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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
John Clements, Professor of Microbiology and Immunology, Tulane University School of Medicine
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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
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*Chair of the NVAC H1N1 Vaccine Safety Risk Assessment Working Group

Table 1: Number of Persons Exposed to H1N1 Vaccine in Monitoring Systems Reviewed by the H1N1 VSRAWG (Gray shading indicated a signal has been detected)

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
H1N1 Vaccine Trials (Manufacturer)	All health events	10,852	10,352[a]	500[a]	10,852[a]	01/25/10	Adjudication and analysis of SAE	No SAE related to vaccine
H1N1 Vaccine Trials (NIAID)	All health events	4,589	-	-	-	04/05/10	Adjudication and analysis of SAE	-
Vaccine Adverse Event Reporting System (VAERS)	All health events	US Population	105,211,620[b]	21,755,200[b]	126,966,820[b]	04/28/10	Comparison of reports for H1N1 versus seasonal influenza vaccines	SAE reporting after H1N1 are comparable to seasonal influenza immunization
							Data-mining with comparison to similar vaccines	No signal
Vaccine Safety Datalink (VSD)	Pre-specified outcomes	9.5 million	1,313,683 [a]	265,135[a]	1,578,818[a]	04/24/10	Rapid cycle analysis	Weak signal (Bell's palsy)
Real-Time Immunization Monitoring System (RTIMS)	All health events	US Population	8,615	1,1134	9,774[a]	04/15/10	Symptoms that trigger an alert	No signal
Defense Medical Surveillance System (DMSS)	Pre-specified outcomes	1.4 million	1,216,545[a]	76,908[a]	1,288,353[a]	04/28/10	Rapid cycle analysis	Weak signal (TP/ITP)
Veteran's Affairs (VA) Databases **1.Enhanced VAERS**	All health events	1.2 million	879,164[b]	-	879,164[b]	03/29/10	Comparison of reports for H1N1 versus seasonal influenza vaccines	No signal
2.Signal Detection	Pre-specified outcomes	918,000	334,897[a]	-	334,897[a]	04/24/10	Rapid cycle analysis	Weak signal (TP/ITP)
Centers for Medicare and Medicaid Services (CMS)	Guillain-Barré syndrome	38 million	-	-	3,089,638[a]	04/27/10	Rapid cycle analysis	No signal
Indian Health Service (IHS)	Pre-specified outcomes	1.4 million	251,288[a]	59,317[a]	321,305[¥]	04/15/10	Rapid cycle analysis	Weak signal (Bell's palsy & TP/ITP)
Post-Licensure Rapid Immunization Monitoring System (PRISM)	Pre-specified outcomes	30 million (17 million registry enhanced)	2,452,482[a]	103,157[a]	2,555,639[a]	04/17/10	Rapid cycle analysis	No signal
Guillain-Barré syndrome (GBS) enhanced surveillance	Guillain-Barré syndrome	45 million	-	-	-	04/26/10	Observed versus Expected Rates of GBS; GBS incidence in vaccinated versus unvaccinated	Weak signal (GBS)

***Vaccines and Medications in Pregnancy Surveillance System (VAMPSS)**	Maternal and fetal outcomes	3,100	-	-	-	-	-	-

[1]H1N1 monovalent inactivated vaccine
[2]H1N1 live attenuated monovalent vaccine
*Data not yet available
[a] Exposed to vaccine; [b] Doses of vaccine distributed
¥ Total is greater than sum of H1N1 MIV and LAMV as some H1N1 exposures are of unknown type