Vaccine 66 (2025) 127842

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Review

Differentiating COVID-19 vaccine-related adverse events from long COVID: A comprehensive review of clinical manifestations, pathophysiology, and diagnostic approaches

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ARTICLE INFO

Keywords:
COVID-19 vaccines
long COVID
vaccine safety
adverse events
differential diagnosis

ABSTRACT

The global deployment of COVID-19 vaccines has introduced diagnostic challenges due to overlapping symptoms with long COVID, or post-acute sequelae of SARS-CoV-2 infection (PASC), prompting a comprehensive review of vaccine safety profiles, long COVID manifestations, and evidence-based differentiation strategies. Through a literature search (PubMed, Scopus, Web of Science) from December 2020 to June 2025, including peer-reviewed studies, clinical trials, and cohort studies, the present review reports that COVID-19 vaccines maintain robust safety, with rare adverse events like myocarditis and thrombosis with thrombocytopenia syndrome, while long COVID affects 10–40 % of SARS-CoV-2 survivors, presenting symptoms such as fatigue, cognitive dysfunction, and dyspnea. Differentiation between these conditions relies on careful analysis of the timing of symptom onset, detailed symptom characterization, and the use of advanced diagnostic tools. Systematic clinical assessment is essential for accurate diagnosis, which is critical for appropriate patient management, maintaining public confidence in vaccination, and guiding future research. Further studies are needed to validate diagnostic biomarkers, develop targeted therapies, and monitor long-term outcomes, with standardized global registries and interdisciplinary collaboration identified as key priorities for improving care and advancing the field.

1. Introduction

The COVID-19 pandemic, caused by the coronavirus SARS-CoV-2, has had an unprecedented impact on global health since its emergence in late 2019 [1,2,3]. The rapid development and deployment of COVID-19 vaccines have been pivotal in mitigating the spread of the virus and reducing the severity of the disease. Vaccines based on mRNA (BNT162b2, mRNA-1273) and viral vector (ChAdOx1, Ad26.COV2·S) platforms have demonstrated high efficacy in clinical trials and real-world settings, leading to their emergency use authorization and widespread administration [4,5,6,7]. These vaccines have significantly reduced hospitalization rates and mortality, marking a crucial milestone in pandemic control.

However, the global rollout of COVID-19 vaccines has also been accompanied by reports of adverse events, ranging from mild and transient symptoms to rare but serious conditions such as thrombotic events, myocarditis, and immune reactions [8,9,10,11]. These adverse events have raised concerns among the public and healthcare professionals, necessitating ongoing pharmacovigilance and robust safety monitoring systems. The rarity of severe adverse events underscores the need for clear communication to maintain public trust in vaccination programs [12,13,14]. Notably, published animal toxicity studies remain scarce, with a significant gap between human adverse event documentation and preclinical data [15].

Concurrently, the emergence of post-acute sequelae of SARS-CoV-2 infection (PASC), commonly referred to as long COVID, has presented a new set of challenges. Long COVID is the official term used by the WHO, CDC, and NIH that refers to the persistent or new symptoms, which are present last weeks or months after the acute phase of SARS-CoV-2 infection. These symptoms can affect multiple organ systems, including neurological, cardiovascular, respiratory, and gastrointestinal systems, significantly impacting the quality of life of affected individuals [16,17,18,19]. The prevalence of long COVID varies widely, affecting an estimated 10–40 % of SARS-CoV-2 survivors, with higher rates observed in individuals who experienced severe acute illness and those who were unvaccinated [20,21].

The temporal overlap between vaccination campaigns and the recognition of long COVID has complicated the clinical landscape,

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https://doi.org/10.1016/j.vaccine.2025.127842
Received 2 July 2025; Received in revised form 10 August 2025; Accepted 4 October 2025
Available online 11 October 2025

making it challenging to differentiate between vaccine-related adverse events and long COVID symptoms [22]. Both conditions can present similar symptoms such as fatigue, cognitive impairment, and cardiovascular issues, and patients may experience both simultaneously [23,24,25]. This overlap has created diagnostic dilemmas for healthcare providers, necessitating the development of advanced diagnostic tools and evidence-based differentiation strategies. Recent studies have highlighted the potential of biomarkers (e.g., spike protein, microclots) and imaging techniques (e.g., PET scans) to improve the accuracy of diagnosis [26,27,28,29]. However, the lack of standardized diagnostic criteria and limited long-term data continue to pose significant challenges. While emerging evidence suggests that vaccination may reduce the risk of long COVID or alleviate symptoms in some patients, the underlying mechanisms remain still unclear [30,31]. Further investigation into the immunological interplay between vaccination and long COVID could elucidate these mechanisms and inform targeted therapies [32].

Understanding the evolving risk-benefit profile of COVID-19 vaccination versus the consequences of remaining unvaccinated has become increasingly important for informed decision-making in both clinical practice and public health policy. The differentiation between vaccine-related adverse events and long COVID symptoms has implications not only for individual patient care, but also for maintaining public confidence in vaccination programs and optimizing resource allocation in healthcare systems. In relation to this, the present manuscript aims to address a critical gap in the current understanding of COVID-19 vaccine safety and long COVID by providing a comprehensive review of their clinical manifestations, pathophysiology, and diagnostic approaches. The differentiation between vaccine-related adverse events and long COVID is of great importance for various reasons. Firstly, accurate diagnosis is essential for appropriate clinical management and patient care. Misdiagnosis can lead to unnecessary treatments, delayed interventions, and increased healthcare costs. Secondly, clear differentiation can help to alleviate public concerns about vaccine safety, thereby enhancing vaccine confidence and uptake. Thirdly, a better understanding of the underlying mechanisms and diagnostic markers can inform the development of targeted therapies and improve long-term outcomes for affected individuals. Finally, addressing these challenges can guide public health policies to better support affected populations and optimize resource allocation [33,34]. A comprehensive framework for clinicians and researchers is provided in the present review, facilitating evidence-based decision-making and advancing the field of COVID-19 research.

2. Methods: search strategy

A comprehensive literature search was conducted across PubMed, Scopus, and Web of Science from December 1, 2020, to June 30, 2025, capturing evidence from initial vaccine authorizations to recent publications. Preprint servers (medRxiv, bioRxiv) were also reviewed for trends, but excluded from primary analysis unless peer-reviewed by June 2025. Search terms included Medical Subject Headings and free-text keywords: (“COVID-19 vaccines" OR “SARS-CoV-2 vaccination” OR “BNT162b2” OR “mRNA-1273” OR “ChAdOx1” OR “Ad26.COV2·S") AND (“adverse events" OR “adverse effects" OR “side effects" OR “harms” OR “harm effects" OR “vaccine safety” OR “pharmacovigilance”) AND (“long COVID” OR “PASC” OR “post-COVID condition”). Searches also targeted specific adverse events (e.g., “myocarditis,” “thrombosis with thrombocytopenia”) and long COVID symptoms (e.g., “fatigue,” “brain fog,” “POTS,” “anosmia”).

Eligible studies included peer-reviewed articles, randomized controlled trials, clinical trials, cohort studies, case-control studies, and systematic reviews in English. Priority was given to randomized controlled trials, population-based surveillance data, and 2024–2025 publications. Exclusions included case reports ($n < 10$), opinion pieces, and methodologically weak studies. Studies from high-impact journals and robust designs were prioritized. Grey literature from regulatory agencies (FDA, EMA, WHO), professional guidelines, and government reports were included. This comprehensive review approach was chosen to synthesize the broad range of evidence available across different study types and populations, recognizing that adverse events may be reported with varying frequencies and methodologies across different research contexts.

3. COVID-19 Vaccine safety profiles

3.1. mRNA Vaccines (BNT162b2, mRNA-1273)

mRNA vaccines have demonstrated robust safety profiles in clinical trials and real-world surveillance [4,35,36,7]. Common side effects include injection site pain, fatigue, and headache [37,38]. Rare adverse events include: a) myocarditis/pericarditis, predominantly in males aged 12–29, with incidence rates of 8–15 cases/million doses (BNT162b2) and 6–10 cases/million doses (mRNA-1273) [39,9], b) anaphylaxis and neurological adverse events [40,41], c) Guillain-Barré syndrome (GBS), which is rare, with 1–2 cases/million doses, primarily in older adults [42,43]. Most cases of myocarditis are mild and resolve with supportive care, though long-term follow-up data are limited [44,45].

3.2. Viral vector vaccines (ChAdOx1, Ad26.COV2·S)

Viral vector vaccines are associated with thrombosis with thrombocytopenia syndrome (TTS), with incidence rates of 4–6 cases/million doses (ChAdOx1) and 2–3 cases/million doses (Ad26.COV2·S) [46,10,47]. TTS occurs 4–30 days post-vaccination, with higher risk in women under 50 years old. Other rare events include GBS (1–3 cases/million doses) and capillary leak syndrome (<1 case/million doses) [48,49]. Recent studies suggest that early recognition and treatment with anticoagulants and immunoglobulin can mitigate TTS severity [50].

3.3. Long-term safety and variant-specific boosters

Pharmacovigilance systems (VAERS, VSD, EudraVigilance) confirm rare long-term adverse events, most occurring within 6 weeks [51,52,53]. Potential links between mRNA vaccines and autoimmune disorders have been recently reported [54,55], while safety profiles remain consistent for boosters targeting Omicron subvariants (BA.5, XBB.1.5, JN.1) [56,57,58]. Ongoing global surveillance is crucial to monitor rare adverse events as new variants and boosters emerge [59].

3.4. Long COVID: clinical manifestations and pathophysiology

3.4.1. Clinical manifestations

Long COVID, or PASC, is defined as symptoms persisting beyond 4 weeks post-infection, with the WHO specifying symptoms lasting ≥2 months, starting ≥3 months post-infection without alternative explanation [60,61]. The prevalence ranges from 10 to 40 % of SARS-CoV-2 survivors, with higher rates in severe cases and unvaccinated individuals [62,63]. Long COVID presents with heterogeneous, multi-system symptoms [16,18]: a) neurological: cognitive dysfunction (“brain fog,” 20–35 %), headaches (40–50 %), peripheral neuropathy (10–20 %), and anosmia/dysgeusia (15–25 %) [64,65,25], b) cardiovascular: chest pain (20–25 %), palpitations (15–25 %), and postural orthostatic tachycardia syndrome (POTS, 10–20 %) [66,67,68], c) respiratory: dyspnea (25–50 %), chronic cough (20–30 %), and pulmonary function abnormalities (20–35 %) [69,70,71], d) systemic: fatigue (58–90 %) with post-exertional malaise (PEM), sleep disturbances (35–50 %), myalgia (25–35 %), and gastrointestinal issues (15–25 %) [72,73,74]. Moreover, psychiatric symptoms (e.g., anxiety, depression) have been reported in 30–40 % of long COVID patients [64,75,76]. In addition, emerging evidence suggests that pediatric and adolescent populations may

experience distinct long COVID symptoms, such as chronic pain and sleep disorders, necessitating tailored diagnostic approaches [77,78].

3.4.2. Pathophysiology

Long COVID's pathophysiology involves multiple interconnected mechanisms ([79]; Santos Guedes de Sa et al., 2024; [80]). Viral persistence represents a key pathway, with SARS-CoV-2 RNA and proteins detected in various tissues including the gut and brain up to 12 months post-infection [81]. Supporting this mechanism, Rong et al. [82] recently demonstrated associations between spike protein presence in plasma and cognitive symptoms. Immune dysregulation constitutes another critical component, characterized by elevated inflammatory markers such as CRP and IL-6, the presence of autoantibodies including anti-neural and anti-nuclear antibodies, and T-cell exhaustion [83,84]. Microvascular dysfunction also plays a significant role, whereby endothelial damage and microclot formation contribute to cardiovascular, neurological, and respiratory manifestations [85,86,87]. Additionally, autonomic dysfunction underlies many cardinal symptoms including fatigue, tachycardia, and cognitive impairment [67,88], while mitochondrial dysfunction and impaired energy metabolism may explain post-exertional malaise and persistent fatigue [89]. Emerging evidence further suggests that gut microbiome dysbiosis contributes to perpetuating systemic inflammation and long COVID symptoms [90,91].

3.5. Clinical differentiation: challenges and approaches

3.5.1. Diagnostic challenges

Distinguishing between COVID-19 vaccine adverse effects and long COVID presents significant clinical challenges due to multiple overlapping factors. The temporal relationship between vaccination and symptom onset is often unclear, as many individuals receive vaccines during active long COVID-19 episodes or while recovering from acute infection [25]. This timing complexity is compounded by substantial symptom overlaps between the two conditions, with fatigue, myalgia, and cognitive dysfunction representing common manifestations in both scenarios [23,24]. Table 1 summarizes the key clinical and temporal parameters that differentiate long COVID from vaccine-related adverse events.

The heterogeneous nature of both conditions further complicates differential diagnosis, as symptom presentation varies considerably across individuals and may evolve over time [17,92]. Additionally, the historical lack of validated biomarkers for either condition has limited objective diagnostic capabilities, though recent advances show promise [29]. The reliance on patient-reported outcomes and potential for self-diagnosis introduces additional diagnostic uncertainty, underscoring the critical need for standardized, objective diagnostic tools and clinical assessment protocols [93,94,95].

It is important to recognize that inadequate reporting of adverse events in clinical trials, particularly those primarily designed to assess efficacy, may contribute to underestimation of certain adverse event frequencies. Many adverse events can only be documented in supplementary materials, or may not be reported at all, when their incidence is low in smaller studies. This limitation highlights the importance of comprehensive post-marketing surveillance and real-world evidence in understanding the full safety profile of COVID-19 vaccines.

3.5.2. Evidence-based differentiation strategies

Effective clinical differentiation relies on systematic analysis of temporal patterns, symptom characteristics, and comprehensive diagnostic evaluation.

Temporal Analysis. The timing of symptom onset provides crucial diagnostic information. Vaccine adverse events typically manifest within hours to days following immunization, presenting as acute, time-limited reactions [9]. In contrast, long COVID symptoms either persist from the acute infection phase or emerge weeks to months post-infection, often following a chronic, fluctuating course [18].

Table 1
Clinical Features and Temporal Characteristics of COVID- 19 Vaccine-Related Adverse Events vs. Long COVID.

Feature	COVID-19 Vaccine-Related Adverse Events	Long COVID (PASC)
Onset Timing	Hours to days post-vaccination (typically within 6 weeks)	Weeks to months post-SARS-CoV-2 infection (≥2 months per WHO definition)
Common Symptoms	• Injection site pain • Fatigue • Headache • Myalgia • Myocarditis/pericarditis	• Fatigue with post-exertional malaise •Cognitive • Dyspnea • Chest pain
Rare/Serious Symptoms	• Thrombosis with thrombocytopenia syndrome • Guillain-Barré syndrome	• Postural orthostatic tachycardia syndrome (POTS) • Peripheral neuropathy • Pulmonary function abnormalities
Symptom Duration	Typically resolves within days to weeks; myocarditis/TTS may require longer recovery	Persistent or relapsing-remitting, lasting months to years
System Involvement	Primarily localized (injection site) or systemic (mild, short-lived); cardiovascular/neurological in rare cases	Multi-system: neurological, cardiovascular, respiratory, gastrointestinal, psychiatric
Key Differentiators	• Acute onset post-vaccination • Localized symptoms • Rare events linked to specific vaccine types (e.g., TTS with viral vector vaccines)	• Relapsing-remitting pattern • Post- exertional malaise • History of confirmed SARS-CoV-2 infection
Emerging Diagnostic Tools	Biomarker assays (e.g., troponin for myocarditis); machine learning for event classification	Biomarkers (e.g., spike protein, microclots, autoantibodies); PET/MRI for neuroinflammation; wearable devices for autonomic monitoring

Symptom Characterization. Distinct symptom patterns further aid differentiation. Long COVID characteristically presents with relapsing-remitting symptoms, post-exertional malaise (PEM), and multi-system involvement affecting neurological, cardiovascular, and pulmonary functions [23,74]. Vaccine reactions, conversely, tend to be either localized to the injection site or present as short-lived systemic symptoms such as fever, fatigue, or myalgia [24].

Comprehensive Diagnostic Workup. A systematic diagnostic approach incorporates multiple assessment modalities. Laboratory evaluation includes complete blood count, inflammatory markers (CRP, ESR), coagulation studies (D-dimer), cardiac biomarkers (troponin), and autoantibody panels to identify systemic inflammation and autoimmune processes [69]. Cardiac assessment through electrocardiography, echocardiography, and cardiac MRI helps detect myocarditis or postural orthostatic tachycardia syndrome [58,68]. Pulmonary function testing, including spirometry, chest CT, and diffusion capacity measurements, evaluates respiratory complications in patients with dyspnea [71].

Advanced neurological imaging using PET or functional MRI can identify neuroinflammatory changes [96,97,98], while autonomic function testing through tilt table tests or orthostatic vital sign monitoring helps diagnose dysautonomia [67,41]. Emerging biomarker assays measuring spike protein levels, microclot formation, or specific autoantibodies offer additional diagnostic precision [99,100,101]. Recent technological advances show promise for improving diagnostic accuracy. Integration of wearable technology for continuous physiological monitoring represents an emerging approach that could further enhance diagnostic precision and enable real-time symptom tracking [102].

3.5.3. Impact of Vaccination on Long COVID

Vaccination reduces long COVID risk by 15–60 % in breakthrough infections, with greater protection from bivalent boosters [103,104,31,105]. Recently, Nguyen et al. [56] found a 40 % risk reduction with JN.1-targeted vaccines. The protective effect is likely mediated by enhanced viral clearance and reduced inflammatory responses [106].

3.5.4. Therapeutic effects

Approximately 20–30 % of long COVID patients report symptom improvement post-vaccination, potentially due to immune modulation or viral clearance [107,108,95]. Although a recent trial of mRNA boosters showed reduced fatigue and dyspnea in long COVID patients [109], the variability in response underscores the need for personalized treatment approaches [110].

3.5.5. Symptom exacerbation

Temporary symptom worsening occurs in 10–15 % of long COVID patients' post-vaccination, resolving within 1–3 weeks, linked to transient cytokine surges [111,112,113]. Careful monitoring during the post-vaccination period is recommended to manage these transient effects [104].

3.5.6. Clinical Management Recommendations

Comprehensive Assessment: history (timeline of infection, vaccination, and symptom onset), physical exam (systematic evaluation of neurological, cardiovascular, and respiratory systems), laboratory/imaging (targeted tests such as inflammatory markers, cardiac MRI, chest CT), and specialist referral (neurology, cardiology, or pulmonology for complex cases) [114,115,116,117].

Supportive care: supportive care for long COVID encompasses a comprehensive, multifaceted approach addressing both symptom management and functional restoration. Symptom-specific interventions form the foundation of treatment, including the use of analgesics for pain management, beta-blockers for postural orthostatic tachycardia syndrome, and cognitive therapy for brain fog [118]. Activity pacing represents a crucial therapeutic strategy, involving gradual exercise progression designed to prevent post-exertional malaise while promoting functional improvement [119]. Effective management requires coordinated multidisciplinary care with seamless integration among specialists to address the complex, multi-system nature of long COVID symptoms. Psychological support constitutes an essential component, with cognitive behavioral therapy and mindfulness-based interventions proving beneficial for managing associated anxiety and depression [64,120]. Patient education plays a vital role in empowering individuals through clear communication regarding prognosis and evidence-based self-management strategies [121]. The integration of telehealth platforms can significantly enhance access to comprehensive multidisciplinary care, particularly benefiting patients in resource-limited settings [122,123].

Monitoring and Follow-up: regular follow-up includes symptom tracking, functional assessment, and treatment optimization, with referrals as needed [104]. Patient registries and mobile health applications could facilitate long-term monitoring and data collection [124].

The clinical approach should also consider the broader context of vaccination decision-making, ensuring that patients receive comprehensive information about both the risks of adverse events, and the protective benefits against long COVID, enabling informed choices based on individual risk profiles and circumstances.

3.5.7. Research Priorities and Future Directions

Research priorities: Several critical research areas require immediate attention to advance our understanding and management of long COVID and vaccine-related adverse events.

Biomarker Development. The identification and validation of reliable biomarkers represents a fundamental research priority. Promising candidates include spike protein levels, microclot formation patterns, autoantibody profiles, and cytokine signatures, which could significantly enhance diagnostic accuracy and enable objective differentiation between conditions [125,85,84,101]. These biomarkers may also provide insights into disease mechanisms and treatment response monitoring.

Mechanistic Understanding. Elucidating the underlying pathophysiological mechanisms driving persistent symptoms remains crucial for developing targeted therapies [27]. Research focusing on viral persistence, immune system dysregulation, and mitochondrial dysfunction could reveal therapeutic targets and explain the diverse symptom presentations observed across patients ([126]; Paul et al., 2024; [79]).

Longitudinal Studies. Comprehensive cohort studies with extended follow-up periods are essential for understanding symptom trajectories, identifying prognostic factors, and determining risk stratification approaches. These studies will provide critical data on natural history, recovery patterns, and long-term outcomes for both conditions ([127]; Lopez-Leon et al., 2025).

Therapeutic Development. Urgent implementation of randomized controlled trials is needed to evaluate potential treatments, including antiviral therapies, immunomodulatory agents, and comprehensive rehabilitation programs. These trials should incorporate standardized outcome measures and consider the heterogeneous nature of symptom presentations [23,128].

Public Health Infrastructure. Establishing standardized diagnostic criteria and implementing global patient registries will improve epidemiological surveillance and facilitate coordinated care delivery. These initiatives require international collaboration to develop harmonized diagnostic protocols and therapeutic guidelines, addressing current global disparities in long COVID recognition and management (Raj et al., 2024; Thompson et al., 2025; [129]).

Comprehensive adverse event surveillance systems should be enhanced to capture the full spectrum of potential vaccine-related outcomes, including those with low incidence rates that cannot be adequately captured in smaller studies or efficacy-focused trials. This includes improved standardization of adverse events reporting across different study types and healthcare settings.

The success of these research initiatives depends on sustained funding, interdisciplinary collaboration, and coordinated international efforts to ensure equitable access to advances in diagnosis and treatment worldwide.

3.6. Future directions

Research should prioritize biomarker validation, mechanistic studies, long-term cohort studies, randomized therapeutic trials, and global standardization of diagnostic criteria [125,130,131,79,84,132,2]. Addressing disparities in access to diagnostics and care, particularly in low-resource settings, is critical for equitable health outcomes [129].

3.7. Limitations

The evolving evidence base may outdate findings. Study heterogeneity, variable long COVID definitions, and potential underreporting of adverse events limit comparisons [133,134], while access to advanced diagnostics (e.g., PET scans) varies globally [135]. Additionally, the lack of diversity in study populations can limit the generalizability of findings to underrepresented groups [20]. It must be acknowledged that adverse event reporting methodologies vary across different study designs, with potential underreporting in investigations focused primarily on efficacy outcomes, which can affect the complete characterization of the safety profile.

4. Conclusions

This comprehensive review examined the clinical differentiation between COVID-19 vaccine-related adverse events and long COVID syndrome, analyzing their distinct pathophysiological mechanisms, temporal patterns, and diagnostic approaches. The analysis yields several key findings with important clinical implications, which are next summarized.

COVID-19 vaccines demonstrate robust safety profiles across both mRNA and viral vector platforms. Common adverse events, including fatigue and injection site pain, typically resolve within days of administration. Serious adverse events remain rare, with myocarditis occurring in 8–15 cases per million doses and thrombosis with thrombocytopenia syndrome (TTS) in 2–6 cases per million doses. Importantly, these severe reactions predominantly manifest within weeks of vaccination, providing a clear temporal framework for clinical assessment (Baden et al., 2021; [39,9,10,7,11]). On the other hand, long COVID affects 10–40 % of SARS-CoV-2 survivors, with higher prevalence observed in patients with severe acute illness and unvaccinated individuals. The syndrome presents with diverse, multi-system manifestations including fatigue (58–90 % of cases), cognitive dysfunction (20–35 %), and dyspnea (25–50 %). These symptoms can persist for months to years, resulting in substantial functional impairment and reduced quality of life ([17,18]; Lopez-Leon et al., 2025; Thompson et al., 2025).

Effective differentiation between vaccine-related adverse events and long COVID relies on systematic evaluation of temporal patterns and symptom characteristics. Vaccine reactions typically occur within hours to days of administration, whereas long COVID symptoms persist or emerge weeks to months following infection [18,9]. Long COVID is distinguished by its characteristic relapsing-remitting course, post-exertional malaise (PEM), and multi-system involvement, contrasting with the localized and time-limited nature of most vaccine reactions ([23,24]; Townsend et al., 2021). Recent advances in diagnostic capabilities have enhanced differentiation accuracy. These include sophisticated laboratory tests, advanced imaging techniques, autonomic function testing, and emerging technologies such as machine learning algorithms and novel biomarkers [136,137]. Table 2 summarizes recommended diagnostic tools and approaches for the systematic evaluation of suspected long COVID versus post-vaccination adverse effects.

Vaccination provides significant protection against long COVID development, reducing risk by 15–60 %. Bivalent and variant-specific booster vaccines offer enhanced protection compared to original formulations (ECDC, 2025; [138]). Among individuals with established long COVID, approximately 20–30 % report symptom improvement following vaccination, though 10–15 % may experience transient symptom exacerbation [103,107,139,106,31].

Vaccination not only provides substantial protection against severe COVID-19, but also significantly reduces the risk of developing long COVID, supporting the favorable risk-benefit profile of COVID-19 vaccines. This information is essential for informed decision-making and maintaining public confidence in vaccination programs. Evidence-based management requires patient-centered care incorporating comprehensive clinical assessment, individualized supportive interventions, and systematic follow-up protocols [140,118,141]. Integration of digital health technologies and participation in global disease registries can optimize care delivery while advancing research understanding of these conditions [124]. This analysis underscores the importance of maintaining vigilant post-vaccination surveillance while developing more sophisticated diagnostic tools for long COVID. Continued research into the mechanistic differences between these conditions will further refine clinical differentiation and inform targeted therapeutic approaches.

Table 2
Diagnostic and Management Approaches for Differentiating Vaccine-Related Adverse Events and Long COVID.

Approach	COVID-19 Vaccine-Related Adverse Events	Long COVID (PASC)
Diagnostic Workup	• History: Timing of vaccination, symptom onset within hours to days • Lab Tests: Blood count, D-dimer, troponin for myocarditis/TTS • Imaging: cardiac MRI for myocarditis; CT angiography for TTS • Point-of-care cytokine assays for rapid assessment	• History: Confirmed SARS-CoV-2 infection, symptom persistence ≥2 months • Lab Tests: CRP, ESR, autoantibody panels, spike protein assays • Imaging: chest CT, PET/MRI for pulmonary/neurological sequelae • Autonomic Testing: tilt table test for POTS • Wearable devices for real-time autonomic monitoring
Advanced Diagnostics	• ECG, echocardiography for cardiovascular events • Machine learning algorithms for event classification (85 % accuracy)	• Functional MRI for neuroinflammation • Pulmonary function tests • Biomarker panels (microclots, cytokines) and machine learning for symptom clustering
Management Strategies	• Supportive Care: analgesics for mild symptoms; anticoagulation/ immunoglobulin for TTS • Monitoring: short-term follow-up for resolution • Patient education on expected symptom duration to reduce anxiety	• Supportive Care: analgesics, beta-blockers for POTS, cognitive therapy for brain fog • Activity Pacing: graded exercise to prevent PEM • Multidisciplinary Care: neurology

CRediT authorship contribution statement

Jose L. Domingo: Writing – review & editing, Writing – original draft, Validation, Methodology, Formal analysis, Data curation, Conceptualization.

Ethics approval

As this is a comprehensive review of published literature, ethics approval was not required.

Funding

This review received no specific funding.

Declaration of competing interest

The author declares that he has no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

This is a Review-manuscript

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