

Invited Commentary

Invited Commentary: Influenza Vaccine and Guillain-Barré Syndrome—Is There a Risk?

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After a new reassortant swine influenza A H1N1 virus caused outbreaks in Mexico and the United States in 2009, a vaccine was prepared from this virus to immunize the entire US population. Surveillance for Guillain-Barré syndrome (GBS) after receipt of this vaccine was carried out in 3 populations: the Vaccine Safety Datalink Project, the 10 Centers for Disease Control and Prevention Emerging Infections Program sites, and a network of large insurance companies. These studies found a small increase of approximately 1 case of GBS per million vaccinees above the baseline rate, which is similar to that observed after administration of seasonal influenza vaccines over the past several years. Enhanced surveillance for GBS was conducted in 2009–2010 because of the experience in 1976 of 362 GBS cases' occurring during the 6 weeks after influenza vaccination of 45 million persons, an 8.8-fold increase over background rates. The 1976 mass immunization had been conducted to prevent an influenza epidemic from another swine influenza A H1N1 recombinant virus. It can be concluded from these recent studies that influenza vaccination overall is of public health benefit, helping to reduce mortality and prevent the thousands of deaths that occur from annual seasonal influenza outbreaks, despite the possibility of a small increased risk of GBS associated with influenza vaccines.

Guillain-Barre syndrome; influenza vaccines; influenza A virus; influenza A virus, H1N1 subtype; population surveillance; safety; vaccines

Abbreviations: CDC, Centers for Disease Control and Prevention; CI, confidence interval; GBS, Guillain-Barré syndrome; PRISM, Post-Licensure Rapid Immunization Safety Monitoring.

In April 2009, untypable influenza A viruses were isolated from persons infected during an influenza outbreak in Mexico (1) and the United States (2–4). The virus was found to be a triple reassortant, including genome segments from avian, swine, and human H1N1 influenza viruses. Experts predicted that this new virus would spread as a worldwide pandemic because few persons younger than age 50 years would have immunity to any of its components (5). Therefore, new vaccines were prepared from this virus to be administered to the entire US population during the fall and winter of 2009 (5). Because more than 400 cases of Guillain-Barré syndrome (GBS), a postinfectious neuroparalytic autoimmune disease, had occurred within 6 weeks following receipt of a swine-origin influenza vaccine in 1976, special attention was focused on surveillance for GBS.

This issue of the *Journal* includes 3 studies on the relative risk of GBS following vaccination with the 2009 pandemic influenza vaccine (pH1N1). Greene et al. (6), using a self-controlled risk interval design that compared GBS onset within 1–42 days following receipt of the pH1N1 vaccine with GBS onset within 43–127 days following receipt of the vaccine, reported a risk difference of 5.0 (95% confidence interval (CI): 0.5, 9.3) cases per million doses; for the seasonal trivalent vaccine, which did not contain the new viral antigens, the risk difference was 1.1 (95% CI: 3.1, 5.4) cases per million doses. However, the monovalent pH1N1 vaccine was given during the influenza season, and 5 of the 9 GBS cases had had a preceding acute respiratory infection, a known GBS risk factor, whereas the seasonal (trivalent) vaccine was given prior to the influenza season and only

1 of 8 cases had had a clinical respiratory infection preceding the onset of GBS (6).

In the second study, Wise et al. (7) conducted active surveillance for GBS at 10 Centers for Disease Control and Prevention (CDC) Emerging Infections Program sites containing a population of 45 million persons. They detected 411 cases of confirmed or probable GBS. The rate of GBS following vaccination with the monovalent vaccine was 57% higher than the background rate of GBS among persons not vaccinated, a rate ratio of 1.57 (95% CI: 1.02, 2.21) (7). This increased risk corresponded to 0.74 excess cases of GBS per million vaccinees during the 6 weeks after immunization.

The third study was based on the Post-Licensure Rapid Immunization Safety Monitoring (PRISM) system, a cohort-based active surveillance network created by the Department of Health and Human Services to supplement other surveillance systems for tracking the safety of the monovalent pandemic 2009 H1N1 influenza vaccine and adverse reactions to it in the United States during 2009–2010 (8). The PRISM system monitored several symptoms, including GBS. In that study, Yih et al. (8) found a relative incidence of 2.5 (95% CI: 0.42, 15.0) for onset of GBS during the 42 days after vaccination.

The experience with GBS following vaccination to prevent swine influenza A H1N1 in 2009 is a welcome contrast to a previous large-scale vaccination campaign against swine influenza. In January 1976, an outbreak of influenza occurred among new US Army recruits at Fort Dix, New Jersey (9). Studies of the influenza viruses associated with these illnesses found that most of the viruses were of the type A/H3N2/Victoria, a virus that had been circulating and causing acute illnesses for several years. However, 4 of the isolates were different, including one isolated from a recruit whose illness was fatal. After detailed study of these influenza viruses, the CDC concluded that they were swine H1N1 viruses which were postulated to be closely related to the virus that caused the 1918 influenza pandemic (10). The 1918 pandemic resulted in over 30 million deaths, including more than 500,000 deaths in the United States (10). Soon thereafter, influenza experts considered and recommended the production of a new vaccine from this A/New Jersey/1976 (pH1N1 swine) strain with which to immunize the entire US population to prevent a recurrence of an epidemic similar to the 1918 pandemic. This program, the National Influenza Immunization Program, was, at the time, the most ambitious and extensive influenza immunization program ever attempted in the United States. The program had bipartisan political support, and Congress appropriated \$135 million for implementation. It was later buttressed by special liability legislation.

The development of a vaccine against this new virus required growing the virus in hens' eggs, inactivating and purifying the virus, and performing safety and immunogenicity trials before producing large quantities of vaccine (11). In addition, the public had to be warned about a possible pandemic and urged to be vaccinated. Dr. David Sencer, the director of the CDC, mobilized federal health agencies to prioritize the effort, and President Gerald Ford was shown being vaccinated on national television.

However, during the 5-month interval while the new vaccine was being prepared, no additional cases of influenza from

this swine virus were reported. All of the influenza cases were from the endemic H3N2 strain. This caused some dissent within the scientific community about the wisdom of proceeding with the program. Nonetheless, most scientists believed that the risks associated with waiting were too great, so mass immunization of the US population began in October 1976. Subsequent surveillance found no cases of influenza from infection with the swine influenza virus until November 19, when a single case was detected in Missouri. This patient did not transmit his infection to others. In November, a case of GBS was reported in a patient in Minnesota who had received the vaccine within the preceding month. In December, additional cases of GBS were reported in Minnesota and Alabama. During the following month, over 50 cases of GBS in persons who had recently received the vaccine were reported from 11 states. On December 16, 1976, the national influenza vaccine campaign was stopped (11).

Because of the reports of GBS following vaccination with the A/New Jersey/1976 (swine) vaccine, the CDC undertook nationwide surveillance for cases of GBS occurring between October 1, 1976, and January 31, 1977. This surveillance uncovered a total of 1,098 patients who contracted GBS during this period, of whom 532 patients had recently received A/New Jersey/1976 (swine) vaccine prior to the onset of GBS (12, 13). The attributable risk for receipt of the swine influenza vaccine within 6 weeks prior to the onset of GBS was 8.8; that is, just under 1 extra case of GBS per 100,000 people who received the vaccine as compared with the background rate in nonrecipients (12). This first mass immunization program, which later became known as "the swine flu affair," had some adverse political repercussions, including the firing of the director of the CDC in 1977. Nevertheless, it also had some beneficial consequences for public health—namely, increased surveillance and reporting of GBS and other adverse effects of immunization, the establishment of an Advisory Committee on Immunization Practices by the CDC, and the development of a federally funded liability mechanism to adjudicate cases and reward persons who experienced inadvertent and unexpected adverse health consequences from receipt of a licensed vaccine (11).

In subsequent years, increased attention was directed at monitoring for GBS and other vaccine-related adverse events. In none of these studies did investigators report a relative risk as high as that seen during the 1976 campaign. In a GBS study conducted in 1992–1993 and 1993–1994, Lasky et al. (14) found a relative risk of GBS during the 6 weeks after receipt of influenza vaccine of 1.7 (95% CI: 1.0, 2.8), or approximately 1 extra case of GBS per million persons vaccinated. In a Canadian study, Juurlink et al. (15) found a relative risk of 1.45 (95% CI: 1.05, 1.99) for GBS 2–7 weeks after receipt of influenza vaccine in comparison with onset 20–43 weeks after vaccination. In contrast with these results, in a United Kingdom study using a self-controlled case series method to analyze cases occurring between 1990 and 2005, Stowe et al. (16) found no increased relative incidence of GBS within 90 days after influenza vaccination (relative incidence = 0.76, 95% CI: 0.41, 1.40). In contrast, the relative incidence of GBS within 90 days of an influenza-like illness was 7.35 (95% CI: 4.36, 12.38). Other reports

from the US Army (17) and the United Kingdom (18) also failed to find a significantly elevated risk of GBS during the 6 weeks following immunization with influenza vaccines in the 2 decades after 1976. However, if the increased risk was only 1 case of GBS per million vaccinees, a large population of subjects would be required in order to detect this risk. In a study using data from the Vaccine Adverse Events Reporting System, which evaluated cases of GBS following influenza vaccination between July 1990 and June 2003, Haber et al. (19) reported a decreased incidence of GBS after vaccination, from 0.17 per 100,000 persons vaccinated in 1993–1994 to 0.04 per 100,000 vaccinees in 2002–2003.

So, what can we conclude from the recent studies about the risk of GBS after receipt of current influenza vaccines? It seems clear that the 1976 influenza vaccine was associated with a substantial, nearly 10-fold, increase in the risk of GBS during the 6 weeks after receipt of that vaccine. It also seems clear that any risk of GBS from current influenza vaccines is no more than approximately 1 extra case of GBS per million persons vaccinated.

The immunopathogenesis of GBS, in at least some cases, is believed to involve anti-ganglioside (anti-GM₁) antibodies and molecular mimicry. In fact, anti-GM₁ antibodies are commonly found in the sera of patients who have developed GBS after a *Campylobacter jejuni* infection, which frequently precedes the onset of GBS (20–22). Furthermore, based on the theory of molecular mimicry and autoimmune pathogenesis of GBS, these patients have been treated, often successfully, with plasma exchange and intravenous immunoglobulin (23).

Although the range of immunopathogenesis mechanisms of the various peripheral neuropathies included in the GBS and neuropathy classification includes cell-mediated causes as well as antibody-mediated causes, an experiment with the A/New Jersey/1976 vaccine was of particular interest. Nachamkin et al. (24) hypothesized that the 1976 influenza vaccine, which was produced in hens' eggs, may have contained contaminating proteins such as *C. jejuni* antigens that mimic human ganglioside, or that the vaccine components may have elicited anti-ganglioside antibodies in some recipients. These investigators found no evidence that the 1976 vaccine induced anti-*Campylobacter* antibodies when injected into mice. The vaccine used in 1976 induced anti-GM₁ antibodies in mice, but so did influenza vaccines from 1991–1992 to 2004–2005 (24). Nachamkin et al. suggested that further studies be done on the components of influenza vaccines that elicit anti-ganglioside antibodies and their role (if any) in GBS that follows influenza vaccination (24).

One possible explanation for the reduced but persistent risk of GBS in more recently produced influenza vaccines is the increased filtration and purification steps required in the preparation of recent influenza vaccines in order to minimize reactions to the vaccine in subjects with egg allergy or other hypersensitivities. It has been my experience that after receipt of the currently highly purified influenza vaccines that have been produced in eggs, local reactions are virtually absent, in contrast to the much more significant postvaccination local inflammatory responses observed several decades ago. Could these additional purification steps have significantly reduced the pathogenic potential for the more recent

vaccines to produce GBS in some persons? I think Nachamkin et al. may have detected one possible pathogenic mechanism for GBS following influenza vaccines in their mouse studies (24). This raises the question as to whether influenza vaccines should be studied in mice before they are licensed. In addition, will cell culture vaccines be free of the ability to produce anti-GM₁ antibodies? Perhaps these questions are worthy of further study in order to further reduce the risk of GBS from influenza vaccines now that we are in an era of widespread annual vaccination of the American public. Importantly, GBS commonly follows an acute respiratory or gastrointestinal infection, including influenza (25, 26). Therefore, influenza vaccination may actually reduce the overall risk of GBS by preventing influenza. Clearly, annual immunization of the population with influenza vaccine is an important public health practice in the United States that needs to be continued and expanded to prevent morbidity and mortality from this important disease (27). The benefits of influenza vaccination in reducing the estimated 5,000–40,000 excess deaths from annual seasonal outbreaks of influenza, despite an occasional mismatch with circulating viruses, definitely outweigh any risks (28, 29).

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REFERENCES

1. Echevarría-Zuno S, Mejía-Arangur JM, Mar-Obeso AJ, et al. Infection and death from influenza A H1N1 virus in Mexico: a retrospective analysis. *Lancet*. 2009;374(9707):2072–2079.
2. Dawood FS, Jain S, Finelli L, et al. Emergence of a novel swine-origin influenza A (H1N1) virus in humans. Novel Swine-Origin Influenza A (H1N1) Virus Investigation Team. *N Engl J Med*. 2009;360(25):2605–2615.
3. Shinde V, Bridges CB, Uyeki TM, et al. Triple-reassortant swine influenza A (H1) in humans in the United States, 2005–2009. *N Engl J Med*. 2009;360(25):2616–2625.
4. Lessler J, Reich NG, Cummings DA. Outbreak of 2009 pandemic influenza A (H1N1) at a New York City school. *N Engl J Med*. 2009;361(27):2628–2636.
5. Fiore AE, Uyeki TM, Broder K, et al. Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010. *MMWR Recomm Rep*. 2010;59(RR-8):1–62.
6. Greene SK, Rett M, Weintraub ES, et al. Risk of confirmed Guillain-Barré syndrome following receipt of monovalent inactivated influenza A (H1N1) and seasonal influenza vaccines in the Vaccine Safety Datalink Project, 2009–2010. *Am J Epidemiol*. 2012;175(11):1100–1109.
7. Wise ME, Viray M, Sejvar JJ, et al. Guillain-Barré syndrome during the 2009–2010 H1N1 influenza vaccination campaign:

- population-based surveillance among 45 million Americans. *Am J Epidemiol.* 2012;175(11):1110–1119.
8. Yih WK, Lee GM, Lieu TA, et al. Surveillance for adverse events following receipt of pandemic 2009 H1N1 vaccine in the Post-Licensure Rapid Immunization Safety Monitoring (PRISM) System, 2009–2010. *Am J Epidemiol.* 2012;175(11):1120–1128.
 9. Kendal AP, Goldfield M, Noble GR, et al. Identification and preliminary antigenic analysis of swine influenza-like viruses isolated during an influenza outbreak at Fort Dix, New Jersey. *J Infect Dis.* 1977;136(suppl):S381–S385.
 10. Top FH Jr, Russell PK. Swine influenza A at Fort Dix, New Jersey (January–February 1976). IV. Summary and speculation. *J Infect Dis.* 1977;136(suppl):S376–S380.
 11. Neustadt RE, Fineburg HV. *The Swine Flu Affair*. Washington, DC: US Department of Health, Education, and Welfare; 1978.
 12. Schonberger LB, Bregman DJ, Sullivan-Bolyai JZ, et al. Guillain-Barre syndrome following vaccination in the National Influenza Immunization Program, United States, 1976–1977. *Am J Epidemiol.* 1979;110(2):105–123.
 13. Langmuir AD, Bregman DJ, Kurland LT, et al. An epidemiologic and clinical evaluation of Guillain-Barré syndrome reported in association with the administration of swine influenza vaccines. *Am J Epidemiol.* 1984;119(6):841–879.
 14. Lasky T, Terracciano GJ, Magder L. The Guillain-Barré syndrome and the 1992–1993 and 1993–1994 influenza vaccines. *N Engl J Med.* 1998;339(25):1797–1802.
 15. Juurlink DN, Stukel TA, Kwong J, et al. Guillain-Barré syndrome after influenza vaccination in adults: a population-based study. *Arch Intern Med.* 2006;166(20):2217–2221.
 16. Stowe J, Andrews N, Wise L, et al. Investigation of the temporal association of Guillain-Barré syndrome with influenza vaccine and influenzalike illness using the United Kingdom General Practice Research Database. *Am J Epidemiol.* 2009;169(3):382–388.
 17. Roscelli JD, Bass JW, Pang L. Guillain-Barré syndrome and influenza vaccination in the US Army, 1980–1988. *Am J Epidemiol.* 1991;133(9):952–995.
 18. Hughes RA, Charlton J, Latinovic R, et al. No association between immunization and Guillain-Barré syndrome in the United Kingdom, 1992 to 2000. *Arch Intern Med.* 2006;166(12):1301–1304.
 19. Haber P, DeStefano F, Angulo FJ, et al. Guillain-Barré syndrome following influenza vaccination. *JAMA.* 2004;292(20):2478–2481.
 20. Rees JH, Soudain SE, Gregson NA, et al. *Campylobacter jejuni* infection and Guillain-Barré syndrome. *N Engl J Med.* 1995;333(21):1374–1379.
 21. Yuki N. Molecular mimicry between gangliosides and lipopolysaccharides of *Campylobacter jejuni* isolated from patients with Guillain-Barré syndrome and Miller Fisher syndrome. *J Infect Dis.* 1997;176(suppl 2):S150–S153.
 22. Willison HJ, O'Hanlon G, Paterson G, et al. Mechanisms of action of anti-GM₁ and anti-GQ_{1b} ganglioside antibodies in Guillain-Barré syndrome. *J Infect Dis.* 1997;176(suppl 2):S144–S149.
 23. Plasma Exchange/Sandoglobulin Guillain-Barré Syndrome Trial Group. Randomised trial of plasma exchange, intravenous immunoglobulin, and combined treatments in Guillain-Barré syndrome. *Lancet.* 1997;349(9047):225–230.
 24. Nachamkin I, Shadomy SV, Moran AP, et al. Anti-ganglioside antibody induction by swine (A/NJ/1976/H1N1) and other influenza vaccines: insights into vaccine-associated Guillain-Barré syndrome. *J Infect Dis.* 2008;198(2):226–233.
 25. Lehmann HC, Hartung HP, Kieseier BC, et al. Guillain-Barré syndrome after exposure to influenza virus. *Lancet Infect Dis.* 2010;10(9):643–653.
 26. Tam CC, O'Brien SJ, Petersen I, et al. Guillain-Barré syndrome and preceding infection with *Campylobacter*, influenza and Epstein-Barr virus in the General Practice Research Database. *PLoS One.* 2007;2(4):e344. (doi:10.1371/journal.pone.0000344).
 27. Osterholm MT, Kelley NS, Sommer A, et al. Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis. *Lancet Infect Dis.* 2012;12(1):36–44.
 28. Simonsen L, Reichert TA, Viboud C, et al. Impact of influenza vaccination on seasonal mortality in the US elderly population. *Arch Intern Med.* 2005;165(3):265–272.
 29. Estimates of deaths associated with seasonal influenza—United States, 1976–2007. *MMWR Morb Mortal Wkly Rep.* 2010;59(33):1057–1062.