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Unexplained post-acute infection syndromes

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SARS-CoV-2 is not unique in its ability to cause post-acute sequelae; certain acute infections have long been associated with an unexplained chronic disability in a minority of patients. These post-acute infection syndromes (PAISs) represent a substantial healthcare burden, but there is a lack of understanding of the underlying mechanisms, representing a significant blind spot in the field of medicine. The relatively similar symptom profiles of individual PAISs, irrespective of the infectious agent, as well as the overlap of clinical features with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), suggest the potential involvement of a common etiopathogenesis. In this Review, we summarize what is known about unexplained PAISs, provide context for post-acute sequelae of SARS-CoV-2 infection (PASC), and delineate the need for basic biomedical research into the underlying mechanisms behind this group of enigmatic chronic illnesses.

Acute infectious diseases are commonly thought of as self-limiting events that lead to either resolution of symptoms or death. Although known for a long time[1], little attention has been paid to the chronic sequelae described in a proportion of exposed individuals following certain infections (Table 1). Despite the significant worldwide impact of such chronic illnesses, they often go undiagnosed owing to the nonspecific nature of symptoms and a lack of objective diagnostic findings. These 'tails' of acute infectious diseases, herein referred to as PAISs, are characterized by an unexplained failure to recover from the acute infection, although studies of objective markers have so far been mostly unrevealing, and the pathogen rarely remains detectable by commonly used methods.

The observation of unexplained chronic sequelae after SARS-CoV-2 — known as post-acute sequelae of SARS-CoV-2 infection (PASC), or 'long COVID' — in a subset of individuals has focused attention on this previously overlooked phenomenon, bringing an opportunity for accelerated progress in biomedical research into PAISs. The risk of chronic sequelae in patients who are hospitalized with COVID-19 is well recognized[2–4]; however, several large cohort studies have shown evidence of chronic symptoms even in SARS-CoV-2-exposed individuals with mild acute illness for up to 6 months or longer after symptom onset[5–13]. Data on chronic sequelae of COVID-19 are also continually being updated in the surveys run by the Office for National Statistics (ONS) in the United Kingdom[14], as well as in a quickly growing body of other epidemiological research. A thorough review of PASC is beyond the scope of this manuscript; however, Box 1 contains a brief overview, and existing detailed reviews have explored the epidemiological findings[15–20] and the potential etiology[21–23] of PASC.

It is remarkable that PASC, especially when it occurs after mild or moderate (rather than severe) COVID-19, shares many similarities with chronic illnesses triggered by other pathogenic organisms, many of which have not been sufficiently explained. These PAISs are characterized by a set of core symptoms centering on exertion intolerance, disproportionate levels of fatigue, neurocognitive and sensory impairment, flu-like symptoms, unrefreshing sleep, myalgia/arthralgia, and a plethora of nonspecific symptoms that are often present but variably pronounced. These similarities suggest a unifying pathophysiology that needs to be elucidated to properly understand and manage post-infectious chronic disability.

To address this need, we have explored the literature to identify overarching themes and concepts that constitute potential common denominators across individual PAISs. We exclude some better-explained syndromes that are known to occur post-infection, including Guillain–Barré syndrome, multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19 or the rare post-measles sequelae of delayed acute encephalitis, and subacute sclerosing panencephalitis (SSPE). Instead, we focus on the unexplained pool of infection-associated chronic disabilities that appear remarkably consistent in their presentation. In this Review, we summarize their common features and provide an overview of this unexplained phenomenon, along with resources for further interrogation of these disabling conditions.

Overview of PAISs

All manner of infectious agents, including bacteria, viruses, and parasites, has been implicated in PAIS pathogenesis. Unfortunately, the association between acute infectious diseases and unexplained chronic disability remains understudied, which leads to poor recognition of these conditions in clinical practice. As a result, patients might experience delayed or a complete lack of clinical care. As of now, the true extent of PAISs remains uncertain, as there is a significant risk that a lot of cases, especially under sporadic circumstances, remain unrecognized. The research that is available concentrates on PAISs in the context of either well-monitored acute infectious diseases, or as a follow-up of outbreaks and epidemics.

Among the more well-established PAISs is Q fever fatigue syndrome, which follows infection by the intracellular bacterium *Coxiella burnetii*[24]. This syndrome lingers in a minority of Q fever survivors for prolonged periods and is associated with substantial morbidity. Another PAIS with significant worldwide impact is post-dengue fatigue syndrome, which can follow infection by the mosquito-borne dengue virus[25]. With the publication of the Partnership for Research on Ebola Virus in Liberia III (PREVAIL III) study[26] in 2019, renewed interest has been sparked in the post-Ebola syndrome[27,28].

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Table 1 | Overview of unexplained PAISs associated with documented infections

Pathogen	Name of PAIS
Viral pathogens	
SARS-CoV-2	Post-acute sequelae of SARS-CoV-2 infection (PASC) Post-acute COVID-19 syndrome (PACS) Long COVID
Ebola	Post-Ebola syndrome (PES) Post-Ebola virus disease syndrome (PEVDS)
Dengue	Post-dengue fatigue syndrome (PDFS)
Polio	Post-polio syndrome (PPS)
SARS	Post-SARS syndrome (PSS)
Chikungunya	Post-chikungunya chronic inflammatory rheumatism (pCHIK-CIR) Post-chikungunya disease
EBV	No name
West Nile virus	No name
Ross River virus[a]	No name
Coxsackie B[a]	No name
H1N1/09 influenza[a,b]	No name
VZV[a,b]	No name
Non-viral pathogens	
Coxiella burnetii	Q fever fatigue syndrome (QFS)
Borrelia[c]	Post-treatment Lyme disease syndrome (PTLDS)
Giardia lamblia[a,d]	No name

[a]Limited or very limited evidence base. [b]Association with increased use of ME/CFS diagnosis in health registry. [c]Contradicting or unclear evidence base. [d]Supporting evidence derives from a single outbreak in Norway.

In the past 10 years, substantial evidence has been presented for a PAIS with fatiguing and rheumatic symptoms in a subset of individuals infected with chikungunya virus, a mosquito-borne virus that causes fever and joint pain in the acute phase[29,30]. Some evidence suggests the possibility of similar post-acute symptoms following infections with other arthritogenic alphaviruses, such as Ross River virus[31–34].

The importance of considering the emergence of post-acute sequelae, sometimes after a very long delay, following infectious diseases is highlighted by studies of post-polio syndrome[35]. This syndrome can emerge as many as 15–40 years after an initial poliomyelitis attack. It has been found that some other neurotropic microbes, such as West Nile virus, might lead to persistent effects similar to those reported in post-polio syndrome or other PAISs[36].

It is important to note that the occurrence of PAISs is not limited to serious or life-threatening infectious agents. Prolonged, debilitating, chronic symptoms have long been reported in a subset of patients after common and typically non-serious infections — for example after mononucleosis, a condition generally caused by Epstein–Barr virus (EBV)[31,37–41], and after an outbreak of *Giardia lamblia*, an intestinal parasite that usually causes acute intestinal illness. In fact, several studies identified the association of this outbreak of giardiasis with chronic fatigue[42], irritable bowel syndrome (IBS)[43], and fibromyalgia[44] persisting for many years.

Post-treatment Lyme disease syndrome (PTLDS) has long been a subject of debate[45,46], as views expressed in the literature regarding both the frequency and the validity of PTLDS are divided. Although substantial evidence[47–53] points to persistence of arthralgia, fatigue, and subjective neurocognitive impairments in a minority of patients with Lyme disease after the recommended antibiotic treatment, some of the early studies have failed to characterize the initial Lyme disease episode with sufficient rigor. Owing to these methodological shortcomings, prevalence estimates of PTLDS are uncertain and potentially inflated[54,55]; some studies even dispute the existence of PTLDS at all[56]. The most recent prospective studies that include well-characterized patient cohorts recruited in the early phases of Lyme disease offer more modest prevalence numbers[47,52].

Several epidemiological studies using health-registry data have looked for post-infection registration of a diagnosis of ME/CFS as a surrogate for chronic post-infection sequelae. One study found that infection with the pandemic H1N1/09 influenza A virus (but not receipt of vaccine) was associated with a more than twofold increase in ME/CFS diagnosis in a Norwegian health registry[57]. Similarly, another longitudinal registry study identified an association between varicella zoster virus (VZV) infection and an increased risk of an ME/CFS diagnosis[58], supporting the concept that the correlation between exposure to certain infections and development of chronic sequelae is indeed not uncommon.

Lastly, one published case series noted the development of ME/CFS in two women and one man after documented infection with Coxsackie B, an enterovirus[59]. However, the possibility of a connection between enteroviruses and PAISs is not new, as these viruses have long been implicated in early outbreaks of ME/CFS occurring in the 1930s to 1960s[60].

Symptoms and signs

Many PAISs have been called 'fatigue syndromes,' although this term is likely too reductionistic to encompass the complex clinical picture typically seen in such disorders. Although the clinical presentation of PAISs is heterogeneous, often including long and varied symptom lists, there is significant overlap, and several characteristic symptom clusters can be identified as a common denominator. The prime manifestations include an overall poor functional status, exertion intolerance, debilitating fatigue, and unrefreshing sleep. Other characteristic features include neurocognitive and sensory impairments, dysautonomia, musculoskeletal complaints, flu-like symptoms, and other feelings of illness. Irritability, mood swings, and signs of depression, as well as a wide range of other nonspecific neurological and immunological symptoms (Box 2), are frequently present.

Although the similarities are considerable, there appear to be differences in the relative frequencies of these symptom groups across the PAISs, seemingly mirroring the tropism of the triggering pathogen or underlying pathogenesis of the related acute disease. For example, individuals with Q fever fatigue syndrome or with complaints after infectious mononucleosis seem to emphasize post-exertional symptom exacerbations and interfering fatigue, whereas complaints of rheumatic symptoms[29] are more prominent in post-chikungunya sequelae, and of IBS[43] in post-giardiasis sequelae.

Moreover, there are trigger-specific symptoms and signs that might be superimposed on the systemic sequelae. For example, ocular symptoms and signs are well recognized in post-Ebola syndrome[61–63]. Chronic inflammatory conditions of the eye, with uveitis being the most common, can appear for prolonged periods in Ebola survivors and can lead to vision loss and other substantial complications. Motor disturbances and marked muscle weakness are characteristic of post-polio syndrome as well as post-West Nile virus syndrome. Another unique complex of symptoms comprises persistent anosmia and ageusia, features that can linger in individuals after SARS-CoV-2 exposure for many months and that appear to be relatively independent of the fatiguing or painful systemic illness. These findings suggest that, unlike the systemic sequelae, trigger-specific clinical features are correlated with the pathogen

Box 1 | Post-acute sequelae of SARS-CoV-2 infection

PASC, also called long COVID, is an umbrella term used to describe chronic outcomes of SARS-CoV-2 infection[192]. It has been postulated that the total morbidity resulting from PASC could be comparable to, or even greater than, the acute outcomes of the infection[193].

Individuals with PASC can be stratified into several subsets. Those recovering from severe COVID-19 may have lung or other organ damage as a result of pneumonia or acute respiratory distress syndrome, or they may have lingering symptoms consistent with post-ICU syndrome.[2] Prolonged or incomplete recovery has been described for this group of individuals, and seems to be more common among older adults, particularly men[194].

Another prominent subset of patients with PASC includes those who experience a syndrome characterized by unexplained exertion intolerance, debilitating fatigue, cognitive and sensory disturbances, headaches, myalgia, and recurrent flu-like symptoms. The core features of this syndrome share remarkable similarities with other PAISs discussed in this review, as well as with myalgic encephalomyelitis/chronic fatigue syndrome[195,196]. This syndrome is not linked to the severity of acute COVID-19 and frequently appears after mild or moderate initial illness, or even after asymptomatic infection — and has predominantly been identified in females[197].

Thoracic and respiratory-system symptoms of dyspnea, chest pain/tightness, and cough are present across the post-COVID-19 population. Other symptoms, such as anosmia and ageusia, are also reported at high rates, but seem to occur relatively independently of other persistent symptoms[198,199]. It has also been postulated that COVID-19 might unmask or trigger other disorders, such as Guillain–Barré syndrome[200], postural orthostatic tachycardia syndrome (POTS)[201], or even diabetes[202]. Post-COVID-19 clotting issues resulting in thrombotic events have also been recognized[203]. Moreover, mental health issues are being reported either primarily as a direct result of the pandemic or secondarily as a result of new health problems[204].

Clinical case definitions:

- World Health Organization[205]: Post-COVID-19 condition occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms and that last for at least 2 months and cannot be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, and cognitive dysfunction but also others and generally have an impact on everyday functioning. Symptoms may be new onset following initial recovery from an acute COVID-19 episode or persist from the initial illness. Symptoms may also fluctuate or relapse over time.
- US Centers for Disease Control and Prevention[206]: Post-COVID conditions are a wide range of new, returning, or ongoing health problems people can experience four or more weeks after first being infected with the virus that causes COVID-19. Even people who did not have COVID-19 symptoms in the days or weeks after they were infected can have post-COVID conditions. These conditions can present as different types and combinations of health problems for different lengths of time.
- UK National Institute for Health and Care Excellence[207]: (1) Ongoing symptomatic COVID-19 for people who still have symptoms between 4 and 12 weeks after the start of acute symptoms; and (2) post-COVID-19 syndrome for people who still have symptoms for more than 12 weeks after the start of acute symptoms. The guideline also makes recommendations for clinical investigations of patients presenting with new or ongoing symptoms 4 weeks or later after acute infection.

tropism and its mechanisms of pathogenesis, though we note that the specifics might be more evident for the more active areas of research for a given PAIS.

Myalgic encephalomyelitis/chronic fatigue syndrome

Another frequent consideration in PAISs is the diagnosis of ME/CFS. This disease is characterized by systemic exertion intolerance that manifests mainly as neurological and immunological symptoms and is accompanied by chronic fatigue that is not relieved by sleep or rest. Patients with this disorder experience worsening of symptoms following physical, cognitive, or emotional exertion above their tolerated limit. These episodes of symptom worsening are characterized by the terms 'post-exertional malaise' or 'post-exertional symptom exacerbation' and can last for several days, weeks, or months, and they can even be associated with irreversible decline. Other prominent features frequently observed in ME/CFS are neurocognitive impairments (colloquially referred to as 'brain fog'), unrefreshing sleep, pain, sensory disturbances, gastrointestinal issues, and various forms of dysautonomia. Several symptom-based case definitions of ME/CFS have been proposed. Currently, the most commonly used criteria include the 1994 Centers for Disease Control and Prevention criteria (the Fukuda criteria)[64], the Canadian Consensus Criteria[65], and the diagnostic criteria of the National Academy of Medicine[66].

Up to 75% of ME/CFS cases report an infection-like episode preceding the onset of their illness. However, other cases report triggers that are not apparently infectious or that appear to reflect a gradual build-up of symptoms. It has repeatedly been found that a proportion of people with PAISs triggered by various pathogens fulfill the diagnostic criteria for ME/CFS. Notably, the terms ME and CFS were both originally coined to describe post-epidemic occurrence of this disorder, emphasizing the conceptual overlap with PAISs.

The terms post-infectious fatigue syndrome and post-viral fatigue syndrome are sometimes used to describe debilitating fatigue following an infection, often accompanied by other signs and symptoms. Post-infectious and post-viral fatigue syndromes were originally postulated as subsets of 'chronic fatigue syndrome,' in which the triggering infectious agent is objectively documented[67]. However, there appears to be no clear consensus at present about the distinctions across these concepts. It is thus unclear whether these terms should be considered synonymous to the ME/CFS label, any of its subsets, or include a wider range of post-infectious fatigue conditions.

Prevalence and prognosis

Data on the prevalence and prognoses of unexplained PAISs remain limited, making their interpretation difficult. The fate of cases is often unclear owing to the shortage of prospective, well-powered studies with long-term follow-up examinations and objective measures, absence or inappropriateness of control groups, or small sample sizes. Few longitudinal studies have been undertaken in fully representative population-based cohorts, raising concerns about generalizability, adequacy of case ascertainment, and various biases, including those relating to retrospective recall. Differences in methods and in criteria used to characterize symptoms often complicate the comparison of clinical status and prevalence estimates across studies. Therefore, it is often difficult to draw definitive conclusions about the accuracy of prevalence estimates and long-term

prognosis. This represents a serious data gap in the foundational knowledge required to design clinical studies and assess the impact of interventions on the occurrence and management of chronic disease and disability after infectious exposures.

Despite the above limitations, reasonably consistent results have been reported for the prognosis of individuals experiencing post-acute symptoms in association with infectious mononucleosis (Fig. 1a). Available longitudinal studies of adolescents and young adults using the 1994 US Centers for Disease Control and Prevention (CDC) criteria for ME/CFS or its modification show that, from the initial 30–40% of cases with persisting symptoms for several weeks[68,69] after onset of illness, the prevalence drops to around 8–14% at 6 months[31,37,39,41,68,69] and 7–9% at 12 months[31,37]. However, in a study of 301 adolescents by Katz et al.[37], 4% of the participants were found to still be experiencing debilitating symptoms at 2-year follow-up and described themselves as unrecovered. This result suggests that ongoing disability might be present in a minority of patients for more than 2 years. Unfortunately, the longer-term prognosis of this minority cannot be determined owing to a lack of data.

Longitudinal estimates of post-West Nile virus symptoms are available from the 8-year observation of a cohort in Texas[70]. In this cohort, the frequency of persistent symptoms was dependent on the initial diagnosis (West Nile-related fever, meningitis or encephalitis). The typical decay of symptom prevalence was observed in the 2-year period directly after the infection. After that, a plateau was reached at which the prevalence of persistent symptoms remained constant in all 3 groups, ranging from 40% to 70% of participants. A different study of the same cohort found that, of the 31% of participants who reported post-infectious fatigue for at least 6 months after West Nile virus exposure, 64% met the 1994 CDC diagnostic criteria for ME/CFS at 5 years. Comparable prevalence of post-acute symptoms associated with West Nile virus infection compared with unexposed controls was also reported in other cohorts[36,71,72].

A similar drop in the prevalence of post-acute symptoms is observed in the first few months after COVID-19. Available estimates by the ONS show a marked decrease in PASC prevalence, measured either as the presence of at least 1 of 12 selected typical symptoms (Fig. 1b) or as self-reported 'long COVID' with or without activity limitation (Fig. 1c). Currently, the long-term prognosis and relationship of PASC with SARS-CoV-2 variants, immunization status, or breakthrough infections remain unknown.

An Australian primary-care surveillance study that monitored long-term outcomes after infection with EBV, *C. burnetii*, and Ross River virus in 253 prospectively selected participants found similar time-dependent decreases in the prevalence of persistent illness for all 3 types of infection: 35%, 27%, 12%, and 9% were unrecovered after 1.4, 3, 6, and 12 months, respectively (see Fig. 1a, light blue trace). When criteria for ME/CFS were applied at 6-month follow-up, 11% of study participants were found to conform to the definition[31].

Alarmingly, however, several case–control and cohort studies of Q fever fatigue syndrome with even longer follow-up periods found that disability associated with *C. burnetii* infection persisted for many years. Longitudinal observation of a cohort exposed to a Q fever outbreak in the United Kingdom, mostly consisting of adult men, found that, 5 years after the outbreak, typical features of Q fever fatigue syndrome, such as increased sweating, breathlessness, and blurred vision, as well as ME/CFS diagnoses, were more prevalent among the 71 exposed cases compared with 142 sex- and age-matched controls[73]. Ten years post-outbreak, fatigue-related features of Q fever fatigue syndrome were still present, and ME/CFS criteria were met by 19.4% of cases compared with 4.2% of controls[74]. In another analysis of the same cohort, wherein individuals with co-morbid conditions were excluded, the prevalence of ME/CFS was 8.2% in cases versus 0% in controls[75]. Association of a different Q fever outbreak with chronic symptoms was also reported in a smaller case–control study at the 6-year time point[76]. Moreover, in yet another Q fever outbreak involving a UK cohort of slaughterhouse workers, ME/CFS criteria were fulfilled by 28% of participants 5–14 years after Q fever but by none of the matched controls[77]. In contrast, a recent study from Germany found a significantly higher frequency of unrefreshing sleep, but not of other typical post-acute features, in cases relative to seronegative household contacts 6 years after Q fever, on the basis of assessments by the Short Form Symptom Inventory questionnaire[78]. This result suggests that assessment methods and the choice of appropriate questionnaire might play an important role in ascertaining infection-associated chronic disability.

Quality-of-life measures can provide insight into the impact of PAISs. In a cross-sectional survey analyzing quality of life associated with a well-characterized Q fever outbreak in the Netherlands, higher rates of disability and health-related work absence were

Box 2 | Symptoms and signs of post-acute infection syndromes

Main categories of symptoms and signs:

- Exertion intolerance, fatigue
- Flu-like and 'sickness behavior' symptoms: fever, feverishness, muscle pain, feeling sick, malaise, sweating, irritability
- Neurological/neurocognitive symptoms: brain fog, impaired concentration or memory, trouble finding words
- Rheumatologic symptoms: chronic or recurrent joint pain
- Trigger-specific symptoms: for example, eye problems post-Ebola, IBS post-*Giardia*, anosmia and ageusia post-COVID-19, motor disturbances post-polio and post-West Nile virus

Symptoms and signs found to be significantly elevated compared to healthy controls (symptoms are listed by the number of studies that found them to be significantly elevated compared to controls):

- Post-Ebola syndrome: fatigue[26,86,87,132], arthralgia[26,85–88,132], myalgia[26,85,86,88,132], ocular symptoms[86–88,132], headache[26,87,88,132], neurocognitive deficits[26,86], sleep problems[87,88], hearing loss[87], stiffness in joints[87], muscle weakness[87], difficulty swallowing[87], fever[88], urinary frequency[26], numbness/tingling[88], nonsensical vocal outbursts[88]
- Q fever fatigue syndrome: fatigue[31,73,77,79], arthralgia[31,77,79], myalgia[31,73,79], sweating episodes[73,77,79], blurring of vision[73,77,79], neurocognitive deficits[31,79], irritability[31,79], headache[31,79], fever[31], breathlessness on exertion[73], alcohol intolerance[77], lymph nodes[77], fasciculation[77], teeth or gums problems[79]
- Post-chikungunya: fatigue[30,89–92], arthralgia[30,89,92], myalgia[30,89–91], joint stiffness[30,92], joint swelling[92], neurocognitive deficits[91], sleep problems[30,91], hair loss[89], depression[30,89], irritability[30], hearing loss[91], blurred vision[91]
- Post-treatment Lyme disease syndrome: arthralgia[48–50,52,54], neurocognitive deficits[48–50,52,54], myalgia[50,52,54], fatigue[49,50,52], distal paresthesias[49], sleep problems[50], irritability[50]
- Post-acute sequelae of SARS-CoV-2 infection (based on studies meeting the following criteria: >50% non-hospitalized patients, >6-month follow-up, mean age >18 years) : changes in taste and smell[7,8,11–13], fatigue[7,8,11,12], dyspnea[7,8,11,12], neurocognitive deficits[7,8,11,12], memory issues[7,8,11], sleep issues[7,11,12], palpitations[7,11,12], tightness/pain[7,11,12], arthralgia[8,12], myalgia[7,8], chest cough[7,11], blurred vision[11,12], headache[7,12], dizziness[7,12], anxiety[7,12], loss of appetite[11], reduced lung function[7], wheezing[12], 'other symptoms'[13]

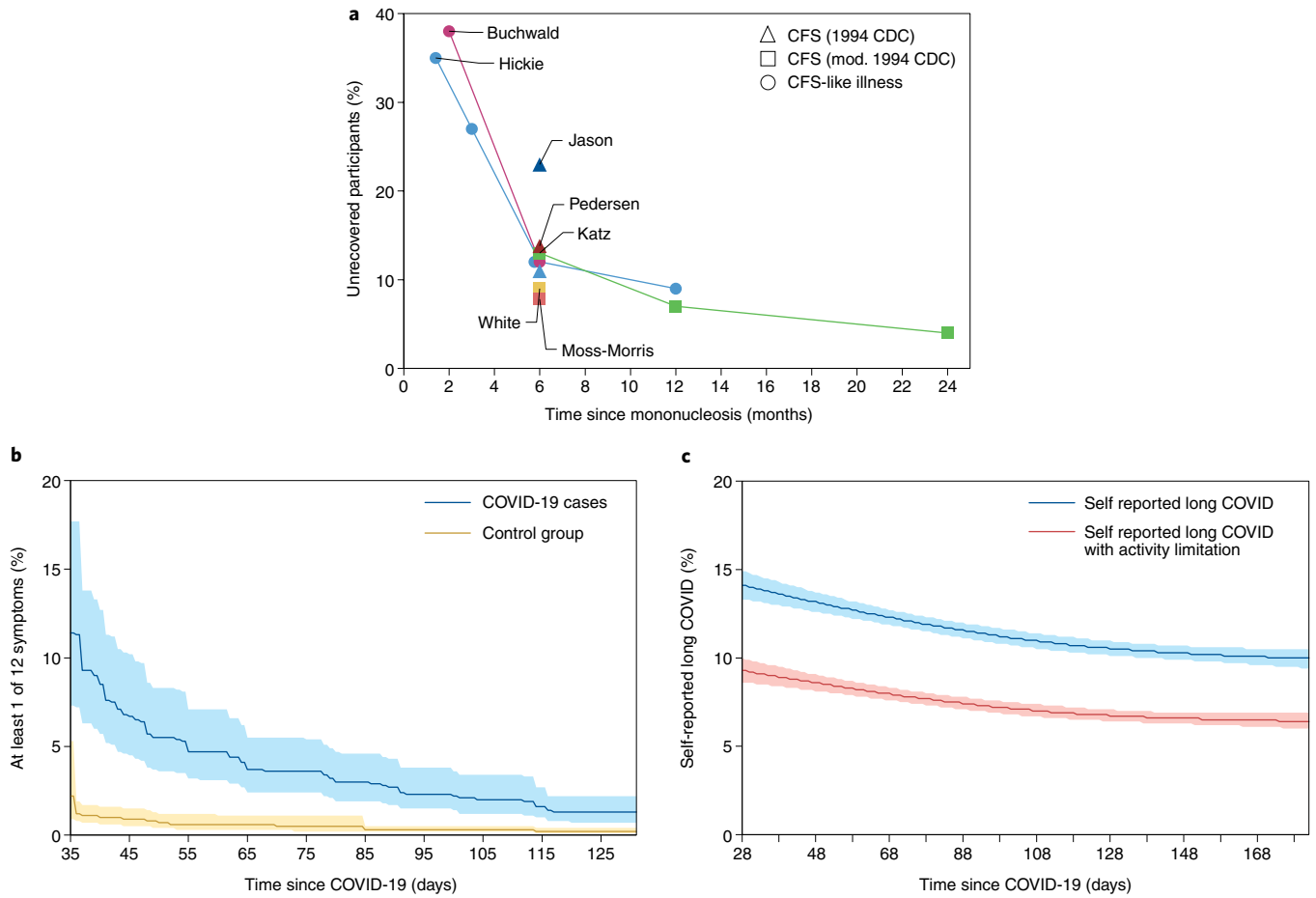

Fig. 1 | Prevalence and prognosis estimates of selected PAISs. a, Comparison of available estimates of persistent symptoms after infectious mononucleosis, based on the 1994 CDC criteria for CFS (Hickie et al.[31,38], Jason et al.[38], Pedersen et al.[39]), its modification (Katz et al.[37,41], White et al.[41], Moss-Morris et al.[68]), or self-reported CFS-like illness (Hickie et al.[31], Buchwald et al.[69]). **b**, Prevalence of at least 1 of 12 selected symptoms following COVID-19 (blue) compared with healthy unexposed controls (orange). **c**, Prevalence of self-reported 'long COVID' of any severity (blue) and with activity limitation (red). Plots in **b** and **c** are adapted from the estimate of Office for National Statistics (ONS)[192]. Lighter-colored bands around plotted lines show 95% confidence intervals. Plots in **b** and **c** contain public sector information licensed under the Open Government License v3.0.

reported at 10 years post-infection in 282 individuals with Q fever fatigue syndrome, compared with 52 patients with chronic Q fever and 144 survivors with less prominent post-acute sequelae[79]. Overall, these studies suggest that, similar to patterns of fatigue that follow infectious mononucleosis, there is a marked drop in the prevalence of post-acute complaints in the first several months or few years after Q fever; however, a significant level of disability continues for longer periods in a subset of patients.

Post-acute symptoms were also found to be present for several years in association with some other pathogens. For example, several studies investigated long-term outcomes of a well-characterized outbreak of water-borne *Giardia* in Norway. In a cohort of 576 exposed participants, the prevalence of post-infectious IBS following this outbreak stagnated at 40% at 6 years and 43% at 10 years follow-up, while the prevalence of chronic fatigue (according to the Chalder fatigue scale) decreased just slightly from 31% at 6 years to 26% at 10 years after infection. Unexposed healthy control participants ($n = 685$) reported significantly lower rates of both IBS and chronic fatigue (14% and 11% at 10 years, respectively)[43]. Among study participants reporting excessive levels of post-infectious chronic fatigue, 41.5% met diagnostic criteria for ME/CFS 5 years after the outbreak[80]. For context, the prevalence of IBS in the general population is reported to be around 11% (ref. [81]), and the prevalence of ME/CFS is usually reported to be under 1% (ref. [82]), although rates vary with diagnostic criteria and assessment method. It is important to note that these results are based on a single *Giardia* outbreak and therefore might not be generalizable.

Comparably, long-term data from studies of PTLDS show ongoing disability even after many years. A study that examined a cohort of 128 individuals after culture-confirmed Lyme disease reported that 4.7% had PTLDS at clinical examination 11–20 years after contracting erythema migrans (a typical circular rash occurring at the site of the tick bite)[83]. Remarkably, a case–control study of 61 cases and 26 controls found the symptoms of PTLDS to be associated with physician- or laboratory-confirmed Lyme disease for up to 27 years[50]. It was also reported that post-*Borrelia* symptoms mimicking fibromyalgia, such as musculoskeletal pain, tender points, dysesthesias, memory difficulties, and debilitating fatigue persisted in some individuals for at least 10 years[84]. Additionally, post-Ebola syndrome[26,85–88] or post-chikungunya sequelae[30,89–94] were found to be associated with the initial infection for periods ranging from many months to several years compared with the prevalence of those symptoms in a control group of healthy individuals. See Table 2 for further resources.

In relation to the current SARS-CoV-2 pandemic, it is interesting to note that the epidemic of SARS in 2002–2004 led to post-acute effects that might, owing to the similarity of the two viruses, provide clues into what post-acute effects can be expected after COVID-19, at least at the severe end of the disease spectrum. Among the most

Table 2 | Studies of post-acute infection syndromes after documented viral and non-viral infections

Viral pathogens		
Pathogen	Type of study	Reference
Ebola	Prospective cohort	**PREVAIL III**[26], **Tozay**[129], **Rowe**[85], Etard[130], Kibadi[131]
	Retrospective cohort	**Clark**[87], **Jagadesh**[86], Shantha[62]
	Case–control	**Steptoe**[63]
	Cross-sectional	**Bond**[88], Wilson[132], Mattia[133], Qureshi[134], Tiffany[135], Nanyonga[136]
	Case series	Howlett[137]
	Review	Rojas[27] (general), Carod-Artal[28] (general), Shantha[61] (ophthalmologic)
Dengue	Prospective cohort	**Halsey**[138], **Sigera**[139], Seet[140], Teixeira[141]
	Cross-sectional	**García**[142]
	Descriptive	Kularatne[143], Umakanth[144], Gonzáles[145]
	Review	Hung[25] (burden)
Chikungunya	Prospective cohort	**Duvignaud**[90], **Kularatne**[94], Chang[146], Couturier[147], Bouquillard[148], Moro[149], Manimunda[150], Schilte[151]
	Retrospective cohort	**Gérardin**[91], **Soumahoro**[89], **Marimoutou**[92], Javelle[152], Sissoko[153]
	Cross-sectional	**Ramachandran**[93], Rahim[154], Blettery[155]
	Review	Rodríguez-Morales[29] (prevalence), Paixão[30] (prevalence), Dupuis-Maguiraga[156] (pathogenesis)
EBV	Prospective cohort	**Petersen**[40], **Katz**[37], **Jason**[157], **Jason**[38], **Pedersen**[39], **White**[41], **Hickie**[31], **Katz**[158], Moss-Morris[68], Buchwald[69], Katz[159]
Polio	Retrospective cohort	Ragonese[160], Ramlow[161],
	Case–control	**Berlly**[162], **Nollet**[163], **Romigi**[164], **On**[165]
	Cross-sectional	Takemura[166], Marin[167]
	Review	Shing[35] (general)
West Nile	Prospective cohort	Nolan[168], Murray[70], Loeb[169], Yeung[170], Garcia[171]
	Retrospective cohort	**Balakrishnan**[71], Carson[172], Klee[173]
	Cross-sectional	**Sejvar**[72], Patnaik[174], Cook[175], Samaan[176]
	Descriptive	Sadek[177]
	Case series	Kuberski[178], Leis[179]
	Review	Patel[36] (general)
SARS	Prospective cohort	Tansey[180], Guo[181]
	Case–control	**Moldofsky**[97]
	Cross-sectional	Lam[96]
	Review	Rogers[95] (neuropsychiatric)
Ross River	Prospective cohort	**Hickie**[31], Mylonas[33], Harley[32]
	Retrospective cohort	Condon[34]
H1N1/09	Prospective cohort	**Magnus**[57]
	Case report	Vallings[182]
VZV	Prospective cohort	**Tsai**[58]
Coxsackie B	Case series	Chia[59]
Non-viral pathogens		
Pathogen	Type of study	Reference
Coxiella burnetii	Prospective cohort	**van Loenhout**[183], **Wildman**[74], **Ayres**[75], **Ankert**[78], **Hickie**[31], **Hatchette**[184]
	Case–control	**Ayres**[73], **Marmion**[77], **van Woerden**[76]
	Cross-sectional	Bronner[79]
	Case report	Leung-Shea[185]
	Review	Morroy[24] (general)
Borrelia	Prospective cohort	**Ursinus**[52], **Seltzer**[54], **Aucott**[47], **Cerar**[56], **Bechtold**[53], **Wormser**[55], Dinerman[84], Weitzner[83], Smith[186], Nowakowski[187], Aucott[188]
	Retrospective cohort	**Adrion**[189], **Shadick**[48], **Shadick**[49]
	Case–control	**Rebman**[50], **Fallon**[51]
	RCT	Klempner[190]
	Review	Rebman[45] (general), Mac[46] (general)
Giardia lamblia	Prospective cohort	**Litleskare**[43], **Hunskar**[44]
	Cross-sectional	Mørch[80]
	Descriptive	Naess[42], Stormorken[191]

Studies including a control group are in bold. Studies of pediatric cohorts (mean age < 18 years) are not included. Studies are listed according to the presence of control group and decreasing *n*.

prominent post-SARS sequelae were the typical systemic PAIS-like features of fatigue along with neuropsychiatric symptoms, such as sleep problems, irritability, depression, anxiety, and memory impairment. The prevalence of post-SARS sequelae was estimated by a recent meta-analysis[95] to be 10–20%, based on studies with a follow-up of 2 months to 12 years. The prevalence of post-SARS fatigue was 19.3% in the same meta-analysis, making it the most prevalent post-acute symptom. Systemic chronic symptoms similar to those reported in other PAISs were also noted. For example, a long-term study of 233 SARS survivors in Hong Kong reported that 27.1% met criteria for ME/CFS 4 years after acute infection[96]. Another smaller study of 21 healthcare workers in Canada who were unable to return to work 1–3 years after SARS infection owing to health complications concluded that the symptoms of these individuals overlapped with the symptoms of ME/CFS and fibromyalgia[97].

Pathogenesis of post-acute infection syndromes

PAISs are largely unexplained and understudied. Multiple mutually non-exclusive biomedical explanations for their pathogenesis can be hypothesized[21], which alone or in combination might be responsible for the development of PAISs. These leading hypotheses are outlined in Fig. 2.

First, it is possible that, even though conventional methods such as peripheral blood or nasopharyngeal swab sampling may fail to detect any ongoing presence of the pathogen, the original pathogen may nonetheless establish a persistent infection or leave non-infectious remnants in deep tissues (Fig. 2a). Such a persistent pathogen reservoir or remnants will generate pathogen-associated molecular patterns (PAMPs), such as viral RNA or bacterial cell wall, and these can engage various host pattern recognition receptors (PRRs) to trigger innate immune activation. Persistent pathogen or remnant antigens can also trigger T and B cells. If the effector functions of T cells and antibodies are insufficient to clear the pathogen, chronic stimulation of these lymphocytes can cause inflammatory conditions. For example, prolonged shedding of viral RNA is being reported in the semen of a subset of male Ebola survivors for up to 3 years after the infection. In several studies, this prolonged positivity in semen was noted to be associated with higher rates of chronic ocular symptoms and joint pain[26,98,99]. Moreover, symptoms of post-Ebola syndrome have been linked to Ebola-specific $CD8^+$ and $CD4^+$ T cell responses[100] as well as to lasting innate immune dysfunction[101] compared with survivors without symptoms. It was also found that, in a proportion of Ebola survivors, there is a periodic restimulation of Ebola-virus-specific antibody levels[102]. Recent reports[103,104] of new Ebola outbreaks being seeded by survivors of prior outbreaks after many years raise the possibility of a viable virus reservoir in immune-privileged sites, with reactivation capabilities. Thus, the role of a chronic inflammatory response to a persistent virus should be considered as a possible contributor to post-Ebola syndrome.

Similarly, it has been found that a subset of convalescents after West Nile virus infection, including those with chronic symptoms, had positive RT–PCR tests from urine 1.6 to 6.7 years after the acute illness, suggesting a persistence of viral RNA[105]. There is also emerging evidence of viral persistence in COVID-19. Analysis of endoscopy biopsies of 14 COVID-19 patients revealed that 5/14 patients had positive staining for SARS-CoV-2 antigen, and 3/14 tested positive by RT–PCR for viral RNA 3 months after the initial COVID-19 diagnosis[106]. In addition, SARS-CoV-2 nucleocapsid protein, as well as viral RNA, was found in the colon, appendix, ileum, hemorrhoids, liver, gallbladder, and lymph nodes of five patients who recovered from COVID-19, between 9 and 180 days after testing negative for SARS-CoV-2 by nasopharyngeal swab[107]. Of note, the viral remnants do not have to localize to the tissues putatively impacted by the PAIS for such effects to be observed. In a mouse model of mild respiratory-confined SARS-CoV-2 infection, inflammatory cytokines are elevated in the circulation as well as in the cerebrospinal fluid for at least 7 weeks, resulting in reactive microglia, oligodendrocyte loss, and demyelination[108]. Whether viral persistence and/or viral remnants trigger PASC is currently unknown.

Second, PAISs can be caused by autoimmune activation resulting either from the immune system trying to target the pathogen or from bystander autoimmune activation unrelated to pathogen structure (Fig. 2b). Autoimmune responses against self-antigens are known to occur after acute infections. This can happen because autoreactive T and B cells that are normally under suppression may temporarily become activated owing to impaired regulatory T cell function or to stimulation by high levels of cytokines in their milieu. Autoimmune lymphocytes can become activated if the pathogen-derived antigens mimic self-antigens, leading to so-called 'molecular mimicry.' This was postulated as a possible mechanism in several important autoimmune diseases such as Guillain–Barré syndrome, multiple sclerosis, type 1 diabetes, and systemic lupus erythematosus[109]. For example, new evidence indicates that the central nervous system (CNS) of patients with multiple sclerosis contains antibodies to a viral protein of EBV (known as EBV nuclear antigen 1 (EBNA1)) that cross-reacts with the CNS protein glial cell adhesion molecule (GlialCAM), and this molecular mimicry is enhanced by a post-translational modification of GlialCAM[110]. A longitudinal analysis of more than 10 million military personnel revealed a strong link between EBV and multiple sclerosis — with a 32-fold-higher risk after infection with EBV, but not other viruses[111]. Collectively, molecular mimicry may provide a mechanistic link between viral infection and autoimmune disease.

There is now abundant evidence for the development of autoantibodies in patients with COVID-19 during acute disease[112–120]. Whether such autoantibodies persist and cause long-term symptoms is being investigated. To this end, a study[121] that examined sera from 31 patients after recovery from RT–PCR confirmed acute disease — including 29 who were still experiencing post-COVID-19 symptoms and 2 who were symptom-free — found that all had autoantibodies against multiple different G-protein-coupled receptors (GPCRs). Autoantibodies to GPCRs have been shown to disturb the balance of neuronal and vascular processes. It is intriguing to note that PAISs are more common in women, and women are at a much higher risk of developing autoimmune diseases than men. Whether there are genetic and/or hormonal links between PAISs and autoimmunity remains to be determined.

A third possible mechanism of PAIS pathogenesis is dysregulation of the microbiome, virome, or mycobiome induced by the initial infection or immune responses generated thereafter (Fig. 2c). PAISs can be accompanied by reactivation of latent DNA viruses, including EBV, cytomegalovirus, and herpes simplex virus (HSV). A recent study found EBV viremia at the time of diagnosis to be one of the four risk factors for PASC development[122]. Reactivation can cause damage through multiple mechanisms, including ones mediated by the immune system. Memory $CD4^+$ T cells triggered by HSV-2 reactivation could induce transient opening of the blood–brain barrier[123]. An impaired blood–brain barrier might exacerbate the impact of inflammatory cytokines and leukocytes within the neural tissues. It has also been shown that translocation of certain pathobionts from gut to systemic tissues can drive autoimmunity in both mice and predisposed humans[124]. Long-term consequences of infection might also be a result of chronic epigenetically-mediated changes in the functional status of microglia[125].

PAISs may be caused by an inability to repair tissue damage imposed by the infection and subsequent immunopathologic effects (Fig. 2d). For instance, vascular damage and fibrosis in the lung that occur during acute respiratory infection, when not repaired properly, will lead to long-term respiratory dysfunction[126]. This may be particularly applicable for example in the chronic sequelae of severe cases of COVID-19 with considerable lung damage.

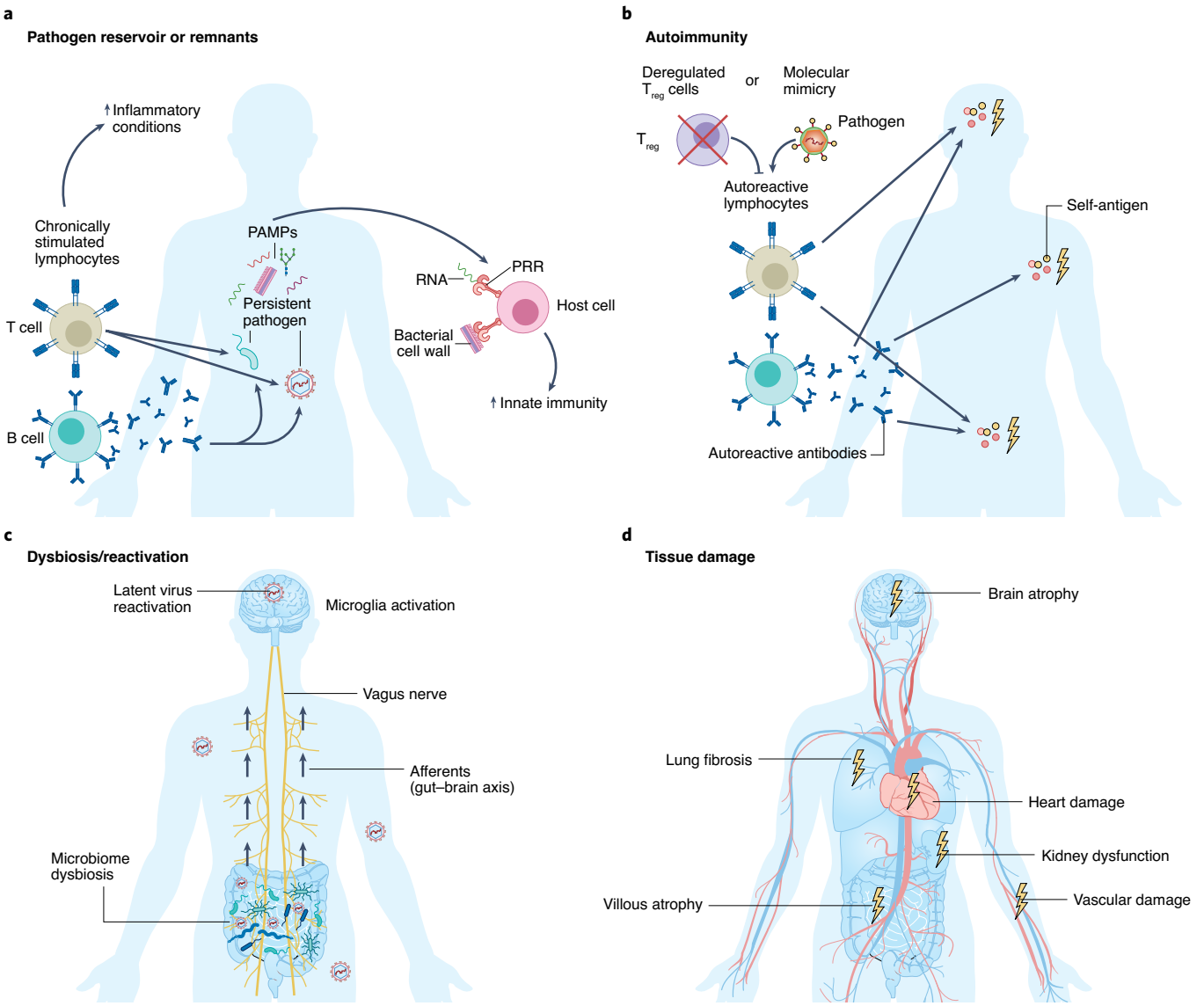

Fig. 2 | Commonly suggested biomedical hypotheses explaining PAISs. a, Possible pathogenic mechanisms might include chronic stimulation of the immune system as a result of persistent infection or persistent unviable pathogen structures. **b**, Alternative modes of immune activation might involve targeting self-antigens either due to infection-triggered impairment of regulatory T (T_{reg}) cell function, molecular mimicry, or other mechanisms. **c**, Chronic pathology might also result from dysregulation of the microbiota–gut–brain axis. **d**, Some features of PAISs could be explained by permanent organ damage. These processes are not mutually exclusive and could exist in combination or be pronounced with varied intensity in different PAIS subsets. Created with BioRender.com.

We note that the hypotheses discussed in Fig. 2 are likely not exhaustive and that pathways leading to the clinical and pathological findings in PAISs may also be overlapping and interdependent. Other mechanisms that are not outlined here might take place and contribute to etiopathogenesis of PAISs. For example, excessive microthrombi were recently reported in PASC[127] and might contribute to the development of this and possibly other PAISs by driving vascular inflammation, or by directly causing hypoperfusion in certain tissues. Nevertheless, the root cause of micro-clotting might still fall within one of the mechanisms considered above.

Predictors of post-acute symptoms remain largely unknown or insufficiently validated. One predicting factor that is consistently reported throughout the literature is female sex. Being a woman has repeatedly been found to be associated with a significantly higher reported prevalence of PAIS symptoms in all of the discussed syndromes. Although ascertainment bias must be excluded, it is interesting to note that this finding might provide clues for etiologic understanding, as women are generally more susceptible to immune-mediated conditions[128]. Severity of the initial infection is often reported to be predictive of higher risk of post-acute sequelae; however, PAISs are not at all limited to severe infections and frequently occur even after mild initial illness. Immunological abnormalities, such as levels of some circulating cytokines during or prior to the acute illness, have also been reported as predisposing factors, but these findings remain mostly unconfirmed.

Limitations and methodological obstacles

Epidemiologic research on PAISs faces several important methodological challenges. First, the lack of mechanistic understanding and of objective markers poses a major problem. At the moment, most research studies rely on self-reporting and subjective measures, which translates to greater risk of bias. In addition, diagnostic

criteria may vary across studies and could be a subject of controversy. Basic research into the underlying pathophysiologic processes and objective diagnostic markers is urgently needed and should be prioritized.

Second, the involvement of an appropriate control group is critical to ensure that the prevalence of symptoms in the post-infectious group is put into context with the background prevalence of symptoms in the general population or in relevant comparator groups. Selection of appropriate control groups, such as sedentary controls, may also be important in distinguishing the pathogenic mechanisms underlying PAISs from those that may be secondary to lifestyle adaptations, such as deconditioning (loss of stamina). These comparisons should include not only the presence of symptoms, but ideally also the intensity, course, and constellation of symptoms within an individual, as the individual symptoms and symptom trajectories of PAISs vary over time, rendering a mere comparison of symptom presence at a single time point misleading.

When a diagnosis of ME/CFS is made, attention should be given to the choice of diagnostic criteria. Some older studies of Q fever fatigue syndrome using the 1994 CDC criteria reported prevalence rates of ME/CFS in the control group to be 4.2% (ref. [74]) or even 26% (ref. [73]). These results are likely to be overestimated, as a recent meta-analysis[82] found a mean prevalence of ME/CFS in the general population, according to 1994 CDC criteria, to be 0.89% (95% confidence interval, 0.60–1.33). The use of more conservative ME/CFS diagnostic criteria, such as the Canadian Consensus Criteria[65] or the criteria of the National Academy of Medicine[66] and their cautious application should be encouraged.

Moreover, epidemiological studies of PAISs are often centered predominantly on the symptom of fatigue. Given the widespread occurrence of fatigue in the general population as well as in other illnesses, this can provide an overly reductionistic view and can be misleading. Studies should include features such as post-exertional symptom exacerbation and other characteristic symptoms and signs to better capture the complex clinical picture seen in PAISs.

Conclusion

Unexplained post-acute infection syndromes (PAISs) appear to be an under-recognized feature of a spectrum of infectious diseases in a minority of patients. At present, our understanding of the underlying pathophysiologic mechanisms and etiologic factors is poor and there are no known objective markers or effective therapeutic options. More basic biomedical research is needed. The overlap of symptoms, signs, and general features of the individual PAISs suggests the involvement of shared pathological pathways and the possibility that common diagnostic markers, or even a unified etiological model, might be established.

However, some symptoms or clinical characteristics seem to be trigger-specific or more prevalent in one PAIS than in others, emphasizing the need for cohorts with a well-documented infectious trigger. The overall clinical picture of many PAISs often overlaps with the presentation of post-infectious ME/CFS or fibromyalgia, or resembles other fatiguing, neurological, or rheumatic disorders. Exploiting existing knowledge of these conditions might help guide future scientific discovery and progress in clinical care.

The SARS-CoV-2 pandemic uncovered a significant gap in knowledge about post-acute sequelae of infectious diseases and identified the need for better diagnostic care and clinical infrastructure for patients experiencing these long-term effects. In addition to basic biomedical research, more needs to be done to refine diagnostic criteria and obtain more reliable estimates of the prevalence and societal burden of these disorders to help shape health-policy decisions. Moreover, we call for unified nomenclature and better conceptualization of post-acute infection symptoms.

There is much to be done, but the unprecedented amount of attention and resources that have recently been allocated to the study of COVID-19-related pathology brings a promise of much-needed progress in the wider field of unexplained infection-associated chronic disability.

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Author contributions

J. C. performed the literature search. J. C. and V. J. evaluated and cross-checked epidemiological parameters of the included studies. J. C. and A. I. wrote the initial draft of the manuscript and conceived the figures and tables. J. C., V. J., M. H., and A. I. edited and improved the manuscript.

Competing interests

J. C. receives financial support from Gilead Sciences & IOCB Research Centre and is involved in running Czech Association of patients with ME/CFS — a volunteer non-profit initiative supporting patients with ME/CFS (no funds involved). V. J. declares no competing interests. M. H. serves on the scientific advisory boards of PaxMedica and Simmaron Research. A. I. consults for 4BIO Capital, BlueWillow Biologics, Healthspan Technologies, Revelar Biotherapeutics, RIGImmune, and Xanadu Bio.

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