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Vaccines and Guillain-Barré Syndrome

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Abstract

Guillain-Barré syndrome (GBS) is the leading cause of acute flaccid paralysis in developed countries and is characterized by various degrees of weakness, sensory abnormalities and autonomic dysfunction. Although the underlying aetiology and pathophysiology of GBS are not completely understood, it is broadly believed that immune stimulation plays a role in its pathogenesis. Thus, since vaccines have an effect on the immune system it is biologically plausible that immunizations may be associated with subsequent GBS.

The objective of this article is to review the current body of evidence that either supports or does not support a causal, rather than just temporal, association between various vaccines and GBS, and to provide an evidence-based review of this issue. The scope of the article includes published reports that,

regardless of method of case ascertainment, appeared in peer-reviewed literature between 1950 and 2008.

Our review indicates that, with rare exceptions, associations between vaccines and GBS have been only temporal. There is little evidence to support a causal association with most vaccines. The evidence for a causal association is strongest for the swine influenza vaccine that was used in 1976–77. Studies of influenza vaccines used in subsequent years, however, have found small or no increased risk of GBS.

Older formulations of rabies vaccine cultured in mammalian brain tissues have been found to have an increased risk of GBS, but newer formulations of rabies vaccine, derived from chick embryo cells, do not appear to be associated with GBS at a greater than expected rate.

In an earlier review, the Institute of Medicine concluded that the evidence favoured a causal association between oral polio vaccine and tetanus toxoid-containing vaccines and GBS. However, recent evidence from large epidemiological studies and mass immunization campaigns in different countries found no correlation between oral polio vaccine or tetanus toxoid-containing vaccines and GBS.

Spontaneous reports to the US Vaccine Adverse Events Reporting System shortly after the introduction of quadrivalent conjugated meningococcal vaccine (MCV4) raised concerns of a possible association with GBS. Comparisons with expected rates of GBS, however, were inconclusive for an increased risk, and lack of controlled epidemiological studies makes it difficult to draw conclusions about a causal association.

For other vaccines, available data are based on isolated case reports or very small clusters temporally related to immunizations, and no conclusion about causality can be drawn.

There are certain circumstances in which immunizing individuals, particularly those with a prior history of GBS, may require caution. However, the benefit of vaccines in preventing disease and decreasing morbidity and mortality, particularly for influenza, needs to be weighed against the potential risk of GBS.

Guillain-Barré syndrome (GBS) is the leading cause of acute flaccid paralysis in developed countries and is characterized by various degrees of weakness, sensory abnormalities and autonomic dysfunction. The syndrome includes a spectrum of clinical conditions in which idiopathic peripheral neuropathy causes acute or subacute weakness of limbs and/or cranial nerve-innervated muscles. GBS is believed to be an immune-mediated disorder resulting from the generation of autoimmune antibodies that cross-react with epitopes on peripheral nerves, leading to nerve damage. Autoantibodies may form in response to a variety of antigenic stimuli, such as bacterial or viral infections. About two-thirds of GBS cases occur several days or weeks after an apparent infectious illness, commonly a diarrhoeal illness or upper respiratory tract infection.[1] Based primarily on biological plausibility and temporal associations, some vaccines have also been suggested to cause GBS.

In this article, we review the evidence for a possible causal association between vaccination and GBS. We first present our review methodology. Next we provide a brief overview of the epidemiology and pathophysiology of GBS, including possible biological mechanisms related to vaccination. We then review the evidence for the specific vaccines for which concerns about a possible association with GBS have been raised. Individual vaccines are discussed in the order of the strength of the evidence. We also include a

section on the risk of relapse of GBS associated with vaccination. We conclude with a summary of the evidence and implications of our findings.

1. Search Methodology

We sought original articles on GBS associated with all vaccines. Articles were identified from searches of health literature databases, including PubMed, the Excerpta Medica Database (EMBASE) and Cumulative Index to Nursing and Allied Health Literature (CINAHL). The literature search covered the period 1950–2008 and there were no language restrictions. We used the following algorithm of medical subject heading (MeSH) terms combined with text words: ('Guillain-Barre Syndrome' OR 'Guillain Barre' OR 'inflammatory demyelinating polyradiculoneuropathy' (AIDP) OR 'Fisher Syndrome') AND ('Vaccines' OR 'Vaccines/adverse effects' OR 'Vaccines/complications'). We also identified articles through the reference lists of previous reviews, especially those conducted by the Institute of Medicine (IOM).[2,3] We identified 67 references relevant to our review. In addition, we reviewed reports to the US Vaccine Adverse Event Reporting System (VAERS), a national voluntary reporting system for vaccine adverse events, for the period of 1990–2007.[4,5]

2. Overview of Guillain-Barré Syndrome Epidemiology and Pathophysiology

2.1 Epidemiology

GBS has been reported to have an annual incidence of between 0.4 and 4.0 cases per 100 000 population per year, with most studies reporting 1–2 cases per 100 000 population per year.[1] Several population-based studies indicated that the annual incidence of GBS in children is 0.1 case per 100 000 population between the ages of 5 and 14 years, and 0.62 per 100 000 population between the ages of 10 and 19 years.[6,7] GBS is far more common in adults and the incidence steadily increases with age, with an annual incidence in people over the age of 75 years estimated at upwards of 4 per 100 000. Studies have consistently suggested that men are more likely to be affected than women. Overall, GBS is associated with a favourable outcome, with most patients experiencing improvement. In children, recovery is more rapid and tends to be complete, with fatalities rare. Elderly patients have a worse prognosis; requirement of mechanical ventilation, severe weakness at nadir and rapid onset of weakness have been identified as adverse prognostic factors. Treatment with either plasmapheresis or intravenous immunoglobulin has been shown to improve outcome, and these are considered the gold standard for treatment, although data are lacking for treatment of children.

Various subtypes of GBS have been described, with the most common form in the Western world being acute inflammatory demyelinating polyradiculoneuropathy (AIDP), a predominantly demyelinating peripheral neuropathy. Other forms of GBS, including acute motor axonal neuropathy (AMAN) and Fisher syndrome (involving the triad of ophthalmoplegia, areflexia and ataxia) are less common.

2.2 Pathophysiology

GBS is believed to be an immune-mediated disorder resulting from the generation of autoimmune antibodies that cross-react with epitopes on peripheral nerves, leading to nerve damage. Autoantibodies may form in response to a variety of antigenic stimuli, such as bacterial or viral infections. About two-thirds of GBS cases occur several days or weeks after an apparent infectious illness, commonly a diarrhoeal illness or upper respiratory tract infection.[1] The gastrointestinal bacterium *Campylobacter jejuni* has been found to stimulate cross-reactive antibodies that can result in GBS, particularly AMAN. Other infectious agents that have been temporally associated with GBS include influenza viruses, *Mycoplasma pneumoniae*, human immunodeficiency virus, Epstein-Barr virus, cytomegalovirus and the vaccinia virus used in smallpox vaccination. Other stimuli that appear to be temporally associated with GBS include surgical procedures and some malignancies, particularly Hodgkin's disease and other lymphomas. Various vaccines have also been temporally associated with GBS.

2.3 Immunizations and Guillain-Barré Syndrome: Potential Biological Mechanisms

Active immunization by a vaccine stimulates the immune system to produce antigen-specific humoral and/or cellular immunity.[8,9]

Thus, immune stimulation induced by vaccination could theoretically result in GBS through a variety of possible mechanisms:

1. The concept of 'molecular mimicry', involving a situation in which the epitopes of a live or attenuated vaccine could initiate the development of antibodies and/or T cells that could cross-react with epitopes on myelin or axonal glycoproteins of peripheral nerves. Activated macrophages could potentially be targeted to antigens on myelin sheath and subsequently invade the basement membrane or, alternatively, in the case of AMAN, invade at the nodes of Ranvier to result in axonal degeneration with relative sparing of myelin. Alternatively, the initial event could be the binding of cross-reactive antibodies, with subsequent fixation of complement and damage to the Schwann cell or axon. Perturbation of immunoregulatory mechanisms, interfering with self-tolerance of host myelin or axon proteins, could lead to immune-mediated damage.
2. Destruction of the axonal or myelin membranes could presumably be mediated directly by vaccine virus or vaccine-associated products, or infection or damage of surrounding supporting cells by virus could lead to insertion of virus-specified polypeptides into host cell membranes, resulting in a humoral or cell-mediated autoimmune response to the infected cell. Finally, axons or myelin cells could potentially be damaged by the introduction of sequestered myelin antigens into the circulation, inciting autoimmunity.
3. Moreover, it is likely that host factors and genetic polymorphisms may result in a predisposition to GBS in some individuals. Several studies have suggested that various polymorphisms, including genes of the T-cell glycolipid CD1, are more frequent in individuals developing GBS.[10-13] While specific human leukocyte antigen (HLA) types have not been found definitively to be associated with a higher risk of GBS, it is possible that other host factors may predispose to illness in individuals exposed to certain antigenic stimuli.

It is important to realize that a causal association of any particular vaccine or other antecedent event with subsequent GBS is difficult to demonstrate. In general, specific biological markers indicative of a cause-and-effect association with a particular pathogen or vaccine are absent in GBS. Challenge-rechallenge data or dose-response data, while possible to assess in animal models, are not available in the setting of natural human disease. Thus, in general, the association of a prior infection or vaccination with development of GBS is based upon a close temporal relationship and additional supportive epidemiological evidence. With extremely rare exceptions, direct laboratory data supporting a causal biological association are lacking. Convincing evidence for the presence of cross-reactive antibodies to peripheral neural tissue and several infectious organisms has been demonstrated in only a few instances; this evidence is particularly strong for antecedent infection with *C. jejuni*, cytomegalovirus and *M. pneumoniae*. However, proof that any one of these agents causes GBS awaits definitive substantiation. Among vaccines, the strongest evidence for causality exists for the formulation of influenza vaccine used in the 1976 swine flu immunization campaign and Semple rabies vaccine and rabies vaccine derived from suckling mouse brain (SMB) [section 3.2]. Despite strong epidemiological data of an association for both vaccines, biological mechanisms remain to be demonstrated, although a recent study found that remnant samples of 1976 swine flu vaccines induced antibodies to ganglioside GM1 in mice, as did vaccines from 1991–92 and 2004–05.[14] The possible causal mechanism, if any, of these antibodies in vaccine-associated GBS requires further research.

3. Evidence Findings for Specific Vaccines

3.1 Influenza Vaccine

Influenza vaccines have generated the most study regarding a possible association with GBS.

Vaccination is the primary means of reducing the morbidity and mortality associated with influenza, either by preventing illness or by reducing its severity. Because of the continual antigenic changes of influenza viruses, new influenza vaccines are formulated each year. Vaccines formulated since 1979 are trivalent – produced using strains of influenza A (H1N1), influenza A (H3N2) and influenza B viruses.

Concerns about the risk of developing GBS following influenza vaccination first surfaced during a mass vaccination programme with a swine influenza vaccine in the US in 1976–77.[15-17] In 1976, an outbreak of influenza was caused by swine-type influenza A (H1N1) virus in Fort Dix, New Jersey, USA. The US Department of Health and Human Services and other experts, concerned about the possibility of a large epidemic or pandemic caused by swine-type influenza, recommended mass vaccination of the entire US population. Over 45 million people were vaccinated in a short period from October to December 1976. During this time, over 500 cases of GBS, including 25 deaths, were reported. A statistically significant elevated risk of GBS was found among swine flu vaccinees relative to non-vaccinees within 6–8 weeks after vaccination, with relative risks ranging from 4.0 to 8.0. In controlled observational studies, the overall attributable risk was estimated to be slightly less than 1 excess case of GBS per 100 000 vaccinees.[15] In January 1977 the swine flu vaccination programme was suspended owing to the elevated GBS risk.

Questions were raised about the association of GBS with the swine flu vaccine, but a subsequent study to reassess the association substantiated the original findings.[18,19] The IOM has concluded that "the evidence favored acceptance of a causal relationship between the 1976 swine influenza vaccine and GBS in adults".[3] The pathophysiological basis for the elevated risk for GBS with the swine flu vaccine, however, has not been established, although studies are ongoing[20] and a recent study reported that swine influenza vaccine can induce anti-GM1 antibodies in mice.[14]

Evidence for a causal relationship between GBS and other influenza vaccine formulations is less clear (IOM). Studies of the three influenza seasons during 1978–81 found nonsignificant relative risks of GBS of 1.4 (95% CI 0.7, 2.7) in 1978–79,[21] 0.6 (95% CI 0.45, 1.32) in 1979–80 and 1.4 (95% CI 0.80, 1.76) in 1980–81.[22] A retrospective study of more than 5.6 million US Army personnel receiving the influenza vaccine during the 1980–88 seasons did not detect an increase in the incidence of GBS,[23] although the background rate of GBS in this population (4.08 per 100 000 person-years) appeared to be higher than that found among civilians (1.16 per 100 000 person-years).[15] During the 1990–91 influenza season, an elevated risk was found among vaccinated persons aged 18–64 years (relative risk 3.0; 95% CI 1.5, 0 6.3), but not among persons 65 years or older.[24]

An apparent increase in the number of GBS reports to VAERS in 1993–94 prompted a large, multistate case-control study[25] assessing the association with influenza vaccine during that season and the 1992–93 seasons. The study found a combined relative risk of 1.7 (95% CI 1.0, 2.8; $p = 0.04$) within 6 weeks following influenza vaccination, suggesting an attributable risk of less than one additional case of GBS per million persons vaccinated.[25,26]

Recently, there was an observed decline in reporting rates of GBS following influenza vaccine within VAERS beginning with the 1994–95 influenza season.[27] As VAERS is a voluntary, passive reporting system, it is difficult to draw conclusions about what may have accounted for the observed trend. One proposed explanation is that the trend is a reflection of a decrease in coincidental cases associated with *C. jejuni* infections. As noted, infection with the enteric bacterium *C. jejuni* has been strongly associated with subsequent development of GBS. Infections with *C. jejuni* in the US declined in the mid 1990s, suggesting a possible role in the noted decrease in overall number of reported cases of GBS coincidentally following influenza vaccination.[28]

More recent studies have found inconclusive results on the association between influenza vaccine and GBS. Juurlink et al.[29] conducted two studies using population-based healthcare data from the province of Ontario, Canada. In one analysis, the authors identified a statistically significant association between receiving influenza

vaccination and subsequent hospitalization for GBS; the relative incidence compared with controls was 1.45 (95% CI 1.05, 1.99; p = 0.02). However, a separate time-series analysis in the same publication demonstrated no evidence of seasonality or a statistically significant increase in hospital admissions due to GBS after the introduction of a universal influenza immunization programme in Ontario.[29] A study in the UK examined the association between immunization and GBS in the UK from 1992 to 2000. The database included 253 general practices with a mean of 1.8 million registered patients. The authors identified new occurrences of GBS and estimated age- and sex-specific and age-standardized incidence rates. Of 228 incident cases, seven occurred within 42 days after receipt of any vaccine and only three followed influenza vaccination. The adjusted relative risk of GBS within 42 days after influenza immunization was 0.99 (95% CI 0.32, 3.12; p = 0.99).[30]

3.2 Rabies Vaccine

GBS has been associated with two rabies vaccines – the Semple rabies vaccine, which was produced by inoculation of rabies virus into mature sheep or goat brain and inactivated with phenol, and the SMB rabies vaccine. Approximately 7% of individuals hospitalized with adverse events from Semple strain developed a neuroparalytic adverse event characteristic of GBS.[31,32] This was presumed to be due to the presence of brain protein in the formulated vaccine, owing to involvement of brain inoculation in the manufacturing process, with the possible generation of antibodies strongly cross-reactive to neural tissue, and led to discontinuation of the vaccine in 1980 in the US and other countries, although the vaccine continues to be used to a limited extent in some countries mainly in Southeast Asia. The rabies vaccine produced from inoculation of SMB has been associated with an incidence of flaccid paralysis, including GBS, in approximately 1 in 7500 vaccinees,[33,34] Newer formulations of rabies vaccine, derived from chick embryo cells, do not appear to be causally associated with subsequent GBS. Although case reports of neuroparalytic illness following newer formulations of rabies vaccine have appeared, the overall occurrence does not appear to be elevated above recognized background rates, based on currently available data.[35-37]

3.3 Oral Polio Vaccine

Oral polio vaccine (OPV) is another vaccine for which there has been evidence of a possible causal association with GBS. Poliomyelitis is an acute infectious disease caused by poliovirus, an enterovirus. There are three serological types of poliovirus, based on slight differences in virus capsid epitopes, and each can cause paralytic disease. OPV consists of live attenuated viruses that multiply in the intestinal tract, mimicking a natural process of exposure to virus which results in immunity to the disease. Vaccinees excrete live virus for several weeks, and recipients or contacts may become infected with the virus. Although the vaccine virus is attenuated, approximately 1 in 1 million vaccinations with attenuated virus lead to paralytic disease, known as vaccine-associated paralytic poliomyelitis (VAPP). VAPP may occur among OPV recipients and contacts of OPV recipients.[38] VAPP may be differentiated from GBS on the basis of clinical and laboratory diagnostic features.

Two controlled observational studies conducted in Finland assessed the potential association between OPV and GBS. The first study was in a southern province of Finland (Usimaa), where continuing surveillance of GBS from 1981 to 1986 found an increase in the incidence of GBS following nationwide immunization of children and adults against polio.[39-40] At that time, Finland had been using inactivated polio vaccine (IPV), which had not been associated with an increased risk of VAPP; however, an outbreak of ten cases of poliomyelitis between August 1984 and January 1985 led to the decision to carry out mass immunization with OPV, which, unlike IPV, induces mucosal immunity and can thus prevent virus transmission. Ninety-four percent of the Finnish population was vaccinated with OPV during a 5-week period between 10 February and 15 March 1985. During and shortly after the

immunization campaign, hospitals in Usimaa province (population about 1.17 million) admitted high numbers of patients with GBS. Ten cases occurred in the first quarter and six in the second quarter of 1985, the time periods corresponding to the immunization campaign. At the same period, Uhari et al.[40] conducted a study covering the entire paediatric population of Finland. They identified 27 cases of GBS in children aged 0.4–14.3 years over a 7-year period from 1980 to 1986, with an average incidence of 3.9 cases per year. They also noted a peak of ten cases in 1985, which was statistically significantly elevated compared with the other years ($p = 0.0042$).

Based largely on the above findings, in 1994 the IOM concluded that the evidence favours a causal association between OPV and GBS.[2] More recent studies, however, cast doubt on this conclusion. In 1998, Kinnunen et al.[41] published results of an extended study from their earlier study which included hospital records from the whole of Finland for 1981–86. Monthly reports suggested that the number of GBS cases started to rise before the OPV campaign. Since there had been an influenza epidemic between December and April that year, in addition to the outbreak of wild-type poliovirus, the authors concluded that the rise of GBS could also have been associated with the circulation of wild-type poliovirus or of influenza virus in addition to OPV.

Epidemiological studies in California by Rantala et al.[42] in 1994 and in Kuwait by Ismail et al.[43] in 1998 that evaluated immunization programmes with high numbers of vaccinations found no correlation between OPV and GBS.

The association between OPV immunization and GBS has also been studied in South America, where surveillance for poliomyelitis has focused on detection of cases of acute flaccid paralysis in children younger than 15 years and where large annual OPV campaigns were implemented. In a study of 3112 cases of GBS from 1989 to 1991 in South America, no temporal association or increased incidence of GBS during mass vaccination with oral poliovirus was detected.[40] Based on the more recent data from Finland,[40] and South America,[44] whether OPV is associated with increased risk of GBS remains uncertain. Salisbury[45] points out that failure to detect an association in different countries and at different times, which also may be due to different vaccination programmes and study designs, argues against a causal association.

3.4 Diphtheria and Tetanus Toxoid Vaccine

In surveying the medical literature, the IOM found 25 case reports describing a possible association between GBS and tetanus toxoid, diphtheria tetanus (DT) and tetanus diphtheria (Td).[2] In 1978 Pollard and Selby[46] described a case of a 42-year-old man who received tetanus toxoid on three occasions and developed GBS after each vaccination (over a 13-year period). This man also experienced multiple subsequent episodes of GBS following acute viral illness. A more recent report described the case of a 22-year-old college student who developed GBS 4 days after tetanus diphtheria toxoid vaccine.[47] In 1994, the IOM, based on biological plausibility and the case report of the relapsing illness in one patient, concluded that there was sufficient evidence from this case to suggest causality between tetanus toxoid (DT and Td) and GBS. The committee added that since the conclusion was not based on controlled studies, no estimates of incidence or relative risk were available; however, the risk appeared to be low.[2]

Tuttle et al.[48] reviewed the findings of two active surveillance studies: (i) a study in children based on the Rantala polio study[42] in California in 1980–86 that looked at the relationship between administration of OPV and GBS; and (ii) a Centers for Disease Control and Prevention (CDC) assessment using retrospective active surveillance to detect new onset of GBS cases among 8.1 million vaccinated adults.[24] The investigators in the Rantala study[42] reviewed medical records of all children from 22 hospitals in Los Angles and Orange counties. The study included 1.2 million vaccinated children aged <15 years who had received diphtheria tetanus toxoid pertussis (DTP) vaccine simultaneously with other vaccines. Tuttle et al.[48] compared the number of cases observed after tetanus toxoid-containing vaccine with the number that would

be expected to occur by chance alone. Overall, the authors estimated that 2.4 cases of GBS would be expected among all children aged 5 years or younger within 6 weeks of DTP vaccination and only 2 cases were observed. According to the authors' calculation, 1.3–2 cases of GBS would be expected by chance alone within 6 weeks of tetanus toxoid and only 1 case of GBS was observed within this time. Both of the preceding studies failed to demonstrate an association of GBS within 6 weeks following administration of tetanus toxoid-containing vaccine. These results suggest that GBS following tetanus toxoid vaccine administration is rare and potentially due to individual genetic susceptibility,[46] and that the number of GBS cases observed after administration of tetanus toxoid vaccines in both children and adults is not greater than the number expected by chance alone.[48]

3.5 Meningococcal Polysaccharide Diphtheria Toxoid Conjugates Vaccine

In January 2005 a meningococcal polysaccharide diphtheria toxoid conjugate vaccine (MCV4; Menactra®) against the bacterium *Neisseria meningitidis* was licensed in the US for use among persons aged 11–55 years. In February 2005 the Advisory Committee on Immunization Practices in the US recommended MCV4 vaccination for 11- to 12-year-old children and before high school entry for individuals who had not been vaccinated previously.[49] Routine vaccination was also recommended for first-year college students living in dormitories and other persons at increased risk due to crowded living conditions.[49,50] By October 2005, five cases of GBS following MCV4 vaccination had been reported to VAERS[25,50] and the US FDA issued a warning of a possible association between receipt of the MCV4 vaccine and GBS.[50] In April 2006, three additional GBS cases were documented with onset within 6 weeks of vaccination.[51] By September 2006, 17 suspected cases of GBS had been identified among vaccinees aged 11–19 years within 6 weeks of vaccination. A small increased risk for the development of GBS following receipt of MCV4 was estimated after calculating an incidence risk ratio (IRR), the ratio of the reporting rate of GBS within 6 weeks after MCV4 vaccination to the expected incidence rate.[51-53] The calculated IRR from the 17 reported cases of GBS was 1.78 (95% CI 1.02, 2.85), which represents one additional case of GBS per 1 000 000 persons vaccinated. The report indicated that the results should be interpreted with caution, however, owing to the limitations of VAERS data and the imprecise estimated background rate of GBS in adolescents. The CDC did not change recommendations for the use of MCV4, as a subsequent assessment suggested that the benefit of vaccination in reducing the risk for meningococcal disease outweighed the risk of GBS.[52] However, the CDC did issue a warning that individuals with a history of GBS should not be vaccinated with MCV4 unless they are at unusually high risk of meningococcal disease (e.g. microbiologists handling isolates of *N. meningitidis*).

GBS following MCV4 vaccination continues to be monitored through VAERS and the Vaccine Safety Datalink (VSD)[54] at the CDC and FDA, as well as through a manufacturer-sponsored controlled study.[55] A recent study of a mass vaccination campaign with meningococcal C conjugate vaccine in Canada, although not specifically of MCV4, provides some additional related evidence. The study, involving over 1.5 million vaccinees, identified two cases of GBS with onset within 8 weeks of vaccination, which was not greater than the expected background number of cases.[56]

3.6 Measles and Mumps Vaccine

GBS has been described in case reports following natural (wild-type) measles infection[57] and following immunization to measles and mumps. Grose and Spigland[58] in 1976 reported two cases of GBS that developed in patients within 1 week after immunization with measles vaccine. Fescharek et al.[59] in 1990 described three cases of GBS following mumps vaccines. These case reports and small case series represent uncontrolled observations, and although all reports were temporally related to vaccination, absence of clinical details and other antecedent

events precludes a determination of a causal relationship.[2,60] Surveillance during a mass measles vaccination campaign of more than 70 million children aged 9 months to 15 years in South America found no excess in the number of cases of GBS compared with the number of expected cases in the 72 days following measles vaccination, a period that exceeds the 6-week time frame of highest risk suggested by the swine influenza vaccine studies; the authors concluded that, there was no statistically significant association between measles vaccination and GBS.[61]

A 14-year follow-up of adverse events associated with measles-mumps-rubella (MMR) vaccination in Finland detected two cases of GBS within the 6-week risk period. Both cases were in 18-month-old boys, resulting in an incidence of 0.07 per 100 000 vaccine doses, which is not higher than the background incidence of 0.22 per 100 000 18-month-old children.[62] Patja et al.[63] reported results of a study based on linkage of a nationwide hospital discharge register and individual vaccination records from 1983 to 1986 in Finland. No cases of GBS were reported following over 600 000 doses of MMR vaccine.

3.7 Hepatitis Vaccines

GBS has been infrequently reported following vaccination against hepatitis B. Since the introduction of plasma-derived hepatitis B vaccine in 1982[64] and later the recombinant hepatitis B vaccine,[65] several case reports of hepatitis B vaccine-associated GBS have appeared in the literature. Khamaisi et al.[66] reported on a 52-year-old woman who developed GBS 10 weeks after the second dose of recombinant hepatitis B vaccine. Khamaisi et al.[66] also reported 19 cases in which hepatitis B vaccination preceded the onset of symptoms of GBS. Nine cases occurred within 7 weeks following vaccination; five of these were associated with plasma-derived hepatitis B vaccine and four with recombinant vaccine.

In 1997, Kakar and Sethi[67] reported a 3-year-old girl diagnosed with GBS after recombinant hepatitis B vaccination. In 2000, Sinsawaiwong and Thampanitchawong[68] reported a 17-year-old woman who developed progressive quadriparesis with bilateral facial diplegia 3 days after hepatitis B vaccination; other potential causes of GBS were ruled out.

The temporal associations noted in the above case reports have not been substantiated in the only epidemiological investigation of hepatitis B vaccine and GBS. In an uncontrolled observational study of 43 618 Alaskan native vaccinees, no relationship between hepatitis B vaccination and GBS was demonstrated.[69]

GBS has been observed to be associated temporally with natural infection with hepatitis A virus (HAV), suggesting a possible biological rationale for development of GBS following the HAV vaccine.[70] Blumenthal et al.[71] reported a case of an 18-month-old previously healthy child diagnosed with GBS 10 days after hepatitis A vaccination. There have been no other case reports or epidemiological studies of HAV and GBS.

3.8 *Haemophilus influenzae* Type B Vaccines

Individual case reports form the only evidence of a possible association of *Haemophilus influenzae* type b (Hib) vaccine with GBS. D'Cruz et al.[72] reported three GBS cases following immunization with three different Hib conjugate vaccines and none of the children had antecedent infection. A fourth case was reported by Gervaix et al.[73] of a 4-year-old girl who developed signs of GBS 10 days after receiving Hib vaccine; serological tests were negative for cytomegalovirus, herpesvirus, Epstein-Barr virus, *Borrelia burgdorferi* and *Campylobacter* species. Three cases of GBS following Hib vaccination were reported to VAERS from 1990 to 1992, but two of the three children had antecedent illness.[5]

In 2001, Nejmi et al.[74] described a case of an 18-month-old boy in Casablanca, Morocco, who was hospitalized with extensive paralysis consistent with AIDP, with onset within 48 hours of Hib vaccination. There was no history of antecedent illness and serological evaluations, and stool cultures for numerous infectious agents, including *C. jejuni*, were unremarkable There have been no cases of GBS reported in any controlled observational studies of Hib vaccine.[75-77]

3.9 Yellow Fever and Japanese Encephalitis Vaccines

Recently, cases of neurological disease after yellow fever vaccine 17D-204 have been reported to VAERS. Six cases of GBS, including one Fisher variant, were classified by an international yellow fever vaccine working group as 'suspect' vaccine-associated disease.[78] The authors defined the reporting rate as the number of people with neurological adverse events occurring within 30 days of vaccination that were reported to VAERS during the study period divided by the number of doses of vaccine distributed to the US civilian population during the same study period. In studies covering the period 1990–2004, five cases of GBS following yellow fever vaccination were reported, corresponding to a reporting rate of 1.9 cases within 30 days of vaccination per million doses distributed in the US.[78,79] The expected incidence of GBS from all causes used in this report was 0.8–3.3 per 30 days per million population. There was a similar reporting rate from the UK, with another 17D-204-based vaccine and a similar expected rate.[80] The findings of these studies did not suggest an elevated risk of GBS following YF 17D vaccine when compared with baseline estimates.

For Japanese encephalitis (JE) vaccine, one case of GBS temporally related to JE vaccination has been reported in the US since 1984; however, this patient also had pharyngitis 3 weeks before the onset of weakness and had a positive rapid antigen test for mononucleosis due to Epstein-Barr virus test. A causal relationship between JE vaccination and neurological events has not been established in this US case or other cases reported worldwide.[79-81]

3.10 Smallpox Vaccine (Vaccinia)

At least three cases of GBS following smallpox vaccination had appeared in the literature in the pre-eradication era. Glanders[82] reported in 1950 a case of apparent GBS in a 27-month-old occurring 1 week after vaccination. Drouet et al.[83] reported an apparent case in 1956. Kisch[84] reported a case of GBS in a 52-year-old woman with onset 16 days after her third receipt of smallpox vaccine.

In 2002, the US reinstituted smallpox vaccination among selected groups. An assessment of VAERS data performed in 2004 found three reported cases of GBS occurring over a 27-month period; the estimated reporting rate of GBS of 0.5 per 100 000 vaccinees was determined not to be above reported background rates.[85]

4. Immunization and Relapse of Guillain-Barré Syndrome

The association of GBS following swine influenza vaccination in 1976 led to heightened awareness and caution when recommending vaccination for individuals with a history of GBS. Currently CDC influenza vaccine recommendations contain the following precaution: "[avoiding] vaccinating persons who are not at high risk for severe influenza illness complications and who are known to have experienced GBS within 6 weeks after a previous influenza vaccination is prudent".[86] Recently, CDC issued a warning for MCV4 – persons with a history of GBS should not receive MCV4 vaccine unless at particularly high risk for meningococcal disease.[51] The recommendation is based primarily on theoretical concerns, and there is currently little empirical evidence to support the possibility that MCV4 vaccination increases the risk of GBS recurrence. However, individuals with a history of GBS have a greater likelihood of subsequently experiencing GBS than those without such a history[86-88] and therefore their risk of coincidentally experiencing a recurrence of GBS following vaccination is increased.

An audit of the recurrence of GBS and chronic inflammatory demyelinating polyneuropathy following immunization among members of a British GBS patient organization suggests that the risk of relapse of GBS requiring treatment or hospitalization following any immunization is low. Only 11 of 311 patients with GBS (3.5%) who were immunized reported recurrence of symptoms, which is much higher than the baseline risk of 2 per 100 000 population per year.[1,89]

Influenza, tetanus and typhoid were the most common immunizations that preceded a relapse.

5. Discussion

Immunizations have dramatically reduced vaccine-preventable diseases, including hospitalizations and death.[90] By their nature, immunizations are intended to stimulate the human immune system, and that stimulation could, at least theoretically, increase the risk of autoimmune diseases. Although the underlying aetiology and pathophysiology of GBS are incompletely understood, it is broadly believed that immune stimulation plays a role in its pathogenesis. Thus, it is biologically plausible, and perhaps not altogether surprising, that in rare cases, immunizations may lead to subsequent GBS. To date, however, with rare exceptions, causal associations between vaccines and GBS have not been substantiated.

The IOM has conducted reviews of the association of influenza and other vaccines with GBS.[2,3] The totality of the evidence for causality was reviewed taking into account quality of the studies, strength and consistency of the association, temporality, potential biases and confounding, statistical chance, and possible biological mechanisms. The most research has been conducted on influenza vaccine, and the IOM has concluded that the evidence favoured acceptance of a causal relationship between the 1976 swine influenza vaccine and GBS in adults.[3] The evidence is inadequate, however, to accept or reject a causal relationship between GBS in adults and influenza vaccines administered after 1976.[3] In its 1994 review, IOM also found that evidence favoured a causal association with GBS for both OPV and tetanus toxoid-containing vaccines. More recent population-based studies, however, cast doubt on these conclusions. In particular, data from large OPV campaigns in South America have not indicated an increased risk of GBS, and large US studies have found that the occurrence of GBS following immunization with tetanus toxoid (DT and Td) was not above the expected background rate. Based upon the limited body of evidence, the IOM concluded in 1994 that it was unable to accept or reject a causal association between hepatitis B or Hib vaccines and GBS.[2] We have identified no additional studies that would change this conclusion.

Older rabies vaccines that were cultured in mammalian brains also had an association with GBS, but the risk of GBS following newer rabies vaccines does not appear to be increased above background rates. For other vaccines not included in the IOM reviews, the available evidence is extremely limited. Only the MMR vaccine has been evaluated using population-based data; large MMR immunization campaigns in South America did not find an increased occurrence of GBS. For other vaccines, including MCV4, HAV vaccine, JE vaccine, yellow fever vaccine and smallpox vaccine, the evidence of a possible association with GBS has been based on case reports or voluntary reports to VAERS. Individual case reports or case series, however, cannot address whether the frequency of cases is higher than the expected background rate and are of limited value for causality assessment.

Our findings point out the need for additional research in several areas. First, because of the causal association identified with swine flu vaccine and the slight increased risk found in three other studies, the association between influenza vaccine and GBS deserves close monitoring with each influenza season's new vaccine and especially when there is a major change in the antigenic composition of the vaccine. Second, the evidence for a causal association between OPV and GBS, including recent studies, should be reassessed and, if necessary, additional studies undertaken in countries in which OPV is still being used. Third, a similar reassessment of the evidence should be undertaken for tetanus toxoid-containing vaccines. Fourth, ongoing studies should continue to try to quantify to the extent feasible the relative risk of GBS associated with MCV4. Fifth, consideration should be given to conducting controlled observational studies for the other vaccines that have been suggested to be associated with GBS in published case reports or reports to VAERS. Finally, additional laboratory and clinical research is needed to better understand the pathophysiology of GBS and the possible role of immunizations.[11,14]

In the studies cited in this review, many undoubtedly employed passive methods of surveillance and case identification, which have several significant inherent limitations. Additionally, cases of GBS were identified differently in various studies, and differing definitions and methods of diagnosis of GBS are present in the various studies. Any current or future studies of risk of a rare adverse event, such as GBS, associated with a particular vaccine will require data on (i) age-specific background rates of GBS (or a large comparison group of unvaccinated individuals); (ii) complete reporting of GBS following immunization; (iii) the use of standardized, validated case definitions and criteria for GBS; and (iv) a knowledge of the total number of persons vaccinated. Obtaining such data requires a well established surveillance system or the conduct of large epidemiological cohort and case-control studies. Large linked databases such as VSD can fulfil these requirements, although they may not be large enough to ascertain significant numbers of rare events such as GBS,[54] and larger populations may have to be studied, as is happening with the ongoing industry-sponsored study of MCV4. Standardization of procedures, including case definitions, is vitally important for the validity of individual studies and to allow comparisons across studies. Standardized case definitions for GBS are currently under development and may aid in the classification of suspected GBS cases following immunizations in clinical and epidemiological studies.[91]

6. Conclusions

GBS is a rare disease that has been rarely associated with vaccination. The most convincing evidence of a causal association is for swine flu vaccine and older rabies vaccines. Although the IOM concluded that the evidence favoured a causal association for OPV vaccine, more recent data cast doubt on this conclusion. Similarly, for tetanus toxoid-containing vaccines, the IOM favoured a causal association based on a single unique but well documented case report, but subsequent epidemiological studies did not demonstrate an increased risk of GBS. There are certain circumstances in which immunizing individuals, particularly those with a prior history of GBS, may require caution. However, the benefit of vaccines in preventing disease and decreasing morbidity and mortality, particularly for influenza, needs to be weighed against the small potential risk of GBS.

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