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REVIEW

# Acute and post-acute neurological manifestations of COVID-19: present findings, critical appraisal, and future directions

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## Abstract

Acute and post-acute neurological symptoms, signs and diagnoses have been documented in an increasing number of patients infected by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which causes Coronavirus Disease 2019 (COVID-19). In this review, we aimed to summarize the current literature addressing neurological events following SARS-CoV-2 infection, discuss limitations in the existing literature and suggest future directions that would strengthen our understanding of the neurological sequelae of COVID-19. The presence of neurological manifestations (symptoms, signs or diagnoses) both at the onset or during SARS-CoV-2 infection is associated with a more severe disease, as demonstrated by a longer hospital stay, higher in-hospital death rate or the continued presence of sequelae at discharge. Although biological mechanisms have been postulated for these findings, evidence-based data are still lacking to clearly define the incidence, range of characteristics and outcomes of these manifestations, particularly in non-hospitalized patients. In addition, data from low- and middle-income countries are scarce, leading to uncertainties in the measure of neurological findings of COVID-19, with reference to geography, ethnicity, socio-cultural settings, and health care arrangements. As a consequence, at present a specific phenotype that would specify a post-COVID (or long-COVID) neurological syndrome has not yet been identified.

**Keywords** COVID-19 · SARS-CoV-2 · Neurological diseases · Post-COVID

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## Background

The current pandemic caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the coronavirus responsible for the Coronavirus Disease 2019 (COVID-19) infection, has led to the identification of a complex phenotype that includes, among others, several neurological disorders (symptoms, signs or diagnoses) characterizing the acute phase of the disease [1–9]. These disorders are believed to be either a result of direct viral infection of the nervous tissue or an indirect consequence of the activation of immune-mediated and vascular mechanisms [10–13]. However, very little is known about the short-term and long-term consequences of COVID-19.

An increasing number of case reports illustrate the occurrence of differing neurological disorders [3–7, 9]. Several of these reports refer to well-defined immune-mediated disorders, including Guillain–Barre syndrome (GBS), post-infectious immune encephalitis, Central Nervous System (CNS) vasculitis, and myelitis. These neurological conditions and similar disorders have been reported after previous viral outbreaks, including infections caused by other coronaviruses [14–30] and might reflect common complications of viral action and even of vaccines [31, 32].

The overall picture is further complicated by three factors that must be considered when testing the purported association between COVID-19 and specific neurological manifestations:

- Identification of neurological symptoms, signs or diagnoses occurring after the acute phase of COVID-19, which might result from indirect effects of the infection and should be differentiated from chance association with comorbidities;
- Neurological sequelae from the acute phase (including post-intensive care syndrome) which must be distinguished from newly ascertained occurrences during follow-up; and
- Post-acute neurological manifestations in COVID-19 patients that might be associated with known and/or unknown genetic, demographic and/or environmental factors.

Any new neurological manifestation, documented after the development of symptoms due to SARS-CoV-2 should, therefore, undergo critical appraisal and be investigated with the appropriate methods.

### Key questions

To investigate the above factors, the following research questions should be posed:

- Are there specific new-onset neurological symptoms, signs or diagnoses occurring after the acute phase of COVID-19 symptoms that can be interpreted as sequelae of COVID-19?;
- Are there any neurological symptoms, signs or diagnoses that arise during and persist after the acute phase of COVID-19?; and
- What are the factors associated with the persistence and/or any new-onset post-acute neurological manifestations?

## Methods

For the purposes of this Rapid Review, we searched PubMed for appropriate articles to address the three key questions above, which were drawn from articles that were published up to January 28, 2021. As our aim was not to perform a systematic review of the literature and we wanted to exclude the effects of vaccines, we deliberately did not include articles published after that date.

Using MeSH terms for COVID-19 and neurological disorders, and filtering for study types in humans, two separate searches were performed (see Online Appendix for details).

### First search

The first search focused on studies related to the incidence, outcome (with risk factors), and sequelae of neurological manifestations in patients with COVID-19. Eligible articles were those focusing on neurological sequelae of COVID-19 or incident neurological manifestations at the end of the acute phase or during follow-up. Three types of cohort studies were considered: the first comparing patients confirmed positive with real-time polymerase chain reaction assays (RT-PCR) (COVID +) with contemporaneous RT-PCR negative patients (COVID-); the second comparing COVID + patients with neurological manifestations with those without; and the third (with nested case–control studies) comparing those who survived with those who did not.

### Second search

The second search focused on neurological symptoms, signs or diagnoses identified in case reports of patients with

COVID-19. Psychiatric/Neuropsychiatric conditions were not the focus of this report.

The original research articles found in these focused searches were examined to determine:

- Incident neurological symptoms, signs or diagnoses occurring after the onset or the end of the acute phase of COVID-19;
- Prevalent neurological symptoms, signs or diagnoses persisting after the acute phase; and
- Identification of patients who are at higher-than-expected risk of developing neurological sequelae or neurological symptoms, signs or diagnoses occurring during follow-up.

## Results

### First search

The results of this search led to the identification of 444 studies, of which 28 were found eligible for detailed review (e-Table 1). Eligible studies were those whose abstracts included matched or unmatched comparison groups and those with follow-up after discharge. 21 cohort studies (18 retrospective and 3 prospective), 6 case–control studies and 1 case series with follow-up were included. Each study is illustrated in the table in terms of population, setting, main demographics, exposed vs. unexposed individuals (cases vs. controls), outcome measures, results and quality assessment. With few exceptions [33–35], all patients who were COVID + had tested positive with RT-PCR.

In the two studies that included up to a six-month follow-up after hospital discharge, neurological sequelae were frequently present. In a retrospective cohort of 1733 COVID + patients discharged from the hospital, 19.6% of cases (340) reported neurological manifestations after a median follow-up of 186 days [36]. The commonest reported complaints were fatigue or muscle weakness (63%, 1038/1655) and sleep difficulties (26%, 437/1655). Anxiety and depression were reported by 23% (367/1617) of patients and difficulty walking by 24% (103 of 423). Common complaints at discharge included amnestic dysfunction (30%, 18/61), dysexecutive syndrome (33%, 20/61), ataxia (11%, 7/61) and tetraparesis (18%, 11/61) [37].

Overall, even with different incidence rates, the presence of neurological manifestations during or after the acute phase of COVID-19 was associated with a more severe disease and a worse outcome, with higher proportions of in-hospital deaths, longer length of stay, and persistent neurological sequelae (functional disability, transfer to rehabilitation/nursing facilities) at discharge (see e-Table 1) [35, 38–40].

In a large prospective hospital cohort ($N = 4491$), 88% (948/1072) of patients seen by neurologists had a new neurological manifestation and 64% (606/948) of these tested positive for COVID-19 [40]. The prevalence of neurological disorders among all hospitalized patients was 13.5% (606/4,491). The most common disorders among COVID + patients who were seen by neurologists were toxic/metabolic encephalopathy (51%, 309/606), stroke (14%, 84/606), seizures (12%, 74/606), and hypoxic/ischemic brain injury (11%, 65/606). Forty-six percent (34/74) of seizures were incident events. The median time from onset of the first COVID-19 symptom to the onset of neurological symptoms was 2 days (interquartile range, IQR 0–13). Fifty-four percent of cases ($N = 326$) had neurological symptoms after a median of 12 days (IQR 5–22). These patients were older, more severely ill, and less likely to be discharged home [40].

In a retrospective cohort of 509 hospitalized COVID + patients, 19.6% of cases developed neurological manifestations after hospital admission [38]. In another large retrospective cohort of COVID + patients ($N = 574$), two-thirds developed neurological manifestations during the course of the disease [39]. Of these, 9.8% presented new neurological symptoms/signs or diagnoses while in hospital. The authors classified neurological manifestations into major (encephalopathy, 8.4%, 48/574; critical illness neuropathy/myopathy, 0.9%, 5/574; ischemic stroke, 0.5%, 3/574) or minor (myalgia, 5.4%, 31/574; headache, 5.2%, 30/574; dizziness, 4.5%, 26/574; dysgeusia, 3.8%, 22/574; anosmia, 2.4%, 14/574). In-hospital mortality was 28.7% in patients with a history of neurological disorders and 15.3% in patients who presented with both neurological manifestations and COVID-19, whereas in those with incident symptoms during their hospital stay it was 22.5%. Patients with major neurological manifestations at any time experienced a higher mortality (37.4%) compared to those who had no major neurological manifestations during COVID infection (11.9%).

The presence of any neurological symptom, sign or disease was a significant predictor of death (Hazard Ratio 2.1) in a population-based sample of COVID + patients [41]. Additional findings from other studies revealed that the occurrence of any neurological complications was also associated with the need for acute rehabilitation and transfer to nursing homes [40]. The occurrence of major neurological signs/diseases (encephalopathy, seizures, ischemic stroke, critical illness neuropathy, cerebral venous thrombosis, and even posterior reversible encephalopathy syndrome) carried a high mortality risk [39]. Concurrent neurological diseases (mostly pre-existing dementia) carried a 32.6 timed higher risk of death in a large population-based cohort ($N = 7057$) [42].

Stroke was the most commonly reported neurological disease among hospitalized patients. Stroke risk ranged from 0.5% (33) to 1.6% [43]. The interval between onset of COVID-19 symptoms and stroke varied from 1 to 27 days (predominantly 6–10 days) [43–49]. Stroke occurred during a hospital stay in 56.2% (18 of 32) of cases in one study [44] and in 74.2% in another study (23/31 with acute ischemic stroke) [43]. Ischemic stroke predominated, followed by haemorrhagic stroke. Of ischemic stroke cases, those of undetermined etiology (cryptogenic stroke) or due to involvement of large vessels were commonly reported [43–45, 47–49]. Patients with symptomatic COVID-19 + and stroke were compared with asymptomatic COVID-19 + patients with stroke or with contemporary or antecedent COVID-19 negative stroke patients. COVID-19 was associated with a higher incidence of ischemic stroke than influenza infection (OR 7.6; 95% CI 2.3–25.2) [43]. Compared to COVID-negative individuals, COVID-positive patients had higher rates of hospital admissions for cerebrovascular diseases [34]. Compared to historical or concurrent controls, patients with stroke associated with COVID-19 presented a higher risk (up to 40-fold) of in-hospital mortality and functional disability at discharge [42, 45–48]. Risk factors for stroke in COVID + patients included disease severity and ischemic heart disease [32]. Along with cerebral infarction, intracerebral and subarachnoid haemorrhage were more frequently documented among hospitalized COVID-19 + than in COVID-19 negative subjects [50]. Disease severity was higher in older than in younger cohorts, with 32.1% (85/265) in-hospital mortality and 36.4% (96/265) institutionalization rate in the oldest elderly subjects who had a stroke during the course of their COVID-19 infection [49].

Delirium was another neurological manifestation associated with higher disease severity, as shown by the higher proportion of cases with a prolonged hospital stay, admission to the intensive care unit (ICU) or in-hospital mortality [34, 51]. In one study [34] delirium was present in 73.3% (22 of 30) of COVID + patients with pre-existing dementia. Elderly patients experiencing delirium were at higher risk of functional disability requiring rehabilitation [52].

Disorders of consciousness, when present, were also a significant predictor of death [2]. In one study, 10% of patients who did not improve while in the hospital experienced the loss of consciousness (LoC) [53]. In this cohort, in-hospital death was more than tenfold higher than in patients without LoC.

In contrast, the presence of syncope did not result in increased mortality [54] while anosmia (isolated or in combination with ageusia) was accompanied by a favourable outcome [55].

When SARS-CoV-2 was compared to other influenza viruses, despite an overall higher severity, data on any neurological manifestations were not significantly different [56], but ischemic stroke was significantly more frequent in COVID + patients (Relative Risk 3.1) compared to those with influenza [57].

Compared to hospital-based studies, population-based studies provide different results. GBS is an acute post-infectious immune-mediated polyradiculoneuropathy typically occurring a few days to few weeks after bacterial or viral infections, including coronaviruses. In a population-based cohort of GBS patients from the UK National Immunoglobulin Database, 47 cases of GBS were reported with definite (13), probable (12), or no (22) COVID-19 infection [58]. However, there were no between-group differences in all measures (incidence, severity, and outcome) and GBS fell in the UK during the pandemic. This finding is an argument in favour of the use of population-based studies to confirm the external validity of the results of cohort or case–control studies performed in hospital studies.

## Second search

The second search focused on case reports of neurological manifestations associated with COVID-19. The results of this search led to the identification of 950 studies, 431 of which fulfilled our criteria for eligibility and presented data on neurological diagnoses, symptoms, or clinical or instrumental signs (e-Table 2). Acute ischemic stroke was the most commonly reported disease (71 cases, 16.5%), followed by GBS (67, 15.5%), cranial neuropathies (33, 7.7%), encephalitis/meningitis (30, 7.0%), cerebral venous thrombosis (17, 3.9%), intracerebral haemorrhage (16, 3.7%), myelitis/myelopathy (14, 3.2%), parainfectious (autoimmune) encephalopathies (13, 3.0%), other peripheral neuropathies (2.8%), posterior reversible encephalopathy syndrome (11, 2.5%), acute necrotizing encephalopathy, and seizures/epilepsy (10 each, 2.3%). Cerebrovascular disorders predominated, followed by (immune-mediated) peripheral neuropathies. Neurological manifestations occurred during both the acute and post-acute phase and presented differing COVID-19 severities and outcomes. Other manifestations (see e-Table 2) were occasionally reported and, in a few instances, even symptoms, signs or subclinical findings with no link to a specific diagnosis were documented (for a total of 36 case reports).

The results of case reports are implicitly limited because the role of chance cannot be excluded, particularly for manifestations that are apparently unrelated to the infectious disease. However, case reports can be indicators of a possible association that could require further investigation if considered biologically plausible.

In summary, based on the above findings, a number of adverse effects of SARS-CoV-2 on the central and peripheral nervous system have been documented. The robustness of the association between COVID-19 infection and neurological manifestations is supported by the strength and the

consistency of findings and by a biological (dose–response) gradient (ie, a more severe disease should generally lead to a greater incidence of neurological findings). The underlying mechanisms of the viral action on the vascular and nervous system, that might reflect persistent brainstem dysfunction, make the association biologically plausible [10–13]. In addition, in most instances the findings were confirmed even after adjusting for major confounders like older age and chronic comorbidities that have been repeatedly found to adversely affect the outcome of COVID-19. However, published reports have important limitations that can have significant effects on the external validity of the results and, more specifically, the number and type of immediate, short-term and long-term neurological complications. These limitations are inherent in the study design, the population at risk, the accuracy and reliability of the diagnoses, the duration of follow-up, and the definition of the outcome measures.

## Limitations of published reports (Box 1)

There is still variability in measuring the risk of neurological manifestations, which is mostly explained by the differing study populations and the use of different, often suboptimal study designs [59]. Limited knowledge about the mechanisms of COVID-19 infection and the complexity of the interactions between various viral and non-viral factors are the most likely explanations for our present lack of understanding regarding the impact of COVID-19 on the nervous system. Information about the phenotype of COVID-19 has been mostly obtained from referral series, and predominantly from hospitalised patients. For this reason, the spectrum of the disease tends to reflect the most severely affected cases. These findings, in the absence of well-defined study populations, might mask the true incidence and spectrum of neurological complications. Data from low- and middle-income countries are also scarce, leading to underreporting of neurological findings of COVID-19 overall, particularly in the post-acute phase, with reference to geography, ethnicity, age and sex, and socio-cultural environment. Other limitations that should be further emphasized include variability in clinical case definition (use of differing diagnostic criteria), low level of control for confounders (risk factors and comorbidities), and variable and generally short follow-up periods.

Additionally, some studies included asymptomatic patients in their control groups who were not screened with molecular or serological tests to exclude SARS-CoV-2 exposure. This bias might have resulted in the dilution of any reported differences. Screening methods and diagnostic ascertainment also varied across studies depending on the clinical background of local investigators (nurses *vs.* doctors; neurologists *vs.* non-neurologists), number and type of contacts during follow-up and, importantly, attrition (number of contacts with patients during follow-up) and patients' consent and compliance. Missing information is not at random and, as such, can bias the external validity of the study results, especially when post-acute disorders are investigated. In addition, most of the reviewed studies were done under surge conditions, leading to incomplete diagnostic assessments. The present data are mostly based on patients' self-reports, clinically relevant manifestations, and with more attention paid to symptoms, signs and diseases illustrated in previous reports, leading to a reporting bias. In other regards, however, information is extremely limited regarding signs that can only be documented through testing, imaging or biochemical or pathological investigations.

Another limitation intrinsic to the nature of an infectious disease that affects the nervous system is the inclusion of the entire spectrum of symptoms, signs and even diseases that may be part of the underlying infectious disease process, like headache, myalgias, asthenia and even meningoencephalitis. In addition, even if different underlying mechanisms are present, acute and post-acute symptoms can hardly be separated, making it difficult to define a neurological syndrome characterized by manifestations persisting at the end of the acute phase and/or occurring during follow-up as a separate nosological entity.

With the current background of research, the knowledge of the outcome and long-term impact of SARS-CoV-2 on the nervous system is at present limited, as insufficient time has elapsed for any long-latency effects to appear in the majority of cases.

At the time of writing, two systematic reviews on post-COVID syndrome were published.

The first [60] identified studies published from January 1, 2020, to March 11, 2021, that examined persistent symptoms after COVID-19 infection, defined as those persisting for at least 60 days after diagnosis, symptom onset, or hospitalization or at least 30 days after recovery from the acute illness or hospital discharge. 45 studies reporting 84 clinical signs or symptoms were included in the systematic review. There were 9751 total participants. The median proportion of individuals experiencing at least 1 persistent symptom was 72.5%. Individual symptoms occurring most frequently included, among others, sleep disorders or insomnia, followed by headache, memory loss and cognitive deficits. However, the authors noted wide variations in the design and quality of the studies, which had implications for interpretation and often limited direct comparability and combinability. The second systematic review [61] collected studies on long-term COVID-19 symptoms published until February 15, 2021. 145 reports met authors' selection criteria. 24.1% of reports were on neurologic complaints and olfactory dysfunctions. The commonest manifestations include headache

and, to a lesser extent, anosmia/ageusia, sleep disorders, distal paresthesiae and cognitive impairment. A relatively high heterogeneity of the reviewed.studies was confirmed also in this review.

Changes in exposure to the virus, virulence and virus mutation (with special reference to the delta variant), mediated by changing disease control measures and alterations in the organization of healthcare systems, as well as the evolution of therapeutic strategies for COVID-19, can also have an impact on the disease outcome and its complications, even within the same country. In addition, data on the follow-up of patients with COVID-19 are at present insufficient to demonstrate that any incident neurological manifestation that occurs at the end of the acute phase of COVID-19 is higher than expected in the broader population.

## Box 1: Limitations of published reports

- Data collected from selected case reports or clinical series.
- Very limited data from low-income countries.
- Predominant assessment of more severe disease varieties.
- Under-reporting of data from non-hospitalized patients.
- Focus on selected disease aspects (e.g., neurological, pneumological) and not to the full spectrum of the COVID-19.
- Unclear separation of direct complications of infection (headache, acute CNS infection) from diseases attributable to other pathogenic mechanisms.
- Use of differing disease definitions.
- Variable degree of diagnostic assessment.
- Unknown interaction between SARS-CoV.2 and preexistent comorbidities.
- Limited follow-up observation.
- Non-standardized investigation of sequelae/complications.
- Patient-reported vs. investigation-driven outcome measures.
- Inadequate assessment of the risk attributable to COVID-19 (lack of adequate controls).
- Uncontrolled effects of treatments.

## Knowledge gap

In light of the present reports, there is a substantial gap in the knowledge of the association between COVID-19 and the large majority of neurological manifestations, if stroke and immune-mediated disorders of the central and peripheral nervous system are excluded. More specifically (see also Table 1):

- Neurological manifestations occurring during the acute phase of the infection cannot be easily disentangled from those with onset in the post-acute phase;
- Existing reports are flawed by selection and reporting bias. Available data reflect the spectrum of neurological manifestations in patients with the more severe forms of COVID-19;
- The information on patients who were not hospitalized is almost completely missing;
- Neurological symptoms, signs and diagnoses cannot be always differentiated from symptoms and signs that belong to the clinical spectrum of an infectious disease;
- Neurological symptoms or diagnoses occurring de novo during follow-up cannot yet be identified or quantified due to the very limited number of reports with prolonged follow-up;
- Subclinical findings (e.g. minor cognitive impairment) are still rarely investigated and might require the use of specific diagnostic instruments (eg, neuropsychological tests; imaging studies);
- Pathological studies are still insufficient to provide an exhaustive picture of the organ-systems (including the nervous system) involved by the pathologic process.

**Table 1** Recommendations for studies on neurological sequelae associated with SARS-CoV-2 infection

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|---|
| *Study population* should be clearly defined in terms of clinical or community-based cohorts, sociodemographic characteristics, comorbidities, linkage to external registries as a data source (e.g., mortality) |
| As diagnostic and therapeutic resources/approaches are varying among and within countries and changes can happen over time, the study timeframe should be specified and linked to relevant information on the pandemic in the country(ies) of origin of the study population |
| *Outcome neurological measures* prevalent and incident neurological disorders (signs, symptoms, syndromes, diseases) should be distinguished. Clinical case definitions should be reported (e.g., diagnostic procedures, laboratory, neuroimaging, and other diagnostics tools used) |
| *Time of onset* of incident neurological disorders, from early signs/symptoms of SARS-CoV-2 infection or confirmed infection, should be specified. This would facilitate the identification of short, medium, and long-term neurological disorders |
| *Outcome, non-neurological measures* relevant measures that can be reported include duration of hospitalization, disability, need for rehabilitation or long-term treatment, institutionalization, and mortality |
| *Missing information* from baseline and follow-up, should be adequately discussed, including considerations on how they could have affected the reported measures of occurrence/associations, as well as in terms of effects on the external validity of the study findings |

## Future directions (Box 2)

Based on this Rapid Review, we need a more extensive systematic and updated review of the available evidence to address the above key questions and put more emphasis on the long-term aspect, which is difficult to assess at present due to lack of appropriate studies. Each study will be assessed for quality using the risk of bias measures.

Although the investigation of neurological manifestations associated with COVID-19 in population-based samples with accurate follow-up and limited attrition is difficult to obtain, adequate inception cohorts can be still identified, which should be drawn from the different clinical settings in which a patient is assessed (e.g., outpatient services, emergency rooms, ICU admissions).

Ongoing (neuro)COVID registries [62–64], data banks [65] and surveillance systems [66] with active follow-up (including the upcoming WHO follow-up tool) (https://www.who.int/publications/i/item/global-covid-19-clinical-platform-case-report-form-(crf)-for-post-covid-conditions-(post-covid-19-crf-) can provide useful information for the identification of incident neurological manifestations (types and frequency) in large cohorts of patients enrolled during the acute phase of the disease. In these registries and surveillance modules, the ascertainment of COVID-19 complications during follow-up should be made using accurate measures, valid and reliable diagnostic criteria, and standardised methods for the characterisation of any signs or symptoms. Additional screening instruments (neuropsychological tests, imaging studies) should be used to investigate subclinical events.

Consensus is also needed regarding how to classify manifestations in the post-acute period. A pragmatic approach has been proposed to classifying phenotypes and severity of post-acute COVID-19 syndrome [67].

The potential for presently unknown long-term and delayed-onset emergent neurological complications must also be recognised. Matched controls must be used to distinguish unrelated clinical conditions from those caused directly or indirectly by the virus, or by an associated prophylaxis (vaccines or drugs), treatment, or the broader psychosocial impact of the pandemic. As symptoms perceived by patients and/or physicians might not require immediate neurological consultation, follow-up visits (face-to-face or virtual) should be planned by those in charge of the initial consultation for a period of at least 12 months.

## Box 2: Future directions

- Studies in well-defined populations or inception cohorts.
- Involvement of and comparison between high-income and low-income countries.
- Use of standard definitions for target diseases and risk factors.
- Use of valid and reliable diagnostic and outcome measures.
- Adoption of prospective designs.
- Accurate definition of the patients' profiles at baseline (with inclusion of socio-demographic, psychosocial characteristics, and comorbidities).
- Data collection on treatment schedules (including vaccinations).
- Screening instruments (neuropsychological tests, imaging studies) to be used in ad-hoc studies.
- Comparison with matched unexposed individuals.
- Prolonged follow-up with predefined periodic contacts for the investigation of sequelae and new manifestations.
- Minimization of drop-outs (time-consuming data collection to be avoided to encourage participation and improve compliance).
- Longitudinal assessment of the pandemic to verify whether variants are associated with differing phenotypes and disease severity.
- All studies to be performed in compliance with high-quality standards following available guidelines.

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