Guillain-Barré Syndrome and Vaccinations

Daniel A. Salmon and Neal A. Halsey
Institute for Vaccine Safety, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland

(See the Major Article by Baxter et al on pages 197–204.)

Keywords. GBS; Guillain-Barré Syndrome; vaccine; H1N1; influenza vaccine.

Questions have been raised about Guillain-Barré syndrome (GBS) after vaccinations since the 1976 Swine flu vaccine was associated with a 7- to 8-fold increased risk for GBS in the 6 weeks after vaccination, resulting in about 1 excess case of GBS per 100 000 vaccinees. There is evidence to support several possible biological mechanisms for the development of GBS, but no one has been able to determine the mechanism responsible for the association with the 1976 Swine influenza vaccine [1, 2]. The only other vaccine that has been associated with an increased risk of GBS is the mouse brain-produced rabies vaccine [3]. Several infections, including Campylobacter jejuni [4, 5], cytomegalovirus [6], and influenza-like illnesses [7–9], have been associated with an increased risk of GBS.

Influenza vaccines since 1976 have not been associated with the level of risk seen in 1976; however, it is not clear if post-1976 influenza vaccines had any increased risk of GBS. Most epidemiologic studies since 1976 found no associations between GBS and influenza vaccines, and some studies found a statistically significant but very small risk of about 1 excess case of GBS per million vaccinated persons. In 2011, the Institute of Medicine (IOM) reviewed data through the 2008–2009 influenza seasons and concluded that “the evidence is inadequate to accept or reject a causal relationship between influenza vaccine and GBS” [10]. The IOM report further stated that “[w]hile the weight of epidemiological evidence does not support a causal link between influenza vaccinations evaluated over the last 30 years, an association cannot be confidently ruled out, particularly for future vaccine strains” [10]. The 2009–2010 H1N1 vaccine program included the most comprehensive safety monitoring program for any vaccine ever used, including 6 active surveillance systems monitoring for GBS among about 23 million persons in the United States [11]. An increased risk for GBS was seen in each of these 6 surveillance systems in the 6 weeks after vaccination; however, some systems and not others had results that were statistically significant. A meta-analysis of GBS cases across these 6 systems found a significantly increased risk of about 2.35, translating into about 1–2 excess cases per million persons vaccinated. This risk ratio was consistent across age groups, although the attributable risk was higher among persons >65 years of age because of a higher background of GBS in this age group. Risk did not vary among persons who did or did not receive seasonal influenza vaccine or reported influenza-like symptoms. A multinational European case-control study of 2009 H1N1 vaccine found an increased risk of GBS after adjuvanted vaccines in an unadjusted analysis; however, the risk no longer existed after adjusting for influenza-like illness or upper respiratory tract infection and seasonal influenza vaccination [12].

There have been case reports of GBS after other vaccinations [13], but the IOM concluded in 2011 that there was inadequate evidence to draw conclusions for measles, mumps, rubella, varicella, hepatitis A or B, human papillomavirus, and diphtheria toxoid, tetanus toxoid, or acellular pertussis-containing vaccines [10]. Concerns were raised when 17 suspected cases of GBS were reported to the Vaccine Adverse Event Reporting System, a passive reporting system, within 6 weeks of a meningococcal vaccine (Menactra) among adolescents 11–19 years of age; however, an epidemiologic study including 18 million person-years and 1.4 million Menactra vaccines identified no cases within 6 weeks of vaccination, excluding a risk of ≥1.5 cases per million vaccines [14].

In this issue of Clinical Infectious Diseases, Baxter and colleagues [15] examined the risk of GBS after administration...
of various vaccines, including influenza, tetanus, diphtheria, pneumococcal polysaccharide, and others, and they found no evidence of an association between GBS and vaccination. This study is an important contribution to this body of evidence. The study was conducted at the Northern California Kaiser Permanente site with an excellent electronic medical record system and considerable expertise developed over decades in conducting these sorts of studies. The use of a 13-year ascertainment period and >30 million person-years of observation identified 415 GBS cases that were confirmed through review of the medical record by a neurologist using a standardized case definition. This study used a case-centered approach that has the advantages of other self-controlled risk interval designs, which eliminate potential biases that could result from undetectable differences in populations and confounding due to individual-level factors such as genetic susceptibility, previous illness, or demographics. The case-centered approach, in contrast to other self-controlled risk interval designs, addresses the potential for seasonality to bias study findings. The Baxter study examined multiple immunizations, whereas most controlled studies of GBS after vaccination have focused only on influenza vaccines. These study strengths lend considerable weight to the findings of no association between vaccines and GBS.

However, with any study trying to evaluate a very small risk for a disease that is rare, there are important limitations to the Baxter study. The authors acknowledge limitations to power and the potential for investigator bias to impact case ascertainment. Additionally, the case-centered methodology is dependent on a valid measure of vaccine coverage in the study population [16, 17]: bias in vaccine coverage estimates would impact study results. Although Baxter et al state that “[v]accinations are provided at no additional cost to members [and] are almost all received with the system,” the Kaiser system likely underestimates vaccine coverage. A study conducted to assess the accuracy of data on influenza vaccination at 4 Vaccine Safety Datalink sites, of which Northern California was one, found suboptimal sensitivity (51%–89%) and negative predictive value (46%–87%) [18]. As data from this publication blinded readers as to which site had corresponding sensitivity and negative predictive value, it is not possible to ascertain how much potential bias would exist for the Northern California Kaiser site. Even if one assumes the highest sensitivity and negative predictive value for Northern California among the 4 sites, there is the potential for underascertainment of vaccination.

Identifying a small increased risk of GBS after vaccination is extremely difficult given the rarity of GBS. Even with 30 million person-years of data, only 18 cases of GBS were identified within 6 weeks of influenza vaccine (compared with 54 cases identified in the meta-analysis of 2009 H1N1 influenza vaccine). Using some reasonable assumptions, Baxter et al [15] reported they can rule out a risk of approximately 2 or more GBS cases per million trivalent inactivated influenza vaccinees. These findings are not consistent with other studies, including the US 2009 H1N1 meta-analysis, which found an increased risk of 1–2 excess cases in the 6 weeks after influenza vaccination. Similarly, null findings between GBS and other vaccines must be interpreted with an appreciation for the limits of even large studies. One can conclude with reasonable confidence that if a risk of GBS is causally attributable to vaccination, the magnitude of that risk is extremely low and no greater than 1 or 2 cases per million persons vaccinated. Even if there was a risk of 1–2 cases per million for GBS, this risk is greatly outweighed by the benefits of vaccination.

For routine influenza vaccines, further epidemiologic studies to refine a risk of such small magnitude may not be justified; however, it is important to continue routine surveillance to identify signals of possible higher levels of risk of GBS or other serious illnesses in a timely manner, such as the recently identified problem of narcolepsy following the AS03 adjuvanted influenza vaccine used in Europe [19–23].

Further research should focus on understanding the biological mechanisms to explain why GBS occurred at a higher rate following the 1976 vaccine, if there are differences in the risk of GBS following infection by different strains of influenza, and host factors that predispose to GBS.

Note

Potential conflicts of interest. Both authors: No reported conflicts.

Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References


