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SARS-CoV-2 Vaccination and Neuroimmunological Disease
A Review

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IMPORTANCE The temporal association between the occurrence of neurological diseases, many autoimmune diseases, and vaccination against SARS-CoV-2 has been topically interesting and remains hotly debated both in the medical literature and the clinic. Given the very low incidences of these events both naturally occurring and in relation to vaccination, it is challenging to determine with certainty whether there is any causative association and most certainly what the pathophysiology of that causation could be.

OBSERVATIONS Data from international cohorts including millions of vaccinated individuals suggest that there is a probable association between the adenovirus-vectored vaccines and Guillain-Barré syndrome (GBS). Further associations between other SARS-CoV-2 vaccines and GBS or Bell palsy have not been clearly demonstrated in large cohort studies, but the possible rare occurrence of Bell palsy following messenger RNA vaccination is a topic of interest. It is also yet to be clearly demonstrated that any other neurological diseases, such as central nervous system demyelinating disease or myasthenia gravis, have any causative association with vaccination against SARS-CoV-2 using any vaccine type, although it is possible that vaccination may rarely trigger a relapse or worsen symptoms or first presentation in already-diagnosed or susceptible individuals.

CONCLUSIONS AND RELEVANCE The associated risk between SARS-CoV-2 vaccination and GBS, and possibly Bell palsy, is slight, and this should not change the recommendation for individuals to be vaccinated. The same advice should be given to those with preexisting neurological autoimmune disease.

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Supplemental content

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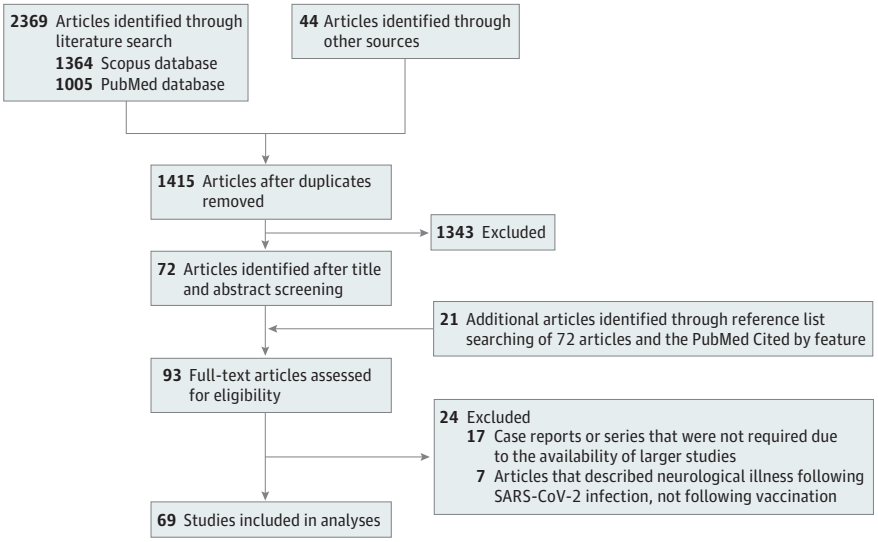
Infection with SARS-CoV-2 results in COVID-19 in many, which can be severe in some. After a year of variable worldwide government-mandated social restrictions, the arrival in 2021 of vaccines against SARS-CoV-2 was very welcome. These used new medical technologies, and there was public and medical concern about any potential serious neurological adverse effects that might occur. As a result, passive and active academic and international clinical surveillance systems focused on public reassurance and ensuring pharmacological safety. The neurological diseases of concern, including specific adverse events of special interest, are all individually rare. Most occur with a background incidence of naturally occurring disease recorded with variable accuracy in nonpandemic historical cohorts. Furthermore, a heterogeneity of ascertainment, recording, and coding strategies have hampered efforts to identify or refute causality. The reporting systems in place are by necessity usually passive, with variable ability to corroborate reports and clean data. Rarely, reliable active ascertainment methods can generate more accurate data.[1] In general, evidence that vaccination is causally significant in the pathogenesis of autoimmune neurological syndromes is rarely validated even by large, well-conducted epidemiological studies.[2] An almost unique exception to this is the cerebral venous sinus thrombosis, now termed *vaccine-associated immune thrombosis and thrombocytopenia* (VITT), identified as a rare and specific complication of the adenoviral vector (AV) ChAdOx1 (Oxford/AstraZeneca) and Ad26.COV2.S (Janssen) vaccines.[3,4] An increased risk of developing other neurological autoimmune disorders has been extensively sought, but only the very low incidence of Guillain-Barré syndrome (GBS) following AV vaccine administration has been supported by significant evidence.

Methods

Study Selection

We performed an extensive literature search for this narrative review in the PubMed and Scopus databases, with no limitation on the time period searched, using the MeSH search terms "COVID-19" OR "SARS-CoV-2" AND "vaccination" AND "autoimmune," returning 1005 articles in PubMed and 1364 articles in Scopus (**Figure 1**; eMethods 1 in the Supplement). Relevant studies for inclusion were identified by A. G. W. and M. P., who independently screened all titles and abstracts. A hierarchical selection was used where only high-quality epidemiological studies exploring millions of participants or vaccine doses were included to review the highest certainty evidence. Case studies have only been included where no or very few large studies were identified.

Figure 1. PRISMA Flow Diagram



The first phase of screening excluded 1343 articles. Articles that did not include millions of vaccine doses of millions of vaccinated patients were removed if there existed articles including this number of patients or vaccinations, for example, for Guillain-Barré syndrome. If, as was the case of myasthenia gravis, there was insufficient evidence including millions of patients or vaccine doses, the articles evaluating the largest cohort of patients were included in the analysis. Articles were screened for a focus on neurological disease occurrence or worsening following SARS-CoV-2 vaccination. Neurological disease included central and peripheral nervous system complications, including but not limited to autoimmune diseases, cerebrovascular disease, and psychiatric disease.

Statistical Analysis

The forest plot (Figure 1) was created using data hand-extracted from 10 articles that recorded cases of GBS following an AV vaccine, the background incidence in their cohort—or, where the background incidence could be taken from another cohort, which was possible for the British data—and the number of vaccinated individuals for that specific vaccine. Articles containing GBS data not included in the plot did not include the parameters needed to calculate the excess cases per 100 000 vaccines—for example, only the total number of GBS cases for a given vaccine with no expected or background rate available or without the total number of individuals vaccinated using a specific vaccine. The excess cases per 100 000 vaccines and the 95% CI were calculated from the number of vaccinated individuals for a given vaccine as well as the number of excess GBS cases in that population. The parameters were calculated in Excel version 16.69 (Microsoft), and the plot was created in RStudio version 2022.12.0 (Posit) using the ggplot2 package.

Limitations of the Current Evidence

These data are all particularly vulnerable to small study effects, publication bias, outcome reporting bias, and clinical heterogeneity, as neurological disease following SARS-CoV-2 vaccination is rare, event numbers are small, and public interest due to the COVID-19 pandemic is huge. We therefore preferentially selected large cohort studies for this review. Even in these studies, acquisition bias is important, as the interest in GBS, facial palsy, and other neurological diseases likely led to significant overreporting or duplicate reporting. As illustrated in data from the UK, cohorts often interrogated the same data sets, and so cohorts reporting the same participant were reported in more than 1 article. Multiple reporting of patients also occurred in the passively reported Yellow Card system in the UK and possibly Vaccine Adverse Events Reporting System (VAERS) in the US; these systems have limited cross-checking and data cleaning methods, unlike the National Health Service England (NHSE) Intravenous Immunoglobulin (IVIG) used by Keh et al.[1] The risk of overrepresenting the incidence of neurological disease following vaccination is further increased by the background rates of relatively mild diseases being underestimated in some epidemiological cohorts. People with mild GBS or mild Bell palsy may not present to hospital, and so the true background rate may well be higher than the background rate estimated by the literature. This imbalance is problematic for then understanding true incidences following vaccination. Additionally, the diagnostic certainty of GBS, Bell palsy, myasthenia gravis, and other diseases is often very limited in passive systems, and to our knowledge, only the NHSE IVIG database had some prospective diagnostic check. In the Yellow Card UK data set, fewer than 20% of patients were in a diagnostic certainty category or had a Brighton score of 1 to 3.

Observations: Neuroimmunological Complications of SARS-CoV-2 Vaccination

GBS

The most frequently investigated temporal association between an autoimmune neurological disease and SARS-CoV-2 vaccination was GBS, an acute-onset immune-mediated postinfectious polyradiculoneuropathy.[5] The background incidence of GBS in North America and Europe is approximately between 0.8 and 1.9 (median, 1.11) cases per 100 000 person-years.[6] GBS usually occurs within 4 weeks of a triggering infection, but an interval of up to 6 weeks was established following swine flu vaccination in 1976/1977, and the consensus is to consider this period of vaccination-attributable risk the same as the infection's at-risk period.[1,7] Numerous studies based on national or insurance-based surveillance systems have been published, many including millions of vaccines or vaccinated individuals (**Table 1**).[1,8-17] We present these separated by country. The major differences in certainty of the conclusions are diagnostic categorization (from patient-reported passive reporting to dedicated clinician-identified and criterion-supported

Table 1. Association Between Vaccination and Guillain-Barré Syndrome (GBS)

Source	Study type	Vaccinated individuals/ administered doses, No.	Postvaccination risk window of interest	Country	Period of data collection	Possible associations
Walker et al,[8] 2022	Self-controlled case series	Vaccinated individuals: 7 783 441 with ChAdOx1, 5 729 152 with BNT162b2, and 255 446 with mRNA-1273	4-42 d for GBS; 4-28 d for Bell palsy	UK	July 2020-July 2021	ChAdOx1 and GBS
Patone et al,[9] 2021	Self-controlled case series	Vaccinated individuals: 20 417 752 with ChAdOx1 and 12 134 782 with BNT162b2	1-28 d	UK	December 2020-May 2021	ChAdOx1 and GBS
Hanson et al,[10] 2022	Cohort study of surveillance data	Vaccinated individuals: 7 894 989; administered doses: 483 053 Ad.26.COV2.S doses, 8 806 595 BNT162b2 doses, and 5 830 425 mRNA-1273 doses	1-21 d vs 22-42 d	US	December 2020-November 2021	Ad.26.COV2.S and GBS
Abara et al,[11] 2023	US Vaccine Adverse Event Reporting System	Administered doses: 17 944 515 Ad26.COV2.S doses, 266 859 784 BNT162b2 doses, and 202 847 486 mRNA-1273 doses	0-21 d; 1-42 d	US	December 2020-January 2022	Ad26.COV2.S and GBS
García-Grimshaw et al,[12] 2022	Retrospective study of a nationwide registry	Administered doses: 81 842 426 ChAdOx1, rAd26-rAd5, Ad5-nCoV, Ad26.COV2.S, mRNA-1273, BNT162b2, and CoronaVac doses	0-42 d	Mexico	December 2020-October 2021	Ad26.CoV2-S and GBS; BNT162b2 and GBS
Le Vu et al,[13] 2023	Self-controlled case series	Administered doses: 107 000 000 BNT162b2 doses, 23 000 000 mRNA-1273 doses, 7.7 000 000 ChAdOx1 doses, and 1 000 000 Ad26.COV2.S doses	1-42 d	France	December 2020-May 2022	ChAdOx1 and GBS; Ad26.COV2.S and GBS
Osowicki et al,[14] 2022	Enhanced spontaneous surveillance system following COVID-19 vaccination	Administered doses: 3 749 291 ChAdOx1 doses	0-42 d	Australia	February 2021-September 2021	ChAdOx1 and GBS
Woo et al,[15] 2021	US Vaccine Adverse Event Reporting System	Administered doses: 13 209 858 Ad26.COV2.S doses	1-21 d and 1-42 d	US	February 2021-July 2021	Ad26.CoV2-S and GBS
Maramattom et al,[16] 2021	Observed cases within 3 districts of Kerala, India	Vaccinated individuals: 1 200 000 with ChAdOx1	28 d	India	March-April 2021	ChAdOx1 and GBS
Li et al,[17] 2022	Population-based historical rate comparison study and self-controlled case series	Vaccinated individuals: 4 376 535 with ChAdOx1, 3 588 318 with BNT162b2, 244 913 with mRNA-1273, and 120 731 with Ad26.COV.2.S	0-21 d After the first vaccine dose	UK and Spain	December 2020-May 2021 in the UK and December 2020-June 2021 in Spain	No evidence of increased incidence
Keh et al,[1] 2023	National Immunoglobulin Database retrospective case identification and prospective case collection in UK multicenter surveillance database	Administered doses: 20 300 000 ChAdOx1 doses, 11 500 000 BNT162b2 doses, and 300 000 mRNA-1273 doses	Within 6 wk	UK	December 2021-July 2021 for retrospective data; January 2021-November 2021 for prospective data	ChAdOx1 and GBS

diagnoses) and study size; the latter is crucial in rare associations where huge populations are required to identify low event numbers reliably.

UK

A UK self-controlled case series including unverified coding data of hospital admissions assessed GBS incidence 1 to 28 days postvaccination. A total of 20 417 752 individuals vaccinated with a first dose of ChAdOx1 were included. An increased incidence rate ratio (IRR) for hospital admission or death due to GBS was reported from 15 to 21 days (IRR, 2.90; 95% CI, 2.15-3.92) and 22 to 28 days (IRR, 2.21; 95% CI, 1.59-3.09) after vaccination. An increased risk of GBS in the 1 to 28 days postvaccination (IRR, 2.04; 95% CI, 1.60-2.60) equated to an excess of 38 GBS cases per 10 million exposed to ChAdOx1.[9] No association was demonstrable with BNT162b2. A Scottish validation cohort supported these findings.[9] A subsequent self-controlled English case series looking for GBS, transverse myelitis, and Bell palsy using a very similar (possibly the same) data set coded in primary care from emergency department and secondary institutions but using slightly different methodology included 7 783 441 individuals vaccinated with ChAdOx1.[8] New coded but diagnostically unverified episodes of GBS logged from 4 to 42 days after vaccination were used in the analysis. A total of 517 cases of GBS resulted in an increased post–ChAdOx1 vaccination IRR of 2.85 (95% CI, 2.33-3.47), corresponding to 11 excess cases of GBS per 1 million vaccines. The excess was again after the first dose only, and the relative increase in GBS cases was highest among individuals aged 40 to 64 years.[8] There was no association with the BNT162b2 (BioNTech/Pfizer) vaccine.[8]

Significantly more reliable GBS diagnosis and case ascertainment using the UK National Immunoglobulin Database/NHSE IVIG database paired with known immunization type and date allowed

for the evaluation of criteria-supported GBS diagnosis in relation to 20 300 000 ChAdOx1 doses, 11 500 000 of BNT162b2 doses, and 300 000 mRNA-1273 (Moderna) doses.[1] Only 90 to 140 excess UK GBS cases above the background rate could be identified, distributing in a peak about 24 days after a first dose of the ChAdOx1 vaccine.[1] The excess risk of GBS in the first 42 days following vaccination using ChAdOx1 was 0.576 cases (95% CI, 0.481-0.691) per 100 000 doses, and this risk is established with higher certainty from this study. Using a prospective case collection in a multicenter UK surveillance database, no specific vaccine-associated GBS phenotype was identified, illustrating how hard it is to identify cases with causal association from background occurrences.[1] Tamborska et al[18] also identified that ChAdOx1 may be associated with GBS using an independent online open-access passive reporting national surveillance system, but it should be noted that the the cases in their study are a subset of those in the study by Keh et al.[1]

Germany

Cases of GBS occurring between 3 and 42 days postvaccination reported to the German national surveillance system were analyzed.[19] Following vaccination with ChAdOx1 and Ad.26.COV2.S, the expected number of GBS cases was exceeded by a factor of 3.1 and 4.2, respectively. This was not observed for messenger RNA (mRNA) vaccines or for the additionally included influenza vaccine. Lehmann et al[19] also suggested a higher frequency of bilateral facial paresis in GBS cases occurring after vaccination; however, acquisition may have been overestimated by the inclusion of Bell phenomenon (normal upward elevation of the ocular globe on voluntary eye closure) as well as Bell palsy and its synonyms as a search criterion for identifying cases.

France

Using data from the French national health data system (Système National des Données de Santé), with 139 million doses of 4 vaccinees (BNT162b2, mRNA-1273, ChAdOx1, and Ad26.COV2.S), an excess of approximately 6 cases of GBS per million persons occurred within 42 days of the first dose of each of the AV vaccines.[13] There was no evidence of an increased risk after the second or third doses. An increased risk following Ad26.COV2.S was only observed in individuals 50 years or older. This cohort only included cases of GBS for patients requiring hospitalization, possibly underestimating the true incidence.

US

US reporting systems are smaller in size compared with the UK, as they frequently rely on insurance-based monitoring, as no true nationwide systems exist. Hanson et al[10] performed a cohort study of surveillance data (Vaccine Safety Datalink) from 7 894 989 individuals. An increased incidence of GBS following the Ad.26.COV2.S AV vaccine (only 483 053 doses) was observed in this cohort calculated from the 11 reported and confirmed GBS cases following this vaccine. The unadjusted incidence rate of GBS cases per 100 000 person-years (32.4; 95% CI, 14.8-61.5) in the 1 to 21 days following vaccination was highest in the first 14 days. This figure is 15-fold to 30-fold the background GBS rate[10]; subsequent cases of GBS that have clearly not occurred at this frequency in larger vaccinated cohorts and overestimated risk illustrates the problems of small studies with low event numbers. As a further illustration of this, 91% of patients had facial weakness or paralysis in addition to limb weakness, and Hanson et al[10] suggested that AV vaccines may precipitate a form of GBS that has distinct facial involvement. This was not borne out in practice or other larger more reliable series. The slightly larger VAERS reported a small but statistically significant safety concern for GBS following Ad26.COV2.S vaccination.[15] The estimated crude reporting rate was 1 case of GBS per 100 000 doses of Ad26.COV2.S. Woo et al[15] calculated in the worst-case-scenario analysis that the estimated absolute rate increase of GBS was 6.36 per 100 000 person-years following Ad26.COV2.S vaccination. From these small studies, neither the high incidence of facial paralysis nor GBS has occurred. A more recent publication from Abara et al[11] also used VAERS to identify GBS cases among 487 651 785 SARS-CoV-2 vaccine doses (17 944 515 Ad26.COV2.S doses, 266 859 784 BnT162b2 doses, and 202 847 486 mRNA-1273 doses) within 21 days and 42 days of vaccination. The data indicated an association between Ad26.COV2.S and an increased risk of GBS (observed-to-expected [OE] ratio at 21 days, 3.79; 95% CI, 2.88-4.88; OE ratio at 42 days, 2.34; 95% CI, 1.83-2.94), which was not observed for the mRNA vaccines (OE ratio less than 1 for both mRNA vaccines).[11]

Mexico

Mexico administered 81 842 426 doses of ChAdOx1, rAd26-rAd5 (Sputnik V, AV vaccine), Ad5-nCoV (Convidecia, AV vaccine), Ad26.COV2.S, mRNA-1273, BNT162b2, and CoronaVac (Sinovac, inactivated whole virus). Using CoronaVac as a comparator, higher incidences of GBS per 1 000 000 administered doses were observed among those vaccinated with Ad26.COV2.S (3.86; 95% CI, 1.50-9.93) and BNT162b2 (1.92; 95% CI, 1.36-2.71).[12] GBS incidence per 1 000 000 administered doses was higher among mRNA-based vaccine recipients in this cohort (1.85; 95% CI, 1.33-2.57). This is the only study to suggest a risk from BNT162b2, but it is one of the largest population studies reported.

Australia

In Victoria, Australia, an enhanced passive (spontaneous) and active surveillance system was used to identify GBS cases following vaccination against SARS-CoV-2. Within 42 days of vaccination, the observed GBS incidence rate was 1.85 per 100 000 doses of ChAdOx1 following the first dose, with the expected rate given as 0.39 presentations per 100 000 adult population.[14] The rate was not increased for BNT162b2 or mRNA-1273.

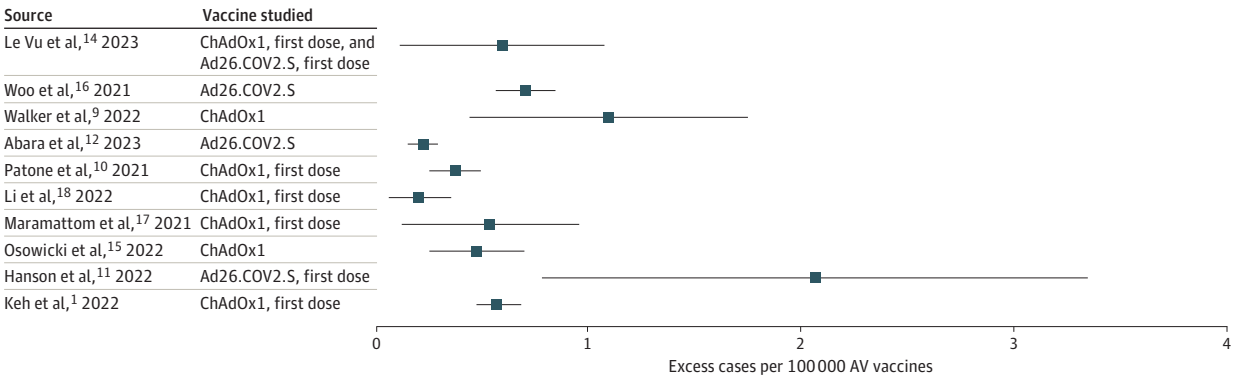
India

Maramattom et al[16] reported a case series in which they observed a 1.4-fold to 10-fold increase in the incidence of GBS during a 4-week period between mid-March to mid-April 2021 in 3 districts of Kerela, India. The number of individuals in this cohort was estimated at only 1.2 million. In the UK, Singapore, and other countries with comprehensive pre–COVID-19 pandemic reporting of GBS cases, the case numbers remained largely the same as pre–COVID-19 pandemic, and reported significant increases in cases in small series is probably artifactual.

South Korea

Lee et al[20] performed a nationwide time series correlation study using data collected from the National Health Insurance Service and Korea Disease Control and Prevention Agency databases to assess

Figure 2. Excess Cases of Guillain-Barré Syndrome per 100 000 Adenoviral Vector (AV) Vaccines



The forest plot was created using data hand-extracted from 9 articles that recorded cases of Guillain-Barré syndrome following an AV vaccine, the background incidence in their cohort—or where the background incidence could be taken from another cohort, which was possible for the British data—and the number of vaccinated individuals for that specific vaccine. Articles containing Guillain-Barré syndrome data not included in the plot did not include the parameters needed to calculate the excess cases per 100 000 vaccines, for example, only the total number of Guillain-Barré syndrome cases for a given vaccine with no expected or background rate available or without the total number of individuals vaccinated using a specific vaccine. The excess cases per 100 000 vaccines and the 95% CIs were calculated from the number of vaccinated individuals for a given vaccine as well as the number of excess Guillain-Barré syndrome cases in that population. All the articles identified an excess of GBS cases following AV vaccination.

incidence of GBS prior to and during the COVID-19 pandemic. The cumulative incidence rate of GBS was significantly lower during the COVID-19 pandemic (2.1 per 100 000 population in 2020 to 2021 vs 2.4 per 100 000 population in 2017 to 2019), but time series correlation analysis demonstrated a strongly positive temporal association between SARS-CoV-2 vaccination and GBS in 2021. Lee et al[20] did not specifically assess whether this could be attributed to a single vaccine. In a prospective surveillance study including 38 828 691 total vaccine doses, of which 6 465 097 were AV vaccines (ChAdOx1 and Ad26.CoV2.S), Ha et al[21] concluded AV vaccines were associated with a 3-fold to 4-fold increased risk of developing GBS than mRNA vaccines in the same cohort, with GBS following the AV vaccine associated with the first dose.[21]

International (Mixed Countries)

Li et al[17] evaluated 4 376 535 ChAdOx1, 3 588 318 BNT162b2, 244 913 mRNA-1273, and 120 731 Ad26.CoV2 vaccinated individuals compared with a historical cohort of 14 330 080 individuals in the general populations of the UK and Spain. The authors did not identify an increased risk of GBS following any vaccine 0 to 21 days after the first dose. Using the World Health Organization global pharmacovigilance database (VigiBase), Kim et al[22] also found no association between GBS and SARS-CoV-2 vaccination compared with the influenza vaccines but warned regarding the heterogeneity of sources of information in the database. However, a further case report from VigiBase suggested that there is a risk of GBS following AV vaccines.[23]

Summary of GBS Data

The 4 UK studies highlight the major difficulties of the rush to study and, subsequently, of any systematic synthesis. Estimates of risk were generated with differing reliability, and for any future synthesis, significant numbers of the cases in these 4 studies are likely the same case reported multiple times but with variable diagnostic certainty. We calculated and demonstrated the excess number of cases of GBS per 100 000 vaccines for 10 studies that evaluated AV vaccines (**Figure 2**).[1,8-11,13-17] The data demonstrate a relatively equivalent number of cases of excess GBS per 100 000 vaccinations using AV vaccines. One limitation of this graph is that the observed postvaccination time period varies as follows: Keh et al,[1] 42 days; Hanson et al,[10] 21 days; Osowicki et al,[14] 28 days; Maramattom et al,[16] 28 days; Li et al,[17] 21 days; Patone et al,[9] 28 days; Abara et al,[11] 42 days; Walker et al,[8] 4 to 42 days; Woo et al,[15] 42 days; and Le Vu et al,[13] 42 days.

Bell Palsy

Studies including millions of vaccines or vaccinated individuals have been included (**Table 2**).[8,9,17,24] The unilateral lower motor neuron facial nerve palsy, often referred to as *Bell palsy*, describes paralysis of the facial nerve that occurs in the absence of an identifiable cause, with an annual incidence of 15 to 30 per 100 000 persons.[25] The phase 3 clinical trials of the mRNA vaccines identified a numerical imbalance between Bell palsy occurrence in the vaccinated group compared with placebo, which instigated investigation into whether there was an association of Bell palsy with SARS-CoV-2 vaccination.[26,27] This safety signal concern raised from the mRNA vaccine clinical trials was investigated in a disproportionality analysis using the World Health Organization VigiBase, and the reporting rate of facial paralysis was not found to be higher than that observed with other vaccines.[28] This finding of no association was supported by an interim analysis of surveillance data from 6.2 million individuals in the US vaccinated with 11.8 million doses of mRNA vaccine.[29] However, following separate, independent analyses of the clinical trial data, Cirillo and Doan[30] and Ozonoff et al[31] both suggested a higher risk of developing facial palsy associated with the mRNA vaccines compared with the background population. A safety assessment by Sato et al[32] using the VAERS database then demonstrated that the incidence of Bell palsy following SARS-CoV-2 vaccination was lower than or equivalent to the rates associated with influenza vaccines; however, there was a statistically significant relationship between SARS-CoV-2 vaccination and BNT162b2 or

Table 2. Association Between Vaccination and Bell Palsy

Source	Study type	Vaccinated individuals/ administered doses, No.	Postvaccination risk window of interest	Country	Period of data collection	Possible associations
Walker et al,[8] 2022	Self-controlled case series	Vaccinated individuals: 7 783 441 with ChAdOx1, 5 729 152 with BNT162b2, and 255 446 with mRNA-1273	4-42 d for GBS; 4-28 d for Bell palsy	UK	July 2020-July 2021	ChAdOx1 and Bell palsy
Patone et al,[9] 2021	Self-controlled case series	Vaccinated individuals: 20 417 752 with ChAdOx1 and 12 134 782 with BNT162b2	1-28 d	UK	December 2020-May 2021	ChAdOx1 and Bell palsy
Shibli et al,[24] 2021	Retrospective cohort study with noncurrent historic comparative group	Administered doses: 2 594 990 first doses and 2 434 674 second doses of BNT162b2	Within 21 d of the first vaccine and 30 d of the second vaccine	Israel	December 2020 (first dose) and January 2021 (second dose)-April 2021, followed until May 2021	BNT162b2 and Bell palsy
Li et al,[17] 2022	Population-based historical rate comparison study and self-controlled case series	Vaccinated individuals: 4 376 535 with ChAdOx1, 3 588 318 with BNT162b2, 244 913 with mRNA-1273, and 120 731 with Ad26.COV.2	0-21 d After the first vaccine dose	UK and Spain	December 2020-May 2021 in the UK and December 2020-June 2021 in Spain	No evidence of increased incidence

mRNA-1273 vaccination above the background prevalence.[32] An important major flaw in the data is the inclusion of Bell phenomenon in the search criteria.[33] A full analysis of the articles evaluating the association between Bell palsy and vaccination is available in eMethods 2 in the Supplement. In summary, an association of vaccination with Bell palsy is unclear.

Myasthenia Gravis, Multiple Sclerosis and Central Demyelination, Neuromyelitis Optica Spectrum Disorders, and Myelin Oligodendrocyte Glycoprotein Antibody–Associated Disease

An association between vaccination and myasthenia gravis, multiple sclerosis and central demyelination, neuromyelitis optica spectrum disorders, and myelin oligodendrocyte glycoprotein antibody–associated disease occurrence is not clearly supported by the literature. A detailed analysis is included in eMethods 2 in the Supplement.

Discussion

GBS remains the neurological condition with the clearest evidence of a causal link with SARS-CoV-2 vaccination. However, neither SARS-CoV-2 nor adenoviruses have been convincingly associated with GBS pathogenesis. Whether the vaccine data indicate that adenovirus may be of undetermined pathogenic importance in GBS is unclear,[34] but it would not be impossible. Discussion of the underlying pathogenesis of AV vaccine–driven GBS remains purely hypothetical owing to rarity, unstructured case ascertainment, and absence of widespread clinical biomarker sampling.

Identifying the molecular agent driving autoimmunity aids in any discussion of pathogenesis. This concerns some or all of the spike protein, the AV components, and the immune response to vaccination or infection. The autoimmune diseases that are reported to occur following COVID-19 only very rarely involve the peripheral nervous system.[35] The studies and data suggesting an association between SARS-CoV-2 infection and self-reactivity are dependent on temporal associations and have little else to support a proven causality.[35] Unlike vaccination, it is difficult to pinpoint an infection date or time of immune response in infection adding additional uncertainty to coassociation. Given the unprecedented conditions of the COVID-19 pandemic and the inherent complexity of autoimmunity, finding an autoimmunity and SARS-CoV-2 link will be challenging. It does not appear that the spike protein is a causal trigger of autoimmunity; if it were, then autoimmune diseases and GBS would occur with equal frequency in all vaccines. Repeated stimulation of C57B1/6 mice with recombinant SARS-CoV-2 spike protein does not induce any measurable autoimmunity.[36] It follows that the vaccine component common to the AV vaccines is the stimulus associated with the development of GBS. Despite the likelihood that AV components are the causative stimulus, it is then unclear if it is the inflammatory response to the vaccination, host genetic factors such as HLA haplotypes, autoreactivity of the adenovirus particles, or any or all of these could therefore be involved in the pathogenesis of GBS.

Identified adenoviral infection does not classically precede GBS onset in a frequency higher than background rates of infection and has not often been linked to GBS pathogenesis.[37] One study stands out as finding very high seroconversion rates,[38] but this finding has never been replicated. The adenoviral serotypes used in vaccinations are deliberately selected for their low virulence in humans. AV vaccines, in part due to the broad tissue tropism of adenovirus, are nonetheless potently immunogenic. The ChAdOx1 vaccine is based on the chimpanzee adenovirus (ChAd) Y25, and Ad26.COV2.S is based on species D human adenovirus serotype 26 (Ad26). Ad26 has a low seroprevalence in humans,[39] and a notable benefit to using ChAds is also the circumventing of any more generic preexisting human adenoviral immunity in the general population; the presence of antibodies against a given adenovirus serotype would greatly impede the immunogenicity of the vaccine antigen.[40] Whether this potent and distinctive immunogenicity of AV vaccination could be linked to driving autoimmunity through, for example, activating anergic B cells or activation of bystander T cells in susceptible individuals is pure speculation.[41,42] To our knowledge, both processes have yet to be associated with GBS. In addition, while there have been no known genetic associations when studying GBS as a group, there is little known about individual precipitating infections for HLA linkage, for example. Further investigation of this topic could aim to identify distinctive antibody or T-cell receptor signatures to AV fragments in individuals with post–AV vaccine GBS compared with unaffected AV vaccine–immunized controls, a unique HLA haplotype in those with post–AV vaccine GBS compared with controls, or

specific neural/myelin-centric molecular targets for AV antibodies in those with post–AV vaccine GBS.

The occurrence of VITT following vaccination with ChAdOx and Ad26.COV2.S has a clearer pathomechanism.[43] VITT is estimated to occur in 3 to 15 persons per million first doses of AV vaccine, with some rare cases occurring after a second vaccination. Biomarkers such as thrombocytopenia, D-dimer elevation, and reduced plasma fibrinogen were identified in many cases. VITT was also associated with immunoglobulin G antibodies directed against platelet factor 4, which leads to greatly enhanced platelet activation.[44] Whether cross-reactivity of AV components and peripheral nerve (glyco-)proteins could similarly lead to GBS has been suggested in the literature. However, the electrostatic interaction of platelet factor 4 that initiates VITT is not easily replicated by peripheral nerve components. Further research is needed to investigate the cross-reactivity of antibodies against different vectors after immunization as well as the possible interaction between components of adenoviruses and surface molecules of peripheral nerve structures.

Conclusions

In this review, we found there was a small increased risk of GBS following AV-based SARS-CoV-2 vaccines. High-quality UK studies of large cohorts convincingly reproduced consistent similar numerical associations for the AV-based ChAdOx1 vaccine, and these have been replicated in other international studies. The risk of Bell palsy following SARS-CoV-2 vaccination was unclear. No quantifiable excess risk was identified for myasthenia gravis, multiple sclerosis, or neuromyelitis optica spectrum disorders.

There are substantial confounding factors in all of the studies, limiting the certainty of their conclusions. Vaccination of a substantial proportion of the world's population happened after a year of severe pandemic illness and restricted interperson mixing, with background health and environmental risk substantially modifying health and immune exposures. The global search for a vaccine solution was met in many quarters by suspicion and criticism of new technology. There were many motivations for physicians, the public, and politicians to report any perceived complication. The lack of many organized, effective, and highly accurate national surveillance systems was quickly realized, and the data generated by multiple, heterogeneous acquisition and diagnosis-based systems are of questionable certainty for these rare and difficult-to-diagnose events. It is very unlikely that the risks of vaccination for any associated condition have been underestimated. But it is very clear that the reductions in illness episodes, hospitalizations, and deaths were the result of the huge, conferred benefits of SARS-CoV-2 vaccination at the individual and societal levels.[45]

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