Occurrences of the Guillain–Barré Syndrome (GBS) After Vaccinations with the 1976 Swine A/H1N1 Vaccine, and Evolution of the Concern for an Influenza Vaccine-GBS Association

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Abstract Implementation of a public vaccination program with A/New Jersey (A/NJ) vaccines in 1976 led to the recognition of an increased risk among vaccinated persons of developing the neurological disorder known as Guillain–Barré Syndrome (GBS). The attributable risk was 8.8 among adults in the 6-week period after vaccination or about 1 case per 100,000 vaccinations. Skepticism of the statistically significant association was resolved with a subsequent careful assessment in two states in the USA that confirmed the association. Subsequent efforts to confirm an association between other influenza vaccines and occurrence of GBS have mostly failed to identify an association but a suggestion of about one case of GBS per one million vaccinations has been reported. GBS has been associated with various other infections, illnesses, vaccinations, and other disorders. *Campylobacter jejuni* infections are accepted as inducing a risk for GBS and evidence suggests antiganglioside immune responses that react with the nerve myelin sheath as the mechanism. To assess this possibility, A/NJ and some other influenza vaccines were all shown to induce antiganglioside antibodies in mice; however, a relation of this finding in mice to GBS in humans has not been provided.

More recently, reports have indicated a risk of GBS after clinical influenza that is greater than the risk after influenza vaccination, suggesting that influenza vaccination may actually protect against GBS. Influenza, influenza vaccinations, and their role in the occurrences of GBS are evolving subjects. At present, however, occurrence of GBS cannot be considered an inherent risk of influenza vaccination.

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1 Introduction

In the fall of 1976, the USA implemented a public health program of vaccination of the population with influenza A/New Jersey/76 (A/H1N1) vaccines so as to prevent a pandemic from the swine-like (H1N1) virus that had emerged at Fort Dix, New Jersey, USA. That program led to recognition of a risk for occurrence after vaccination of the neurological disorder known as the Guillain–Barré Syndrome (GBS). That experience and the current status of understanding of an influenza vaccine-induced risk for GBS are summarized in this chapter.

2 The A/New Jersey Vaccine Experience

The nationwide campaign for immunization of all citizens in the USA in 1976 with influenza A/New Jersey (A/NJ) vaccine encountered numerous difficulties during the decision, organization, and implementation [1]. The final event that led to discontinuation of the public health program was the apparent increase in GBS among vaccine recipients in the setting of no apparent spread of the swine A/H1N1 virus in the population.

A subsequent organized GBS surveillance effort in the USA identified 1098 cases during the vaccination period, 532 of which had occurred after vaccination with the A/NJ vaccine [2]. Calculations of the risk of GBS after A/NJ vaccination indicated a significant attributable risk of 8.8 among adults in the 6-week period after vaccination. This corresponds to about one case per 100,000 vaccinations; almost 50 million vaccinations were performed. Additional convincing data for this association was the pattern of an increase in the GBS rate after vaccination with a peak in weeks two and three and a subsequent return to the baseline rate for unvaccinated persons (Fig. 1). Risk appeared about the same for all four vaccines distributed; a number of potential confounding variables were excluded.

Subsequent to this landmark report, substantive questions were raised about the quality of the data leading to the "conclusive" epidemiologic association [4, 5]. Additionally, other reports appeared that confirmed and did not confirm the association [3, 6, 7]. In an attempt to resolve the concerns, a new study was mounted to review all cases of GBS in the states of Michigan and Minnesota during the vaccination period using neurologists for formulating diagnostic criteria and reviewing all cases [8]. Some cases used in the earlier association report were discarded but the relative risk for GBS after A/NJ vaccination remained about as proposed in the initial report. Overall, these various reports provide very strong evidence that vaccination with A/NJ vaccine in 1976 increased the risk for developing the GBS in a 6–8 week period after vaccination; the reason(s) for this epidemiological association are unknown.

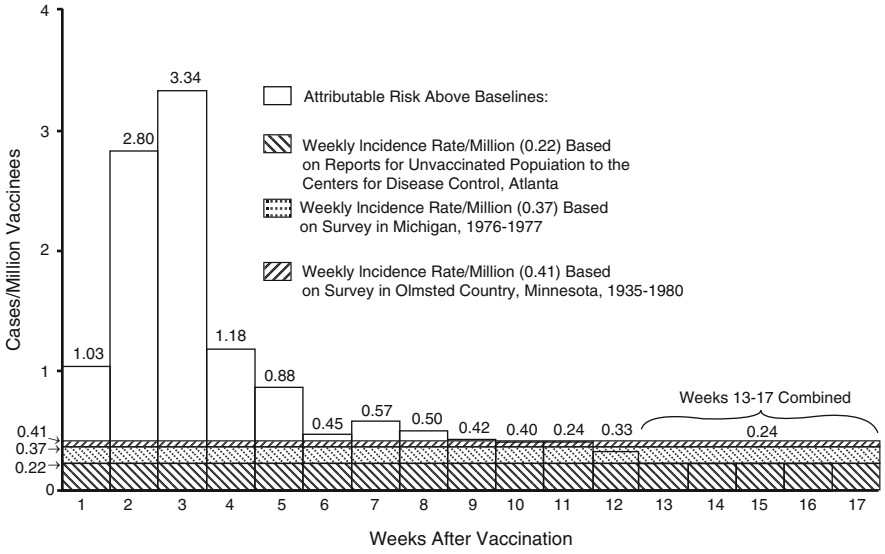

Fig. 1 Guillain–Barré syndrome, relative risks for population 18 years of age and over, by week of onset, after A/New Jersey/76 influenza vaccination, United States. Attributable risk and expected incidence evaluated from Olmsted County, Minnesota, Michigan, and USA data. Reprinted from Beghi et al. [3] with permission

3 The Guillain–Barré Syndrome

GBS is a neurologic disorder consisting of a constellation of neurological signs and symptoms of unknown cause. There are no objective tests available for establishing the diagnosis in a suspect case. Because of lack of uniformity in reported cases, the National Institute of Neurological and Communicative Disorders in the USA and the Brighton Collaboration provided definitions of the syndrome that have, for the most part, been followed [9–11]. The syndrome is an acute illness characterized by progressive motor weakness of more than one limb that tends to be symmetrical and is accompanied by areflexia. Mild sensory findings and cranial nerve involvement may be present and recovery generally occurs. Strong support for a diagnosis of GBS is provided by finding an albumin-cytologic dissociation (elevated protein and reduced cell concentration) in cerebrospinal fluid and typical electrophysiologic abnormalities.

Descriptions of GBS over many years have specified that most cases (about two-thirds) seemed to follow an episode of illness [12, 13]. In a review of GBS, Lineman identified 1,100 cases with about 60% having followed an infection, most commonly a nonspecific acute viral or bacterial infection of the respiratory tract [14]. Subsequently, reports have emphasized enteric infections and noted association with cytomegalovirus infections, infectious mononucleosis and numerous other infections and maladies. Until recently (see later), it was thought that influenza

infections did not convey a risk for GBS despite the fact that a history of an acute viral-like respiratory illness was known to be the most common preceding event [15–17]. Associations with immune disorders and events have included GBS after vaccinations; in earlier reports this association was seen more commonly after rabies vaccinations or use of tetanus antitoxin. Many vaccinations have now been followed by GBS and caused some concern; these have included various live and inactivated vaccines, viral and bacterial vaccines, protein and carbohydrate vaccines, and adjuvanted and nonadjuvanted vaccines (references available upon request).

Incidence rates of GBS have varied but are generally about one case per 100,000 persons per year [17, 18]. This low rate has compounded the problem of identifying and proving a specific cause for the GBS. Clusters of cases have been noted, sometimes associated with a discrete preceding outbreak such as acute gastroenteritis [19]. The GBS rate increases with increasing age is somewhat more common in males and, possibly, in whites.

4 A/New Jersey Vaccine and Pathogenesis of GBS

The GBS is primarily a polyradiculopathy of spinal nerve roots. The major histopathology is edema and disorganization of the myelin sheath that progresses to a mild inflammatory reaction and to Swann cell proliferation in the late stages [20]. Although the specific pathogenesis of the GBS is unknown, it is thought by most to be induced by an aberrant immune response that leads to reaction with the nerve myelin sheath or other axonal sites and results in impaired transmission of impulses through peripheral nerves [13, 21–23]. This possibility is most completely explored for GBS following *Campylobacter*-associated enteric infections [24, 25].

Campylobacter jejuni apparently has surface polysaccharides that are similar to gangliosides of nerve sheaths. Molecular mimicry is proposed as the mechanism for induction of ganglioside antibodies that react with nerve tissue and induce the pathology that impairs nerve impulse transmissions [24, 25]. Clusters of GBS associated with *Campylobacter* infections and gastroenteritis outbreaks that could be from *Campylobacter* infections are compatible with this specific infection being a precipitating event for GBS [24–26].

Whatever the exact relationship between infection, antiganglioside antibody, and GBS, it is clear that ganglioside antibody is not useful as a diagnostic test for GBS. Whether this antibody, in conjunction with cofactors or coevents, describes a pathogenetic circumstance for all cases of GBS is uncertain.

In an effort to assess ganglioside antibody induction and GBS after A/NJ vaccinations in 1976, residual A/NJ vaccines were used for immunizing mice and testing for ganglioside antibodies [27]. All of the A/NJ/76 vaccines induced anti-GM1 antibodies, the antibody of interest. If this antibody mediates GBS, it would be reasonable to suggest that a high frequency of responses occurs but that antibody mediates clinical disease in only a low percentage of cases. On the other hand, this

same report immunized mice with two different seasonal influenza vaccines and two A/H5N1 vaccines and all induced ganglioside antibodies. Although the number of H5 vaccinations is too small for detecting a GBS relationship, no relationship was noted for the two seasonal vaccines evaluated. Unfortunately, this provocative report has apparently not been followed by the indicated studies that would further clarify the significance of the finding. Thus, at present, it seems most reasonable to regard the influenza vaccination–ganglioside antibody–GBS relationship as no more than an interesting, suggestive observation that could use resolution for significance.

5 GBS and Influenza Vaccines Other than the A/New Jersey Vaccine

In order to verify whether the A/NJ–GBS association was an inherent risk of influenza vaccination, the American Center for Disease Control conducted surveillance for an association in 3 years subsequent to the A/NJ vaccination period. For three separate vaccination years, 1978–1979, 1979–1980, 1980–1981, no association of GBS and prior influenza vaccination was detected [28–30]. However, a borderline significant increased risk for GBS was reported after an investigation of influenza vaccinations in 1992–1994 that was precipitated by reports to the vaccine adverse event reporting system (VAERS) in the USA; the validity of this association has been questioned [31, 32]. Some other reports of an association between influenza vaccination and GBS have appeared as well as reports of no association [32–38]. Reports utilizing VAERS data to support an association between influenza vaccinations and GBS have been refuted by the CDC with the strong statement "the rate of an adverse event cannot be approximated from VAERS data" [39]. Thus, although it is possible that a small increase in risk for the GBS may follow vaccination with seasonal influenza vaccines, present knowledge suggests it is equally plausible to believe that there is no increased risk.

6 Recent Contributions

The most significant recent data on the influenza vaccine–GBS relationship are data supporting a risk for GBS after influenza infections [32, 40, 41]. Using the self-controlled case series method, an approach thought superior to cohort and case–control studies, Stowe et al. [32] found the relative incidence of GBS after influenza vaccination in the UK General Practice Database to be 0.76 within 90 days while GBS after an influenza-like illness was 7.35 within 90 days and 16.67 within 30 days. A similar relationship for GBS and clinical influenza-like illness was reported by Sivaden-Tardy et al. (Fig. 2), which was further supported by

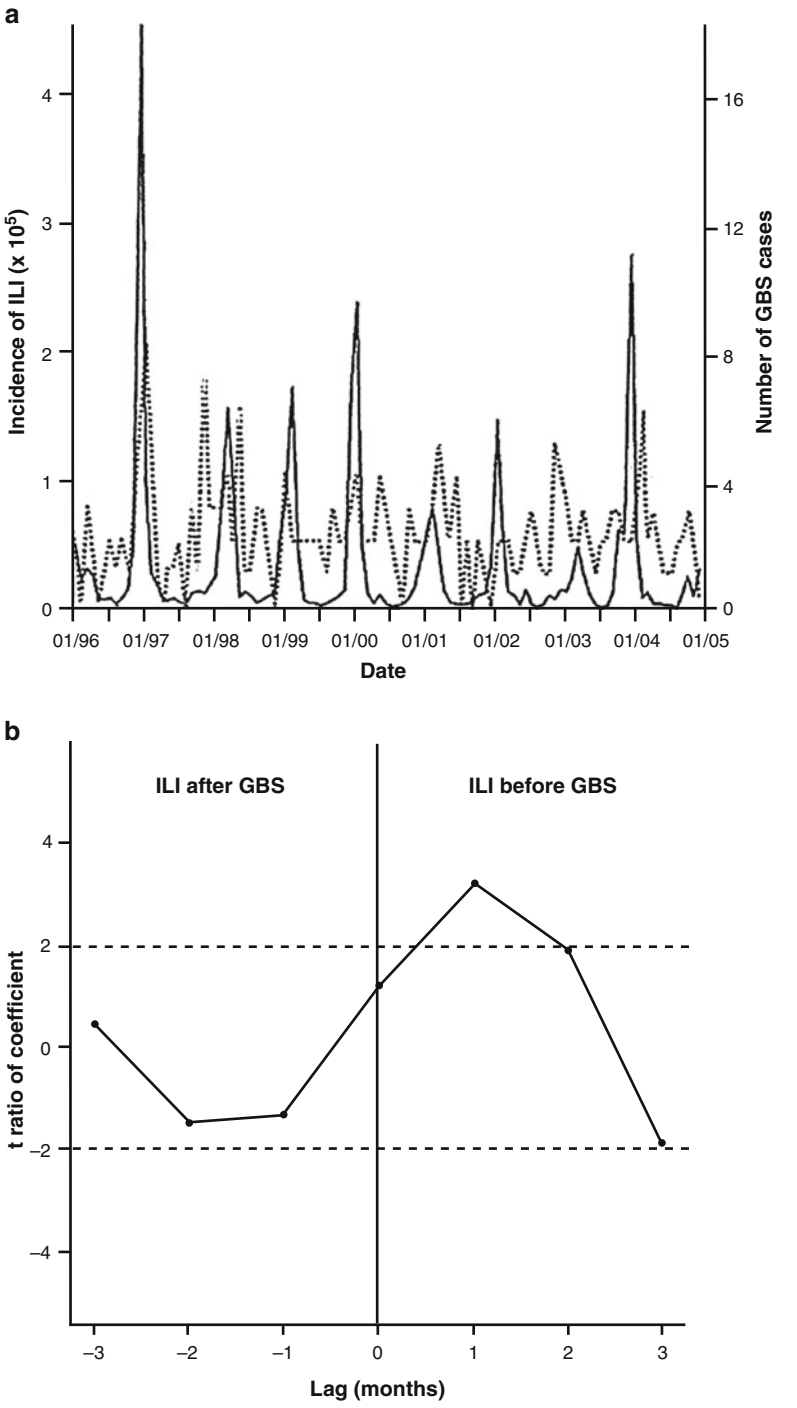

Fig. 2 (**a**) Monthly incidence of influenza-like illness (ILI; *solid line*) and Guillain–Barré syndrome (GBS; *dashed line*) caused by an unidentified agent. (**b**) *t* Ratios of lagged-regression

objective evidence of actual influenza virus infection in the GBS cases [41]. Also of interest is the fact that none of the GBS cases after influenza infection developed ganglioside antibodies. These recent reports offer the intriguing possibility that influenza vaccinations may protect against any increased risk for development of GBS after clinical influenza that might exist.

7 Comment

A summary of the evolution of the influenza vaccine-GBS association is provided in Table 1. It seems clear that vaccination with the A/NJ influenza vaccine in 1976 increased the risk for developing GBS; however, numerous efforts since 1976 have failed to confirm a risk for GBS attributable to influenza vaccination. Thus, it seems reasonable to conclude that GBS does not constitute an inherent risk from influenza vaccinations. It remains possible that influenza vaccinations may, on rare occasions, serve as a contributing factor to occurrences of GBS and account for the reports that have suggested a minor increase in risk; for some unknown reason, a contribution of significance occurred in the fall of 1976 when a nationwide vaccination campaign was conducted to prevent a pandemic with swine influenza

Table 1 Summary of the Influenza vaccine Guillain–Barré Syndrome (GBS) Association

- There was a significant increased risk for developing GBS in the 6–8 week period after vaccination with the swine influenza A/H1N1 vaccine in 1976. The reason(s) for this increase are unknown.
- The GBS is a paralytic syndrome of unknown cause that is presumed to be an immunopathologic disorder resulting from an immune reaction with nerve tissue.
- Ganglioside antibodies are proposed as the mediator for the immunopathological reaction leading to GBS and data are available to support this hypothesis, particularly for GBS after *Campylobacter* infections. Available data are insufficient to support this as a mechanism for an influenza vaccine-induced GBS.
- The many studies reported on influenza vaccinations and GBS since 1976 have either failed to identify a risk for GBS or have reported a very low frequency risk (~one per million vaccinations).
- Recent studies of influenzal illnesses and GBS have reported a significant risk for GBS after clinical influenza. GBS after a nonspecific acute viral-like respiratory illness has been an accepted association for decades.
- Influenza, influenza vaccinations, and their role in occurrences of GBS are evolving subjects. At present, occurrence of GBS cannot be considered an inherent risk of influenza vaccination.

Fig. 2 (continued) coefficients between residual cases of GBS caused by an unidentified agent at month t and ILI at month t – lag, for lags of -3 to 3. Horizontal dashed lines indicate 5% significance level of a two-sided test of association. Reprinted from Sivadon-Tardy et al. [41] with permission

A/H1N1 viruses. The similarities between the swine influenza A/H1N1 experience in 1976 and that ongoing at the present time (2009), with swine influenza A/H1N1 vaccinations are obvious. The magnitude of the current vaccination effort should clarify any relationship between influenza vaccination and occurrence of the GBS.

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References

1. Sencer DJ, Millar JD (2006) Reflections on the 1976 swine flu vaccination program. Emerg Infect Dis 12:29–33
2. Schonberger LB, Bregman DJ, Sullivan-Bolyal JZ, Keenlyside RA, Ziegler DW, Retailliau HF, Eddins DL, Bryan JA (1979) Guillain–Barre syndrome following vaccination in the National Influenza Immunization Program. United States, 1976-1977. Am J Epidemiol 110:105–122
3. Johnson DE (1982) Guillain-Barre syndrome in the US Army. Arch Neurol 39:21–24
4. Beghi E, Kurland LT, Mulder DW, Wiederholt WC (1985) Guillain-Barre syndrome: clinicoepidemiologic features and effect of influenza vaccine. Arch Neurol 42:1053–1057
5. Kurland LT, Wiederholt WC, Kirkpatrick JW, Potter HG, Armstrong P (1985) Swine influenza vaccine and Guillain-Barre syndrome. Epidemic or Artifact? Arch Neurol 42:1089–1092
6. Marks JS, Halpin TJ (1980) Guillain-Barre syndrome in recipients of A/New Jersey influenza vaccine. JAMA 243:2490–2494
7. Breman JG, Hayner NS (1984) Guillain-Barre syndrome and its relationship to swine influenza vaccination in Michigan, 1976-1977. Am J Epidemiol 119:880–889
8. Safranek TJ, Lawrence DN, Kurland LT, Culver DH, Wiederholt WC, Hayner NS, Osterholm MT, O'Brien P, Hughes JM, Expert Neurology Group (1991) Reassessment of the association between Guillain-Barre syndrome and receipt of swine influenza vaccine in 1976-1977: Results of a two-state study. Am J Epidemiol 133:940–951
9. Asbury AK, Arnason BG, Karp HR, McFarlin DE (1978) Criteria for diagnosis of Guillain-Barre syndrome. Ann Neurol 3:565–566
10. Asbury AK, Cornblath DR (2004) Assessment of current diagnostic criteria for Guillain-Barre syndrome. Ann Neurol 27:S21–S24
11. Sejvar J, Cornblath D, Hughes R, The Brighton Collaboration Guillain-Barre Syndrome Working Group. (2008) The Brighton Collaboration case definition for Guillain-Barre syndrome as an adverse event following immunization. Inflammatory Neuropathy Consortium Meeting, Paris, France, July 2008
12. Kennedy RH, Danielson MA, Mulder DW, Kurland LT (1978) Guillain-Barre Syndrome. A 42-year epidemiologic and clinical study. Mayo Clin Proc 53:93–99
13. van Doorn PA, Ruts L, Jacobs BC (2008) Clinical features, pathogenesis, and treatment of Guillain-Barre syndrome. Lancet Neurol 7:939–950
14. Leneman F (1966) The Guillain-Barre syndrome. Arch Intern Med 118:139–144
15. Melnick SC, Flewett TH (1964) Role of infection in the Guillain-Barre syndrome. J Neurol Neurosurg Psychiatry 27:385–407
16. Langmuir AD (1979) Guillain-Barre syndrome: the swine influenza virus vaccine incident in the United States of America, 1976-77: preliminary communication. J R Soc Med 72:660–669

17. Schonberger LB, Hurwitz ES, Katona P, Holman RC, Bregman DJ (1981) Guillain-Barre syndrome: its epidemiology and associations with influenza vaccination. Ann Neurol 9:31–38
18. Black S, Eskola J, Siegrist C-A, Halsey N, MacDonald N, Law B, Miller E, Andrews N, Stowe J, Salmon D et al (2009) Importance of background rates of disease in assessment of vaccine safety during mass immunization with pandemic H1N1 influenza vaccines. Lancet 374 (9707):2115–2122
19. Sliman NA (1978) Outbreak of Guillain-Barre syndrome associated with water pollution. Br Med J 1:751–752
20. Haymaker W, Kernohan JW (1949) The Landry-Guillain-Barre syndrome: a clinical pathologic report of 50 fatal cases and a review of the literature. Medicine 28:59–141
21. Zhu J, Mix E, Link H (1998) Cytokine production and the pathogenesis of experimental autoimmune neuritis and Guillain-Barre syndrome. J Neuroimmunol 84:40–52
22. Ariga T, Miyatake T, Yu RK (2001) Recent studies on the roles of antiglycosphingolipids in the pathogenesis of neurological disorders. J Neurosci Res 65:363–370
23. McCarthy N, Giesecke J (2001) Incidence of Guillain-Barre syndrome following infection with *Campylobacter jejuni*. Am J Epidemiol 153:610–614
24. Yuki N (2001) Infectious origins of, and molecular mimicry in, Guillain-Barre and Fisher syndromes. Lancet Infect Dis 1:29–37
25. Rees JH, Soudain SE, Gregson NA, Hughes RAC (1995) *Campylobacter jejuni* infection and Guillain-Barre syndrome. BMJ 333:1374–1379
26. Bereswill S, Kist M (2003) Recent developments in *Campylobacter* pathogenesis. Curr Opin Infect Dis 16:487–491
27. Nachamkin I, Shadomy SV, Moran AP, Cox N, Fitzgerald C, Ung H, Corcoran AT, Iskander JK, Schonberger LB, Chen RT (2008) Anti-ganglioside antibody induction by swine (A/NJ/19976/H1N1) and other influenza vaccines: Insights into vaccine-associated Guillain-Barre syndrome. J Infect Dis 198:226–233
28. Hurwitz ES, Schonberger LB, Nelson DB, Holman RC (1981) Guillain-Barre syndrome and the 1978-1979 influenza vaccine. New Engl J Med 304:1557–1561
29. Kaplan JE, Katona P, Hurwitz ES, Schonberger LB (1982) Guillain-Barre syndrome in the United States, 1979-1980 and 1980-1981. JAMA 248:698–700
30. Kaplan JE, Schonberger LB, Hurwitz ES, Katona P (1983) Guillain-Barre syndrome in the United States, 1978-1981: Additional observations from the national surveillance system. Neurology 33:633–637
31. Lasky T, Terracciano GJ, Magder I, Koski CL, Ballesteros M, Nash D, Clark S, Haber P, Stolley PD, Schonberger LB et al (1998) The Guillain-Barre syndrome and the 1992-1993 and 1993-1994 influenza vaccines. New Engl J Med 339:1797–1802
32. Stowe J, Andrews N, Wise L, Miller E (2009) Investigation of the temporal association of Guillain-Barre syndrome with influenza vaccine and influenzalike illness using the United Kingdom general practice research database. Am J Epidemiol 169:382–388
33. Roscelli JD, Bass JW, Pang L (1991) Guillain-Barre syndrome and influenza vaccination in the US Army, 1980-1988. Am J Epidemiol 133:952–955
34. Centers for Disease Control and Prevention (2003) *Surveillance Summaries*, January 24, 2003. Surveillance for Safety after immunization: vaccine adverse event reporting system (VAERS) – United States, 1991–2001. *MMWR* 52 (No. SS-1)
35. Geier MR, Geier DA, Zahalsky AC (2003) Influenza vaccination and Guillain Barre syndrome. Clin Immunol 107:116–121
36. Haber P, DeStefano F, Angulo FJ, Iskander J, Shadomy SV, Weintraub E, Chen RT (2004) Guillain-Barre syndrome following influenza vaccination. JAMA 292:2478–2481
37. Souayah N, Nasar A, Fareed M, Suri K, Qureshi AI (2007) Guillain-Barre syndrome after vaccination in United States. A report from the CDC/FDA vaccine adverse event reporting system. Vaccine 25:5253–5255

38. Juurlink DN, Stukel TA, Kwong J, Kopp A, McGeer A, Upshur RE, Manuel DG, Moineddin R, Wilson K (2006) Guillain-Barre syndrome after influenza vaccination in adults. Arch Intern Med 166:2217–2221
39. Haber P, Slade B, Iskander J (2007) Letter to the editor. Vaccine 25:8101
40. Tam CC, O'Brien SJ, Petersen I, Islam A, Hayward A, Rodrigues LC (2007) Guillain-Barre syndrome and preceding infection with *Campylobacter*, influenza and Epstein-Barr virus in the general practice research database. PLoS ONE 2(4):e344. doi:10.1371/journal.pone.0000344
41. Sivadon-Tardy V, Orlikowski D, Porcher R, Sharshar T, Durand M-C, Enouf V, Rozenberg F, Caudie C, Annane D, van der Wert S et al (2009) Guillain-Barre syndrome and influenza virus infection. Clin Infect Dis 48:48–56