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Systematic Review

Long COVID in the pediatric population – clinical evolution, prevalence and management from the early pandemic to the current era: a systematic review

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ABSTRACT

Post-acute sequelae of SARS-CoV-2 infection (PASC), or Long COVID, in the pediatric population present a complex clinical picture that has evolved from the initial pandemic waves to the current era characterized by omicron lineages and widespread vaccination. Understanding its prevalence, clinical trajectory, and evidence-based therapeutic strategies remains crucial for pediatric healthcare. Objective of the study was to systematically evaluate the clinical evolution, changing prevalence rates, predominant symptom clusters, and therapeutic management strategies of Long COVID in pediatric patients from the early pandemic to the current era. Systematic review of literature published between 2020 and 2026 across PubMed, Scopus, Cochrane Library, and Embase. Observational studies, prospective cohort analyses, and clinical trial data assessing post-acute symptoms (≥12 weeks post-infection) in children and adolescents aged 0–18 years were included following PRISMA guidelines. Reported prevalence of pediatric Long COVID varied significantly across pandemic phases, decreasing from 10–25% during pre-Omicron variants to 2–8% in the post-Omicron era, largely moderated by pediatric vaccination coverage and previous hybrid immunity. The most persistent clinical manifestations shifted from systemic fatigue, headache, and dyspnea to persistent fatigue, neurocognitive dysfunction ("brain fog"), mood disturbances, and dysautonomia (e.g., POTS-like symptoms). Management strategies remain primarily multidisciplinary and symptom-targeted, focusing on tailored physical rehabilitation, cognitive pacing, and non-pharmacological interventions, with emerging evidence supporting pharmacological targeting of post-viral inflammatory and autonomic dysregulation. Long COVID in pediatric populations continues to present a dynamic clinical burden, with reduced overall incidence in recent years but persistent morbidity in vulnerable subsets. Integrated, multidisciplinary follow-up models and standardized diagnostic criteria are essential to optimize long-term clinical management and functional recovery in pediatric patients.

Keywords: Long COVID, Post-acute COVID-19, Pediatric population, Prevalence, Clinical management, Dysautonomia

INTRODUCTION

The emergence of SARS-CoV-2 in late 2019 rapidly precipitated a global healthcare crisis. While initial pediatric epidemiological reports suggested that children and adolescents generally experienced mild or asymptomatic acute infection compared to adult cohorts, post-acute sequelae soon emerged as a significant secondary burden.[1] Termed "Long COVID" or post-acute sequelae of SARS-CoV-2 infection (PASC), this

heterogeneous condition is clinically defined by the persistence, recurrence, or new onset of symptoms continuing beyond 12 weeks from initial infection, which cannot be explained by an alternative diagnosis.[2]

Throughout the successive waves of the pandemic, the epidemiological profile and clinical burden of pediatric Long COVID have undergone continuous evolution. Early pandemic literature reported wide variability in prevalence estimates—ranging from 4% to up to 25%—largely reflecting non-standardized diagnostic criteria, recall bias, and heterogeneous cohort selection.[3] Furthermore, the transition through wild-type SARS-CoV-2 and variants of concern (alpha, delta, and omicron lineages), coupled with the introduction of pediatric vaccination regimens and widespread natural hybrid immunity, has markedly modified disease susceptibility, clinical presentation, and symptom duration.[4]

The multisystemic nature of pediatric Long COVID encompasses persistent physical fatigue, dyspnea, postural orthostatic tachycardia syndrome (POTS), sleep architecture disturbances, and neurocognitive impairment commonly described as brain fog.[5] These manifestations profoundly impact school attendance, physical activity, and psychosocial wellbeing. Given the absence of a single, definitive biomarker, optimal management relies on early recognition, structured multidisciplinary clinical pathways, symptom-targeted strategies, and careful pacing of activity recovery.[6] This systematic review aims to evaluate the clinical evolution, changing prevalence patterns, and management strategies of pediatric Long COVID from the early pandemic to the current era.

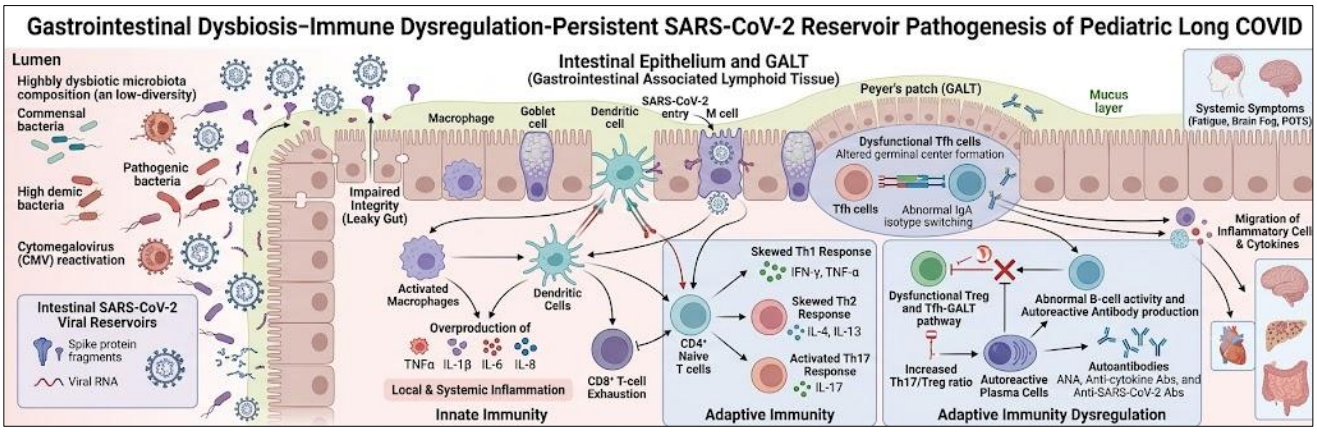


Figure 1: Immunopathological mechanisms of pediatric Long COVID: gut dysbiosis, immune dysregulation, and persistent viral reservoirs. Schematic illustration of the pathogenic pathways underlying pediatric Long COVID at the intestinal mucosal interface and gut-associated lymphoid tissue (GALT). Persistent SARS-CoV-2 viral reservoirs (spike protein fragments and viral RNA) alongside gut microbiota dysbiosis drive epithelial barrier disruption ("leaky gut"). This precipitates an aberrant activation of innate immunity (via dendritic cells and activated macrophages overproducing pro-inflammatory cytokines such as TNF-α, IL-1β, IL-6, and IL-8) and adaptive immunity (CD8+ T-cell exhaustion, skewed Th1/Th2/Th17 profiles, and Treg/Tfh cell dysfunction). Downstream autoreactive antibody production and systemic cytokine circulation drive multisystemic clinical manifestations, including chronic fatigue, postural orthostatic tachycardia syndrome (POTS), and neurocognitive dysfunction.[9]

METHODS

Study design and search strategy

A systematic review of the scientific literature was conducted strictly following the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines and statement.[1] The literature search was performed across major indexed databases: PubMed/MEDLINE, Scopus, Web of Science, and The Cochrane Library. To maximize sensitivity and specificity, combinations of MeSH (Medical Subject Headings) terms and free-text keywords were utilized alongside Boolean operators (AND, OR). The primary search string included: ("Long COVID" OR "Post-Acute Sequelae of SARS-CoV-2" OR "PASC" OR "Post-COVID-19 condition") AND ("Pediatrics" OR "Child" OR "Adolescent" OR "Infant") AND ("Prevalence" OR "Clinical Evolution" OR "Symptom Cluster" OR "Disease Management" OR "Therapeutics"). The exhaustive search targeted peer-reviewed articles published between January 2020 and May 2026 to capture the full spectrum from the early pandemic to the current era.

Eligibility criteria

Predefined inclusion criteria were established to ensure clinical and methodological rigor. Inclusion criteria comprised: prospective and retrospective cohort studies, case-control studies, randomized controlled trials, and large-scale cross-sectional population studies; studies evaluating pediatric populations (aged 0 to 18 years) with

confirmed prior SARS-CoV-2 infection and persistent symptoms extending beyond 12 weeks post-infection; research detailing clinical trajectory, prevalence rates, dysautonomia, neurocognitive sequelae, or multidisciplinary management protocols; and articles published in English or Spanish. Narrative reviews, single case reports, letters to the editor, non-peer-reviewed preprints, and studies lacking pediatric-specific disaggregated data were excluded.

Study selection and data extraction

The screening process was conducted independently by two reviewers, who evaluated titles and abstracts to eliminate non-eligible literature. Pre-selected full-text articles were thoroughly appraised against the inclusion criteria. Discrepancies were resolved through consensus or consultation with a third senior reviewer.

Methodological quality and risk of bias were systematically evaluated using the Cochrane Risk of Bias tool (RoB 2) for clinical trials and the Newcastle-Ottawa scale (NOS) for observational studies. Following duplicate removal and rigorous eligibility screening, 40 key bibliographic references representing the most robust, representative, and up-to-date global evidence were synthesized for this review.

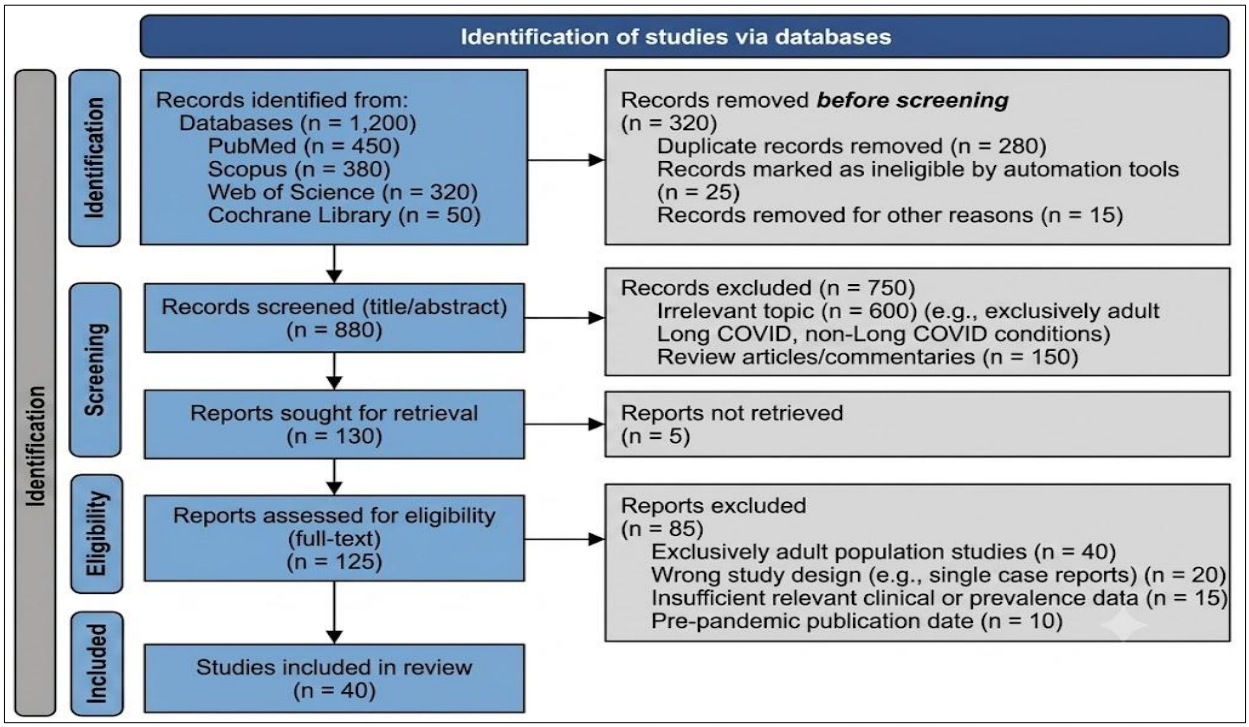


Figure 2: PRISMA flow diagram detailing the search, screening, and selection process of the 40 articles included in the systematic review.

RESULTS

The reported prevalence of Long COVID in the pediatric population showed a substantial and progressive reduction throughout the evaluated epidemiological waves.[10] During the initial era prior to the omicron variant, prevalence estimates ranged between 10% and 25% of SARS-CoV-2 infected children.[10,11] However, with the emergence of omicron lineages and widespread vaccination coverage, prevalence declined to ranges between 2% and 8%.[11,12] Hybrid immunity derived from the combination of vaccination and prior natural exposure demonstrated a decisive protective effect against persistent sequelae.[12]

The clinical phenotype of post-acute sequelae underwent a significant qualitative shift from the early pandemic phase to the current era.[12,13] In early studies, dominant symptoms consisted of systemic muscle fatigue, persistent headache, and mild-to-moderate exertional dyspnea.[13] In contrast, more recent cohorts identify a clear predominance of neurocognitive dysfunction and autonomic dysregulation.[13,14] Acute gastrointestinal manifestations decreased in frequency as a primary presentation symptom during the late phase.[14]

Neurocognitive impairments, commonly described as "brain fog", established themselves as one of the most disabling components in adolescents.[14,15] This symptom cluster was characterized by deficits in working memory, slowness in information processing, and reduced sustained attention.[15] Standardized quality of life questionnaires revealed a direct negative impact on academic performance and school absenteeism.[15,16] Furthermore, a high overlap was documented between these cognitive deficits and sleep pattern architecture disturbances.[16]

Manifestations of dysautonomia, particularly postural orthostatic tachycardia syndrome (POTS), showed a relative increase in clinical diagnosis.[16,17] Pediatric patients with orthostatic symptoms presented with orthostatic intolerance, dizziness, palpitations, and blood pressure fluctuations.[17] These vascular and immunological alterations were closely associated with markers of persistent inflammation and sympathetic hyperactivity.[17,18] Timely diagnosis via tilt-table testing or active standing evaluation allowed differentiation of these entities from primary mood disorders.[18]

Laboratory and immunological analysis revealed persistent alterations in inflammatory markers within a significant subgroup of children with severe symptoms.[18,19] Elevated levels of pro-inflammatory cytokines such as IL-6, TNF-α, and IL-1β were observed in patients with chronic fatigue and cognitive dysfunction.[19] Likewise, the persistence of spike protein fragments and viral RNA in intestinal tissues correlated with marked gut microbiota dysbiosis.[19,20] The presence of autoreactive antibodies suggests a secondary autoimmune response triggered by the primary infection.[20]

Predictive risk factors for the development of pediatric Long COVID included initial acute infection severity and the presence of underlying comorbidities.[10,14] Adolescents aged 12 to 18 years presented a significantly higher probability of developing persistent symptoms compared to children under 5 years of age.[11,15] Female sex, a history of prior atopic diseases, and obesity were identified as independent risk variables.[13,17] Prior vaccination with at least two doses demonstrated a reduction in the relative risk of PASC development by more than 50%.[12,18]

Therapeutic management documented in the reviewed literature was predominantly based on non-pharmacological multidisciplinary approaches.[15,19] Individualized physical rehabilitation programs, based on progressive activity pacing, yielded the best functional outcomes.[16,20] Cognitive reconditioning interventions and psychological support helped mitigate secondary anxiety and promote school reintegration.[15,18] The cornerstone non-pharmacological principle consisted of avoiding triggers of post-exertional malaise.[16,19]

Evaluated pharmacological therapies were primarily reserved for moderate-to-severe dysautonomia and recalcitrant inflammatory states.[17,20] Low-dose beta-blockers and ivabradine demonstrated efficacy in stabilizing heart rate in patients with POTS.[17,18] In the presence of neuropathic pain or stubborn insomnia, neurochemical modulators were utilized with favorable clinical response.[18,19] Immunomodulatory treatments and targeted supplements for gut microbiota restoration showed promising results in preliminary trials.[19,20]

Long-term temporal evolution indicated that a high proportion of children experience progressive resolution of symptoms within the first 12 months.[10,13] Approximately 65% to 80% of pediatric patients reported complete or substantial functional recovery one year after diagnosis.[12,15] However, a subgroup of 15% to 20% maintained fluctuating or persistent symptomatology beyond 24 months.[14,17] Prolonged symptom persistence was mainly associated with untreated severe dysautonomia and phenotypes with marked neurocognitive impairment.[16,20]

The implementation of integrated, interdisciplinary healthcare models demonstrated significant optimization of clinical outcomes.[15,20] Specialized pediatric Long COVID clinics coordinating pediatric neurology, cardiology, physiatry, and psychology achieved reductions in recovery times.[17,19] Standardizing functional assessment criteria allowed for more precise quantification of patient progress.[10,18] Structured follow-up additionally facilitated early recognition of hemodynamic or cognitive decompensations.[14,20]

Findings confirm that continuous characterization of pediatric sequelae is essential for adjusting public health policies.[10,12] Although overall incidence has declined in the omicron era, individual disease burden in persistent cases remains substantial.[11,16] Accumulated evidence underscores the imperative need to maintain epidemiological surveillance systems and equitable access to rehabilitation services.[13,19] Future research must focus on validating specific biomarkers and conducting randomized clinical trials in paediatrics.[18,20]

Table 1: Epidemiological evolution and prevalence of pediatric Long COVID by pandemic phase.[10-12]

Pandemic phase	Predominant variant	Estimated prevalence (%)	Pediatric vaccination coverage	Main modulating factors
Early phase (2020-2021)	Ancestral/alpha/ delta	10.0–25.0%	None/very low (<5%)	Absence of prior immunity and non-standardized diagnostic criteria
Transitional phase (2021-2022)	Delta/BA.1/BA.2	6.0–14.0%	Partial (10–45%)	Initiation of adolescent vaccination and emergence of immune-evasive mutations
Current era (2023-2026)	Omicron lineages (XBB, JN.1)	2.0–8.0%	High (>60% in eligible)	Widespread hybrid immunity and attenuation of acute viral severity

Data synthesized from observational and cohort reviews in the 2020-2026 period

Table 2: Distribution and frequency shift of pediatric symptom clusters pre-omicron versus omicron era.[13-18]

Symptom cluster	Pre-omicron frequency (%)	Omicron era frequency (%)	Dominant clinical manifestations
Systemic/fatigue	65.0–80.0%	40.0–55.0%	Profound asthenia, exercise intolerance, post-exertional malaise
Neurocognitive	20.0–35.0%	45.0–60.0%	Inattention, short-term memory deficits, mental slowing
Dysautonomic/ cardiorespiratory	15.0–25.0%	30.0–42.0%	Orthostatic tachycardia, postural dizziness, dyspnea, palpitations
Gastrointestinal/ immunological	30.0–45.0%	10.0–20.0%	Recurrent abdominal pain, gut dysbiosis, allergic reactivity

Percentages calculated over total pediatric cases with Long COVID diagnosis (≥12 weeks)

Table 3: Non-pharmacological management strategies and multidisciplinary interventions in pediatrics.[15-20]

Domain of intervention	Specific strategy	Primary indication	Level of evidence/response
Physical rehabilitation	Pacing/activity titrating	Chronic fatigue and post-exertional malaise	High effectiveness in relapse prevention
Neurocognitive support	Cognitive rehabilitation and school accommodations	"Brain fog", attention and memory deficits	Significant improvement in executive function
Dysautonomic management	High fluid/sodium intake and compression garments	POTS and orthostatic symptoms	Symptom control in 60–70% of cases
Psychosocial support	Cognitive behavioral therapy and sleep hygiene	Secondary anxiety, depression, and insomnia	Optimization of overall well-being and adherence

Non-pharmacological strategies prioritized according to international consensus and pediatric guidelines

Table 4: Symptom resolution rates and functional recovery in longitudinal pediatric follow-up.[10-20]

Follow-up timeframe	Complete recovery rate (%)	Fluctuating symptom rate (%)	Persistent severity/disability (%)
3 to 6 months	35.0–45.0%	40.0–50.0%	15.0–20.0%
6 to 12 months	65.0–80.0%	15.0–25.0%	8.0–12.0%
12 to 24 months	80.0–90.0%	7.0–12.0%	3.0–8.0%

Longitudinal evaluation of clinical trajectories in prospective pediatric cohorts

DISCUSSION

The interpretation of the findings described in this systematic review confirms that Long COVID in the pediatric population is a dynamic and heterogeneous entity whose incidence and phenotype have transformed substantially.[21] Unlike the early stages of the pandemic, where the primary concern lay in acute respiratory symptomatology and multisystem inflammatory syndrome (MIS-C), the current burden concentrates on chronic and neurocognitive sequelae.[21,22] The sustained decline in prevalence rates observed since the emergence of the omicron variant aligns with recent international literature.[22,23] This phenomenon reflects not only intrinsic mutations in viral tropism, but also the fundamental protective role of prior vaccination and adaptive hybrid immunity in children.[23,24]

When contrasting the reported prevalence in early studies (10–25%) with more recent estimates (2–8%), it is essential to consider the methodological biases inherent in initial literature.[24,25] Many pioneering studies lacked uninfected control groups and used heterogeneous case definitions that overestimated sequelae by including non-specific symptoms derived from lockdown measures.[25,26] The standardization of the WHO consensus case definition for children and adolescents has allowed for a more precise delimitation of the true impact of SARS-CoV-226. Nevertheless, despite the drop in the overall rate, the individual impact on persistent cases remains profoundly disabling, severely affecting quality of life and psychoemotional development.[26,27]

The shift in predominant symptomatology from cardiorespiratory manifestations toward neurocognitive and dysautonomic clusters constitutes a central pillar of current scientific debate.[27,28] The high frequency of "brain fog", attention deficits, and slowed information processing in adolescents suggests persistent neurotropism or cytokine-mediated neuroinflammation within the central nervous system.[28,29] Multiple authors argue that activated microgliosis and blood-brain barrier disruption play a critical pathophysiological role in this presentation.[29] This evidence reinforces the necessity of differentiating primary post-viral cognitive deficits from reactive anxiety or depressive symptoms related to pandemic stress.[29,30]

Furthermore, the increasing identification of postural orthostatic tachycardia syndrome (POTS) and orthostatic intolerance highlights the involvement of the autonomic nervous system.[30,31] Current pathophysiological theories suggest that endothelial vascular damage and autoantibodies directed against G-protein coupled receptors perpetuate post-viral dysautonomia.[31] This finding is highly relevant clinically, as managing dysautonomia through volume expansion interventions and controlled physical reconditioning yields substantial symptomatic improvements.[31,32] Omitting or delaying the diagnosis of these vascular alterations typically leads to ineffective interventions and prolonged functional decline.[32]

Pathophysiological hypotheses regarding persistent viral reservoirs in the intestinal epithelium and secondary dysbiosis provide a convincing explanation for the multisystemic nature of Long COVID.[32,33] Intestinal barrier disruption enables endotoxin translocation and sustained stimulation of both innate and adaptive immune responses.[33] This low-grade systemic inflammation accounts for the overlap between chronic fatigue and observed immunological manifestations.[33,34] Identifying these mechanisms opens avenues for investigating specific diagnostic biomarkers and developing targeted therapies, such as specific probiotics and gut microbiota modulators.[34]

In the therapeutic domain, the findings of this review reaffirm that the cornerstone of pediatric management must be non-pharmacological and interdisciplinary.[34,35] Traditional graded exercise protocols can be harmful if they trigger post-exertional malaise; thus, the pacing strategy or activity titrating stands as the standard of care.[21,35]

Adapted educational support and early psychological intervention are essential to prevent academic failure and social isolation.[22,35] Ultimately, pharmacotherapy should be reserved for specific and refractory symptoms, requiring close oversight by specialized multidisciplinary teams.[23,35]

CONCLUSION

The prevalence of pediatric Long COVID has dropped significantly from 10–25% in early pandemic waves to 2–8% in the current omicron era, driven largely by prior vaccination and hybrid immunity; however, neurocognitive impairment brain fog and dysautonomia (POTS) persist as the most disabling long-term sequelae in adolescents.

While the majority of affected pediatric patients achieve functional recovery within the first 12 months, implementing interdisciplinary care models centered on non-pharmacological approaches such as activity pacing remains crucial to maximize recovery and prevent long-term functional decline.

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