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A narrative review and perspectives of PANDAS/PANS in the COVID-19 age: Impact of the infection and vaccination

Abstract

Background/Objectives: The COVID-19 pandemic has significantly affected mental health worldwide. In children and adolescents with neuropsychiatric conditions, especially those with Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS) and its subtype Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS), factors such as infection, social isolation and disrupted routines, might exacerbate symptoms. This narrative review examines the impact of the COVID-19 pandemic, including the role of infection, social restrictions, and vaccination, on the clinical course of PANS/PANDAS, highlighting potential underlying immunological mechanisms.

Methods: A comprehensive literature search was conducted across seven databases (PubMed, PsycINFO, PsycARTICLES, Scopus, MEDLINE, Web of Science and Google Scholar), covering publications from January 2020 to May 2025. The review included peer-reviewed empirical studies involving children or adolescents with PANS/PANDAS, while reviews, purely qualitative studies and studies on general population were excluded. Fourteen empirical studies that met the inclusion criteria were analyzed to understand the effects of the COVID-19 pandemic on symptom severity and disease course in PANS/PANDAS.

Results: The majority of reviewed studies indicate that SARS-CoV-2 infection can trigger new onset or exacerbate pre-existing PANS/PANDAS symptoms, with more frequent flare-ups reported post-infection than post-vaccination. Additional stressors such as lockdowns and reduced access to care also contributed to worsening symptoms. Preliminary evidence suggests that neuroinflammation, immune dysregulation, and possible Epstein–Barr virus reactivation may mediate these effects.

Limitation: Findings should be interpreted with caution, as most available studies are cross-sectional, rely heavily on caregiver's surveys and lack control groups, thereby limiting causal inference. More longitudinal and biomarker-based research is essential to guide targeted interventions and improve long-term outcomes.

Conclusion: The pandemic has imposed a substantial burden on PANS/PANDAS patients. Early identification of at-risk children and adolescents, integration of hybrid care models, and a neuroimmune-informed clinical approach are critical for mitigating adverse consequences. While vaccination was a concern for some families, current data do not show significant post-vaccine adverse effects in the population which was allowed to receive the vaccination (75%).

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Keywords: PANDAS; PANS; COVID-19; Neuroinflammation; Immunology.

Introduction

Several studies have shown that children and adolescents experienced a significant worsening of Obsessive-Compulsive Disorder (OCD) symptoms during the COVID-19 pandemic [1-3] with contamination obsessions and compulsive behaviors increasing markedly. Adults with pre-existing OCD proved especially vulnerable, experiencing a considerable intensification of their symptoms, with age also playing a moderating role. The core clinical feature of OCD includes intrusive and distressing obsessions, along with compulsion performed to neutralize anxiety. While relevant for contextualizing PANS/PANDAS, full DSM5TR diagnostic criteria are not reported here, as the focus of this review is on infection-related neuropsychiatric presentation.

Despite children and adolescents being among the least likely to suffer severe COVID-19, multiple large-scale studies documented a significant uptick in anxiety symptoms for these younger cohorts [5-7].

An online survey, conducted on a sample with age range of 11-88 years, revealed that nearly 60% of respondents reported the onset of OCD symptoms during the pandemic, and these new-onset cases frequently presented co-occurring generalized anxiety disorder and depression [8].

Consequently, this mental health deterioration has driven a surge in demand for both psychological and pharmacological treatments. Prior outbreaks, such as Severe Acute Respiratory Syndrome (SARS), have demonstrated long term psychiatric morbidity in survivors, including depression and OCD [9] reported in Table Building on this precedent, COVID-19 is uniquely relevant to PANS/PANDAS because of its dual role as a potential infectious trigger and as a major psychosocial stressor through lockdowns, school closures and routine disruption.

Table 1: Psychiatric outcomes in SARS survivors (4-year follow-up) [9].

Condition	Prevalence
Posttraumatic stress disorder	54.50%
Depression	39.00%
Somatoform pain disorder	36.40%
Panic disorder	32.50%
Obsessive-compulsive disorder	15.60%

Furthermore, we delve into potential underlying pathogenic mechanisms. To our knowledge, no previous review has synthesized the multifaceted impact of COVID-19, including infection, vaccination and psychosocial stressor, on the clinical trajectory of PANS/PANDAS. The aim of this narrative review is to synthesize the multifaceted impact of COVID-19, including infection, vaccination, and psychosocial stressors, on the clinical trajectory of PANS/PANDAS, and to highlight potential underlying mechanisms and clinical perspectives.

Materials and methods

This article, a narrative review, aims to capture and describe the complexity of PANS/PANDAS during the COVID-19 era. We included peer reviewed empirical studies published between January 2020 and May 2025 that involved children or adolescents with PANS/PANDAS. While the emerging nature of this topic and there was not strict inclusion or exclusion criteria were applied, reviews, purely qualitative studies and studies on general population were excluded. This review was not registered in PROSPERO or similar databases, as it is a narrative rather than a systematic review. A comprehensive literature search was conducted using the following databases: PsycINFO, PsycARTICLES, MEDLINE, Scopus, Web of Science, PubMed and Google Scholar. An example of PubMed query used: (PANS OR PANDAS OR "pediatric acute-onset neuropsychiatric syndrome") AND (COVID-19 OR SARS-CoV-2 OR coronavirus) AND (children OR adolescents). Similar combinations were applied across PsycINFO, Scopus, and Google Scholar. Keywords used in various combinations included: "OCD, "Obsessive-Compulsive Disorder," "OCD symptoms," "PANS", "Pediatric Acute-Onset Neuropsychiatric Syndrome", "PANDAS", "Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections", "Immunopsychiatry", "Neuroimmunology", "Neuroinflammation", "Immunology", "Coronavirus," "Pandemic," "COVID-19," "SARS-CoV-2,", "Social distancing", "Lockdowns", "Psychological well-being", "Children" "Adolescents" and "Adults". The selection of studies adhered to specific inclusion criteria: articles had to be peer-reviewed and between January 2020 and May 2025; present empirical data on clinical OCD samples examining the impact of the COVID-19 pandemic in children, adolescents, and/or adults; utilize either cross-sectional or longitudinal designs; and provide accessible abstracts and full texts. Qualitative studies were excluded to focus on measurable clinical outcomes and mechanisms; however, such studies could provide valuable insights into caregiver experiences and warrant inclusion in future reviews. Thus, the final corpus of 14 studies reflects the paucity of empirical work in this field rather than restrictive selection. Exclusion criteria included: non-original contributions (e.g., reviews, commentaries, letters to the editor), studies reporting exclusively qualitative data, and those focusing on the general population. Variables such as treatment type, comorbidities, publication status, language, gender composition, ethnicity, and nationality were not considered exclusionary.

After screening, a total of 102 articles were initially identified. Of these, 88 were excluded based on the outlined criteria, primarily because they were literature reviews, essays, or did not focus on the target population. Ultimately, 14 empirical studies met all inclusion criteria and were selected for in-depth analysis. The key characteristics of these studies are summarized in the PRISMA flowchart (Figure 1).

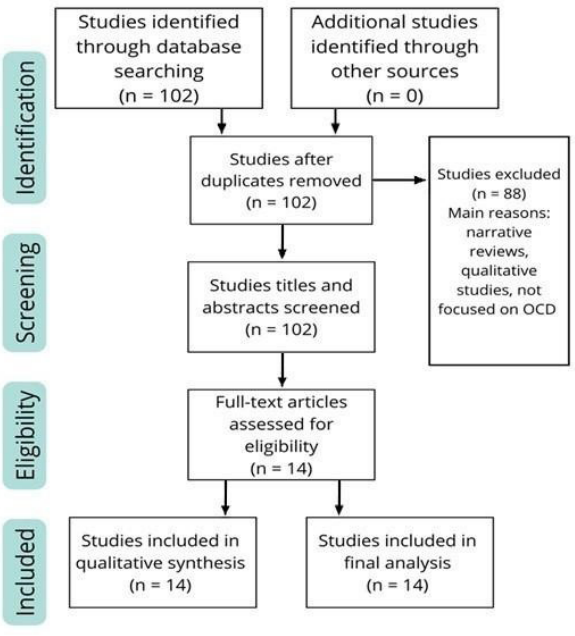

Figure 1: PRISMA flowchart selection of studies.

In line with PRISMA recommendations, we added a table summarizing the principal reasons for exclusion of screened records (Table 2). Of the 102 full-text articles assessed, 34 were excluded as reviews or pespectives, 28 for wrong population, 16 for insufficient clinical data and 10 for other reason (editorials, duplicated cohorts).

Table 2: Reasons for exclusion of articles during the full-text screening stage (in line with PRISMA guideline).

Reason for exclusion	Number of records
Review/perspective articles	34
Wrong population	28
Insufficient clinical data	16
Editorials/duplicates	10
Total excluded	88

Risk of bias assessment

To evaluate the methodological quality of the included studies, we applied standard risk-of-bias tools based on study design. For survey-based studies, we used the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for analytical cross-sectional studies [10]. For observational research (non-randomized), we employed the ROBINS-I tool (Risk of Bias in Non-Randomized Studies - of Interventions) [11]. Wherever applicable, the RoB 2.0 tool was used for randomized controlled trials. Risk of bias result were synthesized in a traffic-light plot (Figure 2) generated according to JBI, ROBINS-I and RoB 2.0 guidelines. Survey-based studies were consistently rated as high risk of recall and selections bias whereas observational cohort showed moderate concerns regarding confounding and outcome assessment. The single RCT included was judged at low risk of bias. Overall, study quality was heterogeneous, and our conclusion are therefore weighted more heavily toward the higher-quality observational and interventional reports.

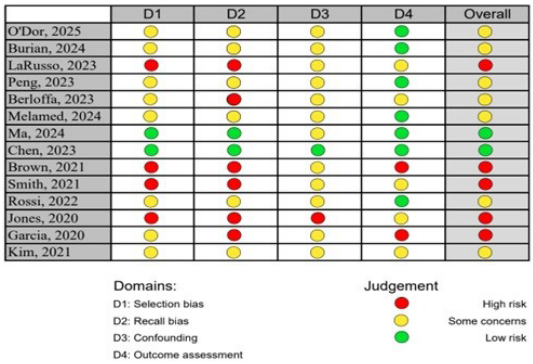

Figure 2: Traffic-light plot.

Each study was independently assessed by two reviewers, and disagreements were resolved through consensus. Overall, most survey-based studies were judged at high risk of recall and selection bias according to the JBI checklist, while observational cohort studies showed moderate internal validity when assesses with ROBINS-I.

COVID-19 impact on children and adolescents

The COVID-19 pandemic had a profoundly disruptive impact on the mental well-being of children and adolescents. Meta-analyses involving nearly 23,000 young people reported that almost 80% experienced adverse psychological effects - such as anxiety, depression, irritability, and inattention - during lockdowns and quarantine periods [12]. One global synthesis of 29 studies, totaling over 80,000 individuals under 18 years, found that for the first year of the pandemic, about one in four (25.2%) exhibited clinically elevated depressive symptoms and one in five (20.5%) showed clinically significant anxiety [13]. In addition to these changes, children displayed increased irritability, difficulty maintaining attention, and heightened attachment to caregivers as routines were disrupted and social contact was limited [14,15]. More specifically, among children already diagnosed with OCD, there was a pronounced increase in contamination obsessions and cleaning/washing compulsions [16], along with and adolescents.

Table 3: Summary of pandemic-related mental health outcomes in children and adolescents.

Domain	Key findings	References
Psychological impact	Worsened well-being during lockdowns (~80%)	Panda et al. 2021 [12]
Depressive symptoms	Clinically elevated in the pandemic's first year (25.2%)	Racine et al. 2021 [13]
Anxiety symptoms	Clinically elevated (20.5%)	Racine et al. 2021 [13]
Behavioral changes	Increased irritability, inattention, caregiving attachment	Loades et al. 2020 [15]
OCD exacerbation	Greater contamination obsessions and cleaning compulsions in subjects with OCD	Tanir et al. 2020 [16]
Clinical cohorts	Worsened anxiety/OCD symptoms in subjects with neuropsychiatric Nissen et al. 2020 disorders [17]; Conti et al. 2020 [18]	

Further research highlighted environmental and familial risk factors that were strongly associated with the onset of symptoms in children. Elevated parental stress, pervasive fear of infection, disruption of daily routines and enforced social isolation emerged as key contributors during lockdown [14,19,20].

This evidence paints a clear, scientifically grounded, picture: the COVID-19 pandemic profoundly affected young people's mental health worldwide, increasing the burden of mood and anxiety disorders, straining familial systems and exacerbating neuropsychiatric vulnerabilities.

PANS/PANDAS

In 1998, Swedo and colleagues issued the first report of 50 children who developed abrupt onset of OCD or tic symptoms shortly after a Group A Streptococcus (GAS) infection, coining the term "PANDAS" which stands for Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections [21].

These cases were defined by five core criteria: prepubertal onset of OCD and/or tics, an episodic course with sudden exacerbations, a clear temporal link to GAS, and the presence of subtle neurological signs such as choreiform movements [21]. However, clinicians soon observed that many children presented with a nearly identical clinical picture - sudden-onset of OCD or tics without a preceding GAS infection. Therefore, to encompass these cases, Swedo and colleagues introduced the new term Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS) in 2012 [22].

While retaining the hallmark features of sudden OCD onset or severe food restriction, PANS expands the criteria to include any of a range of acute neuropsychiatric symptoms, such as anxiety, mood lability, irritability, regression, or motor/sensory abnormalities, showing up within 48 hours, without requiring evidence of streptococcal infection (Table 4 for the diagnostic criteria of PANS).

Table 4: Pediatric Acute-Onset Neuropsychiatric Disorders (PANS) diagnostic criteria. Modified from Swedo et al. (2012) [22].

	Criteria
1	Abrupt onset of OCD or restricted food intake
2	Presence of at least 2 of the following symptoms:
a.	Anxiety
b.	Emotional lability and/or depression
c.	Irritability, aggression
d.	Behavioral regression
e.	Worsening of school performance
f.	Sensory or motor abnormalities Sleep disturbances, enuresis, or urinary frequency
3	Symptoms not better explained by another disorder, such as Sydenham chorea, Tourette disorder, or others

PANS recognizes triggers beyond GAS, including other infections such as influenza (e.g., H1N1), Epstein-Barr Virus (EBV), Borrelia burgdorferi (Lyme disease), and even 193 non-infectious stressors like metabolic imbalances or environmental factors. This shift reflects a more comprehensive understanding of acute-onset neuropsychiatric syndromes in children, one that is rooted in clinical phenotype rather than a single etiological agent [23-27].

To further support the autoimmune basis of PANS, several studies have identified heightened rates of autoimmune conditions within families and among affected children themselves. Approximately 80% of patients report first-degree relatives with autoimmune disorders [28]. Among children, inflammatory conditions are frequently comorbid, most commonly comprising inflammatory back pain (21%) and reactive or persistent arthritis (28%) [29].

The evolution from PANDAS to PANS illustrates a shift from a narrowly defined, infection-based syndrome to a broader clinical construct (see Table 5 for some comparative characteristics between PANDAS and PANS). It acknowledges diverse triggers and immune-related vulnerabilities, offering a more inclusive framework for research, diagnosis, and ultimately, intervention.

Table 5: Comparative summary: PANDAS vs PANS.

Feature	PANDAS PANS
Primary	Group A Streptococcus infection Broad triggers: GAS, other infections (e.g., influenza,
trigger	[21] Lyme), and non-infectious factors [22,27]
Symptom	Abrupt, episodic with acute Abrupt onset (<48 h) of OCD or strict eating and at least
onset	exacerbations [21] two additional neuropsychiatric symptoms [22,27]
Diagnostic	Temporal link to strep is required No specific pathogen required-diagnosis based on
requirement	[21] clinical phenotype [22]
Autoimmune	Not emphasized in original criteria Prominent family and personal history of
comorbidity	[21] autoimmune/inflammatory disorders [34]

Inflammation hypothesis

While data remain limited on chronic inflammation in children meeting PANS/PANDAS diagnostic criteria, emerging evidence from related conditions such as OCD and tic disorders suggests the immunological involvement. Gray and Bloch (2012) and Walls et al. (2015) [30,31] reviewed multiple studies reporting elevated pro-inflammatory cytokines, specifically Tumor Necrosis Factor-alpha (TNF-α) and interleukin 6 (IL-6, in patients with OCD and PANS. Neurological imaging further bolsters the neuroinflammatory hypothesis. Magnetic Resonance Imaging (MRI) analyses have shown increased volumes of basal ganglia structures, including the caudate, putamen, and globus pallidus, in children with early- stage PANDAS compared to matched controls [27]. A pioneering Positron Emission Tomography (PET) study, using the microglial tracer 11C-[R]-PK11195, demonstrated elevated Translocator Protein (TSPO) binding, a marker of microglial activation, in the basal ganglia of 17 children with PANDAS versus controls. While the Tourette's syndrome cohort also showed increased binding, the pattern in PANDAS was more widespread, indicating a broader neuroinflammation [32]. Murgia, Gagliano et al. (2021) found a unique plasma metabolic profile in PANS, suggesting also the involvement of a state of neuroinflammation in this disorder [33].

The autoimmune nature of PANDAS is further supported by immunological studies, which reveal serum and Cerebrospinal Fluid (CSF) autoantibodies targeting basal ganglia regions. Williams and Swedo (2015) reported reactivity against postmortem human caudate and putamen tissues, providing direct evidence of immune-mediated neural targeting basal ganglia antibodies, reinforcing the hypothesis of molecular mimicry between streptococcal antigens and basal ganglia proteins [34].

However, it is essential to acknowledge that these kinds of findings are not without limitations. In fact, the cited studies rely on, for example, small sample sizes, lack uniform diagnostic criteria for PANS/PANDAS and use heterogeneous populations [30-34].

In sum, while a body of converging evidence, including cytokine elevations, neuroimaging and autoantibody studies, supports the role of neuroinflammation in PANS/PANDAS, the field still requires larger, methodologically rigorous studies to confirm causality and clinical relevance.

PANS and COVID-19

The following results are derived from heterogeneous evidence sources. Controlled cohort studies provide stronger support, whereas caregiver-reported surveys and case reports

represent lower levels of evidence and should be interpreted with caution.

A descriptive quantitative summary of the included studies in provided in (Table 6). Across the 14 studies, the median age of participants was 11.5 years (range 4-17) and the median follow-up duration was 8 months (range 1-24). Approximately 42% of patients experienced a symptom flare following SARS-CoV-2 infection, while 18% reported exacerbation after vaccination. Caregiver-based surveys consistently indicated higher relapse rates compared to clinician-assessed cohorts.

The 14 empirical studies included in this review were conducted across multiple countries, providing an international perspective on the relationship between COVID-19 and PANS/PANDAS. Specifically, several studies originated from the United States [35,38], while Italy contributed observational and clinical data [1]. Research from China also provided important evidence [59], complemented by contributions from Germany [61]. This distribution demonstrates that most data are concentrated in North America, Europe, and East Asia, highlighting the global relevance of the issue but also the need for more geographically diverse research.

Table 6: A descriptive quantitative summary of the included studies.

Parameter	Summary (14 studies)
Median age (range)	11.5 years (4-17)
Median follow-up duration (range)	8 months (1-24)
Flare-ups after infection	42%
Exacerbation after vaccination	18%
Evidence source	Caregiver survey vs. clinician cohorts (higher relapse rates in surveys)

PANDAS and PANS both describe the abrupt manifestation of neuropsychiatric symptoms in children, which include the presence of OCD. Since the COVID-19 pandemic began, individuals with pre-existing OCD, both adults and youth, have reported a significant worsening of their symptoms, accompanied by increased anxiety and depression [1,35-37].

Yet, only a handful of studies have specifically examined the impact of COVID-19 on PANS/PANDAS.

A global survey of families affected by PANS/PANDAS, involving 496 caregivers, revealed that, among 178 children infected with SARS-CoV-2 virus, 43% experienced severe symptom relapses and 23% reported mild flares; in contrast, 30% had no change, and only 5% experienced improvement after COVID-19 infection [38].

Strikingly, flare-ups were significantly more frequent after infection than after vaccination, highlighting COVID-19 as a likely trigger in vulnerable children [38].

Additionally, another survey of 670 PANS/PANDAS families conducted by the PANDAS Network showed nearly 41-58% of children, with confirmed or suspected COVID-19, experienced exacerbations in mood, OCD symptoms, anxiety, and sensory sensitivities following infection. Although it did not include a control group, the study clearly establishes a link between infection and symptom escalation [39].

O' Dor et al. (2022) [40] and Guido et al. (2021) [41] reached the same conclusions.

One case report described adolescent twins developing PANS after COVID-19 infection [36,37]. However, as an isolated observation, this should be regarded as anecdotal and cannot establish causality.

In adult clinical subjects suffering from OCD, statistical comparisons between pre- quarantine and quarantine periods showed significant increases in total Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) scores, and in both obsession and compulsion Subscales, highlighting a measurable surge in symptom severity during lockdowns [42,43]. In their narrative review, Zaccari and colleagues (2021) [44] systematically evaluated 39 clinical studies - 14 with empirical data - published between January 2020 and early 2021 on the impact of COVID-19 on OCD in adults, adolescents and children. They found a clear pattern of symptom exacerbation across most studies, particularly for contamination and washing compulsions. In adults, eight studies reported a significant increase in symptoms, while two noted minimal effects and one even slight improvement; among youth, two of three studies showed worsening OCD, even in those already undergoing treatment. However, Zaccari et al. also emphasized notable methodological limitations that temper the strength of the findings. These included heterogeneous samples spanning wide age ranges, inconsistent use of standardized instruments such as the Y-BOCS, unclear treatment contexts (e.g., ongoing Cognitive Behavioral Therapy "CBT" and Exposure and Response Prevention "ERP" or pharmacotherapy), and varying monitoring periods that challenged cross-study comparisons. Despite these constraints, their review underscores the pronounced impact of COVID-19, especially about symptom subtypes directly tied to infection fears, and calls for more rigorous, longitudinal, and treatment- contextualized research [44]. Among the five primary studies examining symptom recurrence post-COVID-19, three reported significant symptom flares in over 50% of cases. It could therefore be highlighted that survey data and case reports consistently indicate increased neuropsychiatric burden during the pandemic, especially in those with confirmed COVID-19 infections. While these findings are noteworthy and consistent with clinical impressions, they must be interpreted with caution. We acknowledge that the reliance on caregiver surveys and case reports may introduce bias and limit the strength of conclusions. These tools are valuable for hypothesis generation but should be complemented by longitudinal clinical studies with objective measures. These surveys are subject to significant limitations, including 'selection bias' (families experiencing more severe or worsening symptoms may be more likely to participate), 'lack of standardized diagnostic verification', and 'absence of control groups', which limits causal inference. Additionally, the data often rely on subjective caregiver impressions rather than clinician- administered assessments. Interestingly, a minority of caregivers (5-10%) reported symptom improvement post-COVID-19. Potential explanations may include reduced social pressures, increased structure at home, or placebo effects; however, these cases were rare. These caregiver-based surveys are inherently subject to recall bias and lack objective clinical confirmation. While they provide preliminary insights, their findings must be interpreted with caution and ideally compared with clinician-verified cohort data. By contrast, data from studies on 'non-PANS OCD populations', such as adults and adolescents without immune-mediated triggers, also report symptom exacerbation during the pandemic, particularly in domains related to contamination fears and compulsive cleaning [42-44]. These patterns support the idea that pandemic stressors

may aggravate a wide range of neuropsychiatric conditions, though the underlying mechanisms may differ. Isolated case reports, such as adolescent twins developing PANS post-COVID Infection, offer intriguing clinical observations [36,37], but these must be viewed as 'anecdotal evidence'. Without larger, controlled studies, such reports cannot be generalized. In summary, while early surveys and case reports raise critical clinical questions about the intersection between COVID-19 and PANS/PANDAS, the current evidence base is preliminary. A more rigorous methodological framework, including validated diagnostic tools, control groups, and objective clinical measures, is necessary to draw reliable conclusions.

Possible mechanisms: inflammation, epstein-barr virus, and psychosocial stressors The mechanisms behind COVID-19's neurological and psychiatric impact are complex and multifaceted. It has been hypothesized that SARS-CoV-2 may induce systemic inflammation and autoimmunity [45], consistent with the pathology of cytokine storm [46], which may activate microglia, suppress neurotrophic signaling, elevate glutamate, and provoke excitotoxic injury, thereby amplifying pre-existing neuropsychiatric conditions [47,48]. The immunological profile of PANS patients has also shown some, not univocal, alterations [31]. (Figure 2) presents a conceptual hypothesis of shared cytokine pathways between COVID-19 and PANS. This model is speculative and has not yet been empirically validate.

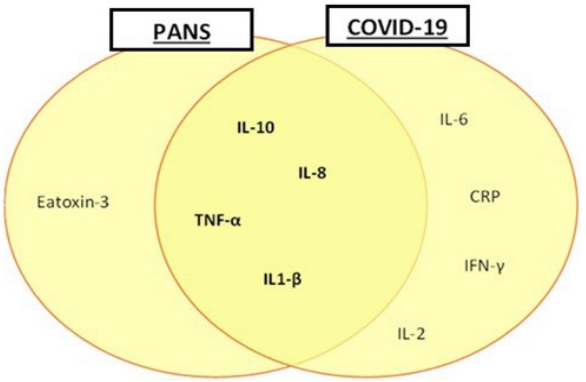

Figure 3: Proposed model of cytokine alterations in PANS and COVID-19 [31,46,49].

Another critical possible mechanism is herpesvirus reactivation: COVID-induced immune compromises can reactivate latent Epstein-Barr virus (EBV), detected in 66.7% of long COVID patients [50], who may exhibit elevated titers of anti-EBV antibodies [51]. A small case series involving five pediatric PANS patients found EBV reactivation in three cases [52]. While intriguing, this evidence remains preliminary and does not establish causality In addition to these immune-mediated pathways, psychosocial mechanisms may also play a significant role in symptom exacerbation considering the involvement in inflammatory processes. Prolonged social isolation, disruption of daily routines, increased caregiver stress and anxiety related to health fears, were all considered important factors of psychological distress in children and adolescents during the pandemic [53-55]. These stressors can independently trigger or worsen neuropsychiatric symptoms, even in the absence of viral infection or prior immune activation, by increasing emotional dysregulation, sleep disturbance, and behavioral instability in vulnerable individuals.

Indeed, inflammatory markers such as Interleukin-6 (IL-6) have been shown to rise even in uninfected individuals following lockdown-related loneliness and stress [55], suggesting a possible interaction between psychosocial distress and immune signaling.

Thus, COVID-related neuropsychiatric impacts likely stem from multiple interacting pathways: direct viral neuroinflammation, herpesvirus reactivation, and 'pandemic-related psychosocial stress'. A comprehensive, integrative research approach, encompassing clinical, immunological, and psychological assessments, is essential to fully understand the multifactorial nature of symptom exacerbation in PANS/PANDAS.

New onset or exacerbation of symptoms

Two caregiver surveys, performed by Guido et al. (2021) [41] and O'Dor et al. (2022) [40], assessed symptom severity in children and adolescents with PANS/PANDAS during the COVID-19 pandemic. Both studies reported that the majority of respondents observed declines in their children's social relationships, school performances, and overall mental well-being, consistent with broader findings of pandemic-associated psychological distress in youth. Guido et al. found that 71% of the sample experienced worsening of pre-existing symptoms during lockdown, while nearly one-third developed new symptoms. Key factors associated with these declines included sleep disruption, heightened anxiety and pandemic-related stress especially fear of SARS-CoV-2 infection [41]. In O'Dor and colleagues' subset of 12 children with confirmed COVID-19, 58% exhibited pronounced mood lability following infection, further supporting the hypothesis that new infections can trigger or intensify PANS/PANDAS symptomatology [3], consistent with the early descriptions by Swedo et al. (1998) [21]. Not only did SARS-CoV-2 exacerbate existing conditions, but it may also have precipitated new cases of PANS; in fact, two independent case series [36,37] reported two adolescent cases of PANS temporally linked to COVID-19 infection. Notably, post-COVID "long-hauler" symptoms, such as fatigue, cognitive impairment (brain fog), sleep disorders, mood swings, and memory issues, have been reported in pediatric populations at rates between 20-33%, with approximately 25% developing chronic symptoms lasting more than 12 weeks. Although no studies have yet directly examined these long-term sequelae in children with PANS/PANDAS, the overlap with known long-COVID symptomatology suggests an essential avenue for future research.

Access to healthcare

In addition to symptom exacerbation, the COVID-19 pandemic notably disrupted access to healthcare for children with PANS/PANDAS. O'Dor and colleagues (2022) reported that 35.9% of caregivers found it more challenging to obtain medical care during the early pandemic period [40].

Travel restrictions, clinic closures, and safety concerns led to a reduction of in-person evaluations and missed follow-ups, posing additional stress to already vulnerable families. In response, telehealth emerged as a vital alternative, particularly suited for routine medication management and monitoring of patients with milder symptom profiles. Among surveyed families, 83.6% used telehealth services, with 78.7% reporting that remote consultations made care more accessible. Nearly 29% indicated a clear preference for continuing telehealth post-pandemic, while around 61% said their preference depended on appointment type [40]. Interestingly, families with children exhibiting milder forms of PANS/PANDAS were more

enthusiastic about telehealth. In contrast, those managing more severe symptoms often required in-person visits, particularly during acute flare-ups. This suggests that while telehealth can broaden access and reduce travel burden, especially given that over 60% of families typically travel more than 50 miles for care, it cannot fully replace in- person assessments for complex cases. The move to remote care had important implications not only for patient well-being but also for caregiver burden. Most respondents reported pre-existing high levels of parental stress and burnout, a state that was, however, further exacerbated by pandemic pressures such as homeschooling, social isolation, and financial strain [56].

Caregivers who found telehealth easy to use and effective reported slightly improved emotional resilience, although overall stress levels remained high, highlighting the need for comprehensive, family-centered support systems.

Vaccine hesitancy and vaccine-related neuroinflammation

In their survey of 2022, O'Dor et al. reported that approximately 25% of caregivers of children with PANS/PANDAS indicated no intent to vaccinate their child against COVID-19 [38]. This refusal rate aligns closely with that of other chronic pediatric conditions, where parental hesitancy ranges from 28% to 33%. A significant concern underlying this hesitancy is the fear that vaccination might exacerbate underlying autoimmune or inflammatory conditions in their children, an understandable reaction rooted in the syndromes' pathophysiology and caregiver anxiety. Parental hesitancy was often rooted in fear of autoimmune flare-ups, general vaccine mistrust, concerns over long-term effects, and conflicting messages about efficacy against new variants. These concerns mirror those found in other chronic pediatric and autoimmune populations [57-60].

However, emerging evidence is reassuring. In a large cohort of over 1,000 patients with neuroinflammatory conditions compared to 500 controls, Epstein et al. (2022) and Burian et al. (2024) found no significant differences in vaccine-related side effects or disease exacerbation post-vaccination [58].

Specifically, within PANS/PANDAS, most children either remained stable or improved following vaccination; only mild side effects, such as fatigue in 30-56% of cases, were reported, with no severe clinical flare-ups observed [40].

While rare autoimmune reactions following vaccination, such as Guillain-Barré syndrome or myocarditis, have been documented, these remain extremely uncommon and do not alter the overall favorable safety profile [60] In contrast, larger-scale studies [59] have found that COVID-19 vaccination is associated with a reduced long-term risk of developing autoimmune disorders, such as Graves' disease, lupus, and autoimmune arthritis, underscoring not only safety but also potential protective benefits. Recent evidence further suggests that vaccine hesitancy may be specifically predicted by an inflexible thinking style, as individuals with objective deficits in cognitive flexibility—such as perseveration on the Wisconsin Card Sorting Test—show a significantly higher resistance to immunization. This suggests that for a subgroup of the population, hesitancy is less about education and more a manifestation of stable, rigid cognitive traits [61].

Caregiver hesitancy is influenced by several factors, including a perceived lack of sufficient scientific evidence (84.8%), concerns about safety and side effects (76.9%), and doubts over vaccine efficacy against viral variants (36.7%) [62].

Similarly, Goldman et al. (2020) [63,64] reported that about two-thirds of caregivers intended to vaccinate, citing the protection of their child as the primary motivation, while those opposed labeled the vaccine as "too novel" and uncertain. Additional determinants included the child's age, chronic illness, prior vaccination history, and caregiver characteristics (e.g., gender, personal vaccine attitude, and perceived infection risk).

Taken together, these findings define a precise framework: although significant minority of caregivers harbor genuine concerns that vaccination may exacerbate PANS/PANDAS symptoms, the balance of evidence supports both the safety and long- term benefits of COVID-19 vaccination in this population [60]. Clinicians should prioritize open communication, presenting data on minimal adverse reactions, immunological reassurance, and the preventive value of vaccination, while empathetically addressing caregiver anxiety.

Limitations

This review has some limitations. First, the diagnostic criteria for PANS/PANDAS were not uniformly applied across the included studies, introducing heterogeneity in case definition. Second, most of available evidence is based on caregiver surveys, which are prone to recall and selection bias and lack clinician-verified diagnostic confirmation. Third, most studies were cross-sectional or descriptive, with few prospective or controlled designs, which limits causal inference. Fourth, many findings relied on small samples and anecdotal case reports, such as single-family descriptions, which cannot be generalized. Finally, evidence on potential mechanisms, such as cytokine dysregulation or Epstein-Barr Virus (EBV) reactivation, remains preliminary and largely speculative, often derived from small uncontrolled series rather than well-powered studies.

Taken together, these methodological constraints highlight the urgent need for prospective, controlled, and biomarker-informed research to clarify the relationship between COVID-19 and PANS/PANDAS.

Conclusion and perspectives

This narrative review highlights preliminary but concerning evidence that COVID-19 may act as a trigger or exacerbator factor in children with PANS/PANDAS [36,37]. While observational data and caregiver reports suggest infection related relapses in up to 40% of cases [38,40,41], these findings remain associative rather than casual.

Importantly, even children who were not infected showed increased symptom burden, suggesting that pandemic-related psychosocial stressors, such as social isolation and routine disruption, may contribute independently to clinical worsening [55]. These non-directly inflammatory mechanisms mirror trends also observed in non-PANS OCD populations [42-44].

The likely mechanisms behind symptom exacerbation appear to be multifactorial, including:

Neuroinflammation: SARS-CoV-2 may provoke systemic cytokine responses and microglial activation, potentially worsening neuropsychiatric vulnerability [45-48].

Herpesvirus reactivation: EBV reactivation has been observed in long COVID and suggested in small case series involving PANS patients [50-52], but these findings remain inconclusive.

Psychosocial stress: Independent of infection, pandemic stressors such as disrupted routines, loneliness, and caregiver burden may trigger or amplify symptoms through behavioral and emotional dysregulation [53-55].

Given these converging factors, a biopsychosocial framework is necessary to understand and manage COVID-era exacerbations in PANS/PANDAS. Clinicians should adopt a multidimensional approach, monitoring not only infectious exposures and immune responses, but also psychological and environmental stressors. Notably, approximately 25% of the population is excluded from vaccination due to documented medical or other valid reasons, underscoring the need for individualized risk assessment and management. Telemedicine has emerged as a valuable tool for maintaining continuity of care, particularly in cases of mild to moderate severity. However, complex or acute presentations still require in-person assessment. Additionally, vaccine hesitancy remains a concern: although some families report fear of immune exacerbation, current evidence suggests no significant increase in adverse outcomes post-vaccination in this population [58-60].

It remains to be clarified whether vaccine hesitancy is due to a lack of information or whether it may represent the correlate of a specific perception of the disorder, associated with particular hypersensitivity; this highlights the need to further investigate this population.

A significant limitation of the current literature is its reliance on retrospective, non-controlled data, often based on caregiver report. To move beyond speculation, future research must include:

Well-powered and prospective cohort studies; Control groups. Standardized diagnostic tools; Biomarker and neuroimaging correlates; Implications of the stress-related exacerbations.

In conclusion, COVID-19 may play a role, as a potential trigger or aggravating Factor, in a subset of vulnerable children with PANS/PANDAS, but definitive evidence of specificity or causality is lacking. A cautious, evidence-based approach is essential. Moving forward, integrated, structured caregiver support systems, routine IL-6 and cytokine monitoring post-infection, and neuroimaging follow-up in clinically worsening cases. Clinically, children with PANS/PANDAS should be monitored for SARS-CoV-2 infection as well as possible EBV reactivation and inflammatory markers such as IL-6. Telehealth service should be integrated into long-term care for milder cases, while acute flare-ups require in person evaluation.

In interpreting the findings, it is essential to consider the moderate to high risk of bias present in many of the included studies. Common limitations included small sample sizes, reliance on caregiver reports, absence of control groups, and heterogeneous diagnostic criteria. While some observational studies demonstrated acceptable internal validity (assessed using the ROBINS-I), most survey-based reports (assessed using the JBI checklist) had limited generalizability due to selection bias.

These factors further support the need for more rigorously designed prospective studies in the field. Future studies should also include translational research such as animal models of PANS-like neuroinflammation post-viral exposure, as well as studies investigating biomarkers and cytokine signatures to clarify causal mechanism.

Declarations

Author contributions: Conceptualization, methodology, investigation, S.P., L.A., and N.M..; writing—original draft preparation, S.P. and N.M..; writing—review and editing, S.P., M.G.T. and D.M.; supervision, S.P. All authors have read and agreed to the published version of the manuscript.

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Abbreviations: The following abbreviations are used in this manuscript: PANS: Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS); PANDAS: Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infecti; OCD: Obsessive-Compulsive Disorder; COVID-19: Coronavirus Disease 2019; SARS: Severe Acute Respiratory Syndrome; DSM-5-TR: Diagnostic and Statistical Manual of Mental Disorders, 5th ed. Text Revision; JBI: Joanna Briggs Institute; ROBINS-I: Risk of Bias in Non-Randomized Studies - of Interventions; GAS: Group A Streptococcus; EBV: Epstein-Barr Virus; TNF-α: Tumor Necrosis Factor-Alpha; IL-6: Interleukin 6; MRI: Magnetic Resonance Imaging; PET: Positron Emission Tomography; TSPO: Translocator Protein; CSF: Cerebrospinal Fluid; Y-BOCS: Yale-Brown Obsessive Compulsive Scale; CBT: Cognitive Behavioral Therapy; ERP: Exposure and Response Prevention.

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