



Australian Government

Department of Health and Ageing

Australian Technical Advisory Group on Immunisation (ATAGI) advice regarding influenza, influenza vaccines and Guillain-Barré Syndrome

Summary of advice

Guillain-Barré Syndrome (GBS) is a demyelinating polyneuropathy which typically causes an ascending paralysis. **Receipt of pandemic H1N1 2009 influenza vaccine is not expected to result in any increased risk of GBS.** Relevant considerations include:

1. The annual incidence of GBS in developed countries including Australia is 1.0 to 2.0 per 100,000 population, equating to approximately 400 cases per year in Australia.
2. There is evidence of preceding infection in most cases of GBS, most commonly *Campylobacter* enteritis. Less than 5% have laboratory-proven influenza infection.
3. In the USA in 1976, following receipt of the A/New Jersey/76 influenza vaccine, a statistical association suggested the excess risk of GBS due to the vaccination was about 9 in every million vaccinees in the 6 weeks after vaccination. However, studies conducted since 1976 have not found an excess risk of GBS associated with influenza vaccines. Indeed some studies have suggested a possible protective effect of influenza vaccination against GBS.
4. The pandemic H1N1 influenza vaccine registered by the TGA in Australia is an inactivated monovalent influenza vaccine, manufactured using the same techniques as conventional seasonal influenza vaccines currently available in Australia.
5. Although the H1N1 2009 influenza vaccine has the same favourable safety profile as seasonal vaccines, additional surveillance for adverse events will be conducted to ensure comprehensive safety monitoring, including monitoring for GBS.

Background

Concern has been raised whether recipients of the new pandemic H1N1 2009 influenza (swine flu) vaccine might have a small increased risk of developing Guillain-Barré Syndrome (GBS), such as was observed with an H1N1 vaccine against 'swine flu' in 1976–1977 in the USA. This ATAGI advice addresses the concern, based on available evidence.

The disease: Guillain-Barré Syndrome

GBS is a neurological syndrome characterised by acute flaccid paralysis (AFP), first described in 1916 by French neurologists.^{1,2} There are several clinical subtypes of GBS, with

acute inflammatory demyelinating polyradiculoneuropathy (AIDP) being the predominant subtype especially in North America and Europe.

Clinical features and prognosis

Generalised muscle weakness (flaccid paralysis) is the dominant clinical feature of the AIDP subtype of GBS. An Australian study reported a spectrum of peak disability, ranging from ambulant with weakness (32%) to bed-bound (29%) to respiratory weakness requiring intensive care (38%).³ Overall, mechanical ventilation is required in about 25% of patients.^{1,2}

The disease usually lasts for weeks, with the functional nadir occurring within 2 weeks from onset for most cases and 4 weeks for almost all cases. About 10–20% of patients have residual disabling motor deficits, and more require re-adjustment to their work or social activities due to residual functional deficits. Older age is associated with poorer prognosis.^{1,2}

Association between infection and GBS

About two-thirds of GBS cases report a history consistent with infection in the 6 weeks prior to onset of neurological symptoms, with respiratory tract symptoms or gastroenteritis being most common. Laboratory evidence for a recent infection is often not found. The most commonly identified agents are *Campylobacter jejuni*, cytomegalovirus (CMV), *Mycoplasma pneumoniae*, and Epstein-Barr virus (EBV).^{1,4}

Influenza and GBS

In one retrospective case-control study of 154 GBS patients,⁴ evidence of infection with influenza A virus and influenza B virus was found in about 1% of cases for each type, not significantly greater than in controls, although power to detect an association was limited. A much larger nested case-control study, using data from the UK General Practice Research Database between 1991 and 2001, found that 14 of 553 GBS cases reported an influenza-like illness in the preceding 2 months compared with 9 of 5445 controls. This yielded an odds ratio of 18.6 (95%CI 7.5–46.4, $p < 0.001$). In contrast, influenza vaccination was associated with a non-significantly lower risk of GBS (1/553 cases, 47/5445 controls, odds ratio 0.16 (95%CI 0.02–1.25, $p = 0.08$).⁵

A more recent study using data from the UK General Practice Research Database over a longer time period (1990 to 2005) found a relative incidence of GBS within 90 days of an influenza-like illness (ILI) of 7.4 (95%CI 4.4–12.4), increasing to 16.6 (95%CI 9.4–29.5) within 30 days.⁶ There was again a non-significant negative association between reported influenza vaccination and GBS of 0.76 (95%CI 0.41–1.40).

A time-series analysis of 405 French GBS patients between 1996 and 2004 showed a statistically significant association with ILI incidence at both 1 and 2 months before onset of GBS, and also identified 10 cases with serological evidence of recent influenza A, and 4 with influenza B infection. Influenza-related GBS cases were found to occur mainly during major influenza seasons and involved circulating epidemic strains.⁷

The available evidence supports an association between infection and GBS, and specifically between influenza infection and GBS which, although accounting for only a small proportion of GBS cases, is significant at the population level. On the other hand, these studies did not find any statistically significant increase in GBS associated with influenza vaccination, with the direction of effect consistent with protection.

Acute neurological complications (encephalopathy and seizures) associated with pandemic H1N1 2009 influenza A virus infection were reported in four children in the USA, but none of them were diagnosed with GBS.⁸ In Australia to date, there has been one case of GBS in a child with confirmed pandemic H1N1 2009 influenza A infection. This case was identified

through the Paediatric Active Enhanced Disease Surveillance system¹ among 288 fully documented influenza cases admitted in three NSW hospitals during the pandemic period June–September 2009 inclusive (personal communication, E. Elliott, Australian Paediatric Surveillance Unit, 30 Sept 2009). The majority of those influenza infections for which sub-typing information is available, constituting about two-thirds of NSW cases, were due to influenza A (H1N1).

Pathogenesis of GBS

In GBS, there is inflammation of the peripheral nervous system with patchy multifocal mononuclear cell infiltration and subsequent demyelination. The mechanism of inflammation is complex, involving both cellular and humoral immune responses and varying among different GBS subtypes.^{1,2} The pathology of the AIDP subtype of GBS closely resembles autoimmune neuritis induced by inoculating experimental animals with peripheral nerve myelin.

In both animal studies and human cases, there is evidence that antibodies cross-reacting with neural antigens, leading to inflammatory neuropathy like GBS, is induced by some infections. Molecular mimicry between some antigens, such as lipo-oligosaccharides on the bacterial wall of *C. jejuni* and gangliosides on peripheral nerves, has been demonstrated.^{1,9} However, although anti-ganglioside antibodies are implicated in the pathogenesis of some subtypes of GBS, they are not found in patients with AIDP, the commonest subtype of GBS.^{1,2} It is possible, although unproven, that immune responses to influenza virus, or to influenza vaccines, could be implicated in GBS.

An excess of GBS cases was observed in recipients of the 1976 swine flu vaccine (see also section below on *GBS and the 1976 swine flu vaccination in the United States*). Cross-reacting antibodies induced by that particular influenza vaccine have been studied as a possible pathogenetic link to immune nerve injury. A recent study examined a number of hypotheses related to the development of anti-ganglioside antibodies by immunising mice with either the 1976 vaccine or one of two other more contemporary influenza vaccines.¹⁰ They found that mice developed both anti-ganglioside antibodies and anti-haemagglutinin (HA) activity following immunisation. However, there was no difference in antibody induction in mice given the A/New Jersey/76 H1N1 vaccine compared with those given the 1992-93 or 2004-05 vaccines. The latter two vaccines have not been associated with an excess of GBS cases. The authors also speculated that lower neuraminidase (NA) activity in the 1976 vaccine, as reported in one study, could be responsible for leaving residual sialic acid on the HA leading to the presence of sialic acid-HA complexes that mimic the GM1 ganglioside. However, this may be due to inactivation of the NA rather than low activity during virus maturation and the hypothesis remains unsubstantiated. Also, of note, there is a low level of homology between the A/New Jersey/76 virus and the current pandemic strain with respect to both HA and NA antigens.¹¹ Whether the presence of anti-ganglioside antibodies predicts GBS in humans is unknown.¹²

Population-based incidence estimates

The incidence of GBS has been estimated to be 1.2–1.9/100,000 population in Europe, based on well-controlled population-based studies, and 0.6–4/100,000 worldwide.^{1,2} A male predominance is observed (male:female ratio ~1.5:1). Incidence increases several fold with age, with rates of <1/100,000 in younger age groups. Most cases are sporadic, but small clusters have been associated with outbreaks of bacterial enteritis.

Australian incidence estimates and current GBS surveillance

¹ The Paediatric Active Enhanced Disease Surveillance system is funded by the Australian Government Department of Health and Ageing and an NHMRC Influenza grant.

Australian data on the incidence of GBS are limited to studies based on hospitalisation records and extrapolation from acute flaccid paralysis surveillance.

The estimated crude annual incidence of GBS from admissions in teaching hospitals in Perth between 1980 and 1985 was 1.35/100,000 population, with a male:female ratio of 1.2:1.¹³ The estimated rate for children aged 0–9 years was 1.13/100,000. Victorian teaching hospital data from 1980–1984 reported an annual incidence of 0.9/100,000 in adults (age ≥15 years), with a male:female ratio of 1.3:1.³

Data from the Australian Paediatric Surveillance Unit (APSU) suggest that the incidence of GBS in children is lower than in adults although it is the most common single cause of AFP in children (47% of AFP cases).¹⁴ The annual incidence of GBS from hospitalisation records in addition to APSU data has been estimated to be 0.71/100,000 for NSW and 1.02/100,000 for WA in children aged <15 years in 1995–1998.¹⁵ Using the capture-recapture method based on APSU and hospitalisation data in Victoria between 1998 and 2000, the estimated true incidence of AFP was 1.4/100,000 (95%CI 1.1–1.7).¹⁶ Imputing from the reported proportion of GBS among the AFP cases, the annual incidence of GBS would be approximately 0.5/100,000 among children aged <15 years in Victoria.

The overall crude average annual rate of hospitalisation (excluding same-day separation) with GBS coded as the principal diagnosis was 2.5 episodes/100,000 population in the period July 1998–June 2003, and 2.4/100,000 in the period July 2003–June 2008, based on data from the Australian Institute of Health and Welfare. These estimates are likely to exceed true disease incidence, as hospitalisation episodes include transfers between hospitals. An incidence of 2.5 per 100,000 represents approximately 500 cases per year.

There are limitations in estimating baseline population incidence rates of GBS through routinely collected data, in particular the problems of small case numbers and under-ascertainment. Clustering of cases is sometimes described.¹³ Heightened awareness and increased reporting could result in a spurious increase in the detected incidence of GBS in post-marketing surveillance of adverse events over short time periods following introduction of a new vaccine.

Guillain-Barré Syndrome and vaccines

GBS and the 1976 swine flu vaccination in the United States (USA)

In October 1976, a mass influenza campaign was conducted in the USA because of an impending influenza pandemic, following an outbreak caused by swine-type influenza A in New Jersey. Over 45 million people were vaccinated over a 3-month period, with more than 500 cases of GBS reported and 25 deaths. The vaccination program was halted in December 1976.^{17,18} It later became evident that the new strain of virus was not capable of epidemic spread and that the initially predicted pandemic of influenza did not occur.

An active and intense surveillance system for reporting of GBS cases was established in all states of the USA. An epidemiologic study reported a significantly increased risk of GBS in people receiving the A/New Jersey/76 influenza vaccine.¹⁸ The study reported a relative risk of 7.6 (95%CI 6.7–8.6), and an estimated excess of 9 cases of GBS per million vaccinations in the 6 weeks after vaccination. The authors suggested increased risk of GBS was greatest within 5 weeks after vaccination, and could last for up to 10 weeks.

Further studies were conducted to reassess the association of GBS and the 1976 swine flu vaccine.^{19,20} The results support the main findings of the original research, with reported relative risks that ranged from 4.0 to 7.8. One of the later studies found no increase in relative risk for GBS beyond 6 weeks post vaccination.²⁰ Based on these findings, the Institute of Medicine concluded “the evidence favored acceptance of a causal relationship between the 1976 swine influenza vaccine and GBS in adults”.²¹

GBS and seasonal influenza vaccination

Since 1976, a number of epidemiologic studies have assessed the association between GBS and subsequent seasonal influenza vaccines. Overall, the results have been inconclusive, finding no or marginally increased risk of GBS.

Several US studies of seasonal influenza vaccines between 1978 and 1988 did not detect a significant increased risk of GBS in people receiving influenza vaccine. The reported relative risk of GBS in vaccine recipients was 1.4 (95%CI 0.7–2.7) in 1978–79,²² and 0.6 (95%CI 0.45–1.32) in 1980–81.²³ A study of the US army's mandatory influenza vaccination program in 1980 to 1988 found no detectable increase in the incidence of GBS in army soldiers.²⁴ For the 1992–93 and 1993–94 seasons, a large case-control study found that there was no increased risk of vaccine-associated GBS in either of these two years. However, for the two seasons combined, the relative risk was 1.7 (95%CI 1.0–2.8). This is consistent with slightly more than one extra case of GBS per million persons vaccinated.²⁵

The link between GBS and influenza vaccine has also been studied in other countries. Analysis of patient-level data in a Canadian study reported a statistically significant temporal association between receiving an influenza vaccine and subsequent hospitalisation with GBS, with a relative risk of 1.45 (95%CI 1.05–1.99).²⁶ However, the same study reported no significant increase in the incidence of GBS at the population level following a mass influenza vaccination program. A UK study using a large general practice database found no association between influenza vaccination and GBS, with a relative risk of 0.99 (95%CI 0.32–3.12) within 6 weeks of influenza immunisation.²⁷

In summary, all epidemiologic studies since 1976 have found no or only slightly elevated relative risk of GBS following influenza vaccination, with a maximum estimated attributable (excess) risk of 1 in 1 million compared with 9 in 1 million from the 1976 vaccine.

In Australia, the Adverse Drug Reactions Advisory Committee (ADRAC) of the Therapeutic Goods Administration (TGA) conducted an epidemiologic investigation in 2002, after receiving a number of reports of GBS following immunisation with the influenza vaccine. They found that the number of Australian cases of GBS following immunisation with the influenza vaccine was lower than that expected in an unimmunised population.²⁸

GBS and other vaccines

Numerous studies have been conducted to evaluate the relationship between GBS and a range of other vaccines. A recent review has assessed the current available evidence and no causal association was identified.²⁹

GBS was associated with early formula rabies vaccines derived from animal brain material, though the newer formulations of rabies vaccine (cell derived) do not appear to be causally associated with GBS.²⁹ For oral polio virus vaccine (OPV), two controlled observational studies conducted in Finland in the 1980s found an increase in the incidence of GBS following a mass OPV immunisation campaign. However, subsequent studies conducted in the USA, Kuwait and South America did not detect any correlation between OPV and GBS. The study findings argue against a causal association between OPV and GBS.²⁹ Neither the older formula rabies vaccine nor OPV are currently in use in Australia.

The current evidence suggests there is no increased risk of GBS following vaccination with diphtheria and tetanus toxoid vaccine, tetravalent meningococcal conjugate vaccine, measles-mumps-rubella vaccine, hepatitis vaccines, *Haemophilus influenzae* type b vaccines, yellow fever vaccine, or Japanese encephalitis vaccine.²⁹

Safety of the pandemic H1N1 2009 vaccine

As of September 2009, there is only one pandemic H1N1 influenza vaccine registered by the TGA for use in Australia, i.e. Panvax (CSL Limited, Parkville, Australia). The vaccine is a monovalent purified inactivated split virion vaccine that contains 15µg haemagglutinin antigen of the virus per 0.5mL dose.³⁰ The antigenic content is the same as that used for each of the three strains of vaccine virus that are included in the annual seasonal trivalent influenza vaccines (TIV). The vaccine is prepared in embryonated chicken eggs with the same standard techniques used for the manufacture of the seasonal TIV vaccines administered annually in Australia.³¹ Panvax is a non-adjuvanted vaccine, unlike some other pandemic H1N1 influenza vaccines registered in other countries.

The safety and immunogenicity of the pandemic H1N1 influenza vaccine was studied in adult subjects (aged 18–64 years) similar to annual assessment of each new seasonal TIV vaccine.³¹ The type and frequency of adverse effects seen in adults after the administration of the H1N1 influenza vaccine were consistent with those seen with seasonal TIV vaccines, namely injection site reactions (in 46% of vaccine recipients) and mild to moderate systemic adverse events (such as headache, myalgia, malaise) seen in 45% overall. The sample size in this study, as in all pre-licensure studies of the seasonal TIV vaccines, was calculated for assessing the primary immunogenicity end points and detecting common adverse events. No pre-licensure studies of TIV vaccines have included sufficient subjects to ascertain differences in rare outcomes, such as GBS, which would require the inclusion of tens of thousands if not hundreds of thousands of vaccine and placebo recipients. Population-based, post-licensure surveillance is needed for this purpose.

Surveillance for Guillain-Barré Syndrome and other adverse events following immunisation

As with all other vaccines, post-licensure surveillance is important for monitoring vaccine safety in the field. In Australia, reports of serious or unusual adverse events following immunisation (AEFI) are assessed by the ADRAC of the TGA. In addition to this usual passive surveillance system, the TGA, State/Territory and Commonwealth Health Departments are establishing systems for enhanced monitoring of AEFI with the H1N1 vaccine, including monitoring for rare conditions such as GBS. Active surveillance systems are also in place in the UK, USA, and Canada.

Influenza immunisation in people with a history of Guillain-Barré Syndrome

Only two studies have examined the risk of recurrent GBS after influenza vaccination in people with a history of GBS. In a UK study that relied on self-reporting of immunisation history (with verification by general practitioners), only 3.5% (11 of 311 people) who had a history of a previous episode of GBS and reported receiving at least one immunisation at some time since their illness, had any symptom relapse in the week post immunisation. Most reports of symptom relapse were mild and resolved spontaneously, and there was no association with any particular vaccine.³² In a similar study conducted in The Netherlands, none of 106 GBS patients who received an influenza vaccination (775 in total) had a recurrence of GBS.³³

For patients in whom GBS onset was not related in time to recent influenza immunisation, the benefit of influenza immunisation outweighs the risk of symptom relapse. This is in accord with the statement in the 9th edition of *The Australian Immunisation Handbook*: “patients with a history of Guillain-Barré Syndrome (GBS) with an onset related in time to influenza vaccination may be at increased risk of again developing GBS if given influenza vaccine. The risk should be weighed against the benefits to the individual patient of influenza vaccination.”³⁴

Influenza immunisation in family members of people with a history of Guillain-Barré Syndrome

Occurrence of GBS in people with a family history of GBS is rare. There have only been a small number of case reports of familial GBS occurring,^{35,36} including three siblings who developed GBS at an unusually young age born to healthy consanguineous parents.³⁷ The number of reported families is insufficient to prove that there is a familial occurrence of GBS.³⁵ Genetic susceptibility to GBS is plausible, but environmental factors like antecedent infections play an important role in the pathogenesis.³⁵ Particular human leucocyte antigen (HLA) types that are consistently associated with developing GBS have not been identified.^{36,38}

Given the rarity of occurrence of familial GBS, the absence of consistently identified genetic risk markers, and the lack of clear evidence of excess risk of GBS due to seasonal influenza vaccines, there is currently no evidence to suggest that family members of persons who have a history of GBS are at an increased risk of developing GBS due to vaccination against seasonal influenza or pandemic H1N1 influenza A, compared with those without this family history.

References

1. Hughes RA, Cornblath DR. Guillain-Barre syndrome. *Lancet* 2005;366:1653-1666.
2. Vucic S, Kiernan MC, Cornblath DR. Guillain-Barre syndrome: an update. *Journal of Clinical Neuroscience* 2009;16:733-741.
3. Storey E, Cook M, Peppard R, Newton-John H, Byrne E. Guillain-Barre syndrome and related conditions in Victorian teaching hospitals 1980-84. *Australian & New Zealand Journal of Medicine* 1989;19:687-693.
4. Jacobs BC, Rothbarth PH, van der Meche FG, Herbrink P, Schmitz PI, de Klerk MA, et al. The spectrum of antecedent infections in Guillain-Barre syndrome: a case-control study. *Neurology* 1998;51:1110-1115.
5. Tam CC, O'Brien SJ, Petersen I, Islam A, Hayward A, Rodrigues LC. Guillain-Barre syndrome and preceding infection with campylobacter, influenza and Epstein-Barr virus in the general practice research database. *PLoS ONE [Electronic Resource]* 2007;2:e344.
6. Stowe J, Andrews N, Wise L, Miller E. Investigation of the temporal association of Guillain-Barre syndrome with influenza vaccine and influenza like illness using the United Kingdom General Practice Research Database. *American Journal of Epidemiology* 2009;169:382-388.
7. Sivadon-Tardy V, Orlikowski D, Porcher R, Sharshar T, Durand MC, Enouf V, et al. Guillain-Barre syndrome and influenza virus infection. *Clinical Infectious Diseases* 2009;48:48-56.
8. Evans AS, Agadi S, Siegel JD, Chung WM, Carlo JT, Uyeki TM, et al. Neurologic complications associated with novel influenza A (H1N1) virus infection in children - Dallas, Texas, May 2009. *MMWR - Morbidity & Mortality Weekly Report* 2009;58:773-778.

9. Yuki N. Ganglioside mimicry and peripheral nerve disease. *Muscle & Nerve* 2007;35:691-711.
10. Nachamkin I, Shadomy SV, Moran AP, Cox N, Fitzgerald C, Ung H, et al. Anti-ganglioside antibody induction by swine (A/NJ/1976/H1N1) and other influenza vaccines: insights into vaccine-associated Guillain-Barre syndrome. *Journal of Infectious Diseases* 2008;198:226-233.
11. Eisen DP, McBride ES. The necessity of avoiding Guillan-Barré Syndrome following swine origin pandemic H1N1 influenza vaccination. *Journal of Infectious Diseases* 2009; In press.
12. Evans D, Cauchemez S, Hayden FG. "Prepandemic" immunization for novel influenza viruses, "swine flu" vaccine, Guillain-Barre syndrome, and the detection of rare severe adverse events. *Journal of Infectious Diseases* 2009;200:321-328.
13. Hankey GJ. Guillain-Barre syndrome in Western Australia, 1980-1985. *Medical Journal of Australia* 1987;146:130-133.
14. Morris AM, Elliott EJ, D'Souza RM, Antony J, Kennett M, Longbottom H. Acute flaccid paralysis in Australian children. *Journal of Paediatrics & Child Health* 2003;39:22-26.
15. D'Souza RM. Retrospective hospital-based searches for cases of acute flaccid paralysis. *Australian & New Zealand Journal of Public Health* 2002;26:45-49.
16. Whitfield K, Kelly H. Using the two-source capture-recapture method to estimate the incidence of acute flaccid paralysis in Victoria, Australia. *Bulletin of the World Health Organization* 2002;80:846-851.
17. Langmuir AD. Guillain-Barre syndrome: the swine influenza virus vaccine incident in the United States of America, 1976-77: preliminary communication. *Journal of the Royal Society of Medicine* 1979;72:660-669.
18. Schonberger LB, Bregman DJ, Sullivan-Bolyai JZ, Keenlyside RA, Ziegler DW, Retalliau HF, et al. Guillain-Barre syndrome following vaccination in the National Influenza Immunization Program, United States, 1976-1977. *American Journal of Epidemiology* 1979;110:105-123.
19. Langmuir AD, Bregman DJ, Kurland LT, Nathanson N, Victor M. An epidemiologic and clinical evaluation of Guillain-Barre syndrome reported in association with the administration of swine influenza vaccines. *American Journal of Epidemiology* 1984;119:841-879.
20. Safranek TJ, Lawrence DN, Kurland LT, Culver DH, Wiederholt WC, Hayner NS, et al. Reassessment of the association between Guillain-Barre syndrome and receipt of swine influenza vaccine in 1976-1977: results of a two-state study. Expert Neurology Group. *American Journal of Epidemiology* 1991;133:940-951.
21. Stratton K, Alamaro DA, Wizemann T, McCormick MC, eds. Immunization safety review: influenza vaccines and neurological complications. Washington, DC: Institute of Medicine, 2004.
22. Hurwitz ES, Schonberger LB, Nelson DB, Holman RC. Guillain-Barre syndrome and the 1978-1979 influenza vaccine. *New England Journal of Medicine* 1981;304:1557-1561.

23. Kaplan JE, Katona P, Hurwitz ES, Schonberger LB. Guillain-Barre syndrome in the United States, 1979-1980 and 1980-1981. Lack of an association with influenza vaccination. *JAMA* 1982;248:698-700.
24. Roscelli JD, Bass JW, Pang L. Guillain-Barre syndrome and influenza vaccination in the US Army, 1980-1988. *American Journal of Epidemiology* 1991;133:952-955.
25. Lasky T, Terracciano GJ, Magder L, Koski CL, Ballesteros M, Nash D, et al. The Guillain-Barre syndrome and the 1992-1993 and 1993-1994 influenza vaccines. *New England Journal of Medicine* 1998;339:1797-1802.
26. Juurlink DN, Stukel TA, Kwong J, Kopp A, McGeer A, Upshur RE, et al. Guillain-Barre syndrome after influenza vaccination in adults: a population-based study. *Archives of Internal Medicine* 2006;166:2217-2221.
27. Hughes RA, Charlton J, Latinovic R, Gulliford MC. No association between immunization and Guillain-Barre syndrome in the United Kingdom, 1992 to 2000. *Archives of Internal Medicine* 2006;166:1301-1304.
28. Isaacs D, Lawrence G, Boyd I, Ronaldson K, McEwen J. Reporting of adverse events following immunization in Australia. *Journal of Paediatrics & Child Health* 2005;41:163-166.
29. Haber P, Sejvar J, Mikaeloff Y, Destefano F. Vaccines and Guillain-Barre syndrome. *Drug Safety* 2009;32:309-323.
30. CSL Limited. Panvax® H1N1 Vaccine Product Information. 2009.
31. Greenberg ME, Lai MH, Hartel GF, Wichems CH. Response after one dose of a monovalent influenza A (H1N1) 2009 vaccine - preliminary report. *New England Journal of Medicine* 2009; electronic publication ahead of print. Available at <http://content.nejm.org/cgi/content/full/NEJMoa0907413>
32. Pritchard J, Mukherjee R, Hughes RA. Risk of relapse of Guillain-Barre syndrome or chronic inflammatory demyelinating polyradiculoneuropathy following immunisation. *Journal of Neurology, Neurosurgery & Psychiatry* 2002;73:348-349.
33. Kuitwaard K, Bos-Eyssen ME, Blomkvist-Markens PH, van Doorn PA. Initial symptoms, intercurrent events and long-term disability in GBS and CIDP. *Journal of the Peripheral Nervous System* 2009;14:s2 [abstract]
34. National Health and Medical Research Council. The Australian immunisation handbook. 9th ed. Canberra: Australian Government Department of Health and Ageing, 2008.
35. Geleijns K, Brouwer BA, Jacobs BC, Houwing-Duistermaat JJ, van Duijn CM, van Doorn PA. The occurrence of Guillain-Barre syndrome within families. *Neurology* 2004;63:1747-1750.
36. Wilmshurst JM, Pohl KR, Vaughan RW, Hughes RA. Familial Guillain-Barre syndrome. *European Journal of Neurology* 1999;6:499-503.
37. Bar-Joseph G, Etzioni A, Hemli J, Gershoni-Baruch R. Guillain-Barre syndrome in three siblings less than 2 years old. *Archives of Disease in Childhood* 1991;66:1078-1079.

38. McCombe PA, Csurhes PA, Greer JM. Studies of HLA associations in male and female patients with Guillain-Barre syndrome (GBS) and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). *Journal of Neuroimmunology* 2006;180:172-177.