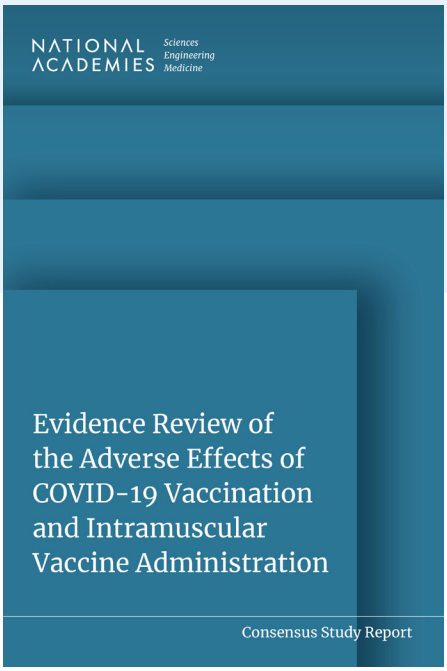
Evidence Review of the Adverse Effects of COVID-19 Vaccination and Intramuscular Vaccine Administration



Vaccines are a public health success story, as they have prevented or lessened the effects of many infectious diseases. However, to address the concerns of individuals asserting that they or their children were injured by vaccines, the Health Resources and Services Administration (HRSA) administers the Vaccine Injury Compensation Program (VICP), which provides compensation to those who assert that they were injured by routine vaccines. HRSA also administers the Countermeasures Injury Compensation Program, which provides compensation related to injuries from pandemic, epidemic, or security countermeasures, such as COVID-19 vaccines. The National Academies of Sciences, Engineering, and Medicine (the National Academies) have contributed to the scientific basis for VICP's compensation decisions for decades.

Therefore, HRSA asked the National Academies to convene an expert committee to review the epidemiological, clinical, and biological evidence about the relationship between COVID-19 vaccines and specific adverse events, as well as the relationship between intramuscular administration of routinely administered vaccines and shoulder injuries. The committee's report, *Evidence Review of the Adverse Effects of COVID-19 Vaccination and Intramuscular Vaccine Administration*, presents its conclusions.

Evidence Review of the Adverse Effects of COVID-19 Vaccination and Intramuscular Vaccine Administration draws 85 conclusions about the causal relationship between these vaccines and possible harms. The committee found significant evidence for 20 conclusions to establish, favor acceptance of, or favor rejection of a causal relationship between vaccines and possible harms. The evidence was insufficient to establish, favor acceptance of, or favor rejection of 65 potential relationships. The committee did not address the benefits of vaccines, which have been well established for both COVID-19 vaccines and all vaccines covered by VICP.

SCOPE OF REVIEW

The National Academies appointed a committee of experts in epidemiology, causal inference, cardiology, rheumatology, gynecology, audiology, neurology, infectious disease, pediatrics, internal medicine, hematology, orthopedics, and immunology to perform this study. The committee evaluated evidence about COVID-19 vaccines used in the United States, the scope of which includes four vaccines—BNT162b2 (Pfizer/BioNTech), mRNA-1273 (Moderna), Ad26.COV2.S (Janssen), and NVX-CoV2373 (Novavax). For the COVID-19 vaccine analysis specifically, the committee reviewed a list of possible harms requested for inclusion by HRSA, including:

- Guillain-Barré syndrome;
- chronic inflammatory demyelinating polyneuropathy;
- Bell's palsy;
- transverse myelitis;
- chronic headache;
- postural orthostatic tachycardia syndrome (added after the committee's first public meeting);
- sensorineural hearing loss;
- tinnitus;
- thrombosis with thrombocytopenia syndrome;
- immune thrombocytopenic purpura;
- capillary leak syndrome;
- myocardial infarction;
- ischemic stroke;
- hemorrhagic stroke;
- deep vein thrombosis, pulmonary embolism, and venous thromboembolism;
- myocarditis;
- pericarditis without myocarditis;
- sudden death; and
- female infertility.

The committee also reviewed evidence about vaccines administered intramuscularly—including but not limited to COVID-19 vaccines—and shoulder injuries to help VICP better understand whether vaccination can cause specific types of shoulder injuries or a more general syndrome designated as Shoulder Injuries Related to Vaccine Administration (SIRVA). The committee identified nine shoulder injuries for review.

CATEGORIES OF CAUSATION

The committee adopted categories of causation that have been used by other National Academies reports on vaccine safety, including:

- *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. Future research demonstrating a clear mechanism of action, or research demonstrating increased risk among vaccinated people compared with unvaccinated people, could lead to a different conclusion.

COVID-19 VACCINE CONCLUSIONS

Most of the evidence available was for BNT162b2 (Pfizer/BioNTech), followed by mRNA-1273 (Moderna). Janssen (Ad26.COV2.S) was approved later than the first two vaccines, had less uptake, and eventually had its U.S. Food and Drug Administration (FDA) authorization revoked on June 1, 2023; therefore, only a small number of studies were available for examination. NVX-CoV2373 (Novavax) was the last available vaccine in the United States, and as of the literature search cutoff date of October 17, 2023, there was not enough evidence to draw conclusions about its potential adverse effects.

Because Ad26.COV2.S (Janssen) was administered to fewer people and its authorization was revoked by FDA in the United States, only a small number of studies were available for review. To supplement the evidence base, the committee reviewed and considered studies of the COVID-19 vaccine manufactured by Oxford-AstraZeneca (ChAdOx1-S). As Ad26.COV2.S (Janssen) and ChAdOx1-S (Oxford-AstraZeneca) share the same vaccine platform—adenovirus vector—their profile of potential adverse events is likely similar so associations could be made. It is partially due to studies on ChAdOx1-S (Oxford-AstraZeneca) that some of this report's conclusions about Ad26.COV2.S (Janssen) could be drawn.

The conclusions with sufficient evidence to establish, favor rejection of, or favor acceptance of a causal relationship are as follows:

CONCLUSIONS RELATED TO BNT162b2 (PFIZER/BioNTech) AND mRNA-1273 (MODERNA)

The committee concluded that evidence **establishes a causal relationship** between both BNT162b2 (Pfizer/BioNTech) and mRNA-1273 (Moderna) and myocarditis.

The committee concluded that the evidence **favors rejection of a causal relationship** between both BNT162b2 (Pfizer/BioNTech) and mRNA-1273 (Moderna) and:

- Guillain-Barré syndrome,
- Bell's palsy,
- thrombosis with thrombocytopenia syndrome,
- myocardial infarction, and
- infertility.

The committee concluded that the evidence **favors rejection of a causal relationship** between BNT162b2 (Pfizer/BioNTech) and ischemic stroke

CONCLUSIONS RELATED TO Ad26.COV2.S (JANSSEN)

The committee concluded that sufficient evidence exists to **favor acceptance of a causal relationship** between Ad26.COV2.S (Janssen) and

- Guillain-Barré syndrome and
- thrombosis with thrombocytopenia syndrome.

CONCLUSIONS RELATED TO NVX-CoV2373 (NOVAVAX)

The committee did not have sufficient evidence to form any conclusions establishing, favoring acceptance of, or favoring rejection of a causal relationship between any adverse events and NVX-CoV2373 (Novavax).

SHOULDER INJURY CONCLUSIONS

The committee reviewed the available evidence regarding vaccines administered intramuscularly and specific injuries to the shoulder. For this section of the report, the term vaccination includes but is not limited to COVID-19 vaccines.

The conclusions with sufficient evidence to establish, favor rejection of, or favor acceptance of a causal relationship follow:

The committee concluded that the evidence **establishes a causal relationship** between vaccination and:

- subacromial/subdeltoid bursitis caused by direct injection into the bursa,
- acute rotator cuff or acute biceps tendinopathy caused by direct injection into or adjacent to a tendon,
- bone injury caused by direct injection into or adjacent to the bone, and
- axillary or radial nerve injury caused by direct injection into or adjacent to the nerve.

The committee concluded that the evidence **favors rejection of a causal relationship** between vaccination and chronic rotator cuff disease.

DATA REGARDING CHILDREN

Potential vaccine-associated harms may differ in children and adults, so the committee conducted an in-depth review of the literature on adverse events to COVID-19 vaccines specifically for individuals under 18. Because the vaccine was available to be administered to young children much later than to adults, there was not enough information in the literature for conclusions to be made about potential harms to children, especially children under 11.

There is also little data available on shoulder injuries and vaccination among the pediatric population. Similarly, this lack of data did not allow for conclusions specific to children to be made.

To learn more about this report, visit our website at www.nationalacademies.org/vaccines-evidence-review.

COMMITTEE TO REVIEW RELEVANT LITERATURE REGARDING ADVERSE EVENTS ASSOCIATED WITH VACCINES **George J. Isham** (*Chair*), HealthPartners Institute; **Anne R. Bass** (*Vice Chair*), Weill Cornell Medicine; **Alicia Christy,** Uniformed Services University and Howard University School of Medicine; **Delisa Fairweather,** Mayo Clinic (Jacksonville, FL); **James S. Floyd,** University of Washington; **Eric J. Hegedus,** Tufts University School of Medicine; **Chandy C. John,** Indiana University School of Medicine; **John Edward Kuhn,** Vanderbilt University Medical Center; **Evan Mayo-Wilson,** University of North Carolina Gillings School of Global Public Health; **Thomas Lee Ortel,** Duke University School of Medicine; **Nicholas S. Reed,** Johns Hopkins Bloomberg School of Public Health and Johns Hopkins University School of Medicine; **Andy Stergachis,** University of Washington; **Michel Toledano,** Mayo Clinic (Rochester, MN); **Robert B. Wallace,** University of Iowa; and **Ousseny Zerbo,** Kaiser Permanente Northern California

NATIONAL ACADEMY OF MEDICINE FELLOW **Inmaculada Hernandez,** University of California, San Diego

STUDY STAFF **Kathleen Stratton,** Study Director; **Ogan K. Kumova,** Program Officer (since February 2023); **Dara Rosenberg,** Associate Program Officer; **Nerissa Hart,** Senior Program Assistant (until May 2023); **Olivia Loibner,** Senior Program Assistant (since June 2023); and **Rose Marie Martinez,** Senior Director, Board on Population Health and Public Health Practice

FOR MORE INFORMATION

This Consensus Study Report Highlights was prepared by National Academies staff based on the Consensus Study Report *Evidence Review of the Adverse Effects of COVID-19 Vaccination and Intramuscular Vaccine Administration* (2024).

The study was sponsored by the Centers for Disease Control and Prevention and the Health Resources and Services Administration. Any opinions, findings, conclusions, or recommendations expressed in this publication do not necessarily reflect the views of any organization or agency that provided support for the project. Copies of the Consensus Study Report are available from the National Academies Press, (800) 624-6242 or https://www.nap.edu/catalog/27746.

Health and Medicine Division

NATIONAL ACADEMIES *Sciences Engineering Medicine*