Headache After Vaccination: An Update on Recent Clinical Trials and Real-World Reporting

Kimberly N. Garces1 · Alexandra N. Cocores1 · Peter J. Goadsby2,3 · Teshamae S. Monteith1

Accepted: 14 October 2022 / Published online: 23 November 2022
© The Author(s), under exclusive licence to Springer Science+Business Media, LLC, part of Springer Nature 2022

Abstract
Purpose of Review The aim of this review is to characterize headache as a vaccine adverse event (VAE) in clinical trials.
Recent Findings Of the recent phase III vaccine RCTs (non-COVID-19), 53 studies reported on headache (13 infectious agents). The median rate (interquartile range) of headache was 15.6% (IQR: 9.6–37.6%). Of these, 24.5% of the RCTs reported headache greater in the vaccine group compared to the placebo/control group. In the herpes zoster vaccination trials, headache was more common in all active groups: median rate 33.9% (IQR: 29.7–40.5%) as compared to placebo: median rate 17.7% (IQR: 15.4–23.8%). Influenza and HPV vaccination trials were the 2nd and 3rd most common to have headache as a VAE. Of the 6 widely distributed COVID-19 vaccinations, median rate of post-vaccination headache was 39% (IQR: 28–50%).
Summary Headache is a common VAE in vaccine trials. Standardized grading methods, predictors of persistence, and treatment regimens are warranted.

Keywords Headache · Migraine · Vaccine/vaccination · COVID-19 · Vaccine adverse event · Reactogenicity/immunogenicity

Introduction

Vaccine programs are one of the most effective public health measures to control the threat of communicable diseases. Phase III clinical trials are performed to study the effectiveness and safety of novel vaccines, with comparison to the gold standard, an established vaccine, or placebo. Vaccine adverse events (VAEs) are important to evaluate. In one meta-analysis, vaccine safety was among the top reasons for COVID-19 vaccination hesitancy in healthcare workers [1]. In post-licensure surveillance, headache is one of the most reported VAEs, which is especially relevant given the high burden of headache disorders in the general population [2].

The aim is to characterize headache as a VAE and summarize the quality of reporting in randomized controlled trials (RCTs). There is focus on COVID-19 vaccinations, due to the novelty of mRNA-based technologies and nanovaccines. As post-vaccination headache is not defined in the International Classification of Headache Disorders (ICHD-3), we also characterize a case presentation, possible mechanisms, and clinical relevance.

Methods

We conducted a search of RCTs involving vaccines from November 30, 2018 through November 30, 2021 which resulted in 1501 articles (PubMed). From these, 1058 were randomized controlled trials (RCTs), of which 211 were phase III RCTs. Of these 211 phase III RCTs, articles were excluded if they pertained to experimental tumor vaccines or mentioned vaccines but did not test safety and immunogenicity. According to these criteria, 185 studies were obtained. We included COVID-19 RCTs but limited our evaluation to those with FDA approval within the USA. Medians, 25th, and 75th percentiles describing rate of vaccination headache and rate of headache due to placebo were calculated.
We reviewed 11 RCTs published within the last 2 years of six widely distributed COVID-19 vaccinations.

**Headache as an Adverse Event in Vaccination Trials**

In the majority of the 148 RCTs (non-COVID-19) reviewed, data on headache as a VAE was either not reported or nonspecific. Ten (6.8%) of the studies reported only the most and least common VAE without mention of all VAEs that occurred.

Of the 148 reviewed studies, headache as a VAE was measured in 56. These 56 studies included testing of vaccines against 13 different infectious agents in total. Fifty-three of the studies reported the headache data (Table 1), while three did not report. Of the 53 which reported headache data, 34 RCTs had active comparison groups while the remaining 19 were placebo controlled.

**Measurement and Report of Headache Occurrence and Frequency**

Of these studies, about one fourth (40/148; 27.0%) reported headache as an individual VAE. Less (13/148; 8.8%) reported headache as combined with other common VAEs (including fatigue, fever, and myalgias): These were defined together as “solicited VAEs,” “solicited systemic VAEs,” “systemic events,” “solicited general symptoms,” “general symptoms,” “solicited systemic reactions,” and “systemic reaction categories.” Often, the specific frequency of headache was recorded in supplemental tables and materials (Table 1).

**Measurement and Report of Headache Severity**

Of the 53 studies reporting headache, 16 measured the intensity of headache as a grading scale. One study defined four grades (the most severe headache outcome as “grade 4”) [27], while all others defined three grades (the most severe and debilitating outcome as “grade 3”). Not all grading scale data was reported: One study reported grades 1, 2, and 4 but did not report grade 3 [27], and 14 studies reported grade 3 only (Table 1).

Additionally, two studies specified headache severity as “mild,” “moderate,” or “severe,” rather than using a grading scale [16, 49]. Three studies specified only when headaches were considered “severe” [13, 14, 34].

Within the RCTs with active comparison groups, 9 described headache using a grading severity system, 3 described headache using severity measures, and 22 did not specify grade/severity. Within the 19 placebo-controlled RCTs, 7 described headache using a grading system, 2 provided headache severity measures, and 10 did not specify headache grade/severity.

**Measurement and Report of Headache Severity in COVID-19 Vaccination Studies**

Because of significant interest due to the COVID-19 pandemic, we evaluated the FDA approved COVID-19 vaccinations separately. Among the six COVID-19 vaccine RCTs reviewed, all but one, CoronaVac, reported data on headache severity. However, the five trials that do report severity also lack consistency. The RCT involving COVID-19 vaccine BNT162b2 classified headache severity outcomes as “any,” “mild,” “moderate,” “severe,” and grade 4 among the “5 to 11,” “12 to 15,” “16 to 55,” and “55 and greater” age groups [56]. The RCT involving vaccine mRNA-1273 categorized headache severity in grades 1–4 and “any” among the “18 to 65” and “65 and greater” age groups [57, 58]. The RCT involving vaccine Ad26 CoV2.S only reported headache severity with grades 3 and 4 and these were assessed in the “18 to 59” and “59 and greater” age groups [59]. This study did not report data on headaches with a grade severity of 1 or 2. The RCT involving ChAdOxInCoV-19/ADZ1222 vaccine also defined headache severity as “any,” “mild,” “moderate,” and “severe” but indicated whether headaches led to hospitalization across the “18 to 55,” “56–69,” and “69 and greater” age groups [60]. Similarly, to the mRNA-1273 vaccine, the RCT involving NVX-CoV2373 also defined headache severity as “any” and grades 1–4, but these were only reported in the “18 to 84” age group [61, 62]. These severity definitions were assessed within 7 days of each vaccination dose except for the Ad26 CoV2.S vaccine RCT, which only administered one dose. All six studies reported headache as an individual VAE and were considered one of the “systemic” VAEs (Table 2).

**Results**

**Findings on Headache Reported Post-Vaccination**

Of the 148 (non-COVID-19) studies reviewed, the top five infectious agents which measured and reported headache as a VAE included herpes zoster, influenza, HPV, meningococcal, and pneumococcal. Of those using placebo as control, 8 of 13 (61.5%) herpes zoster vaccine trials, 11 of 27 (40.7%) of influenza vaccine trials, and 5 of 16 (31.4%) of HPV vaccine trials reported headache as a VAE. Of those using active control, 10 of 26 (38.5%) meningococcal vaccine trials and 3 of 10 (30.0%) of pneumococcal conjugate vaccine trials reported headache as a VAE.

Over a third (38.5%; 19/53) of RCTs reporting headache were placebo controlled. In 13 of these, headache was more...
| Vaccine type | Headache reported in vaccine group | Headache reported in placebo group | Headache grading/severity | Overall headache results/key findings |
|--------------|-----------------------------------|------------------------------------|---------------------------|--------------------------------------|
| 1. Ward et al. [3] | Influenza vaccine | • 18-64 years Quadrivalent virus-like particle vaccine: 1020/5064 (20.1%)<br>• 65 plus years Quadrivalent virus-like particle vaccine: 624/6352 (9.8%)<br>• 65 plus years Quadrivalent inactivated vaccine: 656/6366 (10.3%)<br>967/5072 (19.1%) | • 967/5072 (19.1%)<br>• No grading system reported | • Headache was greater in the quadrivalent virus-like particle vaccine group than in the placebo group but headache was greater in the placebo group than in the quadrivalent virus-like particle vaccine and quadrivalent inactivated vaccine<br>At least one life threatening or vaccine associated headache:<br>• Quadrivalent virus-like particle vaccine: 17 (0.3%)<br>• Quadrivalent virus-like particle vaccine: 10/6352 (0.2%)<br>• Quadrivalent inactivated vaccine: 11/6366 (0.2%)<br>• Placebo: 23/5072 (0.5%)<br> | |
| 2. Chang et al. [4] | Influenza vaccine | IIV4-HD influenza vaccine group reported higher headache than IIV3-HD influenza vaccine | • No placebo reported | Fewer than 1% subjects reported grade 3<br>• Headaches began within 3 days of vaccination<br>• Headaches resolved within 3 days onset<br> | |
| 3. Vesikari et al. [5] | Influenza vaccine | • QIV vaccine group: 24.0%<br>• TIV vaccine group: 20.9% | • No placebo reported | No grading system reported<br>• Local/systemic reactions were analyzed within 7 days post-vaccination<br>• There were no significant differences in reporting of local and systemic adverse reactions between the two vaccine arms<br>• Headache was one of the most common systemic reactions along with fatigue/tiredness and irritability/fussiness<br> | |
| 4. Endo et al. [6] | Influenza vaccine | MA group: 132/369 (35.8%) CI [30.9–40.9] | • No placebo group reported | Grade 3 severity headache: 10.3% Incidence CI [0.0–1.5]<br>• Drug related grade 3 headache: 1 (0.3%) CI [0.0–1.5]<br>• Headache solicited adverse drug reactions: 131 (35.5%) CI [36.6–40.6]<br>• Headache was the second highest solicited systemic adverse events along with myalgia (30% and 40%) | |
| Table 1 (continued) | Vaccine type | Headache reported in vaccine group | Headache reported in placebo group | Headache grading/severity | Overall headache results/key findings |
|---------------------|--------------|-----------------------------------|------------------------------------|---------------------------|-------------------------------------|
| 5. Chu et al. [7]   | Influenza vaccine | • IIV4: 8/1160 (0.69%)<br>• IIV3-BV: 4/580 (0.69%)<br>• IIV3-BY: 1/580 (0.17%) | • No placebo group reported | • No grading system reported | • There was no statistical significance of headache among the three vaccine groups with a P-value: 0.4085<br>• The most common local reaction was pain while fever was the most common systemic reaction<br>• There was no significant difference between vaccine receiving and placebo receiving groups with a P-value of 0.3369<br>• Headache in the placebo group was greater than headache in the vaccine group |
| 6. Lan et al. [8]   | Influenza vaccine | • 121/740 (16.4%) CI [13.76–19.22] | • 29/148 (19.6%) CI [13.53–26.91] | • No grading system reported | • There was no significant difference between vaccine receiving and placebo receiving groups with a P-value of 0.3369<br>• Headache was the most common solicited systemic adverse event in both the younger and older group<br>• Headache was combined with pain, redness, swelling, fever, loss of appetite, fatigue, muscle ache, joint pain, and shivering to make up the solicited adverse events category of adverse events |
| 7. Loebermann et al. [9] | Influenza vaccine | Younger age group: 17%<br>Older age group: 10% | • No placebo group reported | • No grading system reported | Headache was one of the most reported solicited systemic reactions along with muscle aches and fatigue<br>• Incidence rates of TEVAEs were similar across all influenza lot groups |
| 8. Sarkar et al. [10]* | Influenza vaccine | Cohort 1 and 2: less than 5 VAEs among reported solicited VAEs | • No placebo group reported | • No grading system reported | Headache was greater in the vaccine group than the control 2 TIV group but was less than headache in the control 1 TIV group<br>• There was no significant difference in headache across all groups with a P-value: 0.65 |
| 9. Ward et al. [11]* | Influenza vaccine | At least one subgroup: over 20%<br>Headache within adverse events: 11/281 (3.9%)<br>Overall participants: 356/1200 (29.7%) | • No placebo group reported | • No grading system reported | |
| 10. Song et al. [12] | Influenza vaccine | GC3110A vaccine: 91/647 (14.1%)<br>Control 1 TIV: 46/325 (14.2%)<br>Control 2 TIV: 40/326 (12.3%) | • No grading system reported | |
| Vaccine type | Headache reported in vaccine group | Headache reported in placebo group | Headache grading/severity | Overall headache results/key findings |
|--------------|-----------------------------------|-----------------------------------|---------------------------|-------------------------------------|
| 11. Beran et al. [13] * | Influenza vaccine | Systemic solicited VAEs influenza vaccine group: 128/665 (19.2%) | Systemic solicited VAEs non-influenza comparator group: 109/667 (6.3%) | 1 severe headache was reported | Incidence of headache among solicited VAEs vaccine group: 10.8% |
| | | • Systemic solicited VAEs non-influenza comparator group: 109/667 (6.3%) | | • Incidence of headache among solicited VAEs non-comparator vaccine group: 8.3% |
| | | • Headache was combined with arthralgia, chills, diarrhea, fatigue, fever, loss of appetite, myalgia, nausea, and vomiting to make up the solicited systemic adverse events category | | • Headache was greater in the vaccine group than placebo group |
| | | • Headache was combined with arthralgia, chills, diarrhea, fatigue, fever, loss of appetite, myalgia, nausea, and vomiting to make up the solicited systemic adverse events category | | • Headache was greater in the vaccine group than placebo group |
| 12. Yamazaki et al. [14] * | Pneumococcal conjugate vaccine | • Systemic events 6 to 17 year olds: 31/51 (60.8%) | • No placebo group reported | 1 severe headache was reported | • Most common systemic events were fatigue, muscle pain, and headache |
| | | • Systemic events 18 to 64 year olds: 85/145 (58.6%) | | • Headache in 6 to 17 year old group made up 35% of all systemic events |
| 13. Klein et al. [15] * | Pneumococcal conjugate vaccine | • 20-valent pneumococcal conjugate vaccine: Approx. 38% of systemic events | • No placebo group reported | 1 severe headache was reported | • Headache in 18 to 64 year olds made up 34% of all systemic events |
| | | • 13-valent pneumococcal conjugate vaccine: Approx. 40% of systemic events | | Headache was combined with fatigue, muscle pain, joint pain, and fever to make up the systemic events category |
| 14. Song et al. [16] * | Pneumococcal conjugate vaccine | • V114 vaccine: 14.1% and 12.1% | • No placebo group reported | Headaches were defined as mild, moderate, or severe | • VAEs were similar between both vaccine groups |
| | | • PCV13 vaccine: 12.7% and 12.6% | | • Infections were the most common VAE reported post-vaccination |
| 15. Bastidas et al. [17] | Herpes zoster | 302/901 (33.5%) CI [30.4–36.7] | 166/892 (18.6%) CI [16.1–21.3] | Grade 3 vaccine: 26/901 (2.9%) CI [1.9–4.2] | Headache in the vaccine group is greater than headache in the placebo group |
| | | Grade 3 placebo: 10/892 (1.1%) CI [0.5–2.0] | | Grade 3 VAEs were higher after second vaccine dose |
Table 1 (continued)

| Vaccine type          | Headache reported in vaccine group | Headache reported in placebo group | Headache grading/severity | Overall headache results/key findings     |
|-----------------------|-----------------------------------|-----------------------------------|---------------------------|------------------------------------------|
|                       | General symptoms: 206/278 (74.1%) | 134/274 (48.9%)                  | Grade 3 headaches: 43/278 (15.5%) | Headache were combined with fatigue, myalgia and local injection site adverse events to consist of solicited general symptoms
| 16. Dagnew et al. [18]* | Headache in the vaccine group was greater than the placebo group |                                   |                           | Headache in the vaccine group was greater than the placebo group |
|                       | • Grade 3 vaccine: 5%              | • Grade 3 placebo: 2%             |                           | Headache was combined with fatigue, myalgia and local injection site adverse events |
|                       | • Headache in all vaccine groups greater than all corresponding placebo groups |                                   |                           |                           |
| 17. Vink et al. [19]* | RZV vaccine: 45/112 (40%)         | 42/110 (38%)                     |                           |                           |
|                       | • Non-frail RZV grade 3 severity: 74 (3.7%) | • Non-frail RZV grade 3 severity: 53 (2.7%) |                           |                           |
|                       | • Pre-frail RZV grade 3 severity: 17 (3.5%) | • Pre-frail RZV grade 3 severity: 17 (3.5%) |                           |                           |
| 18. Curran et al. [20] |                                    |                                   |                           |                           |
|                       | • Frail RZV group grade 3 severity: 0 | • Frail RZV group grade 3 severity: 0 |                           |                           |
|                       | • Non-frail placebo group grade 3 severity: 8 (0.4%) | • Non-frail placebo group grade 3 severity: 8 (0.4%) |                           |                           |
|                       | • Pre-frail placebo group grade 3 severity: 12 (0.6%) | • Pre-frail placebo group grade 3 severity: 12 (0.6%) |                           |                           |
|                       | • Frail placebo group grade 3 severity: 10 (2.1%) | • Frail placebo group grade 3 severity: 10 (2.1%) |                           |                           |
|                       | • Unknown placebo group grade 3 severity: 0 (0%) | • Unknown placebo group grade 3 severity: 0 (0%) |                           |                           |
Table 1 (continued)

| Vaccine type | Headache reported in vaccine group | Headache reported in placebo group | Headache grading/severity | Overall headache results/key findings |
|--------------|-----------------------------------|------------------------------------|---------------------------|--------------------------------------|
| 19. Ocran-Appiah et al. [21] Herpes zoster | Overall: 679/8687 (7.8%) CI [7.3–8.4] | • No placebo group reported | • Overall grade 3: 98 (1.1%) CI [0.9–1.2] | • During 30 day post-vaccination period 5175 (59.6%) participants reported at least 1 VAE, 4422 (50.9%) were vaccine related. Headache was one of most common VAEs including injection site reactions and pyrexia. Headache related to vaccine: Overall vaccine related: 563 (6.5%) CI [6.0–7.0] • 50–59 year olds vaccine related: 135 (13.0%) CI [11.0–15.2] • 60–69 year olds vaccine related: 207 (9.5%) CI [8.3–10.8] • 70–79 year olds vaccine related: 164 (4.9%) CI [4.2–5.7] • 80 year olds and older vaccine related: 57 (2.7%) CI [2.1–3.5] |
| 20. Schmader et al. [22]* Herpes zoster | 37.5% | • No placebo group reported | Grade 3: 2.8% of vaccine participants | Headache was most common solicited systemic VAE along with fatigue and myalgia. Post-vaccine 1: 30% headache. Post-vaccine 2: 38% headache. 6.5% of participants experienced headache pre-vaccination. Headache was one of the most common solicited systemic reactions along with fatigue and myalgia. |
| 21. Schmader et al. [23]* Herpes zoster | Overall participants: 28.3% | • No placebo group reported | • No grading system reported | |
| 22. Lopez-Fauqued et al. [24]* Herpes zoster | • RZV group: 954 (6.51%) CI [6.12–6.93] • 445 (3.04%) CI [2.76–3.33] | | Grade 3 RZV group: 99 (0.7%) CI [0.5–0.8] Grade 3 placebo group: 27 (0.2%) CI [0.1–0.3] | | |
| 23. Mikamo et al. [25] HPV vaccine | 2/554 (0.4%) | 7/559 (1.3%) | • No grading system reported | Headache in the placebo group was greater than the vaccine group. Headache was one of the most common vaccine-related VAEs along with pyrexia. |
| Vaccine type | Headache reported in vaccine group | Headache reported in placebo group | Headache grading/severity | Overall headache results/key findings |
|--------------|-----------------------------------|-----------------------------------|---------------------------|-------------------------------------|
| HPV vaccine  | • Women 16–26 years of age: 72/570 (12.6%)  
Women 27–45 years of age: 87/640 (13.6%) | • No placebo group reported | • No grading system reported | • Headache was one of the most common systemic VAEs including pyrexia and fatigue  
• Headache related to vaccine 16–26 year olds: 12.6%  
• Headache related to vaccine 27–45 year olds: 13.6% |
| HPV vaccine  | 218/1499 (14.5%) | 193/1496 (12.9%) | Vaccine group severity  
• Grade 1: 203 (13.5%)  
• Grade 2: 14 (0.9%)  
• Grade 4: 1 (0.1%)  
Placebo group severity  
• Grade 1: 176 (11.7%)  
• Grade 2: 17 (1.1%)  
• Grade 4: 0 (0%) | Difference in percent of the vaccine vs placebo group: 1.6% CI [−0.8–4.1]  
Headache in the vaccine group was greater than the placebo group |
| HPV vaccine  | Overall: 7/200 (3.5%) headache VAEs | • No placebo group reported | • No grading system reported | |
| HPV vaccine  | • Vaccine lot 1: 78/1229 (6.3%)  
• Vaccine lot 2: 87/1229 (7.1%)  
• Vaccine lot 3: 94/1228 (7.7%) | • No placebo group reported | 0 grade 3 headaches reported | P-value: 0.45 indicated no significant differences of headache among participants who received the three different lots of HPV vaccines |
| Meningococcal vaccine | • MenACYW-TT vaccine group: 27.9% (730/2618)  
• MCV4-DT vaccine group: 27.8% (171/615) | • No placebo group reported | • No specific grading system reported | • Headache was one of the most common solicited systemic reactions along with myalgia and malaise  
• The majority of solicited reactions began within 3 days post-vaccination and resolved in 1 to 3 days  
• The majority of systemic reactions were a grade 1 or 2 in severity |
| Meningococcal vaccine | • MenACYW-TT vaccine group: 84/442 19.0 [15.5–23.0]  
• MPSV4 vaccine group: 66/451 14.5% [11.5–18.2] | • No placebo group reported | Grade 3 MenACYW-TT: 3/442 0.7 [0.1–2.0]  
Grade 3 MPSV4: 3/451 0.7% [0.1–1.9] | • Headache was one of the most common solicited systemic reactions along with myalgia and malaise |
| Vaccine type                                      | Headache reported in vaccine group | Headache reported in placebo group | Headache grading/severity | Overall headache results/key findings |
|--------------------------------------------------|-----------------------------------|-----------------------------------|---------------------------|--------------------------------------|
| 30. Group MMRS et al. [32] Meningococcal vaccine | Sub-cohort 1 MMR-RIT: 0          | No placebo group reported         | Grade 3 sub-cohort 1 MMR-RIT: 0 (0%) | Solicited VAEs were comparable across all vaccine groups |
| With and without varicella/DTaP                  | Sub-cohort 1 MMRII: 2 (0.7%)      |                                   | Grade 3 sub-cohort 1 MMRII: 0 (0%) |                                      |
|                                                  | Sub-cohort 2 MMR-RIT: 1 (0.1%)    |                                   | Grade 3 sub-cohort 2 MMR-RIT: 0 (0%) |                                      |
|                                                  | Sub-cohort 2 MMRII: 0(0%)         |                                   | Grade 3 sub-cohort 2 MMRII: 0 (0%) |                                      |
|                                                  | Sub-cohort 3 MMR-RIT: 0 (0%)      |                                   | Grade 3 sub-cohort 3 MMR-RIT: 0 (0%) |                                      |
|                                                  | Sub-cohort 3 MMRII: 0 (0%)        |                                   | Grade 3 sub-cohort 3 MMRII: 0 (0%) |                                      |
| 31. Baccarini et al. [33] Meningococcal conjugate vaccine | MenACYW-TT vaccine group: 61/487 12.5% CI [9.7–15.8] | No placebo group reported | No grading system reported | Headache measured was defined as pain or discomfort in the head or scalp but did not include migraine |
|                                                  | MenACWY-CRM vaccine group: 56/486 11.5% CI [8.8–14.7] |                                   |                           |                                      |
| 32. Nolan et al. [34] Meningococcal conjugate vaccine | Primed group: 146/266 (55%)     | No placebo group reported         | Severe headache Primed group: 18/266 (7%) | Over 49% of participants experienced headache |
|                                                  | Naïve group: 125/254 (49%)       |                                   | Severe headache Naïve group: 19/254 (7%) |                                      |
| 33. Vesikari et al. [35] Meningococcal conjugate vaccine | MenACWY-TT toddler group: 4/67 (6.0%) | No placebo group reported | No grading system reported | Headache was one of the most frequently reported solicited systemic VAEs |
|                                                  | MenC-CRM toddler group: 1/67 (6.3%) |                                   |                           |                                      |
|                                                  | MenACWY-TT children group: 3/77 (3.9%) |                           |                           |                                      |
|                                                  | MenACWY-PS children group: 0 (0%) |                                   |                           |                                      |
| 34. Anez et al. [36] Meningococcal conjugate vaccine | MenACYW-TT vaccine group: 151/398 (37.9%) | No placebo group reported | No specific grading system reported | Headache was the most common solicited systemic reaction |
|                                                  | MCV4-DT vaccine group: 156/402 (38.8%) |                                   |                           | All headaches were either grade 1 or grade 2 and transient |
| Vaccine type                                      | Headache reported in vaccine group | Headache reported in placebo group | Headache grading/severity | Overall headache results/key findings |
|-------------------------------------------------|------------------------------------|------------------------------------|---------------------------|--------------------------------------|
| 35. Vesikari et al. [37]*                        |                                    |                                    |                           | • Headache was combined with fever, vomiting, diarrhea, fatigue, chills, muscle pain, and joint pain to make up the systemic events category • Between 68.8 and 76.6% of subjects reported at least one systemic event depending on the study group after 0, 2, and 6 months |
| Meningococcal conjugate vaccine                  | • Primary series vaccine group: 77% after 0, 2, and 6 months • Booster group: 40% after 0, 2, and 6 months | • No placebo group reported | • No grading system reported |                                       |
| 36. Tipton et al. [38]                          |                                    |                                    |                           | • Possibly vaccine related medically attended VAEs associated with headache were reported in 3 participants in the primed vaccine group • Headache onset was on day 1 followed by myalgia at day 4 and anxiety onset at day 22 |
| Meningococcal conjugate vaccine                  | • Primed vaccine group: 31% • Naïve vaccine group: 20% | • No placebo group reported | • No grading system reported |                                       |
| 37. Nolan et al. [39]*                           |                                    |                                    |                           | • Headache was one of the most common solicited general symptom along with fatigue and gastrointestinal symptoms • No VAEs were considered to be related to vaccine, study procedures, or concomitant medication |
| Meningococcal conjugate vaccine                  | • Less than 24.6% of all participants • HibMenC vaccine: 24% • HiB + MCC vaccine: 20% | • No placebo group reported | • Grade 3 HiB + MCC: about 5% |                                       |
| 38. Jiang et al. [40]*                           |                                    |                                    |                           | • Headache in the vaccine group was greater than the placebo group |
| Varicella vaccine                                | 5 (0.84%)                          | 2 (0.67%)                          |                           | Vaccine: • Grade one: 4 (0.67%) Headache • Grade 2: 1 (0.17%) • Grade 3: 0 (0%) Placebo: • Grade 1: 1 (0.34%) • Grade 2: 0 (0%) • Grade 3: 1 (0.34%) |
| 39. Asatryan et al. [41]                         |                                    |                                    |                           | • Headache related to the vaccine group: 18.9 CI [15.3–22.9] • Grade 3 headache was considered if headache prevented normal activity • Headache was one of two most common solicited VAEs • In participants 65 years and older, headache was unrelated to vaccine in 50% of cases |
| Combined diphtheria, tetanus, pertussis vaccine   | 24.9% CI [20.9–29.3]               | • No placebo group reported        | • Grade 3: 2.1% [1.0–3.9] |                                       |
Table 1 (continued)

| Vaccine type | Headache reported in vaccine group | Headache reported in placebo group | Headache grading/severity | Overall headache results/key findings |
|--------------|-----------------------------------|-----------------------------------|---------------------------|-------------------------------------|
| 40. Vesikari et al. [42]* | Hepatitis B vaccine | • Tri-antigenic: 249/572 (31.3%) • Mono-antigenic: 238/811 (29.3%) | No placebo group reported | No specific grading system reported | There was no significant difference in headache reported between the two vaccine groups with a P-value of 0.678 |
| 41. Chaparro et al. [43]* | Hepatitis B vaccine | • Fendrix vaccine group: 17% • Engerix vaccine group: 4.3% | No placebo group reported | No grading system reported | Data reported only specified 18 participants presented mild VAEs related to the vaccine |
| 42. Lee et al. [44]* | Adult tetanus diphtheria vaccine | • GC1107 vaccine: 22/250 (8.80%) | Control group: 21/125 (16.80%) | No grading system reported | Headache was grouped with pain, pressure, irritation, swelling, fever, vomiting, nausea, diarrhea, fatigue, and myalgia and reported as solicited VAEs. Headache in the control group was greater than headache in the GC1107 vaccine group. |
| 43. Arredondo et al. [45]* | Concomitant dengue and HPV vaccine | • Concomitant vaccine group: 185/231 (80.1%) • Sequential Concomitant vaccine group: 196/234 (83.8%) • Sequential vaccine group: 129/151 (85.4%) | No placebo group reported | No grading system reported | Headache was combined with fever, malaise, myalgia, and asthenia to make up solicited systemic reactions category. There was no difference in safety outcomes across vaccine groups. |
| 44. Shen et al. [46] | Rabies vaccine | • Zagreb group: 33/600 (5.5%) • Essen group: 37/398 (9.4%) | 23/600 (4.5%) | No grading system reported | 97/918 (5.4%) of total adverse events were due to headache. Headache in both vaccine groups was greater than control. |
| 45. Matson et al. [47]* | Rabies vaccine | • HRIG vaccine group: 8/59 13.6% • Comparator vaccine group: 9/59 15.3% • Drug-related TEVAEs in HRIG: 3.4% • Drug-related TEVAEs in comparator group: 5.1% | No placebo group reported | No grading system reported | Overall 17/118 (14.4%) reported headache in the trial. Overall 5/118 (4.2%) of participants reported drug-related headache. |
| 46. de Bruyn et al. [48]* | C. diff vaccine candidate | • 302/1196 (25.3%) CI [21.5–26.4] • 115/586 (19.6%) CI [16.5–23.1] | No grading system reported | No grading system reported | Headache was combined with fever, malaise, myalgia, arthralgia to make up the systemic reaction category. Headache in the vaccine group greater than placebo. |
| Vaccine type                         | Headache reported in vaccine group | Headache reported in placebo group | Headache grading/severity | Overall headache results/key findings |
|-------------------------------------|------------------------------------|------------------------------------|---------------------------|--------------------------------------|
| 47 McCarty et al. [49]*             | Oral cholera vaccine               | • 60/296 (20.3%)                  | • 30/99 (30.3%)           | Vaccine group severity               |
|                                     |                                    |                                    |                           | • Mild headache: 41/296 (13.9%)      |
|                                     |                                    |                                    |                           | • Moderate headache: 17/296 (5.8%)   |
|                                     |                                    |                                    |                           | • Severe headache: 2/296 (0.7%)      |
|                                     |                                    |                                    |                           | Placebo group severity              |
|                                     |                                    |                                    |                           | • Mild headache: 39/99 (19.2%)       |
|                                     |                                    |                                    |                           | • Moderate headache: 11/99 (11.1%)   |
|                                     |                                    |                                    |                           | • Severe headache: 0/99 (0%)         |
| 48 Gray et al. [50]                 | HIV vaccine                         | • 0 (0%)                           | • 15.7%                   | No grading system reported          |
| 49 Brogan et al. [51]*              | Canakinumab vaccine                 | CAPS vaccine: 6/17 (35%)           | No placebo group reported  | No grading system reported          |
| 50 Riveau et al. [52]*              | Schistosomiasis vaccine            | 23/787 (2.92%)                     | 28/733 (3.82%)            | No grading system reported          |
| 51 Markman et al. [53]              | Pregabalin vaccine                 | 12/274 (4.4%)                      | 8/265 (3.0%)              | No grading system reported          |
| 52 Song et al. [54]                 | Hantaan virus vaccine               | 1st dose vaccine group: 21 (6.8%)  | No placebo group reported  | Injection site pain and myalgia     |
|                                     |                                    | 2nd dose vaccine group: 12 (3.8%)  |                           | were the most frequently local and   |
|                                     |                                    | 3rd dose vaccine group: 12 (3.8%)  |                           | systemic VAEs                       |
|                                     |                                    | Booster vaccine group: 14 (4.53%)  |                           | No vaccine-related VAE were         |
|                                     |                                    |                                    |                           | reported                              |
|                                     |                                    |                                    |                           | No significant differences in        |
|                                     |                                    |                                    |                           | headache were noted with a P-value   |
|                                     |                                    |                                    |                           | of 0.1818 across all doses           |
| 53 Halperin et al. [55]             | Ebola virus envelope glycoprotein   | ZEBOV-GP recipients reported higher rates of injection site pain, erythema, swelling, fever, headache, arthralgia, pain, chills and fatigue recipients | No placebo group reported | The majority of reported VAEs were  |
|                                     | vaccine                             |                                    |                           | considered mild to moderate          |
|                                     |                                    |                                    |                           | No reported VAEs were related to     |

*Headache data reported from supplemental table and other information
common after vaccination than placebo. These included studies of vaccines against herpes zoster, influenza, varicella, rabies, and c. difficile. In the remaining six, headache was more common in the placebo group than vaccine group. These included studies of vaccines against influenza, HPV, diphtheria, HIV, and schistosomiasis (Table 1). In one study, more than one vaccine group was compared to a single placebo group [3]. Headache was greater in the quadrivalent virus-like particle vaccine group in adults 18–64 than in the placebo group. However, headache was greater in the placebo group when compared to the quadrivalent virus-like particle vaccine with adults 65 plus and quadrivalent inactivated vaccine of both age groups [3]. In another, one vaccine group was compared to two different control groups [12]. Headache was greater in the vaccine group than in the control 2 trivalent inactivated subunit group but was less than headache in the control 1 trivalent inactivated subunit group.

Of the herpes zoster vaccine trials, five of eight found post-vaccination headache to be more common in the vaccine group compared to placebo: 33.5% (active) vs. 18.6% (placebo) [17]; 74.1% (active) vs. 48.9% (placebo) [18]; 40% (active) vs. 38% (placebo) [19]; 41.8% (active) vs. 14.1% (placebo), 34.3% (active) vs. 15.8% (placebo), 30.1% (active) vs. 19.0% (placebo), 28.6% (active) vs. 16.7% (placebo) [20]; 6.51% (active) vs. 3.04% (placebo) [24] while the others found no significant difference. Of the influenza vaccine trials, 27.3% (3/11): 20.1% (active) vs. 19.1% (placebo) [3]; 14.1% (active) vs. 12.3% (placebo) [12]; and 19.2% (active) vs. 6.3% (placebo) [13] found headache to be more common in the vaccine group and 9.1% (1/11): 16.4% (active) vs. 19.6% (placebo) [8] found headache to be more common in the placebo group. Of the HPV vaccine trials, 20% (1/5): 14.5% (active) vs. 12.9% (placebo) [27] found headache more common in the vaccine group and 20% (1/5): 0.4% (active) vs. 1.3% (placebo) [25] found headache more common in the placebo group. Overall, median rate of headache in non-COVID-19 vaccines was 15.6% (IQR: 6.4–30.6%) (active) vs. 15.7% (IQR: 5.4–19.1%) (placebo) (Table 1).

**Headache as an Adverse Event Following COVID-19 Vaccination Studies**

The coronavirus disease (COVID-19) pandemic resulting from infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) has affected and continues to affect hundreds of millions of people. In response, multiple vaccines were developed, of which clinical trial and prospective data have revealed headache to be one of the most commonly reported VAEs (Table 2). Headache was the third most common symptom after vaccination [68].

The initial messenger RNA-based COVID-19 vaccines were the first of their approach to be approved [56, 57]. For these vaccines, the majority of headache events were rated as “mild” or “grade 1” across doses and age groups and systemic reactogenicity (including headache) was more common and severe after the second dose than after the first dose and among younger than older recipients [56, 57, 61]. The median rate of headache post-vaccination for mRNA COVID-19 vaccines dose one, two, and combined was 30.3% (IQR: 4.7–40.3%) (active) vs. 26.6% (IQR: 20.5–32.5%) (placebo), 49% (IQR: 40.8–60%) (active) vs. 21.4% (IQR: 18–24.3%) (placebo), and 40.5% (IQR: 27.3–52.6%) (active) vs. 24.1% (IQR: 18.5–26.2%) (placebo) respectively. When compared, median rate of headache due to placebo was lower by 3.7%, 27.6%, and 16.4%. In the BNT162b2 study, headache was one of only two systemic events reported as severe after either dose in at least 2% of recipients [57].

Data from the mRNA-1273 study reveal headache to have a mean duration of 2.1 days after the first dose and 2.3 days after the second dose, with only 4.8% persisting beyond 7 days [57]. Similarly, mean duration of headache was 1.6 days after the first and 2.0 days after the second dose in the NVX-CoV2373; no headache extended past 7 days after the second dose [61].

The median rate of headache vaccination of vaccines using a recombinant nanoparticle was calculated for dose 1, 23% (active) vs. 30% (placebo), dose 2, 46% (active) vs. 29% (placebo), and combined, 34.5% (active) vs. 29.5% (placebo). When compared, median rate of headache due to placebo was 7% higher for dose one, yet was 17% lower for dose two, and 5% lower for both doses combined [61, 62].

The median rate of headache vaccination for adenovirus vectored vaccines [59, 60] was calculated for dose 1, 45.5% (IQR: 40.5–53.8%), dose 2, 31% (IQR: 25.5–32.5%), and combined, 38.9% (IQR: 32.5–45.5%). No rate of headache due to placebo was reported for comparison.

For the COVID-19 vaccines reviewed (Table 2), overall median rate of headache vaccination and IQR was calculated among first, second, and both doses combined. This resulted in medians: 38.9% (IQR: 24.9–46%) (active) vs. 29% (IQR: 21.7–31.9%) (placebo), 42.5% (IQR: 31.8–50.3%) (active) vs. 24.1% (IQR: 18.2–24.9%) (placebo), and 39% (IQR: 28–50%) (active) vs. 24.3% (IQR: 18.8–29%) (placebo). This demonstrates a 10%, 18.4%, and 14.7% increase in headache post-vaccine when compared to placebo.

**VAE Case Description: Headache Associated with COVID-19 Vaccination**

A 23-year-old woman presented for follow up of migraine with aura and menstrual migraine; she had been diagnosed 3 years prior and had comorbid anxiety and irritable bowel syndrome. She had reported two migraine attacks in the...
6 months prior to COVID-19 vaccination. Following vaccination, she experienced increased severity and frequency. Of note, she did have a history of chronic migraine (up to 22 headache days per month) in years prior.

The patient received the first dose of the BNT162b2 mRNA vaccine on January 14, 2021. Two days after, she experienced a series of severe migraine attacks for with pain intensity of 7–10 out of 10 on a 0–10 numeric rating scale. The attacks were lasting 7 to 8 h with reoccurrence, for 1.5 weeks. The migraine attacks alternated between unilateral and bilateral locations and were throbbing and sharp in pain quality. Symptoms occurring with her post-vaccination headache included more severe photophobia and nausea and vomiting compared to baseline, as well as her typical photophobia, sensitivity to movement, lightheadedness, confusion, and difficulty thinking and concentrating. She reported an increased frequency of visual auras consisting of flashing lights with about half of these migraine attacks. The visual auras lasted about 4 h and were prolonged compared to her usual episodes of 45 min duration. Numbness with tingling also occurred in the face, arms, and sometimes legs during her attacks. In the past, she had experienced word substitution and weakness but had not had these symptoms for 6 years.

She treated her migraine attacks with rizatriptan, metoclopramide, and NSAIDs daily; however, they were treatment resistant. To alleviate the pain, the patient stayed in a dark room but had difficulty falling asleep. Due to the constant pain, she was not able to work or socialize. After 1.5 weeks, the migraine attacks subsided.

The patient received dose 2 of the vaccine three weeks later. A few hours after the vaccine, she experienced a mild headache in the center frontal region of the head, with pressure-like pain that lasted 2 h in duration and did not interrupt her daily activities. She did not have any associated symptoms and did not require treatment. About 15 h following the second dose, she experienced mild chills, a low-grade fever, and mild myalgias which resolved 5 h later. About 10 days after receiving dose 2, the patient reported no new symptoms or recurrences in headaches or migraine attacks.

In clinical practice, the risk of getting a headache after vaccination is a commonly asked question. A recent systematic review and meta-analysis of 84 papers concluded that COVID-19 vaccines are associated with a two-fold risk of developing headache within 7 days from injection (compared with placebo) [68].

Similar trends have been shown in real-world, cross-sectional survey-based studies conducted after vaccine approval: “Headache/fatigue” was the most common systemic side effect (48.1% in mRNA-based vaccines and 74.4% in viral vector-based vaccines) in one [69] and the third most common (45.6%) behind fatigue in another [70]. Data according to the database of Adverse Drug Reactions in Italy has been compared to epidemiologic data according to the Global Health Data Exchange and revealed that the cumulative rate of headache/migraine episodes after receiving all COVID-19 vaccines was 2.25-fold higher than the daily frequency of headache disorders [71].

**Discussion**

**Pathophysiology of Headache Post-Vaccination**

Headache secondary to vaccination is likely due to systemic reactogenicity, the physical and systemic manifestations of the immune response to the vaccine. Headache following vaccination is proposed to occur via prostaglandin E production, release of cytokines such as IL-6, and C-reactive protein [72] which could lead to activation of trigeminal nociceptors. In a similar fashion, immune mediators and products of inflammation could exacerbate symptoms and induce headache persistence in patients with primary headache disorder. Taken together, individuals with migraine have been shown to have clinical evidence of peripheral and central sensitization of the trigeminovascular system, in addition to enhanced sensitivity to inflammatory stimuli [73, 74]. Although inflammation is debated as a mechanism of migraine, our case suggests that the immune response to vaccination may induce cortical spreading depression in individuals with a predisposition to migraine aura. The association between headache, other non-headache symptoms of reactogenicity such as fever, fatigue, and malaise, and immunogenicity should be evaluated in future studies.

**Characteristics of Post-Vaccination Headache**

Prior to the emergence of COVID-19 vaccinations, specific characteristics of headache following vaccination were not systematically examined. Still, HPV vaccination had been identified as a trigger for new daily persistent headache (NDPH) [75]. In our clinical practice, persistent and unremitting headache of at least 3-month duration, consistent with NDPH following vaccination has also been seen in rare circumstances.

An understanding of the characteristics and risk factors related to post-vaccination headache has been further elucidated with recent investigations focused on COVID-19 vaccination. Three questionnaire-based studies have revealed similar timelines with mean intervals of 1.8 ± 3.5 days [76], 18.0 ± 27.0 h [77], and 14.5 ± 21.6 h [78] following vaccination. The mean duration of the attacks has been reported as 14.2 ± 21.3 h [77], 16.3 ± 30.4 h [78], and majority less than 3 days [76]. There is one published case report of status migrainosus lasting 11 days following receipt of vaccination in a patient with history of migraine [79], and status
| Study | Vaccine/technology | Trial details | Within 7 days of first dose | Within 7 days of second dose | Overall headache results |
|-------|--------------------|---------------|-----------------------------|-----------------------------|------------------------|
| 1. Polack et al. [56, 63–65] | BNT162b2 Lipid nanoparticle-encapsulated nucleoside-modified mRNA encoding the prefusion stabilized full-length SARS-CoV2 spike protein [63, 66] | Randomized, observer-blinded, placebo-controlled trial of efficacy and safety Conducted in multiple nations | Age 5–11 years:  
• Any: 22.4% (placebo 24.1%)  
• Mild: 16.5% (placebo 17.5%)  
• Moderate: 5.8% (placebo 6.0%)  
• Severe: 0.1% (placebo 0.5%)  
• Grade 4: 0% (placebo 0%)  
Age 12–15 years:  
• Any: 55.3% (placebo 35.1%)  
• Mild: 32.0% (placebo 22.7%)  
• Moderate: 22.3% (placebo 11.6%)  
• Severe: 1.0% (placebo 0.8%)  
• Grade 4: 0% (placebo 0%)  
Age 16–55 years:  
• Any: 41.9% (placebo 33.7%)  
• Mild: 27.4% (placebo 20.3%)  
• Moderate: 19.9% (placebo 12.6%)  
• Severe: 1.4% (placebo 0.5%)  
• Grade 4: 0% (placebo 0%)  
Age > 55 years:  
• Any: 25.2% (placebo 18.1%)  
• Mild: 19.3% (placebo 13.5%)  
• Moderate: 22.9% (placebo 24.6%)  
• Severe: 0.4% (placebo 0.9%)  
• Grade 4: 0% (placebo 0%) | Age 5–11 years:  
• Any: 28.0% (placebo 18.6%)  
• Mild: 18.7% (placebo 12.6%)  
• Moderate: 9.1% (placebo 6.1%)  
• Severe: 0.2% (placebo 0%)  
• Grade 4: 0% (placebo 0%)  
Age 12–15 years:  
• Any: 64.5% (placebo 24.4%)  
• Mild: 27.5% (placebo 15.7%)  
• Moderate: 35.0% (placebo 8.6%)  
• Severe: 2.0% (placebo 0.1%)  
• Grade 4: 0% (placebo 0%)  
Age 16–55 years:  
• Any: 51.7% (placebo 24.1%)  
• Mild: 25.6% (placebo 15.3%)  
• Moderate: 5.8% (placebo 4.5%)  
• Severe: 0.1% (placebo 0.2%)  
• Grade 4: 0% (placebo 0%)  
Age > 55 years:  
• Any: 39.0% (placebo 13.9%)  
• Mild: 25.4% (placebo 10.0%)  
• Moderate: 13.0% (placebo 3.6%)  
• Severe: 0.5% (placebo 0.2%)  
• Grade 4: 0% (placebo 0%) | Second most commonly occurring solicited systemic event (55.1%), behind fatigue (62.9%)
Table 2 (continued)

| Study | Vaccine/technology | Trial details | Within 7 days of first dose | Within 7 days of second dose | Overall headache results |
|-------|--------------------|---------------|-----------------------------|------------------------------|--------------------------|
| 2. Baden et al. [57, 58] | **mRNA-1273** | Lipid nanoparticle-encapsulated nucleoside-modified mRNA encoding the prefusion stabilized full-length SARS-CoV2 spike protein | Randomized, observer-blinded, placebo-controlled trial of efficacy and safety Conducted at 99 centers across the USA | Age 18–65 years:  
  - Any: 35.3% (placebo 29.0%)  
  - Grade 1<sup>b</sup>: 27.8% (placebo 23.5%)  
  - Grade 2: 5.6% (placebo 4.1%)  
  - Grade 3: 1.9% (placebo 1.4%)  
  - Grade 4: 0% (placebo 0%)  
Age > 65 years:  
  - Any: 24.5% (placebo 19.3%)  
  - Grade 1: 20.7% (placebo 16.8%)  
  - Grade 2: 2.4% (placebo 1.6%)  
  - Grade 3: 1.5% (placebo 0.9%)  
  - Grade 4: 0% (placebo 0%) | Age 18–65 years:  
  - Any: 62.8% (placebo 25.5%)  
  - Grade 1: 33.3% (placebo 20.0%)  
  - Grade 2: 24.5% (placebo 4.1%)  
  - Grade 3: 5.0% (placebo 1.2%)  
  - Grade 4: 0% (placebo 0%)  
Age > 65 years:  
  - Any: 46.2% (placebo 17.8%)  
  - Grade 1: 31.1% (placebo 15.3%)  
  - Grade 2: 12.3% (placebo 1.6%)  
  - Grade 3: 2.9% (placebo 0.9%)  
  - Grade 4: 0% (placebo 0%) | Second most commonly occurring solicited systemic event (63.0%), behind fatigue (68.5%) |
| 3. Sadoff et al. [59] | **Ad26.COV2.S** | Recombinant, replication-incompetent human adenovirus type 26 vector encoding full-length SARS-CoV-2 spike protein in a prefusion-stabilized conformation | Randomized, double-blind, placebo-controlled trial of efficacy and safety Conducted in Argentina, Brazil, Chile, Colombia, Mexico, Peru, South Africa, and the USA | Age 18–59 years:  
  - Any:  
  - Grade 1:  
  - Grade 2:  
  - Grade 3: 0.2% (placebo 0.9%)  
  - Grade 4: 0% (placebo 0%)  
Age > 59 years:  
  - Any:  
  - Grade 1:  
  - Grade 2:  
  - Grade 3: 0.3% (placebo 0.4%)  
  - Grade 4: 0% (placebo 0%) | A single dose of this vaccine was studied | Most commonly occurring solicited systemic event (38.9%) |
| Study | Vaccine/technology | Trial details | Within 7 days of first dose | Within 7 days of second dose | Overall headache results |
|-------|-------------------|---------------|-----------------------------|-----------------------------|-------------------------|
| 4. Ramasamy et al. [60] | ChAdOx1 nCoV-19 / ADZ1222 Replication-defective chimpanzee adenovirus-vectored vaccine expressing the full-length SARS-CoV-2 spike glycoprotein gene | Randomized, single-blind, controlled\(^d\) trial of safety and efficacy Conducted in two trial sites in the UK | Age 18–55 years:  
• Any: 65%  
• Mild: 41%  
• Moderate: 20%  
• Severe: 4%  
• Hospitalization: 0%  
Age 56–69 years:  
• Any: 50%  
• Mild: 50%  
• Moderate: 0%  
• Severe: 0%  
• Hospitalization: 0%  
Age > 69 years:  
• Any: 41%  
• Mild: 35%  
• Moderate: 6%  
• Severe: 0%  
• Hospitalization: 0% | Age 18–55 years:  
• Any: 31%  
• Mild: 24%  
• Moderate: 4%  
• Severe: 1%  
• Hospitalization: 0%  
Age 56–69 years:  
• Any: 34%  
• Mild: 31%  
• Moderate: 3%  
• Severe: 0%  
• Hospitalization: 0%  
Age > 69 years:  
• Any: 20%  
• Mild: 16%  
• Moderate: 4%  
• Severe: 0%  
• Hospitalization: 0% | • Second most commonly occurring solicited systemic event, behind fatigue |
| 5. Heath et al., Keech et al. [61, 62] | NVX-CoV2373 Recombinant nanoparticle contains the full-length spike glycoprotein of the SARS-CoV-2 prototype strain plus Matrix-M adjuvant | Randomized, observer-blinded, placebo-controlled trial of efficacy and safety Phase III trial conducted at 33 sites in the UK | Age 18–84 years:  
• Any: 23% (placebo 30%)  
• Grade 1\(^b\): 19.2% (placebo 21.7%)  
• Grade 2: 3.8% (placebo 8.7%)  
• Grade 3: 0% (placebo 0%)  
• Grade 4: 0% (placebo 0%) | Age 18–84 years:  
• Any: 46% (placebo 29%)  
• Grade 1: 38.5% (placebo 23.8%)  
• Grade 2: 7.7% (placebo 4.8%)  
• Grade 3: 0% (placebo 0%)  
• Grade 4: 0% (placebo 0%) | • Most commonly reported systemic adverse event after both the first (24.5%) and second (40.0%) doses |
| 6. Tanriover et al. [67] | CoronaVac Inactivated whole-virion SARS-CoV-2 vaccine | Randomized, double-blind, placebo-controlled trial of efficacy and safety Phase III trial conducted in Brazil, Indonesia, Chile, and Turkey; data published from Turkey | Age 18–55 years:  
• Any: 23%  
• Grade 1\(^c\): 12%  
• Grade 2: 5%  
• Grade 3: 0%  
• Grade 4: 0% | Age 56–69 years:  
• Any: 31%  
• Grade 1: 19%  
• Grade 2: 6%  
• Grade 3: 0%  
• Grade 4: 0% | • There was no significant difference in report of headache in vaccine (5.91%) versus placebo (5.94%) \((P = 0.9538)\) |

\(^a\)Mild, does not interfere with activity; moderate, some interference with activity; severe, prevents daily activity; grade 4, emergency room visit or hospitalization for severe headache  
\(^b\)Grade 1, does not interfere with daily activity; grade 2, repeated use of OTC pain reliever > 24 h to some interference with activity; grade 3, any use of prescription pain reliever or prevents daily activity; grade 4, requires emergency room visit or hospitalization  
\(^c\)Grade 1 (mild), symptoms causing no or minimal interference with usual social and functional activities (minor headache not requiring medication); grade 2 (moderate), symptoms causing greater than minimal interference with usual social and functional activities (bad headache but able to do most activities with medication); grade 3 (severe), symptoms cause inability to perform usual social and functional activities (severe headache requiring medication and unable to do normal activities during the day); grade 4, symptoms causing inability to perform basic self-care functions OR hospitalization indicated OR headache with significant impairment of alertness or other neurologic function (emergency department or hospital admission required)  
\(^d\)Vaccine was compared with a meningococcal conjugate vaccine (MenACWY) as control
migrainosus following vaccine has also been seen in our clinical practice. According to a recent systematic review and meta-analysis, post-vaccination headache tends to develop within 24 h from injection and usually resolves in less than 24 h [68].

The characteristics of headache after vaccination included a majority with bilateral location [76–78] and often at the forehead and temples [77, 78]. Commonly described pain qualities included pressing, throbbing, and dull [76–78]. Pain intensity was reported most often as moderate (46.2%) or severe (32.1%) in one study [77] and most often as severe (38.7%) or moderate (35.2%) in another [78]. In studies of COVID-19 vaccine, migraine-like features were present in one third of the cases (pulsating quality, phonophobia, and photophobia), and in 40–60% of the cases aggravation with activity was observed [68]. Interestingly, in a cohort of individuals with prior diagnosis of migraine, over half perceived the post-vaccination headache attacks as “different” from those usually experienced; this included higher pain intensity, longer duration, and reduced responsiveness to usually effective pain reliever or prevents daily activity; grade 4, requires emergency room visit or hospitalization. C Grade 1 (mild), symptoms causing no or minimal interference with usual social and functional activities (minor headache not requiring medication); grade 2 (moderate), symptoms causing greater than minimal interference with usual social and functional activities (bad headache but able to do most activities with medication); grade 3 (severe), symptoms cause inability to perform usual social and functional activities (severe headache requiring medication and unable to do normal activities during the day); grade 4, symptoms causing inability to perform basic self-care functions OR hospitalization indicated OR headache with significant impairment of alertness or other neurologic function (emergency department or hospital admission required).

There is one case reporting transient unilateral hemiparesis, sensory deficit, and visual phenomenon followed by headache and lasting 5 days without evidence of cerebral insult on brain imaging which was ultimately attributed to migraine pathology with cortical spreading depression [81]. Another report describes a case of new-onset visual aura phenomenon without headache, although this occurred 127 days after injection; magnetic resonance imaging (MRI) of brain and intracranial vessel imaging were normal [82].

There is one series of 8 patients who experienced lateralized sensory deficits, motor deficits, or both, of 2–14 day duration following CoronaVac vaccination; a history of migraine, female predominance, and abnormal functional brain imaging without structural changes was found and suggestive of migraine aura as pathophysiology [83]. The incidence of aura symptoms related to post-vaccination headache remains unclear at this time.

### Risk Factors for Post-Vaccination Headache

In a web-based questionnaire study, potential risk factors identified for development of headache included female sex,
pre-existing primary headaches (including migraine and tension-type), thyroid disorders, headache during COVID-19, and headache related to the influenza vaccine [76]. However, our review of recent influenza vaccine RCTs includes reported results of trivalent inactivated vaccine and quadrivalent inactivated vaccine, which was mixed.

Another questionnaire-based study also found headache to be more commonly reported in participants who had a prior history of migraine or non-migraine headache compared with healthy controls [84]. Patients who reported headache were more likely to report other systemic VAEs including fever, chills, fatigue, myalgias, joint pain, and nausea or vomiting [76–78].

**Other Secondary Etiologies**

As in the evaluation of all patients presenting with headache complaint, other secondary causes for a post-vaccination headache must be thoroughly considered. Headache was the most common presenting symptom of cerebral venous sinus thrombosis (CVST) following SARS-CoV-2 vaccination, a very rare but severe and potentially fatal complication [85].

There is accumulating evidence supporting an association between (CVST) and adenovirus vector-based vaccines against SARS-CoV-2 (including ChAdOx1 nCov-19 and Ad26.COV2.S); although, one cohort study found no significant association [86]. Development of CVST following vaccination may be mediated by the development of thrombosis and thrombocytopenia syndrome (TTS); one cohort study found that over two thirds of patients who developed CVST within 28 days of SARS-CoV-2 met diagnostic criteria for TTS [87]. A meta-analysis revealed that these thrombotic complications tended to affect predominantly women (69%; 95% CI 60–77%) under age 45, even in the absence of prothrombotic risk factors [88]. Headache related to CVST tended to be delayed compared to the time interval observed in the vaccine safety studies: Studies found the development of CVST-related headache at mean intervals of 8 days [89] and 10 days (within 2 weeks) [88] after exposure.

Suspicion for such an etiology is critical as the pooled mortality rate of TTS-associated CVST was 38% (95% CI 27–49%) [88]. Healthcare providers should be familiar with “red flags” in clinical presentations and the diagnostic criteria for this potential complication and other secondary etiologies (Fig. 1). When suspected, early diagnosis including brain imaging and prompt initiation of treatment can result in more favorable neurologic outcomes.

**Nocebo Effects of Vaccination Trials**

The frequency of headache as a VAE in vaccination trials may be associated with several additional factors, including nocebo effects inherent to clinical trials. VAEs resulting from placebo administration are called nocebo effects. Overall, 12 studies reported headache as a VAE greater within the vaccine group than the placebo. However, 6 studies reported greater headache outcomes in the placebo group than the vaccine group. This may be due to differing sample sizes between the vaccine and the placebo group, with the placebo group being considerably smaller.

The “nocebo effect” has been defined as a negative effect experienced due to the belief that an intervention will cause harm. There is concern that this effect may occur when safety information of a vaccine is updated regularly with spontaneous VAEs, whether they are truly vaccine-related or not [90]. While the nocebo effect is more widely recognized among long-term vaccination efforts of well-described diseases, it has also been observed in recent COVID-19 vaccine trials as a potential factor for bias. In a meta-analysis of VAEs in COVID-19 RCTs, the incidence of nocebo responses was 16.4% while the magnitude was determined to be 0.3% [66]. Nocebo was attributed as a possible contribution for lowered vaccination rates in European countries due to public perception of the vaccine as less effective [91]. Additionally, a nationally representative cross-sectional survey in the UK also documented that side-effect expectation was associated with believing that COVID-19 vaccination was unsafe and ineffective [92].

**Treatment Recommendations**

Given the multitude of potential mediators contributing to vaccine-related headache, these events may require different treatment approaches. In the BNT162b2 mRNA COVID-19 vaccine trial, younger recipients were more likely to report taking an antipyretic or pain medication in response to a moderate or severe headache than older recipients [56]. Based on expert opinion, there is no contraindication to use of NSAIDs and acetaminophen for treatment of headache following vaccination; triptans may also be helpful. Infusion therapies for treatment of status migrainosus may be of particular benefit; anecdotally, we have seen 30–100% response rates with intravenous dihydroergotamine and neuroleptics.

Oral corticosteroids can also be considered after expected immunogenicity is established, especially if other severe non-headache symptoms are also present. There is no consensus on the amount and duration of steroids that will result in suppression of an immunocompetent person [93] but CDC warns of active treatment with high-dose corticosteroids (i.e., 20 or more mg of prednisone or equivalent per day when administered for 2 or more weeks). Moreover, some theoretical guidance is provided by both the Pfizer-BioNTech BNT162b2 mRNA COVID-19 vaccine (28 days after dose 1 and 7 days after dose 2) and the Moderna mRNA-1273 (42 days after day 1 and 14 days after dose 2) [94, 95]. Greater occipital nerve
blocks with corticosteroid may also be effective and corticosteroid sparing when administered peripherally. In general, it is reasonable to delay use for at least 2 weeks, especially in the case of live-virus vaccines [96].

Our clinical practice has shown that it may be beneficial to address the possibility of acute headache triggering after vaccination in patients with a pre-existing primary headache disorder in preparation for vaccination. In addition, for patients with migraine, there are no contraindications to the use of preventive therapies including onabotulinumtoxinA and monoclonal antibodies against calcitonin gene-related peptide [97]. It may be helpful to have a plan to escalate treatment as needed depending on response, including the potential treatment of status migrainosus. Longer term preventive therapies may be indicated for rare cases of headache persistence (e.g., amitriptyline and venlafaxine); treatment options should be guided by the headache phenotype.

**Conclusion**

As both passive surveillance and RCTs have shown, headache is a common although mostly mild and transient VAE following vaccination. There is heterogeneity among randomized controlled trials regarding the grading and scoring of headache severity; therefore, comparison is limited. Often, especially in pediatric trials, headache is not considered or is grouped with other systemic VAEs, which is a limiting factor towards understanding headache as a VAE post-vaccination.

There may be triggering of attacks in patients with baseline primary headache disorders or de novo headache. De novo headache post-vaccination should be considered for inclusion in the next iteration of the International Classification of Headache Disorders. Standardized grading methods, risk factors for persistence, and treatment are warranted in clinical trials, including in open-label phases.

Clinicians including headache specialists play a major role in helping people assess their personal eligibility for a vaccine and weigh the risks and benefits. Communication regarding the relative safety of vaccination and the transient and benign nature of the majority of potential systemic effects including headache can be crucial in the promotion of public health.

**Declarations**

**Conflict of Interest** Kimberly Garces and Alexandra Cocores do not report any significant disclosures or conflicts of interest. Peter James Goadsby reports, over the last 36 months, grants and personal fees from Aeon Biopharma, Allergan/Abbvie, Amgen, Biodelivery Sciences International, Biohaven Pharmaceuticals Inc., CoolTech LLC, Dr Reddys, Epalex, GlaxoSmithKline, Impel Neuropharma, Lundbeck, Novartis, Praxis, Sanofi, Satsuma and Teva Pharmaceuticals, and personal fees for advice through Gerson Lehrman Group, Guidepoint, SAI Med Partners, Vector Metric, and fees for educational materials from CME Outfitters, Omnia Education, WebMD, and publishing royalties or fees from Massachusetts Medical Society, Oxford University Press, UpToDate and Wolters Kluwer, and for medicolegal advice in headache. Teshamse Monteith has received personal compensation for serving on advisory boards for Biohaven, Allegan/Abbvie, Lundbeck, Amgen, Teva, Linpharma and Impel Neuropharmaceuticals. She has also served as a site principal investigator without direct compensation for Teva, Eli Lilly, Electrocore, Amgen, Novartis.

**References**

1. Biswas N, Mustapha T, Khubchandani J, Price JH. The nature and extent of COVID-19 vaccination hesitancy in healthcare workers. J Community Health. 2021;46(6):1244–51. https://doi.org/10.1007/s10900-021-00984-3.
2. Stovner LJ, Hagen K, Linde M, Steiner TJ. The global prevalence of headache: an update, with analysis of the influences of methodological factors on prevalence estimates. J Headache Pain. 2022;23(1):34. https://doi.org/10.1186/s10194-022-01402-2.
3. Ward BJ, Makarkov A, Seguin A, Pillet S, Trepainier S, Dhaliwall J, et al. Efficacy, immunogenicity, and safety of a plant-derived, quadrivalent, virus-like particle influenza vaccine in adults (18–64 years) and older adults (>/>=65 years): two multicentre, randomised phase 3 trials. Lancet. 2020;396(10261):1491–503. https://doi.org/10.1016/S0140-6736(20)32014-6.
4. Chang LJ, Meng Y, Janosczyk H, Landolfi V, Talbot HK, Group QHDS. Safety and immunogenicity of high-dose quadrivalent influenza vaccine in adults (>/>=65years of age: a phase 3 randomised clinical trial. Vaccine. 2019;37(39):5825–34. https://doi.org/10.1016/j.vaccine.2019.08.016.
5. Vesikari T, Nauta J, Lapini G, Montomoli E, van de Witte S. Immunogenicity and safety of quadrivalent versus trivalent inactivated subunit influenza vaccine in children and adolescents: a phase III randomized study. Int J Infect Dis. 2020;92:29–37. https://doi.org/10.1016/j.ijid.2019.12.010.
6. Endo M, Tanishima M, Ibaragi K, Hayashida K, Fukuda T, Tanabe T, et al. Clinical phase II and III studies of an AS03-adjuvanted H5N1 influenza vaccine produced in an EB66(R) cell culture platform. Influenza Other Respir Viruses. 2020;14(5):551–63. https://doi.org/10.1111/irv.12755.
7. Chu K, Xu K, Tang R, Tian X, Hu J, Yang T, et al. Immunogenicity and safety of an inactivated quadrivalent influenza vaccine: a randomized, double-blind, controlled phase III study in healthy population aged >/=4 years. Vaccine. 2020;38(37):5940–6. https://doi.org/10.1016/j.vaccine.2020.06.071.
8. Lan PT, Toan NT, Thang HA, Thang TC, Be LV, Thai DH, et al. A phase 2/3 double-blind, randomized, placebo-controlled study to evaluate the safety and immunogenicity of a seasonal trivalent inactivated split-virion influenza vaccine (IVACFLU-S) in healthy adults in Vietnam. Hum Vaccin Immunother. 2019;15(12):2933–9. https://doi.org/10.1080/21645515.2019.1613127.
9. Loebermann M, Fritzsch C, Geerdes-Fenge H, Heijnen E, Kirby D, Reisinger EC. A phase III, open-label, single-arm, study to evaluate the safety and immunogenicity of a trivalent, surface antigen inactivated subunit influenza virus vaccine produced in mammalian cell culture (Optalflu(R)) in healthy adults. Infection. 2019;47(1):105–9. https://doi.org/10.1007/s15010-018-1233-2.
10. Sarkar S, Bokade C, Garg K, Kumar R, Sannukkani J, Mittal R. Immunogenicity and safety of the first indigenous developed Indian tetravalent influenza vaccine (split virion) in healthy children (6 months to 17 years of age): a randomized, multicenter, phase III clinical trial. Hum Vaccin Immunother. 2021;17(3):681–9. https://doi.org/10.1080/21645515.2020.1794683.
11. Ward BJ, Seguin A, Couinard J, Trepanier S, Landry N. Phase III: randomized observer-blind trial to evaluate lot-to-lot consistency of a new plant-derived quadrivalent virus like particle influenza vaccine in adults 18–49 years of age. Vaccine. 2021;39(10):1528–33. https://doi.org/10.1016/j.vaccine.2021.01.004.

12. Song YJ, Lee J, Woo HJ, Wie SH, Lee JS, Kim SW, et al. Immunogenicity and safety of an egg-based inactivated quadrivalent influenza vaccine (GC3110A) versus two inactivated trivalent influenza vaccines with alternate B strains: a phase randomized clinical trial in adults. Hum Vaccin Immunother. 2019;15(3):710–6. https://doi.org/10.1080/21645515.2018.1553659.

13. Beran J, Reynales H, Poder A, Yu CY, Pitsuttithum P, Yuan LL, et al. Prevention of influenza during mismatched seasons in older adults with an MF59-adjuvanted quadrivalent influenza vaccine: a randomised, controlled, multicentre, phase 3 efficacy study. Lancet Infect Dis. 2021;21(7):1027–37. https://doi.org/10.1016/S1473-3099(20)30402-4.

14. Yamazaki Y, Ikeda M, Imada T, Furuno K, Mizukami T, de Solom R, et al. A phase 3, multicenter, single-arm, open-label study to assess the safety, tolerability, and immunogenicity of a single dose of 13-valent pneumococcal conjugate vaccine in Japanese participants aged 6–64 years who are considered to be at increased risk of pneumococcal disease and who are naive to pneumococcal vaccines. Vaccine. 2021;39(43):6414–21. https://doi.org/10.1016/j.vaccine.2021.08.106.

15. Klein NP, Peyrani P, Yacisin K, Caldwell N, Xu X, Scully IL, et al. A phase 3, randomized, double-blind study to evaluate the immunogenicity and safety of 3 lots of 20-valent pneumococcal conjugate vaccine in pneumococcal vaccine-naïve adults 18 through 49 years of age. Vaccine. 2021;39(38):5428–35. https://doi.org/10.1016/j.vaccine.2021.07.004.

16. Song YJ, Chang CJ, Andrews C, Diez-Domingo J, Oh MD, Dagan R, et al. Safety, tolerability, and immunogenicity of V114, a 15-valent pneumococcal conjugate vaccine, followed by sequential PPV23 vaccination in healthy adults aged =/50 years: a randomized phase III trial (PNEU-PATH). Vaccine. 2021;39(43):6422–36. https://doi.org/10.1016/j.vaccine.2021.08.038.

17. Bastidas A, de la Serna J, El Idrissi M, Oostvogels L, Quittet P, Lopez-Jimenez J, et al. Effect of recombinant zoster vaccine on incidence of herpes zoster after autologous stem cell transplantation: a randomized clinical trial. JAMA. 2019;322(2):123–33. https://doi.org/10.1001/jama.2019.9053.

18. Dagnen AF, Bhan O, Lee WS, Kosczuk D, Kwak JY, Bowcock S, et al. Immunogenicity and safety of the adjuvanted recombinant zoster vaccine in adults with haematological malignancies: a phase 3, randomised, clinical trial and post-hoc efficacy analysis. Lancet Infect Dis. 2019;19(9):988–1000. https://doi.org/10.1016/S1473-3099(19)30163-X.

19. Vink P, Delgado Minorgoraj H, Maximiano Alonso C, Rubio-Viqueira B, Jung KH, Rodriguez Moreno JF, et al. Immunogenicity and safety of the adjuvanted recombinant zoster vaccine in patients with solid tumors, vaccinated before or during chemotherapy: a randomized trial. Cancer. 2019;125(8):1301–12. https://doi.org/10.1002/cncr.31909.

20. Curran D, Kim JH, Matthews S, Dessart C, Levin MJ, Oostvogels L, et al. Recombinant zoster vaccine is efficacious and safe in frail individuals. J Am Geriatr Soc. 2021;69(3):744–52. https://doi.org/10.1111/jgs.16917.

21. Ocran-Appiah J, Bourtay C, Herve C, Soni J, Schuind A, Group Z-S. Safety of the adjuvanted recombinant zoster vaccine in adults aged 50 years or older: A phase IIIb, non-randomized, multinational, open-label study in previous ZOE-50 and ZOE-70 placebo recipients. Vaccine. 2021;39(1):6–10. https://doi.org/10.1016/j.vaccine.2020.10.029.

22. Schmader KE, Levin MJ, Chen M, Matthews S, Riley ME, Woo W, et al. Impact of reactogenicity after two doses of recombinant zoster vaccine upon physical functioning and quality of life: an open phase III trial in older adults. J Gerontol A Biol Sci Med Sci. 2021;76(3):485–90. https://doi.org/10.1093/gerona/lga127.

23. Schmader KE, Levin MJ, Grupping K, Matthews S, Butuk D, Chen M, et al. The impact of reactogenicity after the first dose of recombinant zoster vaccine on the physical functioning and quality of life of older adults: an open-label, phase III trial. J Gerontol A Biol Sci Med Sci. 2019;74(8):1217–24. https://doi.org/10.1093/gerona/gly218.

24. Lopez-Fuqued M, Campora L, Delgado Mingorance I, Maximiano Alonso C, Rubio-Gerona/Gly218.

25. Mikamo H, Yamagishi Y, Murata S, Yokokawa R, Han SR, Wakana A, et al. Efficacy, safety, and immunogenicity of a quadrivalent HPV vaccine in Japanese men: a randomized, phase 3, placebo-controlled study. Vaccine. 2019;37(12):1651–8. https://doi.org/10.1016/j.vaccine.2019.01.069.

26. Joura EA, Ulied A, Vandenmeulen C, Rua Figueroa M, Seppa I, Hernandez Aguado JF, et al. Immunogenicity and safety of a nine-valent human papillomavirus vaccine in women 27–45 years of age compared to women 16–26 years of age: an open-label phase 3 study. Vaccine. 2021;39(20):2800–9. https://doi.org/10.1016/j.vaccine.2021.01.074.

27. Chen W, Zhao Y, Xie X, Liu J, Li J, Zhao C, et al. Safety of a quadrivalent human papillomavirus vaccine in a Phase 3, randomized, double-blind, placebo-controlled clinical trial among Chinese women during 90months of follow-up. Vaccine. 2019;37(6):889–97. https://doi.org/10.1016/j.vaccine.2018.12.030.

28. Thiem VD, Quang ND, Tuan NH, Cheon K, Gallagher N, Luxembourg A, et al. Immunogenicity and safety of a nine-valent human papillomavirus vaccine in Vietnamese males and females (9 to 26 years of age): an open-label, phase 3 trial. Hum Vaccin Immunother. 2021;17(7):1980–5. https://doi.org/10.1080/21645510.2020.1865739.

29. Su YY, Lin BZ, Zhao H, Li J, Lin ZJ, Qiao YL, et al. Lot-to-lot consistency study of an Escherichia coli-produced bivalent human papillomavirus vaccine in adult women: a randomized trial. Hum Vaccin Immunother. 2020;16(7):1636–44. https://doi.org/10.1080/21645515.2019.1691413.

30. Dhingra MS, Peterson J, Hedrick J, Pan J, Neveu D, Jordanov A. Immunogenicity, safety and inter-lot consistency of a meningococcal conjugate vaccine (MenACYW-TT) in adolescents and adults: a phase III randomized study. Vaccine. 2020;38(33):5194–201. https://doi.org/10.1016/j.vaccine.2020.06.013.

31. Estelles-Jaramillo A, Koehler T, Jeanfreau R, Neveu D, Jordanov E, Singh DM. Immunogenicity and safety of a quadrivalent meningococcal tetanus toxoid-conjugate vaccine (MenACYW-TT) in >=56-year-olds: a phase III randomized study. Vaccine. 2020;38(28):4405–11. https://doi.org/10.1016/j.vaccine.2020.04.067.

32. Group MMRS. A second dose of a measles-mumps-rubella vaccine administered to healthy four-to-six-year-old children: a phase III, observer-blind, randomized, safety and immunogenicity study comparing GSK MMR and MMR II with and without DTaP-IPV and varicella vaccines co-administration. Hum Vaccin Immunother. 2019;15(4):786–99. https://doi.org/10.1080/21645515.2018.1554971.

33. Baccarini CI, Simon MW, Brandon D, Christensen S, Jordanov E, Dhingra MS. Safety and immunogenicity of a quadrivalent meningococcal conjugate vaccine in healthy meningococcal-naive children 2–9 years of age: a phase III, randomized study. Pediatr Infect Dis J. 2020;39(10):955–60. https://doi.org/10.1097/INF.0000000000002832.

34. Nolan T, Santolaya ME, de Looze F, Marshall H, Richmond P, Henein S, et al. Antibody persistence and booster response in
adolescents and young adults 4 and 7.5 years after immunization with 4MenB vaccine. Vaccine. 2019;37(9):1209–18. https://doi.org/10.1016/j.vaccine.2018.12.059.

35. Vesikari T, Peltola H, Lyytikainen O, Peltola H, et al. Meningococcal A/CYWY-WP vaccine in adolescents and adults: a phase III randomized study. Hum Vaccin Immunother. 2020;16(6):1292–8. https://doi.org/10.1080/21645515.2020.1738367.

36. Vesikari T, Östergaard L, Beeslaar J, Absalon J, Eiden JJ, Jansen KU, et al. Persistence and 4-year boosting of the bactericidal response elicited by two- and three-dose schedules of MenB-HFp: a phase 3 extension study in adolescents. Vaccine. 2019;37(12):1710–9. https://doi.org/10.1016/j.vaccine.2018.11.073.

37. Tipton M, Daly W, Senders S, Block SL, Lattanzi M, Mzolo T, et al. MenACYW-CRM conjugate vaccine booster dose given 4–6 years after priming: results from a phase IIIb, multicenter, open-label study in adolescents and adults. Vaccine. 2019;37(42):6171–9. https://doi.org/10.1016/j.vaccine.2019.08.065.

38. Nolan T, Booy R, Marshall HS, Richmond P, Nissen M, Ziegler JB, et al. Immunogenicity and safety of a quadrivalent meningococcal ACWY-tetanus conjugate vaccine 6 years after MenC priming as boosters. Pediatr Infect Dis J. 2019;38(6):643–50. https://doi.org/10.1097/INF.0000000000002334.

39. Jiang F, Zhang R, Guan Q, Mu Q, He P, Ye X, et al. Immunogenicity and safety of a live attenuated varicella vaccine in children 1–12 years of age: a randomized, blinded, controlled, non-inferiority phase 3 clinical trial. Contemp Clin Trials. 2021;107:106489. https://doi.org/10.1016/j.cct.2021.106489.

40. Asatryan A, Meyer N, Scherbakov M, Romanenko V, Osipova I, Galustyan A, et al. Immunogenicity, safety, and reactogenicity of combined reduced-antigen-content diphtheria-tetanus-acellular pertussis vaccine administered as a booster vaccine dose in healthy Russian participants: a phase III, open-label study. Hum Vaccin Immunother. 2021;17(3):723–30. https://doi.org/10.1080/21645515.2020.1796423.

41. Vesikari T, Langley JM, Segall N, Ward BJ, Cooper C, Poliquin G, et al. Immunogenicity and safety of a tri-antigenic versus a mono-antigenic hepatitis B vaccine in adults (PROTECT): a randomised, double-blind, phase 3 trial. Lancet Infect Dis. 2021;21(9):1271–81. https://doi.org/10.1016/S1473-3099(20)30780-5.

42. Chaparro M, Gordillo J, Domenech E, Esteve M, Barreiro-de Acosta M, Villoria A, et al. Fendrix vs Engerix-B for primovaccination against hepatitis B infection in patients with inflammatory bowel disease: a randomized clinical trial. Am J Gastroenterol. 2020;115(11):1802–11. https://doi.org/10.1033/j.ajg.0000000000000926.

43. Lee J, Choi JH, Wie SH, Park SH, Choi SM, Lee MS, et al. A phase III study to evaluate the immunogenicity and safety of GC1107 (adult tetanus diphtheria vaccine) in healthy adults. J Korean Med Sci. 2019;34(4):e31. https://doi.org/10.3346/jkms.2019.34.e31.

44. Arredondo JL, Villagomez Martinez SM, Concepcion Morales M, Meyer S, Toth ML, Zocchetti C, et al. Immunogenicity and safety of a tetravalent dengue vaccine and a bivalent HPV vaccine given concomitantly or sequentially in girls aged 9 to 14 years in Mexico. Vaccine. 2021;39(25):3388–96. https://doi.org/10.1016/j.vaccine.2021.04.064.

45. Shen H, Wang Z, Yang B, Cai K, Jiang C, Xie R, et al. Immunogenicity and safety of purified vero cell-cultured rabies vaccine under Zagreb 2–1–1 or 5-dose Essen regimen in the healthy Chinese subjects: a randomized, double-blind, positive controlled phase 3 clinical trial. Hum Vaccin Immunother. 2021;17(2):351–7. https://doi.org/10.1080/21645515.2020.1778408.

46. Matson MA, Schenker E, Stein M, Zamfirina V, Nguyen HB, Bergman GE. Safety and efficacy results of simulated post-exposure prophylaxis with human immune globulin (HIG: KEDRAB) co-administered with active vaccine in healthy subjects: a comparative phase 2/3 trial. Hum Vaccin Immunother. 2020;16(2):452–9. https://doi.org/10.1080/21645515.2019.1659697.

47. de Bruyn G, Gordon DL, Steiner T, Tambah Y, Cogrove C, Martens M, et al. Safety, immunogenicity, and efficacy of a Closstrioides difficile toxoid vaccine candidate: a phase 3 multicentre, observer-blind, randomised, controlled trial. Lancet Infect Dis. 2021;21(2):252–62. https://doi.org/10.1016/S1473-3099(20)30331-5.

48. McCarty JM, Lock MD, Bennett S, Hunt KM, Simon JK, Gurwitz M. Age-related immunogenicity and reactogenicity of live oral cholera vaccine CVD 103-HgR in a randomized, controlled clinical trial. Vaccine. 2019;37(11):1389–97. https://doi.org/10.1016/j.vaccine.2019.01.077.

49. Gray GE, Bekker LG, Laher F, Malahlela M, Allen M, Moodie Z, et al. Vaccine efficacy of ALVAC-HIV and bivalent subtype C gp120-MFS9 in adults. N Engl J Med. 2021;384(12):1089–100. https://doi.org/10.1056/NEJMoa2101499.

50. Brogana HA, Hofer M, Kuenmerle-Deschner JB, Koh-Paut I, Roessler J, Kallinich T, et al. Rapid and sustained long-term efficacy and safety of canakinumab in patients with cryopyrin-associated periodic syndrome ages five and younger. Arthritis Rheumatol. 2019;71(11):1955–63. https://doi.org/10.1002/art.41004.

51. Riveau G, Schacht AM, Dompnier JP, Deplagne D, Seck M, Waucquier N, et al. Safety and efficacy of the rSf282R GST urochistosomiasis vaccine: a phase 3 randomized, controlled trial in Senegalese children. PLoS Negl Trop Dis. 2018;12(12):e0006968. https://doi.org/10.1371/journal.pntd.0006968.

52. Markman J, Resnick M, Greenberg S, Katz N, Yang R, Scavone J, et al. Efficacy of pregabal in post-traumatic peripheral neuropathic pain: a randomized, double-blind, placebo-controlled phase 3 trial. J Neurol. 2018;265(12):2815–24. https://doi.org/10.1007/s00415-018-9063-9.

53. Song JY, Jeong HW, Yun JW, Lee J, Woo HJ, Bae JY, et al. Immunogenicity and safety of a modified three-dose priming and booster schedule for the Hantaan virus vaccine (Hantavax): a multi-center phase III clinical trial in healthy adults. Vaccine. 2020;38(30):8016–23. https://doi.org/10.1016/j.vaccine.2020.10.035.

54. Halperin SA, Ras D, Onorato MT, Liu K, Martin J, Grant-Klein RJ, et al. Immunogenicity, lot consistency, and extended safety of rSVS/DELAg-ZEBOV-GP vaccine: a phase 3 randomized, double-blind, placebo-controlled study in healthy adults. J Infect Dis. 2019;220(7):1127–35. https://doi.org/10.1093/infdis/jiz241.

55. Polack FP, Thomas SJ, Kitchin N, Absalon J, Kurtman A, Lockheed S, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med. 2020;383(27):2603–15. https://doi.org/10.1056/NEJMoa2034577.

56. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med. 2021;384(5):403–16. https://doi.org/10.1056/NEJMoa2035389.

57. Moderna TX I. Vaccines and related biological products advisory committee meeting, December 17, 2020: FDA Briefing Document. 2020. Available from: https://www.fda.gov/media/144443/download.

58. Sadoff J, Gray G, Vandenbosh A, Cardenas V, Shahkave G, Grinsztejn B, et al. Safety and efficacy of single-dose Ad26 COV2-S vaccine against Covid-19. N Engl J Med. 2021;384(23):2187–201. https://doi.org/10.1056/NEJMoa2105144.

59. Ramasamy MN, Minassian AM, Ewer KJ, Flaxman AL, Folegatti PM, Owens DR, et al. Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults (COV002): a
single-blind, randomised, controlled, phase 2/3 trial. Lancet. 2021;396(10267):1979–93. https://doi.org/10.1016/S0140-6736(20)32466-1.

61. Heath PT, Galiza EP, Baxter DN, Boffito M, Browne D, Burns F, et al. Safety and efficacy of NVX-CoV2373 Covid-19 vaccine. N Engl J Med. 2021. https://doi.org/10.1056/NEJMoa2107659.

62. Kheech C, Albert G, Cho I, Robertson A, Reed P, Neal S, et al. Phase 1–2 trial of a SARS-CoV-2 recombinant spike protein nanoparticle vaccine. N Engl J Med. 2020;383(24):2320–32. https://doi.org/10.1056/NEJMoa2026920.

63. Pfizer-BioNTech COVID-19 vaccine BNT162, P. Vaccines and related biological products advisory committee briefing document. 2020. Available from: https://www.fda.gov/media/144434/download.

64. Pfizer-BioNTech COVID-19 Vaccine Reactions & Adverse Events. www.cdc.gov/covid-vaccine/covid-19-info-by-product/pfizer/reactogenicity.html (2021). Accessed 28 Nov 2021.

65. Frenck RW Jr, Klein NP, Kitchin N, Gurtman A, Absalon M, Lockhart S, et al. Safety, immunogenicity, and efficacy of the BNT162b2 Covid-19 vaccine in adolescents. N Engl J Med. 2021;385(3):239–50. https://doi.org/10.1056/NEJMoa2107456.

66. Lee YH, Song GG. Nocebo responses in randomized controlled trials of COVID-19 vaccines. Int J Clin Pharmacol Ther. 2021. https://doi.org/10.5414/CP204028.

67. Tanriover MD, Doganay HL, Akova M, Guner HR, Azap A, Akhan S, et al. Efficacy and safety of an inactivated whole-virion SARS-CoV-2 vaccine (CoronaVac): interim results of a double-blind, randomised, placebo-controlled, phase 3 trial in Turkey. Lancet. 2021;398(10296):213–22. https://doi.org/10.1016/S0140-6736(21)01429-X.

68. Castaldo M, Waliszewska-Prosól M, Koutsokera M, Robotti M, Straburzyński M, Apostolakopoulou L, et al. Headache onset after vaccination against SARS-CoV-2: a systematic literature review and meta-analysis. J Headache Pain. 2022;23(1):41. https://doi.org/10.1186/s10194-021-01400-4.

69. Kular J, Riad A, Mekhemar M, Conrad J, Buchbender M, Howaldt HP, et al. Side effects of mRNA-based and viral vector-based COVID-19 vaccines among German healthcare workers. Biology. 2021;10(8):752.

70. Riad A, Pokorna A, Attia S, Klugarova J, Kosck M, Klugar M. Prevalence of COVID-19 vaccine side effects among healthcare workers in the Czech Republic. J Clin Med. 2021;10(7).

71. Mattuuzzi C, Lippi G. Headache after COVID-19 vaccination: updated report from the Italian Medicines Agency database. Neurol Sci. 2021;42(9):3531–2. https://doi.org/10.1007/s10072-021-05354-4.

72. Herve C, Laupeze B, Del Giudice G, Didierlaurent AM, Tavares Da Silva F. The how’s and what’s of vaccine reactogenicity. NPI Vaccines. 2019;4:39. https://doi.org/10.3814/s14514-019-0132-6.

73. Goadsby PJ, Holland PR. An update: pathophysiology of migraine. Neurol Clin. 2019;37(4):651–71. https://doi.org/10.1016/j.ncl.2019.07.008.

74. Ferrari MD, Goadsby PJ, Burstein R, Kurth T, Ayata C, Charles M, et al. Clinical characteristics of headache after vaccination against COVID-19 (coronavirus SARS-CoV-2) with the BNT162b2 mRNA vaccine: a multicentre observational cohort study. Brain Commun. 2021;3(3):fcab169. https://doi.org/10.1093/braincomms/fcab169.

75. Gobel CH, Heinez A, Karstedt S, Morschek M, Tashiro L, Cirkel A, et al. Headache attributed to vaccination against COVID-19 (coronavirus SARS-CoV-2) with the ChAdOx1 nCoV-19 (AZD1222) vaccine: a multicenter observational cohort study. Pain Ther. 2021;10(2):1309–30. https://doi.org/10.1007/s40122-021-00296-3.

76. Consoli S, Dono F, Evangelista G, D’Apolito M, Travaglini D, Onofrj M, et al. Status migrainosus: a potential adverse reaction to Comirnaty (BNT162b2, BioNtech/Pfizer) COVID-19 vaccine-a case report. Neurol Sci. 2021. https://doi.org/10.1007/s10072-021-05714-x.

77. Silvestro M, Tessitore A, Orollolo J, Sopioz P, Napolitano G, Siciliano M, et al. Headache worsening after COVID-19 vaccination: an online questionnaire-based study on 841 patients with migraine. J Clin Med. 2021;10(24).

78. Rattanawong W, Akaratantawat W, Tempmongsol K, Chutinet A, Santivatan J, Suwanwela NC. Acute prolonged motor aura resembling ischemic stroke after COVID-19 vaccination (CoronaVac): the first case report. J Headache Pain. 2021;22(1):93. https://doi.org/10.1186/s10194-021-01311-w.

79. Salai G, Bilic E, Primorac D, Lakusim DM, Bilic H, Lazarib I, et al. Benign fasciculation syndrome and migraine aura without headache: possible rare side effects of the BNT162b2 mRNA vaccine? A case report and a potential hypothesis. Vaccines (Basel). 2022;10(1).

80. Suwanwela NC, Kijjaisalratan N, Tepmongsol K, Rattanawong W, Vorasanay P, Charnnarong C, et al. Prolonged migraine aura resembling ischemic stroke following COVID-19 vaccination: an extended case series. J Headache Pain. 2022;23(1):13. https://doi.org/10.1186/s10194-022-01385-0.

81. Sekiguchi K, Watanabe N, Miyazaki N, Ishizuki K, Iba C, Tagashira Y, et al. Incidence of headache after COVID-19 vaccination in patients with history of headache: a cross-sectional study. Cephalalgia. 2021;33:31024211038654. https://doi.org/10.1177/03310341221038654.

82. Sharifian-Dorche M, Bahmanyar M, Sharifian-Dorche A, Mohammadi P, Nomovi M, Mowla A. Vaccine-induced immune thrombotic thrombocytopenia and cerebral venous sinus thrombosis post COVID-19 vaccination: a systematic review. J Neurol Sci. 2021;428:e2136-707. https://doi.org/10.1016/j.jns.2021.117607.

83. Pawlowski C, Rincon-Hekking J, Awasthi S, Pandey V, Lenehan M, Baykan B. The characteristics of COVID-19 vaccine-related blood disorders: a single-blind, randomised, controlled, phase 2/3 trial. Lancet. 2021. https://doi.org/10.1016/S0140-6736(20)32462-8.

84. Sekiguchi K, Watanabe N, Miyazaki N, Ishizuki K, Iba C, Tagashira Y, et al. Incidence of headache after COVID-19 vaccination in patients with history of headache: a cross-sectional study. Cephalalgia. 2021;33(10):24211038654. https://doi.org/10.1177/03310341221038654.

85. Sanchez van Kammen M, Aguiar de Sousa D, Poli S, Cordonnier C, Heldner MR, van de Munckhof A, et al. Characteristics and outcomes of patients with cerebral venous sinus thrombosis in SARS-CoV-2 vaccine-induced immune thrombotic thrombocytopenia. JAMA Neurol. 2021;78(11):1314–23. https://doi.org/10.1001/jamaneurol.2021.3619.

86. Palaiodimou L, Stefanou MI, Katsanos AH, Aguiar de Sousa D, Coutinho JM, Lagiou P, et al. Cerebral venous sinus thrombosis is not significantly linked to COVID-19 vaccines or non-COVID vaccines in a large multi-state health system. J Stroke Cerebrovasc Dis. 2021;30(10):105923. https://doi.org/10.1016/j.jstrokecerebrovasdis.2021.105923.

87. Garcia-Azorin D, Do TP, Gantenbein AR, Hansen JM, Souza MNP, Obermann M, et al. Delayed headache after COVID-19 vaccination: a red flag for vaccine induced cerebral venous thrombosis. J Headache Pain. 2021;22(1):108. https://doi.org/10.1186/s10194-021-01324-5.
91. Amanzio M, Cipriani GE, Bartoli M. How do nocebo effects in placebo groups of randomized controlled trials provide a possible explicative framework for the COVID-19 pandemic? Expert Rev Clin Pharmacol. 2021;14(4):439–44. https://doi.org/10.1080/17512433.2021.1900728.

92. Smith LE, Sim J, Amlot R, Cutts M, Dasch H, Sevdalis N, et al. Side-effect expectations from COVID-19 vaccination: findings from a nationally representative cross-sectional survey (CoVAccS - wave 2). J Psychosom Res. 2021;152:110679. https://doi.org/10.1016/j.jpsychores.2021.110679.

93. Rubin LG, Levin MJ, Ljungman P, Davies EG, Avery R, Tomblyn M, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis. 2014;58(3):e44-100. https://doi.org/10.1093/cid/cit684.

94. Hong SM, Park YW, Choi EJ. Steroid injections in pain management: influence on coronavirus disease 2019 vaccines. Korean J Pain. 2022;35(1):14–21. https://doi.org/10.3344/kjp.2022.35.1.14.

95. Spine Intervention Society. Preliminary recommendations on corticosteroid injections and COVID-19 vaccinations friday, January 22, 2021. Available from: https://www.spineintervention.org/news/548668/Preliminary-Recommendations-on-Corticosteroid-Injections-and-COVID-19-Vaccinations.htm.

96. Chow RM, Rajput K, Howie BA, Varhahhatla N. The COVID-19 vaccine and interventional procedures: exploring the relationship between steroid administration and subsequent vaccine efficacy. Pain Pract. 2021;21(8):966–73. https://doi.org/10.1111/papr.13062.

97. Gelfand AA, Poland G. Migraine treatment and COVID-19 vaccines: no cause for concern. Headache. 2021;61(3):409–11. https://doi.org/10.1111/head.14086.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Springer Nature or its licensor (e.g. a society or other partner) holds exclusive rights to this article under a publishing agreement with the author(s) or other rightsholder(s); author self-archiving of the accepted manuscript version of this article is solely governed by the terms of such publishing agreement and applicable law.