Worldwide epidemiology of neuro-coronavirus disease in children: lessons for the next pandemic

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Purpose of review
The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) pandemic has overwhelmed the global community, negatively impacting patient health and research efforts; associated neurological manifestations are a significant cause of morbidity. This review outlines the worldwide epidemiology of neurologic manifestations of different SARS-CoV-2 clinical pediatric phenotypes, including acute coronavirus disease 2019 (COVID-19), multisystem inflammatory syndrome in children (MIS-C) and postacute sequelae of COVID-19 (PASC). We discuss strategies to develop adaptive global research platforms for future investigation into emerging pediatric neurologic conditions.

Recent findings
Multicenter, multinational studies show that neurological manifestations of acute COVID-19, such as smell/taste disorders, headache, and stroke, are common in hospitalized adults (82%) and children (22%), associated with increased mortality in adults. Neurological manifestations of MIS-C are reported in up to 20% of children, including headache, irritability, and encephalopathy. Data on PASC are emerging and include fatigue, cognitive changes, and headache. Reports of neurological manifestations in each phenotype are limited by lack of pediatric-informed case definitions, common data elements, and resources.

Summary
Coordinated, well resourced, multinational investigation into SARS-CoV-2-related neurological manifestations in children is critical to rapid identification of global and region-specific risk factors, and developing treatment and mitigation strategies for the current pandemic and future health neurologic emergencies.

Keywords
Coronavirus disease 2019, epidemiology, multisystem inflammatory syndrome in children, pediatric, severe acute respiratory syndrome coronavirus-2

INTRODUCTION
Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the virus that causes acute coronavirus disease 2019 (COVID-19) and the postinfectious hyperinflammatory shock syndrome, multisystem inflammatory syndrome in children (MIS-C), was declared the source of a global pandemic on March 11, 2020 by the World Health Organization (WHO) [1]. [2] (Fig. 1). Neurological manifestations of SARS-CoV-2 infection were recognized early as a significant cause of mortality and morbidity, similar to influenza, Zika, and other emerging virus outbreaks [3,4]. This review will outline the worldwide epidemiology and clinical manifestations of acute COVID-19, MIS-C, and postacute sequelae of SARS-CoV-2 (PASC) and their respective neurological manifestations in children.

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PEDIATRIC SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS-2
EPIEIMIOLOGY

As of July 12, 2021, the WHO estimates that there have been 186,638,285 confirmed cases of COVID-19 reported worldwide, including 4,035,037 deaths. The WHO estimates that children under 14 years old have thus far accounted for 5,486,503 of reported COVID-19 cases (2.5%) and 2,717 of reported deaths (0.07%) [5]. The United Nations Children’s Fund (UNICEF) estimates that children under 20 years old account for 13% of reported cases (10–15% in high and upper middle income countries [HIC], vs 10–11% in lower middle and low income [LMIC] countries), and 0.3% of reported deaths (0.1% in HIC, 1.1% in LMIC) [6]. The American Academy of Pediatrics (AAP) and the Children’s Hospital Association estimate that children account for 14.2% of total reported cases in the United States (US) [7]. The differences in these estimates are likely related to access to testing and reporting strategies in different regions and countries.

In addition to case counts and mortality rates, the SARS-CoV-2 pandemic has had other significant impacts on overall child health. Modeling estimates from LMICs suggest there has been an increase in child mortality from causes other than SARS-CoV-2 infection due to widespread disruption of healthcare systems [8]. Projections from UNICEF estimate that as a result of the pandemic, 140 million children are living in poverty in developing countries [9], 463 million children have not had access to remote learning during school closures, 80 million children under the age of 1 have not received routine vaccinations [10], and 1.8 billion children are at risk for violence, exploitation and abuse due to disruption of violence prevention and response services [11].

Severe acute respiratory syndrome coronavirus-2 variants

As of July 2, 2021, the WHO has designated four notable SARS-CoV-2 variants of concern (VOC) in widespread global circulation, including: Alpha
Neurology

Severe acute respiratory syndrome coronavirus-2 clinical phenotypes in children

Acute coronavirus disease 2019

Clinical signs and symptoms of acute COVID-19 range in severity. Up to 33% of infected individuals may be asymptomatic [13]. The remainder of children, similar to adults, have symptoms ranging from mild upper respiratory symptoms (fever, chills, cough) to more severe symptoms of hypoxemia, acute respiratory distress syndrome, and shock. Ten percent of children experience more severe illness with acute COVID-19 [14,15], particularly among Black children [16], and those with reported underlying medical conditions [17,18].

Multisystem inflammatory syndrome in children

First described in April 2020, MIS-C is a postinfectious hyperinflammatory syndrome that occurs in <1% of children [19] following confirmed SARS-CoV-2 infection [20]. Previously referred to as atypical Kawasaki disease, pediatric MIS (PMIS), and pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS), MIS-C is a distinct clinical and immunologic entity from COVID-19 [21]. MIS-C manifests primarily with gastrointestinal, mucocutaneous, and cardiovascular symptoms including myocardial dysfunction and shock; respiratory symptoms are less common. About 60% of children with MIS-C require intensive care unit admission. In addition, while children with acute COVID-19 have evidence of active SARS-CoV-2 infection by polymerase chain reaction (PCR), children with MIS-C more often have negative PCR but evidence of past infection by serology [22,23].

As of June 28, 2021, the Centers for Disease Control and Prevention (CDC) reported a total of 4,196 cases of MIS-C in the US, including 37 deaths [24]. Affected children are more likely to be older school age or adolescent (compared to younger age), Black or Hispanic (compared to White) [25,26], and unlike acute COVID-19, children with MIS-C are most often previously healthy [26]. Similar epidemiology has been described in the United Kingdom (UK) [27], Europe [28,29], Canada, and South Africa [30]. Notably, there have been disproportionately fewer MIS-C reports in Asian countries; reasons for this difference are not yet clear [31].

NEUROLOGICAL MANIFESTATIONS OF SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS-2

Multiple human coronaviruses (HCoV) have previously been associated with neurological manifestations [32]. Encephalitis [33] and acute disseminated encephalomyelitis (ADEM) [34] have been reported in association with HCoV-OC43. Headache, seizures, and cerebrovascular disease have been reported in association with SARS [35,36]. Finally, ADEM, Guillain-Barré syndrome (GBS), Bickerstaff encephalitis, intracerebral hemorrhage, vasculopathy, encephalopathy, and seizures have been reported in association with Middle Eastern Respiratory Syndrome (MERS) [35,37–39].

Acute coronavirus disease 2019 and multisystem inflammatory syndrome in children

Neurological manifestations in acute COVID-19 are reported globally in up to 82% of hospitalized adults [40,41,42]. The most commonly reported neurological manifestations are acute encephalopathy (up to 49%) and headache (37%); hospitalized adults with a neurological manifestation have been reported to have 6-fold higher odds of mortality [40]. Smell/taste disorders (anosmia, dysgeusia) have also been reported in 48–80% of all adults with acute COVID-19 [43,44], and ischemic stroke has been reported in 0.4–2.7% adults hospitalized or presenting to an ED [42,45–48]. There have been case reports of peripheral neurologic disorders (including GBS) [49–52], meningoencephalitis [53,54], ADEM and acute hemorrhagic necrotizing encephalopathy [49,55], seizures [56–58], and posterior reversible encephalopathy syndrome [52].

In children, there are fewer data regarding the prevalence of neurological manifestations of acute COVID-19 or MIS-C. Clinical neurologic, neuropsychologic, and neuroimaging data have not been routinely reported in large published epidemiologic cohorts, and cohorts often do not differentiate between acute COVID-19 and MIS-C. One potential reason for this lack of neurologic data is that some of the more subtle neurologic symptoms such as smell/taste disorders, headache, altered mental status, weakness, or paresthesia, may be difficult to identify in young children, and children
may not recognize or volunteer these symptoms unless specifically asked. This ascertainment bias limits the ability of retrospective studies to adequately estimate the burden of neurologic manifestations among children.

The largest epidemiological study to date to examine neurological manifestations in hospitalized children included 1695 children with acute COVID-19 and MIS-C from 61 US hospitals. They found neurological manifestations in 22% of children with acute COVID-19 and 20% of children with MIS-C [59**]. Children with underlying neurological conditions had a higher prevalence of neurological manifestations (42% vs 22% previously healthy children) in the overall mixed cohort. The clinical spectrum of neurological manifestations reported was similar to that seen in adults. About a quarter of children with neurological manifestations presented with altered mental status or confusion, and seizures were more commonly a presenting symptom in younger children (~38% in children <5 years). Among a subset of 43 children with ‘life-threatening’ neurologic manifestations in the mixed cohort, 26% died and 40% of survivors had new neurologic deficits at discharge [59**].

In the broader published pediatric literature, neurological manifestations such as smell/taste disorders, headache, seizures, and stroke appear to predominate in acute COVID-19, whereas headache, encephalopathy, and MRI changes suggesting neuroinflammation predominate in MIS-C. Examples of neurological manifestations in children reported to date are summarized by clinical phenotype in Table 1 [60,61,62**,63*,64,65*,66,67*,68–75,76*,77,78*,79,80**]. As these studies represent different pediatric cohorts (e.g. critically ill vs hospitalized patients), caution should be taken in extrapolating this data.

There are several significant knowledge gaps in the epidemiology of pediatric SARS-CoV-2 neurological manifestations. First, cases of acute COVID-19 and MIS-C are not always clearly differentiated. Second, lack of common data elements and definitions for neurologic signs and symptoms make prevalence estimates difficult to interpret and evaluate in meta-analyses. For example, the term ‘encephalopathy’ is nonspecific; it may include altered mental status, irritability, lethargy, or some combination of the three. Several upcoming studies, including the pediatric arm of the GCS-NeuroCOVID (NCT04379089) may help address this limitation [81] (Table 2). Third, despite limits placed on the conduct of research during the pandemic, increased research resources and preexisting research networks in HIC compared to LMIC led to publication biases, limiting our understanding of the scope of neurological manifestations and outcomes in less resourced regions. Finally, there are limited data regarding the impact of variants, vaccination, and disparities in access to vaccination, on the prevalence of neurological manifestations.

**Postacute severe acute respiratory syndrome coronavirus-2 infection**

Postacute sequelae of SARS-CoV-2 infection among survivors are increasingly recognized, and sometimes referred to as Long COVID or PASC. In a systematic review of English-language cohort studies that included 9,751 adults following acute COVID-19 hospitalization, over 70% reported the persistence of one or more new symptoms such as fatigue (median: 40%), dyspnea (median: 36%), anxiety (median: 22%), anosmia and/or dysgeusia (median: 16%), depression (median: 15%), and cognitive deficits (median: 18%), including memory loss (median: 28%) and concentrating difficulties (median: 22%) [82]. Similar symptoms have been reported six months after acute infection in about 50% of adults with milder disease that did not require acute hospitalization [83].

Children who have had either acute COVID-19 infection and/or MIS-C treated as outpatients or inpatients may also have postacute sequelae of infection [84,85,86*,87*], though estimates of prevalence vary. In a study of 129 children with prior SARS-CoV-2 infection in Italy, 58% had persistent symptoms at a mean of 163 (±114) days follow-up. Risk factors included symptomatic infection and hospitalization. The most commonly reported symptoms were insomnia (18%), respiratory symptoms (15%), nasal congestion (12%), fatigue (11%) and concentration issues (10%) [84]. However, in the UK, <1% of children <17 years old self-reported symptoms of long COVID [88]. Hospitalized children and their families are also at risk of postintensive care/hospital syndrome (PICS) [89], compounding the virus’s effects on functional health domains, health-related quality of life, future development, and participation. Ongoing multicenter studies will provide further information about the long-term sequelae and outcomes associated with acute COVID-19 and MIS-C in pediatrics (Table 2).

**SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS-2 VACCINES AND NEUROLOGIC ADVERSE EVENTS**

In the US and the UK, the first vaccine approved for emergency use in people ≥16 years in December 2020, was Pfizer-BioNTech’s mRNA vaccine
### Table 1. Prevalence of neurologic manifestations reported with children hospitalized with SARS-CoV-2 infection by clinical phenotype\(^a\)

| Mixed cohort (Acute COVID-10 and MIS-C) | Acute COVID-19 | MIS-C |
|----------------------------------------|----------------|-------|
| **Any neurologic sign or symptom**     |                |       |
| 3/33 (9% Peru) [60]                    | 186/577 (32% US) [26**] | 30/99 (30% New York, US) [19] |
| 13/90 (14% Chile) [61]                | 239/1079 (22% US) [59**] | 13/186 (7% US) [23**] |
| 51/1334 (4% UK) [62**]                | 2/48 (8% USA/Canada) [63*] | 218/539 (40% US) [26**] |
|                                       | 2/27 (7% France) [64]   | 126/616 (20% US) [50**] |
|                                       | 186/577 (32% US) [26**] | 24/46 (52% UK) [65*] |
|                                       | 2/27 (7% France) [64]   | 14/36 (39% Turkey) [66] |
|                                       | 2/27 (7% France) [64]   | 4/27 (15% UK) [67*] |
|                                       | 186/577 (32% US) [26**] | 30/99 (30% New York, US) [19] |
| **Myalgias/muscular symptoms**         |                |       |
| 3/33 (9% Peru) [60]                    | 8/90 (9% Chile) [61]   | 17/186 (9% US) [23**] |
| 8/90 (9% Chile) [61]                  | 1/24 (4% Spain) [69]   | 17/43 (16% Spain) [69] |
| 1/10 [10% Mexico] [68]                |                |       |
|                                       | 1/24 (4% Spain) [69]   | 17/43 (16% Spain) [69] |
| **Headache**                           |                |       |
| 5/33 (15% Peru) [60]                   | 3/24 (13% Spain) [69]  | 29/99 (29%, New York, USA) [19] |
| 1/9 (11% India) [71]                  | 4/27 (15% UK) [62**]   | 24/46 (52% UK) [65*] |
|                                       | 4/100 (4% Italy) [73]  | 3/36 (11% India) [71] |
|                                       | 0/21 (0% India) [73]   | 17/45 (16% Iran) [70] |
| **Acute encephalopathy/acute agitation**|                |       |
| 24/46 (54% UK) [65*]                   | 7/1079 (0.6% US) [50**] | 2/99 (2%, New York, USA) [19] |
| 6/9 (66% India) [71]                  | 2/27 (7% France) [64]  | 8/616 (1% US) [30**] |
|                                       | 3/27 (11% Spain) [69]  | 24/46 (52% UK) [65*] |
|                                       | 14/27 (52% UK) [62**]  | 7/36 (19% Turkey) [66] |
|                                       | 1/21 (5% India) [73]   | 3/47 (7% France) [64] |
| **Meningitis and/or encephalitis**     |                |       |
| 2/10 (20%, optic neuritis), 1/10 [10% Anti-NMDA encephalitis, Mexico] [68] | 2/1079 (0.2% US) [50**] | 6/616 (1% US) [30**] |
| **Seizures**                           |                |       |
| 6/9 (66% India) [71]                  | 0/27 (0% Spain) [69]   | 1/46 (2% UK) [63*] |
|                                       | 8/27 (30% UK) [62**]   | 1/45 (2% Spain) [69] |
|                                       | 5/168 (3% Italy) [76*] | 4/25 (16% UK) [67*] |
|                                       | 3/62 (5% Saudi Arabia) [77] | 3/268 (1% UK/Ireland) [74] |
| **Stroke**                             |                |       |
| 8/971 (0.8% multicenter) [78*]        | 9/1079 (0.8% US) [50**] | 3/616 (0.5% US) [59**] |
| 2/10 (20% Mexico) [68]                |                |       |
| **Cerebral edema/intracranial hypertension** |                |       |
| None                                   | 2/1079 (0.2% US) [59**] | 2/616 (0.3% US) [59**] |
|                                        | 4 cases (Philadelphia, US) [79] |       |
| **Myelopathy**                         |                |       |
| 3/10 (30% Mexico, GBS) [68]           | 3/1079 (0.3% US; GBS) [59**] | 1/616 (0.2% US; GBS) [59**] |
|                                        | 5/27 (18.5% UK; GBS) [52**] |       |
| **Brain MRI abnormalities**            |                |       |
| 7/38 (18% international; ADEM-like pattern, myelitis, neuritis, splenial lesions) [80**] | 11/25 (44% UK; abnormal imaging) [62**] | 7/16 (44% UK; splenial changes, microhemorrhages, subcortical white matter lesions) [63**] |
|                                        | 6/12 (50% international; autoimmune presentations), 4/12 (33%, thomboschismic, 4/12 (33% infectious sequelae) [80**] | 4/27 (15% UK; splenial lesions) [67*] |
|                                        | 7/16 (44% UK; splenial changes, microhemorrhages, subcortical white matter lesions) [63**] | 17/23 (74% UK; abnormal imaging) [62**] |
|                                        | 4/11 (64% UK; splenic lesions, ADEM-like lesions) [80**] | 4/11 (64% UK; splenic lesions, ADEM-like lesions) [80**] |

*This table demonstrates the spectrum of neurological manifestations reported. This list is not all-inclusive of the current literature. Caution should be taken in comparing one study to another as each study has a different study population (e.g. all patients with neurological manifestations, all hospitalized patients), study designs, and study definitions. ADEM, acute disseminated encephalomyelitis; MIS-C, multisystem inflammatory syndrome in children; NMDA, N-methylD-aspartate; UK, United Kingdom; US, United States.*
### Table 2. Ongoing/upcoming studies examining neurologic manifestations of SARS-CoV-2

| Study (Country) | Design | Primary Outcomes | Neurology-Pertinent Secondary Outcomes |
|-----------------|--------|------------------|----------------------------------------|
| **COVID-19**: Pediatric Research Immune Network on SARS-CoV-2 and MIS-C (PRISYM) | Study Design: Prospective observational multisite cohort  
Population: Acute COVID-19 and/or MIS-C  
Inclusion criteria: ≥21 years old  
Exclusion criteria: none | Proportion of patients with death, rehospitalization, or complication | Neurologic sequelae up to 1-year postillness  
Health-related quality of life up to 1-year postillness |
| **Global Consortium to Study Neurological dysfunction in COVID-19 (GCS-NeuroCOVID)** (Multisite) | Study Design: Prospective observational multisite registry  
Population: Acute COVID-19 and/or MIS-C  
Inclusion criteria: <18 years old  
Exclusion criteria: none | Overall prevalence of neurological manifestations among hospitalized COVID-19 and/or MIS-C patients  
Health-related quality of life 1-month postdischarge | In-hospital, 30 and 90-day mortality  
Discharge modified Rankin score  
90-day modified Rankin scale |
| **Neurocognitive Impairment in Patients With COVID-19** (France) | Study Design: Observational case control study  
Population: Cohorts of adults and children with (cases) and without (controls) SARS-CoV-2  
Inclusion criteria: Patients admitted to a hospital and SARS-CoV-2 confirmed (cases) or excluded (controls) within 48 h of admission  
Exclusion criteria: none | Incidence of delirium/neurocognitive impairment in adult and pediatric patients with COVID-19  
Change in neuroaxonal injury biomarker levels in patients with COVID-19  
Neurocognitive 3-months outcome in patients with COVID-19 | |
| **CORONERVE**: Neurological complications of COVID-19 (United Kingdom) | Study design: Multisite observational study  
Population: Children with acute onset neurological syndrome including encephalitis, encephalopathy, meningitis, demyelination, myelitis, cerebrovascular, cerebellar, Guillain-Barre syndrome, etc. in eligible population  
Inclusion criteria: Child 0–18 years of age with suspected or proven COVID-19 infection and acute neurological syndrome as above  
Exclusion criteria: No evidence of active or recent COVID-19 infection | To determine the demographic, clinical, laboratory and radiographic features of patients presenting with acute neurological syndromes during or within 6 weeks of virologically proven coronavirus infection | Proportion receiving immune and associated therapies  
Clinical outcomes of patients which each neurological syndrome relative to baseline features and treatments received |
| **NEPyson-COVID**: Assessment of Neurological, Epidemiological, Psychiatric and Psychosocial Consequences during the COVID-19 Pandemic (India) | Study design: Prospective observational study  
Population: All neurological patients [1–70 years] visiting the neurological emergency following the with the criteria.  
Inclusion criteria: a. Patients of neurological disorders with previously described symptoms related to COVID-19 infection (e.g. stroke, acute encephalitis, seizure, Guillain-Barre syndrome, ADEM)  
b. Patients of neurological disorders precipitated or preceded by respiratory symptoms in the last 2–4 weeks  
c. Patients of neurological symptoms not fitting the criteria of a/b but found to have lymphopenia / thrombocytopenia / thrombotic states / elevated D-dimer levels  
Exclusion criteria: neurological disorders of other etiology and lack of consent | Death | Proportions of patients with each neurological diagnosis in the group with neurological disease  
Admission to critical (intensive/high dependency) care unit  
Time to discharge from hospital  
Functional outcome at discharge [or 30 days from admission, if still in hospital] |
| **Perinatal COVID-19 Infection, NO Pathway, and Minipuberty (miniNO-COVID)** | Study Design: Single site prospective observational case-control study  
Population: Newborn infants (24 to 41 weeks gestational age) or young infants (<3 months)  
Inclusion criteria: Group 1: Antenatal or perinatal COVID-19 infection  
Group 2: Severe cardiorespiratory diseases requiring intalled NO treatment  
Group 3: Control group with perinatal COVID-19 infection and no intalled NO treatment [matched]  
Exclusion criteria: <24 weeks gestational age, severe brain lesions: bilateral/ extensive periventricular leucomalacia, intracranial hemorrhage grade 3 or 4 | The follicle stimulating hormone (FSH) plasma concentrations measured at the postnatal age of 3 months  
The rate of negative hearing and olfactory tests  
The developmental scores (ASQ-3, ASQ-2E, Bayley III)  
The time of mutual gaze interactions [vs noninteractive periods] measured by eye-tracking glasses (mother and children) at 9 months | |
This approval was extended to US adolescents 12–15 years of age in May 2021 [92] with ongoing trials for younger children to determine dosing, safety, and efficacy. Multiple other vaccines using mRNA, viral vector, and inactivated virus-based platforms have been introduced since. As of July 12, 2021, over 3 billion vaccines doses had been administered worldwide [5*]. Impact of vaccination and VOC emergence on the frequency and presentation of neurological manifestations remains to be determined.

As of July 2021, there have been no reports of neurologic adverse events following vaccination in children. In adults, GBS variants have been reported following viral vector-based vaccine administration (Oxford-AstraZeneca, Johnson & Johnson’s Janssen), but this is rare [93,94]. Currently, a history of GBS is not considered a contraindication for receiving a SARS-CoV-2 vaccine. In addition, while there was early concern of acute onset peripheral facial nerve palsy following mRNA-based vaccine administration (Pfizer-BioNTech, Moderna) [95,96], subsequent evaluation of 320 million vaccination administrations from the WHO database demonstrated no increase over baseline population incidence following vaccination [97]. These data highlight the importance of reporting and monitoring potential vaccine adverse effects through national and international systems, such as the CDC’s Vaccine Adverse Event Reporting System, to determine if there are true associations between specific vaccines and potential neurologic adverse events.

**KEY LESSONS FOR THE NEXT PANDEMIC**

The emergence of multiple novel pathogens in the 21st century has reinforced the critical need for rapid, prospective, global epidemiologic and clinical data collection when new infectious threats present [3,35,37–39]. Although national and international public health systems in HIC have developed excellent mechanisms to monitor case counts and mortality, most of our understanding of neurological manifestations has initially come from HIC case reports and case series [98]. Prospective global data on neurological manifestations and outcomes of the various SARS-CoV-2 clinical phenotypes are only now beginning to emerge, 17 months into the pandemic, with pediatric data lagging. Investment in research to examine the impact SARS-CoV-2 infection has on the developing brain in the context of the individual and family is greatly needed.

Although the pandemic has highlighted examples of clinical research of good quality despite constraints, it has also highlighted gaps in existing international research infrastructure [99*]. Standardized reporting of clinical data, as used in the ISARIC/WHO clinical characterization protocol

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### Table 2 (Continued)

| Study (Country) | Design | Primary Outcomes | Neurology-Pertinent Secondary Outcomes |
|----------------|--------|------------------|---------------------------------------|
| **Brain imaging in baby study**<br>Trial number: NCT04443179 (United Kingdom) | - Study Design: Prospective observational case control study | - Neurodevelopmental outcomes of children at 3–4 years of age |
| | - Population: Community sampling of eligible cohorts listed below | |
| | - Inclusion criteria: Pregnant mothers with and without confirmed COVID-19. Infants with and without an immediate family history of Autism Spectrum, neurodevelopmental conditions, based in England, UK | |
| | - Exclusion criteria: based on further screening | |
| | - Note: This is not a COVID-19 specific study. COVID-19 cohort was added to an existing study | |
| **CLoCk: Children & young people with Long Covid study**<br>Trial number: ISRCTN34804192 (United Kingdom) | - Study design: A longitudinal cohort analytic study with online questionnaire (3, 6, 12 and 24 months post-COVID test) | - Physical symptoms: ISARIC Pediatric COVID-19 questions |
| | - Population: SARS-CoV-2 positives aged 11–17 years compared with age, sex and region matched SARS-CoV-2 test negative controls | - Emotional and mental health: Strength and Difficulties Questionnaire |
| | - Inclusion criteria: Those that have had a COVID-19 test between 01/09/2020 and 28/02/2021 | - Quality of life/functioning: EQ-5D-Y |
| | - Exclusion criteria: None | - Fatigue: Chalder Fatigue Questionnaire |
| | | - Wellbeing: Warwick Edinburgh Mental Wellbeing Scale (WEMWBS, short version) |
| | | - Loneliness: adapted UCLA 4 items |

SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; COVID-19, coronavirus disease 2019.
and by the Overcoming COVID-19 investigators [23**,26**,59**], provided timely epidemiological, clinical, and prognostic information during the pandemic for children. Large scale interventional trials in adults (e.g., SOLIDARITY, RECOVERY, ACTT, REMAP-CAP) were instrumental in reducing uncertainty at the bedside and improving outcomes [100–103]. However, such large-scale interventional trials in children have not yet emerged.

Single-center studies are locally impacted by patient population demographics (e.g., age, comorbidities, social determinants of health) and by the frequency of neurologic manifestations. There is thus a critical need for multicenter, multinational collaboration to better understand neurologic manifestations of pediatric diseases. Clinical research networks in pediatrics (e.g., PALISI, PCCSSG, ESPNIC, ANZICS-PSG, LaRed, PACCMA, CPCCRN), neurology (e.g., PNCRG, NeuroNEXT), and infectious disease (ISARC) worldwide have produced innovations in epidemiology, pathobiology, and therapeutic efficacy in a variety of disorders. These networks could be leveraged to create a resource previously unavailable to transform pediatric neurologic care worldwide.

We propose establishing an inclusive, global neurology research network platform in advance of the next pandemic to facilitate rapid execution of streamlined and cost-effective neurology-focused pediatric protocols. This platform should incorporate key principles of a Learning Health System, scaled for global application [104]. Necessary steps include: (a) sufficient, equity-oriented funding for platform infrastructure to facilitate participation, (b) coordination among existing and newly created clinical research networks; (c) streamlined, standardized case report form with predefined common data elements; (d) training/education bundles; (e) biorepository with standards for sample collection, transfer, and storage; (f) preexisting and centralized ethical/regulatory approval; and (g) inclusive (e.g., clinical, research, funder, family/patient) and effective leadership structure (Fig. 2). This platform could facilitate swift understanding of the epidemiological scope of the neurologic problem, generate hypotheses, evaluate potential risk factors and outcomes, and support direct public health efforts. When therapeutic interventions are proposed, this platform may provide the springboard for efficient clinical trials using innovative methodologies such as randomized registry trials and a master protocol to test multiple interventions.

CONCLUSION

Neurological manifestations of SARS-CoV-2 infection in children are common, heterogenous, and distinct in each clinical phenotype (acute COVID-19, MIS-C, and PASC). Their potential impact on overall pediatric SARS-CoV-2 morbidity and mortality has yet to be determined. A strategy to create an equitable, global neurology-focused platform for future emergent deployment to capture high-quality data and specimens is critically needed to care for and protect children with neurologic manifestations of disease across the globe.
Neurology

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There are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:
- of outstanding interest
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