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Association of Receipt of the Ad26.COV2.S COVID-19 Vaccine With Presumptive Guillain-Barré Syndrome, February-July 2021

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IMPORTANCE As part of postauthorization safety surveillance, the US Food and Drug Administration (FDA) has identified a potential safety concern for Guillain-Barré syndrome (GBS) following receipt of the Ad26.COV2.S (Janssen/Johnson & Johnson) COVID-19 vaccine.

OBJECTIVE To assess reports of GBS received in the Vaccine Adverse Event Reporting System (VAERS) following Ad26.COV2.S vaccination.

DESIGN, SETTING, AND PARTICIPANTS Reports of presumptive GBS were identified in a US passive reporting system (VAERS) February-July 2021 and characterized, including demographics, clinical characteristics, and relevant medical history.

EXPOSURES Receipt of the Ad26.COV2.S vaccine; the comparator was the background rate of GBS in the general (unvaccinated) population that had been estimated and published based on a standardized case definition.

MAIN OUTCOMES AND MEASURES Presumptive GBS; the reporting rate was analyzed, including calculation of the observed to expected ratio based on background rates and vaccine administration data. Because of limited availability of medical records, cases were not assessed according to the Brighton Collaboration criteria for GBS.

RESULTS As of July 24, 2021, 130 reports of presumptive GBS were identified in VAERS following Ad26.COV2.S vaccination (median age, 56 years; IQR, 45-62 years; 111 individuals [86.0%] were < 65 years; 77 men [59.7%]). The median time to onset of GBS following vaccination was 13 days (IQR, 10-18 days), with 105 cases (81.4%) beginning within 21 days and 123 (95.3%) within 42 days. One hundred twenty-one reports (93.1%) were serious, including 1 death. With approximately 13 209 858 doses of vaccine administered to adults in the US, the estimated crude reporting rate was 1 case of GBS per 100 000 doses administered. The overall estimated observed to expected rate ratio was 4.18 (95% CI, 3.47-4.98) for the 42-day window, and in the worst-case scenario analysis for adults 18 years or older, corresponded to an estimated absolute rate increase of 6.36 per 100 000 person-years (based on a rate of approximately 8.36 cases per 100 000 person years [123 cases per 1 472 162 person years] compared with a background rate of approximately 2 cases per 100 000 person years). For both risk windows, the observed to expected rate ratio was elevated in all age groups except individuals aged 18 through 29 years.

CONCLUSIONS AND RELEVANCE These findings suggest a potential small but statistically significant safety concern for Guillain-Barré syndrome following receipt of the Ad26.COV2.S vaccine. However, the findings are subject to the limitations of passive reporting systems and presumptive case definition, and they must be considered preliminary pending analysis of medical records to establish a definitive diagnosis.

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On February 27, 2021, the US Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for the Ad26.COV2.S (Janssen/Johnson & Johnson) COVID-19 vaccine,[1] followed by interim recommendations by the Advisory Committee on Immunization Practices.[2] The Ad26.COV2.S vaccine uses a replication-incompetent human adenoviral type 26 vector platform (Ad26.COV2.S) and is administered as a single intramuscular dose.[3] The FDA's EUA review focused on a randomized, double-blind, placebo-controlled trial; safety was assessed in 21 895 vaccine recipients and 21 888 individuals who received placebo.[4] In that study, there was one case of Guillain-Barré syndrome (GBS) after Ad26.COV2.S vaccination. A 60-year-old woman developed GBS 16 days after vaccination; she had experienced antecedent chills, nausea, diarrhea, and myalgia.[4] In the placebo group, there was 1 case 10 days after the injection.[4]

As part of postauthorization safety surveillance, the FDA reviews adverse events that have been reported after vaccination. The objective of the case series described herein was to review reports of GBS received in the Vaccine Adverse Event Reporting System (VAERS) following vaccination with the Ad26.COV2.S COVID-19 Vaccine and to assess whether the number of GBS reports associated with vaccination is greater than would be expected based on the background risk of GBS. Safety monitoring for the mRNA vaccines for COVID-19 is simultaneously being conducted, and results will be published elsewhere.

Key Points

Question In a passive reporting system, is there an association between receipt of the Ad26.COV2.S (Janssen/Johnson & Johnson) COVID-19 vaccine and development of Guillain-Barré syndrome (GBS)?

Findings Within the US Vaccine Adverse Event Reporting System (VAERS), 130 cases of presumptive GBS were reported from February 2021 to July 2021. The overall estimated observed to expected rate ratio was 4.18, corresponding to an absolute rate increase of 6.36 per 100 000 person-years.

Meaning These findings suggest a potential small but statistically significant safety concern for Guillain-Barré syndrome following receipt of the Ad26.COV2.S vaccine but are considered preliminary pending analysis of medical records to establish a definitive diagnosis.

Methods

This work was conducted as part of routine vaccine safety activities and public health surveillance. Data are deidentified and patient informed consent was not required.

VAERS is a national passive surveillance system for monitoring vaccine safety.[5,6] Established in 1990, VAERS is jointly managed by the FDA, and the Centers for Disease Control and Prevention (CDC) and, since 2015, has received more than 50 000 reports per year. Reports are submitted by clinicians, vaccine recipients or their parents or guardians, vaccine manufacturers, and other interested parties. FDA physicians review all reports of serious events, defined as events that are fatal, disabling, or life-threatening; require or prolong hospitalization; result in congenital anomalies; require medical intervention to prevent such outcomes; or are deemed to be other medically important conditions.[7]

Exposure

VAERS was searched for US reports received from February 27, 2021, through July 24, 2021, stating that the patient had received the Ad26.COV2.S COVID-19 Vaccine. The comparator was the background rate of GBS in the general (unvaccinated) population that had been estimated and published based on a standardized case definition.

Outcome

Reports of possible GBS were identified by 2 complementary methods: daily review of serious reports by an FDA physician and by an automated query of VAERS for Medical Dictionary for Regulatory Activities preferred terms: *acute polyneuropathy*, *autoimmune neuropathy*, *axonal and demyelinating polyneuropathy*, *demyelinating polyneuropathy*, *Guillain Barré syndrome*, and *Miller Fisher syndrome*. Reports with any of these terms were identified as cases of potential GBS and then individually reviewed by a clinician. Any available medical records were also reviewed.

Cases were retained as presumptive GBS, based on the presence of any combination of the following: clinical signs and symptoms (eg, ascending weakness or paralysis, hyporeflexia or areflexia, and paresthesia), diagnostic testing (eg, nerve conduction studies or electromyography), treatment (eg, intravenous immunoglobulin and/or plasmapheresis), or a physician's diagnosis or impression of GBS. Reports in which clinicians stated that the patient did not have GBS were eliminated from further review. Duplicates were consolidated.

Demographics, clinical characteristics, concomitant exposures, and relevant medical history were reviewed and summarized (**Table 1**). The onset time from vaccination to the initial signs or symptoms of presumptive GBS was noted. Cases were retained regardless of onset time, provided that the clinical presentation was consistent with GBS. Because medical record acquisition is delayed due to the pandemic, many reports lacked sufficient documentation for us to assess the cases using the Brighton Collaboration criteria for GBS at this time.[8] When available, medical records were reviewed to support the categorization of cases as presumptive GBS, and to evaluate relevant characteristics (eg, weakness, areflexia, cerebrospinal fluid, electromyography) when such information was present.

Statistical Analyses

The reporting rate was estimated and observed to expected (O/E) analyses were performed, stratified by age, using vaccine administration data[9] and published background rates,[10-12] for the 42-day and 21-day risk windows; only cases with onset in those windows were included in the O/E analyses. The O/E analyses consisted of comparison of the observed number of cases from spontaneous reporting to the expected

Table 1. Demographics of Patients and Characteristics of Guillain-Barré Syndrome Reports After the Ad26.COV2.S COVID-19 Vaccination (N = 130)

Demographic and report characteristics	No. (%)
Age, y[a]	
No.	129
Median (IQR)	56 (45-62)
18-64	111 (86.0)
≥65	18 (14.0)
Sex[b]	
Men	77 (59.7)
Women	52 (40.3)
Seriousness[c]	
Hospitalized	122 (93.8)
Life-threatening condition	46 (35.4)
Permanent disability	42 (32.3)
Died	1 (0.8)
Relevant medical history	
Recent illness (eg, upper respiratory infection, flu-like symptoms, gastroenteritis)	10 (7.7)
Neuropathologic past medical history[d]	9 (6.9)
Time to onset of presumptive GBS, d[e]	
No.	129
Median (IQR)	13 (10-18)
≤21 d after vaccination	105 (81.4)
≤42 d after vaccination	123 (95.3)
Reported complications of GBS	
Respiratory compromise or failure (eg, patient required endotracheal intubation and/or mechanical ventilation)	18 (13.8)
Dysautonomia/hemodynamic instability (eg, labile blood pressure or pulse)	4 (3.1)
Recovered[f]	
Yes	15 (13.8)
No	94 (86.2)

Abbreviation: GBS, Guillain-Barré syndrome.

[a] For 1 person, age was unknown.

[b] For 1 person, sex was unknown.

[c] Death, life-threatening condition, hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity, or congenital anomaly or birth defect.[7] These designations are defined by the reporter's input. Serious criteria are not mutually exclusive.

[d] For details about relevant comorbidities, please see the Results section.

[e] For 1 person, symptom onset time was unknown. For 6 people, the onset time was more than 42 days: 62, 70, 75, 85, 89, or 94 days after vaccination.

[f] For 21 people, recovery status was unknown.

number of cases based on published background rates. GBS background rates were derived from the work of Sejvar et al,[12] who conducted a meta-analysis of 13 studies in the US and Europe and estimated the mean GBS background rate per 100 000 person-years as a function of age group as exp [−12.0771 + 0.01813 (age in years)] × 100 000, where age was the midpoint of the age group (eg, for the age group of 20-29 years, the midpoint age was 25 years). Thus, for our analyses, for the age group of 18 years or older (assumed age, 18-89 years), the respective rate was estimated as 1.51 per 100 000 person-years; for the age group of 18 to 65 years, the respective rate was estimated as 1.22 per 100 000 person-years; for the age group of 65 years or older (assumed age, 65-89 years), the respective rate was estimated as 2.34 per 100 000 person-years. Additionally, alternative background rates[10,11] were used to illustrate other scenarios: 2 per 100 000 person-years for the age group of 18 to 65 years, and 2.4 per 100 000 person-years for the age group of 65 years or older. A sensitivity analysis was also performed to estimate the O/E based on the assumption that 80% of the reports can ultimately be determined to meet Brighton Collaboration criteria for GBS.[8]

For the 2 risk windows, the person-time at risk for the different age groups was calculated based on the cumulative vaccine administration data per age group (where age was reported), and the available weekly vaccine administration data (any age; **Table 2** and the **Figure**). Approximately 93% of the vaccine doses were administered at least 6 weeks (42 days) prior to the data cutoff date, approximately 2% were administered 5 weeks (35 days) before; 1.5%, 4 weeks (28 days) before; 1.5%, 3 weeks (21 days) before; 1%, 2 weeks (14 days) before; and 1%, 1 week (7 days) before the data cutoff date. For the 42-day and 21-day windows, respectively, the calculations were as follows:

$$\text{person-years (42-day risk window)} = N \times (0.93 \times 42 + 0.02 \times 35 + 0.015 \times 28 + 0.015 \times 21 + 0.01 \times 14 + 0.01 \times 7)/365.25;$$

$$\text{person-years (21-day risk window)} = N \times (0.98 \times 21 + 0.01 \times 14 + 0.01 \times 7)/365.25,$$

where N was the number of vaccine doses administered.

The expected number of cases was calculated as (person-years) × (background rate/100 000), where person-years was

Table 2. Vaccine Administration Data by Week, as of July 26, 2021[a]

Week beginning, 2021	No. of vaccine doses administered
January	
3	228
10	251
17	211
24	180
31	860
February	
7	668
14	745
21	1173
28	364 945
March	
7	1 540 197
14	953 854
21	713 053
28	1 222 508
April	
4	3 052 249
11	651 459
18	9769
25	368 112
May	
2	613 635
9	541 402
16	591 815
23	472 794
30	351 770
June	
6	353 959
13	315 446
20	253 606
27	201 011
July	
4	191 786
11	161 191
18	132 389

[a] The data are updated weekly and are subject to delay.[9]

the accumulated person-time in years and the background rate was the background rate per 100 000 person-years. The respective rate ratio (RR) was then estimated as the number of cases reported (observed) divided by the expected number of cases. The 95% CIs (ie, assuming a 2-sided type I error of 0.05) for the RRs for different age groups were provided. These were based on the exact CIs for the number of observed cases, assumed to be a Poisson random variable and were given as ($\frac{1}{2}\chi^2_{2c;a/2}$,$\frac{1}{2}\chi^2_{2(c+1);\,1-a/2}$) where c was the observed number of cases, $\chi^2_{2c;a/2}$ was the a/-2th quantile of the χ^2 distribution with $2c$ degrees of freedom.[13] The respective CI for the RR was derived by dividing the above CI's limits by the expected number of cases. No adjustment of the type I error for multiple testing was conducted. The calculations were done in R (version 3.6.1).

Results

As of July 24, 2021, the FDA identified 130 reports of presumptive GBS after Ad26.COV2.S vaccination (Table 1). There was a male predominance, and most affected individuals were younger than 65 years. Most cases began within 21 days after vaccination, and nearly all began within 42 days. There was no geographical clustering of reports. Cases of presumptive GBS that began after 42 days or had an unknown onset time, but were otherwise consistent with GBS, were retained in the summaries of demographic and clinical characteristics, but were not included in the O/E analyses. The majority of cases 122 (93.8%) were serious[7] (Table 1).

Ten reports (7.7%) mentioned a recent illness, such an upper respiratory infection, generalized rash, gastroenteritis, or flu-like symptoms, but they did not specifically mention *Campylobacter*. Nine reports (6.9%) described potentially relevant comorbidities or past medical history, such as chronic compression fractures in the thoracic spine, chronic neuropathy, deficiency of vitamins B_{12} and D, remitting and relapsing multiple sclerosis, significant degenerative disease in the spine, static encephalopathy and epilepsy, traumatic brain injury, history of GBS after yellow fever vaccine, or remote history of transverse myelitis. No reports listed concomitant vaccines.

One death was reported. A 57-year-old man developed pain and weakness within a week following vaccination. He was hospitalized, including 6 days on a ventilator. He completed a course of intravenous immunoglobulin but died 25 days after vaccination.

From the date of the EUA[1] through July 26, 2021, approximately 13 209 858 doses of the Ad26.COV2.S vaccine were administered to adults in the US (**Table 3**).

The crude reporting rate for presumptive GBS was 9.84 per million doses administered or approximately 1 per 100 000. Except for adults aged 18 through 29 years, O/E analyses across age groups, using different background rates, indicated elevated RRs for both the 21-day and 42-day risk windows (Table 3). Overall, the RR of the O/E was 4.18 (95% CI, 3.47-4.98) for the 42-day risk window.

In most strata, the lower bound of the 95% CI was greater than 2.0. In Table 3, the results using the highest published background rates for each age group were used (representing a conservative estimate of the potential association with the vaccine). To illustrate other potential scenarios, the O/E results using different background rates are shown in **Table 4**. Additionally, a sensitivity analysis was conducted assuming that only 80% of cases are confirmed as GBS. The O/E estimates for the 21-day and 42-day risk windows remained elevated in most age strata (**Table 5**).

In the worst-case scenario for adults 18 years or older, the reporting rate based on numbers in Table 3 was estimated to be approximately 8.36 per 100 000 person-years (123 per 1 472 162), compared with the background rate of 2 per 100 000 person-years, ie, an absolute rate increase of 6.36 per 100 000 person-years.

Figure. Vaccine Administration Data

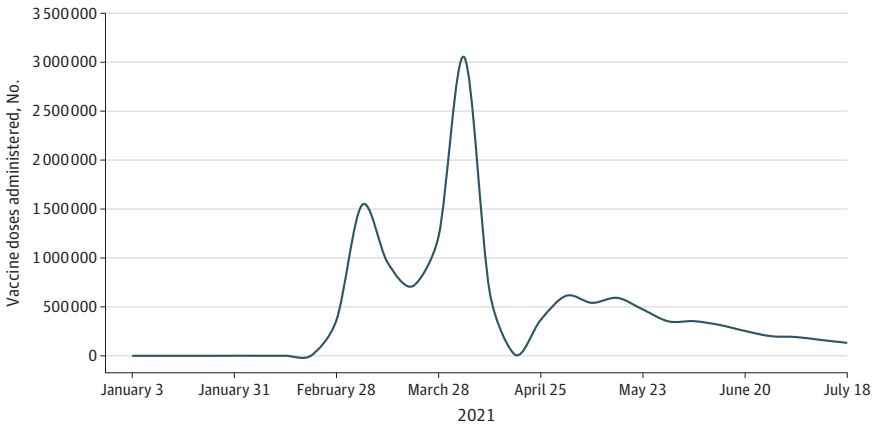

Table 3. Observed to Expected Analysis of Guillain-Barré Syndrome After the Ad26.COV2.S COVID-19 Vaccine[a]

Age groups, y	No.[b]	Vaccine doses administered[c]	Person-years[c]	Background rate per 100 000 person-years	Expected cases	Rate ratio (95% CI)
Onset within 21 days after vaccination						
All (≥18)	105	13 209 858	751 904	2	15.0	6.98 (5.71-8.45)
18-<65	91	11 169 018	635 740	2	12.7	7.16 (5.76-8.78)
18-29	3	2 388 973	135 980	0.88	1.2	2.51 (0.52-7.33)
30-39	10	2 277 609	129 641	1.07	1.4	7.21 (3.46-13.26)
40-49	22	2 345 471	133 504	1.29	1.7	12.77 (8.01-19.34)
50-64	56	4 156 965	236 614	2	4.7	11.83 (8.94-15.37)
≥65	14	2 040 840	116 164	2.4	2.8	5.02 (2.74-8.43)
Onset within 42 days after vaccination						
All (≥18)	123	13 209 858	1 472 162	2	29.4	4.18 (3.47-4.98)
18-<65	105	11 169 018	1 244 722	2	24.9	4.22 (3.45-5.11)
18-29	4	2 388 973	266 237	0.88	2.3	1.70 (0.47-4.37)
30-39	12	2 277 609	253 826	1.07	2.7	4.42 (2.28-7.72)
40-49	25	2 345 471	261 389	1.29	3.4	7.41 (4.80-10.94)
50-64	64	4 156 965	463 270	2	9.3	6.91 (5.32-8.82)
≥65	18	2 040 840	227 440	2.4	5.5	3.30 (1.95-5.21)

[a] In this table, the results using the highest published background rates for each age group were used to illustrate the lowest observed to expected ratio, representing the most conservative estimate of the potential association with the vaccine.

[b] Reports with missing age, missing onset, or onset after 42 days are not included in these calculations. One report had missing age, sex, and onset information but was still deemed a valid report of Guillain-Barré syndrome. For 6 people, the onset time was more than 42 days: 62, 70, 75, 85, 89, or 94 days after vaccination.

[c] Cumulative Vaccine Administration Data.[9] Please see the Methods section. Age-specific dose administration data were obtained from the Centers for Disease Control and Prevention and are shown with permission (F. Lee, MPH, statistician, Centers for Disease Control and Prevention, email September 3, 2021).

Discussion

These findings suggest a potential small but statistically significant safety concern for GBS following receipt of the Ad26.COV2.S vaccine. However, the findings are subject to the limitations of passive reporting systems and presumptive case definition, and they must be considered preliminary pending analysis of medical records to establish a definitive diagnosis.

GBS is a rare, immune-mediated polyneuropathy leading to muscle weakness and paralysis.[10] The condition is thought to result from an aberrant immune response in which antibodies cross-react with peripheral nerve proteins after an exposure or event.[10] Diagnosis is based on clinical features, cerebrospinal fluid testing, and nerve conduction studies.[10,11] The incidence of GBS is approximately 1 to 2 cases per 100 000 person-years.[10,11] The incidence increases by about 20% for every 10-year age increment, and men are almost twice as likely to be affected as women.[10] A respiratory or

Table 4. Observed to Expected Analysis of Guillain-Barré Syndrome After the Ad26.COV2.S COVID-19 Vaccine, Based on Different Background Rates for Selected Age Groups[a]

Age groups, y	No.[b]	Vaccine doses administered[c]	Person-years[c]	Background rate per 100 000 person-years	Expected cases	Rate ratio (95% CI)
Onset within 21 days after vaccination						
All (≥18)	105	13 209 858	751 904	1.51	11.4	9.25 (7.56-11.20)
All (≥18)	105	13 209 858	751 904	2	15.0	6.98 (5.71-8.45)
18-<65	91	11 169 018	635 740	1.22	7.8	11.73 (9.45-14.41)
18-<65	91	11 169 018	635 740	2	12.7	7.16 (5.76-8.78)
18-29	3	2 388 973	135 980	0.88	1.2	2.51 (0.52-7.33)
30-39	10	2 277 609	129 641	1.07	1.4	7.21 (3.46-13.26)
40-49	22	2 345 471	133 504	1.29	1.7	12.77 (8.01-19.34)
50-64	56	4 156 965	236 614	1.63	3.9	14.52 (10.97-18.86)
50-64	56	4 156 965	236 614	2	4.7	11.83 (8.94-15.37)
≥65	14	2 040 840	116 164	2.34	2.7	5.15 (2.82-8.64)
≥65	14	2 040 840	116 164	2.4	2.8	5.02 (2.74-8.43)
Onset within 42 days after vaccination						
All (≥18)	123	13 209 858	1 472 162	1.51	22.2	5.53 (4.60-6.60)
All (≥18)	123	13 209 858	1 472 162	2	29.4	4.18 (3.47-4.98)
18-<65	105	11 169 018	1 244 722	1.22	15.2	6.91 (5.66-8.37)
18-<65	105	11 169 018	1 244 722	2	24.9	4.22 (3.45-5.11)
18-29	4	2 388 973	266 237	0.88	2.3	1.70 (0.47-4.37)
30-39	12	2 277 609	253 826	1.07	2.7	4.42 (2.28-7.72)
40-49	25	2 345 471	261 389	1.29	3.4	7.41 (4.80-10.94)
50-64	64	4 156 965	463 270	1.63	7.6	8.48 (6.53-10.82)
50-64	64	4 156 965	463 270	2	9.3	6.91 (5.32-8.82)
≥65	18	2 040 840	227 440	2.34	5.3	3.38 (2.00-5.35)
≥65	18	2 040 840	227 440	2.4	5.5	3.30 (1.95-5.21)

[a] In this table, different background rates were used to illustrate varying estimates of the observed to expected ratio (O/E). The lowest background rates correspond to higher estimates of O/E (ie, worst-case scenario for a potential association with the vaccine).

[b] Reports with missing age, missing onset, or onset more than 42 days are not included in these calculations. One report had missing age, sex, and onset information, but was still deemed a valid report of Guillain-Barré syndrome. For 6 people, the onset time was more than 42 days: 62, 70, 75, 85, 89, or 94 days after vaccination.

[c] Cumulative Vaccine Administration Data.[9] Please see the Methods section. Age-specific dose administration data were obtained from the CDC and are shown with permission (F. Lee, MPH, statistician, Centers for Disease Control and Prevention, email September 3, 2021).

gastrointestinal infection precedes approximately two-thirds of cases.[10]

The 1976 swine influenza vaccine was associated with GBS, including mortality of 6%,[14] but a causal association with other vaccines has not been established. As of June 27, 2021, more than 200 cases of GBS following receipt of the ChAdOx1 nCoV-19 (Oxford/AstraZeneca) COVID-19 vaccine had been reported to EudraVigilance, the adverse event reporting system for the European Union,[15] and GBS has been included as a warning in the package information.[16] The ChAdOx1 nCoV-19 vaccine, which uses a replication-incompetent chimpanzee adenoviral vector, is not authorized or licensed for use in the US at this time.

In this VAERS review, O/E analyses across age groups and different background rates demonstrated an elevated RR for both the 21-day and 42-day risk windows. Although these cases have not yet been adjudicated based on the Brighton Collaboration case definition,[8] even if 20% of cases are excluded, the sensitivity analysis suggests that the risk would remain elevated. However, the absolute risk of GBS, both in the background population (≈2 per 100 000), and following Ad26.COV2.S vaccination (130 reports per ≈13 million vaccinations), is extremely small and far lower than the risk of COVID-19, which as of August 31, 2021, has led to 39 428 972 cases in the US, including 647 492 deaths.[9]

Strengths

Strengths of VAERS include its national scope, size, timeliness, ability to detect events that were not observed during prelicensure trials, and surveillance among special populations.[5] The FDA and CDC are also conducting active surveillance with large-scale population-based studies, using claims data or electronic health care record data. The population-based data sources include the FDA Biologics Effectiveness and Safety System,[17] the Centers for Medicare & Medicaid Services databases,[18] and the CDC Vaccine Safety Datalink.[19] Under the EUA,[1] the manufacturer is also required to conduct postauthorization observational safety studies. The FDA is conducting continuous safety monitoring for adverse events after all vaccines, including the Ad26.COV2.S COVID-19 Vaccine.

Table 5. Sensitivity Analysis: Observed to Expected Analysis of Guillain-Barré Syndrome After the Ad26.COV2.S COVID-19 Vaccine, Assuming That 80% of Cases Are Ultimately Confirmed Based on Brighton Collaboration Criteria[8]

Age groups, y	No.[a]	Vaccine doses administered[b]	Person-years[b]	Background rate per 100 000 person-years	Expected cases	Rate ratio (95% CI)
Onset within 21 days after vaccination						
All (≥18)	84	13 209 858	751 904	1.51	11.4	7.40 (5.90-9.16)
All (≥18)	84	13 209 858	751 904	2	15.0	5.59 (4.46-6.92)
18-<65	73	11 169 018	635 740	1.22	7.8	9.41 (7.38-11.83)
18-<65	73	11 169 018	635 740	2	12.7	5.74 (4.50-7.22)
18-29	2	2 388 973	135 980	0.88	1.2	1.67 (0.20-6.04)
30-39	8	2 277 609	129 641	1.07	1.4	5.77 (2.49-11.36)
40-49	18	2 345 471	133 504	1.29	1.7	10.45 (6.19-16.52)
50-64	45	4 156 965	236 614	1.63	3.9	11.67 (8.51-15.61)
50-64	45	4 156 965	236 614	2	4.7	9.51 (6.94-12.72)
≥65	11	2 040 840	116 164	2.34	2.7	4.05 (2.02-7.24)
≥65	11	2 040 840	116 164	2.4	2.8	3.95 (1.97-7.06)
Onset within 42 days after vaccination						
All (≥18)	98	13 209 858	1 472 162	1.51	22.2	4.41 (3.58-5.37)
All (≥18)	98	13 209 858	1 472 162	2	29.4	3.33 (2.70-4.06)
18-<65	84	11 169 018	1 244 722	1.22	15.2	5.53 (4.41-6.85)
18-<65	84	11 169 018	1 244 722	2	24.9	3.37 (2.69-4.18)
18-29	3	2 388 973	266 237	0.88	2.3	1.28 (0.26-3.74)
30-39	10	2 277 609	253 826	1.07	2.7	3.68 (1.77-6.77)
40-49	20	2 345 471	261 389	1.29	3.4	5.93 (3.62-9.16)
50-64	51	4 156 965	463 270	1.63	7.6	6.75 (5.03-8.88)
50-64	51	4 156 965	463 270	2	9.3	5.50 (4.10-7.24)
≥65	14	2 040 840	227 440	2.34	5.3	2.63 (1.44-4.41)
≥65	14	2 040 840	227 440	2.4	5.5	2.56 (1.40-4.30)

[a] Reports with missing age, missing onset, or onset more than 42 days are not included in these calculations. One report had missing age, sex, and onset information, but was still deemed a valid report of Guillain-Barré syndrome. For 6 people, the onset time was more than 42 days: 62, 70, 75, 85, 89, or 94 days after vaccination.

[b] Cumulative Vaccine Administration Data.[9] Please see the Methods section. Age-specific dose administration data were obtained from the Centers for Disease Control and Prevention and are shown with permission (F. Lee, MPH, statistician, Centers for Disease Control and Prevention, email September 3, 2021).

Limitations

This study has several limitations. First, although the EUA for this vaccine[1] stipulated mandatory reporting requirements for the manufacturer and clinicians, passive surveillance systems such as VAERS are subject to underreporting and lack of direct and unbiased comparison groups.[5,6] Spontaneous reports may contain incomplete information. Because of these and other limitations, it is usually not possible to verify causal associations between vaccines and adverse events from spontaneous reports to VAERS. Second, this preliminary case series analysis does not include medical record review for assessment with respect to the Brighton Collaboration criteria.[8] Many reports described ascending weakness or paralysis, hyporeflexia or areflexia, paresthesia, nerve conduction studies, electromyography, treatment with intravenous immunoglobulin and/or plasmapheresis, and a time course consistent with GBS. In some cases, a physician listed a diagnosis of GBS or stated that the history and clinical presentation represented probable GBS. Nevertheless, the analysis was constrained by the information available in the initial VAERS reports and limited medical documentation available to date. Additional medical record collection, review, and analyses to determine whether the cases meet the Brighton Collaboration criteria for GBS[8] are in progress. Third, these preliminary analyses compared the observed GBS rates with expected rates that were calculated based on background rates reported in the literature. This approach assumes that the vaccinated population is subject to the same background rate as in the population that was assessed in the literature.[10-12] Fourth, the O/E analyses were stratified by age but not sex. Since the baseline risk of GBS is higher for males than females,[10] future analyses should account for this difference. Fifth, the analyses were not adjusted for multiple testing and are subject to type I error.

Conclusions

These findings suggest a potential small but statistically significant safety concern for Guillain-Barré syndrome following receipt of the Ad26.COV2.S vaccine. However, the findings are subject to the limitations of passive reporting systems and presumptive case definition, and they must be considered preliminary pending analysis of medical records to establish a definitive diagnosis.

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