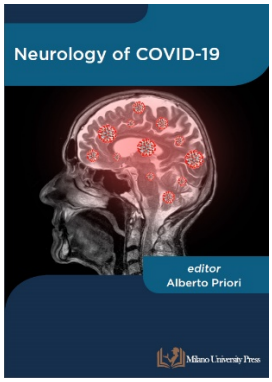

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Chapter 17.
Neurological complications of vaccines for COVID-19

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Chapter 17. Neurological complications of vaccines for COVID-19

Laura Bertolasi, Maria Donata Benedetti

On January 30 2020, the World Health Organization (WHO) declared the outbreak of the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (COVID-19) a public health emergency of international concern, reaching a pandemic status on March 11 2020[1]. In less than 12 months, several research teams rapidly developed candidate vaccines to prevent COVID-19, assessing their efficacy and safety in phases I, II, and, later, in phase III clinical trials[2-10]. Pfizer-BioNTech COVID-19, Moderna COVID-19, and J&J/Janssen COVID-19 vaccines were authorized for emergency use in rapid succession in the US (Food and Drug Administration [FDA]: December 11 2020[11], December 18 2020[12], and February 27 2021[13], respectively) and in Europe (European Medicines Agency [EMA]: December 21 2020[14], January 6 2021[15], and March 11 2021[16]), where a fourth vaccine, AstraZeneca COVID-19, was also authorized on January 29 2021[17]. The WHO recently authorized two vaccines developed in China: Sinopharm COVID-19[18] and Sinovac COVID-19[19]; authorization by the FDA and the EMA is still awaited. Overall, more than 100 candidate vaccines are currently under clinical development, while another three vaccines have been authorized and are used in several parts of the world (Sputnik V, Russia[20,21]; CanSino, China; Bharat Biotech, India[22]). As of June 18 2021, the worldwide cumulative number of COVID-19 cases was 177,108,695, the cumulative deaths 3,840,223, and a total of 2,378,482,776 vaccine doses had been administered worldwide[23]. Currently authorized COVID-19 vaccines are summarized in Table 17.1.

Despite the urgency related to the pandemic state, the safety profiles of candidate vaccine resulting from available clinical trials and all documents and product information submitted by companies, were rigorously and thoroughly evaluated by the WHO and regulatory agencies before authorization[24]. Nevertheless, clinical trials have a limited follow-up time and insufficient power to detect rare adverse events (AEs), or those occurring at a later time, or those emerging after large populations have been vaccinated. Post-marketing safety surveillance and monitoring allow recommendations and advice to be updated and modified.

Table 17.1: The anti-COVID-19 vaccines

Characteristics	Pfizer/BioNTech Vaccine	Moderna Vaccine	Astra-Zeneca Vaxzevria	Jonson & Jonson jNJ-78436735	Sputnik V	Sinopharm	Sinovach Biotech
Type of vaccine	mRNA (BNT 162b2)	mRNA (1273)	Chimpanzee Recombinant adenovirus vectored	Human Recombinant viral vector	Recombinant viral vector (2 different viruses)	Human inactivated coronavirus	Chimpanzee inactivated virus
Approval	Emergency authorization Dec 11, 2020 FDA	Emergency authorization Dec 18, 2020 FDA	Emergency authorization Jan 29, 2021 EMA	Emergency authorization March 12, 2021 EMA	Under evaluation	Under evaluation	Under evaluation
Number of injections	2 shots, 21 days apart	2 shots, 28 days apart	2 shots, 28 days apart	1 shots	2 shots, 21 days apart	2 shots, 21 days apart	2 shots, 21 days apart
Age group for vaccination	16 yrs and older	18 yrs and older	Recommended 60 yrs and older	18 yrs and older			
Effectiveness	95%	94%	62%-90%	77%-85%	91.4%	79.34%	78%
Mechanism of action	Elicits immune response to the S antigen	Elicits immune response to the S antigen	Elicits the immune response to the virus	Elicits the immune response to the virus	Elicits the immune response to the virus	Elicits the immune response to the virus	Elicits the immune response to the virus

Safety definitions

According to the WHO criteria for causality assessment, an AE following immunization (AEFI) is any untoward medical occurrence which follows vaccination and which does not necessarily have a causal relationship with the usage of the vaccine[25]. The AE may be any unfavorable or unintended sign, abnormal laboratory finding, symptom or disease. Serious adverse events (SAE) are untoward events that at any dose result in death, are life-threatening, require hospitalization or prolongation of existing hospitalization, or result in persistent or significant disability/incapacity or birth defect, or AEs requiring medical attention, or leading to withdrawal from the trial. The AE

severity grading scale ranges from grade 1 (mild), grade 2 (moderate), and grade 3 (severe), to grade 4 (life-threatening). Reactogenicity is evaluated in terms of solicited local (injection site pain / tenderness / swelling) and systemic (fatigue, headache, myalgia, nausea, fever) AEs during the 7 days after vaccination, and unsolicited AEs over the 28 days post vaccination. AEs are further classified as AEs of Special Interest (AESI) or according to MedDRA (Medical Dictionary for Regulatory Activities) by system organ classes (SOC), e.g., nervous system disorders. Finally, investigators, independent committees of neurological experts, and regulatory agencies evaluated whether it is plausible that the reported AEs are or are not related to the vaccine under study. For the purpose of this discussion, AEs were searched in published trials and Supplementary Appendices, and FDA and EMA assessment reports.

Neurological complications of COVID-19 vaccines in clinical trials

1. BNT162b2 COVID-19 mRNA-based vaccine

The safety and efficacy of the BNT162b2 candidate vaccine (Pfizer and BioNTech) were assessed in phase I and II/III randomized, placebo-controlled clinical trials[2,7], where local and systemic events were generally milder in older than in younger participants and were greater after the second than after the first dose. The phase III trial enrolled 43,448 subjects aged 16 years and over from July to November 2020, randomized to receive BNT162b2 (n=21,720) or placebo (n=21,728) two doses, 21 days apart[7]. The safety population, followed for a median of 2 months after the second dose, included 37,706 subjects, median age 52 years, while reactogenicity was evaluated in a subgroup of 8,183 subjects. Related AEs were reported more frequently in vaccine recipients (20.7%) than in placebo (5.1%), largely due to reactogenicity events during the 7 days after vaccination. Among them, headache was reported more often after the second dose (52% vs 24% in placebo [16-55 years], and 39% vs 14% in placebo [>55 years]) than after the first dose (42% vs 34% in placebo [16-55 years], and 25% vs 18% in placebo [>55 years]). No severe AEs/SAEs of neurological interest occurred in the safety population. The investigators concluded that no deaths were to be considered to be related to the study interventions. In the FDA and EMA assessment reports (not in the published paper[7]), four cases of Bell's palsy were reported in the vaccine arm versus 0 in placebo, three occurring 3, 9 and 48 days after dose 2, and one 37 days after dose 1; the study investigators considered all four to be related to vaccination[11,14]. Sleep disturbances (insomnia/sleep disorder/abnormal dreams) were more frequent in the vaccine than in the placebo arm, possibly due to local/systemic reactogenicity[11,14]. Overall, systemic reactions

were transient and of short duration, mostly of mild or moderate intensity, and reported more often by younger subjects. The frequency of severe AEs, SAEs and AEs leading to trial discontinuation was low and equally distributed in both study arms.

Comment: the efficacy of Pfizer-BioNTech COVID-19 vaccine (Comirnaty in Europe) was considered high (95%) and the observed safety profile favorable, with a positive benefit-risk balance. The frequency of Bell's palsy in the vaccine group was consistent with the expected rate in the general population[11], with a possible relation to the vaccine[14]. Surveillance for cases of Bell's palsy and allergic (anaphylactic) reactions with deployment of the vaccine into larger populations was recommended.

2. mRNA-1273 MODERNA COVID-19 -based vaccine

This vaccine was evaluated in two small phase I studies[3,4] and in a large phase III, placebo-controlled clinical trial enrolling 30,420 subjects between July 2020 and October 2020, randomized to receive mRNA-1273 (n=15,185) two doses, 28 days apart, or placebo (n=15,166)[8]. The median follow-up after the second injection was 63 days; 25% of participants were ≥65 years of age. Reactogenicity was pronounced for both local and systemic adverse reactions, in particular after the second dose of vaccine, with mostly mild or moderate transient events[12,15]. Headache was more frequently reported in younger than in older persons, and after the second dose: 65.8% versus 25.3% in placebo (18-64 years) and 46.2% versus 17.5% in placebo (≥65 years), than after the first dose: 35.3% versus 29% in placebo (18-64 years) and 24.5% versus 19.3% in placebo (≥65 years). Unsolicited nervous system disorders during the 28 days after vaccination were reported by 4.5% in the vaccine arm (3.1% headache) and 4.1% in the placebo group (3% headache) (Supplementary Appendix: Tables S9-S11)[8]. Moreover, three cases of Bell's palsy were observed in the mRNA-group compared to one case in the placebo group, with timing suggesting a possible causal relationship to vaccination[15]. Treatment-related sensory disturbances (paresthesia, hypoesthesia, hyperesthesia) were more frequent in the vaccine than in the placebo arm (20 vs 7) as well as sleep disorders (insomnia abnormal dreams, nightmare) (30 vs 15). Finally, in vaccine recipients, three SAEs of cerebrovascular accident (1 placebo), 2 SAEs of embolic stroke (none in the placebo group), and 1 SAE of transient ischemic attack (none in the placebo group) were reported; the investigators did not consider any of them to be related to vaccination.

Comments: the efficacy of mRNA-1273 MODERNA COVID-19-based vaccine was high, and the safety profile was favorable, although this vaccine appeared more reactogenic than many of the standard vaccines in use. As for the COVID-19 vaccines, long-term safety data, interaction with other

vaccines, data on use in pregnancy and other subgroups require updates and surveillance for AEs[26].

3. ChAdOx1 nCoV-19 vaccine (AZD1222)

The safety and efficacy of the AstraZeneca COVID-19 vaccine, now called Vaxzevira, were evaluated in a phase I/II trial[5] and in the pooled interim analysis of four ongoing randomized, blinded, controlled trials carried out across the UK, Brazil, and South Africa between April 23 and Nov 4 2020[9]. The safety analysis included 23,745 participants randomly assigned to receive two doses of AZD1222 (n=12,021) or vaccine/placebo (n=11,724). Overall, in the safety population, 91.1% were aged 18-64 years, 8.9% were 65 years or over, 55.8% were female. The median follow-up from the first dose was 105 days in the AZD1222 treatment and 104 days in the control groups. Local and systemic AEs, generally mild or moderate, were reported more frequently in AZD1222 than in controls, and after the first dose than after the second. Headache was the second most frequently reported solicited systemic AE (57.5% vs 42.4% in control) after fatigue (62.3% vs 48% in control)[17], while among the unsolicited AEs, the frequency of nervous system disorders was higher in the vaccine group (9.3%, mostly of grade 1-2) than in controls (5.5%), including headache, lethargy, migraines, somnolence, dizzines[17]. In the category of AESI, five 'potential immune mediated conditions-neuroinflammatory disorders' are reported in the AZD1222 group (three Bell's palsy, one transverse myelitis, one multiple sclerosis) and four in controls (three Bell's palsy, one myelitis), while 'other neurologic events' reported in both vaccinated and control groups, although with a very low frequency (range <0.1 - <0.5%) included paresthesia, hypoesthesia, muscular weakness, visual impairment, followed by sensory disturbance (sensory loss, dysesthesia, hyperesthesia), gait disturbance, neuralgia (Supplementary Appendix Table S7)[9]. Of the six cases of Bell's palsy, only one in the vaccine and one in the control group were considered to be at least possibly related to vaccination based on the timing. Again, among the seven SAEs of neurological interest in the vaccine recipients (facial spasm, ischemic stroke, migraine, multiple sclerosis, transverse myelitis, presyncope, serotonin syndrome; one case each), and the four in controls (myelitis, subarachnoid hemorrhage, syncope, transient ischemic attack; one case each) (Supplementary Appendix Table S6), only the case of transverse myelitis in the AZD1222 group was reported as being possibly related to vaccination, resulting in temporarily pausing the trial, while multiple sclerosis was considered unrelated to study treatment as the MRI showed new and pre-existent brain lesions[9]. One case in each group had generalized convulsion, while a case of neuritis and a case of peripheral neuropathy were reported in the AZD1222 group.

Comment: in this trial the subjects in the control group were administered Meningococcus ACWY vaccine or saline, which complicates the comparison of data[17]. Only 3 of 175 SAEs were considered to be related to the vaccine or control. Thrombotic and neurovascular events were more frequent in controls (8 cases) than in the AZD1222 group.

4. Ad26.COV2.S COVID-19 vaccine

Immunogenicity was studied in a very small phase I trial[6], while the safety and efficacy of a single dose of Ad26.COV2.S (Janssen/Johnson & Johnson) vaccine were evaluated in a multicenter, placebo-controlled, phase III trial, enrolling 43,783 subjects aged 18 years and over from September 2020 to January 2021, randomized to receive a single dose of either Ad26.COV2.S (n=21,895) or saline placebo (n=21,888)[10]. The median follow-up was 58 days (range 1- 124), 66.5% of subjects were aged 18-59 years, 33.5% were 60 years or over. In the safety population (3,356 vaccine recipients and 3,380 placebo recipients), systemic solicited AEs were more frequent in Ad26.COV2.S (55.2%) than in placebo recipients (35.1%), and in the class of study participants aged 18 to 59 years than in those aged 60 years or over. Headache was the most frequently reported solicited AE (39% vs 23.8% in placebo). Among 7 SAEs that the investigators considered to be related to vaccination, 4 were neurological disorders: two Bell's palsy, one brachial radiculitis, one Guillain–Barré syndrome versus 0 in control (Supplementary Appendix Tables S6 and S7)[10]. One case of Guillain-Barré syndrome and two cases of Bell's palsy in the placebo group, as well as another case of Bell's palsy in the vaccine group, were, however, considered to be unrelated. Moreover, four cases of headache in the vaccine group (vs 2 in control) and 1 syncope (vs 0 in control) were reported as AEs of grade ≥3 (Supplementary Appendix Table S6)[10]. One case of transverse sinus thrombosis with cerebral hemorrhage occurring 21 days after the vaccination in a male of 25 years of age was considered unrelated to vaccination; the patient recovered. Finally, six cases of tinnitus were reported in the vaccine arm and none in the placebo group, while seizures occurred in 4 vaccine recipients and 1 placebo recipient. The causal relationship between these events and the vaccine remains undetermined[10].

Comments: EMA recommendations were updated in April and June 2021 with evolving experience of thrombosis with thrombocytopenia syndrome (TTS) following vaccination with Vaxzevria and the Janssen COVID-19 vaccine in people under 60 years of age within three weeks after vaccination, the majority in women[27,28]. On April 23 2021, the FDA recommended resuming the use of the Janssen COVID-19 vaccine in the US after the pause determined by the reports of six cases of a rare and severe type of blood clot following administration[29].

5. Sinovac and Sinopharm inactivated vaccine against COVID-19

Safety, efficacy and immunogenicity data for WHO Sinovac-CoronaVac authorization[19] came from several trials of phase I/II in China[30,31] and ongoing phase III trials in Brazil[32], Turkey, Indonesia and Chile. In the available safety population (n=8,840) who received any dose/schedule of Sinovac, AEs were mild/moderate, and there was no imbalance between vaccine and control group in SAEs, all classified as unrelated/unlikely related to vaccine, or AEs grade 3+[19]. In older subjects, reactogenicity was lower compared to younger adults, while the safety profile was similar. Post-authorization, two neurological SAEs were reported in China (one cerebral hemorrhage and one demyelination) out of over 35.8 million doses[19]. Vaccine efficacy was evaluated to be 51% for symptomatic disease and 100% for severe disease and hospitalization[19]. The WHO authorized Sinopharm BBIBP-CorV COVID-19[18] after assessment of efficacy and safety reported in phase I/II trials in China[33] and an ongoing phase III trial in Bahrain, Egypt, Jordan, and the United Arab Emirates[34]. The available safety population included 16,671 participants who received any dose/schedule of BBIBP-CorV vaccine. Most AEs were mild to moderate, without any imbalance in the number of reported SAEs, AEs of special interest (neurological diseases) or grade 3+ AEs between the BBIBP-CorV and placebo groups. One SAE initially reported as being possibly linked to vaccination was inflammatory demyelination syndrome/acute disseminated encephalomyelitis, later not confirmed. In terms of quality of evidence, the WHO concluded, with a moderate level of confidence, that the risk of SAEs following one or two doses of BBIBP-CorV in adults (age 18-59 years) is low, while for older adults (age ≥60 years) the level of confidence was very low. Vaccine efficacy for symptomatic and hospitalized disease was estimated to be 79% in all age groups combined[18]. No AEs of neurological interest were reported in Sputnik V[20,21] and Covaxin[22] trials.

In summary, neurological AEs were extremely rare in clinical trials of COVID-19 vaccines, and vaccine-induced immune thrombotic thrombocytopenia (VITT) was observed only in a small number of persons receiving AZD1222 and Ad26.COV2.S. However, with mass vaccination, several hundred patients were reported with this syndrome, which is caused by platelet activation and subsequent stimulation of the coagulation system, resulting in thromboembolic complications, as discussed below.

Table 17.2: Neurological adverse events (AEs) in safety populations of trials of COVID-19 vaccines

Vaccine in trials	Randomized population	Safety Population and Safety Time	Headache after dose 1 Vaccine vs placebo/control	Headache after dose 2 Vaccine vs placebo/control	Neurologic SAEs Vaccine vs placebo/control	Neurologic AEs Vaccine vs placebo/control
mR-NA-BNT162b[27] Pfizer and BioNTech Phase II/III**7	N= 43,448	N=37,706 n= 18,860 BNT162b2 n= 18,846 placebo July 27-November 14, 2020 median ≥ 2 months after dose 2	42% vs 34% 16-55 yr 25% vs 18% >55 ys	52% vs 24% 16-55 yr 39% vs 14% >55 ys	0	4 Bell's palsy vs 0 *related* sleep disturbances more frequent in vaccine arm
mRNA-127[38] MODERNA Phase III8	N= 30,420	N = 30,351 n= 15,185 mRNA-1273 n= 15,166 placebo July - November 2020 median 63 days after dose 2	35.% vs 29% 18-64 yr 24.5% vs 19% ≥65 yr	66% vs 25% 18-64 yr 46.% vs 17.5% ≥65 yr	16 vs 10 *not related**	3 Bell's palsy vs 1 *related* sleep disorders 30 vs 15 sensory disturbances 20 vs 7
AstraZeneca[9] (AZD1222) Phase I/II/III (4 RCT pooled)[9]	N= 23,848	N=23,745 n= 12,021 AZD1222 n= 11,724 vaccine/ placebo April - November 2020 median 3.4 months	54.4% vs 38.1%	32.6% vs 25%	1 transverse myelitis vs 0 *related*§ 7 vs 4§§	1 Bell's palsy vs 1 *related* 1 seizures vs 1 1 peripheral neuropathy and 1 neuritis vs 0
Janssen Vaccine[10] (Johnson &Johnson) Ad26. COV2.S Phase III10	N= 43,783	N=6736 n= 3356 Ad26. COV2.S n= 3380 placebo September 2020-January 2021	39% vs 23.8%	-	2 Bell's palsy, 1 Guillain-Barré syndrome, 1 brachial radiculitis *related* 1 transverse sinus thrombosis *not related*	1 Bell's palsy vs 2 *not related* - 1 Guillain-Barré syndrome in placebo *not related* - 6 tinnitus vs 0 and 4 seizures vs 1 *undetermined*

Sinopharm[31] BBIBP-CorV Phase III interim analysis	N= 40,382	n= 13,459 vaccine 1 n= 13,465 vaccine 2 n= 13,458 control median 77 days (1-121)	12.9% vs 13.1% vs 12.6%		1 Acute disseminated encephalomyelitis, 1 Clinically Isolated Syndrome in vaccine 2 *related*°	
Sinovac# CoronaVac Phase III (submitted)	N= 12,396	n= 8,840 n= 6,195 (vaccine) n= 6,201 (placebo) median 77 days	31.4% vs 32.2%	24.7% vs 24.2%	1 transient ischemic attack *not related*	oral paresthesia 5 vs 1
COVAXIN[22] Bharat Biotech India Phase II trial^^	N= 380	n=190 3 μg n=190 6 μg September 5-12, 2020	1% 1%	1% 1%	0	0
Gam-COVID-Vac[20] (Sputnik V) Phase III^	N= 21,977	N= 12,296 n= 14,964 vaccine n= 4902 placebo September-November 2020	2.9% vs 2.6% in those >60 yr (not stated after which dose)		1 vestibular ataxia, 1 syncope vs 0, 1 Multiple Sclerosis recurrence in placebo *not related*	3 metallic taste vs 0 1 paresthesia vs 1

*3 Serious adverse events (SAEs) of cerebrovascular accident (1 in placebo), 2 SAEs of embolic stroke (none in placebo), and 1 SAE of transient ischemic attack (none in placebo).

** Headache was analyzed in 8,183 participants (reactogenicity subset).

§One case of transverse myelitis 14 days after AZD1222 vaccination was judged to be related (the most likely diagnosis to be of an idiopathic, short segment, spinal cord demyelination), resulting in temporarily pausing the trial. The other case of transverse myelitis 10 days after AZD1222 vaccination, initially considered to be related, was later judged as pre-existing, but previously unrecognised, multiple sclerosis. The transverse myelitis in control was judged to be unrelated.

§§ Seven cases in vaccine recipients: facial spasm, ischemic stroke, migraine, multiple sclerosis, transverse myelitis (related), presyncope, serotonin syndrome (one each); 4 cases in controls: myelitis, SAE, syncope, transient ischemic attack. All considered unrelated (multiple sclerosis was considered unrelated to study treatment as the MRI showed new and pre-existent brain lesions).

° From Supplementary Appendix Table 8S: in the text it was instead specified that a man aged 30 years was diagnosed with possible demyelinating myelitis after receiving the first dose, but later pathophysiological tests excluded the possibility of multiple sclerosis and identified that the man was heterozygous for very long-chain acyl-CoA dehydrogenase deficiency variant.

Palacios Ricardo et al.[32] Efficacy and safety of a COVID-19 inactivated vaccine in healthcare 2 professionals in Brazil: The PROFISCOV study (submitted) https://dx.doi.org/10.2139/ssrn.3822780

^ In two small, previous open, non-randomized phase I/II trials with two vaccine formulations in 76 volunteers, no SAEs were reported.[21]

^^ A phase III placebo-controlled, double-blind trial is ongoing on 25,800 randomized subjects.

Post-marketing surveillance of neurological complications of COVID-19 vaccines

Several countries have mandatory reporting systems of AEs following immunization used for post-marketing vaccine monitoring and surveillance. While at the population level there are several criteria to establish causality, temporal relationship (the only criterion necessary), strength of association, dose-response relationship, consistency of evidence, specificity, biological plausibility and coherence, at the individual level it is often impossible to achieve certainty about the cause-and-effect link between a reported AE and the vaccine[22]. After considering all other possible explanations, including coincidence, vaccine-quality defect, and error, the conclusions of systematic assessment establish whether the evidence is consistent with the vaccine being a cause, or is inconsistent, or indeterminate.

The US

The Centers for Disease Control and Prevention (CDC) and the FDA use the Vaccine Adverse Event Reporting System (VAERS) to monitor the safety of vaccines licensed for use in the US. According to the last CDC report (June 14 2021), results from VAERS are reassuring as to the safety and effectiveness of COVID-19 vaccines[35]. Anaphylaxis is rare (2-5 people per million vaccinated). After more than 11.7 million doses of the J&J/Janssen COVID-19 vaccine injected, 36 confirmed TTS have been reported (more than half with cerebral venous sinus thrombosis), nearly all in adult women under 50 years of age, and one confirmed case of TTS following mRNA COVID-19 vaccination (Moderna) after more than 310 million doses of mRNA COVID-19 vaccines administered in US. The clinical features of TTS following vaccination with the Janssen COVID-19 vaccine appear to be similar to those being observed following AstraZeneca COVID-19 vaccination in Europe. However, based on available data, there is no an increased risk for TTS after mRNA COVID-19 vaccination. No other neurological AEs of special interest have been reported. Myocarditis and pericarditis after COVID-19 vaccination are

rare. As of June 14 2021, VAERS has received 511 reports of myocarditis or pericarditis (323 confirmed by the CDC and the FDA) among people aged 30 years and under who received a COVID-19 vaccine, most cases being reported after mRNA COVID-19 vaccination (Pfizer-BioNTech or Moderna), particularly in male adolescents and young adults; investigation into the relationship to vaccination is ongoing. From December 14 2020 through June 14 2021, VAERS received 5,343 reports of death (0.0017%) among recipients of COVID-19 vaccines (more than 310 million doses administered in the US), but a review of available clinical information (death certificates, autopsy, medical records) has not established a causal link to COVID-19 vaccines, even if there is a plausible causal relationship between the J&J/Janssen COVID-19 vaccine and TTS, which has led to deaths.

Europe

According to the EMA/EudraVigilance (the system monitoring all suspected AEs to medicines authorized in the European Economic Area [EEA]), as of April 2021, 169 cases of cerebral venous thrombosis, often associated to thrombocytopenia, were reported in the EEA and the UK after the first dose of Vaxzevria vaccination out 34 million of doses injected (4.9 cases per million)[36]. As occurred with the J&J/Janssen COVID-19 vaccine in the US, also AstraZeneca was paused in several European countries in March, to be restarted (in some countries only in persons over 55-60 years of age) when the EMA concluded that the AE had not increased beyond the expected incidence rate[36]. However, the incidence of all cases of TTS seems to be 1/100,000 vaccinated with Vaxzevria (lower in Italy, at around 0.45 cases)[37]. This thrombotic thrombocytopenia, which is immune in origin, seems to be due to the activation of antibodies against platelet factor PF4 and is clinically similar to the autoimmune heparin-induced thrombocytopenia**37**. Similar findings, with more thrombosis and intracerebral hemorrhage, are described after J&J/Janssen COVID19 vaccine with a frequency of presentation comparable to that described for Vaxzevria[38]. The diagnosis of cerebral venous sinus thrombosis (CVST) is suggested by persistent, worsening headache or blurred vision, focal neurological signs, or subacute encephalopathy. Thrombocytopenia is present, brain computed tomography (CT) or magnetic resonance imaging (MRI) detect CVST, PF4 antibody testing is positive. Therapeutic recommendations include intravenous immunoglobulin, oral anticoagulation or anticoagulants other than heparin.

In the European database there are 122 reported cases of myocarditis in Pfizer (Comirnaty) recipients, 16 in the Moderna COVID-19 vaccine, 38 in Vaxzevria) and 0 for the Janssen COVID-19 vaccine[39]. The reported cases of pericarditis were 126 (Comirnaty), 18 (Moderna COVID-19 vaccine), 47 (Vaxzevria) and 1 (Janssen COVID-19 vaccine). The exposure in the EEA for each vaccine was

around 160 million doses for Comirnaty, 19 million doses for Moderna, 40 million for Vaxzevria, and 2 million for Janssen. Most of these cases were mild, resolving within a few days, mainly affecting males under 30 years of age, and after the second dose of vaccination[39]. Six cases of capillary leak syndrome in people who had received Vaxzevria were reported mostly in women within 4 days of vaccination (one of the 3 with history of capillary leak syndrome died)[40].

Overall, cerebral venous thrombosis is the most relevant neurological SAE reported in the post-marketing findings for the two viral vector vaccines, even if its frequency is not considered to be higher than expected in the general population, and both the FDA (J&J/Janssen) and the EMA (J&J/Janssen and Vaxzevria) concluded that the benefits outweigh the risks. However, especially women under 50 years of age should be aware of the rare but increased risk of this adverse event and that there are other COVID-19 vaccine options available for which this risk has not been seen.

There is no evidence at the present time to suggest that any of the vaccines is associated with AEs of neurological interest in any significant numbers. The only consistent neurological AE clearly associated to COVID-19 vaccines in clinical trials is headache, mostly occurring in mRNA vaccines, in younger people, and after the second dose. However, headache is very common after any vaccination (e.g., against Influenza virus and Hepatitis B virus) and probably reflects reactogenicity, with or without other symptoms such as fever and myalgia, and local reactions. Bell's palsy in clinical trials was rare, but investigators and the EMA considered it to be related to mRNA-vaccines, and even if it usually resolved by itself, surveillance is recommended as part of post-marketing procedures. As for influenza, the risk of Guillain-Barré syndrome after COVID-19 is probably higher than the risk after vaccination.

Take-home message

- The most frequent neurological AE associated with COVID-19 vaccines is headache, which is, however, common after any vaccination.
- Other AEs are rare events and are comparable to those of the usual vaccines.
- Occasional reports concerning extremely serious neurological AEs, such as cerebral venous thrombosis, require careful surveillance and the choice of the safest vaccine for a specific class of age and gender.
- Final considerations are limited by the continuing evolution of this unique global vaccination campaign. But it is evident that, despite the fact that extremely serious but very rare AEs are probably attributable to the vaccines, the benefits far outweigh the risks.

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