

Opinion

# The lingering shadow of epidemics: post-acute sequelae across history

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The SARS-CoV-2 pandemic has drawn global attention to post-acute infection syndromes (PAIS), with millions affected by post-acute sequelae of COVID-19 (PASC, or Long COVID). While Long COVID is newly defined, PAIS have been described for over a century following epidemic infections. Multiple pathogens – including influenza, Epstein-Barr virus, and *Borrelia burgdorferi*, among others – can precipitate persistent, poorly understood symptoms. Chronic illnesses such as myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) have long been linked to infectious triggers. This recurring association highlights critical knowledge gaps and underscores the need for systematic investigation. Unlike prior pandemics, the current era offers advanced technologies and analytic tools to address these gaps. Defining the biology of Long COVID may yield broader insights into host-pathogen interactions and mechanisms of chronic illness.

## Long COVID highlights the complexity of PAIS

Traditionally, infectious diseases were thought to have two potential outcomes: a patient either succumbs to the disease or fully recovers after a period of convalescence. This model assumes infection causes short-term illness followed by full recovery. Coronavirus disease 2019 (COVID-19) has challenged that idea, as many people continue to have symptoms after the initial infection. When recovery does not happen, the illness can become chronic. The incidence of Long COVID is reported to be around 10% globally [1], with highly heterogeneous symptoms that encompass virtually every organ system. Modern research is beginning to unravel the many ways in which severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) exerts long-term effects on the body (Table 1). Long COVID can impact any person of any demographic, but like many autoimmune diseases, it is particularly prevalent in women [2].

Despite these advances, routine clinical tests such as complete blood counts and standard serum chemistry tests typically return in the normal range [3]. Physicians seeing normal lab values may extrapolate these results, concluding erroneously that the absence of evidence of Long COVID is also evidence of absence of underlying biological drivers. In fact, scores of objective biomarkers that reliably distinguish cases of Long COVID and ME/CFS from healthy controls (and, sometimes from disease comparison groups) have been reported [1–7]. These assertions contribute to the high levels of stigma and medical trauma reported by Long COVID patients [5] and reflect a long history of dismissing complex chronic conditions like PAIS.

Nevertheless, a large and growing body of research supports the conclusion that Long COVID is driven by prolonged physiological dysfunction, particularly in the immune system (Table 1). SARS-CoV-2, however, is far from the first pandemic pathogen associated with **chronic illness** (see Glossary). In this review, we outline the historical context of PAIS and argue that this

## Highlights

New or persistent symptoms following COVID-19, known as 'long COVID', occur in an estimated 4–20% of pediatric and 10–20% of adult patients after acute infection with SARS-CoV-2. Long COVID is associated with dysregulation of both innate and adaptive immunity.

While long COVID is a relatively new clinical entity, post-acute infection syndromes (PAIS) have been well documented for over a century.

A wide variety of pathogens are associated with PAIS, including divergent classes of viruses, bacteria, and parasites. While each PAIS has a unique trigger and pathology, similarities in symptom profiles and immunological findings suggest these conditions may share features or involve overlapping biological mechanisms.

Despite being well described in the literature, PAIS remain understudied relative to their high disease burden. Patients often face stigma and psychologization from medical professionals when disease biomarkers are not readily apparent, exemplified by the historic dismissal of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).

## Significance

Long COVID, a chronic multisystemic health condition, impacts hundreds of millions around the world. Long COVID has brought light to other related post-acute infection syndromes (PAIS) that are triggered by a wide array of pathogens. This opinion article highlights historical accounts of PAIS through the centuries and emphasizes the need for integrated approaches to understanding and treating PAIS.



perspective provides crucial context for future research and treatment of these devastating and understudied conditions (Figure 3, Key figure).

### PAIS throughout history

The pandemic of 1889–1890, often referred to as the ‘Russian influenza epidemic’, is believed to have originated in central Asia in May 1889, with the first outbreak occurring in Western Siberia, October 1889 (Figure 1) [6]. By November and December of that year, the pandemic had hit most of Europe [6]. By mid-December the first cases were seen in the USA, and by the spring of 1890 Asia and Africa were affected as well [6]. Although originally attributed to influenza, some modern analyses have proposed that human coronavirus OC43 may have been the causative agent, however, definitive consensus remains elusive [6–8]. In the aftermath of this epidemic, physicians widely reported cases of ‘influenza exhaustion’ – a post-viral condition characterized by prolonged and varied symptoms following **acute illness**. Entire volumes were dedicated to documenting this syndrome, with clinical observations spanning decades prior to their publication. In a notable 1892 publication, physician Thomas Stretch Dowse described a constellation of persistent symptoms – including myalgias, anxiety, neuritis, cranial nerve dysfunction, fatigue, sleep disturbances, and depression – that he termed ‘post-influenza exhaustion’ [9]. Dowse also noted clinical heterogeneity, with some patients presenting with symptoms isolated to a single domain, such as fatigue or neuropathy, while others exhibited **multisystem** involvement. Similarly, Dr J. Samuel Price addressed the Texas Medical Board in 1892, detailing several cases of prolonged convalescence following influenza, marked by recurrent or persistent fevers lasting weeks to months [10]. Though poorly understood at the time, these historical accounts reflect clinical patterns strikingly reminiscent of contemporary descriptions of Long COVID.

Several decades after the 1889 pandemic, the 1918 H1N1 influenza pandemic similarly gave rise to reports of post-acute, persistent neurological sequelae. A particularly striking phenomenon, termed encephalitis lethargica, emerged in a subset of individuals following acute influenza infection (Figure 1). This post-viral syndrome was characterized by a range of symptoms, including encephalitis, catatonia, and states of profound lethargy approaching coma. In a 1932 letter to the *Canadian Medical Journal*, Dr Charles Hunter described pathological findings observed in autopsied cases, noting ‘hemorrhagic areas in the brain... cellular infiltration of the perivascular lymphatic sheaths of certain areas of grey matter, primarily composed of small mononuclear leukocytes, with a conspicuous absence of polymorphonuclear cells’ [11]. Although these individuals exhibited **encephalopathic** symptoms, the pathology lacked hallmark features of encephalitis, such as neutrophilic infiltration.

The prevalence and impact of encephalitis lethargica were significant. Between 1919 and 1927, the British Ministry of Health recorded 15 935 cases with an estimated 48% mortality rate, 20% resulting in chronic disability, and only 14% achieving full recovery [11]. Alarmingly, in 1924 alone, 1136 schoolchildren in England were reported to have been affected, and two-thirds of these children never fully recovered [11].

Treatment options at the time were limited, with care focused primarily on supportive measures. Physicians stressed the importance of ‘absolute rest’ and made specific dietary recommendations such as milk, beans, fat mutton, and fat pork [9]. Some clinical reports described the use of acriflavine – an antiseptic dye discovered in 1912 and initially used for wound care and coma treatment during World War I – as part of a graded dosing regimen with noted responses [11]. By the late 1920s, acriflavine was also being used to treat persistent fevers following brucellosis infection, underscoring its broader role in managing post-infectious condition [12].

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One of the most enigmatic aspects of encephalitis lethargica is its temporally bounded nature – it has not been observed outside the context of the 1918 H1N1 pandemic [13]. While its precise etiology remains unknown, the close temporal association with the influenza outbreak strongly suggests a post-infectious pathogenesis, offering historical precedent for the type of delayed, heterogeneous syndromes seen in contemporary post-viral illnesses such as Long COVID.

During the mid-20th century, poliovirus epidemics began peaking in the Northern Hemisphere globally [14]. In the USA, the 1952 outbreak was particularly severe, with more than 21 000 cases of paralytic polio reported [14]. Approximately 75% of polio cases presented as a mild, influenza-like illness, however up to one-quarter progressed to flaccid paralysis [15]. Additionally, a subset of previously infected individuals developed progressive muscle weakness, profound fatigue, severe myalgias, and, in some cases, recurrent paralysis, years to decades after their initial infection [15]. This constellation of symptoms is now recognized as post-polio syndrome (Figure 1). Although first described in 1875, post-polio syndrome was not widely acknowledged by the medical and scientific communities until the 1980s. Despite decades of investigation, the underlying pathobiology remains poorly understood.

A more recent example of post-acute sequelae followed the original severe acute respiratory syndrome (SARS) outbreak in the early 2000s that infected approximately 8000 globally, with a fatality rate of approximately 10%. Many survivors were left with persistent disabling symptoms or ‘long SARS’ following the acute illness, including pulmonary conditions, muscle wasting, sleep disturbance, severe fatigue, and cognitive deficits that persisted for at least 1 year [16–18]. Despite major differences in the pathobiology of SARS and COVID-19, similarities in presentation between Long COVID and Long SARS have been noted in the literature [19,20].

Following the 2014–2016 West African Ebola outbreak, lingering symptoms were also described in a subset of patients. Ebola virus, an RNA virus of the *Filoviridae* family, causes acute illness marked by fever, myalgias, sore throat, and often progresses to hemorrhage, with a case fatality rate over 40% [21]. Among survivors, many report persistent symptoms – fatigue, musculoskeletal pain, neurocognitive deficits, and particularly ophthalmologic complications [22]. Longitudinal immunophenotyping revealed sustained antiviral activity, chronic inflammation, and immune features resembling systemic lupus erythematosus, including upregulated interferon pathways, cytotoxic T cell expansion, and myeloid activation [22]. These findings suggest that acute viral infections can trigger durable immune alterations leading to chronic dysfunction.

Beyond epidemic outbreaks, several infections cause lasting sequelae in some individuals. Epstein-Barr virus (EBV), a ubiquitous herpesvirus, is a well-established cause of PAIS. Following infectious mononucleosis, 4–10% of children and adolescents develop chronic fatigue lasting months to years [23]. Affected individuals experience persistent fatigue and recurrent symptoms resembling the acute illness. Immunologic studies reveal sustained T cell activation and elevated proinflammatory cytokines [24], though mechanisms remain unclear. The emerging link between EBV and multiple sclerosis further illustrates how infection can drive chronic disease [25–27].

Lyme disease is associated with several Lyme infection-associated chronic illnesses (Lyme-IACI), including post-treatment Lyme disease syndrome (PTLDS) that develops following antibiotic therapy for tick-borne *Borrelia burgdorferi* infection [28]. While the majority of patients recover from the acute *B. burgdorferi* infection with appropriate treatment, 5–10% report persistent symptoms such as fatigue, myalgias, arthralgias, and neuropathic complaints [29]. The etiology of Lyme-IACI and PTLDS remain debated. Proposed mechanisms include persistent bacterial reservoirs undetectable by standard culture due to the spirochete’s motility, pleomorphism, and immune

### Glossary

**Acute illness:** a condition that arises following an infection and is characterized by the onset of symptoms and is typically time-limited.

**Chronic illness:** a condition characterized by persistent or recurrent symptoms lasting months to years after initial infection.

**Encephalopathic:** inflammation of brain tissue causing widespread brain dysfunction.

**Multisystemic:** a condition that affects more than one organ system.

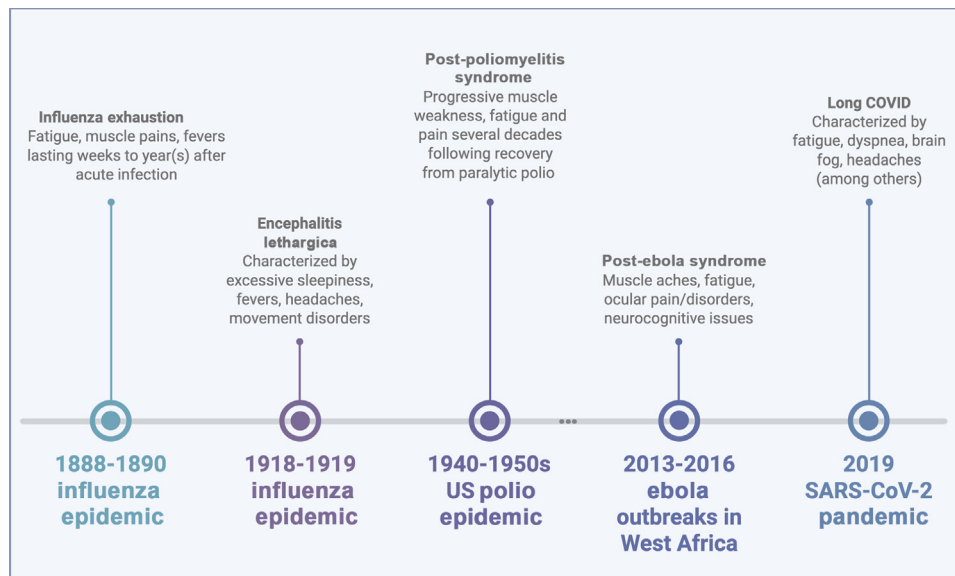
Table 1. Highlighted innate and adaptive immunologic findings of Long COVID and ME/CFS

Dysregulation of innate immunity			
Long COVID		ME/CFS	
Alterations in circulating myeloid cells	Phetsouphanh <i>et al.</i> (2022) [69] Klein <i>et al.</i> (2023) [4]	Prominent monocyte dysregulation that correlates with disease severity	Vu <i>et al.</i> (2024) [70]
Large GWAS <sup>a</sup> identified variants within FOXP4 locus as risk factors for Long COVID, implicating altered regulation of innate immune responses in the lung	Lammi <i>et al.</i> (2025) [71]	Large GWAS identified several loci that act in response to infection including <i>BTN2A2</i> , <i>OLFM4</i> , <i>RABGAP1L</i>	Genetics Delivery Team (2025, preprint) [72]
Increased corneal dendritic cells alongside corneal small nerve fiber loss measured through intravital corneal confocal microscopy	Bitirgen <i>et al.</i> (2022) [73] Cañadas <i>et al.</i> (2023) [74] Azcue <i>et al.</i> (2025) [75]	Small fiber nerve loss observed via corneal confocal microscopy	Azcue <i>et al.</i> (2025) [75]
Elevated plasma CCL11 reported in patients with brain fog	Fernández-Castañeda <i>et al.</i> (2022) [76]	Several plasma cytokines correlate with ME/CFS severity including CCL11, CXCL1, CXCL10	Montoya <i>et al.</i> (2017) [77]
Ongoing neutrophil activity, NETosis in plasma samples	Woodruff <i>et al.</i> (2023) [78] George <i>et al.</i> (2022) [79] Talla <i>et al.</i> (2023) [78]	Exaggerated innate immune responses to microbial stimulation, worse after exercise	Che <i>et al.</i> (2025) [61]
Dysregulation of adaptive immunity			
Long COVID		ME/CFS	
Decreased naïve T and B cell populations compared with recovered individuals, unexposed donors, patients with other coronaviruses	Phetsouphanh <i>et al.</i> (2022) [69]	Increased frequency of total B, naïve T and B cells; decreased frequency of plasmablasts, effector memory and regulatory T cells	Ono <i>et al.</i> (2017) [80]
Alterations in circulating lymphocyte populations	Klein <i>et al.</i> (2023) [4]	Lymphocyte death rate may be useful as a blood-based biomarker for ME/CFS	Missailidis <i>et al.</i> (2020) [81]
Exaggerated humoral responses directed against SARS-CoV-2 and non-SARS-CoV-2 pathogens	Klein <i>et al.</i> (2023) [4]	Reduced humoral response pattern (IgG, IgA, IgM, IgG3, IgG4, mannose-binding lectin, C3c)	Lutz <i>et al.</i> (2021) [82]
Widespread distribution of activated T cells throughout the body up to 910 days post-infection	Peluso <i>et al.</i> (2024) [83]	Abnormal and divergent patterns of T cell activation and cytotoxic T cell frequency in mild/moderate versus severe ME/CFS	Lee <i>et al.</i> (2025, preprint) [84]
Increased frequency of migratory CD4+ T cells and exhausted SARS-CoV-2 specific CD8+ T cells	Yin <i>et al.</i> (2024) [85]	CD8+ T cell dysfunction observed in ME/CFS patients	Iu <i>et al.</i> (2024) [86] Gil <i>et al.</i> (2024) [87]
Higher levels of SARS-CoV-2 antibodies, discordance between SARS-CoV-2-specific T and B cell responses	Yin <i>et al.</i> (2024) [85]	Higher levels of antibodies directed against gut microbiota	Vogl <i>et al.</i> (2022) [88]
Passive transfer of immunoglobulins from Long COVID patients triggers neurological symptoms in mice	Sa <i>et al.</i> (2024, preprint) [89] Chen <i>et al.</i> (2024, preprint) [90]	Elevated autoantibodies directed against neuronal antigens	Loebel <i>et al.</i> (2016) [91] Bynke <i>et al.</i> (2020) [92] Ryabkova <i>et al.</i> (2023) [93]

<sup>a</sup>GWAS, genome-wide association study.

evasion. Alternatively, residual bacterial components may drive chronic immune activation without active infection. Co-infection with other tick-borne pathogens, such as *Rickettsia* and *Babesia* spp., may further contribute to Lyme-IACI [30–32].

Chikungunya virus, a mosquito-borne pathogen endemic to tropical regions, is associated with chronic inflammatory rheumatism resembling rheumatoid arthritis in up to 25% of cases

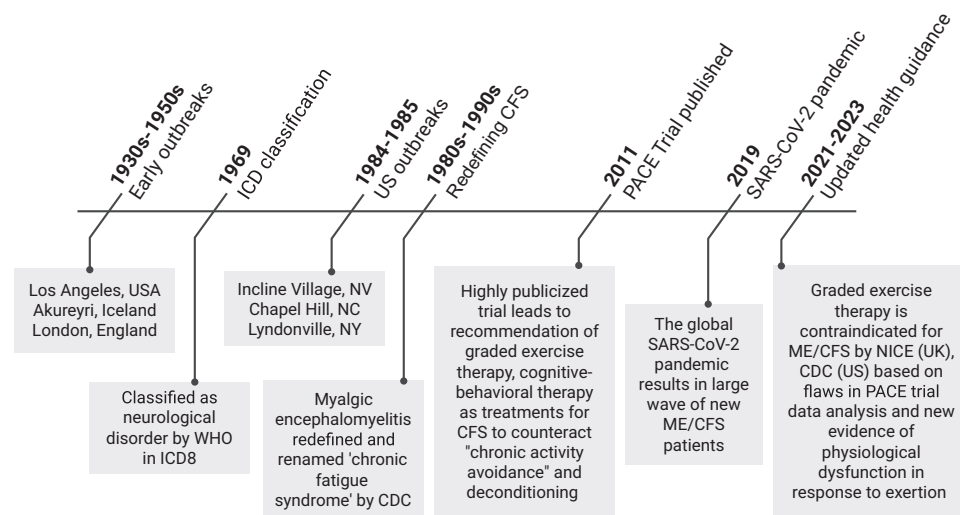


Trends in Immunology

Figure 1. Epidemics and their post-acute sequelae throughout modern history.

[33,34]. Likewise, *Coxiella burnetii*, the agent of Q fever, has been linked to post-acute sequelae. During the 2007–2010 Netherlands outbreak – the largest recorded – 10–28% of patients reported persistent fatigue, pain, neurocognitive impairment, sleep disturbance, and respiratory symptoms, though no unifying mechanism was identified [35].

Bacterial infections such as Group A streptococcal infections have also been well described as having post-acute sequelae. Molecular mimicry between streptococcal antigens and host

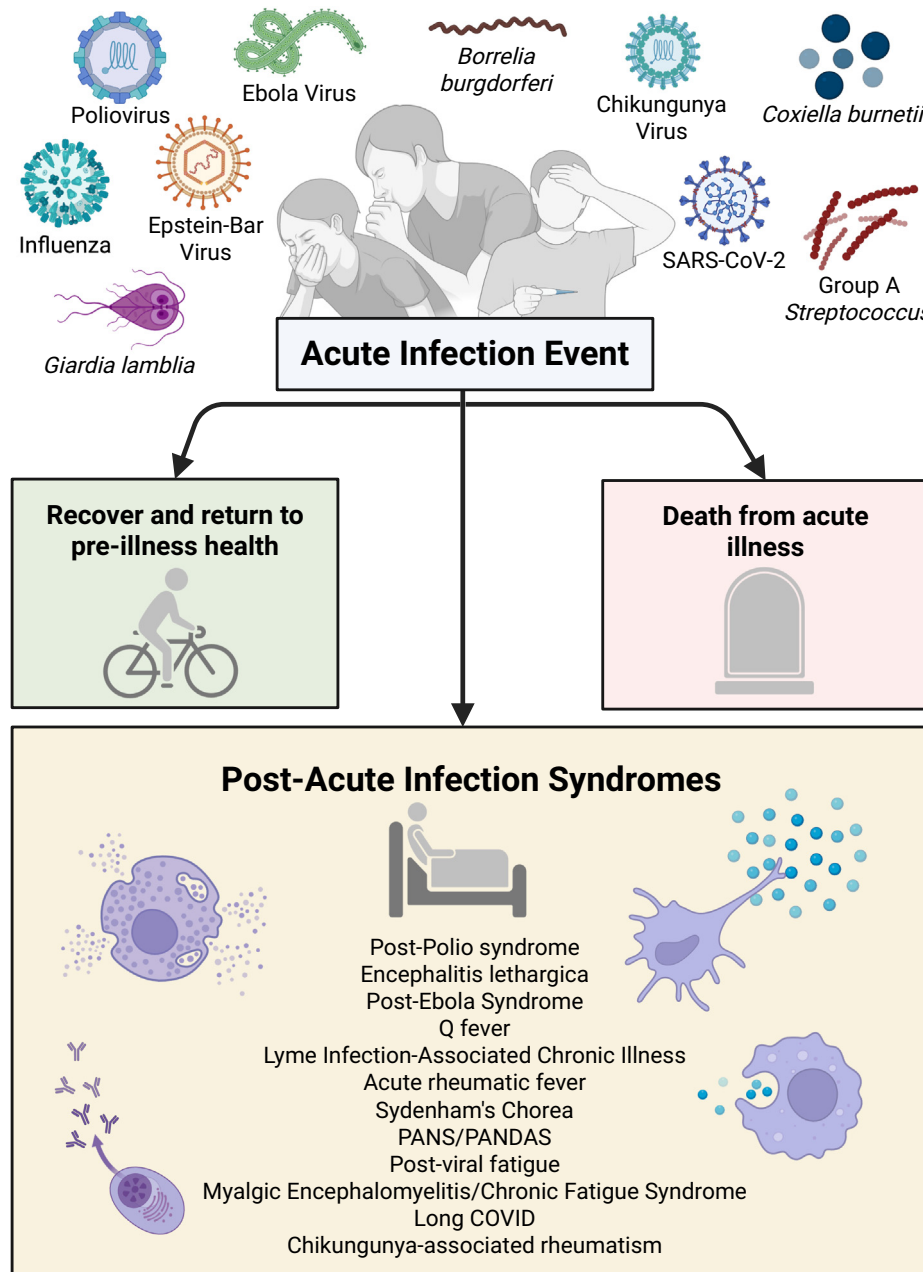


Trends in Immunology

Figure 2. Timeline of major events in ME/CFS history. Abbreviations: CDC, Centers for Disease Control; ICD, International Classification of Diseases; ME/CFS, myalgic encephalomyelitis/chronic fatigue syndrome; NICE, National Institutes for Health and Care Excellence; PACE, pacing, graded activity and cognitive behavior therapy: a randomized evaluation; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

**Key figure**

Graphical summary of acute infections and the subsequent post-acute sequelae



Trends In Immunology

Figure 3. Abbreviations: COVID, coronavirus disease; PANDAS, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections; PANS, pediatric acute-onset neuropsychiatric syndrome; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

proteins drive an immune-mediated response targeting multiple organ systems, resulting in carditis, arthritis, chorea, and cutaneous lesions [36]. Group A streptococcal infections have also been linked to pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS), characterized by abrupt onset of tics, obsessive-compulsive behaviors, anxiety, and other behavioral changes following strep throat [37]. As with other PAIS, no diagnostic biomarkers exist, complicating recognition and diagnosis [38].

### ME and the stigmatization of PAIS

Another longstanding and understudied PAIS is ME, a condition originally described by physician A.M. Ramsay in 1955 following an outbreak of unexplained illness in over 300 staff members of the Royal Free Hospital in London [39] (Figure 2). Although a causative infectious agent was never identified, the disease shared many features of poliomyelitis, including muscle weakness, severe fatigue, recurrent fevers, and neurological symptoms. While some patients fully recovered, others experienced regular relapses or remained seriously ill for decades. Similar epidemic outbreaks were reported internationally since the early 20th century, often centered around hospitals, and sporadic cases were later identified following common viral infections. Different names were given to these illnesses, including Icelandic disease, epidemic neuromyasthenia, and neurocirculatory asthenia [40–42]. Dr Ramsay and colleagues hypothesized that the symptoms may reflect mitochondrial damage and stressed that adequate rest was required for any kind of symptom improvement [42].

Although ME was classified as a neurological disorder by the World Health Organization in 1969 [43], the disease was quickly psychologized. Two 1970 papers published in the *British Medical Journal* attributed the outbreaks to epidemic hysteria, as it occurred primarily in female nurses and hysteria typically occurs in ‘populations of segregated females’ [41,42]. Another large outbreak occurred in the 1980s centered around Lake Tahoe, California. Although early reports suggested that patients may be experiencing a chronic or reactivated EBV infection, serological EBV titers lacked diagnostic specificity and did not correlate with symptom levels [44]. Nevertheless, another study of the same patient community found evidence of structural brain abnormalities, alterations in circulating lymphocytes, and much more frequent reactivation of human herpesvirus 6 [45]. Studies of sporadic, endemic cases of ME/CFS also found that standard serologic testing for EBV was not a useful diagnostic [44,46]. The disease was later renamed ‘chronic fatigue syndrome’ (CFS) and redefined by the Centers for Disease Control in 1988 to de-emphasize an infectious origin and focus on persistent, medically unexplained fatigue [47].

One prominent hypothesis proposed that CFS represented a maladaptive psychological response to an acute infection, in which those experiencing an illness develop a conditioned aversion to exercise that is maintained by deconditioning and ‘unhelpful illness beliefs’ [47]. A randomized clinical trial of graded exercise and cognitive behavioral therapy was reported to show a benefit [48], but the study methodology was heavily criticized by both patients and researchers [49,50]. The highly publicized study reinforced the notion that CFS was a psychogenic illness, contributing to the widespread belief among clinicians, researchers, and funding agencies that CFS was not a distinct clinical entity. An independent analysis using the study’s initial recovery thresholds later reported no significant differences in any outcome measure based on treatment group [51]. Other potential mechanisms investigated include mitochondrial dysfunction, gut microbiome dysbiosis, and autonomic dysfunction [52–55].

The field now generally refers to the condition as ME/CFS, and stricter diagnostic criteria were later proposed that focused on the cardinal symptom of post-exertional malaise (PEM, also known as post-exertional neuroimmune exhaustion) [56–58]. PEM is characterized by new and intensifying symptoms following minimal levels of physical or cognition exertion [57], including

flu-like symptoms such as fever and lymphadenopathy [59]. Emerging evidence shows that PEM involves an abnormal physiological response to exertion, with patients reporting that regular episodes of PEM can cause significant deterioration over time [60,61]. Accordingly, graded exercise therapy is now discouraged for ME/CFS by major health authorities (Figure 2). Although psychological factors may contribute, the historical psychologization of ME/CFS underscores the risks of attributing unexplained illness to purely psychological causes.

ME/CFS is now an established sequela of many pathogens, including Ebola virus, EBV, influenza, giardia, and SARS-CoV-2. A significant percentage of Long COVID patients experience PEM and meet ME/CFS criteria [56–59,62,63], with many reports of overlapping biological abnormalities between these two groups [64]. The condition is highly disabling, with one report finding that health-related quality of life was lower in ME/CFS compared with 20 major medical conditions, including lung cancer, renal failure, and multiple sclerosis [65]. The historic paucity of biomedical research funding means treatment options are generally limited to symptom management and the condition has a long-term recovery rate of less than 10% [66]. Despite evidence pointing toward a biological disease driver, patients still report high rates of misdiagnosis and invalidation from medical professionals [67,68].

### Concluding remarks

These examples illustrate that long-term sequelae following acute infections are not new, nor are they confined to novel pathogens. Across diverse microbial classes similar symptom clusters and immune patterns recur, highlighting that recovery from infection does not always restore baseline health. These historical and biological precedents provide critical context for understanding current challenges in post-acute sequelae of SARS-CoV-2 infection and offer valuable insights into plausible immunopathogenic pathways that merit further investigation. As PAIS global prevalence grows, increased recognition of infection-associated conditions will be crucial in both the laboratory and the clinic to address the many outstanding questions that remain in the field regarding underlying mechanisms, therapeutics, and prevention (see Outstanding questions). Investing in PAIS research is critical to understand underlying host factors that may predispose to long-term sequelae, improve treatment options for these devastating conditions, as well as provide a comprehensive understanding of human health and disease.

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### Declaration of interests

A.I. co-founded RIGImmune, Xanadu Bio, and PanV, and is a member of the Board of Directors of Roche Holding Ltd and Genentech. All other authors have no conflicts of interest.

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### Outstanding questions

How do diverse classes and species of pathogens trigger similar chronic illnesses? Do they act through shared pathways, or converge on similar states of dysfunction through distinct mechanisms?

Why do some patients develop PAIS while others fully recover from an infectious illness? What factors influence vulnerability to PAIS, and how?

What is the role of immune dysregulation in PAIS? While immune dysregulation has been well described in conditions like Long COVID, the root cause of this phenomenon remains unknown. Several factors likely influence immune dysregulation following an acute infection, including pathogen or antigen persistence, chronic systemic or localized inflammation, and direct infection of host tissues.

While myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is typically associated with an infectious trigger, it has also been described following other noninfectious pathologies such as concussion, brain injuries, and severe trauma (i.e., motor vehicle accident). Does immune dysregulation contribute similarly to infection-associated and non-infectious ME/CFS?

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