one extra case of GBS per 1 million persons vaccinated based on currently available data.
2. Bell's palsy
A weak signal linking H1N1 vaccine exposure and BP emerged in two monitoring systems. In one system, several analyses to examine this finding yielded inconsistent results with some comparisons providing support for the signal while others did not.
3. Thrombocytopenia/Idiopathic thrombocytopenic purpura
A weak signal between H1N1 vaccine exposure and thrombocytopenia also emerged in three systems. In these systems the cases are being reviewed to see if the diagnoses are valid. More rigorous comparisons between cohorts with H1N1 vaccine exposure and other vaccines or no exposure are planned.

When assessing the "strength" of the signal, we evaluated factors that are typically considered in assessing the level of concern include: strength of the association (e.g. elevated relative risk in a controlled study), temporal relationship between the receipt of the product and onset of the event, consistency of findings across available data, evidence of a dose response effect, potential biologic mechanisms linking the vaccine and the adverse event, and the rigor of the methodology and analyses being employed. Since many analyses in several systems are being conducted simultaneously, the possibility that temporal associations will arise by chance alone is important to recognize. As designated in Table 1, a "weak signal" implies a low level of risk and/or substantial methodological limitations in data or study design. Before any assessment of the association of vaccine exposure and adverse event is possible, several steps are needed to assure the validity of the findings and to explore potential alternatives that might result in a spurious association.

Appendix 13: VSRAWG Report to the NVAC 6 – June 2010

National Vaccine Advisory Committee

http://www.hhs.gov/nvpo/nvac/reports/vsrawg_repot_may2010.html

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National Vaccine Advisory Committee
Report on 2009 H1N1 Vaccine Safety Risk Assessment
Approved by the National Vaccine Advisory Committee on June 2, 2010
Approved by the Assistant Secretary for Health on June 7, 2010

Background
The National Vaccine Advisory Committee (NVAC) established the H1N1 Vaccine Safety Risk Assessment Working Group (H1N1 VSRAWG) with the charge to conduct independent, rapid reviews of available safety monitoring data for the 2009 H1N1 influenza vaccines. Since the Working Group was created, it has met twelve times to review available data from the federal vaccine safety monitoring systems listed in Table 1. Based on the review and discussion of H1N1 safety data available as of its meeting on May 3, 2010, the Working Group has provided the following assessment for NVAC's consideration on June 2, 2010.

Report
Since our last report, an additional 114,200 doses of inactivated H1N1 have been distributed through the immunization program. A total of 105,211,620 doses of inactivated H1N1 and 21,755,200 doses of live attenuated H1N1 vaccine have been distributed as of April 28, 2010.

At the April 23 NVAC meeting the VSRAWG presented preliminary results from five reporting systems for three adverse events for H1N1 monovalent inactivated vaccine: Guillain-Barré syndrome (GBS), thrombocytopenia/idiopathic thrombocytopenic purpura (TP/ITP) and Bell's palsy (BP). The Working Group requested further investigation and follow-up of these findings, which were reviewed during its meeting on May 3.

Based on the data presented in Table 1, the Working Group concluded that the data are adequate to assess the presence or absence of a signal. With regard to the specific adverse events above, the Working Group concluded the following:

1. Guillain-Barré syndrome
The potential weak signal in the Emerging Infections Program (EIP) data has changed to a weak signal between H1N1 vaccine exposure and GBS. Since the Working Group's last report it has reviewed updated data from the EIP through March in which the elevated relative risk has reached statistical significance. While the signal has reached statistical significance, this has relatively little impact on the interpretation of these data. The slightly elevated risk is highly prone to a number of factors that could lead to a spurious association or incorrect assessment of risk. GBS surveillance is also being conducted in five other systems. Although some systems are reporting elevated relative risks, none, with the exception of EIP, have crossed the threshold for a signal. Of importance is the fact that, even if an association between H1N1 vaccine exposure and GBS were substantiated, the estimate is that the vaccine would account for only one extra case of GBS per 1 million persons vaccinated based on currently available data.
2. Bell's palsy
A weak signal linking H1N1 vaccine exposure and BP remains in two monitoring systems. In one system, several analyses to examine this finding yielded inconsistent results with some comparisons providing support for the signal while others did not.
3. Thrombocytopenia/Idiopathic thrombocytopenic purpura
A weak signal between H1N1 vaccine exposure and thrombocytopenia also remains in three systems. In these systems the medical records are being reviewed to see if the diagnostic codes are valid. More rigorous comparisons between cohorts with H1N1 vaccine exposure and other vaccines or no exposure are planned to be initiated if this signal persists.

When assessing the "strength" of the signal, we evaluated factors that are typically considered in assessing the level of concern include: strength of the association (e.g. elevated relative risk in a controlled study), temporal relationship between the receipt of the product and onset of the event, consistency of findings across available data, evidence of a dose response effect, potential biologic mechanisms linking the vaccine and the adverse event, and the rigor of the methodology and analyses being employed. Since many analyses in several systems are being conducted simultaneously, the possibility that temporal associations will arise by chance alone is important to recognize. As designated in Table 1, a "weak signal" implies a low level of risk and/or substantial methodological limitations in data or study design. Before any assessment of the association of vaccine exposure and adverse event is possible, several steps are needed to assure the validity of the findings and to explore potential alternatives that might result in a spurious association.

The Working Group has reviewed end-of-season analysis plans and anticipates providing its final report after reviewing the results of these planned analyses.

Thus, the Working Group concludes that the evidence continues to suggest a weak signal between receipt of H1N1 vaccine and the indicated adverse events that requires further validation. The end-of-season analyses, which are in progress, will be important for determining whether the signals outlined in this report are spurious or if they represent a true association.

The Working Group does not view these results as necessitating any immediate response by NVAC, but wishes that the NVAC be aware of progress to date. In addition, all relevant federal agencies and departments are aware of these results, as they participate in the analyses and/or review calls. The Working Group recommends that the federal government continue to monitor H1N1 vaccine safety as the body of evidence accumulates.

All recommendations of the NVAC are made to the Department's Assistant Secretary for Health. The recommendation on vaccine safety monitoring listed above will be formally transmitted to the Assistant Secretary for Health, who will review and consider it for potential implementation options to include communications with various components of the Department.

H1N1 Vaccine Safety Risk Assessment Working Group Membership:
Stephen Cantrill, Associate Professor of Emergency Medicine, University of Colorado
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1 of 3

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