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Review article

# Breaking the silence: Recognizing post-vaccination syndrome

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A B S T R A C T

Post-vaccination syndrome has recently gained attention in the scientific community, yet its formal recognition remains elusive. This condition, characterized by long-lasting symptoms similar to long COVID, affects a small percentage of vaccine recipients. Acknowledging post-vaccination syndrome is crucial for ensuring that affected individuals receive proper compensation, care, and research funding. Without recognition, these patients face significant barriers to healthcare and justice, navigating a system unprepared to address their needs. The syndrome presents with symptoms such as dysautonomia, post-exertional malaise, fatigue, neuropathic pain, and cognitive disturbances, overlapping with syndromes like myalgic encephalomyelitis/chronic fatigue syndrome, postural orthostatic syndrome, and small fiber neuropathy. The lack of formal recognition and poor development of diagnostics hampers research funding, treatment development, and compensation processes, leaving patients to navigate without support. Addressing post-vaccination syndrome requires developing rigorous diagnostic criteria, increasing research funding, and improving compensation systems to ensure affected individuals receive appropriate care and support.

## 1. Introduction

Covid-19 vaccines were instrumental in preventing deaths from Covid-19 [1]. Despite their successes, they uncommonly led to adverse events in the recipient population. More uncommonly still, some recipients experience lingering, long covid-like symptoms which persist for months or years after receiving a vaccine [2–6].

Presently, the medical community is in the process of defining this illness, marked by its similarity to long covid [2–7]. Estimates of prevalence vary across several orders of magnitude from approximately 1 % [8] to 0.2 % [9] to 0.003 % [4,10]. At the upper end of these estimates, there is potentially a large unmet need to treat this syndrome and compensate affected individuals.

Barriers currently exist between patients and receiving care, including a lack of disease definition, compensation schemes, research and treatment options. Social factors and potential stigma also affect people bringing up potential safety issues with vaccines [11].

### 1.1. Disease definition and diagnostics

Disease definition for post covid-19 vaccination syndrome (PCVS) has been challenging, owing to different clinical presentations. The terminology ‘acute covid-19 vaccination syndrome’ (ACVS) is adopted to refer to adverse events which occur soon (immediately after up to days) after vaccination [5]. The terminology ‘post-acute covid-19 vaccination syndrome’ (PACVS) refers to a different clinical presentation than PCVS, and refers to lingering symptoms which last typically longer than one month and may last for years [5].

Clinically, PACVS presents as similar to another disease cluster, myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) [2]. Other overlaps with existing syndromes include postural orthostatic syndrome (POTS), mast cell activation syndrome (MCAS) and

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small fibre neuropathy (SFN). PACVS is characterized by dysautonomia, post-exertional malaise, fatigue, and often accompanying neuropathic pain and cognitive disturbances, such as brain fog. In a cohort of 191 PACVS-affected persons, common symptoms are included in Table 1, with their associations with one of the above listed syndromes included.

These disease categories are analogous to the distinction between acute covid-19 infection and post acute covid-19 syndrome (PACS), commonly called 'long covid'(5). These four diseases: acute covid-19, PACS, ACVS, and PACVS, share similar symptoms, which makes sense in light of shared etiological factors. One etiological factor shared between all four conditions is the SARS-CoV-2 spike protein, which is a factor that is present for all conditions [23–26].

Differences between the vaccinal and viral spike are present, and one of the easiest delineable is the co-presence of the nucleocapsid (N) protein, which will be present during natural infection [27], but is not a product of any of the widely used approved Covid-19 vaccines [28–31]. Some vaccines and prospective vaccines do utilize the SARS-CoV-2 nucleocapsid (N) protein, though these are not in wide use [32]. Vaccines utilizing N protein in addition to S protein may be more attractive as the S protein has been the site of selective pressure, and inclusion of another protein may guard against immune escape [33,34].

In several autopsies of individuals deceased in temporal proximity to Covid-19 vaccination, this criteria was used to rule the cases as being causally related tot the vaccine, and to rule out the possibility that the spike observed through immunohistochemical staining was viral in origin [35–37]. One study of patients deceased from acute Covid-19 found spike protein deposited in the brain-meninges axis [38]. While this was not related to long covid pathology, it is possible that interaction of the spike protein with neural tissue may explain some of the neurological symptoms of long covid.

Proteomic-based methods may be used to differentiate vaccinal spike protein from viral spike protein, which is the basis of the protocol in Brogna et al., 2024, which used a protein digestion assay to digest the spike protein to a segment which has a differentiated sequence between vaccinal and viral spike, and uses mass spectrometry to sequence the remaining peptide fragment [39]. The study found circulating spike protein in the blood of vaccinated individuals up to six months after their last vaccination [39].

Persistence of spike protein beyond a few days after vaccination was initially thought unlikely, as typical mRNA degrades, generally within a few days of the injection, and it would cease to produce it's protein products beyond a few days. However, persistent spike protein has been observed in the blood and bodily fluids of individuals post vaccination [24,39,40]. Potential mechanisms for spike protein persistence include long lasting n1-methyl-psueouridinylated RNA, reverse integration into human cells, or genome integration into bacterial cells [39]. One complicating factor is the presence of DNA plasmids, used in the production of the vaccinal mRNA sequences, in vaccine vials [41], and may have implications for explaining persistent spike protein production.

In terms of disease mechanism, spike protein interacts with different receptors in the body, which may explain some of the symptom clusters [42] (Table 1, Fig. 1). So far, few studies have examined diagnostics for PACVS [2,3,43]. Generally, they have discovered a biomarker profile similar to long covid, with minor differences [2,3,43]. Changes in biomarkers in post acute vaccination syndrome and in long covid are included in Table 1 below.

Despite many studies on alterations of biomarkers in both PACS and PACVS (Table 2), both conditions are characterized by a broad clinical phenotype. While diagnostics may help to make a determination, still, a set of rigorous diagnostic criteria eludes researchers and clinicians. Overall, both clinical phenotypes are characterized by inflammation and altered metabolism, which may explain the

**Table 1**
Common symptoms of PACVS and their overlap with existing syndromes. Symptoms are self-reported and/or determined by general practitioner. ME/CFS, myalgic encephalomyelitis/chronic fatigue syndrome; POTS, postural orthostatic syndrome; MCAS, mast cell activation syndrome; SFN, small fiber neuropathy. Potential molecular mechanisms involving spike protein are included in the rightmost column. Adapted from Ref. [2].

| Symptom/Diagnosis | Prevalence (%) | Syndrome Assoc. | Potential Spike Protein mediated mechanisms |
|---|---|---|---|
| Exhaustion | 84.82 | ME/CFS, POTS | Spike protein misfolding/aggregation in brain [12], nicotinic receptor [13,14], reduced blood brain barrier integrity [15], toll-like receptor mediated inflammation [16,17], mitochondrial alterations [18–20] |
| Debility | 83.77 | ME/CFS, POTS | mitochondrial alterations [18–20], spike protein aggregation and microclot formation [21], ACE2 mediated thrombosis [22], TLR mediated inflammation [16,17] |
| Muscle Pain | 80.63 | ME/CFS, POTS, SFN | mitochondrial alterations [18–20], toll-like receptor mediated inflammation [16,17], ACE2 mediated thrombosis [22], spike protein aggregation and microclot formation [21] |
| Unrestful Sleep | 80.63 | ME/CFS | Spike protein misfolding/aggregation in brain [12], nicotinic receptor [13,14], reduced blood brain barrier integrity [15], toll-like receptor mediated inflammation [16,17] |
| Dizziness | 80.10 | ME/CFS, POTS, SFN | Spike protein misfolding/aggregation in brain [12], nicotinic receptor [13,14], reduced blood brain barrier integrity [15], toll-like receptor mediated inflammation [16,17] |
| Tingling/Prickling/ Paresthesia | 79.58 | SFN | toll-like receptor mediated inflammation [16,17], ACE2 mediated thrombosis [22], spike protein aggregation and microclot formation [21] |
| Impairment of Mental Focusing | 78.53 | ME/CFS, POTS | Spike protein misfolding/aggregation in brain [12], nicotinic receptor [13,14], reduced blood brain barrier integrity [15], toll-like receptor mediated inflammation [16,17] |
| Fatigue/Tiredness | 76.96 | ME/CFS, POTS | Spike protein misfolding/aggregation in brain [12], nicotinic receptor [13,14], reduced blood brain barrier integrity [15], toll-like receptor mediated inflammation [16,17], mitochondrial alterations [18–20] |
| Orthostatism | 76.44 | ME/CFS, POTS, SFN | ACE2 mediated thrombosis [22], spike protein aggregation and microclot formation [21] |
| Brain Fog | 76.44 | ME/CFS, POTS | Spike protein misfolding/aggregation in brain [12], nicotinic receptor [13,14], reduced blood brain barrier integrity [15], toll-like receptor mediated inflammation [16,17], mitochondrial alterations [18–20], |

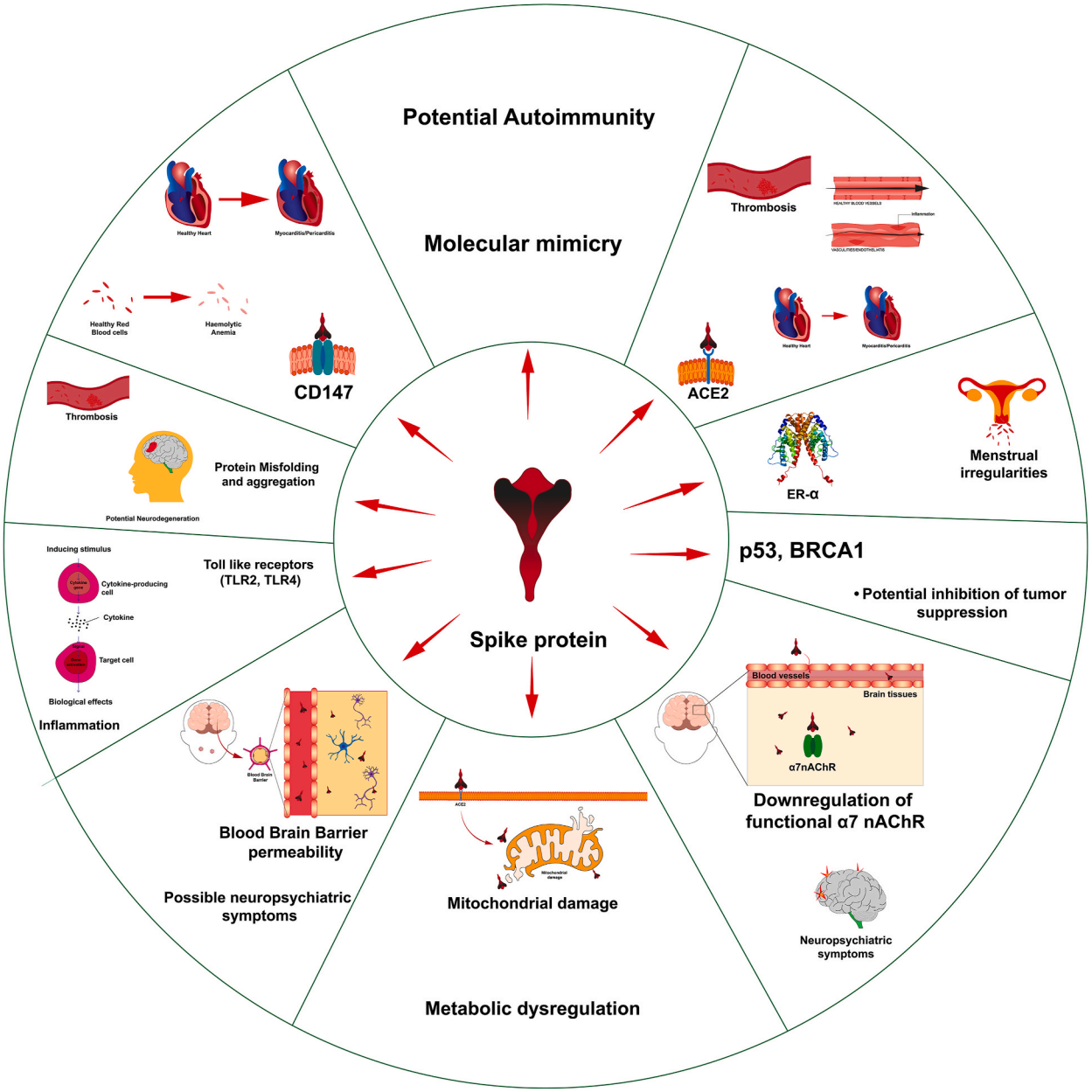


**Fig. 1.** Pathophysiology related to spike protein. Reproduced from (42) under a Creative Commons Attribution 4.0 International License.

fatigue symptoms observed in both PACVS and PACS [2].

Autoimmunity is present in a subset of those with PACVS, and autoantibodies for a particular set of proteins, the G-protein coupled receptors (GPCRs), have been observed in multiple case reports [69–71] and surveys [72,73]. GPCRs are important in autonomic nervous system functioning, relaying extracellular signals inside the cell [74], their autoimmune-mediated destruction is postulated to contribute to the POTS phenotype [75], as the presence and concentration of GPCR autoantibodies is associated with the presence and severity of POTS [76–78].

Autoantibodies for GPCRs can be found during and after Covid-19 infection, and are associated with Covid-19 severity [79,80]. GPCR autoantibodies have also been found in long Covid and correlate with symptom severity [53,80–82]. One published case exists of anti-GPCR autoantibodies found in a cardiomyocyte assay of a young boy with MIS-C following Covid-19 vaccination [70]. The POTS phenotype is observed in both long Covid [83,84] and post-covid vaccination syndrome [83,85–88]. In these cases, autoimmunity to GPCRs may contribute to POTS [78,89].

**Table 2**
Altered biomarkers in PACVS and PACS. * High eGFR (>120 mL/min) with low serum urea (<18 mg/dL).[†] blood urea nitrogen (BUN) was measured in this study. [α]Hypoperfusion in the frontal cortex, parietal and temporal cortex.

| Biomarker | Change in PACVS | Change in PACS ('long covid') |
|---|---|---|
| sCD40L | ↑ [43] | |
| CCL5 | ↑ [43] | |
| Interleukin-6 | ↑ [2,3,43] | ↑ [44] |
| Interleukin-8 | ↑ [2,43] | ↓ [45] |
| Interleukin-17 | | ↑ [46] |
| IP-10 | | ↑ [46] |
| C-reactive protein | | ↑ [46] |
| SARS-CoV-2 S1 | + [43] | |
| SARS-CoV-2 S2 | + [43] | |
| Angiotensin II type 1 receptor antibodies | ↑ [3] | ↑ [3] |
| alpha-2B adrenergic receptor antibodies | ↓ [3] | ↓ [3] |
| eGFR | High eGFR (>120 mL/min) with low serum urea (<18 mg/dL) in 17 % of cases) [2] | ↓ [47] |
| Serum urea | | ↑[†] [47] |
| fT3 | ↓ [2] | Unchanged [48] |
| Ferritin-index | ↓ [2] | ↑ [49] |
| Transferrin | ↓ [2] | |
| sNFL | ↑ [2] | Unchanged [50]<br>↑ [46] |
| IgG-2 | ↓ [2] | Unchanged [51] |
| IgG-3 | ↑ [2] | |
| Total cholesterol | ↑ [2] | |
| Triglycerides | ↑ [2] | |
| HDL cholesterol | | ↓ [52] |
| GPCR autoantibodies | | + [53] |
| Haemoglobin | | ↓ [54] |
| D-dimer | | ↑ [54] |
| NGF (at time of infection) | | ↓ [55] |
| BDNF (at time of infection) | | ↑ [55] |
| TGF-β (at time of infection) | | ↑ [55] |
| Functional memory cells ($CD8^+$ TEMRA cells, CD8±TCRγδ+ cells, and NK cells with $CD56^+CD57$ + NKG2C + phenotype) | | ↑ [56] |
| $CD4^+$ Tregs | | ↑ [56] |
| PD-1 on the surface of $CD3^+$ T lymphocytes | | ↑ [56] |
| FOXP4 rs9367106 C-allele (frequency 4,2 %) | | OR (long covid) = 1.63 [1.40,1.89] [57] |
| Density of amyloid clots | | ↑ [58] |
| Brain blood flow | | ↓[α] [59] |
| Anti-viral (non-Covid) antibody responses | | ↑ [60] |
| Circulating myeloid and lymphocyte populations | | Altered [60] |
| Cortisol | | ↓ [60] |
| Antinuclear antibodies | | + [61] |
| Plasma Kallkrein | | ↓ [62] |
| Platelet factor 4 | | ↑ [62] |
| von Willebrand factor (VWF) | | ↑ [62] |
| α-2 antiplasmin (α-2-AP) | | Marginal increase [62]<br>↑ [63] |
| SARS-CoV-2-S IgG avidity index | | ↑ [64] |
| SARS-CoV-2-IgG titres | | ↑ [65] |
| FMS-related receptor tyrosine kinase 3 ligand (FLT3LG) | | ↑ [66] |
| IP-10 | | ↑ [67] |
| TNF-α | | ↑ [67] |
| IFN-γ | | ↑ [67] |
| IFN-β | | ↑ [68] |
| IFN-λ1 | | ↑ [68] |
| CXCL10 | | ↑ [46] |
| Pentraxin 3 | | ↑ [68] |
| CCL3 | | ↑ [46] |
| CCL2 | | ↑ [46] |
| Lactate dehydrogenase | | ↑ [46] |
| Vascular endothelial growth factor | | ↑ [46] |
| Aspartate aminotransferase | | ↓ [46] |

### *1.2. Pharmacovigilance*

Pharmacovigilance, or post marketing surveillance of vaccine products is accomplished through several systems, including the Vaccine Adverse Event Reporting System (VAERS), the Vaccine Safety Datalink (VSD), V-Safe and the Clinical Immunization Safety

Assessment (CISA) project (Fig. 2).

VAERS is a passive surveillance system, and allows users to submit a report of an adverse event following immunization (AEFI). Reports can be submitted by anybody, allowing VAERS to serve as an early warning system which can quickly detect potential safety signals. VAERS has several limitations, including both underreporting and stimulated reporting [90,91]. The latter refers to elevations in reporting due to media attention and public awareness, and may increase the rates of poorly documented, incorrect or fraudulent reports, the lattermost being rare due to database monitoring by the US Centers for Disease Control (CDC) [92].

VAERS, acting as an early warning system, can identify AEFIs requiring further investigation, which can be accomplished through active monitoring systems including V-Safe, VSD, the biologics effectiveness and safety system (BEST) and the center for Medicare and Medicaid services (CMS) [93]. V-safe is a smartphone based platform which prompts users to complete health surveys after vaccination. Surveys ask about injection site reactions, as well as systemic reactions such as muscle aches, chills or headaches. Participants may also record any other symptoms in a free text field [93].

The VSD is a project founded in 1990, encompassing roughly 3 % of the total US population, which maintains healthcare records of persons who receive care through several centers across the USA [94]. A large majority of the VSD population is immunized, and the VSD largely relies on case-control study designs to evaluate if AEFIs are elevated in the time period soon after vaccination relative to other time windows [95]. The VSD allows for retrospective analysis of anonymized patient medical records to test associations between various diseases and vaccination [96].

CISA, established in 2001, is a collaboration between the US CDC and several academic medical centers, and functions as a research network which investigates emerging issues in vaccine safety [97]. CISA is generally consulted to investigate potential vaccine safety issues, and it draws on its network of experts to study and publish reports related to specific issues in vaccine safety [98].

### 1.3. Causality establishment

Reports in VAERS by themselves are usually insufficient to establish causality, and causality assessment of AEFIs follows an algorithm defined by the World Health Organization (WHO) (Fig. 3) [99,100].

For causality to be established, other causes of the AEFI must be ruled out [99–101]. However, one criticism of this step is that other potential causes being present does not necessarily rule out immunization as a contributing cause, given multifactorial and probabilistic pathology [100,101].

The second step (Fig. 3) evaluates if the AEFI has a known causal association with vaccination. This assessment is contingent on the level of evidence collected for the potential adverse events causally related to the vaccine administration. Fortunately, lack of a known causal association at this step does not rule out causality, as it is possible that a causal association exists but is currently lacking evidence.

If there is a known causal association, the reviewer then assesses if the event falls within the known time window of increased risk. For acute AEFIs, events typically occur immediately after vaccination, or within days or weeks of the vaccine administration date [102]. Some AEFIs, such as autoimmunity, may take months or over one year to manifest [103,104], and may not fall within the accepted time window for AEFIs [100].

Fortunately, AEFIs outside of the accepted time window or lacking an established causal relationship are not disqualified from being causally related to immunization. These AEFIs proceed to step III (Fig. 3), which asks if there is strong evidence against a causal association. Presently, lack of a statistically significant association between an AEFI and immunization in epidemiological studies may be admitted as evidence against causality at the individual level [101]. This is potentially problematic for rare and poorly understood reactogenicity to a particular vaccine or vaccine component [100]. If there is not strong evidence against a causal association, other

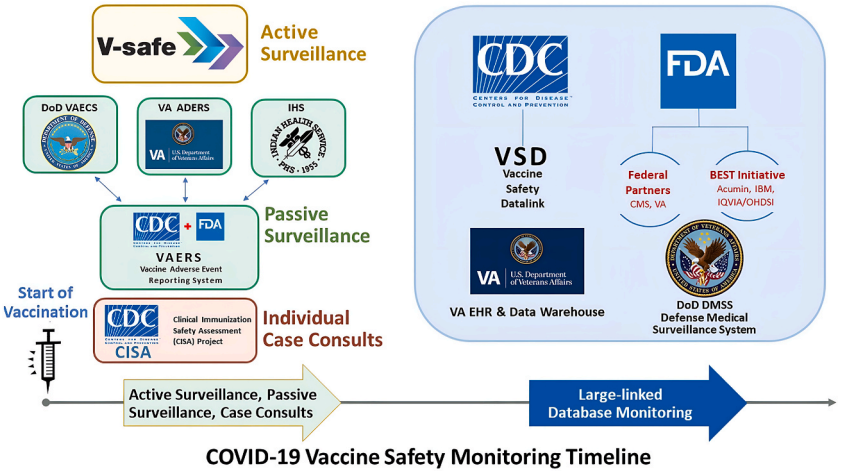


**Fig. 2.** Existing systems for Covid-19 vaccine safety monitoring. Reproduced from (90) under a Creative Commons Attribution 4.0 International License.

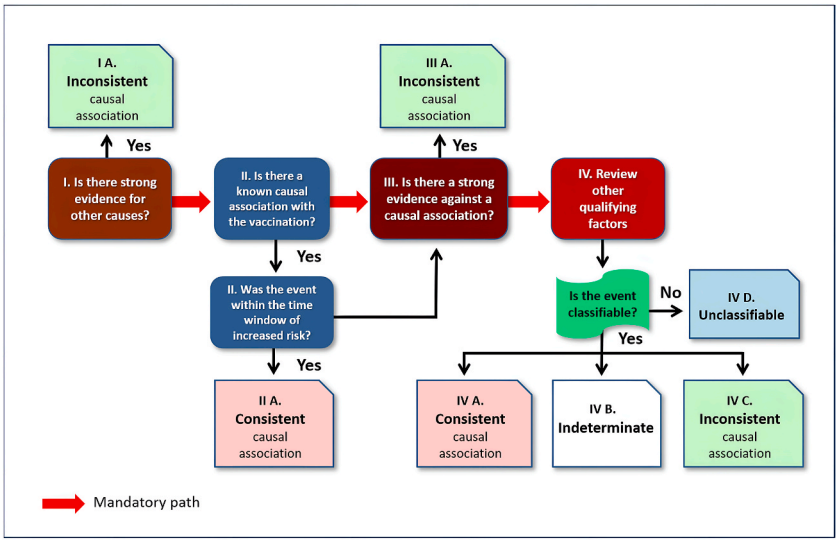


**Fig. 3.** Causality Assessment according to WHO criteria causality assessment of adverse events following immunization. Reproduced from (100) under a Creative Commons Attribution (CC BY) license.

qualifying factors are considered.

The final step to classify the consistency of the event with causal association with vaccination involves reviewing other qualifying factors. Factors such as a pre-existing condition in the patient prior to immunization may be considered factors against a causal relationship of the adverse event with vaccination [99,105]. Given the multifactorial nature of some diseases, this may not be justified [101].

### *1.4. Compensation of vaccine injuries*

The route to receive compensation for vaccine injuries within the childhood schedule [106]proceeds through the Vaccine Injury Compensation Program (VICP), set up through the 1986 Childhood Vaccine Injury Act [107]. Covid-19 vaccines are covered through a separate program, the Countermeasures Injury Compensation Program (CICP) [108,109]. Childhood vaccines receive liability protection through the 1986 National Childhood Vaccine Injury Act [107] and Covid-19 vaccines receive liability protection through the Public Readiness and Emergency Preparedness (PREP) Act [110].

Unlike other medical products where producers can face liability for a product causing injury, Covid-19 vaccine manufacturers for countermeasures covered by the PREP Act are not liable for injuries or deaths occurring through use of their products [110]. For the vaccine injured, this closes one potential route of compensation, leaving the CICP as their only option for compensation.

Despite the well-described relationship between Covid-19 mRNA vaccines and certain conditions, including myocarditis, pericarditis and Guillian-Barre syndrome, Covid-19 Vaccine Injury Tables were not scheduled to be published until November 2024 [111], and no vaccine injury tables for Covid-19 vaccines are published by December 30, 2024 [112]. To elaborate, vaccine injury tables are lists of vaccine injuries causally related to a given vaccine. Vaccine injury tables can speed up the process of adjudicating, as any injuries meeting the definition in the vaccine table and within a certain time period after vaccination may be eligible for compensation. Injuries outside of the vaccine tables may require a more lengthy adjudication.

As of this writing (December 30, 2024), there are no tables published for Covid-19 vaccine injuries [112], despite strong relationships being demonstrated for conditions including myocarditis [113] and coagulopathies [114]. One consequence of the lack of tables is that every claim must be adjudicated in a CICP court, contributing to the slow rate of processing (24 months median value to complete eligibility check and medical review) [111]. According to a government report published Dec. 18, 2024, only 92 vaccine injuries are deemed eligible for compensation, or 3 % of the 13 824 claims [111].

Despite most of the claims being made in 2021 and 2022, only 25 % have been examined, with the remaining 75 % not examined yet [111]. The average time to complete the initial eligibility check and medical review was 24 months. Debilitation may preclude the patient from working, and patients may experience difficulty having their treatments covered with medical insurance. While we cannot assess the validity of each claim, the current compensation system operates far slower than what is practical for people needing to receive medical care.

## 2. Research and treatment

Limited research currently exists for post-vaccination syndrome [42,115–118]. Treatment options have been set out in some articles, but lack studies into their efficacy [42,116–118]. In a survey of the vaccine injured, the median number of individual treatments

tried was 20, suggesting a high degree of experimentation and lack of consistent treatment protocols [115].

The lack of acknowledgement of the condition means that research funding is limited. An estimated $1.5 billion globally has been set aside for long COVID research [119], while only three small trials focusing on vaccine adverse events were registered on clinicaltrials.gov [120–122].

PACVS patients face a unique set of challenges when it comes to receiving care. The lack of diagnostic criteria hampers efforts to identify and treat the condition. As a result, patients are often left to navigate an unregulated market of unsubstantiated treatments, much like those with Lyme disease or chronic fatigue syndrome [123]. This can expose vulnerable patients to health scams and further delay legitimate care. Billing and insurance coverage present additional barriers [124]. Many vaccine injury patients must pay out of pocket for their treatments, as insurance companies often do not recognize the condition.

The experiences of those with post-vaccination syndrome echo the struggles faced by individuals with other misunderstood conditions, such as Lyme disease. Both groups often encounter disbelief and dismissal from medical professionals, even when their cases meet official diagnostic criteria [125]. This lack of recognition has profound consequences, not only for the injured but also for the broader public health landscape.

Recognition is essential for several reasons. It legitimizes the condition, making it easier for patients to receive proper diagnoses and treatment. Moreover, without formal recognition, research into post-vaccination syndrome remains underfunded and limited. The burden of this disease is significant, with where possibly tens of thousands of people experience a highly disabling disease [115].

### *2.1. Public perception and vaccine hesitancy*

Concerns about vaccine safety have contributed to an increase in vaccine hesitancy, particularly following the COVID-19 pandemic, and extending to other vaccines besides Covid-19 [126]. Trust in scientists and medical authorities has decreased since the pandemic, possibly making future public health measures more challenging [127,128].

One oft-cited reason for vaccine hesitancy is the possibility for vaccine adverse events [129–131]. This safety concern has persisted despite consistent messaging on the safety of vaccines by health authorities. One German survey revealed that 42 % of vaccine-hesitant survey participants desired a greater level of detailed and numerical information on vaccine side effects [132]. Communicating with certainty, as opposed to acknowledging uncertainty around vaccine risks, can produce unintended and unwanted backfiring [133].

Vaccine hesitancy may be alleviated by no-fault compensation schemes for vaccine injury which assure potential vaccinees that if a rare serious adverse event occurs, they will be able to access medical care and compensation [134,135]. In practice, however, the process can take years, has a low success rate, and can be laborious. As mentioned previously, the average time to complete the initial eligibility check and medical review for the CICP was 24 months [111].

Perceived health risks are one of the primary reasons for vaccine hesitancy [136]. These concerns may potentially be allayed by providing accessible compensation for rare vaccine injuries when they occur [134,135].

## 3. Conclusion: a roadmap to recognition

The first step in addressing post-vaccination syndrome is to develop rigorous diagnostic criteria. This will involve distinguishing between vaccine injury, COVID-19, and long COVID, all of which can present with similar symptoms [5]. By identifying the specific markers of vaccine injury, such as the presence of spike proteins from vaccines [24], medical professionals can provide more targeted care.

Once diagnostic criteria are established, research funding must follow. Research can focus on identifying diagnostic criteria, unpacking disease mechanisms, and developing treatments to serve PACVS patients.

## CRediT authorship contribution statement

**Matthew Halma:** Writing – review & editing, Writing – original draft, Investigation, Conceptualization. **Joseph Varon:** Writing – review & editing, Supervision.

## Data and code availability statement

No new data was generated for the research described in the article.

## Role of the funding source

Funding from the Frontline Covid-19 Critical Care Alliance paid for the article processing charge. The two authors are affiliated with the Frontline Covid-19 Critical Care Alliance, so the funding source did have a role in the study via their participation.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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