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Preliminary Results: Surveillance for Guillain-Barré Syndrome After Receipt of Influenza A (H1N1) 2009 Monovalent Vaccine — United States, 2009–2010

Guillain-Barré syndrome (GBS) is an uncommon peripheral neuropathy causing paralysis and in severe cases respiratory failure and death. GBS often follows an antecedent gastrointestinal or upper respiratory illness but, in rare cases, can follow vaccination. In 1976, vaccination against a novel swine-origin influenza A (H1N1) virus was associated with a statistically significant increased risk for GBS in the 42 days after vaccination (approximately 10 excess cases per 1 million vaccinations), a consideration in halting the vaccination program in the context of limited influenza virus transmission (*1*). To monitor influenza A (H1N1) 2009 monovalent vaccine safety, several federal surveillance systems, including CDC's Emerging Infections Program (EIP), are being used. In October 2009, EIP began active surveillance to assess the risk for GBS after 2009 H1N1 vaccination. Preliminary results from an analysis in EIP comparing GBS patients hospitalized through March 31, 2010, who did and did not receive 2009 H1N1 vaccination showed an estimated age-adjusted rate ratio of 1.77 (GBS incidence of 1.92 per 100,000 person-years among vaccinated persons and 1.21 per 100,000 person-years among unvaccinated persons). If end-of-surveillance analysis confirms this finding, this would correspond to 0.8 excess cases of GBS per 1 million vaccinations, similar to that found in seasonal influenza vaccines (*2,3*). No other federal system to date has detected a statistically significant association between GBS and 2009 H1N1 vaccination. Surveillance and further analyses are ongoing. The 2009 H1N1 vaccine safety profile is similar to that for seasonal influenza vaccines, which have an excellent safety record. Vaccination remains the most effective method to prevent serious illness and death from 2009 H1N1 influenza infection; illness from the 2009 H1N1 influenza virus has been associated with a hospitalization rate of 222 per 1 million and a death rate of 9.7 per 1 million population.

In addition to existing surveillance systems that routinely monitor vaccine safety in U.S. vaccine recipients, new systems were added in the fall of 2009.* The 2009–10 influenza vaccine safety network consists of the following systems: Vaccine Adverse Event Reporting System (VAERS), Real Time Immunization Monitoring Systems (RTIMS), Vaccine Safety Datalink (VSD), Department of Defense (DoD) Defense Medical Surveillance System (DMSS), Post-Licensure Rapid Immunization Safety Monitoring (PRISM), Indian Health Service (IHS), Department of Veteran Affairs (VA), Centers for Medicaid and Medicare Services (CMS), and CDC's EIP. This report discusses preliminary analyses from EIP.

EIP, an established collaboration among CDC, state health departments, and academic centers in 10 states, initiated a population-based, active surveillance program designed to provide rapid case identification and assessment of risk for GBS following 2009 H1N1 vaccination.† EIP has covered 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 (nearly all GBS patients are hospitalized). Trained surveillance officers reviewed medical charts to confirm the diagnosis and obtain data on antecedent illnesses, vaccinations, and clinical outcomes; primary-care physicians provided further details about vaccination status when possible. Potential cases were classified by surveillance officers, sometimes in consultation with neurologists, using the Brighton Collaboration case criteria for GBS.§ Cases meeting Brighton Levels 1 and 2 were considered

* Information available at http://www.flu.gov/professional/federal/monitor_immunization_safety.html.
† Information available at http://www.cdc.gov/ncpdcid/deiss/eip/index.html.
§ Case definitions and guidelines available at http://www.brightoncollaboration.org/internet/en/index.html.

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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.

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 (*4*). 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 vaccinees by 42 days (or the number of days from vaccination to the end of the surveillance period if <42 days) (*1*). 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 vaccinated within the risk window 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 (*5*). 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 (*6*).

[¶] Recommendations available at http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5839a3.htm.

During October 1, 2009–May 10, 2010, a total of 529 reports of potential GBS were identified by EIP, of which 326 met the GBS case criteria. Of the 326 persons with GBS, 27 had documentation of 2009 H1N1 vaccination in the 42 days preceding illness onset, 274 did not receive vaccine, and the vaccine status of 25 was either unknown (six) or pending ascertainment (19) (Table 1). Sixteen of the 27 (59%) with documentation of 2009 H1N1 vaccination also reported antecedent illness symptoms in the 42 days before GBS onset; 78% of unvaccinated persons with GBS (215 of 274) reported antecedent symptoms (p=0.04). No clustering among vaccinated persons was observed in the period between vaccination and illness onset (p=0.54). Among the 27 GBS patients with 2009 H1N1 vaccination, four required ventilator support, and one remained hospitalized 30 days after GBS onset; among the 274 GBS patients who did not receive 2009 H1N1 vaccination, 37 (14%) required ventilator support, and 34 (12%) remained hospitalized after 30 days. Eight (2%) of the 326 GBS patients died (from any cause); none of the eight had received the 2009 H1N1 vaccine within 42 days of illness onset.

Among patients hospitalized through March 31, 2010, comparison of the incidence of GBS among those who received 2009 H1N1 vaccine and those who did not receive the vaccine revealed an age-adjusted rate ratio of 1.77 (CI = 1.12–2.56) (Table 2). If this preliminary rate ratio is confirmed in end-of-surveillance analyses, the attributable rate of GBS would be 0.71 per 100,000 person-years, corresponding to an attributable risk of 0.8 excess cases of GBS per 1 million vaccinations.[**]

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[**] The number of excess cases per 1 million vaccinations was calculated as the number of excess cases (i.e., attributable rate multiplied by person time-at-risk among the vaccinated population) divided by the number of vaccinations administered.

TABLE 1. Preliminary data regarding 2009 H1N1 vaccination status of persons with confirmed or probable Guillain-Barré syndrome, by case status, age group, and sex — Emerging Infections Program, United States, October 1, 2009–May 10, 2010*

	Documented receipt of monovalent 2009 H1N1 vaccine in the 42 days preceding illness onset							
	Yes		No		Unknown or under investigation		Total	
Characteristic	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Case status								
Confirmed (Brighton Level 1 and 2)	25	(93)	224	(82)	22	(88)	271	(83)
Probable (Brighton Level 3)	2	(7)	50	(18)	3	(12)	22	(17)
Age group (yrs)								
≤24	6	(22)	40	(15)	5	(20)	51	(16)
25–49	9	(33)	84	(31)	3	(12)	96	(29)
50–64	7	(26)	81	(30)	7	(28)	95	(29)
≥65	5	(19)	69	(25)	10	(40)	84	(26)
Sex								
Male	15	(56)	146	(53)	13	(52)	174	(53)
Female	12	(44)	128	(47)	12	(48)	152	(47)
Total	**27**	**(100)**	**274**	**(100)**	**25**	**(100)**	**326**	**(100)**

* Reported by May 10, 2010.

TABLE 2. Preliminary incidence rates* and rate ratios for persons with confirmed or probable Guillain-Barré syndrome, by 2009 H1N1 vaccination status and age group — Emerging Infections Program, United States, October 1, 2009–March 31, 2010†

		Documented receipt of monovalent 2009 H1N1 vaccine in the 42 days preceding illness onset						
		Yes			No			
Age group (yrs)	Vaccination coverage§	No.	Person-years	Rate	No.	Person-years	Rate	Rate ratio (95% CI¶)
≤24	32.5%	6	643,310	0.93	37	6,801,172	0.54	1.71 (0.40–3.61)
≥25	23.0%	21	763,496	2.75	216	14,024,546	1.54	1.79 (1.08–2.68)
Total	**26.1%**	**27**	**1,406,806**	**1.92**	**253**	**20,825,718**	**1.21**	**1.77 (1.12–2.56)****

* Per 100,000 person-years.
† Hospitalization as of March 31, 2010, reported as of May 10, 2010.
§ Vaccination coverage for persons with reported vaccination during October 2009–March 2010 who were interviewed during November 2009–April 24, 2010 (National 2009 H1N1 Flu Survey [NHFS]) or November 2009–April 25, 2010 (Behavioral Risk Factor Surveillance System [BRFSS]), using combined estimates from BRFSS and NHFS with Kaplan-Meier survival analysis procedure. Included in person-year estimates were second doses (22.9%, 95% CI = 18.7–27.1) for children aged 6 months–9 years.
¶ Confidence interval.
** Age adjusted total rate ratio and 95% CI.

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Editorial Note

This preliminary analysis showed an elevated, statistically significant association between 2009 H1N1 vaccination and GBS. If confirmed, the excess risk for GBS associated with 2009 H1N1 vaccine of 0.8 cases per 1 million vaccinations would be comparable to the excess described previously for some trivalent seasonal influenza vaccine formulations (approximately one excess case per 1 million vaccinations) (*2*,*3*), and much smaller than the risk for GBS observed during the 1976 swine influenza vaccine campaign (approximately 10 excess cases per 1 million vaccinations) (*1*). Notably, the high proportion of antecedent illnesses associated with GBS (e.g., gastrointestinal illness or respiratory infection) suggests that a number of the GBS illnesses observed after vaccination might be attributable to other antecedent illness; historically, 40%–70% of GBS patients report experiencing an antecedent infectious illness (*7*). Also, data demonstrating an association between GBS and the 1976

What is known on this topic?

Guillain-Barré syndrome (GBS) is an uncommon peripheral nerve disorder that, in rare cases, can follow vaccination; theoretic concern existed that an increased risk for GBS might occur after vaccination against 2009 pandemic influenza A (H1N1).

What is added by this report?

Preliminary findings from population-based, active surveillance for GBS in CDC's Emerging Infections Program indicate that, if confirmed by end-of-surveillance analysis, the rate of GBS following 2009 H1N1 vaccination receipt is less than one excess GBS case per 1 million vaccinations, similar to the rate following receipt of some formulations of seasonal influenza vaccines.

What are the implications for public health practice?

The incidence of GBS following 2009 H1N1 vaccination is very low, and the benefits of getting influenza vaccines outweigh the risk for GBS; vaccination remains the most important step in preventing serious illness and death from 2009 H1N1 influenza.

swine flu vaccines described a clustering of cases during the second and third weeks following vaccination (*1*). Similarly, a single study of seasonal influenza vaccine and GBS risk using combined data from 1992–93 and 1993–94 seasonal influenza vaccine formulations showed GBS cases peaked at 2 weeks following vaccination (*2*), whereas the EIP data did not demonstrate this same clustering effect for the 2009 H1N1 vaccine.

Safety monitoring is an integral part of any vaccination program. The federal government is using several other systems to monitor 2009 H1N1 vaccine safety, including programs to detect potential associations between GBS and the vaccine. These systems differ in the size of the population under surveillance, methods to identify and verify GBS cases, and methods to determine the vaccine status of persons with and without GBS. Interpreted collectively, these systems provide a comprehensive picture of vaccine safety. Preliminary safety data from VAERS (*8*) indicate that the safety profile of 2009 H1N1 vaccines is similar to the profile for seasonal influenza vaccines, which have an excellent safety record. To date, VSD, PRISM, DoD/DMSS, VA, and CMS have not detected any statistically significant associations between GBS and receipt of influenza A (H1N1) 2009 monovalent vaccine, although some of these systems (DoD, VA, VSD) have found a non-significant but slightly elevated relative risk (C. Vellozzi, CDC, personal communication, 2010).[††]

The findings in this preliminary report are subject to at least five limitations. First, misclassification of some cases might have occurred, particularly in younger patients where the diagnosis of GBS can be difficult, which might result in an underestimate of GBS cases; however, such an underestimate could bias the rate ratio in either direction. Second, some inaccurate reporting of the date of vaccination might have occurred, potentially resulting in an overestimate or underestimate of cases within the risk window. Third, the rate ratio relies on vaccination coverage estimates using BFRSS and NHFS data; based on work from previous seasons studying seasonal influenza vaccine, 2009 H1N1 vaccination coverage estimates might be overestimated by as much as two or three percentage points (*9*), which might produce an underestimate of the rate ratio. Fourth, incomplete case ascertainment or reporting bias might have occurred. However, these likely would have had a minimal effect because active case finding was conducted throughout the surveillance period. Finally, none of the vaccine monitoring systems currently in use, including EIP, can fully account for other confounding risk factors for GBS that might not be measured or accounted for but might be associated with vaccination decisions by patients or providers; thus, the association described above cannot prove a causal relationship between vaccination and GBS.

Further data collection and analyses of information from EIP and other surveillance systems are ongoing; a final analysis of the EIP data, including a self-controlled case series (*10*) that can control for some of the confounding that might exist when comparing vaccinated to unvaccinated persons, is expected to be available in early fall 2010. Persons with a history of GBS should discuss potential risks and benefits with their health-care providers before receiving any influenza vaccine. However, risk assessment should take into account that influenza and influenza-like illnesses are associated with significant morbidity and mortality, including a hospitalization rate of 222 per 1 million population and a death rate of 9.7 per 1 million population for H1N1-associated illness, as well as possible increased risk for GBS (*11*).[§§] Vaccination

[††] Additional information available at http://www.hhs.gov/nvpo/nvac/reports/index.html.

[§§] Information available at http://www.cdc.gov/h1n1flu/hosp_deaths_ahdra.htm.

remains the most effective method to prevent serious illness and death from influenza infection.

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