# Investigating Associations and Outcomes of Vaccines with Guillain-Barré Syndrome: A Review

**Daniel S. Ehlers[1*‡], Gulnar K. Jhaj[1*‡], Leann N. Seidel[1*‡], and Saishravan S. Shyamsundar[1*‡]**
[1]Geisinger Commonwealth School of Medicine, 525 Pine St., Scranton, PA 18510
*Master of Biomedical Sciences Program
‡Authors contributed equally
Correspondence: shyamsundar.sai@gmail.com

## Abstract

Guillain-Barré syndrome (GBS) is a debilitating autoimmune disease that causes demyelination of neurons. This impacts neurotransmission and can lead to muscle impairments. If this disease is not diagnosed and treated, it can be detrimental to an individual's quality of life. Over the past several years, there have been growing concerns of vaccines leading to the onset of GBS. We performed a literature search in PubMed to determine whether there is an association between GBS and several vaccine types, including influenza, hepatitis B, measles-mumps-rubella (MMR), and coronavirus disease of 2019 (COVID-19) vaccines. Overall, most studies concluded that these vaccine types do not exacerbate GBS onset among recipients. We determined that the risk associated with GBS was a rare event, and most studies advocated that administration of a vaccine had a much greater benefit than an associated risk. Based on our review, there were no studies that indicated an elevated risk of GBS after vaccinations. In conclusion, this analysis may contribute to reducing vaccine hesitancy that is prevalent in society.

## Introduction

The Centers for Disease Control and Prevention (CDC) reports that the incidence of Guillain-Barré syndrome (GBS) worldwide is not as common as one may think (1). The incidence of this disease is approximately 1 in 100,000, with around 3,000 individuals in the United States (U.S.) being affected annually (1–4). However, though rare, GBS can impact the quality of life of individuals of various ages (2, 5–8).

GBS is an autoimmune disease in which the body's immune system starts producing antibodies in order to attack itself (9–11). The main target of these antibodies are the body's own nerves and more specifically, the myelin sheath that surrounds these neurons (9–11). The myelin sheath is a fundamental aspect of neurotransmission and acts as an electrical insulator (9). When an action potential is propagated throughout the axon, the myelin sheath prevents current leakage and works to help maintain a high conduction velocity for the action potential to propagate and trigger an effector response (12–13). In unmyelinated neurons, however, one can observe a decrease in the overall conduction velocity (14). Existing literature has suggested structural similarity of the pathogen to the immune system along with a bacterial infection as two possible explanations as to the possible causes of GBS (10–11, 15). For the case of structural similarity, the literature has suggested that the immune system is responding to molecules or even microorganisms that may have morphological and structural similarities to the myelin sheath (15). These structural similarities may prevent the innate or adaptive immune systems from differentiating between the two and so the body may end up attacking itself in the outcome (15). Another plausible explanation for GBS could be linked to the bacterial infection caused by *Campylobacter jejuni* (10–11, 15). The prevalence of this bacteria within the body could be attributed to eating foods that are contaminated, which eventually causes the pathophysiology and symptoms observed in GBS (15).

GBS symptoms are like those for other neurological disorders, ranging from weakness and tingling sensation that begins in the lower extremities and gradually progresses to the upper extremities (2, 16–17). The manifestations of the disease may begin to worsen over time and may lead to partial or complete muscle paralysis (2, 16–17). Though rare, GBS is still considered a life-threatening disease with a mortality rate between approximately 3% and 13% (18). The diagnosis is completed through a nerve conduction test, electromyography (EMG) studies, or through analyzing cerebrospinal fluid (CSF) to look for any increased levels of proteins using a lumbar puncture (2, 19–21). Unfortunately, there is no effective cure for GBS (20). However, symptoms may be managed through a variety of ways such as using non-steroidal anti-inflammatory drugs, carbamazepine, or gabapentin (22–24). Other forms of treatment include the use of plasmapheresis and intravenous immunoglobulin therapy (IVIG) (22, 25–26).

Over the past several years, it has been reported that GBS can occur after vaccine administration (27). This concern has further contributed to the growing vaccine hesitancy (28). The objective of this literature review was to determine the association between GBS with several different types of vaccines.

## Methods

We conducted a literature search using PubMed and an online search engine, Google, to identify studies that discuss any association between vaccines and GBS onset. Particularly, we focused our search on four broad categories. These include any association between GBS with influenza vaccines, hepatitis B vaccines, measles-mumps-rubella vaccines (MMR), or coronavirus disease of 2019 (COVID-19) vaccines. We did not utilize any Medical Subject Headings (MeSH) terms or establish any inclusion or exclusion parameters for our search.

## Discussion

### Vaccine overview

Vaccines have been a vital tool in protecting individuals and communities from infectious diseases for hundreds of years (29,

30–32). Vaccines have a long history and go as far back as Edward Jenner's initial work with addressing smallpox, a disease that ravaged many parts of the world for many years (32–34). Edward Jenner found that individuals affected by cowpox were offered protection against smallpox (35). This was because the antigens developed during a cowpox infection were structurally like that of smallpox and as a result, the body was able to defend against smallpox if it encountered the infection again in the future (36). This provided the basis for understanding more about the body's humoral response (37–38). Edward Jenner's work opened the doors for further vaccine development and its widespread global use (33).

It is important to mention that the immune system can be subcategorized into the innate and adaptive immune system (39). The innate immune system provides the initial response to a pathogen, while the adaptive immune response requires multiple days to occur (39). However, the response is usually more pronounced than that of the innate immune system (39). The idea of the body's own immune system reacting to structurally similar antigens, such as Edward Jenner's observation of the cowpox and smallpox viruses, highlights the concept of cross-reactivity (39-40). Figure 1 shows the concept of cross reaction and how the adaptive immune system can remember the specificity of a previously encountered antigen in order to mount a stronger immune response for all subsequent infections (36, 39–40).

Since the advent of the live-attenuated smallpox vaccine, several other vaccines have been developed such as inactivated, capsular polysaccharide, protein-based and more recently genetically engineered vaccines (12, 41). Throughout time, outbreaks of polio, hepatitis, chickenpox, and influenza have led scientists to find innovative ways to activate the body's immune system through these different vaccines (41).

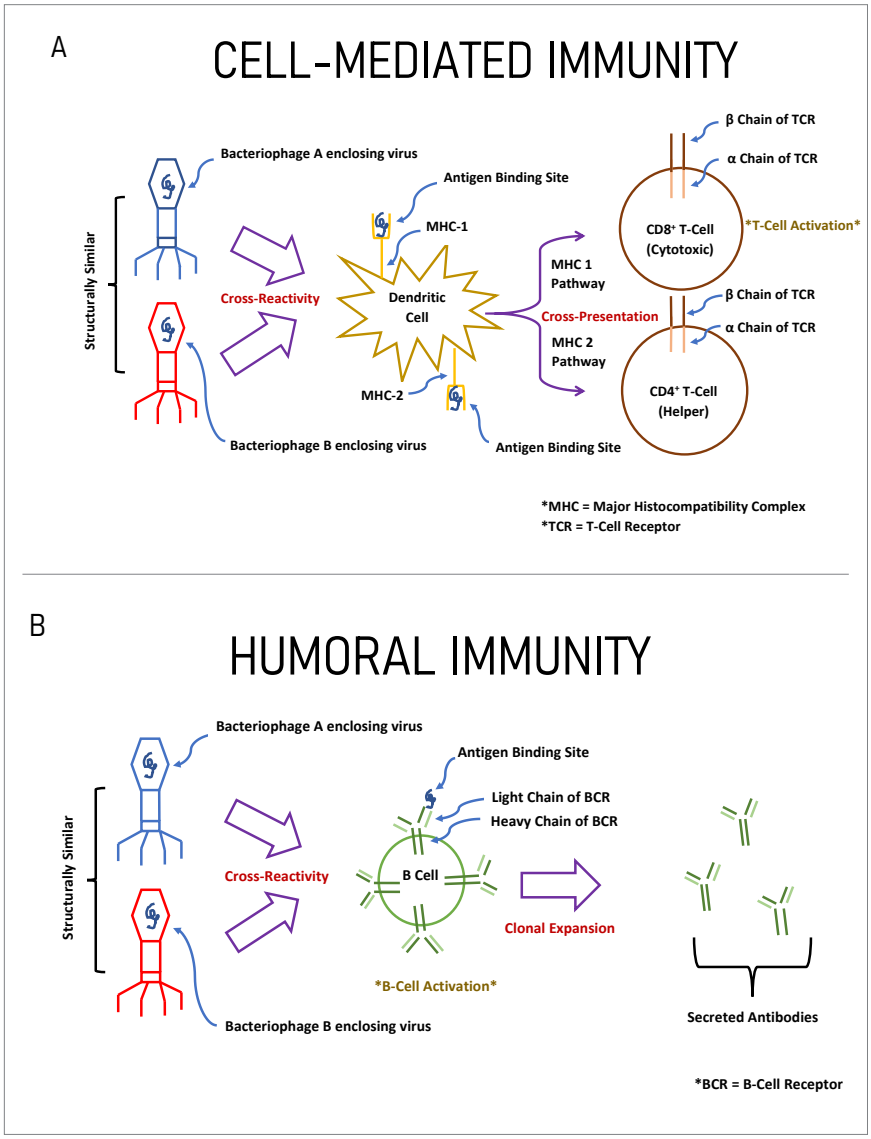


**Figure 1:** Specificity of the adaptive immune response in antigen recognition of two structurally similar pathogens (39). (A) Cell-mediated immunity involves cytotoxic T-cells (CD8+) and helper T-cells (CD4+) (39). There are two main pathways involved for antigen presentation: major histocompatibility complex (MHC I) and/or major histocompatibility complex (MHC II) (39). The antigens are presented to T-cells by these complexes through professional antigen presenting cells such as dendritic cells (39). (B) Humoral immunity is an antibody response to a pathogen (39). Once an antigen is recognized, B-cells can differentiate into plasma cells, undergo clonal expansion, and begin to secrete antibodies to neutralize an infiltrated pathogen (39). Note: Not all signaling molecules and cellular mechanisms are depicted in this figure and were not drawn to scale. Image was adapted from (39).

One valuable aspect of vaccines compared to other options at a physician's disposal is that they go beyond positively impacting the health of the person receiving it (42). They also provide protection to any interactions that a vaccinated person may have by decreasing the rate of transmission among individuals (42). Vaccine development can take a decade or longer, as it undergoes meticulous safety and efficacy monitoring through animal and then human trials before it becomes available to the public (43). Even after widespread distribution of the vaccine, efficacy and adverse events are still monitored among the general population (43). In this review, we focused on inactivated vaccines, subunit vaccines, live-attenuated vaccines, as well as messenger RNA (mRNA) vaccines, and explored any causal risk associated with GBS onset (41).

## GBS and influenza vaccines

A link between GBS and vaccines first arose during the swine flu vaccination effort in 1976 (44). A small rise in cases was seen among those who received the vaccine, with roughly one GBS instance seen for every 100,000 people vaccinated (44). Since this time, the association between influenza vaccines

and GBS has remained inconsistent (44). One study monitored the occurrence of GBS during the H1N1 vaccination initiative in 2009 (44). Surveillance of 23 million vaccinated people revealed the risk of GBS doubled during the 6 weeks succeeding the inactivated influenza vaccine. However, findings were not statistically significant (44). This was an expected finding. Influenza is a known source of GBS, and the vaccine's function is to stop influenza infection, so by preventing infection the vaccine was also preventing any possible emergence of GBS (44). It is also unclear whether the connection between GBS and the H1N1 vaccine was a result of unrevealed H1N1 infections as this vaccine was being administered at a time where infections were widespread (44). Possible similarities between the 2009 H1N1 and 1976 swine flu vaccines could have also led to the belief of an association (44).

The data from the Vaccine Safety Datalink (VSD) concluded that GBS was notably linked to the monovalent inactivated vaccine (MIV) compared to the seasonal trivalent inactivated influenza vaccines (TIV) during 2009–2010 (45). MIV and TIV both contain an identical H1N1 antigen (45). In this particular study, five of the nine GBS cases which occurred in the 6 weeks succeeding an MIV were individuals that had a respiratory infection noted in their medical documentation inside 1 month prior to GBS onset, contrasted by one of eight cases succeeding TIV (45). However, it is important to note the MIV availability stated in the VSD conflicted with the height of a wave of the H1N1 pandemic in October 2009, with the administration of TIV in 2009–2010 mainly occurring prior to this wave possibly leading to prejudiced positive linkage between GBS and 2009–2010 MIV (45). This study examined the linkage between both GBS and administration of MIV and TIV, and the linkage between GBS and medically assisted infections, modifying for MIV or TIV reception (45). Vaccinations occurring in the risk window were defined as the 1 to 42 days before onset of GBS; those in the 43 to 49 days were considered a null interval to give a supplemental week for possible cases occurring during the primary risk window (45). Vaccinations occurring in the 50 through 126 days before emergence of GBS were the control interval. Cases with previous infections were defined as those occurring in the 1 to 42 days before emergence of GBS that experienced a medically assisted respiratory, gastrointestinal, or viral infection (45).

Over 1 million and 2 million MIV and TIV doses were administered, respectively, and over 3 million medically assisted infections were recorded among patients, including over 180,000 influenza infections (45). Noted in the 6 weeks prior to emergence of GBS were 18 cases that had received a vaccine and 44 cases with medically assisted infections. In three of these cases, both exposures occurred in the risk interval and received a diagnosis of acute respiratory infections (45). Four cases also had manifestations of respiratory illnesses, such as bronchitis and cold, which occurred in the risk interval before emergence of GBS (45). Of the 18 individuals that received a vaccination in the risk interval before GBS onset, seven experienced manifestations of a respiratory illness of which three were medically assisted (45). Although statistical significance was not identified between GBS and MIV or TIV, there was a significant relation between GBS and respiratory infection (45).

In a similar study involving data from VSD and Medicare patients, the association between GBS and the high-dose inactivated influenza vaccine (IIV3-HD) was examined during the 2018–19 flu season (46). IIV3-HD is given to those 65 and older due to the increased influenza antigens that aid in preventing hospitalizations and deaths (46). A weekly rapid cycle analysis was performed by the VSD to observe the emergence of GBS among individuals 65 and older in the 6 weeks after receiving the vaccine (46). In the Medicare data, an exposure was designated as the patient's main influenza vaccine amidst the examination time frame, while an incident GBS case was designated as a patient who received the vaccine that had been discharged from the hospital with a diagnosis in the 1 to 84 days post-vaccination (46). This study identified primary and secondary risk windows as the 8 to 21 and 1 to 42 days after a vaccination respectively, and days 43 to 84 as the control window (46). In the early flu season during late 2018, over 600,000 doses of IIV3-HD were administered according to the VSD, with five GBS cases recorded within the risk window versus zero in the control window (46). In the late flu season during April 2019, eight GBS cases were noted in the risk windows and one case within the control window (46). The Medicare early-season examination for IIV3-HD revealed 16 GBS cases in the primary risk window (Odds Ratio [OR], 1.85; 95% Confidence Interval [CI], 0.99-3.44), and 34 in the secondary risk window (OR, 1.31; 95% CI, 0.78-2.18) with 26 GBS claims in the control windows (46). The end-of-season examination for IIV3-HD revealed 18 GBS cases in the primary risk window (OR, 1.64; 95% CI, 0.92-2.91) and 37 claims in the secondary risk window (OR, 1.12; 95% CI, 0.70-1.79) with 33 GBS claims in the control windows (46). Both data source examinations revealed no statistical significance of an elevated risk of GBS following a IIV3-HD vaccine with a p-value greater than 0.05 (46). The overall findings along with the calculated OR indicated the risk between emergence of GBS after a IIV3-HD vaccination in 2018-19 was low and analogous to prior flu seasons, and the advantages of receiving the vaccine were more than enough to rule out the possibility of GBS emergence (46).

Both studies found that the relationship between GBS and influenza vaccinations were not significant, therefore a correlation or association between the two cannot be concluded (45–46). A recorded meta-analysis depicted roughly one GBS case per 1 million vaccine receivers and about 17 GBS cases per 1 million influenza infections, indicating that vaccinations diminish the possibility of GBS emergence (47).

### GBS and hepatitis B vaccines

The hepatitis B vaccine falls under the larger category of subunit vaccines (41). Compared to the inactivated vaccine, subunit vaccines utilize parts of an antigen to trigger an immune response by the body (48). However, more specifically, the hepatitis B vaccine is considered a recombinant vaccine type (a subcategory of subunit vaccine) (41, 48). Hepatitis B has a high prevalence rate and affects upward of 300 million individuals globally (49–53). Serious complications can lead to liver damage (50, 54). Fortunately, due to improvements in immunizations, awareness, medical care, and access, the age-adjusted mortality rate has been reduced over the years to about 0.42 for every 100,000 individuals as of 2019 (55–56).

Similar to an influenza vaccination, the concern of developing GBS after a hepatitis B vaccine is also of public interest (57). Interestingly, this concern is not new but can be dated back

several decades (58). A case report from India detailed that a 3-year old female with no relevant past medical history developed acute onset of extremity weakness after receiving the hepatitis B vaccine one day prior (58). The patient had neurological and psychomotor deficits (58). The clinical findings that were reported were consistent with the presentation of GBS (58–61). The patient showed gradual improvement after being placed on a course of steroidal medications (58). Through their discussion, the authors were not able to pinpoint an exact reasoning as to why this patient developed GBS-like symptoms after vaccination and suggested that more research may be needed to establish causality (58).

It was also important for us to explore if there were any occurrences of GBS after hepatitis B vaccination for the adult population. A 52-year-old female had GBS-like symptoms around 10 weeks after hepatitis B vaccination (62). The patient had a past medical history of renal dysfunction and presented with characteristic neurological deficits as well as abdominal pain (62). Serological tests indicated abnormal findings while EMG as well as nerve conduction tests were not performed on the patient due to worsening symptoms (62). The patient died several months later due to septic shock (62). Following an in-depth literature review of prior work, the authors concluded that GBS onset was a rare adverse event (62). However, the authors advocated that the benefits of the vaccine were greater than any associated risk (62).

Like the Vaccine Safety Datalink study for influenza vaccinations, another study utilized the Vaccine Adverse Event Reporting System (VAERS) to look at GBS occurrence after all types of vaccination between 1990 and 2005 (45, 63). In this 15-year period, out of a total of 1,000 GBS cases, 632 GBS cases were identified after influenza vaccination and occurred during the risk window (63). For this study, the risk window was defined as 6 weeks after vaccination (63). Comparatively, during the same time period, only 94 GBS cases were identified due to a hepatitis B vaccine with a majority also occurring in the same risk window (63). Mortality rate after GBS onset was higher among influenza vaccine recipients, whereas hepatitis B vaccine recipients had a slightly higher percentage of disability (63). However, the authors noted that both mortality and disability rates caused by vaccinations were comparable to the general population affected by GBS (63).

It was surprising to note, however, that in our PubMed search, we did not find other relevant studies that explored hepatitis B vaccine and GBS further with surveillance data. The most recent study that we found completed a nested case-control study in three Chinese cities from 2011 to 2015 (64). No significant increase in risk for GBS in the pediatric population (OR, 0.94; 95% CI, 0.54–1.62) and the adult population (OR, 1.09; 95% CI, 0.88–1.32) was found after vaccination, including against hepatitis B (64). From our search, we were not able to find any age differences that would exacerbate GBS onset. It would be beneficial if future studies investigated whether geographical or ethnic differences contribute to the prevalence of GBS after hepatitis B vaccinations.

### GBS and measles-mumps-rubella vaccines

The measles-mumps-rubella (MMR) vaccine is a trivalent, live-attenuated vaccine administered to individuals beginning in the 1970s (41, 65). After extensive outreach and education of the diseases and vaccines, measles cases were reduced by 80% in 1981 compared to the previous year (66). This was attributed in part to a two-dose vaccination regimen with the first vaccine being administered between 12 and 15 months of age and the second dose between 4 and 6 years of age (67). Like the above-mentioned vaccines, the question of whether the MMR vaccine is associated with an increased risk of GBS is worth asking given the dramatic impact GBS can have on an individual's life. A retrospective study conducted in Finland evaluated the risk of GBS and the MMR vaccine using data from 630,000 vaccine recipients from 1982 through 1986 (68). The target population was represented by 24 patients diagnosed with GBS, of which 20 patients were administered the MMR vaccine (68). This represents no statistically significant difference between administration of the MMR vaccine and the typical incidence of GBS (68). Of note, respiratory or gastrointestinal infections were present in 83% of the 24 patients prior to the diagnosis of GBS, which is in line with other reported cases (68).

Data involving post-mass vaccination campaigns can be utilized to test the association between MMR vaccines and GBS (69). One such study drew the number of GBS cases from the Poliomyelitis Eradication Surveillance System of the Pan American Health Organization in which 73 million children received the measles immunization between 1990 and 1994 in the countries of Argentina, Brazil, Chile, and Colombia (69). The number of GBS cases was 2,296, indicating there was no significant increase in GBS cases versus the expected (69). A similar outcome was observed in Turkey during a mass vaccination campaign where 325,000 individuals were administered measles vaccines (70). An incidence of 0.615 per 100,000 doses was detected which was believed to be coincidental (70). Again, during a vaccination campaign in Iran from 2002 to 2004, GBS incidence rates ranged between 0.65 to 0.76 per 100,000 individuals, which was not a significant increase (71).

The U.S. Institute of Medicine has stated there is not enough evidence to either accept or reject a causal relationship between MMR vaccination and GBS (72). Additional studies involving many individuals could highlight a potential link between the MMR vaccine and GBS. The MMR vaccine has proved to be effective in reducing the incidence of infectious diseases specifically, 96% effective against measles, 86% effective against mumps and 95% effective against rubella (73). While each individual should consult with their healthcare provider prior to receiving a vaccination, it was also important for us to assess the risks of not receiving a vaccination. Measles is a highly contagious disease — so much so that an estimated 90% of individuals in close proximity to the infected individual will become infected (74). Given the current data, we do not feel the use of MMR vaccines should be reduced due to a concern of developing GBS.

### GBS and COVID-19 vaccines

Coronavirus disease of 2019, widely known as COVID-19, is a disease caused by the agent SARS-CoV-2 (75). SARS-CoV-2 has been identified as a severe acute respiratory syndrome coronavirus (76). SARS-CoV-2 is spread primarily by droplets, and it has impacted lives around the world by causing millions of infections and deaths (75, 77). At the end of 2020, two mRNA vaccines became available in the U.S. and other countries for

protection against COVID-19. These two vaccines were the Pfizer-BioNTech and Moderna vaccines. This was the first time mRNA vaccines were authorized for use; however, this technology had been under development since the late 1970s (78). There were challenges to developing mRNA vaccines, which included that mRNA was too prone to degradation, its production was too expensive, the ubiquitous presence of ribonucleases, and the lack of scalability (77–78). However, companies such as BioNTech and Moderna had already been developing mRNA vaccines and therapeutics for other diseases and cancers when COVID-19 struck. These two companies were able to develop, conduct clinical trials, and gain emergency use authorization within a year's time for mRNA vaccines for COVID-19 (78).

Such mRNA vaccines can be considered gene-based vaccines because an RNA vector is delivered to a host cell, which will then express the RNA to produce antigens that will then cause an immune response (77). These mRNA vaccines contain sequences that encode a form of the SARS-CoV-2 spike, S, protein, which induces an adaptive immune response against an antigen (77–78). The mRNA is injected intramuscularly, and it is taken up by muscle cells via endocytosis (77). Once inside the cell, the mRNA is translated and S proteins form (77). Some S protein will be presented on the plasma membrane of cells, or it is secreted out of the cell (77). However, most of the S protein will be degraded by the endosome-derived proteasome where the fragments will be presented to CD8+ cells via MHC I molecules (77). Antigen presenting cells (APC) will be attracted to the muscles and these will help present the S protein antigens by MHC II molecules to CD4+ cells (77). However, mRNA vaccines also involve the humoral immune response by activating B cells, which will either form memory B cells or antibody-secreting plasma cells (77). Antibodies that are secreted from plasma cells are circulating and will look for their antigen in the body (77). If the antibody finds its specific antigen, then it will bind to it to neutralize it so it cannot infect cells (77).

There are other vaccines that have been approved for use against COVID-19. These vaccines include Johnson & Johnson, Novavax, and Oxford-AstraZeneca (79). These three other vaccines are not mRNA vaccines. The Johnson & Johnson and Oxford-AstraZeneca vaccines operate similarly to previously developed vaccines for other diseases; they contain an adenovirus as a shell that carries the genetic code for the S protein to the cells, and once inside the cells, S protein is made, and the immune system responds (79). Novavax is different, as it contains the S protein of SARS-CoV-2 as a nanoparticle, which can elicit an immune response (79). Administration with any of the five vaccines can cause side effects such as injection site pain, muscle pain, headaches, fever, nausea, tiredness, and chills and normally these side effects last a few days (79). More severe side effects in the mRNA vaccines include myocarditis, inflammation of the heart muscle, and pericarditis, inflammation of the outer lining of the heart, in adolescents and young adults (79). In July 2021, the FDA attached a warning to the Johnson & Johnson vaccine that there is an increased risk of GBS with the Johnson & Johnson vaccine (79). This warning came after approximately 100 suspected cases of GBS were identified among 12.8 million people who received the Johnson & Johnson vaccine (80). These cases were reported through the Vaccine Adverse Event Reporting System (VAERS); 95 of the cases were serious and required hospitalization and only one death was reported (80). Most of the cases occurred within 42 days after administration of the Johnson & Johnson vaccine, and these cases were more frequent in men, and many of the men were over 50 years old (79–80). However, the FDA stated that even though there is an increased risk of GBS with the Johnson & Johnson vaccine, it was insufficient to establish a causal relationship (80). The Johnson & Johnson vaccine also has an FDA attached warning to it regarding the risk of blood clots (79).

The Oxford-AstraZeneca vaccine also has a warning attached to it regarding the risk of blood clots with low blood platelets, which can occur within two weeks of receiving the vaccine (79). The Oxford-AstraZeneca COVID-19 vaccine was also found to have an increased risk of GBS after vaccination, which led to the European Medicines Agency (EMA) to attach a warning to the Oxford-AstraZeneca COVID-19 vaccine in September 2021 (80–81). This warning was added after 833 cases of GBS were reported with the Oxford-AstraZeneca COVID-19 vaccine worldwide by July 31, 2021 (81). By July 25, 2021, approximately 592 million doses of the Oxford-AstraZeneca COVID-19 vaccine were given worldwide (81). The EMA's Pharmacovigilance Risk Assessment Committee (PRAC) concluded that a causal relationship between the Oxford-AstraZeneca COVID-19 vaccine and GBS should be considered at least a reasonable possibility (81). The EMA PRAC listed GBS as very rare for the Oxford-AstraZeneca COVID-19 vaccine, which is the lowest frequency category that can be given, meaning it occurs in less than 1 in 10,000 people (81).

A study conducted in three districts of Kerala, India over a 4-week period from mid-March 2021 to mid-April 2021 found that seven patients developed GBS within 2 weeks of receiving their first dose of the AstraZeneca COVID-19 vaccine (82). The subjects were mostly female, with a ratio of female to male of six to one and they were in their fifth to seventh decades of life (82). All patients progressed to areflexic quadriplegia, had bilateral facial paresis, and six of the seven patients required mechanical ventilation (82). Additionally, four subjects developed other cranial neuropathies, including abducens palsy and trigeminal sensory nerve involvement (82). The researchers reported that the incidence of GBS in India was approximately 6 to 40 cases per million per year (82). Since the study was conducted over a 4-week period, the researchers broke this down into cases per 4-week period. Out of the 1.2 million people administered with the AstraZeneca COVID-19 vaccine in three districts of Kerala, India, the expected cases of GBS in a 4-week period was between 0.58 and four cases (82). Seeing seven cases in 1.2 million people is a 1.4- to 10-fold rise in the incidence of GBS (82). The study found that there was a risk of 5.8 per million, which could be considered relatively low, however, even with a risk of developing GBS, the benefits of vaccinations outweigh the risk (82).

Another investigation performed in the United Kingdom also included the AstraZeneca vaccine. In this investigation, four cases of GBS were reported, each having bifacial weakness with paresthesia and symptoms occurred 11 to 22 days after vaccination (83). The investigators presented that the typical occurrence of GBS is less than four cases per month (83). Even though a risk for developing GBS is seen, it is difficult to describe a causal relationship (83). The investigators did provide

a hypothesis on why vaccines can lead to the development of GBS. They hypothesized that the generation of host antibodies could cross-react with proteins present in peripheral myelin (83). These antibodies could be in response to the S protein, however, a less specific immune response, such as what is seen in vaccines that use adenovirus was also possible (83).

The SARS-CoV-2 S protein can bind to sialic acid-containing glycoproteins and gangliosides on cell surfaces (83). Antibody cross-reactivity of the S protein and peripheral nerve glycolipids may be involved in the pathogenesis of GBS, either from the COVID-19 vaccine or an infection of COVID-19 (83).

| Vaccine | Study Identifier | Principal Findings |
|---|---|---|
| Influenza | Salmon DA *et al.* (2021) | Observance of GBS cases among those who received the H1N1 vaccine concluded statistically insignificant results (44). While the risk of GBS appeared to double in the six weeks following the vaccine, the authors anticipated this result as influenza is a known cause of GBS (44). The vaccine's function was to suppress influenza infection, and by doing this it was also suppressing emergence of GBS (44). |
| | Greene SK *et al.* (2013) | Data collected from the VSD depicted GBS was linked to MIV versus TIV during 2009-2010 (45). The study also examined the relationship between GBS and medically assisted infections (45). A majority of patients who had an emergence of GBS and received MIV or TIV were also found to have had recent infections (45). While no significance was found between GBS and MIV or TIV, it was proven between GBS and respiratory infection (45). |
| | Perez-Vilar S *et al.* (2021) | The authors used VSD and Medicare data to analyze the relationship between GBS and IIV3-HD in 2018-2019 (46). Medicare early and end-of-season examinations followed IIV3-HD showed no statistical significance with p-values higher than 0.05 in both periods (46). |
| Hepatitis B | Kakar A *et al.* (1997) | The authors discussed the association between hepatitis B vaccination and GBS onset in a three-year old female in India who developed acute onset extremity weakness (58). They concluded that GBS is a rare adverse event and suggested more research may be needed to establish causality (58). |
| | Khamaisi M *et al.* (2004) | A literature review in the case of a 52-year-old female who presented with GBS-like neurological deficits ten weeks post-hepatitis B vaccination revealed that the GBS onset was a rare adverse event (62). The authors recommended that the benefits of vaccine administration outweighed any associated risks (62). |
| | Souayah N *et al.* (2009) | Using the Vaccine Adverse Event Reporting System between 1990-2005, 632 GBS cases that occurred after influenza vaccination and 94 cases that occurred after hepatitis B vaccination were identified (63). GBS-related mortality or disability rates post-vaccinations were comparable to the general population affected by GBS (63). |
| | Chen Y *et al.* (2020) | In a nested case-control study in three Chinese cities from 2011-2015, no significant increase in GBS cases for the pediatric population (OR, 0.94; 95% CI, 0.54-1.62) and adult population (OR, 1.09; 95% CI, 0.88-1.32) post-vaccination were found (64). |
| MMR | Patja A *et al.* (2001) | A retrospective study using hospital discharge diagnoses and vaccination data in Finland found no causal association between MMR vaccine administration and GBS (68). Those diagnosed with GBS developed symptoms between 80 days and several years after receiving a vaccine, greater than the risk period of 6 weeks (68). |
| | da Silveira CM *et al.* (1997) | The frequency of GBS cases were observed by the Poliomyelitis Eradication Surveillance System of the Pan American Health Organization during a five-year period in which 73 million children took part in a mass measles vaccination campaign (69). No statistically significant association was found between measles vaccination and GBS (69). |
| | Koturoglu G S *et al.* (2008) | A national measles vaccination campaign in Turkey vaccinated 325,000 individuals leading to two cases of GBS (70). This calculates to an incidence of 0.615 per 100,000 cases prompting the authors to list the association as coincidental (70). |
| | Esteghamati A *et al.* (2008) | The incidence of GBS cases of five fourteen-year-olds in Iran during an MMR vaccination campaign were evaluated by the national surveillance system (71). Incidence rates over the three-year period ranged from 0.65 to 0.76 per 100,000 population (71). No statistically observable increase of GBS cases were noted during or after the MMR vaccination campaign (71). |
| COVID-19 | Maramattom BV *et al.* (2021) | The frequency of GBS with the AstraZeneca vaccine was found to be 1.4-to-ten-fold higher than the expected rate of developing GBS in Kerala, India (82). All cases had bilateral facial paresis, which usually occurs in less than 20% of GBS cases (82). However, the benefits of vaccination outweigh the risk of developing this relatively rare outcome (82). |
| | Allen CM *et al.* (2021) | In the United Kingdom, four cases of GBS were reported after the AstraZeneca vaccine, and the typical occurrence is less than four cases (83). The researchers did suggest monitoring bifacial weakness with paresthesias post-SARS-CoV-2 vaccination (83). |
| | Woo EJ *et al.* (2021) | Following vaccination with the Johnson & Johnson COVID vaccine, 130 presumptive GBS cases were reported in the United States (84). It was found that the rate ratio was increased for both the 21-day and 42-day risk windows, except for adults aged 18-29 years old (84). Although these findings suggest a potentially small, but statistically significant risk of developing GBS post vaccination with Johnson & Johnson, this risk is far smaller than the risk of COVID-19 infection (84). |
| | García-Grimshaw M *et al.* (2021) | In Mexico, the observed incidence of GBS post vaccination with Pfizer was 0.18 per 100,000 administered doses, while the reported incidence of GBS is between 0.2 to 0.71 per 100,000 per year (85). Four out of the seven cases reported did have GI or systemic infections, which could have also caused the development of GBS (85). Due to these concurrent infectious triggers being present, there was a lack of mechanistic connection between mRNA vaccines and GBS (85). |

**Table 1:** Summary of principal findings of different studies investigating vaccination outcomes and GBS onset (44–46, 58, 62–64, 68–71, 82–85).

An additional study examined patients who received the Johnson & Johnson COVID-19 vaccine in the U.S. from Feb. 27, 2021, through July 24, 2021, using VAERS to monitor GBS cases in those who received the vaccine (84). The researchers identified 130 cases of presumptive GBS after receiving the Johnson & Johnson vaccine in this time period (84). Most of the cases were males, and most were younger than 65 years old (84). Most of the cases occurred within 21 days post-vaccination, and almost all of the cases occurred within 42 days post-vaccination, with a majority of the cases being severe (84). The investigators did list other items that could have caused GBS in some patients, such as other illnesses in these patients or comorbidities in patients, however, there were no concomitant vaccines (84). Except for adults aged 18–29 years old, the respective rate ratio was found to be increased for both the 21-day and 42-day risk windows (84). These researchers also stated that even though these findings suggest a potentially small, but statistically significant risk for GBS following vaccination with the Johnson & Johnson COVID-19 vaccine, this risk was far smaller than the risk of COVID-19 infection (84).

In Mexico, Pfizer-BioNTech's COVID-19 vaccine and the risk of GBS during the period from Dec. 24, 2020, to March 19, 2021, was analyzed (85). During this time, 3,890,250 people received at least one dose of the Pfizer-BioNTech vaccine (85). Of these approximately 3.9 million vaccines, only seven cases of GBS post vaccination were reported (85). All of these cases occurred after the first dose (85). This led to an observed incidence of 0.18 per 100,000 administered doses of the vaccine (85). The reported incidence of GBS in Mexico was 0.2 to 0.71 per 100,000 per year (85). The authors did report that four of the cases did have a previous gastrointestinal or systemic infection (85). While the researchers did see a slight increased risk of developing GBS after Pfizer-BioNTech vaccination, it was stated that in most cases concurrent infectious triggers were detected, which could have been the cause of the development of GBS rather than due to the vaccine (85). Due to concurrent infectious triggers being present, there was a lack of a mechanistic connection between mRNA vaccines and GBS (85).

Collectively, the studies reviewed regarding COVID-19 vaccines and GBS development indicated a slight increased risk, however, a causal relationship between the two was not established (82–85). Certain vaccines seem to have an increased risk of developing GBS post-vaccination, which include the Johnson & Johnson and AstraZeneca COVID-19 vaccines (82–84). While GBS and the mRNA vaccines, specifically the Pfizer-BioNTech mRNA vaccine, were examined, it was found that they are not likely to have an increased risk of GBS onset after vaccination due to the concurrent infectious triggers that were found in most of the cases reported in that analysis (85). All studies analyzed in this review stated that the risk of GBS onset from COVID-19 vaccines were small and the benefits of being protected from COVID-19 far outweigh the risks of GBS development (82–85). Table 1 summarizes the principal findings of all the studies for the different vaccine types that were discussed (44–46, 58, 62–64, 68–71, 82–85).

## Conclusion

Our objective was to determine if there were any associations between vaccine types and GBS onset. Our search on influenza, hepatitis B, MMR, and COVID-19 vaccines concluded there was no elevated risk of GBS onset among vaccinated individuals. Increased surveillance of vaccination efforts may reveal differing results regarding emergence of GBS, but based on a current review of the literature, the advantages of receiving each vaccine exceed the minimal to no risk of onset. Although more research is required in this area, these findings should aid in decreasing vaccine hesitancy among individuals, which has become a major talking point in our present society. Some limitations of this review include broad inclusion and exclusion criteria along with possible search bias. Both limitations could have impacted the results that were obtained. Future iterations of this rapid review should include a more comprehensive review with finer, specified search parameters to provide an additional long-term and global analysis that would allow for a more thorough understanding of the GBS-vaccine correlation.

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