NATIONAL ACADEMIES *Sciences Engineering Medicine*

Evidence Review of the Adverse Effects of COVID-19 Vaccination and Intramuscular Vaccine Administration

ACCV
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Committee

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Statement of Task

The National Academies of Sciences, Engineering, and Medicine will convene an ad hoc committee to review the epidemiological, clinical, and biological evidence regarding the relationship between

- COVID-19 vaccines and specific adverse events i.e., Guillain-Barré Syndrome (GBS), chronic inflammatory demyelinating polyneuropathy (CIDP), transverse myelitis, Bell's palsy, hearing loss, tinnitus, chronic headaches, infertility, sudden death, myocarditis/pericarditis, thrombosis with thrombocytopenia syndrome (TTS), immune thrombocytopenic purpura (ITP), thromboembolic events (e.g., cerebrovascular accident (CVA), myocardial infarction (MI), pulmonary embolism, deep vein thrombosis (DVT)), capillary leak syndrome, (and POTS) and

- intramuscular administration of vaccines and shoulder injuries.

The committee will make conclusions about the causal association between vaccines and specific adverse events.

The committee reviewed evidence regarding 19 potential harms from each of the 4 COVID-19 vaccines and regarding 9 specific shoulder injuries subsequent to any vaccination.

Background

- Congress passed the National Childhood Vaccine Injury Act (NCVIA) (P.L. 99-660) in 1986. Among many provisions, the Act mandated two reports by the Institute of Medicine, published in 1991 and 1994.

- The Vaccine Injury Compensation Program (VICP) has used reports from the National Academies of Sciences, Engineering, and Medicine (the National Academies) as an important scientific contribution to its compensation decisions
    - Adverse effects of pertussis and rubella vaccines (1991)
    - Adverse events associated with childhood vaccines: Evidence bearing on causality (1994)
    - Immunization safety review series (2001-2004)
    - Adverse effects of vaccines: Evidence and causality (2012)

- The National Academies has NEVER recommended for or against inclusion on the Vaccine Injury Table or on compensation.

Causality Conclusions

The committee adopted the wording of the causality conclusions developed by National Academies/Institute of Medicine committees and approached the evaluation of evidence from a position of neutrality, presuming neither causation nor lack of causation.

- **Evidence establishes a causal relationship**—The totality of the evidence suggests that vaccination can cause this harm. *Further research is unlikely to lead to a different conclusion.*

- **Evidence favors acceptance of a causal relationship**—The totality of the evidence suggests that vaccination might cause this harm, but meaningful uncertainty remains. *Studies that better minimize bias and confounding, and studies that estimate effects more precisely, could lead to a different conclusion.*

- **Evidence is inadequate to accept or reject a causal relationship**—The available evidence is too limited (e.g., few studies in humans, biased, imprecise) or inconsistent to draw meaningful conclusions in support of or against causality. *Future research could lead to a different conclusion.* This conclusion also applies to situations in which no studies were identified.

- **Evidence favors rejection of a causal relationship**—The totality of the evidence suggests that vaccination does not cause this harm, but *meaningful uncertainty remains*. The committee acknowledges that individual causal effects are difficult to ascertain and the *limitations of applying population average effects to draw conclusions about the causes of specific events in individual people.*

Literature search

Epidemiological, clinical literature search:

- The COVID-19 adverse events literature search included literature published between January 1, 2020- October 17, 2023.
  - The committee restricted its review to U.S. vaccine platforms but included studies conducted outside of the United States.
    - mRNA (Pfizer, Moderna)
    - Adenoviral vector (Janssen)
    - Protein subunit (Novavax)

- The shoulder injury literature search included literature published since the last NASEM vaccine evidence review (2012), January 1, 2011-October 17, 2023.

Mechanisms literature search:

- Included literature published between January 2020- September 2023.
- An ad hoc search included literature published between January 2000–April 2023 and explored general mechanisms underlying vaccine–immune interactions, focusing on non-SARS-CoV-2 messenger ribonucleic acid (mRNA) and adenovirus-vector (AV) vaccines.

Sufficient evidence for 20 of 85 conclusions

Shoulder injury conclusions (n=9)

- Evidence establishes a causal relationship (*n* = 4)
- Evidence favors rejection of a causal relationship (*n* = 1)

COVID-19 vaccine conclusions (n=76)

- Evidence establishes a causal relationship (*n* = 2)
- Evidence favors acceptance of a causal relationship (*n* = 2)
- Evidence favors rejection of a causal relationship (*n* = 11)

SIRVA

"SIRVA represents a clinical syndrome, is not a specific diagnosis, and may have a number of causes. There are no specific objective tests to diagnose the condition and no specific ICD-10 codes exist for "SIRVA" (Zheng et al., 2022). In fact, "SIRVA represents a constellation of different pain-causing diagnoses" (Atanasoff et al., 2010; Cagle, 2021; MacMahon et al., 2022; Slette et al., 2022; Wood and Ilyas, 2022; Wright et al., 2023). As a result, "SIRVA" is considered confusing (Petrakis et al., 2023), is controversial (MacMahon et al., 2022), leads to conflicting reports in the literature (Leopold, 2022), and may be best described as a medico-legal term instead of a diagnosis (Mackenzie et al., 2022). The American Academy of Orthopedic Surgeons offered a position statement (AAOS, 2017) that does not use the term "SIRVA"…."

Shoulder Injuries

- Identified potential mechanisms of injury:
  - **Direct Trauma:** From improper injection technique leading to incorrect placement within the arm.
  - **Reaction to Injection:** Needle or fluid-related injuries that occur despite correct vaccination placement, indicating technique-independent reactions.
  - **Vaccine Constituents:** Harms induced by vaccine ingredients, such as antigens or adjuvants, irrespective of administration accuracy.
- Nine specific injuries assessed

Despite being regarded as the lowest level of evidence, well-defined case reports can provide compelling evidence, which is what the committee aims to present in this context.

Subacromial/subdeltoid bursitis

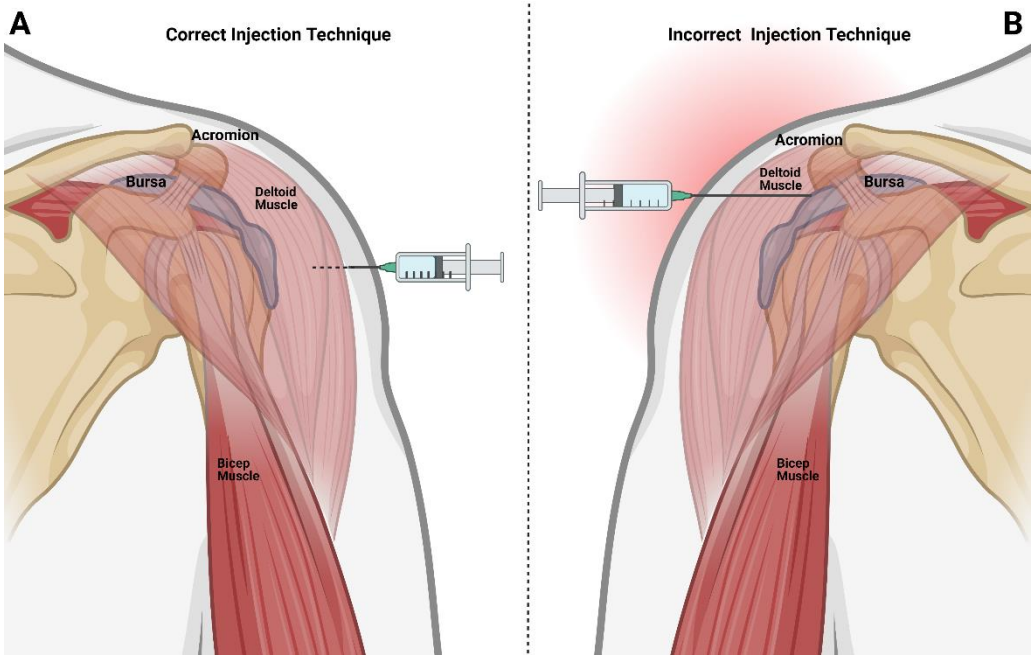

FIGURE 10-1 Illustration of intramuscular injection techniques.
NOTES: A. Correct Injection Technique: Demonstrates proper administration of an intramuscular vaccine into the deltoid muscle, utilizing an appropriate anatomical approach for effective delivery. Dotted line indicates needle inside the deltoid muscle. B. Incorrect Injection Technique: Depicts an erroneous injection leading to inadvertent administration into the subdeltoid bursa, potentially inducing deltoid or subdeltoid bursitis. Solid needle line indicated breach into the bursa. Created with BioRender.com.

Subacromial/subdeltoid bursitis

- The committee conclusion is derived from a body of evidence, as demonstrated in the 15 case reports described in Table 10-1, that consistently features ultrasound or MRI imaging and symptom onset in the ipsilateral shoulder occurring within a biologically significant time window (typically 0–48 hours after vaccination).
    - Studies that lacked pertinent imaging data or extend beyond this critical time frame present a less compelling connection to vaccination.
- Many patients report that the injection was “too high” or “too deep,” which would put the vaccine material in the subdeltoid bursa.
    - The mechanism behind subacromial/subdeltoid bursitis following vaccine administration is closely tied to the incorrect placement of the needle, particularly when it is higher than expected.

Conclusion 10-1: The evidence establishes a causal relationship between vaccine administration and subacromial/subdeltoid bursitis caused by direct injection into the bursa.

Acute rotator cuff or acute biceps tendinopathy

- The committee's decision is derived from a body of evidence, as demonstrated in the case reports provided (Table 10-2).
- Injection of a vaccine into the biceps or rotator cuff tendon can produce an acute tendinosis characterized by edema and increased signal on ultrasound or MRI imaging.

Conclusion 10-2: The evidence establishes a causal relationship between vaccine administration and acute rotator cuff or acute biceps tendinopathy caused by direct administration of vaccine into or adjacent to the tendon

Bone injury

- The conclusion is derived from a body of evidence, as demonstrated in the case reports (Table 10-5), which consistently feature imaging and symptom onset within a biologically significant time window (typically 0–72 hours after vaccination).
    - Studies that lacked pertinent imaging data or extend beyond this critical time frame present a less compelling connection to vaccination.

- Patients who develop shoulder pain after vaccination will rarely demonstrate bone erosions, new-onset avascular necrosis, or bone marrow edema. These changes occur at the site of the injection and appear acute on imaging.

- Although the mechanistic data is limited, it does suggest that bone erosions in patients with shoulder pain may have T cell activation of osteoclasts, which would produce these erosions.

Conclusion 10-6: The evidence establishes a causal relationship between vaccine administration and bone injury caused by direct injection of vaccine into or adjacent to the bone.

Axillary or radial nerve injury

- The committee conclusion is derived from a body of evidence, as demonstrated in the case reports provided (see Table 10-6), which consistently feature imaging or EMG/NCS and symptom onset occurring within a biologically significant time (typically 0–24 hours after vaccination).
  - Studies that lack pertinent imaging data or extend beyond this critical time frame are likely to present a less compelling connection to vaccine administration.

- The axillary and radial nerves are potentially at risk for deltoid vaccine injections.
  - A direct injection of vaccine material into or near a nerve could damage it, producing pain and weakness for its sensory and motor portions. Damage can be confirmed by diagnostic studies.

Conclusion 10-7: The evidence establishes a causal relationship between vaccine administration and axillary or radial nerve injury caused by direct injection into or adjacent to the nerve.

Chronic rotator cuff disease

- Chronic rotator cuff disease is typically a degenerative age-related condition and ubiquitous in the adult population. An injection into tendon material may produce increased signal on MRI imaging and an acute tendinosis but not acute rotator cuff tears or corresponding rotator cuff muscle atrophy.

- Although it is common for patients with shoulder pain to undergo imaging and identify degeneration in the rotator cuff, these findings are more likely pre-existing and not related to a vaccine.

- The committee found the lack of a mechanistic explanation for chronic rotator cuff disease compelling.

Conclusion 10-3: The evidence favors rejection of a causal relationship between vaccine administration and chronic rotator cuff disease.

Shoulder injuries, continued

The committee concluded the evidence was inadequate to accept or reject a causal relationship for:

- Adhesive capsulitis
- Septic arthritis
- Parsonage-Turner syndrome
- Complex regional pain syndrome

Questions on Shoulder Injuries?

Next section will be a brief overview of the COVID-19 vaccine conclusions.

COVID-19 vaccine conclusions:

establishes a causal relationship (n=2)

Myocarditis

The committee identified consistent findings of a large relative risk of myocarditis after either mRNA vaccine (Pfizer, Moderna) in numerous high-quality observational studies, an absolute risk that is orders of magnitude greater than the background rate in certain age and sex subgroups, and a plausible biological mechanism for mRNA vaccines. The strong and substantial body of evidence indicates that the risk of harm varies by age and sex, but it does not exclude the presence of a causal effect in any particular group defined by age or sex.

Conclusion 7-1: The evidence establishes a causal relationship between the BNT162b2 (Pfizer) vaccine and myocarditis.

Conclusion 7-2: The evidence establishes a causal relationship between the mRNA-1273 (Moderna) vaccine and myocarditis.

COVID-19 vaccine conclusions:

favors acceptance of a causal relationship (n=2)

Guillain-Barré syndrome

- The totality of evidence for Ad26.COV2.S (Janssen) includes two well-designed, positive epidemiological studies and pharmacovigilance data.
- Five studies observed an increased risk of GBS and ChAdOx1-S (AstraZeneca).
- The epidemiological association between GBS and ChAdOx1-S (AstraZeneca) but not mRNA vaccines (Pfizer, Moderna) suggests that the mechanism is unlikely to relate to immune responses to the spike protein itself. In addition, the reported increased rates after AV vaccines suggest a potential shared mechanism, although no definitive one was identified by the committee in the mechanistic literature.

- **Conclusion 3-3: The evidence favors acceptance of a causal relationship between the Ad26.COV2.S (Janssen) vaccine and Guillain-Barré syndrome.**

Thrombosis with thrombocytopenia syndrome (TTS)

- TTS is a syndrome of blood clotting at unusual sites, together with low platelet counts.
- Initial cases of TTS post-vaccination (ChAdOx1-S (AstraZeneca)) revealed an almost universal presence of platelet activating (anti-PF4) antibodies. Anti-PF4 antibodies were also demonstrated in people with TTS after the Ad26.COVS.S (Janssen) vaccine.
- The notable association of TTS with adenovirus vaccines versus the rare incidence following mRNA (Pfizer, Moderna) vaccination suggests a potential platform effect specific to adenovirus vectors.
- No cross reactivity of these antibodies with the COVID spike protein.

Thrombosis with thrombocytopenia syndrome

The committee was not able to identify any data from comparative epidemiology studies on the association between Ad26.COV2.S (Janssen) and TTS.

The presence of anti-PF4 antibodies in individuals presenting with TTS after Ad26.COV2.S (Janssen) was deemed strong mechanistic evidence associating that vaccine with TTS, particularly when similar mechanistic data associating the ChAdOx1-S (AstraZeneca) vaccine with TTS is taken into consideration.

Conclusion 5-3: The evidence favors acceptance of a causal relationship between the Ad26.COV2.S (Janssen) vaccine and thrombosis with thrombocytopenia syndrome.

COVID-19 vaccine conclusions:

favors rejection of a causal relationship (n=11)

Guillain-Barré syndrome

Epidemiologic evidence

- Observational studies (9)
- Pharmacovigilance and surveillance (5)

The totality of the evidence included several large self controlled or concurrent cohort studies, or studies relied on chart review for case ascertainment; none of the epidemiological studies reported a significant risk of GBS after BNT162b2 (Pfizer). This is reinforced by the pharmacovigilance data.

Conclusion 3-1: The evidence favors rejection of a causal relationship between the BNT162b2 (Pfizer) vaccine and Guillain-Barré syndrome.

Relatively few mRNA-1273 (Moderna) doses were included in the studies. Only one study reported an increased risk of GBS after the first and second dose, although the CIs for the measure of association were very wide and the excess number of cases was very small (<1 case per 100,000 doses) (Morciano et al., 2023).

Conclusion 3-2: The evidence favors rejection of a causal association between the mRNA-1723 (Moderna) vaccine and Guillain-Barré syndrome.

Bell's Palsy

Epidemiological evidence

- Observational studies (11)

Only one of 11 studies reported a significantly increased risk of BP after the first dose of BNT162b2 (Pfizer) (Shibli et al., 2021), although its results are prone to confounding because it used historical rates as the comparator; studies using concurrent comparators did not find an association between BP and mRNA vaccines (Pfizer, Moderna).

Conclusion 3-9: The evidence favors rejection of a causal relationship between the BNT162b2 (Pfizer) vaccine and Bell's Palsy.

Conclusion 3-10: The evidence favors rejection of a causal relationship between the mRNA-1273 (Pfizer) vaccine and Bell's Palsy.

TTS

The three observational studies failed to find an association between mRNA (Pfizer, Moderna) vaccinations and TTS.

An analysis of cases of TTS reported to VAERS found only three after mRNA vaccination (See et al., 2022), translating into a reporting rate of 0.00855 per million doses which the committee interpreted as likely representative of the background rate in the general population (compared to 3.83 per million with Ad26.COV2.S (Janssen)).

Conclusion 5-1: The evidence favors rejection of a causal relationship between the BNT162b2 (Pfizer) vaccine and thrombosis with thrombocytopenia syndrome.

Conclusion 5-2: The evidence favors rejection of a causal relationship between the mRNA-1273 (Moderna) vaccine and thrombosis with thrombocytopenia syndrome.

Myocardial Infarction

All eight studies showed no important statistical evidence of increased risk of MI associated with either dose of BNT162b2 (Pfizer). Several of these studies were large and adequately powered to detect small increases in risk.

Conclusion 6-1: The evidence favors rejection of a causal relationship between the BNT162b2 (Pfizer) vaccine and myocardial infarction.

Only two studies evaluated the association between mRNA-1273 (Moderna) and MI; neither showed evidence of increased risk (Botton et al., 2022; Shoaibi et al. 2023), but the findings aligned with those for BNT162b2 (Pfizer).

Conclusion 6-2: The evidence favors rejection of a causal relationship between the mRNA-1273 (Moderna) vaccine and myocardial infarction.

Ischemic stroke

All six studies showed no important evidence of increased risk of ischemic stroke associated with either dose of BNT162b2 (Pfizer). Several of these studies were large and adequately powered to detect small increases in risk.

Conclusion 6-5: The evidence favors rejection of a causal relationship between the BNT162b2 (Pfizer) vaccine and ischemic stroke.

Female infertility

The 8 studies reviewed reported no effect of COVID-19 vaccines on fertility. The donor oocyte studies provide the strongest clinical evidence, although the sample sizes were small (Bosch et al., 2023; Karavani et al., 2022). The lack of an adverse impact on ovarian function further suggests no effect on fertility. This conclusion was further supported by animal and human data that disprove a hypothesized mechanism (Lu-Culligan et al., 2022; Prasad et al., 2021).

Conclusion 9-1: The evidence favors rejection of a causal relationship between the BNT162b2 (Pfizer) vaccine and infertility.

Conclusion 9-2: The evidence favors rejection of a causal relationship between the mRNA-1273 (Moderna) vaccine and infertility.

Inadequate evidence: conclusions of note

- Transverse myelitis
- Sensorineural hearing loss
- Tinnitus
- Immune thrombocytopenic purpura
- Hemorrhagic stroke
- Deep vein thrombosis, pulmonary embolism, venous thromboembolism

Pediatrics

- **Potential Adverse Events in Children Under 12:**
  - The absolute increase in risk from BNT162b2 and mRNA-1273 in the 5–11 age group appears to be less than in the 12–17 years and young adult age groups, but because of the epidemiological evidence, the magnitude of risk in this age group is uncertain.
  - VAERS data show no myocarditis cases after hundreds of thousands of doses in children 6 months to 4 years.
  - Limited data on immune-mediated reactions, neurological syndromes, and thromboembolic events.
- **Potential Adverse Events in Children Over 12:**
  - Increased myocarditis risk identified, especially in males aged 12–17, with cases exceeding population norms.
  - Larger surveillance studies include children over 12 but often lack pediatric-specific analyses.
- **Shoulder Injuries Post-Vaccination:**
  - Case reports in children are scarce, indicating very rare occurrences of specific shoulder injuries post-vaccination

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