

A SYSTEMATIC LITERATURE SURVEY OF COVID-19 VACCINE ADVERSE EVENTS

A REACT19 Research Project

EXECUTIVE SUMMARY

(Survey period ending May 1, 2025)

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React19 is a 501(c) charitable organization founded on November 19, 2021, to support research, education, and therapeutic development related to COVID-19 vaccine adverse events (AEs). The organization derives its name from the words **research, educate, action, and therapeutics**. Over 36,000 people who have experienced COVID-19 vaccine AEs have contacted React19 for assistance. This document presents findings from a systematic literature survey examining peer-reviewed publications and research related to COVID-19 vaccine adverse events, with a survey period ending May 1, 2025.

In this document, we use the term “adverse event” (AE) to refer to symptoms or signs of disease states that emerged following COVID-19 vaccination. Where individuals experience multiple persistent symptoms, we may use the term “post vaccine syndrome” (PVS) or “unresolved post vaccine injury.” The focus of this survey is on significant, persistent adverse events that began shortly after vaccination, typically within one month of injection, and that interfere with activities of daily living. This literature survey was conducted by React19 volunteers and includes: (1) a repository of 3,752 peer-reviewed case reports of COVID-19 vaccine AEs, (2) ongoing monitoring of research publications and preprints pertinent to understanding the pathogenesis of AEs, (3) original questionnaire-based studies conducted in cooperation with the University of Maryland Baltimore, and (4) an audit of VAERS report follow-up procedures. The document organization and contents are described in detail in the Introduction.

Notation for readers: If you want more information about immunological terms which appear in this paper, we recommend you obtain a copy of *Cellular and Molecular Immunology: Tenth Edition*, by Abul K Abbas, Andrew H. Lichtman, and Shiv Pillai (©2022), 587 pp. This textbook has an excellent glossary and superb illustrations. We have found that querying search engines such as Google and Bing will return excellent information about many of the terms used.

The COVID-19 pandemic emerged in late 2019 with the appearance of SARS-CoV-2 in Wuhan, China, rapidly spreading worldwide. In response, multiple vaccine platforms were developed under emergency use authorization (EUA) programs in the United States and similar expedited processes in other countries.

The most widely used COVID-19 vaccines employ a modified mRNA lipid nanoparticle platform, where the mRNA sequence encodes the SARS-CoV-2 spike protein. The two primary examples are the Pfizer BNT162b2 vaccine (Pfizer-BioNTech, brand name Comirnaty) and the Moderna mRNA-1273 vaccine (brand Spikevax). These vaccines remain the most widely administered in the USA, and much of this literature survey focuses on adverse events associated with these agents.

Additional vaccines were developed using adenovirus vector platforms containing DNA encoding the spike protein, including the Oxford-AstraZeneca ChAdOx1 (brand Covishield) vaccine and the Janssen Ad26.COV.S (brand Jcovden) vaccine. Following detection of significant adverse event signals—including thrombotic thrombocytopenia syndrome (TTS), intracranial sigmoid vein thrombosis, various thrombotic and hemorrhagic strokes, and thromboembolic episodes—AstraZeneca withdrew their vaccine from production in May 2024, and Janssen suspended production in 2022. Currently, the CDC recommends the Pfizer vaccine, Moderna vaccine, and Novavax (a recombinant SARS-CoV-2 spike protein vaccine with proprietary adjuvant).

Technical Background on mRNA Vaccine Platform

The mRNA lipid nanoparticle platform represents a novel approach to vaccine development. This technology builds upon a decade of research into nucleic acid delivery systems for therapeutic purposes. The platform addresses several technical challenges:

First, the spike protein-encoding mRNA requires encapsulation in a delivery vehicle capable of cellular uptake and intracellular release. Lipid nanoparticle (LNP) technology, previously validated in drugs such as patisiran (licensed in 2018), provides this delivery mechanism.

Second, maintaining mRNA stability within cells required modification of the standard nucleotide composition. The replacement of uridine with N1-methyl-pseudouridine in the mRNA sequence reduces susceptibility to degradation by cellular nucleases and diminishes innate immune responses that would otherwise rapidly degrade foreign RNA. This modification allows sufficient spike protein production to generate an adaptive immune response. The pseudouridine modification also affects translation fidelity, resulting in production of both intended spike protein and additional peptide sequences, which has implications for understanding potential immune responses.

Third, the biodistribution characteristics of lipid nanoparticles are not restricted to immune system cells. The nanoparticles distribute throughout the body rather than

targeting specifically to antigen-presenting cells. This distribution pattern is relevant to understanding the range of adverse events reported following vaccination. Viral vector vaccines similarly lack tissue-specific targeting, with adenoviral vectors taken up by dendritic cells, myocytes, and hepatocytes distributed throughout the body. These vaccines deliver DNA encoding the spike protein, which cells then transcribe into mRNA for protein production. The mRNA produced from viral vector delivery does not contain modified nucleotides, but the total amount and duration of spike protein synthesis cannot be precisely controlled.

Research Environment Context

Research into COVID-19 vaccine adverse events has occurred in a complex environment. Public health priorities have emphasized maximizing vaccine uptake, which has influenced institutional support for adverse event research. Funding for comprehensive studies of post-vaccination syndromes has been limited, and research proposals in this area continue to face challenges in securing institutional review board approval and grant funding. Social media content policies have restricted discussion of adverse events, complicating communication among researchers, clinicians, and affected patients. While peer-reviewed case reports and mechanistic studies have accumulated—particularly since 2023—large-scale epidemiological investigations of post-vaccine syndrome remain difficult to conduct and publish. This environment has made systematic, independent compilation and analysis of published literature particularly important for advancing understanding of these conditions.

Survey Context and Purpose

As COVID-19 vaccines were deployed at an unprecedented scale and speed, reports of adverse events began accumulating in the medical literature. Case reports of various adverse events following vaccination appeared in peer-reviewed journals, documenting a range of symptoms and conditions temporally associated with vaccination.

Characterization of these adverse events has developed through multiple complementary approaches: individual case reports documenting specific clinical presentations, cohort studies examining incidence rates, mechanistic investigations exploring pathophysiological pathways, and surveys assessing symptom patterns and patient experiences.

This literature survey was conducted to systematically compile and analyze published research related to COVID-19 vaccine adverse events. The survey includes peer-reviewed case reports, mechanistic studies, clinical investigations, and epidemiological research published through May 1, 2025. The goal is to provide a comprehensive

resource for understanding the spectrum of reported adverse events, current knowledge of their pathogenesis, and gaps in the existing literature.

The survey complements existing pharmacovigilance systems by systematically organizing published research findings and identifying patterns across multiple organ systems and clinical presentations. It provides a foundation for further investigation into diagnostic approaches, treatment strategies, and understanding of post-vaccination syndrome.

Document Organization

The document is organized into three main sections:

Section 1 presents the literature survey findings, beginning with a repository of 3,752 peer-reviewed case reports and continuing with analysis of selected publications relevant to understanding vaccine adverse events and their pathogenesis.

Section 2 describes original research projects conducted by React19, including a questionnaire-based study conducted in cooperation with the University of Maryland Baltimore and an audit of VAERS reporting procedures.

Section 3 discusses NIH-sponsored research relevant to vaccine adverse events, including publications where NIH representatives served as authors or co-authors.

The **Discussion** section synthesizes findings across sections 1-3. It discusses their implications for pathogenesis, recognition, diagnosis, and management of COVID-19 adverse events. This will be followed by

Concluding Remarks that briefly describe what we know about COVID-19 vaccine injury, implications for the mRNA lipid nanoparticle platform, gaps in current knowledge, and future directions for research in this area.



SECTION 1
SUMMARY OF SURVEY CONTENTS

SECTION 1—SUMMARY OF SURVEY CONTENTS

This portion of this presentation will provide an overview of React19's survey of publications pertinent to COVID-19 vaccine AEs. There are three sections, each of which is divided into subsections. When appropriate individual papers within each subsection will be identified by a citation number. Subsection/citation numbers can be used to identify a paper being discussed as part of the survey. For each citation the reader will be provided with a link where the paper corresponding to a given citation can be downloaded in its entirety.

SECTION 1—COVID-19 VACCINE INJURY PUBLISHED RESEARCH

1.0 Study Repository of Over 3752 Peer Reviewed Publications on COVID Vaccine AEs

Shortly after its founding React19 volunteers developed a searchable data base comprised of case reports of AEs associated with COVID-19 vaccination. The case report genre of medical literature has been important for hundreds of years. When physicians encounter a patient with signs and symptoms which appear novel and important, they publish case reports. Numerous syndromes have been identified by this technique. Case reports can alert both practitioners and the public to diseases and complications of treatment. Case reports are written by trained observers (usually physicians) and typically describe patient demographics, history, presentation, major signs and symptoms, laboratory studies, treatments used, a discussion of pathogenesis, and often references to similar cases. React19 volunteers reasoned creating a searchable data base of case reports could help the vaccine injured. They could see if they were experiencing the same post vaccination problems described in case reports. They could come to an appointment with their doctor bringing abstracts of case reports which fit their complaints. Also, awareness of case reports in respected journals should stimulate researchers to determine how often such AEs are occurring and to investigate diagnostic and treatment pathways.

Thus, React19 volunteers queried PubMed for published, peer reviewed reports of AEs produced by COVID-19 vaccines. A variety of paired search terms were used, where the first member of a search

1.0 Study Repository of Over 3752 Peer Reviewed Publications on COVID Vaccine AEs



pair used a vaccine identifier: COVID-19 vaccines, BNT16b2 mRNA vaccine, mRNA-1273 vaccine, ChAdOx1 vaccine, Ad26.COV.S, Pfizer vaccine, Moderna vaccine, Astra-Zeneca vaccine, or Jansen vaccine and the second member of the pair were words designed to detect case reports of particular AEs, such as:

adverse event, allergy, autoimmune, brain, cancer, case report, cardiac, cardiomyopathy, dermatology, encephalitis, endocrine, eye, gastroenterology, Guillain barre, hematology, hypertension, hypotension, inflammation, injury, kidney, lymphadenopathy, liver, menses, miscarriage, myocarditis, neurology, neuropathy, nose, oncology, ophthalmology, pericarditis, platelet, pulmonary, renal, rheumatology, side effect, stroke, tachycardia, thrombocytopenia, thrombosis, thyroid, transverse myelitis.

Volunteers entered the title, authors, publication (volume, issue, date), and Pubmed linkage identifiers into an excel spreadsheet. They then looked for “repeats,” where the same paper was listed two or more times and eliminated repeated citations. Then they settled on a list of main categories (primary descriptors) which could be applied to describe a given case report, namely:

Allergic, Autoimmune, Cardiac, Dermatologic, Ear Nose & Throat, Endocrine, Gastroenterology, Hematology, Infectious Disease, Immunology, Lymphatic, Multi System Inflammatory Syndrome, Neurological, OB-GYN, Oncology, Ophthalmology, Pulmonary, Renal, Rheumatology.

These categories enable interested parties to search the database for useful information. Subcategory (secondary descriptors) were also applied to each case report with the same goal in mind. There was no uniform list used for the secondary modifiers, which were applied at the discretion of the individual volunteers. At the end of the day a database containing 3,752 references was compiled. At that point volunteers decided to continue monitoring published accounts dealing with COVID vaccine AEs and focus on providing précis of particularly useful ones.

The nature of our search may have influenced the distribution of case reports placed in the database. Classification of AEs into categories and subcategories is in many ways arbitrary. There is considerable overlap such that the same diagnosis could end up under different categories or subcategories. The purpose of this case report survey was to systematically document reported vaccine adverse events in the peer-reviewed literature and provide accessible information for patients and healthcare providers.

This spreadsheet database has been posted at <https://www.react19.org/science>. The database can be downloaded as a CVS file by using the “Download data table” button under the first page displayed.

The leading categories for case reports were Rheumatologic (709), Neurologic (707), Dermatology (562), and Cardiac (460). It is interesting that case reports for cardiac AEs came in fourth for number of case reports identified in the database by our volunteers. This is interesting because most of the public attention regarding COVID-19 vaccine injuries has centered upon cardiac problems. This simple survey conducted early during the pandemic points towards injuries involving many organ systems besides the cardiovascular system. Many of the cases in the Rheumatologic category could also be described as autoimmune phenomena.

There were large number of cases categorized as neurologic. This category included reports of Guillain barre syndrome, transverse myelitis, encephalitis, and painful neuropathies. We were surprised to see the large numbers of dermatological lesions reported. Many of these were mild and self-limited; however, some were very severe and life threatening. For example, Singh et al. (item 105 in the downloadable CVS table) described a case of severe pemphigus vulgaris occurring in an 18 yr old male less than 7 days after receiving a second dose of the Oxford-Astra-Zeneca ChAdOx1 nCoV-19 vaccine. He was treated with systemic steroids, parenteral antibiotics, and intravenous immunoglobulins and only started improving one month post onset.

Scanning through the case reports one soon gets the impression there are a variety of AEs which present as a range of damage to a given organ. Renal AEs, for example, involve a spectrum of findings such as various glomerular changes (e.g. items 1532, 1540 1607), interstitial nephritis (1541), and IgA vasculitis with severe glomerulonephritis (1617). Similarly, there was a range of AEs involving the eye, for example reactivated herpes corneal keratosis (8), varicella acute retinal necrosis (210), acute arterial uveitis (295), unilateral or bilateral optic neuritis (221, 397), bilateral central serous chorioretinopathy (492), acute macular neuroretinopathy (565, 567-572), and even cortical blindness (403). Such a brief skimming of the case report repository suggests a variety of mechanisms for the reported AEs: possible vaccine induced transient immunosuppression, autoimmune phenomena, vascular phenomena (inflammation or coagulopathy), or targeted toxicity towards a particular cell type. In any case, vaccination triggered one or multiple events presenting with a particular sentinel pathology. Researchers should see investigation of AEs as a fruitful avenue of research.

There are some common themes which apply to case reports in the repository:

- ▶ **All Reports indicate onset of the reported AE occurred shortly after the receipt of a COVID-19 vaccine,** generally within a month and often within days. This makes sense because the authors of the papers would not consider a vaccine causality unless there was “temporality” (criteria 4 of the Bradford Hill criteria for causality). Peer reviewers would likely reject any case report which did not portray this pattern.
- ▶ **The authors often present the case AE as a rare or very rare event;** however, there are often multiple case reports describing the same AE. This could be due to the huge number of vaccine doses given; however, it is still reasonable to speculate some of these rare AEs are not as rare as one might think. In any case, from the standpoint of a vaccine injured individual, a particular AE has a frequency of 100%. The case reports should stimulate research to determine how it happens the vaccine appears to be making otherwise rare events less rare.
- ▶ **Several of the case reports suggest a dose-response relationship,** with the AE occurring in a mild form or not at all with the first dose of vaccine and occurring with great intensity after the second dose. This fits well with the testimony of many vaccine injured people. A biological gradient (dose-response relationship) is another Bradford Hill criterion for causality. The observed dose-response relationship warrants further investigation through well-designed studies of vaccine-associated adverse events.

Since our volunteers completed this survey of vaccine AE case reports we know many thousands more have been reported. As previously noted, after completing this initial work, React19 volunteers have been surveying the medical/scientific literature for information describing particularly significant COVID-19 vaccine AEs or plausible mechanisms underlying the AEs. They have conducted their own patient-guided research to obtain a description of what is best called COVID-19 post vaccine syndrome (PVS). They audited a sampling of reports made by vaccine injured individuals to the CDC Vaccine AE Reporting system (VAERS) to determine what became of their reports.

As the survey proceeded it became possible to reach a better understanding of persistent symptoms in vaccine injured individuals. There were individuals who sustained serious organ specific damage which persisted and in some cases was irreversible. On the other hand there were individuals who developed a common pattern of persistent symptoms post vaccination and thus were suffering from COVID PVS. Finally, there were individuals who suffered significant organ specific damage post vaccination and who also developed PVS. This will become self-evident as we continue this presentation.

1.1 Vaccine Lipid Nanoparticle, mRNA, and Spike Protein Biodistribution Studies

Early Biodistribution Data

Early nonclinical reports on lipid nanoparticle biodistribution:

- ▶ These confidential reports of research done by Pfizer were submitted to the Japanese and Australian governments and eventually made public.
- ▶ The reports used laboratory animals to assess the tissue distribution of radiolabeled lipid components from the vaccine formulation.
- ▶ Two links are provided for the Japanese report: they differ somewhat in presentation and readability. The two links are provided because one cannot be certain how long these English translations will be held in internet archives.

Citations/links:

Report to Japanese government: *SARS-CoV-2 mRNA Vaccine (BNT162, PF-07302048) 2.6.4 Summary statement of pharmacokinetic study* [English translation. 2020/2021]. Anonymous:

<https://ia902305.us.archive.org/28/items/pfizer-confidential-translated/pfizer-confidential-translated.pdf>

<https://dn790008.ca.archive.org/0/items/pfizer-confidential-translated/pfizer-confidential-translated.pdf>

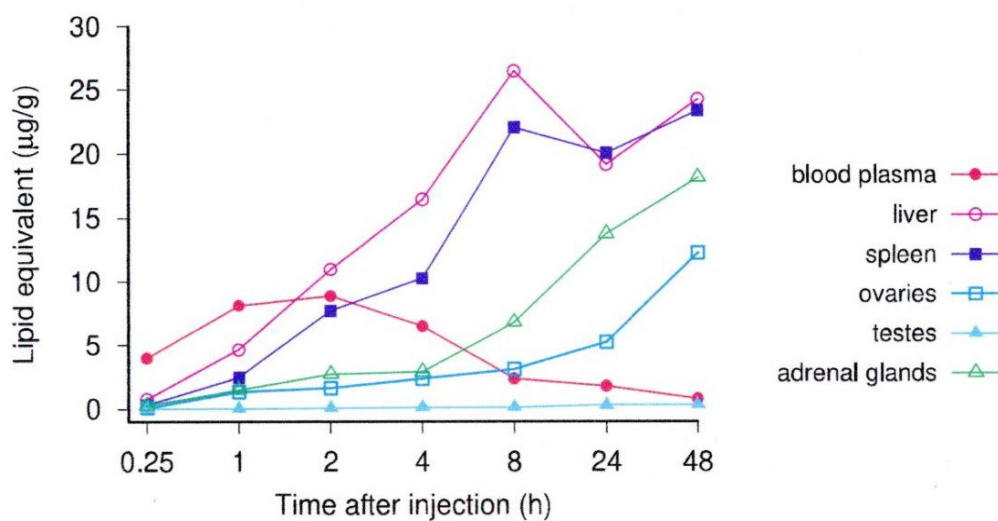
Report to Australian government: *Nonclinical Evaluation Report BNT162b2 [mRNA] COVID-19 vaccine (COMIRNATY™)*. 2021. Anonymous <https://www.tga.gov.au/sites/default/files/foi-2389-06.pdf>

These nonclinical reports were designed to track the biodistribution of the novel lipid components in the vaccine formulation. The LNP formulation contains four lipids: two that are naturally present in the body and two novel synthetic lipids (ALC-0315 and ALC-0159). The study focused on tracking these novel lipid components using tritium labeling. The radiolabel used was specifically described as a 'nonexchangeable, nonmetabolizable lipid marker used to monitor the disposition of the LNPs.' This means the radioactive signal detected in tissues represents intact

lipid nanoparticles containing their mRNA cargo, not dissociated lipid components.

Fifty microgram doses were injected intramuscularly into Wistar rats, and animals were sacrificed at intervals after injection. The radioactive signal from tissues was used to estimate the concentration of lipid components in various tissues, expressed as micrograms of lipid per gram of tissue.

The concentration of labeled lipid components in multiple tissue types increased steadily throughout the 48 hours of the experiment. The highest concentration was at the injection site (165 $\mu\text{g/g}$). However, significant uptake was also found in liver (24.3 $\mu\text{g/g}$), spleen (23.4 $\mu\text{g/g}$), adrenal glands (18.2 $\mu\text{g/g}$), and ovaries (12.3 $\mu\text{g/g}$). Smaller amounts were detected in virtually every tissue analyzed, including bone marrow, heart, kidneys, eyes, brain, and spinal cord. Here is a graphic presentation of some of these data:



This figure, based on Table 2.6.5B of the Japanese Pfizer nonclinical research report, is reproduced from [mRNA Vaccine Toxicity – Doctors for COVID Ethics](#) under an international creative commons attribution license ([ref.](#)). The study's design was focused on tracking novel lipid biodistribution rather than mRNA or spike protein distribution. The researchers operated under the assumption that mRNA would be delivered to cells and subsequently degraded, which is the intended mechanism. However, the study did not investigate where mRNA was delivered, how long it persisted in various tissues, or whether spike protein was expressed in off-target locations.

These reports were significant because they demonstrated that the novel lipid components of the vaccine formulation distribute systemically rather than remaining localized at the injection site, contradicting some public health messaging. However, the question of whether mRNA delivery and spike protein expression occur

in off-target tissues—and what cellular and molecular consequences result—required different experimental approaches to address, as described below.

mRNA Delivery and Protein Expression Study

The same Japanese Pfizer report included a separate study (Report R-0072) that directly measured protein expression after intramuscular injection. Lipid nanoparticles containing luciferase-encoding mRNA (formulated identically to the vaccine) were injected intramuscularly into BALB/c mice, and bioluminescence imaging was used to detect where mRNA was translated into protein.

Key Findings:

- **Injection site:** Protein expression detected from 6 hours to 9 days post-injection
- **Liver:** Protein expression detected from 6 hours to 48 hours post-injection

This study provides direct evidence that after intramuscular injection, mRNA-loaded LNPs reach the liver and the mRNA is translated into protein. Combined with the radiolabeled study showing LNP distribution to ovaries, spleen, and other organs, these findings demonstrate that mRNA delivery and protein expression occur beyond the injection site—contradicting public messaging that the vaccine remains localized.

Investigating mRNA Delivery and Spike Protein Expression in Off-Target Tissues

Citation/link:

Jio Luo, et al. (40 authors, corresponding author Ali Erturk). Nanocarrier imaging at single-cell resolution across entire mouse bodies with deep learning. *Nature Biotechnology*. January 14, 2025. <https://www.nature.com/articles/s41587-024-0252-8-1>

This publication describes very detailed, expansive work done at the Institute for Intelligent Biotechnologies, Helmholtz Center, University Munich, Neuherberg, Germany.

This highly sophisticated paper investigates mRNA delivery and spike protein expression throughout the body at single-cell resolution. The work directly demonstrates whether mRNA is delivered to off-target tissues and whether cellular and molecular consequences result from such delivery.

The authors of this paper explicitly note that a major problem with nanoparticle delivery of mRNA vaccines is ensuring delivery occurs only to desired target cells. In the case of SARS-CoV-2 spike protein-encoding mRNA vaccines, the target should be immune system cells in the immediate vicinity of the injection site. Modified mRNA delivered to “off-target” tissue cells will produce “off-target effects” that could include triggering vaccine adverse events.

The authors developed a methodology called “Single Cell Precision Nanocarrier Identification (SCP-Nano),” which they describe as “a pipeline for mapping and quantifying the biodistribution of any fluorescence-labeled nanocarrier throughout the entire mouse body with single-cell resolution and high sensitivity.” This technique is far more sensitive than the methods used in the earlier Pfizer reports.

The authors attached bioluminescent tags to lipid nanoparticles structurally equivalent to those used in the Pfizer and Moderna COVID vaccines. The methodology is so sensitive they could use intramuscular lipid

nanoparticle doses in their laboratory mouse model ($\mu\text{g}/\text{kg}$) equivalent to those used in human vaccination. They used total body scanning coupled with AI computer programs to obtain three-dimensional imaging of organs where nanoparticles were delivered, with resolution down to the cellular level. The reader should examine the color photographs produced by their technique—they are nothing short of breathtaking. They documented lipid nanoparticle delivery to a variety of tissues (head, heart, lungs, kidneys, liver, lymph nodes, and spleen) after intramuscular injection. Critically, they then demonstrated that mRNA was successfully delivered and translated in off-target tissues. They concentrated on the heart as an example of off-target tissue where mRNA was delivered and spike protein was expressed.

To identify cells where mRNA was being translated into spike protein, they stained heart tissue slices from mice injected with modified mRNA lipid nanoparticles with “Nanobodies” against spike protein. They also used immunohistology to determine the cell types synthesizing spike protein. They found that spike protein was being synthesized primarily within endothelial cells of cardiac capillaries, rather than in cardiomyocytes, immune cells, or arterial smooth muscle cells. It requires little imagination to conceive of a similar situation occurring in other organs throughout the body where endothelial cells of capillaries express spike protein. This observation is highly relevant to understanding why adverse events occur across multiple organ systems.

The authors then employed mass spectrometry to identify the spectrum of molecular changes induced by mRNA expression in off-target tissues, again centering their work on heart tissue. They found changes in the expression of hundreds of proteins comprising a portion of the cardiac tissue “proteome” in regions where spike protein was expressed. Hundreds of proteins were upregulated (expressed more) and downregulated (expressed less). Uptake of mRNA also produced proteomic changes related to vascular formation and maintenance. The authors summarize their main findings in the discussion section:

The ability of SCP-Nano to reveal even minor off-targeting and to assess their consequences by combining imaging with spatial proteomics analysis has direct implications for clinical translation. **Our findings of changes in the expression of immune and vascular proteins in heart tissue after LNP spike mRNA delivery aligns with reports of myocarditis and pericarditis in a subset of individuals who received mRNA vaccines.....**these results highlight the need to investigate the biodistribution and off-target effects of LNP-based therapeutics with cell-level sensitivity across entire animal bodies. This approach enhances targeting precision and supports toxicity risk assessment by uncovering off-target activity and its implications

As of January 2025, this research provides direct experimental evidence using a sophisticated mouse model that: (1) COVID vaccine modified mRNA lipid nanoparticles distribute to tissues throughout the body, (2) modified mRNA in cells throughout the body is successfully delivered and translated, and (3) large-scale proteomic changes occur in these off-target tissues. These findings include changes indicative of cellular stress and inflammatory/immune activation. The combination of the earlier lipid biodistribution data with this direct demonstration of mRNA delivery, spike protein expression, and resulting proteomic changes provides a comprehensive picture of off-target effects. The pattern of off-target effects observed in this experimental model corresponds well with the various organ system adverse events documented in the case report literature. The implications for understanding vaccine-associated adverse events across multiple Bradford Hill criteria (consistency, specificity, plausibility, coherence, and analogy) are substantial.

1.2 Spike Protein Clearance/Persistence

Citations/links:

- ▶ 1. Detection of recombinant spike protein in the blood of individuals vaccinated against SARS-CoV-2: possible molecular mechanisms. Carlo Brogna, et al. *Proteomics Clin Appl*. 17:2300048 (2023).
- ▶ [Detection of recombinant Spike protein in the blood of individuals vaccinated against SARS-CoV-2: Possible molecular mechanisms - PubMed](#)
- ▶ 2. Persistence of S1 spike protein in CD16+ Monocytes up to 245 days in SARS-CoV-2 negative post COVID-19 vaccination individuals with post-acute sequelae of COVID-19 (PASC)-like symptoms. Bruce K. Patterson, et al. (14 authors). Posted March 24, 2024. *medRxiv*. [<https://www.medrxiv.org/content/10.1101/2024.03.24.24304286v1>]{.under line}
- ▶ 3. Immunological and antigenic signatures associated with chronic illnesses after COVID-19 vaccination. Bornali Bhattacharjee et al. (28 authors). Posted February 18, 2025. *medRxiv*. [<https://www.medrxiv.org/content/10.1101/2025.02.18.25322379v1>]{.under line}

Brogna et al. used high pressure liquid chromatography (HPLC) coupled with mass spectrometry (MS) to detect traces of spike protein in 20 modified mRNA vaccine recipients. They noted the vaccine mRNA of both Pfizer and Moderna vaccines code for a spike protein which has two amino acids at positions 986 and 987 substituted with prolines (P-P spike). They could distinguish P-P spike from the spike produced by COVID-19 infection by the distinctive HPLC/MS profile. In this way they could say with certainty they could detect P-P spike from the vaccines in sera of vaccinees obtained between 69 and 187 days post vaccination. Thus the vaccine mRNA is producing spike protein which is circulating in vaccinee blood well beyond the short periods of time (a few days to 2 weeks) claimed in many media statements about the vaccines.

Patterson et al. (citation 2) comprised a working group from multiple institutions. It appears IncelDx of San Carlos, CA provided much of the bench level technology. They studied 50 individuals who developed post COVID-19 vaccine AEs lasting at least 30 days after receiving one of the approved COVID-19 vaccines (Pfizer, n=27; Moderna, n=15; Janssen, n=7, and AstraZeneca, n=1). They stated the symptomatic vaccine subjects had a symptom complex analogous to infected patients having long COVID, or PASC (post-acute sequelae of COVID). These subjects with AEs tested negative for past infection with the virus (negative anti-nucleocapsid antibody and T-detect testing). Forty-five controls also had received vaccinations but had not developed any AEs. Controls were also negative for past COVID-19 infection. They obtained blood samples from all subjects an average of 105 days after vaccination (up to 245 days maximum). They screened peripheral blood cells from 14 subjects and 10 controls by flow cytology with fluorescent tagged antibodies designed to sort and analyze cells which were simultaneously CD16+ (monocytes) and S1+ (expressing S1 protein). They found a statistically significant elevation of S1 in cells of the AE group compared to the control group (P = 0.006). Essentially, they were saying controls had negligible staining for presence of S1 compared to the subjects with AEs. They further analyzed CD 16+, S1 positive cells from the AE group by high pressure liquid chromatography and mass spectroscopy. They standardized their mass spectroscopy by digesting recombinant SARS-CoV-2 spike protein. They were able to detect S1 peptides, S1 mutant peptides, and S2 peptides in these specimens. They said more study would be needed to understand the presence of S1 mutant peptides. One could speculate there was misreading of the spike mRNA as time passed in the subjects who had developed AEs.

The main take away from the paper by Patterson et al. is that spike protein was being expressed in peripheral blood monocytes from individuals who suffered AEs post COVID vaccination up to 245 days post vaccination. We

will discuss this in more detail in **subsection 1.8**, which discusses post vaccine syndrome (PVS) and its pathogenesis.

A working group based at Yale University School of Medicine performed the work described in the paper by Bhattacharjee et al. This is a very detailed, complex study. They established a case cohort, comprised of 42 subjects who had received one of three commercial vaccines (Pfizer, n=14; Moderna, n=21, or J&J, n= 4) and developed prolonged AEs post vaccination. They termed the complex of symptoms observed as post-vaccination syndrome (PVS). **This is a unique and important step in that the authors were correlating clinical observations to make a syndrome diagnosis, namely, PVS.** The control cohort contained 22 individuals. They noted that 15 (35.7%) of the PVS subjects had also sustained a COVID-19 infection. Ten of the control cohort had also been infected. Thus this group was in a position to look at the detections of spike protein in the PVS patients and see if prolonged detection of spike protein was due primarily to mechanisms producing the PVS or to a COVID-19 infection which had intervened. They used a remarkably sensitive testing method to look for the presence of S1 spike protein and S (whole spike) in sera of all the study participants. This method, called successive Proximity Extension Amplification Reaction (SPEAR) can detect S1 spike protein levels as low as 5.64 femtoMolar (fM, 10^{-15} M). They found the PVS group were more likely to have circulating S1 than individuals in the control group. Moreover PVS subjects tended to have higher S1 levels than those seen in controls irrespective of any intervening infection. Thus, one could not say that elevated S1 levels in PVS individuals was due to an intervening infection. The elevation appeared to be related to having PVS. This suggests vaccine causality. We don't have space to explore this further. In their own words the group concluded:

...in our study, significantly elevated levels of circulating S1 and S were observed in a subset of PVS participants both in the infection-naïve and infection-positive groups up to 709 days post-exposure. This is in line with the findings of S1 persistence in monocytes in people with PVS.

They found the PVS patients, even those who had been infected, had much lower anti-S antibody levels than controls and conclude “Why persistent spike antigen fails to elicit an antibody response, and what the source of persistent spike in circulation is, requires further investigation.”

1.3 Frame shifting

Citations/links:

1. Thomas E. Mulrone et al. (20 authors). Nature 625:189-194 (2024). N1-methylpseudouridylation of mRNA causes +1 ribosomal frameshifting
<https://www.nature.com/articles/s41586-023-06800-3>

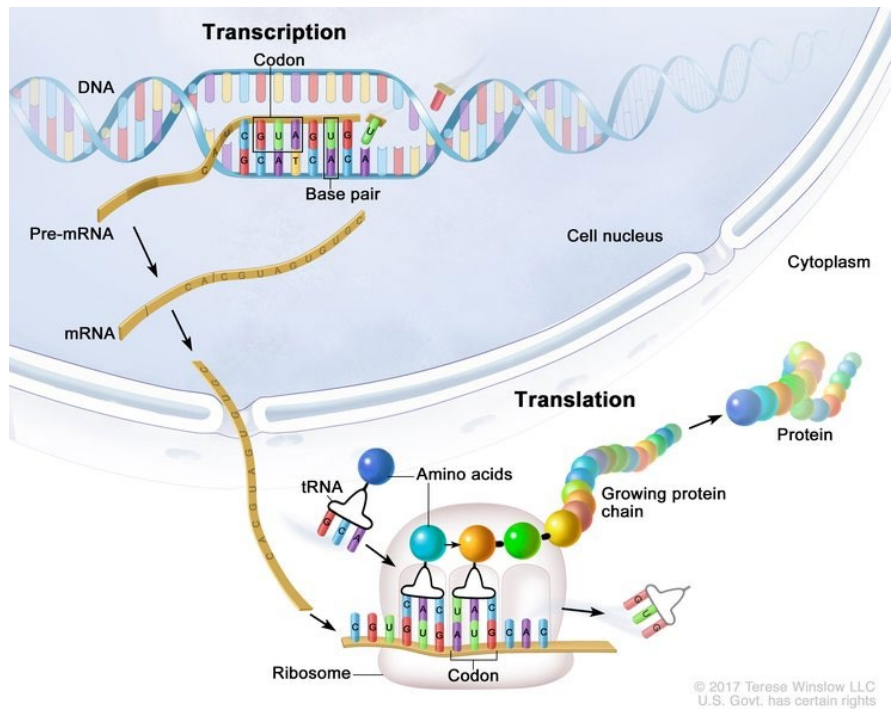
This research group included scientists and clinicians from Cambridge and Oxford Universities and their respective medical schools.

To understand this paper, we need to review briefly the central dogma of DNA-mRNA-protein interactions. It is represented in this cartoon ->

Messenger RNA (mRNA) is transcribed from DNA in the cell nucleus and exits the cell nucleus, entering the cytoplasm. There, the mRNA feeds through the ribosome. Within the ribosome there is an area which holds one of a succession of three nucleic acid groups, called codons, in place. This is the reading frame within the ribosome. Each codon of the mRNA is comprised of a combination of three possible ribonucleosides—uridine, guanosine, cytidine, or adenosine.

Transfer RNA (tRNA) bearing an amino

acid and having a three nucleotide anticodon matching the one in the reading frame of the ribosome area docks there. As the mRNA moves through the ribosome, the amino acid on the tRNA is added to a growing protein exiting the ribosome and the reading frame shifts to the next codon. The same process repeats itself, translating the mRNA into a completed protein.



Now we can consider the various COVID vaccines. The Oxford-AstraZeneca ChAdOx1 (brand Covishield) vaccine and the Janssen Ad26.COV.S (brand Jcovden) vaccine use an adenovirus vector to deliver DNA coding for the SARS-CoV-2 spike protein to human cells. The DNA is translated to mRNA corresponding to the spike protein and this mRNA undergoes translation to spike protein, which is then expressed by this cell. One can consider the resultant protein “error-free,” with all the copies of spike protein being the same. An immune response against spike protein is triggered. On the other hand, the Pfizer BNT16b2 vaccine (Pfizer-BioNTech, brand name Comirnaty) and Moderna mRNA-1273 vaccine (brand Spikevax) vaccine use lipid nanoparticles to deliver modified mRNA to human cells. The modified mRNA is produced using molecular engineering methods to replace uridine in the mRNA with N¹-methylpseudouridine. Recall the modified mRNA is used in the Pfizer and Moderna vaccines to prevent rapid elimination of mRNA delivered to cells, allowing enough time for antigen expression and an immune response to occur.

Mulrone et al. hypothesized spots in mRNA containing pseudouridine could be “slippery,” meaning the reading frame in the ribosome would skip occasionally at these positions. This skipping is called a “reading frame shift.” When a reading frame shift happens, the amino acids incorporated downstream into the protein are now inaccurate. One can end up with proteins close in structure to what would happen with regular RNA; however, in some instances such frame shifts would produce nonsense proteins with structure far from what was intended. According to their hypothesis, the modified mRNA of the Pfizer and Moderna vaccines would produce proteins other than the intended spike protein. They verified this is what happens.

They used appropriate tissue culture methods to isolate spike protein (denoted S) and reading frame shifted spike protein products from modified mRNA caused by one or two reading frame shifts (denoted S+1 and S+2). In other words they had evidence pseudouridine produced at least two slippery areas in the spike modified mRNA and these spots caused reading frame shifts. Immune T-cells, which recognize a specific protein will produce interferon when stimulated by the protein. They could detect interferon production by such cells using the IF N_γELISpot assay. They vaccinated mice with either Pfizer BNT162b2 or AstraZeneca ChAdOx1. Spleen cells from these mice were stimulated with S or S+1 proteins and interferon production was measured. They found mice vaccinated with either vaccine produced interferon in response to S antigen as expected. However only the splenocytes from the Pfizer vaccinated animals produced interferon in response to S+1 proteins. This meant the modified mRNA in cells of the mice synthesized S+1 proteins, thus stimulating an anti-S+1 immune response. Next, they compared interferon responses from lymphocytes of 21 individuals vaccinated with BNT62b2 with responses from 20 individuals vaccinated with ChAdOx1. Neither group had experienced AEs. They found the cells from the BNT162b2 vaccinated individuals reacted to the S protein; however, the interferon response of cells from these individuals was just as high when they were stimulated with a mixture of S+1 and S+2 proteins. The cells of humans vaccinated with the Pfizer vaccine must have produced significant amounts of S+1 and S+2 proteins. Lymphocytes from the ChAdOx1 vaccinees responded only to S protein.

They concluded:

We show that 1-methylpseudouridine is a modified ribonucleotide that significantly increases +1 ribosomal frameshifting during mRNA translation and that cellular immunity to +1 frameshifted products can occur following vaccination with mRNA containing 1-methylpseudouridine....Alongside this impact on host T cell immunity, the **off-target effects** of ribosomal frameshifting could include increased production of new B cell antigens.
[emphasis added]

From this paper and the papers in 1.1 discussed above, it is clear the modified mRNA lipid nanoparticle vaccines produce two important off target effects: (1) the mRNA is delivered to cells throughout the body, not just to regional antigen presenting cells, T cells and B cells and (2) along with spike protein multiple altered proteins will be expressed in and on cells containing the modified mRNA. In appropriate individuals, one can certainly speculate AEs could occur because of these factors. The data in **subsection 1.2** indicate the production of all these proteins may persist longer in individuals with AEs. In any case, none of these studies compare individuals with AEs to those without AEs to see if peak antigen expression in various tissue differs between the groups.

1.4 Neurotoxicity linked to autoantibodies

1. React19 Research: The Spike Protein Problem

<https://www.react19.org/science-and-research/lit-reviews-and-surveys/react19-research-the-spike-protein-problem>

2. SARS-CoV-2 vaccination complicated by small fiber neuropathy, mast cell activation syndrome, and pericarditis. *Clinics (Sao Paulo)*. Danice Hertz et al. 78:100304 (2023).

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10681913/>

3. Post-SARS-CoV-2 infection and post-vaccine-related neurological complications share clinical features and the same positivity to anti-ACE2 antibodies. Belluci M et al *Frontiers in Immunology* 15:1398028 (2024).

<https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2024.1398028/full#B7y>

4. Functional autoantibodies against G-protein coupled receptors in patients with persistent Long-COVID-19 symptoms. Gerd Wallukat, et al. *Journal of Translational Autoimmunity* 4:100100 (2021).

<https://www.sciencedirect.com/science/article/pii/S2589909021000204>

5. Autoantibodies in COVID-19: implications for disease severity and clinical outcomes. Yannick Galipeau, et al. *Frontiers in Immunology* 15:1509289 (2025).

https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2024.1509289/full?utm_source=F-NTF&utm_medium=EMLX&utm_campaign=PRD_FEOPS_20170000_ARTICLE

6. Severity of neurological long-COVID symptoms correlates with increased level of autoantibodies targeting vasoregulatory and autonomic nervous system receptors Seibert F et al. *Autoimmunity Reviews* (Sept 2023).

[Severity of neurological Long-COVID symptoms correlates with increased level of autoantibodies targeting vasoregulatory and autonomic nervous system receptors - PubMed](#)

7. Autoantibodies Targeting G-Protein-Coupled Receptors and RAS-Related Molecules in Post-Acute COVID Vaccination Syndrome: A Retrospective Case Series Study. Montovani M et al. *Biomedicines* 12(12):2852 (2024).

<https://pubmed.ncbi.nlm.nih.gov/39767757/>

8. High serum prevalence of autoreactive IgG antibodies against peripheral nerve structures in patients with neurological post-COVID-19 vaccination syndrome. Friederik A. Arlt, et al. (13 authors). *Frontiers in Immunology* 15:1404800 (2024).

<https://doi.org/10.3389/fimmu.2024.1404800>

Citation 1 references an extended presentation discussing the COVID spike protein, its fundamental toxicity as well as the way autoimmune responses to it may have contributed to long COVID syndromes and COVID vaccine AEs. The reader can explore this internet location. **Citations 2 through 7** discuss primarily neurological problems which have resulted either from COVID-19 infection (long COVID) or COVID vaccines (persisting AEs).

Citation 2 is a case report of a 66-year-old female with three major diagnoses presenting within 3 months of the first dose of BNT162b2 Pfizer vaccine: small nerve fiber neuropathy (SFN), mast cell activation syndrome, and pericarditis. The case was typical of the presentation of many with SFN or mast cell activation syndrome post

vaccination. Symptoms often begin within minutes of vaccine injection, suggesting some sort of direct toxicity or preexistent priming of targeted tissues. This patient developed facial tingling, oral numbness, blurred vision, dizziness, and elevated blood pressure 30 minutes after vaccination. One day later she developed severe dysesthesias of the entire integument (“burning skin”), predominantly of the face and head, as well as diffuse numbness, tingling, twitching, electrical feelings throughout, internal vibrations, tinnitus, blurred vision, tremors, trouble speaking, profound weakness, post-exertional malaise and brain fog. She had watery diarrhea for the first two weeks followed by severe constipation. By this time she had obvious dysautonomia manifested by dizziness, imbalance, postural tachycardia syndrome (POTS), urinary hesitancy, and profuse sweating. Although she did not have decreased intra-epidermal nerve fiber density, SNF neuropathy was diagnosed based upon clinical presentation and normal peripheral nerve conduction studies. The usefulness of quantifying small nerve fiber density in skin biopsies for diagnosis of SFN will be discussed later. Elevated tryptase levels pointed towards mast cell activation syndrome. Chest pain prompted echocardiography which showed moderate pericardial effusion. Despite all of the above Westergren sedimentation rate and C-reactive protein remained normal, showing how routine testing can fail to diagnose inflammatory disease in such patients. Therapies tried for mast cell issues included low histamine diet, diamine oxidase supplements with meals, cromoglicic acid, loratadine, and famotidine. Gabapentin 1200 mg daily did not impact pain. Naltrexone was used to modulate inflammation (reduction of TNF α). Aspirin and colchicine were used for pericarditis.

Citation 3 shows how a peculiar twist of the immune response following either COVID-19 infection or COVID-19 vaccination can lead to autoimmune attack against ACE2 receptors, producing neurological complications. Sometimes antibody response to a specific antigen (Ab1) can result in a secondary antibody response (Ab2) directed against the primary antigen-specific antibody. Ab2 antibodies are called **anti-idiotypic antibodies**. These anti-idiotypic antibodies can play a down regulatory role of the immune response. However, when anti-idiotypic antibodies can bind to a particular cellular receptor they can lead to a disease state. Obviously both COVID-19 infection and COVID-19 vaccination produce anti-spike antibodies. Some individuals produce anti-idiotypic antibody against the anti-spike antibody combining site. Because the anti-idiotypic antibody fits within the binding site of the anti-Spike antibody these anti-idiotypic antibodies have a 3-dimensional structure similar to spike protein. Binding of anti-idiotypic (anti-ACE2) antibodies to ACE2 can produce neurological AEs. This study describes four patients who suffered neurological complications due to anti-ACE2 specific anti-idiotypic antibodies—two post infection and two post vaccination. Both patients who had AEs post vaccination had extensive neurological evaluation. They tested negative for known autoantibodies which could produce neurological symptoms (autoantibodies against AQP-4, MOG, Gly-R, GAD, and amphiphysin, as well as onconeural antibodies). They tested positive for anti-ACE2 antibodies. The first patient presented with symptoms 7 days post Moderna vaccination with back pain and distal burning paresthesia and dysesthesia of the lower limbs. The patient was improved after a course of intravenous methylprednisolone. The second patient was an 80-year-old male who developed lower limb hypoesthesia and rigidity three days post Pfizer vaccination. One month later he received a second dose of vaccine and rapidly developed progressive worsening of gait due to stiffness of his lower limbs; he had a spastic-ataxic gait. Please note this second patient showed a dose-response phenomenon pointing to vaccine causality. He failed to respond to methylprednisolone treatment. Both patients developed initial symptoms quite rapidly post vaccination. One can speculate these individuals had a genomic repertoire of Ig variable regions such that they had clones of B cells producing low levels of antibodies which had an anti-idiotypic fit with anti-spike antibody when they were vaccinated; therefore, they had rapid surge of ACE-2 antibodies producing their AEs.

Citations 4 through 6 deal with the pathogenesis of long COVID, particularly where long-term neurological complications occur. However, the same autoantibodies have been implicated in long term cardiovascular and cutaneous symptoms. Those of particular interest are autoantibodies against G-protein-coupled receptors. These include β_2 -adrenoceptor, α_2 -adrenoceptor, angiotensin II AT1-receptor, nociception-like opioid receptor (NOC), muscarinic M₂-receptor (M₂), MAS-receptor, and ETA receptor. This is pertinent because there is evidence analogous autoantibody production likely occurs in patients suffering severe neurological AEs post vaccination.

Citation 7 looked at 17 subjects who had a combination of 19 possible AEs, which they referred to as a post acute COVID vaccination syndrome (PACVS). Only two had received the AstraZeneca vaccine. The rest had received either Pfizer or Moderna vaccines. Number of injections ranged from one (n=7) through 3 (n=7). These researchers looked at antibody titers against a panel of G-protein-coupled receptors (as in citations 4-6) and also looked at serum levels of anti-ACE-2 autoantibodies (anti-idiotypic antibodies) as in citation 3. They found detection of anti-ACE-2 positive subjects had a higher percentage of cases in 17 of 19 symptoms considered. Anti ACE-2 positive patients had a four-fold risk of having more symptoms compared to anti ACE-2 negative patients. Presence of elevated antibodies against MAS1 correlated with burning sensation of this skin (p = 0.009).

1.5 Genetic Integration

Citations/links:

1. Intracellular Reverse Transcription of Pfizer BioNTech COVID-19 mRNA Vaccine BNT162b2 In Vitro in Human Liver Cell Line. Markus Aldén et al. *Curr. Issues Mol. Biol.* 44(3):1115-1126 (2022).
<https://www.mdpi.com/1467-3045/44/3/73>
2. DNA fragments detected in monovalent and bivalent Pfizer/BioNTech and Moderna modRNA COVID-19 vaccines from Ontario, Canada: Exploratory dose response relationship with serious adverse events. David L. Speicher, J. Rose, M. Gutsch, D. Wiseman, and K. McKernan. *OSF Preprints*, last ed. Oct, 2023.
<https://doi.org/10.31219/osf.io/mjc97>
3. A Rapid Detection Method of Replication-Competent Plasmid DNA from COVID-19 mRNA Vaccines for Quality Control. Tyler J. Wang, Alex Kim, and Kevin Kim. *Journal of High School Science* 8(4):427-39 (2024).
<https://jhss.scholasticahq.com/article/127890-a-rapid-detection-method-of-replication-competent-plasmid-dna-from-covid-19-mrna-vaccines-for-quality-control>

Citation 1, Swedish investigators from Lund University recalled that liver is a major site of uptake of modified mRNA lipid nanoparticles (see discussion under **subsection 1.1** above). Transient signs of hepatitis occur with lipid nanoparticle uptake. They noted a recent study which had shown SARS-CoV-2 mRNAs can be reverse-transcribed and integrated into the genome of human cells. Therefore, they exposed Huh7 cultured human liver cells to BNT162b2 Pfizer vaccine and determined modified mRNA was rapidly taken up by these cells. Then

increased gene expression of long interspersed nuclear element (LINE1), which is an endogenous reverse transcriptase, occurred. PCR testing of Huh7 cells exposed to BNT162b2 amplified the DNA sequence unique to BNT162b2. Thus DNA corresponding to the modified mRNA sequence was inserted into cellular DNA of these cells. The modified mRNA was reverse transcribed intracellularly into DNA as fast as 6 hours post vaccine exposure.

The abstract from [citation 2](#), summarizes the rationale for work done by these Canadian researchers:

In vitro transcription (IVT) reactions used to generate nucleoside modified RNA (modRNA) for SARS-CoV-2 vaccines currently rely on an RNA polymerase transcribing from a DNA template. Production of modRNA used in the original Pfizer randomized clinical trial (RCT) utilized a PCR-generated DNA template (Process 1). To generate billions of vaccine doses, this DNA was cloned into a bacterial plasmid vector for amplification in *Escherichia coli* before linearization (Process 2), expanding the size and complexity of potential residual DNA and introducing sequences not present in the Process 1 template. It appears that Moderna used a similar plasmid-based process for both clinical trial and post-trial use vaccines. Recently, DNA sequencing studies have revealed this plasmid DNA at significant levels in both Pfizer-BioNTech and Moderna modRNA vaccines. These studies surveyed a limited number of lots and questions remain regarding the variance in residual DNA observed internationally.

They examined 27 vaccine vials associated with 12 lots of Pfizer and Moderna modified mRNA vaccines. Their data demonstrate the presence of billions of DNA molecules per dose in both the Pfizer and Moderna modified mRNA COVID-19 products tested. For the lots studied they presented preliminary evidence of a dose-response effect between the residual DNA in vaccine dose versus AEs reported to VAERS. They note DNA could trigger an unwarranted innate immune response and may be prothrombotic. Also, dsDNA may be a significant factor in ischemic diseases including stroke. They found readily detectable amounts of SV40 promoter DNA in 4 lots of Pfizer vaccine. This has implications with respect to long term oncogenic effects which require further investigation. They noted there could be enhanced cumulative effects from vaccinating with these DNA contaminated products. This would include any use of the modified mRNA lipid nanoparticle platform when a plasmid based manufacturing process is used.

[Citation 3](#) was interesting in that it was performed as a high school research project in a laboratory overseen by FDA scientists. They could not find evidence of DNA capable of self-replication in 2 lots of Pfizer COVID-19 vaccine. The DNA they detected in the six vials they studied was all less than 100 base pairs long. On the other hand the samples they tested had 40-110 nanograms DNA per dose, well above the current recommended limit set for continuous cell line-derived DNA by the World Health Organization, namely <10ng/dose, DNA length <200 bp.

1.6 Reproductive Health

Citations/Links: *

1. Covid-19 vaccination BNT162b2 temporarily impairs semen concentration and total motile count among semen donors. Itai Gat, et al. *Andrology* 10:1016-1022 (2022). <https://onlinelibrary.wiley.com/doi/epdf/10.1111/andr.13209>
2. Comprehensive evaluation of inactivated SARS-CoV-2 vaccination on sperm parameters and sex hormones. Yehoa Dong, et al. *Fron Immunol* 15:1321406 (2024). 10.3389/fimmu.2024.1321406
3. Menstrual changes following COVID-19 vaccination: a cross-sectional study. Nahid Ibrahim Fallatah, et al. *Medicina* 60:206 (2024). <https://pmc.ncbi.nlm.nih.gov/articles/PMC10890281/#B3-medicina-60-00206>

* Over 300 references involving impact of COVID vaccines on reproductive health can be found in the React19 Studies Database. We also refer readers to the book edited by Naomi Wolf with Amy Kelly, *The Pfizer Papers, ©2024*, in which study groups analyzed documents released by the FDA in response to a Federal FOIA court order. These documents (450,000 pages) contain adverse event reports made to Pfizer during the first 90 days (beginning December 1, 2020) after the Pfizer vaccine was rolled out for general use. There are analyses of the AEs produced by the Pfizer vaccine on pregnancy (including miscarriages), menstrual changes, and secondary effects upon infants (breast feeding).

Citation 1, came from a group working at Tel Aviv University, Israel. Israel had very high vaccine uptake and Israelis have provided many AE studies. Here they examined the effect of the Pfizer BNT162b2 vaccine on semen parameters among 37 semen donors that provided 216 samples. These were included in a retrospective longitudinal cohort study. They had donor samples taken pre-vaccination to act as controls. Samples were taken 15-45 days (T1), 75-125 days (T2), and over 145 days (T3) after donors received a second dose of vaccine. They found a 15.4% sperm concentration decrease in T2 samples ($p=0.01$) leading to a total mobile count -22.1% compared to T0. At T3 there was overall recovery.

Citation 2, from Brazilian investigators, looked at a cohort of 409 men before and after vaccination. The vaccines were inactivated protein component-aluminum hydroxide adjuvant ones, approved for use in China, Brazil, and other countries (Sinovac/CoronaVac and Sinopharm BBIBP-CorV). They found minimal changes post vaccination. There were slight elevations in follicular stimulating hormone and prolactin post vaccination. There was significant transient decreases in sperm mobility after one and two doses of vaccine compared to before vaccination.

Citation 3 is a cohort study from the Saudi Arabia Ministry of Health of 472 students and staff at a university in Saudi Arabia (age range 18-39 years). Recipients received the Pfizer or Moderna modified mRNA vaccines or the AstraZeneca or Janssen adenovirus vector vaccines. There were limitations in study design. Nevertheless, they found changes in menstrual cycle in 54.7% of vaccine recipients. The most common change was in cycle length, followed by the number of menstruation days and bleeding flow. The overall changes did not reach solid statistical significance. Changes in menstrual bleeding were more frequent after the third dose of the Pfizer vaccine compared to the Moderna vaccine ($p = 0.014$).

1.7 Cardiovascular

Citations/Links: *

1. Intramyocardial inflammation after COVID-19 vaccination: an endomyocardial biopsy-proven case series. C. Baumeir, et al. *Int J Mol Sci*.23:6940 (2022).
<https://pubmed.ncbi.nlm.nih.gov/35805941/>
2. A case report: multifocal necrotizing encephalitis and myocarditis after BNT162b mRNA vaccination against COVID-19. Michael Mörz . *Vaccines* 10:1651 (2022)
[Moerz_Encepahilits-and-Myocarditis-after-C19-mRNA-vax-in-a-77yo.pdf](https://pubmed.ncbi.nlm.nih.gov/35805941/)
3. Autopsy-based histopathological characterization of myocarditis after anti-SARS-CoV-2-vaccination. Constantin Schwab et al. *Clinical Research in Cardiology* 10:1007 (2022)
<https://pubmed.ncbi.nlm.nih.gov/36436002/>
4. Case of Myocarditis, Pericarditis, and Fatal Aortic Dissection Following COVID-19 mRNA Vaccination. E. J. Balbona et al. *Biomed Sci Clin Res* 3(3), 01-08
[case-of-myocarditis-pericarditis-and-fatal-aortic-dissection-following-covid19-mrna-vaccination.pdf](https://pubmed.ncbi.nlm.nih.gov/36436002/)
5. 'Spikeopathy': COVID-19 spike protein is pathogenic, from both virus and vaccine mRNA. P. Parry et al. *Biomedicines* 11:2287 (2023)
'Spikeopathy': COVID-19 Spike Protein Is Pathogenic, from Both Virus and Vaccine mRNA - PubMed
6. Cardiovascular manifestations of the BNT162b2 mRNA COVID-19 vaccine in adolescents. S. Mansanum et al. *Trop. Med. Infect. Dis* 7(8):196 (2022).
<https://pubmed.ncbi.nlm.nih.gov/36006288/>
7. Increased emergency cardiovascular events among under-40 population in Israel during vaccine rollout and third COVID-19 wave. Christopher Sun et al. *Nature Scientific Reports*. 12:6978 (2022)
<https://pubmed.ncbi.nlm.nih.gov/35484304/>
8. Sex-specific differences in myocardial injury incidence after COVID-19 mRNA-1273 booster vaccination. Natacha Buergin, et al. *European Journal of Heart Failure* 25:1871-1881 (2023).
<https://doi.org/10.1002/ejhf.2978>
9. Apparent risks of postural orthostatic tachycardia syndrome diagnoses after COVID-19 vaccination and SARS-CoV-2 infection. Alan C. Kwan, et al. *Nature Cardiovascular Research* 1:1187-1194 (2022)
<https://www.nature.com/articles/s44161-022-00177-8>
10. Myocarditis after SARS-CoV-2 infection and COVID-19 vaccination: epidemiology, outcomes, and new perspectives. Review. N. Nathaniel Mead, Jessica Rose, William Makis, Kirk Milhoan, Nicolas Hulscher and Peter A. McCullough. *International Journal of Cardiovascular Research and Innovation*
<https://publichealthpolicyjournal.com/breaking-landmark-study-proves-covid-19-vaccine-myocarditis-is-more-common-and-more-severe-than-sars-cov-2-infection-myocarditis/>

Baumeier et al. ([citation 1](#)) obtained endomyocardial biopsies from 15 patients (ages 18-68, 6 females, 9 males) with significant myocarditis (cardiac ejection fractions $\leq 30\%$) developing shortly after COVID-19 vaccination. Eleven received Pfizer, 2 AstraZeneca, and 2 Janssen vaccine. They analyzed endomyocardial biopsies from all patients and documented myocardial inflammation in 14/15 patients. They looked at CD markers of infiltrating cells and found predominance of CD4+ compared to CD8+ lymphocytes in 15 cases. CD8+ cells are often found in acute myocarditis. They surmised the elevation of CD4+ cells indicated an autoimmune inflammatory response. Histochemical staining showed presence of spike protein in sites of myocardial inflammation from two Pfizer vaccine recipients and one AstraZeneca vaccine recipient. This pointed towards inflammation stimulated by spike protein in the etiology of myocarditis in these patients.

Mörz ([citation 2](#)) presents details of a 76-year-old man who died three weeks after receiving the Pfizer vaccine. At autopsy he found evidence of acute, predominantly lymphocytic vasculitis in the brain. There was multifocal necrotizing encephalitis of unknown cause associated with pronounced glial and lymphocytic reaction. Mild acute myocarditis was found as well. We cite his paper because only spike protein (and not nucleocapsid) protein could be detected within foci of inflammation in both brain and heart, particularly in the endothelial cells of small blood vessels. The reader can refer to **subsection 1.1**, where Luo found in their mouse model that endothelial cells of blood vessels was a main site for vaccine induced spike protein expression. Inflammation mounted against blood vessel lining cells expressing spike protein could affect any organ system. This can occur in the nervous system as well as the cardiovascular system.

The autopsy study by Schwab ([citation 3](#)) is yet another paper by German pathologists examining specimens of patients with AEs post vaccination. We know of only one American pathologist who has stained specimens of inflamed tissues post vaccination for spike protein. One wonders, why aren't there many curious American pathologists who might consider histochemical staining of such patients? In any case, these pathologists did autopsies on 25 people who had died unexpectedly and within 20 days after COVID-19 vaccination. In four patients who received an mRNA vaccination, they identified acute myocarditis without detection of another significant disease or health constellation that may have caused an unexpected death. Histology showed patchy interstitial myocardial T-lymphocyte infiltration, predominantly of the CD4+ subset, associated with myocyte damage. They conclude their findings indicated death due to acute arrhythmogenic cardiac failure. The issue of a likely epidemic of sudden death events being related to administration of COVID-19 vaccines has been treated exhaustively in Edward Dowd's book, *"Cause Unknown": The Epidemic of Sudden Deaths in 2021 and 2022* ©2022.

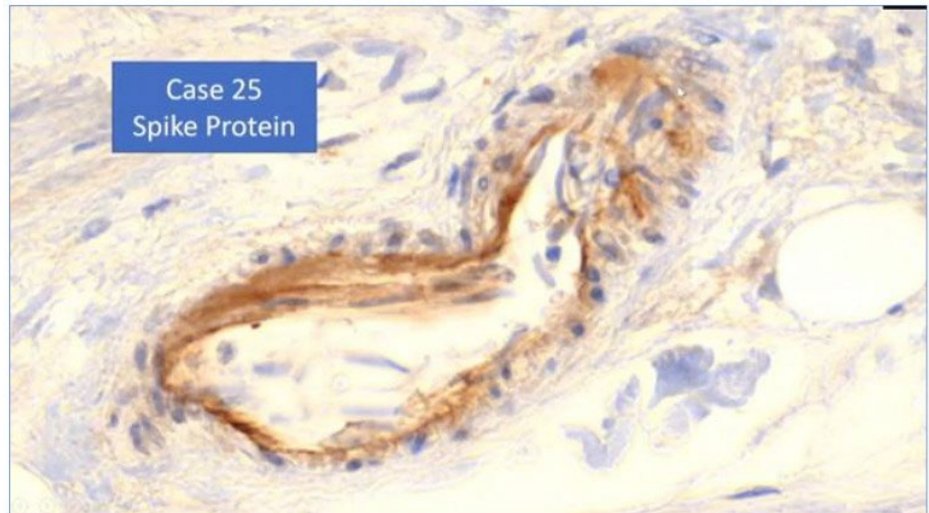
Balbona et al. ([citation 4](#)) reported a case study of a 34-year-old male who developed acute myopericarditis and aortic dissection 16 days after vaccination with a modified mRNA lipid nanoparticle vaccine. Autopsy of his tissues showed histiocytic and lymphocytic myocarditis. Anti-CD3 and antiCD68 antibodies were used to verify the nature of infiltrative cells. Remarkably, the vasa vasorum supplying the media of his aorta featured edematous endothelial lining cells which led to enough ischemia in this area to trigger fatal aortic dissection. There was granular deposition of spike subunit 1 (S₁) in endothelial cells of these arterioles, which were surrounded by macrophages. None of his tissues stained for COVID-19 nucleoprotein, indicating the S₁ was being expressed by translation of vaccine mRNA. Once again we have evidence that the mRNA can trigger intense vasculitis of small arterioles. This could be a final common pathway for myocarditis, aortic dissection, or possibly necrosis of small autonomic nerve fibers and POTS. One must also keep in mind that autoimmune processes are associated with vaccine induced neurologic injury as well (**subsection 1.4**). It is conceivable that vasculitis and



This illustration is reproduced from **citation 5**, an open access article, under the conditions of the Creative Commons Attribution (CC BY) license ([ref.](#)). ->

inflammation could trigger release of cellular debris which triggers autoimmune reactions. Hypothetically both mechanisms could operate together as a pathogenic mechanism.

Citation 5 is an extensive review article fifty pages in length by Australian investigators which shows the many ways in which the COVID-19 spike is toxic irrespective of source—infection or vaccination. We include it here because it contains stunning photomicrographs of tissues from individuals who died after receiving modified mRNA vaccines. These were obtained from a German group headed by Dr. Arne Burkhardt. Page 36 of this paper shows a high magnification photomicrograph of a large capillary blood vessel surrounded by inflammation. The tissue was immunostained with enzyme conjugated anti-spike antibody and an appropriate enzyme substrate was used. The brown granules signal presence of spike protein within the capillary endothelial cells.



Citation 6 is a remarkable study from Mahidol University, Bangkok, Thailand. Parenthetically, one can say, based upon the source of this paper and the above papers, it is amazing how many American academics and government institutions seem to ignore competent research done outside the USA. In any case, Mansanguam et al. did a prospective cohort study of students aged 13-18 years who received a second dose of BNT162b2 modified mRNA (Pfizer) vaccine. They enrolled 314 patients and lost only 13 patients to follow-up (67% of subjects were male). Data included demographics, symptoms, vital signs, ECG, echocardiography, and cardiac enzymes collected at baseline, and days 3, 7, and 14 after vaccination. The most common cardiovascular signs and symptoms were tachycardia (7.64%), shortness of breath (6.64%), palpitation (4.32%), chest pain (4.32%), and hypertension (3.99%). One participant could have more than one sign and/or symptom. Seven subjects (2.33%), all male, exhibited at least one elevated cardiac biomarker or positive lab assessment. Cardiovascular manifestations were found in 29.24%

pg. 25

of patients, ranging from tachycardia or palpitation to myopericarditis. Myocarditis was confirmed in one patient after vaccination (signs, lab data, and MRI changes). Two patients had suspected pericarditis and four patients had suspected subclinical myocarditis. They found all cases fully recovered within 14 days. There are many papers dealing with mRNA vaccine induced cardiac damage which conclude such events are very rare and imply such events may not even exceed what would be expected by chance. This paper should pose the question to such writers: How carefully have you looked for cardiac damage? Alternatively, it is often stated the rate of cardiac damage cause by COVID-19 infection must surely exceed the rate produced by vaccines. Again, we pose the question: Show us your data and tell us how carefully have you looked at vaccinated cohorts prospectively? From React19's point of view, we are only concerned with having people accept the fact vaccines can produce cardiac injury. We are not involved in a debate about whether the risk of cardiac injury from vaccines never exceeds the risk of cardiac injury from infection. This becomes a diversion from addressing the fact that the COVID vaccines can produce myocardial injury. Irrespective of the position one takes in this debate it is very clear that risk-benefit of vaccination must be carefully weighed by considering the age and comorbidities of individuals (e.g. obesity, low vitamin D levels, etc.) These authors say all vaccinees recovered completely within 14 days of onset of signs and symptoms. Nevertheless, when we are dealing with cardiac damage in 12–18-year-olds, one must have some concern about what the long term effects of the vaccine injuries uncovered here will be.

Sun et al. ([citation 7](#)) analyzed a dataset from Israel Emergency Medical Services (EMS) from 2019 to 2023. Israel administered only BNT162b2 Pfizer vaccine to its population. Their study aimed to evaluate the association between the volume of cardiac arrest and acute coronary syndrome EMS calls in the 16-39-year-old population with potential factors including COVID-19 infection and vaccination rates. An increase of over 25% was detected in both call types during January-May 2021, compared with the years 2019-2020. Using negative binomial regression models, the weekly emergency call counts were significantly associated with the rates of first and second vaccine doses administered to this age group but were not associated with COVID-19 infection rates. They concluded, “While not establishing causal relationships, the findings raise concerns regarding vaccine-induced undetected severe cardiovascular side-effects and underscore the already established causal relationship between vaccines and myocarditis, a frequent cause of unexpected cardiac arrest in young individuals.” Pulse vaccination of large segments of a population make it easier to spot adverse events due to vaccines.

Buergin et al. ([citation 8](#)) looked at Swiss hospital employees scheduled to undergo Moderna mRNA-1273 booster vaccination for vaccination-associated myocardial injury, defined as acute dynamic increase in high-sensitivity cardiac troponin (hs-TnT) at a concentration above the sex-specific limit normal on day 3 (48-96 hours) after vaccination. The subjects lacked any evidence of an alternative cause for elevated troponin. To explore possible mechanisms, they evaluated antibodies against an array of antigens and inflammatory cytokines. Among 777 participants (mean age 37 years, 69.5% women) 40 subjects (5.1%) had elevated hs-cTnT concentration and mRNA vaccine associated myocardial injury was adjudicated in 22 participants (20 in women and 2 in men). Those with vaccine associated myocardial injury had lower concentrations of interferon (IFN- λ -1, IL-29) and granulocyte-macrophage colony-stimulating factor (GM-CSF). Depending upon the population, one can find evidence of transient post mRNA vaccination injury in women as well as men.

We include [citation 9](#) here even though it could be considered as focused on a neurologic problem, namely malfunction of the autonomic nervous system; however, fluctuation of blood pressure and tachycardia are

certainly cardiovascular signs. However, as will be discussed elsewhere POTS and dysautonomia have been linked to depletion of fine (small diameter) nerve fibers in the autonomic nervous system. Also, some have speculated the vasculitis produced in organs such as the heart and the aorta (discussed above) could be going on in autonomic nerve bundles, leading to dysautonomia and POTS. This study looked at 284,592 COVID-19-vaccinated individuals (~73% had received Pfizer or Moderna mRNA vaccines and 7% Janssen vaccine). They used a sequence-vaccine analysis such that they looked at the likelihood of POTS occurring 90 days prior to vaccination and then the likelihood of developing POTS within 90 days post vaccination. They used the frequency of conventional primary care diagnoses as a referent. They found odds of myocarditis, dysautonomia, POTS, and mast cell activation syndrome were elevated post vaccination.

The review by Mead et al., [citation 10](#) (48 pp., 341 references), will likely stand as a monumental paper in the discussion of benefit versus risk evaluation of modified mRNA lipid nanoparticle COVID-19 vaccines. Published in the latter part of 2025, it represents a detailed analysis of a large number of papers which have accumulated since roll out of the vaccines beginning December of 2020. This paper makes it impossible to ignore acute and probable long-term effects of myocarditis induced by these vaccines. This is a very detailed paper which the reader can consult on this subject. We will provide the abstract from this paper, provide a few bullet points summarizing some of their key findings, and reproduce two illustrations from the paper. First, the paper abstract:

Myocarditis, typically manifesting as myopericarditis, is among the serious cardiac consequences observed over the course of the COVID-19 pandemic. We performed a comprehensive, evidence-based literature synthesis of findings from clinical trial data reanalyses, post-marketing surveillance, large observational studies, and other diverse research sources that help shed light on the phenomenon of myocarditis post SARS-CoV-2 infection versus COVID-19 vaccine-induced myocarditis. Our conclusions refute several claims previously made by public health agencies and professional associations, namely the following: (1) the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and Omicron infections have caused more cases of myocarditis than the COVID-19 mRNA immunizations; (2) mRNA vaccine-induced myocarditis is typically mild, transient, and rare, with no long-term sequelae; and (3) the risk-benefit calculus favors continued use of these products despite evidence of more iatrogenic cases. We address each of these misconceptions by applying a combination of epidemiological, clinical, and immunological perspectives. We urge government to remove the COVID-19 mRNA products from the market due to the well-documented risk of myocardial damage, a risk that is strongest for younger males (<40 years old).

We summarize a few findings from their paper:

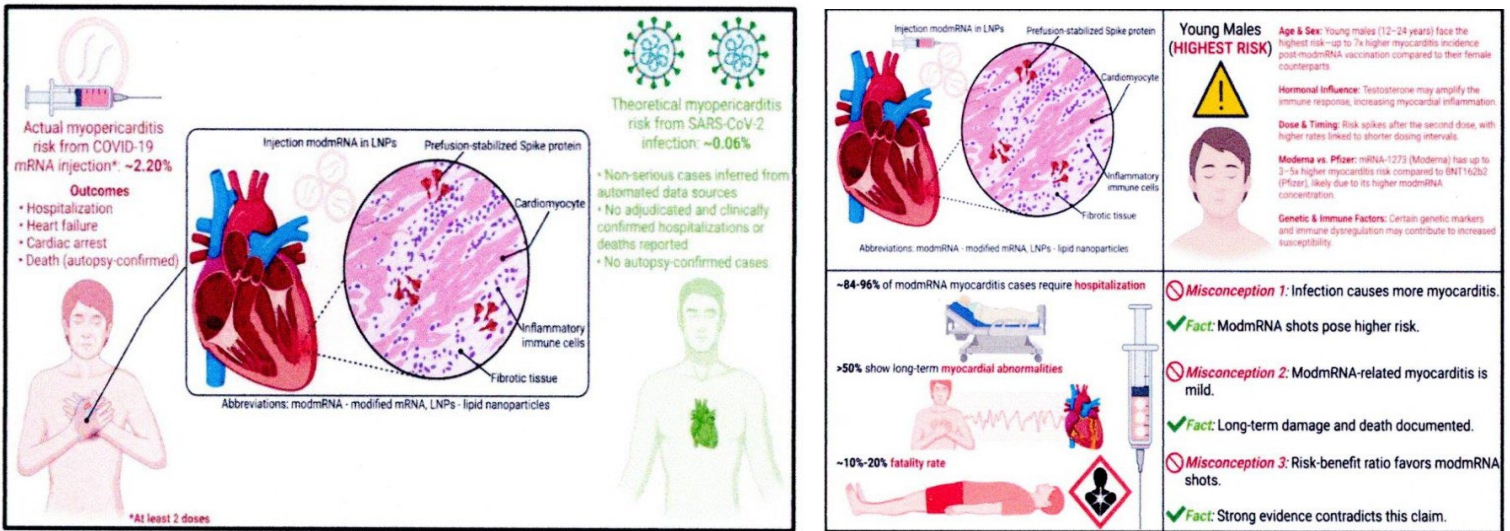
- ▶ Warning signs regarding the ability of mRNA vaccines to produce unacceptable rates of significant myocarditis are evident in diverse epidemiological sources. This was evident using re-analyses of Pfizer and Moderna trial data, confidential post-EUA safety data, prospective measurements of cardiac function and cardiomyocyte injury, autopsy data, U.S. military data (Defense Medical Epidemiology Database, DMED), U.S. life insurance data (U.S. Society of Actuaries), VAERS data, case report data, and sudden deaths in athletes data.

- ▶ Professional medical organizations such as the American College of Cardiology and government health agencies continue to maintain COVID-19 infections produce more cases of myocarditis compared to COVID-19 vaccines. Unadjudicated cases of myocarditis related to COVID-19 infection were suspected in 2020, i.e. studies using strict diagnostic criteria were not used to confirm these cases. Following mass vaccination, many clinically adjudicated and confirmed cases of mRNA vaccine-attributable myocarditis were reported. However, in an attempt to avoid vaccine hesitancy, most public health authorities continue to claim that coronavirus infections cause more myocarditis than the mRNA vaccines. Mead et al. contend this claim is incorrect. They develop at length six main explanations supporting their opinion: (1) hospitalized COVID-19 patients with cardiovascular conditions and elevated troponins triggered clusters of ICD diagnostic codes, with the troponin testing enabling codified data to then be analyzed and reported as false positive “COVID-related” myocarditis; (2) overreliance on data from hospitalized COVID-19 cases without clinical confirmation of myocardial inflammation (CMR, biopsy); (3) lack of autopsy confirmation; (4) differences in how myocarditis incidence is calculated in relation to the coronavirus infection versus the mRNA injection, resulting in an underestimation of the latter’s impact; and (5) failure to consider that the SARS-CoV-2 infection is a “breakthrough” infection which is (by definition) superimposed on a baseline of failed COVID-19 vaccination.
- ▶ Data from hospitalized COVID-19 cases tend to greatly undercount the true number of infections, thus overestimating the relative contribution of infection-related myocarditis in the general population. This theme is developed at length.
- ▶ Many studies purporting to show incidence of vaccine induced myocarditis is much less than myocarditis produced by infection failed to adequately stratify subjects under observation, especially by age and sex.
- ▶ Determining myocarditis incidence post-SARS-CoV-2 infection is very challenging and not very reliable, as the total number of infections remains unknown and cannot be accurately calculated, regardless of the number of RT-PCR tests done. Basically, one can play around with the denominator for total number of COVID cases to get the incidence of myocarditis you want. On the other hand, vaccine-associated risk estimates use well-defined denominators—often total vaccinated individuals—ensuring a more accurate reflection of exposure. Myocarditis linked to COVID-19 infection is typically associated with active viral replication or immune-mediated damage occurring during the acute phase of infection (7-14 days from onset of symptoms). This is a very brief exposure when compared to that associated with COVID-19 mRNA vaccinations, where up to 245 days of mRNA spike protein exposure occurs (see **subsection 1.2, citation 2**).
- ▶ “COVID-related myocarditis” was falsely diagnosed in athletes in 2021-2023. The way this happened is discussed.
- ▶ Multiple studies are discussed which showed the frequent occurrence of subclinical myocarditis results in an undercounting of injection-related myocarditis and an overcounting of infection-related cases.
- ▶ Flawed study methodologies and misreporting issues have distorted the infection-vs-injection argument. Take for example the CDC definition of “vaccination status”: the individual is considered “unvaccinated” until 14 days after dose 2. Conversely, individuals are counted as “vaccinated” only 14 days after the second dose of a two-dose vaccination series. They note, “This has two fundamental implications: (1) individuals testing positive for SARS-CoV-2 before this period, any time prior to the 14 days after dose 2, are considered “unvaccinated”, or not sufficiently protected; and (2) any AE occurring after the first dose or within 14 days of the second dose will be classified as occurring among the “unvaccinated” and counted as such. Implication #2 represents an obvious misclassification that, in turn results in two major distortions. First, with regard to the “vaccinated” individuals in an observational study, this results in consistently lower number of reported myocarditis cases following the first mRNA dose and 14 days up to the second dose, as early post mRNA injection events will not be accurately captured. Second, all myocarditis cases occurring in the first 3-4 weeks of the first injection, or in the first 2 weeks following the second injection, will be

classified as “unvaccinated.” This outcome has resulted in the common yet erroneous belief that the mRNA vaccines prevent more myocarditis than they cause, and therefore mRNA-attributable myocarditis is rare. This problem is intrinsic to many studies adhering to the CDC definition of vaccination status.

- ▶ They observe the modified mRNA dose is different for the Pfizer and Moderna agents, with Moderna’s 1273 vaccine having the highest concentration of mRNA lipid nanoparticles. At the same time reviews have found that Moderna’s 1273 resulted in twice the risk of myocarditis or pericarditis when compared to Pfizer’s BNT162b2 (RR, 4.15, CI=1.87-9.22). This is further evidence of a dose gradient effect pointing towards vaccine causality of myocarditis.
- ▶ The authors develop at length why it is foolish to dismiss any episode of myocarditis as “mild” or “completely reversible.” For example, “mild clinical cases” can involve severe cardiac fibrosis with permanent damage to the heart muscle and lifelong risk of potentially fatal arrhythmias. They point to studies centered upon mild symptoms as opposed to careful cardiac monitoring post vaccination. Thus many studies fail to pick up potentially important cardiac damage.
- ▶ The authors develop a detailed risk-benefit analysis which shows, especially for younger men, risk definitely exceeds benefit. In the process they expose significant conflicts of interest of investigators who authored papers which dismiss concerns about the likelihood of myocarditis post COVID vaccination..

The important features of their arguments are summarized in two figures. We reproduce them below, noting they are taken from **citation 10**, Mead et al. *International Journal of Cardiovascular Research and Innovation* 3(1);1-43 (2025) under the Creative Commons Attribution License ([ref.](#))



Studies of vaccine induced myocarditis have been biased towards minimizing the true importance of this problem. As will become clear in the next section, we do not have good data on the incidence of post COVID vaccine syndrome (PVS) because there has been resistance to validating reports of multiple symptom vaccine injury. One cannot dismiss these vaccine injuries as rare when an acceptable definition for PVS has not been developed and methodical studies have not been performed to determine PVS incidence.

1.8 Post vaccine syndrome (PVS) definitions

Citations/Links: *

1. Post-vaccination syndrome: a descriptive analysis of reported symptoms and patient experiences after COVID-19 immunization. Harlan Krumholz, et al, (20 authors). Posted on medRxiv November 10, 2023 <https://www.medrxiv.org/content/10.1101/2023.11.09.23298266v1>
2. Immunological and antigenic signatures associated with chronic illnesses after COVID-19 Vaccination. Bornali Bhattacharjee, et al. (28 authors). Immunological and antigenic signatures associated with chronic illnesses after COVID-19 vaccination. Posted on medRxiv February 18, 2025 <https://www.medrxiv.org/content/10.1101/2025.02.18.25322379v1>
3. Clinical and diagnostic features of post-acute COVID-19 vaccination syndrome (PACVS) blood markers for COVID vaccine injury. Anna Kathrina Mundorf et al. (13 authors). *Vaccines* 12:790 (2024). <https://doi.org/10.3390/vaccines12070790>
4. Chronic fatigue and dysautonomia following COVID-19 vaccination is distinguished from normal vaccination response by altered blood markers. Amelie Semmler, et al. (14 authors) *Vaccines* 11:1642 (2023). <https://doi.org/10.3390/vaccines11111642>
5. High serum prevalence of autoreactive IgG antibodies against peripheral nerve structures in patients with neurological post-COVID-19 vaccination syndrome. Friederike A. Arlt, et al. (13 authors). *Frontiers in Immunology* 15:1404800 (2024). <https://doi.org/10.3389/fimmu.2024.1404800>
6. Neurological symptoms after COVID-19 vaccination: a report on the clinical presentation of the first 50 patients. *Journal of Neurology* 270:4673-4677 (2023) <https://doi.org/10.1007/s00415-023-11895-9>
7. Persistence of SARS CoV-2 S1 protein in CD16+ monocytes in post-acute sequelae of COVID-19 (PASC) up to 15 months post-infection. Bruce Patterson et al. (17 authors) *Frontiers in Immunology* 12:746021 (2022). Persistence of SARS CoV-2 S1 Protein in CD16+ Monocytes in Post-Acute Sequelae of COVID-19 (PASC) up to 15 Months Post-Infection - PubMed

In many instances, newly identified disease states have not had underlying causal mechanisms determined. However, useful descriptions of these entities must be used to identify cases of disease, do epidemiological studies (determine incidence and prevalence), and to use as a starting point for developing an understanding of underlying causes. We call such descriptions syndromes. *Stedman's Medical Dictionary* defines *syndrome* as the aggregate of signs and symptoms associated with any morbid process, and constituting together a picture of the disease.

All the literature surveyed to this point certainly points towards an entity we could call **post vaccine syndrome (PVS)**. Some are using the term **post-acute vaccine syndrome (PAVS)**, to emphasize the syndrome goes beyond the normal period of around 2-3 days during which one may have “reactive” symptoms after vaccination (e.g. pain at injection site, low grade fever, malaise). What we are describing is signs and symptoms which typically have onset shortly after vaccination but which continue to be severe or grow in severity over time, lasting weeks, months, or indefinitely. We like applying the simplified term “**post vaccine syndrome**” (PVS) to this entity.

This group of papers shows work which identifies signs and symptoms typical of PVS and paves the way for laboratory testing useful in diagnosing PVS. Papers in all the other subsections of this survey have often pointed towards developing a definition of PVS.

Citations 1 and 2 really act as two parts to one study. We have previously discussed **citation 2** in **Subsection 1.2** where we discussed spike protein clearance and persistence. In **citation 1** Krumholz et al. describe the Yale Listen to Immune, Symptom and Treatment Experiences Now (LISTEN) Study conducted from May 2022 to July 2023. This part of their study was intended to determine a reasonable syndrome diagnosis for post vaccine syndrome by surveying individuals who self-reported having PVS symptoms. It included 241 individuals aged 18 and older (median 46 years) who self-reported PVS after COVID-19 vaccination. 92% received modified mRNA (Pfizer or Moderna) vaccines. The investigators administered online surveys and summarized demographics, health status, symptoms, treatments tried and overall experience. Median time from index vaccination to symptom onset was 3 days (interquartile range IQR: 1 day to 8 days). Time from vaccination to completion of the survey was 595 days (IQR: 417-661 days). The median Euro-QoL visual analogue score was 50, indicating significant disruption of daily activities. Space does not allow for a total presentation of their data. Mean number of symptoms attributed to PVS was 22 (IQR: 13-35). The most common symptoms reported were exercise intolerance by 170 (71%), excessive fatigue by 167 (69%), numbness by 153 (63%), brain fog by 151 (63%), neuropathy by 151 (63%), insomnia (61%), palpitations by 145 (60%), myalgia by 132 (55%), tinnitus or humming in ears by 131 (54%), headache by 128 (53%), burning sensations (50%), and dizziness by 121 (50%). It is notable that the FDA and CDC have only admitted myocarditis as an important vaccine AE whereas many of the symptoms described by these PVS patients might best be termed “neurological”; however, this does not rule out cardiovascular events underlying the symptoms. Total number of unique treatments was 209, which they grouped into 40 categories. The median number of treatments tried was 20 (most common being oral steroids, gabapentin, low-dose naltrexone, ivermectin, propranolol, and bronchodilators). The most common non-pharmacological treatment included limiting exercise or exertion (124 [51%]), quitting alcohol or caffeine (105[44%]), hydration and increasing salt intake (105 [44%]), and intermittent fasting (95[39%]). In their discussion they note:

This observational study of self-referred individuals cannot determine causality or provide estimates of the incidence and prevalence of PVS. Although there is a background rate for conditions unrelated to vaccination that can produce many symptoms reported by participants, these individuals do not have other diagnoses to explain their symptoms. Many participants did not have chronic conditions before the pandemic. Also, we excluded LISTEN participants who reported long COVID.... [Also] the syndrome could be unrelated to the vaccination, occurring by chance during the vaccination period. However, the temporal relationship with clustering of symptom onset within the first 1-18 days from the index vaccine suggests a potential relationship.

The possibility that the syndrome may be related to vaccination has implications for future vaccine development and safety surveillance.

Research in this area has the risk of being embroiled in debates about vaccinations. The net benefit of the COVID-19 vaccination program is clear, and there are concerns about vaccine hesitancy. But **fears of inciting vaccine hesitancy should not impede efforts to research this condition—and make progress for people who are suffering.**

They conclude:

In conclusion, people reporting PVS after COVID-19 vaccination in this study are highly symptomatic, have poor health status, and have tried many treatment strategies without success. As PVS is associated with considerable suffering, there is an urgent need to understand its mechanism to provide prevention, diagnosis, and treatment strategies.

[emphasis added]

The same group who conducted the work just reviewed (**citation 1**) then proceeded to look for immunologic and antigenic signatures associated with PVS (**citation 2**). This was a cross-sectional study which involved 42 PVS participants from the LISTEN study along with 22 healthy controls (vaccinated with no AEs).

First, they compared circulating immune system cells from PVS subjects with controls. This was done using tagged antibodies reactive with cell cluster definition (CD) markers and IgD, with cell numbers enumerated by flow cytometry. Briefly, in PVS subjects, they found changes in B cell numbers: increased switched memory B cells (IgD+CD27+) and reduced double negative B cells (DN B cells—IgD-CD27-). For T cells PVS subjects had reduced CD4+ T cells (Th1 and Th2), increased exhausted CD8+T cells. For innate cells (myeloid origin) PVS subjects had increased non-classical monocytes (CD14 low, CD16 high). Staining for intracellular cytokines in PVS subjects showed alterations in IL-7 and IL-21 (B and T cell support). PVS subjects showed increased numbers of TNF α CD8+Tcells; IL-6 pattern changes (IL-4 decreased and IL-4, IL-6 combination were decreased in stimulated CD4+T cells). These findings may be helpful in our future understanding of pathogenesis of PVS but it is unlikely doing such comprehensive testing would be practical for everyday diagnosis of PVS.

Overall, anti-S (spike) IgG levels were lower in PVS compared to controls mainly due to the limited vaccine doses received. It should be pointed out these investigators looked at subgroups of controls and PVS subjects who had experienced COVID infection. They used a SPEAR technique capable of detecting the S1 (spike) segment and full S (spike) molecules at minute femtomolar levels (fM). Significantly elevated S1 and S levels were found in PVS patients and detectable antigen was observed up to 709 days post exposure in PVS subjects. This was true whether they looked at a subgroup of PVS which had only vaccination as last exposure to mRNA coding for spike or a subgroup with onset of PVS and then infection (PVS-I). In the PVS-I group, anti-S antibody levels were lower in those with circulating S1. For some reason, persistent spike antigen failed to elicit an expected antibody response. They state they do not know what the source of persistent spike in the circulation is. This begs the question—the most obvious answer is that modified mRNA is persisting in tissues of PVS individuals and producing S1. Given what we know about the distribution of mRNA lipid nanoparticles, a variety of tissues could be harboring mRNA producing spike. Clearly a study looking at S1 production in various tissues of PVS patients is needed to determine the mechanism for spike productions.

They looked for seropositivity which could point towards reactivation of any of the family of Herpes viruses. They found elevated antibodies against the Epstein-Barr (EBV) surface protein gp42 compared to controls, suggesting EBV reactivation in PVS patients.

They used a micro-array procedure to compare autoantibody levels in PVS subjects and controls. They examined 120 potential autoantigens; however, their panel did not include G protein-coupled receptors. This resulted in a complex picture which showed significant increases in antibody levels for multiple antigens in the PVS group versus the control group and vice versa. It did not appear they could find a particular elevation in the PVS group which would be diagnostic of PVS. They examined circulating hormones, neuropeptides, and immune modulator levels as well.

They used machine learning in an attempt to combine all their data and this process selected 21 features which together separated the PVS subjects from controls. These were in turn grouped into six modules. The reader will need to consult their paper to see a complete discussion of these. However, it was important that one module of variables involved hormones synthesized by the hypothalamus, pituitary glands, and the peripheral nerves which are involved in nociception and stress responses. Oxytocin, neurotensin, β endorphin, melanocyte-stimulating hormones (MSH), and substance P were negatively associated with PVS and formed a separate module (module 6) for separating PVS patient characteristics from controls. This was interesting given the symptomatology found in PVS patients (brain fog, fatigue, neuropathic pain, etc.). The machine learning program identified three features positively associated with PVS: anti-EBV gp42 IgG titers (EBV reactivation), anti MMP1 (matrix metalloproteinase-1), and increased TNF α CD8+T cells. MMP is involved in breakdown of extracellular matrix in normal physiological processes, such as embryonic development but can also be active in disease processes, such as arthritis and metastases. The authors do not comment on this finding, but one wonders about chronic inflammation exposing more of this enzyme and its disintegrated peptides, triggering an autoimmune response. TNF α induces inflammation.

In summary, Bhattacharjee et al. measured multiple parameters and found PVS patients have distinctive symptoms and signs. These are associated with complex changes in cells of their immune system, autoantibody distribution, and inflammatory cytokines. No simple marker was obtained but anti-EBV gp42 and anti-MMP1 are feasible markers. Although they did not detect notable titers of anti-ACE2 (anti-idiotypic) antibodies, the microarray technique they used to look for autoantibodies was likely not of the same quality as the techniques used by investigators looking carefully for anti-ACE2 antibodies. They could not explain why they found low IL6 levels in their PVS subjects whereas other investigators had found the opposite. Timing of specimen acquisition or small sample size could be factors. They were looking for IL-6 expression in mononuclear cells by cell sorting whereas other investigators have measured elevated free IL-6 in serum of PVS subjects. The study was limited by sample size; however, the complex technologies used to produce their study were time consuming and expensive. It is a shame **citations 1 and 2** remain on preprint servers. This is testimony to the tendency of journal editors to dismiss any data describing PVS irrespective of the credentials of the investigators and their care in work. Preprint sources have become more important during the COVID pandemic because of this factor. One can identify a few simplified lessons from their work:

- ▶ The novel modified mRNA lipid nanoparticle vaccines alter innate and adaptive immune systems and in certain individuals this can lead to a constellation of signs and symptoms which can be used to make a clinical diagnosis of PVS.

- ▶ Individuals with severe life-changing PVS can have problems which interfere with normal activities for at least 1.6 years.
- ▶ Detecting elevated S1 and S (spike) proteins and detection of S1 up to 709 days post vaccination should put to bed the myth that the effects of mRNA vaccines are short lived. It would be of interest to determine the tissue sites where spike is being synthesized.
- ▶ Vaccine causality is suggested by a median time to onset of symptoms of 3 days.
- ▶ COVID infection post onset of PVS does not seem to change the underlying changes in the immune system or symptoms and signs of PVS patients.
- ▶ Immune tolerance is complex, given the array of autoantibodies found in PVS and normal controls, respectively. Giving these vaccines can cause reverberating changes in the immune system.
- ▶ An appreciable number of PVS patients had evidence of EBV reactivation confirmed by anti-gp42 IgG. This is a possible laboratory marker to be assessed in people presenting with PVS. Anti-MMP1 is another possible PVS marker.
- ▶ TNF α was a uniting factor in their profile, indicating a chronic inflammatory state. TNF α is capable of producing malaise, joint pain, fatigue, mood changes, etc. A major goal of treatment must be reversing chronic inflammation and normalizing the profile of cells of the immune system. Also, cytokines such as TNF α can be elevated while routine screening markers for inflammation such as C reactive protein may be normal.

In conclusion, people reporting PVS after COVID-19 vaccination in this study are highly symptomatic, have poor health status, and have tried many treatment strategies without success. As PVS is associated with considerable suffering, there is an urgent need to understand its mechanism to provide prevention, diagnosis, and treatment strategies.

Citations 3 and 4 represent work of a German team which was also seeking to describe symptoms and signs of PVS and looking for blood markers of PVS. In their first paper they use the term post-acute COVID-19 vaccination syndrome (PACVS) to refer to chronic fatigue/dysautonomia with onset shortly after vaccination. We will use the term PVS in place of PACVS in this précis of their work. They recruited 191 PVS subjects from self-help groups using online questionnaires. Participants had been diagnosed with myeloencephalitis/chronic fatigue (ME/CFS), POTS, or overlapping syndromes (fibromyalgia, chronic pain syndrome, small nerve fiber (SNF) neuropathy and mast cell activation syndrome (MCAS). PVS subjects exhibited at least three symptoms conforming to these syndromes at least 5 months post vaccination. They explored receptor autoantibodies and IL-6 levels as correlates of PVS. Blood markers determined before and six months after first-time vaccination of healthy controls (n = 89) were compared with corresponding values of PVS subjects. Both the PVS subjects and normal controls (no signs or symptoms of PVS) had received either Pfizer or Moderna modified mRNA lipid nanoparticle vaccines. Those with clinical complaints consistent with COVID-19 infection or serologic evidence of infection had been excluded from their study groups. They used a German manufactured test kit to look for antibodies against 12 receptors. Here they were using ELISA wells coated with native plasma membranes of cells overexpressing the respective receptors. IL-6, IL-8, and CRP were measured in serum of PVS patients and controls using standard laboratory protocols. Note, in both cases these are different from techniques used in citation 2 work. In particular, **citation 2** was looking at IL-6 expression on cell surfaces by flow cytometry.

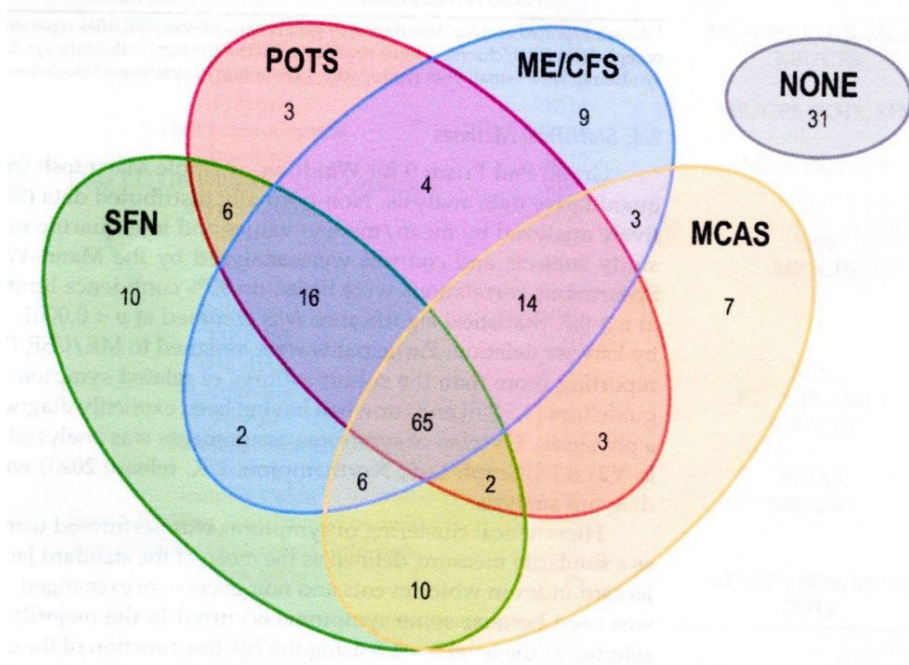
They found normal vaccination response encompassed decreases in 11 receptor antibodies, increases in two

receptor antibodies ($p < 0.0001$) and normal IL-6. In PVS subjects the receptor antibody array was significantly altered ($p < 0.0001$), allowing discrimination from normal post-vaccination state (sensitivity = 90%, $p < 0.0001$) by increased Angiotensin II type 1 receptor antibodies (anti-ACE2 antibodies), decreased alpha-2 β adrenergic receptor antibodies, and increased IL-6 serum levels (cut-off ≥ 2.3 U/ml). Interestingly CRP was similar in PVS

subjects and controls, indicating how worthless this screening measurement is for diagnosis of PVS. In practical terms, IL-6 was identified as a discriminatory marker for PVS.

In a second paper (**citation 4**) they sought to establish a clinical phenotype for PVS using data obtained from the 191 PVS subjects described in their first paper. They used an online registry for 90 symptoms found in MF/CSF, POTS, MCAS, and SFN. They recorded the frequency of each symptom and grouped them into quartiles for percent of PVS subjects reporting a given symptom (i.e. less than 25% subjects reporting, 26-50% reporting, 51-75% reporting, and 76% or more reporting). Wherever possible they also indicated the registry syndrome or syndromes which included a given symptom (i.e. index syndromes: MF/CSF, POTS, MCAS, and SFN). The most frequently reported symptoms (upper quartile) were exhaustion, debility, muscle pain, unrestful sleep, dizziness, tingling/prickling/paresthesia, impairment of mental focusing, fatigue/tiredness, orthostatism, and brain fog.

They used a computer program to transform these data into this Venn diagram:



Reproduced from Mundorf et al. Vaccines 12:790 (2024); open access article distributed under terms and conditions of the Creative Commons Attribution license (<https://creativecommons.org/licenses/by/4.0/>)

The majority (131/191) of cases qualified simultaneously for more than one of the index syndromes. One third of cases even qualified simultaneously for all four syndromes. They say, “These observations support the previous proposition that PACVS [their term for PVS] constitutes a disease or syndrome, *sui generis*, that shares features with, but is distinct from ME/CFS, POTS, MCAS, or SFN.” “*Sui generis*” means “unique.” Having concluded this they used software to perform Jaccard distance statistics for similarities and dissimilarities in the data in a hypothesis-free (non-biased) manner. They obtained eight clusters of symptoms and then looked at the number of PVS subjects fitting each cluster. Almost no subjects fit into symptom cluster 1 or cluster 8, which therefore were deemed as nonspecific symptoms not truly characteristic of PVS. Almost all PVS participants fit into cluster 3— Chronic Fatigue and Malaise. This cluster comprised exhaustion, debility, fatigue-tiredness, weakness, and post exertional malaise. Also heavily represented in the PVS cohort, and overlapping with symptoms of Cluster 3, was Cluster 5—Cognitive Impairment, Headache, Visual and Acoustic Dysfunction: dizziness (153), impairment of mental focusing (150), orthostatism (146), brain fog (146), impairment of short-term memory (125), hyper-sensitivity to noise, diffuse headache (121), amnesic aphasia, anosmia (116) and 12 other symptoms reported by PVS subjects 40-60% of the time. Clusters 3 and 5 appear to comprise a core syndrome definition of PVS. The remaining clusters show a predominance of particular organ system which can be used to more completely define PVS, namely Cluster 2—Peripheral Nerve Dysfunction, Dysesthesia, Paralysis, Pain, Vasomotor Dysfunction; Cluster 4—Cardiovascular Impairment; Cluster 6—Psychomotoric Dysfunction, Anxiety, Disturbed Body Perception, Gastrointestinal Dysfunction; or Cluster 7—Sleep Disturbance, Cutaneous Symptoms. In practical terms, a patient developing symptoms within days of a modified mRNA vaccine with a desired cut-off number of symptoms could meet a case definition for PVS. This diagnosis could be modified, depending upon other symptoms reported. For example, one could have a patient with PVS and Cluster 2 symptoms, PVS with Cluster 4 symptoms, or PVS with 2 or more of the Cluster 2, 4, 6, or 7 symptoms.

They then analyzed data to look for useful serum markers associated with PVS. We tabulate the most useful ones:

Parameter	Normal range (n.r.)	Below n.r.(%)	Above n.r. (%)	Remarks
FT3 , free tri-iodine thyroxine	F2,6-5,M2-4.4 ng/ml	65 (34)		
IL-6	≤6 pg/ml		115 (60)	IL-6 up to 50,000
IL-8	≤62 pg/ml	172 (90)	172 (90)	IL-8 up to 2,000,000
IGG3	24-125 mg/dL	88 (46)		
IgG4			21 (11)	
Transferrin	200-360 mg/dL	34 (18)		
Transf. Saturation	16-45%	27 (14)		
Sol. Transf. Recept	0.81-1.75 mg/L	36 (19)		
Ferritin index	0.63-2.2	117 (61)		

sNFL seroneurofilament light chain	<1.5 (zScore)	39 (20)	Adjusted for age, BMI, GFR
sNFL	10-90 percentile	52 (27)	

They point out the laboratory markers were not significantly associated with specific subsets of symptoms. Note CRP elevation is not helpful in diagnosis. PVS patients have elevated levels of Serum

Neurofilament Light Chain (sNFL), a marker for neuroaxonal damage. Also the changes in fT3 could be an epiphenomenon of chronic critical illness. Changes in iron storage parameters were not significantly associated with chronic fatigue and likely again reflect a chronic disease state.

In summary, [citations 3 and 4](#) provide a useful start to providing an instrument useful in making a core diagnosis of PVS with modifiers for particular organ involvement. They provide several possible laboratory markers as well: elevated anti-ACE2 antibody levels, increased serum IL-6 level, and significant levels of serum sNFL.

We consider the work of Friederike et al. ([citation 5](#)) here because it shows the presentation of PVS may be viewed differently by different providers. This group was based in a neurology practice and examined 50 patients reporting new-onset neurological symptoms post vaccination. Thus their population had predominantly peripheral neurological symptoms, with 56% (n = 28) reporting paresthesia, 46% fatigue, and 36% cognitive impairment. They used teased mouse nerve fibers as targets to identify autoantibodies against neural structures, finding them in 9/50 subjects. They found antibodies against paranodes (n = 5), axons (n=4), Schmidt-Lanterman incisures (n = 2) and Schwann cell nuclei (n=1). In a population rich in a primary complaint of paresthesia, appropriate testing can find autoantibodies against neural structures. This could be useful in diagnosis.

In [citation 6](#) Gerhard et al. from Humbolt-Universität Zu Berlin report their experience with the first 50 patients presenting to their clinic with neurologic symptoms after COVID-19 vaccination. Nearly all had received Pfizer or Moderna mRNA vaccines. Median latency between vaccine administration and symptoms was three days. Most frequent self-reported central nervous symptoms were fatigue, cognitive impairment, and headache. Peripheral nervous symptoms included paresthesia, fasciculations, myalgia, and neuropathic pain. We include this report because they used standardized questionnaire instruments to evaluate their patients. These included one for fatigue (Fatigue Severity Scale, FSS), depression (Beck Depression Inventory BDI), anxiety disorder (Generalized Anxiety Disorder Scale-7, GAD-7), risk of somatic symptom disorder (Somatic Symptom Disorder—C Criteria Scale, SSD-12), and cognitive deficits (Montreal Cognitive Assessment Scale, MoCA). They also used the Short-Form-36 Health Survey to assess impact of symptoms on activities of daily living. They found 73% of patients showed substantial impairment due to fatigue (≥ 4 points), 16% had moderate to severe depression (≥ 20 points), and 25% moderate to severe anxiety (≥ 10 points). Increased risk of somatic symptoms occurred in 75%. SF-36 scores were significantly worse compared to normal controls ($p < 0.05$) with patients having low scores for physical functioning, physical pain and scores showing limitations due to problems with emotional well-being, social functioning, energy/fatigue, and general health. They state “SF-36 showed low percentages in all scores, especially regarding physical health, underlining the severe impact on

patient’s quality of life.” Such standardized testing could assist providers in documenting a PVS diagnosis.

The work by Patterson et al. (**citation 7**) deals with possible pathogenesis of long COVID; however, it centers on the association of non-classical monocytes (CD14Low, CD16+) with long COVID and proposes the persistence of S1 spike protein in these cells is important in the pathogenesis of long COVID. Please recall, we discussed data from this group in **subsection 1.2, citation 2**. There they reported S1 persisting in CD16+ cells in subjects with PVS up to 245 days post vaccination. There are obvious parallelisms here. People with long COVID and PVS may share similarities in the processing of mRNA in monocytes, the maturation of these cells, and their interactions with endothelial cells which make sense.

To make this discussion more meaningful we need to briefly review definitions for macrophages and monocytes as well as their functions and maturation. By macrophages, we really mean tissue resident macrophages. Many of these circulate and are put in place during embryonic development. For example, alveolar macrophages in lung tissue are derived from stem cells in the liver; these liver stem cells become the liver’s Kupffer cells by birth. These resident macrophages are in the tissues, available to function as sentinel cells that sense the presence of microbes and respond by secreting cytokines that initiate and then amplify a protective response against microbes. Some of these cytokines act on endothelial cells lining blood vessels to enhance recruitment of blood monocytes and other leukocytes from blood into sites of infection. It is difficult to know exactly what these tissue macrophages are doing without analyzing tissue biopsies. On the other hand, there are bone marrow derived monocytes circulating in the blood stream. All have potential to act as phagocytes and they can squeeze between endothelial cells of capillaries to gain access to underlying tissue where they can participate in an inflammatory response as macrophages. We can readily obtain blood samples to study these monocytes. All blood monocytes express CD14 (cluster definition 14) on their cell surfaces; however, many believe these monocytes undergo a maturation process yielding monocytes which have differing functions. We tabulate these differences below.

Blood Monocyte		
Subset	CD Markers	Description
Classical Monocyte	CD14++, CD16-	Strong phagocyte activity (readily become activated as tissue macrophages), produce high levels ROS and pro-inflammatory markers IL-6, IL-8, CCL2, CCL3, and CCL5; circulate ~1 day before either migrating into tissues, dying, or turning into intermediate and subsequently non-classical monocytes.
Intermediate Monocyte	CD14+, CD16+	Express highest level of CCR5; pronounced antigen presentation capabilities; secrete TNF- α , IL-1 β , IL-6, CCL3 upon Toll-like receptor stimulation.
Non-classical Monocyte	CD14Low, CD16+	Express high levels of CX3CR1 and are involved in complement and FC gamma-mediated phagocytosis and anti-viral responses. CD16 is the most mature phenotype.

They crawl along endothelial cells (patrolling), where they eliminate circulating microbes and debris. In the context of SARS-CoV-2 infection and long COVID, Patterson et al. note they could phagocytize virally infected apoptotic endothelial cells with subsequent degradation of the RNA and presentation of the S1 protein. Please see our comments below regarding how this cell type is likely important in PVS.

We propose it is reasonable to speculate endothelial cells which might be damaged/killed when they have taken up mRNA lipid nanoparticles, expressed spike protein, and undergone innate immune attack or adaptive immune attack (e.g by auto-antibodies) could also be taken up by non-classical monocytes

The principal findings/conclusions of Patterson et al. were:

- ▶ Long COVID patients had statistically increased intermediate and non-classical monocytes in their blood.
- ▶ These non-classical monocytes contained S1 protein and fragments of RNA encoding spike but no RNA encoding full length S1.
- ▶ Since non-classical monocytes do not have RNA capable of producing complete copies of S1, the S1 must have been in damaged cells (endothelial or otherwise) which were taken up by these monocytes.
- ▶ Persistence of non-classical lymphocytes containing S1 contribute to a chronic inflammatory state.

Although non-classical monocytes are often seen as anti-inflammatory, these authors note this subset can acquire a proinflammatory phenotype when they become senescent and are not eliminated ([ref.](#)). This secretory phenotype is characterized by high basal NF- κ B activity and production of pro-inflammatory cytokines TNF α , IL-1 α , and IL-8 ([ref.](#)). TNF α and TNF- γ can produce malaise, cachexia, etc. Also, in **citation 2**, Battacharjee et al. found increased numbers to TNF α CD8+T cells. Remember TNF α and TNF- γ both are important mediators in chronic inflammation, producing malaise, fatigue, etc. Endothelial cells enter this rather complex picture as well. We now realize endothelial cells have phagocytic properties. They have been called “non-professional phagocytes.” Moreover, they participate in the innate immune system. They have Toll-like receptors and NOD-like receptors, which activate intracellular inflammatory pathways and lead to the production of cytokines, including TNF α ([ref.](#)). They are activated by phagocytosis. In looking at the pathogenesis of vaccine induced chronic inflammation (PVS), we speculate fusion of mRNA lipid nanoparticles would be a phagocytic process activating endothelial cells. Patterson et al., in discussing long COVID, note senescent non-classical monocytes could very well activate endothelial cells as well. Furthermore, TNF- α and TNF- γ induce CX3CL1/Fractalkine by endothelial cells. CX3CL1/Fractalkine inhibits apoptosis of non-classical monocytes, promoting survival of non-classical monocytes.

Perhaps we are seeing evidence for a positive feedback loop here favoring chronic inflammation—activated endothelial cells participate in inflammation, senescent non-classical mononuclear cells activate endothelial cells, and activated endothelial cells produce CX3CL1/Fractalkine to slow elimination of non-classical monocytes. This positive feedback loop favors chronic inflammation. It may be an important mechanism underlying both long COVID and PVS.

Patterson et al. also cite several papers which indicate increased mobilization of CD Low, CD16+ monocytes with exercise. They think this could explain reports of worsening long COVID symptoms in individuals resuming pre-COVID exercise regimens. We think the same could very well be occurring in PVS individuals.

This information may have practical implications. Patterson et al. speculate, “our data suggests that interruption of CX3CR1/fractalkine pathway could be a potential therapeutic target to reduce the survival of S1-containing non-classical monocytes and the associated vascular inflammation previously discussed. What is felicitous for treating long COVID could very well be so for individuals with PVS.

1.9 Pharmacovigilance

Citations/Links:

1. The post-acute COVID-vaccination syndrome in the light of pharmacovigilance. Barbar Platschek and Fritz Boege.

Posted on *Preprints.org* on October 31, 2024

[.https://www.preprints.org/manuscript/202410.2497/v1](https://www.preprints.org/manuscript/202410.2497/v1)

2. Serious adverse events of special interest following mRNA COVID-19 vaccination in randomized trials in adults. Joseph Fraiman et al. (7 authors) *Vaccine* 40(40):5798-5805.

<https://pubmed.ncbi.nlm.nih.gov/36055877/>

Fritz Boege is one of the senior coauthors of the *Vaccine* articles discussed above (**citations 3 and 4 in 1.8 Post vaccine syndrome (PVS) definition**). Not surprisingly, this opinion article has not made it into a peer review journal. We think this demonstrates continued resistance by journal editors in recognizing COVID post vaccine

Background/Objectives: Clinical studies show that SARS-Cov-2 vaccination sometimes entails a severe and disabling chronic syndrome termed post-acute-Covid-vaccination syndrome (PACVS). PACVS shares similarities with long COVID. After more than three years, PACVS is still not officially recognised, while long Covid has been registered by health authorities within little over a year. Here we address possible reasons for that discrepancy. Methods: We analyse to which extent common symptoms of PACVS have been registered by European pharmacovigilance as adverse vaccination reactions and which consequences have been drawn thereof. Results: (i) **PACVS is distinguished from normal vaccination reactions solely by prolonged duration.** (ii) **Symptom duration is poorly monitored by post-authorization pharmacovigilance.** (iii) **PACVS-specific signals were faithfully recorded by health authorities but haven't prompted appropriate reactions.** (iv) The most widely applied SARS-Cov-2 vaccine has been modified after roll-out without renewed phase III evaluation; the modification has increased DNA-contamination, which is thought to aggravate the spectrum of adverse events. (v) Crossing of Pharmacovigilance data with corresponding estimates of applied vaccine doses suggest a **PACVS-prevalence of 0.003 % in the general population. In contrast, occupational surveillance studies suggest a PACVS-prevalence of 0.9 % in young and middle-aged persons.** Conclusions: (a) Denial of official recognition of PACVS is unjustified. (b) PACVS seems to target preferentially young and middle-aged persons. (c) Without official disease recognition, access to public health care and welfare services is made difficult for PACVS-affected persons, which creates considerable socio-economic problems. (d) Without official disease recognition, development and evaluation of therapies for PACVS is impaired.

syndrome (PVS), or, as these authors prefer, post-acute COVID vaccine syndrome (PACVS). However, is there any way to escape the validity of their main points? We will let their abstract serve as a précis of their presentation:

They admit it is difficult to estimate the prevalence of PACVS. After all, none of the mechanisms in place for surveilling for mRNA COVID vaccine AEs is really equipped to enumerate the number of vaccine recipients who have been left with severe symptoms months after vaccination. Platscheck and Boege must use surrogate markers and best guess data on the percent of individuals where PVS symptoms continue or eventually stop. We are left with a very wide range of estimates for prevalence, between 0.003% and 0.9%.

Citation 2 is important for the number of times the authors must note the “limitations” of their analysis. Fraiman et al. set out to analyze serious adverse events (SAEs) reported in the placebo-controlled, phase III randomized trials (RCT) of Pfizer and Moderna mRNA vaccines in adults. SAEs were death; life-threatening AE at the time of the event; inpatient hospitalization or prolongation of existing hospitalization; persistent significant disability/incapacity; a congenital anomaly/birth defect; or medically important event, based on medical judgment. They also focus on a list of adverse events of special interest (AESIs) likely to occur post vaccination provided by the Brighton Collaboration. They did find significant increases in SAEs and AESIs in the variable group of the RCT. Unfortunately, it is clear:



- ▶ Pfizer and Moderna RCT were supposed to follow trial participants for two years but after EUA status for their vaccines was approved they immediately began vaccination their control groups. This makes it essentially impossible to evaluate long-term AEs typically seen in PVS. They could use only interim datasets that were the basis of EUA in December 2020, about 4 months after trials commenced.
- ▶ The AEs examined by Pfizer and Moderna were all assumed, by definition, to be short term reactions typical after vaccination, so-called vaccine reactivity signs. Thus, symptoms such as myalgia or malaise, which are among the markers for PVS were dismissed as only short-term problems. Also, given the fact the observation period for SAEs for the RCT was <4 months for all subjects, it was impossible to measure “persistent or significant disability/incapacity” in any meaningful way. You cannot measure what you set up by design not to measure!
- ▶ The Brighton AESIs were meaningless when one considers the typical AEs associated with PVS. Virtually all of these involve looking at AEs which would be expressed transiently or which are hopelessly incapable of looking at typical symptoms of permanent organ damage or prolonged symptoms. Once again, what they chose to examine was irrelevant with respect to injuries fitting a PVS category.

Most of the discussion of this paper is devoted to the limitations of the study—they discuss five in detail. This paper indicts the typical surveillance being used to track vaccine injuries. One could refer to this paper as evidence that “peer reviewed literature” carefully examining the Pfizer or Moderna RCTs failed to show any evidence of prolonged AEs or a PVS. However, this is a dishonest thing to do. You cannot use a study design which prevents any detection of prolonged, life ruining events as evidence these post vaccination problems do not exist.



SECTION 2
REACT19 COVID VACCINE INJURY RESEARCH

SECTION 2 – REACT19 COVID VACCINE INJURY RESEARCH

React19 Covid vaccine injury study in partnership with University of Maryland Baltimore

React19 investigators presented preliminary data pertinent to defining post vaccination syndrome as a poster session at a meeting, “Demistifying Long COVID International International Conference:”

Characterizing post COVID-19 vaccination syndrome in an international cohort: similarities and differences with long COVID. A collaborative project of React 19 with the University of Maryland School of Medicine. Eduardo Galli, Danice Hertz, and Linda Simoni Wastila. [Poster DLGCG Edoardo Galli 50.pdf](#)

We will not present a detailed description of this investigation in this literature survey since the resultant paper is in the process of being considered for publication in a peer reviewed journal. This paper will greatly enhance the working definition of post COVID vaccine injury discussed in **Concluding Remarks**.

However in **Section 2.1** we will discuss what React19 volunteers discovered when they investigated how VAERS was being used to document vaccine injuries.

2.1 - REACT19 VAERS Audit

Citations/Links:

1. React 19 audit of reports to VAERS. Alberto Benavides, Brianne Dressen, Joel Wallskog, MD, and Linda Wastila,, PhD) Posted on React19.org, November, 2022.

<https://www.react19.org/research-studies-surveys/react19-research-vaers-audit>

2. The above audit is discussed in BMJ Investigation: Is the US’s vaccine adverse event reporting system broken? Jennifer Block, *BMJ* 1383:2582 (November 10, 2023)

<https://www.bmj.com/content/383/bmj.p2582>)

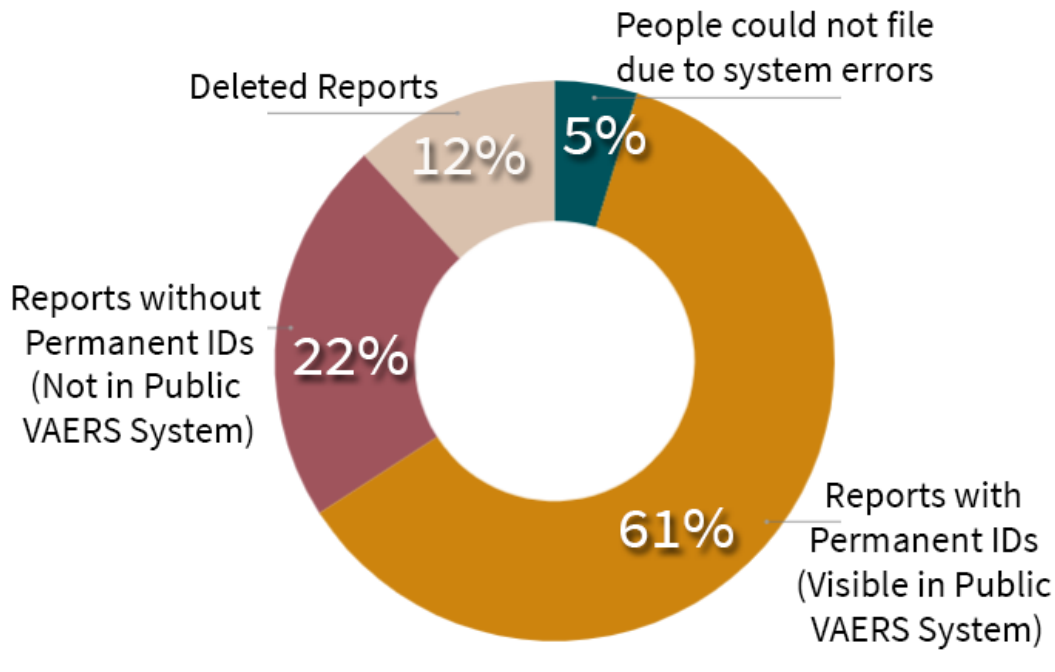
In **citation 1** (Benavides et al.), React19 volunteers reviewed 126 VAERS report numbers filed by 103 independent COVID vaccine-injured individuals. By this time React19 had been contacted by over 20,000 individuals describing COVID vaccine AEs. They conducted this audit due to concerns raised by members that they never received permanent VAERS report Identification Numbers, they could not find their VAERS reports published on the VAERS website, and/or their reports had been altered, combined with previous reports, or removed. The scope of the audit was to understand how CDC and FDA were following up with VAERS reports filed by those who persistently suffer after their COVID vaccine injury. They recruited React19 members to the audit between October 17 and November 7, 2022. They advertised this through a support group. React19 individuals who agreed to the audit provided their name and report number(s). The audit captured the following information: Temporary ID, link to the live VAERS report (publicly available reports online), VAERS permanent ID,

State, Age, Gender, Vaccination Date, Symptom on-set date, Date entered, date published, date deleted, and any commentary by injured who filed the report.

Findings:

Of 126 verified true instances where VAERS reports were submitted regarding COVID-19 vaccine injury or death:

- ▶ 61% of the reports were logged and published in the public VAERS system correctly (provided a permanent ID#);
- ▶ 22% of the reports do not have a permanent ID and, therefore, are not publicly visible;
- ▶ 12% of the reports have been outright deleted and, therefore, not publicly visible;
- ▶ 5% could not file a report or their report number remains unknown.

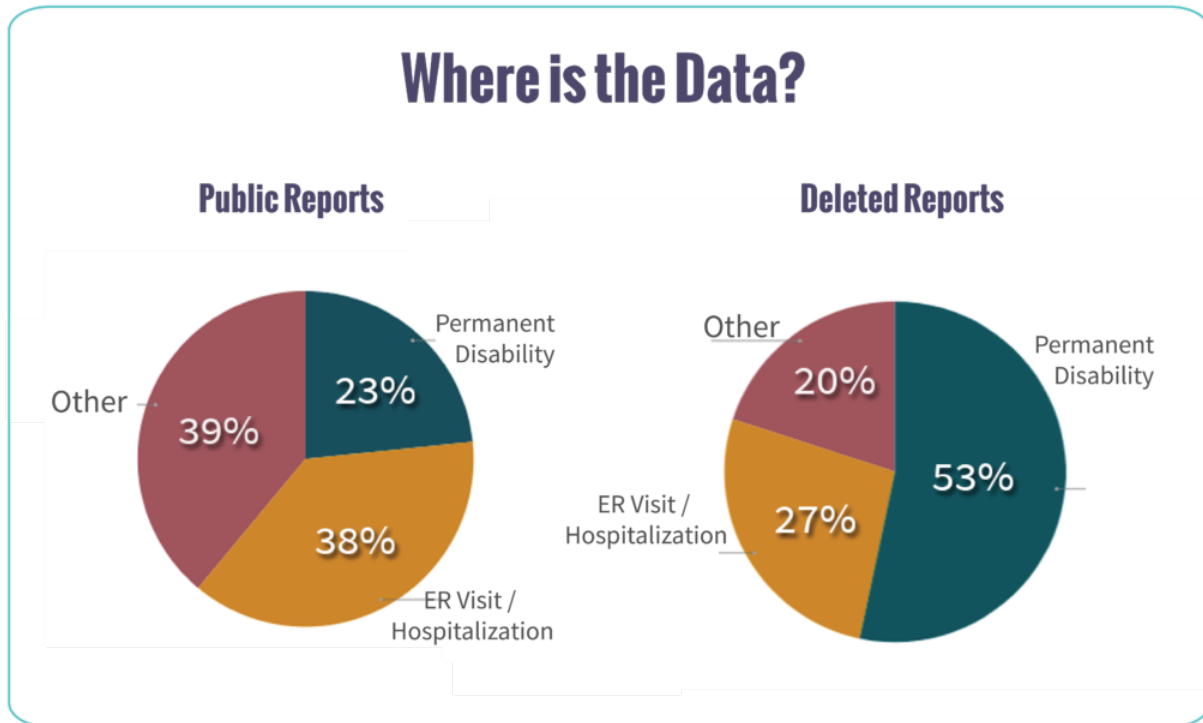


Medical status of the 15 deleted reports:

- ▶ 53% are reports of permanent disability
- ▶ 27% are reports of ER/hospital visits
- ▶ 20% are “other”

Medical status of the 89 reports currently visible in the VAERS system.

- ▶ 23% are Reports of Permanent Disability
- ▶ 38% are Reports of ER/Hospital Visits
- ▶ 39% are “Other”



Individuals who received only temporary IDs (their reports are not visible to the public) reported that they were not aware that their report was not officially in the system, nor were they aware VAERS would need to issue a second permanent ID. During the audit, these individuals were encouraged to call the VAERS office to inquire about the status of their report. Examples of the responses follow. Individuals whose reports were deleted called the VAERS office as well.

Sample responses of telephone calls to the VAERS system/call log from individuals asking VAERS about their temporary reports:

"Basically, she [VAERS representative] didn't have an answer why some of us are stuck in temporary mode. She said when we filed originally, we should have gotten an email as an acknowledgment letter with a permanent ID. Seems it's up to us to know that, look out for the email and if we don't get one, we are to call them to figure it out. As of now she says two of my temp IDs will be merged into one and I should get an email from them in the next week that will have my permanent ID."

"I called VAERS and they [the representative] were cagey when I said I heard my report was deleted. After being placed on hold while she checked, I was told they had my info. Neither denied or confirmed my report was deleted. Told me they would contact me if they need anything. Basic response each time I dug for more details."

Example of investigation of 2 reports, with one deleted:

First report, which was not updated:

"I called, emailed, and faxed updates as they [VAERS representatives] instructed when I repeatedly reached out to update the lot# and medical diagnostics. Nothing was ever updated. I tried every possible avenue even though my hands didn't work. Months later I got the standard automated updated request from them which I always filled out and again, no update to anything. I called again and they said you cannot update any reports at all ever, I must put in a new report."

Report 2 deleted:

"They [VAERS representatives] instructed me to file this report when refusing to do updates to report #1. My report #2 has my medical proof of SFN (small fiber neuropathy), bilateral ulnar neuropathy on EMG, brain spots on MRI, and the lot #. The second report is clearly more important and shows specific medical findings. Yet they silently deleted it and never updated the misleading and weak first report which was too early for diagnostics."

Example of death report NOT listed as a death report (two reports filed):

First report after HLH diagnosis was classified as "life threatening" and second report filed after his death was misclassified as "hospitalized."

[Per healthcare provider] Family called to request a correction to the second report to be fatality and was instructed to file another report and was sent a form condolence letter from the CDC. (fatality was May 2021, form letter received December 2022. After their initial complaint inquiring about why his report is not indicated as a death, they subsequently received the following email:

"Good afternoon, Thank you for contacting the Vaccine Adverse Event Reporting System (VAERS) program. Thank you for taking the time to file the report. VAERS data available to the public include only the initial report data to VAERS. Updated data which contains data from medical records and corrections reported during follow up are used by the government for analysis. However, for numerous reasons including data consistency, these amended data are not available to the public. You can find the above information on our website at <https://vaers.hhs.gov/data.html>. Should you require assistance in the future please visit our website or contact us. Sincerely, VAERS Staff"

Example of death report with NO follow up:

“My condolence letters [received] from the CDC. Despite claims of safety monitoring they never contacted me, never asked for death certificate, autopsy report, medical records. They were not looking for any “signals.” I called several times to ask why no one had contacted me to investigate why a young healthy 34 year old passed 2 weeks after Pfizer vaccine and the only thing I got was those insulting letters.”

Summary:

The React19 audit found that 1 in 3 reports are either not processed through the system for the public to review due to lack of assignment of a permanent ID and/or deleted after original publication. This lack of public visibility is psychologically hurtful and disrespectful to the injured and their families who filed the reports. A ratio of 1 in 3 reports not being visible to the public due to being deleted or incorrectly processed in the VAERS system is far above the margin of error anyone would expect. It also suggests problems of omission of data and under-reporting of VAERS reports may be even greater than estimated. In sum, React19’s audit illustrates a wide-spread issue with reports not being processed by the CDC appropriately. The VAERS system insists they have the information for each report, but when asked they do not provide the information, only stating that they can see it on the private side and that it is combined with the original report. This makes it impossible for submitters to verify and/or validate their reports. The original report in public-facing VAERS does not reflect any updates given. This also illustrates the lack of transparency of the VAERS system, co-managed by the FDA and CDC.

Various estimates indicate the number of AE reports to VAERS 10-20-fold less than reality. This passive system is broken and neither the CDC nor the FDA appear capable or inclined to accept and investigate a relative reporting ratio >2 in VAERS symptom/sign reporting categories for COVID-19 vaccines. These are red flags for frequency of AEs well beyond what has been reported for all other vaccines combined. Dysfunction of VAERS is analyzed independently here:

Rose J. Critical appraisal of VAERS pharmacovigilance: Is the U.S. vaccine adverse events reporting system (Vaers) a functioning pharmacovigilance system? *Science, Public Health Policy, and the Law* October 2021; 3:100-129

[Dr Jessica Rose PhD - Pharmacovigilance VAERS Paper FINAL OCT. 1, 2021.pdf](#)

Citation 2. Jennifer Block, reporting in the *BMJ INVESTIGATION* segment of *BMJ*, published a critique of VAERS comanagement by the CDC and FDA. She found the same defects with respect to management of VAERS discovered by React19. She notes the operation is grossly understaffed and there seems to be no effort to fix this problem. She states, “*The BMJ* has found the FDA and CDC essentially maintain two separate VAERS databases: a public facing database, containing only initial reports; and a private, back-end system containing updates and corrections—such as a formal diagnosis, recovery, or death.” FDA representatives (Peter Marks and Narayan Nair) claim information from a person’s medical record cannot be publicly disclosed by law; therefore,

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such crucial information cannot be publicly posted. This begs the question: Why are CDC and FDA unable to devise a method to anonymize their data? Epidemiologic studies are often done using medical records with identity of the subjects not revealed. The reporting individuals are the ones given an ID number for reference. For example, their identity could be kept anonymous but identifiable for their own purposes by the ID number. Her report also makes clear VAERS has not bothered to develop a method to look for chronic, persistent symptoms/signs, which is pathognomonic for COVID PVS. Thus, practitioners have no way of knowing when they encounter a person with symptoms of chronic AEs or PVS. In essence there is a negative feedback loop embedded in VAERS which works to prevent recognition of PVS and its reporting.



SECTION 3
NIH VACCINE INJURY RESEARCH

SECTION 3—NIH VACCINE INJURY RESEARCH

Citations/Links:

1. ANA investigates: neurological complications of COVID-19 vaccines. Adeline Goss et al. *Ann Neurol* 89(5):856-7 (2021)

[ANA Investigates: Neurological Complications of COVID-19 Vaccines - PMC](#)

2. COVID-19 and vaccination in the setting of neurologic disease, an emerging issue in neurology. Elizabeth B. Marsh et al. *Neurology* 97 (15):720-712 (2021).

[COVID-19 and Vaccination in the Setting of Neurologic Disease | Neurology](#)

3. Neurologic complications with vaccines: what we know, what we don't, and what we should do. Avindra Nath. *Neurology* 101 (14):621-626

<https://pmc.ncbi.nlm.nih.gov/articles/PMC10573146/>

4. Neuropathic symptoms with SARS-CoV-2 vaccines. Farinaz Safavi et al. posted on *medRxiv* May 17, 2022.

[Neuropathic symptoms with SARS-CoV-2 vaccination - PMC](#)

Given the rising number of case reports describing prolonged symptoms following COVID-19 vaccinations, publication of papers pointing towards likely pathogenesis of the persistent generalized symptom, permanent damage to particular organ systems, and descriptions of clusters of symptoms which can be used as case definitions for a post vaccination syndrome (PVS), **output of actual research from the National Institutes of Health looking into complications of COVID-19 vaccination has been quite meager**. The output which has occurred has involved primarily work of Avindra Nath MD, a physician-scientist who specializes in neuroimmunology. Research findings of a group including Nath (**citation 4**) are visible only as a preprint publication nearly 3 years since its original posting. Dr. Nath serves as the intramural clinical director of the National Institute of Neurological Disorders and Stroke (NINDS) and chief of the Section of Infections of the Nervous System at NINDS. **The NIH research output from NINDS regarding long COVID is also scant**. A clinical trial with Dr. Nath as Primary Investigator was registered under ClinicalTrials.gov ID NCT04564287. This would have looked at persisting symptoms and signs post COVID-19 infection. It was to start 10-28-2020, reach primary completion 4-12-2023, and have actual completion 4-4-2023. The last update was posted 11-25-25 and the registration record says, "no results posted." One must assume this study did not go forward

In summary Dr. Nath has authored or co-authored three publications which comment on the topic of COVID vaccine injury. However, it appears only one study of vaccine injured patients involving the NIH Clinical Center has occurred and the results of this study, as noted above, were posted as a preprint on May 17, 2022. The work has not been published in a peer reviewed journal.

Citation 1 is a condensed, edited version of a podcast dealing with complications of COVID-19 vaccines. It is guidance offered to an audience of neurologists. It was submitted March 4 of 2021 and should be regarded as

very preliminary in its assessment of vaccine safety. Post vaccination AEs were starting to come into VAERS. It attempts a balanced analysis in assessing likely COVID vaccine AEs. On the one hand Nath says:

“Concern about neurological complications from COVID-19 vaccines escalated in the fall of 2020, when 2 patients developed transverse myelitis after receiving the Oxford/AstraZeneca vaccine. ¹ 1 One case was ultimately deemed unlikely to be related to the vaccination (the patient had pre-existing multiple sclerosis), whereas the other was determined to be possibly related. ² **Data from the mRNA vaccine clinical trials showed that 7 cases out of 37,000 vaccine recipients developed Bell's palsy and none developed Guillain-Barré syndrome (GBS). “[emphasis added]**

But this is immediately countered with: “The US Food and Drug Administration (FDA) concluded that the rate of Bell’s palsy was not higher than expected in the general population. In the DNA-based Johnson & Johnson vaccine trial, one patient each in the vaccinated and placebo group developed GBS.” The scant data at that time failed to appreciate dangers in two of the vaccines discussed. Because of safety concerns AstraZeneca formally removed their vaccine from production and distribution in May of 2024 and Janssen suspended production of its vaccine in 2022; both are no longer available in the USA.

The paper notes that only 9,443 reports had been submitted to VAERS as of March 2, 2021. As of April 13, 2025, there have been 1,662,446 post COVID vaccination AE reports registered on VAERS. This includes 38,541 deaths and many reports point to a neurologic risk, e.g., there are 5,500 reports of Guillain Barre/transverse myelitis (see openvaers.com). When this podcast occurred, the neurologic AEs reported to VAERS were noted but there was a strong disclaimer for any possible causal link between vaccination and the AEs.

Similarly, **Citation 2** is a short review which deals with the safety of COVID vaccinations in individuals with neurological conditions. It was submitted for publication July 29, 2021. The paper does note, “a number of neurologic complications of these [COVID] vaccines are now being reported in the most comprehensive registry, ...VAERS database.” The authors provide a short list of complications but conclude, “These complications are rare when compared to the large number of vaccinated individuals; however, it is too early to know the true incidence and risk factors for these complications.” This paper is essentially a position paper of the Quality Committee of the American Academy of Neurology which endorses universal vaccination. They conclude, “Based on existing evidence, neurologists should recommend COVID-19 vaccinations to their patients.”

Citation 3 discusses neurologic complications after vaccinations in a general way. For example, they include a table of 17 vaccines and associated complications. There is limited discussion of COVID-19 vaccines. They discuss challenges in determining neurologic complications of vaccines:

The published literature has a large list of case reports and case series with a wide variety of neurological manifestations attributed to vaccines. **While most side effects of vaccines are benign and transient, such as headache or fatigue, more serious side effects, including devastating neurological complications may occur....**The same data set [VAERS] reveals that serious neurologic complications after vaccine administration across all vaccine types are extremely rare. **Nonetheless neurological manifestations that are potentially attributed to vaccines include immune mediated syndromes; major categories of which include Guillain Barre Syndrome, small fiber neuropathies, transverse myelitis and acute disseminated encephalomyelitis....**

There is a great need to conduct research for identifying the underlying factors and subcellular mechanisms that result in neurologic manifestations from vaccines. Questions that could be addressed include identification of comorbidities or genetic factors that increase susceptibility to these side effects; epidemiologic studies to determine what manifestations are common to most vaccines, which are unique and which may occur just by chance alone, develop in vitro models, and clinical studies to understand the immunopathogenesis of these illnesses and to determine the impact of the vaccines on individuals with underlying systemic or neurologic illnesses; and finally, conduct clinical trials that target these pathways to either pretreat individuals to prevent the side effects or treat after the manifestations. Research may also guide the development of safer vaccines.

Many of the comments in this paper touch on COVID-19 vaccines. **The proposed research discussed looks like a plan for what NIH and other government entities should have been pursuing cooperatively at scale during the COVID-19 pandemic.** Some groups of investigators have been making efforts. The papers discussed in **SECTION ONE** of this survey serve as witnesses to this. There have been missed opportunities because many projects, particularly epidemiologic studies of vaccinated versus unvaccinated populations will be more difficult as multiple vaccine boosters have been given and waves of COVID infection have occurred, and COVID vaccine uptake rates have plummeted. Nath notes:

Vaccine adverse event monitoring is not the portfolio of the NIH, which is focused on disease-oriented and fundamental research. The US Food and Drug Administration (FDA) evaluates the risks of the vaccines before approval....Once the vaccines are approved, active surveillance continues through the FDA's biologic effectiveness and safety (REST) system and through the Center for Disease Control and Prevention (CDC)'s vaccine safety datalink program. The scope of these programs needs to be expanded to be able to capture the rare neurologic complications. **No one has primary responsibility for investigating the mechanisms of side effects of vaccines.**

The last sentence is truly amazing! From the standpoint of vaccine injured individuals, major reforms are needed in the way the NIH, FDA, and CDC must work together regarding vaccine development, safety approval, and post marketing surveillance. Nath says no one has primary responsibility for investigating the mechanisms of side effects of vaccines. He says NIH is only "focused on disease-oriented and fundamental research." It seems to us that vaccine AEs and PVS are disease states. They just happen to be produced by vaccines. Like any disease vaccine AEs and PVS are diseases which can be subjected to fundamental research defining the pathogenetic mechanisms responsible for producing these disease states at the cellular and molecular level. If NIH does not see this as part of its present portfolio, maybe there needs to be an adjustment regarding what their portfolio includes. Certainly researchers identified in Section One of this survey have been pursuing this goal.

Dr. Nath makes some cogent comments about the Public Readiness and Emergency Preparedness (PREP) Act and the Countermeasures Injury Compensation Program (CICP):

The bill [PREP Act] provided immunity to drug companies from being sued for any unforeseeable side effect of vaccines, but they can be held responsible if there was any willful misconduct (42US code 247-6d). The PREP Act created the CICP. This provides compensation to the people who may have been injured from the vaccine. This was performed to incentivize companies to take on the risk for development of vaccines. However, **no funds were obligated to provide any provisions for studying the underlying mechanisms of these side effects, for developing ways to prevent them or for treating them. As a result, there is a gap in knowledge about the postmarketing neurologic side effects of vaccines, and lack of an organized effort to provide a definitive diagnosis or develop treatments for these patients.** A simple solution might be to convene all stakeholders preferably at a global level to investigate the side effects and provide funding to conduct research to study and treat them.

REACT19's stance is that the CICP is woefully underfunded with regard to reimbursing vaccine injured individuals and does not provide transparent due process to injured individuals who file claims.

Dr. Nath tabulates steps needed to adequately study neurologic complications of vaccines:

1. **Expansion of active surveillance programs**
2. **Develop tools for gathering precise information on neurologic complications**
3. **Genetic susceptibility studies**
4. **Immune profiling of individuals with neurologic manifestations**
5. **Determine association with comorbidities**
6. **Develop animal models**
7. **Conduct clinical trials for the prevention and treatment of adverse events.**

We observe that none of these steps will occur without a change in attitude at our Federal agencies, research universities, and medical journal editors. There must be openness for discussing vaccine AEs as real phenomena. As noted at the beginning of this literature survey there are strong economic incentives among vaccine manufacturers for dismissing AEs produced by modified mRNA lipid nanoparticle vaccines as vanishingly small in frequency or denying their existence all together. If manufacturers are to be given legal immunity for AEs produced by their products, it stands to reason they should contribute funds to CICP and towards the seven steps identified by Dr. Nath. Investigators who want to study vaccine injuries need funding and, equally as important, some reassurance that their work will be published in peer reviewed journals rather than languishing indefinitely in online preprint journals or even face retraction without explanation.

Citation 4 has 12 coauthors, with Avidra Nath as senior author. Seven authors were based at NIH and five at three medical schools. As noted above, the report was posted on *Medrxiv* on May 16, 2022, and remains there. React19's Danice Hertz and Brianne Dressen were participants in this study. One subject received the AstraZeneca (ChAdOx1 nCoV19), one Janssen (JNJ-78436735), nine Moderna (mRNA-1273), and 12 Pfizer

BioNTech (BNT162b2) vaccine. In this observational study, they “studied 23 patients (92% female; median age 40 years) reporting new neuropathic symptoms beginning within 1 month after SARS-CoV-2 vaccination. 100% reported sensory symptoms comprising severe face and/or limb paresthesia, and 61% had orthostasis, heat intolerance and palpitations.” Eleven subjects were identified as “in person visits,” which we conclude means they were seen at the NIH Clinical Center. They do not report whether the patients were queried to determine presence of a variety of other symptoms associated with PVS (see the discussion in **section 1.8** and **section 2.1**). In any case, they had accepted only individuals with these particular symptoms for study.

Results:


Autonomic testing in 12 subjects	7 showed reduced distal sweat production (iontophoresis) 6 positional orthostatic tachycardia syndrome (POTS, by tilt table data)
Lower-leg skin biopsies in 16 subjects	31% diagnostic/subthreshold epidermal neurite densities ($\leq 5\%$) and 13% borderline (5.01-10%) 19% abnormal axonal swelling
5 Randomly selected biopsies compared to 9 age/sex matched healthy controls; immunohistopathology	More C4d deposition on endothelial cells in all patients
CSF analysis	All with normal cell counts, protein, glucose and IgG synthesis. Two with oligoclonal bands, one with pattern 2 and another with pattern 3.
Nerve conduction study	Normal nerve conduction verifies pure small fiber axonal neuropathy
Brain/spinal MRI in 16 subjects	Normal

Treatments attempted were 0.75-1 mg/kg prednisone with varying tapers. Improvement was variable. Three patients who had been symptomatic for 5-9 months were given intravenous immunoglobulin (IVIg, 2g/kg divided over 5 days). All three had dramatic improvement within 2 weeks. Of 11 patients who never received immunotherapy, seven (64%) had partial recovery, three (27%) had no improvement, and one (10%) had complete recovery by 12 weeks post-onset by subjective assessment.

In their discussion they note a likely priming effect was observed in multiple patients (17% reported mild/transient symptoms after the initial vaccination with full onset after the second dose) “The circumstantial evidence here suggests that in some individuals SARS-CoV-2 vaccination neuropathy may be dysimmune. The fact that participants were screened, and common causes of neuropathy eliminated, the presence of oligoclonal bands in the CSF of two of five participants, deposition of immune complexes on skin biopsy and apparent response to immunotherapy supports possible immune involvement.”

React19 was founded in an environment where there was resistance to accepting COVID vaccine AEs as real in order to prevent vaccine hesitancy in the American population (see **Introduction**). From the point of view of scientific understanding of a problem it is important government institutions, academia, and scientists adopt the appropriate null hypothesis to test in investigating a problem. Unfortunately, all these groups began with a null hypothesis which said, “COVID vaccine injuries are nonexistent to exceedingly rare, short lived, and mild.” This meant the onus was on those suffering from vaccine injuries to prove this hypothesis false. The injured lacked the human and financial capital to produce such proof. This null hypothesis was the **opposite** from the one which had been operative in past years to investigate vaccine injuries to assure vaccine safety, namely, **reports of COVID vaccine injuries should be assumed to be real, COVID vaccine injuries are unacceptably frequent, and they can produce severe life changing illness.** To disprove this hypothesis the CDC, FDA, NIH, and academics should have cooperated at scale to investigate COVID vaccine AEs with appropriate data collection, epidemiologic analysis, appropriate data transparency, and investigation of injury pathogenesis. Based on such work, potential vaccinees would have been provided meaningful information for making an informed consent regarding COVID vaccination soon after roll out of the COVID vaccines to millions of people. Meaningful observational studies and RCTs for early treatment of AEs would likely have resulted.

In 1976, the CDC embarked on a program to mass vaccinate 213 million Americans against swine influenza. This led to over 450 reports of Guillain Barre syndrome (GBS) post vaccination. The CDC ultimately admitted that the vaccination produced GBS at a rate of about 1 per 100,000 doses given ([ref.](#)). This program was cancelled as GBS case reports accumulated. Pulse mass vaccinations, where very large populations are vaccinated over a short period of time, inevitably make it much easier to spot vaccine injury red flags. This has most certainly been the case for COVID-19 vaccinations. Interestingly, both the Oxford-AstraZeneca CHAdOx1 and Janssen Ad26.COV.S virus vector vaccines were quietly removed from the American market after a relatively small number of dramatic AEs occurred, leaving the mRNA lipid nanoparticle vaccines in wide use. Now when we examine reports of COVID-19 vaccine AEs to VAERS in mid-April, 2025, we see 35,488/38,541 (92%) of total reports of death, 4785/5500 (87%) of total reports of GBS/transverse myelitis, and 28,304/28,908 (98%) of reports of myocarditis were associated with modified mRNA lipid nanoparticle vaccines.



Reports of COVID vaccine injuries should be assumed to be real, COVID vaccine injuries are unacceptably frequent, and they can produce severe life changing illness.

Soon after roll out of the COVID-19 vaccines, case reports of vaccine AEs began appearing in the literature at a rapid clip. As discussed above (see **Introduction**), one could count on the introduction of each case report paper to say COVID infection produces the same pathology as the vaccine AE being reported in the given paper and that such vaccine AEs are of course “rare.” The authors had to make this nearly creedal statement to get their paper published. In effect the authors had to endorse the unproven null hypothesis described above, something to the effect, “ AEs from COVID vaccines are very rare, short lived, mild, etc., but we thought you would like to know about this case anyway.” Within a year, there were now thousands of case reports in the literature and VAERS was reporting unprecedented numbers of AEs associated with COVID-19 vaccinations (see **Introduction** and **subsection 1.0**). There were 5,500 cases of GBS/transverse myelitis among the 1,662,426 COVID vaccine AEs reported to VAERS by April 13, 2025. This dwarfs anything seen with any prior vaccination program even when one looks at all vaccines administered since VAERS reporting began. We now have arrived at a situation where case reports in the literature are likely three to four times the 3,572 publications catalogued in the early days of React19’s literature survey (see **subsection 1.0**). We also know VAERS is a broken system. Neither the CDC nor FDA has devoted enough resources to reliably record AEs or to follow up on them in a meaningful way (see **subsection 1.9** and **subsection 2.1**). With over 38,541 deaths reported, this is a sad situation. Also, VAERS is not operated in a way which can identify long term injuries due to the vaccines. Thus getting any meaningful accurate assessment of how many people are suffering long term injuries from the COVID vaccines from our government agencies is really impossible. Few investigators have even dared to make estimates (see **subsection 1.9, citation 1**). One estimate ([ref.](#)) puts the number of COVID-19 vaccine doses administered in the United States at 676.73 million as of May, 2023. Even with 1-3 AEs per 100,000 doses one could predict 67,000-201,000 AEs had occurred from doses given by that time. Although we are discussing mainly AEs in the American population, it is worth noting COVID vaccine injury is an international problem. React19 used an international pool of participants to determine symptoms indicative of PVS.

The assembled literature surveyed here suggests there are likely three major groups of COVID vaccine injured individuals suffering persistent symptoms which seriously affect their quality of life:

- 1. Individuals who had prominent damage involving a particular organ system soon after exposure to vaccine such that they have residual, unrelenting problems.** These individuals may not report PVS symptoms or may neglect reporting PVS symptoms. The damage to the organ system overshadows their lives.
- 2. Individuals who develop a constellation of symptoms which denote COVID post vaccine syndrome (PVS), best described as a chronic inflammatory state.**
- 3. Individuals who have residuals of prominent damage to an organ system (like the first subgroup) and report symptoms of PVS as well**

A good example of group 1 would be individuals who experienced severe myocarditis and were left with chronic heart failure. When someone is left with stage D heart failure that person may not be able to distinguish their general malaise from symptoms of PVS. For that matter, an individual who develops myocarditis and vaccine

injury which triggers aortic dissection will die before reaching a point where PVS would be obvious. A study looking specifically at acute cardiovascular events post vaccination will not query its study population for a spectrum of chronic symptoms (see **subsection 1.7**). Scanning through the React19 repository of case reports (**subsection 1.0**) one will find cases which began with symptoms in a specific organ system (e.g. myocarditis, transverse myelitis) where patients went on to develop symptoms falling within the bounds of PVS (e.g. autonomic dysfunction diagnosed as POTS, etc.).

From one perspective, the specialty of the provider seeing a vaccine injured patient often determines the nature of the AE with which a patient presents (see **Subsection 1.0**). For example, a dermatologist might be confronted with a patient having severe pemphigus refractory to treatment beginning less than 7 days after his second dose of vaccine. A cardiologist might see a teenage boy with myocarditis or an individual with postural hypotension and tachycardia syndrome (POTS) (see **Subsection 1.7**). An Ob-Gyn specialist might see a woman complaining of changes in menstrual bleeding, perhaps miscarriage shortly after vaccination, or infertility (see **Subsection 1.6**). A neurologist might see a patient complaining of severe burning paresthesia with a rather predictable distribution (see **Subsection 1.4**). An ENT practitioner might see a patient complaining of severe tinnitus which was noticeable after a first vaccination and became unbearable after the second vaccine dose (see **Subsection 1.8**). An alert pathologist might detect the footprints of foci of myocarditis in victims of sudden death (**Subsection 1.7**). A general practitioner might see a patient who began having fatigue within a few days after vaccination which proceeded to worsen to the point employment is impossible.

In spite of the vagaries of how and to whom a particular vaccine injured person was presenting, organizations such as React19 and healthcare providers seeing many of these patients concluded they were seeing substantial numbers of vaccine injured patients with similar predictable symptom patterns. Identifying the most common symptoms would enable a description of post COVID vaccine syndrome (PVS). It became possible to do studies where hundreds of people with chronic suffering post COVID vaccination could be readily recruited and queried to determine symptoms identifying PVS.

We presented work by two groups who have conducted observational studies which define common aspects of PVS

- ▶ Investigators Mundorf et al. (**Subsection 1.8, citation 3**) based at Heinrich-Heine-University in Düsseldorf, Germany. We will refer to their work as the “**HHU Group**.” They studied questionnaire responses from 191 subjects..
- ▶ Investigators Krumholz et al. (**Subsection 1.8, citation 1**) based primarily at Yale School of Medicine. They referred to their study as the “**LISTEN**” study and we will use the same name. They had 241 respondents.
- ▶ Investigators Galli, Hertz, and Wastila (**subsection 2.0**), from React19 had 867 respondents. We will refer to this study as “**React19**.”

These three groups used their own independently developed symptom questionnaires. **LISTEN** had the highest number of symptom questions and did the most sophisticated sorting of symptoms into groups. **LISTEN** grouped the reported symptoms into clusters of symptoms. Clusters 3 and 5 had the most overlap of symptoms and they saw these as defining the main features of PVS. Clusters 2, 6, and 7 provided additional clusters of symptoms which they ascertained pointed more towards specific organ systems. We looked for instances in which symptoms in **LISTEN** clusters 3 and 5 were shared with symptoms listed by both **HHU**. We then looked at instances where symptoms reported by >50% of the respondents in **LISTEN** clusters 2, 6, and 7 were shared with

symptoms with **HHU**. This resulted in a list of 14 symptoms. See the tabulation below. For each of these 14 symptoms, we provide in parentheses slightly different terms used by either study to denote this symptom. We then listed these 14 symptoms in descending order of reporting, with the first symptom listed the most frequently in these two studies. This process enabled us to create a table useful as a checklist for identifying individuals with PVS.

COMMON SYMPTOMS OF POST COVID VACCINATION SYNDROME (PVS)

Symptoms begin <30 days post vaccine exposure, greatly decrease quality of life, and persist for months to indefinitely

LISTEN Clusters of PVS Symptoms

Major clusters of PVS symptoms:

Cluster 3: Chronic fatigue, malaise (5 items)

Cluster 5: Cognitive impairment, headache, visual and acoustic Dysfunction (20 items)

Clusters of PVS symptoms pointing towards organ systems:

Cluster 2: Peripheral nerve dysfunction, dysesthesia (17 items)

Cluster 6: Psychomotor dysfunction, anxiety, disturbed body perception, gastrointestinal dysfunction (16 items)

Cluster 7: Sleep disturbance, cutaneous symptoms. (14 items)

Symptoms shared by **LISTEN** clusters 3 &5 and **HHU** as well as **React19**, and symptoms shared by >50% respondents in **LISTEN** clusters 2, 6, and 7 and by **HHU** and **React19**

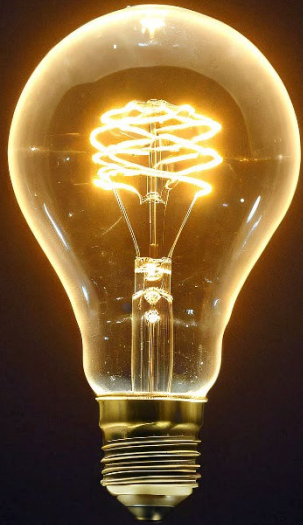
1. Fatigue, tiredness (excessive fatigue)
2. Brain fog
3. Post exertional malaise (exercise intolerance)
4. Neuropathy (tingling, prickling-needles, paresthesia)
5. Insomnia (sleep disturbance, unrestful sleep, sleep onset insomnia)
6. Dizziness
7. Numbness
8. Joint pain
9. Tinnitus (humming)
10. Anxiety (panic attacks, feelings of doom)
11. Muscle or body aches (flu symptoms)
12. Impairment of ocular focusing (visual disturbance)
13. Diffuse headaches (headaches, migraine)
14. Heat intolerance (heat/cold intolerance, altered temperature perception)

We will pause here to review information we have in hand about pathogenesis of persistent organ specific AEs and PVS. Then we can outline possible tests which will strengthen the diagnosis of PVS. We will be discussing primarily what we have learned about the pathogenesis of injuries produced by Pfizer/Moderna mRNA lipid nanoparticle agents rather than those produced by viral vector vaccines. As noted, the mRNA agents have turned out to be responsible for ~90% of the vaccine injuries since use of the viral vector vaccines has stopped. Unfortunately, we have very little information in print focusing on pathogenesis of AEs by viral vector vaccines. Therefore, we will be discussing the behavior of mRNA vaccines unless otherwise noted. But what we say with respect to off target effects of mRNA vaccines producing vaccine injuries and PVS certainly should be applicable to the viral vector vaccines as well.

Each dose of vaccine administered intramuscularly involves deposition of trillions of modified mRNA lipid nanoparticles at the injection site (see **subsection 1.5, citation 2**). This particle mass does not remain solely at the injection site. Particles are rapidly taken up by lymphatics in the area and transit through regional lymph nodes where some are captured. But an appreciable number of particles are conveyed by the lymphatic system into the blood stream where they reach every tissue in the body. This process is ongoing within the first few hours post injection. Pre-clinical studies using rats and mice documented uptake of lipid nanoparticles by liver, spleen, heart, adrenal glands, ovaries, testes, brain, spinal cord, eyes, and bone marrow as well as other tissues. This is true whether a radioactive label is placed on the lipid nanoparticle or the mRNA encoding spike protein. The obvious conclusion is that tissues throughout the body become involved in spike protein production. In **subsection 1.1** we discuss in detail the distribution of nanoparticles and expression of spike protein. Just the uptake of lipid nanoparticles can result in an inflammatory response; such an inflammatory response has been documented for the liver (see **subsection 1.5, citation 1**). If the injection happens to slice through a small blood vessel, particles will reach the blood stream immediately and we can anticipate distribution to various tissues beginning within minutes, analogous to results of preclinical models using intravenous injections of lipid nanoparticles into rats. In susceptible individuals this may result in acute onset of organ specific symptoms. There are case reports of severe tinnitus beginning within minutes to hours of vaccination.

Although industry (Pfizer) preclinical studies looked at presence of mRNA lipid nanoparticle content in tissues, more sensitive studies have been done looking at expression of spike protein from vaccine modified mRNA at the cellular level. The murine model used by Luo et al. looked carefully at the expression of spike protein in the cells of the heart post vaccination and found spike was being produced by endothelial cells and not by myocytes. The resultant endothelial activation was nevertheless producing an inflammatory response in the area surrounding the endothelial cells and resulting in a change in the proteomes of adjacent myocytes. This fits with what we have observed in human endomyocardial biopsies and autopsy specimens from patients with myocarditis (see **subsection 1.7**). In these specimens it is possible to use immunostaining to demonstrate spike protein in capillary cells, which are comprised of a single layer of endothelial cells. This endothelial expression is easily demonstrated in such one-cell thick capillaries. However, it is important to keep in mind that all our blood vessels (arteries, arterioles, capillaries, venules, and veins) are lined with endothelial cells. It is quite logical to conclude that throughout the body these cells are taking up the mRNA lipid nanoparticles of the vaccine and expressing spike protein. In fact, spike has been detected in endothelial cells of larger arteries. It is known lipid nanoparticles can cross the blood brain barrier, fusing with cell membranes of phagocytic glial cells. However, nanoparticles can be taken up by endothelial cells in small vessels of the brain and gain access to neural tissue by this route as well. Subsequent inflammation can then produce symptoms. Multifocal encephalitis along with myocarditis following vaccination has been reported (see **subsection 1.7, citation 2**).

A case can be made that uptake of modified mRNA lipid nanoparticles by endothelial cells throughout the body, irrespective of tissue location, followed by transcription of the modified mRNA to produce spike protein and frame shift nonsense proteins can result in a generalized inflammatory state by multiple mechanisms. Not surprisingly, nanoparticle uptake and expression of spike protein induces an inflammatory phenotype in endothelial cells ([ref.](#)). For years we have known endothelial inflammation can produce coagulopathy ([ref.](#)). Also CD14+ mononuclear cells, activated by uptake of nanoparticles or spike protein will act as effector cells for inducing an endothelial inflammatory phenotype, either by direct contact with endothelial cells or secretion of cytokines ([ref.](#)). Finally, endothelial cells expressing spike protein can undergo attack by the innate and adaptive immune system. The debris of killed endothelial cells will be taken up by blood monocytes, activating their effector status. In **subsection 1.8** we discussed the importance blood monocytes could have in promoting a



chronic inflammatory response in PVS individuals. Increased numbers of CD14^{Low}, CD16⁺⁺ non-classical monocytes have been found in blood of both PVS individuals and those with long COVID.

Early post vaccine injection, uptake of lipid nanoparticles by endothelial cells at particular organ sites can lead to organ specific damage. Intense expression of spike protein and nonsense peptides by endothelial cells in specific organs can produce both acute and chronic inflammation. Tissue destruction results. In susceptible individuals the damage results in severe, persistent or irreversible symptoms. Severe myocarditis with heart failure is a classic example of this. Transverse myelitis residuals, stroke, etc. are other examples. The important thing to note is that we are left with individuals with chronic, possibly irreversible, injuries.

With respect to PVS one can paint a picture whereby a positive feedback loop produces a chronic inflammatory state with persistent symptomatology. This appears to involve both endothelial cells and non-classical monocytes. This positive feedback loop is comprised of activated endothelial cells participating in inflammation, senescent non-classical mononuclear cells activating endothelial cells, and activated endothelial cells producing CX3CL1/Fractalkine to slow elimination of non-classical monocytes. This positive feedback loop favors chronic inflammation. It may be an important mechanism underlying both long COVID and PVS (see the discussion of **citation 7 in subsection 1.8, including the table** depicting maturation of blood monocytes).

What we have presented is perhaps an important feature of PVS. However cells other than endothelial cells undoubtedly also take up lipid nanoparticles with adverse results. We know that autoantibodies are important in vaccine injury (see **subsections 1.3, 1.4 and 2.1.**)

Autoimmune responses occur by several mechanisms. Any inflammatory response produces cellular debris. Also, the expression of spike protein and nonsense peptides mistranslated from vaccine modified mRNA on the surface of various cells is an important factor. Innate immune or adaptive immune attack on cells expressing these antigens leads to lysis or apoptosis of these cells, releasing their contents. In susceptible individuals the cellular debris will stimulate production of autoantibodies. Altered patterns of autoantibodies against G-protein receptors occur (see **subsection 1.4, citations 4-6**). Anti-idiotypic antibodies against anti-spike antibodies can function as anti-ACE2 autoantibodies. Unless these processes dissipate quickly persistent symptoms will result.

We cannot ignore the importance of injury to the autonomic nervous system as an especially malignant aspect of chronic vaccine injuries. Many

We cannot ignore the importance of injury to the autonomic nervous system as an especially malignant aspect of chronic vaccine injuries. Many of the enumerated symptoms of PVS point towards dysautonomia. We cannot biopsy autonomic nerves.

of the enumerated symptoms of PVS point towards dysautonomia. We cannot biopsy autonomic nerves. These nerve bundles are supplied with tiny arterioles and capillaries which penetrate the surface of the nerve sheath to nourish the small diameter nerves deep in the nerve bundles.

The neurons deepest from the surface of the nerve sheath are at greatest risk for ischemic damage. When inflammation surrounding the endothelial cells of these tiny, deeply located vessels occurs, microclots can form with resultant ischemic drop out of neurons. Staining skin biopsies for small nerve fiber drop out is a surrogate for detecting such a process on a larger scale. Inflammatory coagulopathy produces both cardiovascular injury and neural injury. Excess complement (C4d) deposition has been observed in capillaries adjacent to fine nerve fibers in skin biopsies from patients with post COVID vaccine neuropathy, indicating immune mediated damage. Serum antibodies against neural structures have also been demonstrated in patients with post vaccination chronic neuropathy.

It is also important to keep in mind that basophils are present in their largest numbers in the skin and mucous membranes. There they lay on the tissue side of capillary endothelium. Normally they help maintain vessel patency. However, they also are near autonomic nerve fibers. By interacting with mast cells, autonomic nerve fibers influence fluid content and inflammatory status of skin and mucous membranes. Dysfunctional discharge of autonomic nerve fibers can lead to mass discharge of mast cells contributing to cutaneous and visceral symptoms (**subsection 1.4, citation 2**). Thus, we find PVS patients who have puzzling chronic skin rashes, malfunction of the gastrointestinal tract with diarrhea and/or disorganized intestinal motility, and even problems with contraction of the urinary bladder.

Having explored likely mechanisms for chronic AEs and PVS, we can turn to possible diagnostic testing based upon the data on hand. These tests could help confirm a diagnosis of PVS. Here we will be basing suggestions **only** on the literature we have surveyed. There is much we don't know.

DIAGNOSTIC TESTS USEFUL IN DIAGNOSIS OF PVS BASED SOLELY ON THIS LITERATURE SURVEY

PARAMETER	TEST/COMMENTS/CITATION
Quantitating symptoms:	Euro-QoL Visual Analog score
Quality of life	Short Form-36 Health Survey
Fatigue	Fatigue Severity Scale
Depression	Beck Depression Inventory
Brain Fog	Montreal Cognitive Assessment Scale
Somatic complaints	Somatic System Disorder Scale
Anxiety	Generalized Anxiety Disorder Scale
Thorough physical examination	Especially detailed neurologic examination and attention to supine, sitting, and standing pulse and blood pressure.
Routine laboratory work and screening tests	Clinical diagnosis requires formulation of a differential diagnosis and excluding many diagnoses by screening tests and following data developed. Please see the suggestions for evaluating patients where PVS is a serious consideration at Diagnostic Workup Guide - React19 .

Viral re activation	Anti-EBV early antigen (gp42)
Neuropathy, Dysautonomia, POTS W/U	Tilt table examination Iontophoresis (sweat production) Skin biopsy analysis: <ul style="list-style-type: none"> • Neurite density • Axonal swelling • C4d deposition on endothelial cells CSF for oligoclonal bands (weigh risks) MRI (transverse myelitis residuals, normal in dysautonomia (weigh risks of contrast)) Elevated serum neurofilament light chain (sNFL) (subsection 1.8, citation 4) Indirect fluorescent antibody test for autoantibodies against neural structures (subsection 1.8, citation 5)
Mast cell release phenomena	Histamine levels Tryptase level
Hypercoagulable state	D-dimer levels, fibrinogen levels
Chronic inflammation/Immune imbalance	ESR and CRP are often normal Elevated IL-6 Elevated IL-8 Increased TNF α Flow cytometry: <ul style="list-style-type: none"> • Increased CD14LowCD16++ cells • Detectable S1 positive CD16+ cells IgG subclasses (IgG3 low, IgG4 high) Ferritin index low Free tri-iodine thyroxin (fT3) low (subsection 1.8, citation 3)
Anti-spike antibody levels	Paradoxically low in PVS patients compared to normal vaccinated controls (subsection 1.8, citation 2)
Autoantibodies	Anti-G-protein linked receptors by target; levels relative to asymptomatic vaccinated controls (subsection 1.8, citation 4): <ul style="list-style-type: none"> • ACE2 (ACE-II), [also called anti-Angiotensin II type 1 receptor]; ACE-II: increased Ab levels • MAS-1 receptor (MAS1) increased • $\alpha 2\beta$ adrenergic receptor decreased • Interleukin-1 receptor type 2 (IL-Rb:) decreased Ab levels Anti-MMP-1 (matrix metalloproteinase-1) noted in subsection 1.8, citation 2 . Routine auto-antibody assays—caution is advised—In subsection 1.4, citation 7 , ANA, ENA, APCA, ANCA, ASMA, and CMA were negative or failed to discriminate PVS patients from controls
Spike protein detection	HPLC plus mass spectroscopy (subsection 1.2: citation 1) Flow cytometry to detect S1+ CD16+ cells Subsection 1.2: citation 2 SPEAR technique for fM spike levels (subsection 1.2: citation 3)

Please note React19 has posted several suggestions for diagnostic workup of individuals where PVS is a strong diagnostic consideration. We reemphasize the tests in this table are suggested based upon only the literature in this survey. Unfortunately, the tests based upon flow cytometry, autoantibodies, and detection of minute amounts of spike protein have only reached the literature in 2024. Using them at appropriate scale would require commercial reference laboratories to evaluate appropriate control groups to standardize the test results, especially when looking at elevations or depressions of autoantibody levels. Many more PVS subjects should be studied to evaluate positive and negative predictive values or various tests in this table.

CONCLUDING REMARKS

This systematic literature survey documents the accumulation of published research on COVID-19 vaccine adverse events through May 1, 2025. The survey encompasses 3,752 peer-reviewed case reports and analysis of mechanistic studies, clinical investigations, and original research relevant to understanding post-vaccination adverse events.

Bradford Hill Criteria for Causality

The literature reviewed demonstrates several Bradford Hill criteria supportive of a causal relationship between vaccination and reported adverse events:

Strength and Consistency: The substantial number of case reports across multiple organ systems and clinical presentations, published by independent research teams worldwide, demonstrates consistent patterns of adverse events following vaccination.

Temporality: The close temporal relationship between vaccination and symptom onset is well-documented across the case report literature, with severe adverse events typically occurring within hours to days of vaccination, and most presenting within 30 days.

Biological Gradient (Dose-Response): Evidence for dose-response relationships appears in multiple contexts. Some individuals experience mild symptoms after first vaccine dose and severe persistent symptoms after the second dose. Additionally, the Moderna vaccine, which contains higher mRNA concentrations than the Pfizer vaccine, produces higher rates of myocarditis, demonstrating a dose gradient effect.

Plausibility and Coherence: The reviewed literature describes plausible pathogenic mechanisms for adverse events and post-vaccine syndrome, including spike protein persistence, immune dysregulation, autoantibody formation, and inflammatory responses. The common symptom patterns observed by multiple independent research teams provide coherence to the definition of post-vaccine syndrome.

Analogy: Mechanistic parallels between long COVID and post-vaccine syndrome support understanding of both conditions as related post-viral/post-spike protein syndromes involving immune dysregulation and inflammation.

Specificity: While adverse events affect multiple organ systems, distinct patterns emerge including characteristic autoantibody profiles, specific inflammatory markers, and identifiable clinical phenotypes that distinguish post-vaccine syndrome from other conditions.

Implications for the mRNA Lipid Nanoparticle Platform

The mechanisms identified in this literature survey relate to fundamental characteristics of the modified mRNA lipid nanoparticle vaccine platform, including:

1. Non-targeted biodistribution of lipid nanoparticles throughout the body rather than specific localization to immune system cells
2. Modified nucleotide (N1-methyl-pseudouridine) effects on translation fidelity, resulting in both intended spike protein and additional peptide products
3. Potential for prolonged spike protein presence and immune stimulation

These platform characteristics suggest that similar adverse event profiles may occur with future mRNA vaccines targeting different antigens. Understanding the relationship between platform design and adverse event mechanisms is important for future vaccine development using this technology.

Adenovirus vector vaccines (Oxford-AstraZeneca ChAdOx1 and Janssen Ad26.COV.S) also demonstrated non-targeted uptake throughout the body and produced serious adverse events leading to their withdrawal from use in the U.S. Both platforms interact with toll-like receptors on cells throughout the body and show uptake by myocytes, hepatocytes, and other non-immune cells.

Diagnostic and Research Implications

This survey identifies diagnostic approaches that may assist in evaluation of individuals with suspected post-vaccine syndrome, including:

- Flow cytometry for spike protein detection on immune cells
- Specific autoantibody testing (anti-G-protein coupled receptors)
- Inflammatory marker panels (IL-6, IL-8, TNF- α)
- Advanced techniques for ultra-low level spike protein detection

However, many of these diagnostic approaches have only recently appeared in the literature (2024) and require further validation through standardized testing protocols and appropriate control group comparisons. Large-scale studies are needed to establish positive and negative predictive values for these diagnostic modalities.

Gaps in Current Knowledge

Several important questions remain inadequately addressed in the existing literature:

1. **Incidence and Prevalence:** Large-scale epidemiological studies are needed to accurately determine the frequency of post-vaccine syndrome and specific adverse events in vaccinated populations. Such studies remain challenging to fund and conduct. The research environment continues to reflect tension between public health goals of maintaining vaccine confidence and scientific imperatives to thoroughly investigate adverse events. While mechanistic and diagnostic research has increased substantially in

2023-2024, comprehensive population-based studies with adequate sample sizes and long-term follow-up remain scarce. This research gap reflects ongoing institutional constraints rather than lack of clinical or scientific importance.

2. **Risk Factors:** Research is needed to identify genetic, epigenetic, or clinical factors that may predispose individuals to severe adverse events following vaccination.
3. **Natural History:** Long-term follow-up studies would clarify the progression and resolution patterns of post-vaccine syndrome.
4. **Treatment:** Systematic evaluation of therapeutic interventions for post-vaccine syndrome remains limited.

Future Directions

The substantial body of case reports and mechanistic studies compiled in this survey provides a foundation for several research priorities:

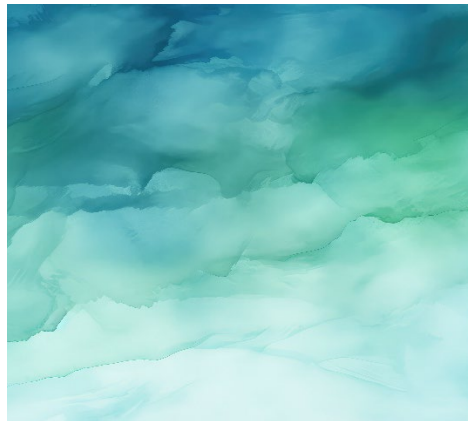
- ▶ Well-designed cohort studies with appropriate control groups to establish incidence rates
- ▶ Mechanistic investigations to further elucidate pathogenic pathways
- ▶ Development and validation of diagnostic biomarkers
- ▶ Therapeutic trials evaluating potential treatment approaches
- ▶ Studies to identify pre-vaccination risk factors
- ▶ Long-term safety assessment for future applications of mRNA and viral vector platforms

It is likely individuals who developed severe injuries following exposure to the COVID vaccines widely used during the COVID pandemic share certain genomic or epigenetic traits. Research is needed to be able to detect such individuals prior to vaccination. Having a definition for PVS provides a starting point. Also, the mechanisms responsible for severe vaccine AEs and PVS appear to involve basic properties of modified mRNA lipid nanoparticle vaccines. Therefore, if this platform is widely applied to produce immune responses against microbial antigens other than spike protein of SARS-CoV-2, one can predict with reasonable certainty similar vaccine injuries will occur. The same problems will occur involving nontargeted uptake of lipid nanoparticles and widespread off target immune attack against cells expressing the antigen or its frame-shift nonsense peptides. We know less about potential risks inherent in adenovirus vector vaccines: however, it is clear both adenovirus vector (Ad25Y in Oxford-AstraZeneca ChAdOx1 and Ad26 in Janssen Ad26.COV.S) COVID-19 vaccines produced severe AEs prompting their eventual removal from use in the U.S. Adenovirus vectors interact with cells throughout the body having toll like receptors, activating innate immunity. Viral vectors show major off-target uptake by myocytes and hepatocytes. Careful consideration regarding potential vaccine injuries must occur before either platform is used again as a vaccine on millions of recipients. Very large RCTs with prolonged observation periods to assess safety should occur prior to considering approval of such agents.

This survey has not discussed the treatment of PVS. However, it has established a working syndrome diagnosis for PVS and explored the pathogenesis of severe COVID-19 vaccine induced AEs and PVS. This should help clinicians attempting to help people suffering from these problems.

Conclusion

This systematic literature survey documents a substantial body of peer-reviewed research on COVID-19 vaccine adverse events and post-vaccine syndrome. The literature demonstrates consistent patterns across multiple clinical presentations, plausible pathogenic mechanisms, and fulfillment of multiple Bradford Hill criteria for causality. Recognition of post-vaccine syndrome as a distinct clinical entity, understanding of its pathogenesis, and development of diagnostic and therapeutic approaches represent important areas for continued medical research and clinical attention.



“Facts do not cease to exist because they are ignored.”
— *Aldous Huxley*