Feedback from operational stakeholders who manage or respond to outbreaks is that they are often too busy to review literature or obtain relevant background information to assist them with acute response. Unlike a traditional analytical outbreak investigation report, ***Watching Briefs*** *are intended as a rapid resource for public health or other first responders in the field on topical, serious, or current outbreaks, and provide a digest of relevant information including key features of an outbreak, comparison with past outbreaks and a literature review. They can be completed by responders to an outbreak, or by anyone interested in or following an outbreak using public or open source data, including news reports.*

Watching brief

Title	**COVID-19-associated encephalitis**
Authors	Braidy Sutton, Damian Honeyman, Adriana Notaras, Ashley Quigley
Date of first report of the outbreak	In February 2020, the first report of encephalitis arising from a positive SARS-CoV-2 infection was reported in Japan (male, 24, clinical outcome not reported) (1).
Disease or outbreak	COVID-19-associated encephalitis has been described as a neurological complication that can occur at all stages of a positive SARS-CoV-2 infection (2, 3) and considered a medical emergency requiring urgent care, with complications encompassing severe disability and death (3-6). Encephalitis is an inflammatory condition of the brain consisting of encephalopathy (altered consciousness, lethargy, irritability and/or a change in personality/behaviour); diagnostic evidence of central nervous system (CNS) inflammation, and a combination of the following symptoms and diagnostics: fever, seizures, focal neurological deficits attributable to brain parenchyma inflammation, cerebrospinal fluid (CSF) pleocytosis, neuroimaging results and electroencephalogram (EEG) results (7, 8).

Origin (*country*, *city*, *region*)	The first confirmed case of COVID-19-associated encephalitis was reported in Japan in a 24-year-old male in February 2020 (index case) (1).
Suspected Source (specify food source, zoonotic or human origin or other)	SARS-CoV-2 is a zoonotic coronavirus, with bats the most likely reservoir of the virus with high rates of human-to-human transmission (9). COVID-19 associated encephalitis is a relatively rare secondary infection of severe COVID-19 disease.
Date of outbreak beginning	The first case of COVID-19 associated encephalitis was reported in February 2020 (1).
Date outbreak declared over	Cases of COVID-19 associated encephalitis continue to be reported during the ongoing COVID-19 pandemic.
Affected countries & regions	As of 4th December 2022, COVID-19-associated encephalitis has been reported in the following countries: India, Italy, Spain, the United States of America, Germany, the United Arab Emirates, Iran, Japan, the United Kingdom, Belgium, Republic of Macedonia, Egypt, Sweden, Brazil, France, China, and Japan (4).
Number of cases (specify at what date if ongoing)	A multinational retrospective analysis performed in 2021 concluded that from 610 studies with a combined patient population of 129,008 across seventeen nations, there were 138 cases of COVID-19-associated encephalitis (4). The average incidence of encephalitis is therefore low, at 0.215%, however significant regional variation does occur, with a similar study in the United Kingdom recording an incidence rate of 18% (5). A large retrospective cohort study reported encephalitis incidence in adults of between 0.11% and 0.12%, increasing in older adults to 0.14% (10). To ascertain the true incidence and prevalence of COVID-19-associated encephalitis, particularly if the infection emerges in individuals with post-acute sequelae of COVID-19 (PASC) (also known as 'post-covid' or 'long-covid'), further investigation is required (11, 12).

Clinical features	Encephalitis is marked by elevated levels of proinflammatory cytokines, chemokines, interleukin-6, interleukin-1, interleukin-18, TNF-α, CXCL10, with serological abnormalities of c-reactive protein, procalcitonin, D-dimer, and ferritin being particularly associated with increased risk of severity and mortality (13-17). Additionally, COVID-19-associated encephalitis can produce hyperintensities in the mesial temporal lobe, subcortical white matter, brainstem, and claustrum (14). The inflammatory response can be the result of a peripheral immune response, leading to microglia activation, BBB-impairment, an ingress of autoantibodies into the brain (16), and widespread neuronal damage (16-19). Injury biomarkers (such as TNFRS12A) remain elevated up to four months post-infection (16, 20), and there has been a report of encephalitis developing 41 days after initial SARS-CoV-2 infection (21). Some severe infections of COVID-19 may only be evident through direct observation of neurological sequelae, without respiratory dysfunction or failure (1, 16-18, 21). Indeed, the index case described here did not initially present to hospital with symptoms of COVID-19, but rather with encephalitis (1). Diagnosis of COVID-19-associated encephalitis requires a combined approach utilising a range of diagnostic techniques (7, 8) ranging from neuroimaging, serology, bronchoalveolar lavage, magnetic resonance imaging, computed tomography, electroencephalograms, and lumbar punctures for cerebrospinal fluid (CSF) testing. Definitive COVID-19-associated encephalitis diagnosis requires isolation of the virus, or virus particles, from cerebrospinal fluid (1, 18).
Mode of transmission (dominant mode and other documented modes)	The high invasiveness of SARS-CoV-2 into multiple brain regions, nearly simultaneously, may explain the diverse and varied clinical symptoms and neurological manifestations in the absence of respiratory failure (1, 4, 6, 13-15, 17, 19, 20). The CNS consists of vast neural networks and is usually protected from viral infection by complex external multilayer cellular barriers, effective immune responses, and the blood-brain-barrier (BBB) (22, 23).

	Typically, SARS-CoV-2 is found in the nasopharyngeal cavity, due to both the airborne transmission of the virus and the (24) olfactory sensory neurons possessing high concentrations of angiotensin-converting enzyme-2 (ACE2), which is a gateway to further cell invasion (25, 26). Subsequent coordination of dynein and kinesin proteins facilitates axonal transport directly to the CNS (26). Another available route of transmission is known as the 'Trojan-horse' method, where the virus binds to leukocytes circulating within the CNS, without activating an immune response, and turning the leukocytes into vectors, before circulating from the CNS (18). The virus can also bind to cells in the circulatory system (hematogenous), and travel through the BBB in this way (26). Additionally, the BBB can be breached paracellularly by disruption to neuronal tight junctions in the endothelial cells (most often caused by inflammation resulting from viremia) (18). SARS-CoV-2 can also infect endothelial cells via transcytosis of the choroid plexus of either cerebral ventricle directly breaching the blood-cerebrospinal fluid barrier (26).
Demographics of cases	The mean age of patients with COVID-19-associated encephalitis is approximately 59.4 years (4); (the index case was 35.4 years younger) (1), with a relatively even proportion of males and females affected (49.3% to 50.7%) (4). The average days of onset from the initial COVID-19 diagnosis to an encephalitis diagnosis was 14.5 days, though range from 3.9 days to 41 days (14, 21). Of patients diagnosed with COVID-19-associated encephalitis, 71.7% of cases reported at least one comorbidity, with a maximum of 3 comorbidities, while 23.8% of patients were COVID-19 asymptomatic (4). Of these patients, 83.8% were previously diagnosed with severe COVID-19 (requiring hospitalisation in an intensive care unit with mechanical ventilation), representing an incidence rate of 6.7% (4). Total mortality for all patients with COVID-19 associated encephalitis was 13.4% (4). A similar retrospective descriptive study reported COVID-19-associated encephalitis in hospitalised individuals with an average onset of 8-9 days (27). In this study onset

	for women was approximately 7.41 days, 1.01 days earlier than for men (27), though this difference was not explored and is a potential source of further research.
Case fatality rate (CFR)	The CFR for COVID-19-associated encephalitis is difficult to determine, given the range of symptom expression and high similarity with other diseases, a recent systematic review and meta-analysis determined a CFR of 13.4% (4). One American health risk analysis determined that at twelve months post-infection, the excess burden of deaths per 1,000 due to COVID-19-associated encephalitis was 0.07%; while the health risk of encephalitis was 1.82% (27).
Complications	The index case returned a negative result from a nasopharyngeal swab, and this clinical sign has since been observed by research (1). When COVID-19-associated encephalitis was diagnosed, negative RT-PCR tests were returned 50% of the time (14). Interestingly, the secondary worsening of the inflammatory response after a period of days is likely a key aspect and indicator of severe SARS-CoV-2 infection (14). Why RT-PCR tests are negative 50% of the time and how vaccination status impacts on diagnosis are two key questions for future research. COVID-19-associated encephalitis-produced hyperintensities (ranging from punctate to diffuse) have been reported in multiple regions of the brain (subcortical white matter, brainstem, and claustrum) (14), though deterioration within the claustrum (''Claustrum Sign'') is usually only present in immune-inflammatory-mediated encephalopathy or autoimmune epilepsy (28). Clinical overlap also exists with herpes simplex encephalitis (HSV encephalitis) (29, 30). These clinical similarities between a range of diseases requires diagnosis to be conferred by a wide array of techniques (as previously stated) and could go some way to explain the time between onset and time of diagnosis (14, 21, 27). This remains a key unanswered question. Interestingly, COVID-19-associated encephalitis can lead to viral replication in the neurons of cognitive centres, and trigger αβ, and p-tau depositions, neuronal

	degeneration, microglia activation and elevated cytokine levels in mimicry of Alzheimer's Disease (31). Infectious limbic encephalitis (32) can also be confused with COVID-19-associated encephalitis. When normal functioning of the limbic system (encompassing memory, learning, and emotional regulation) is affected an infection, clinical manifestations currently described may be produced (particularly encephalopathy) (33).
Available prevention	Though there are treatments currently available to reduce the chance of developing both severe infection and the secondary risk of developing encephalitis, there is no current prophylactic treatment for COVID-19-associated encephalitis. Vaccinations currently reduce the chance of infection progressing to severe (34), however, a snapshot from the Institute of Health Metrics and Evaluation (IHME) reveals vaccine efficacy at preventing severe disease from the Ancestral/Alpha/Beta/Gamma/Delta/Omicron variants ranges from 37% to 97% (34). How effective these vaccines are, particularly when immunity wanes, is a key question deserving of future research efforts.
Available treatment	Available treatment is highly dependent on clinical presentation and specific symptomology. Biological mimicry and differential diagnoses that emerge during PASC may require broad range of available treatment options. The most reported supportive treatment regimens are (6, 27): 1. Prescription of antibiotics and antivirals 2. Administration of corticosteroids – hydroxychloroquine and high-dose methylprednisolone boluses 3. Immunomodulating therapies – convalescent's serum, plasmapheresis, tocilizumab, intravenous immunoglobulin (IVIG) 4. Antiepileptics – levetiracetam, clonazepam, lamotrigine, lacosamide, eslicarbazepine acetate

	Additionally, there is a promising emergent therapy involving pharmacological inhibition of receptor interacting protein kinase 3 (RIPK 3) which blocks the main protease (M^{PRO}) involved in COVID-19-induced microvascular pathology (35). As such, RIPK 3 may be a potential prospective treatment option for COVID-19-associated encephalitis. Unfortunately, whether these treatments produce long-term efficacious reversal of the deleterious effect of neuropathology remains to be seen and requires further study and analysis (36). Current evidence suggests that monoclonal antibodies are likely to result in meaningful reductions in progression of the disease to severe, hospitalisations, and mortality among high-risk individuals, but the overall magnitudes of reductions are uncertain (37, 38). Similarly, a recent systematic literature review found that antivirals are effective for symptom management and reducing disease severity when administered early in the disease course, but not effective in reducing mortality (39). Despite emerging evidence, significant clinical and research debate remains over the most efficacious treatment options (39).
Comparison with past outbreaks	COVID-19-associated encephalitis is less prevalent than other types of encephalitis (4, 29, 40). Herpes simplex encephalitis is the most common cause of all encephalitis, though has a low incidence of between 1% to 2% albeit with significant regional variation (41); Japanese encephalitis has a similar population-level incidence to herpes simplex encephalitis (1.8%) (Table 1) (42). Autoimmune encephalitis presents with a similar incidence at 1.0% (43). These incidence levels compare to the 0.22% incidence rate of COVID-19-associated encephalitis (4). With a high average age of onset (59.4 years) (4), lack of an endemic population (such as with Japanese encephalitis) (42), the absence of dormant SARS-CoV-2 viral particles in humans (such as in herpes simplex encephalitis) (41), and the ability to mimic delayed onset (21), COVID-19-associated encephalitis requires significant surveillance and treatment post-infection, similar to autoimmune encephalitis (44-

46), which relies on symptomatic and maintenance therapy, and bridging immunotherapy.

Table 1: Comparison of incidence, case fatality rate and age at onset of COVID-associated encephalitis, Japanese encephalitis, autoimmune encephalitis, and herpes simplex encephalitis.

Measurement	COVID-associated encephalitis	Japanese encephalitis	Autoimmune encephalitis	Herpes simplex encephalitis
Incidence (per 100,00) (%)	0.22 (though ranging up to 69%) *	1.8	1.0	1 - 2
Case fatality rate (%)	13.4	32.0	7.0	5.0 - 15.0
Average Age at onset (years)	59.4	All ages	43.0	0-3 and >50

**Percentage reported in severe infections in individuals already hospitalised in intensive care units*

Unusual features

Clinical evidence has suggested that COVID-19-associated encephalitis can emerge weeks after initial infection, even after mild infection, and include a secondary period of deterioration, which is a feature not common to other types of encephalitis, and potentially unique to the pathophysiology of COVID-19 (1), though an underlying unifying biological mechanism is yet unknown (47).

Vaccine-induced encephalitis can also occur following COVID-19 vaccination (48, 49) with the Pfizer-BioNTech mRNA vaccine recording a 2 per 10 million doses incidence of vaccine-induced encephalitis, and the AstraZeneca ChAd0x1 nCoV-19 recording a much higher incidence of 8 per 10 million doses (48). Despite a recent case study (49) reporting the same pathophysiology of COVID-19-associated

	encephalitis (delayed onset, secondary worsening, and negative detection of viral particles) further research is required to determine cohort characteristics of onset.
Critical analysis	COVID-19-associated encephalitis requires treatment that is individualised, context-specific, and supportive. This requires specialised imaging and diagnostic equipment, and coordinated economic, human, and medical resources, which can place additional strain on already-burdened health systems. Additionally, six-month health risks for developing COVID-19-associated encephalitis have been reported in clinical research, and longer-term research is required to fully understand the risk mechanism (50). Encephalitis is an indicator of severity of infection and requires consistent monitoring during the acute and post-acute phases. With the ability to emerge up to and beyond six-weeks post-infection, and requiring a lumbar puncture for definitive diagnosis, sustained surveillance is required – though in an already resource-constrained health system, the likelihood of this occurring is already reduced. Subsequently, reinfection with variants of interest and/or variants of concern (51, 52, 53), recombinant infection, co-infection, post-infection, and delayed onset are all possible following initial diagnosis. This requires substantial healthcare resources for detection, monitoring, and treatment, and complicates the diagnostic process. COVID-19-associated encephalitis mimics herpes simplex encephalitis and other immune encephalitis illnesses (41-45) and therefore can be misdiagnosed where viral encephalitis' are endemic (such as Japanese encephalitis). It can also mimic a generalised immune response and present as Alzheimer's disease (31). Diagnosis requires extensive diagnostic elimination and delays the onset of appropriate treatment. Despite this, it is suggested that the presence of anosmia and ageusia can be a clinical marker of differentiation between different forms of encephalitis (17).

	Additionally, elevated levels of tumour necrosis factor receptor superfamily member 12A (TNFRSF12A) is strongly positively associated with COVID-19 (16, 20) severity and may prove to be a reliable diagnostic indicator of encephalitis. Identification of this elevated level may shorten time to treatment, though further research and clinical evidence is required to establish veracity. Additionally, when examining the differences between the three human coronavirus outbreaks (SARS-CoV-2, SARS-CoV, and MERS-CoV), this study (55) recorded prevalence rates for the following symptoms during SARS-COV-2 infection (compared to SARS-COV infection): nausea/vomiting = 5.0% (19.4% - 19.6%); dizziness = 3.7% (4.2% - 42.8%); and headache = 8.0% (35.4% - 55.8%). Despite there being evidence of structural genomic changes to the virus and significant epidemiological differences in incidence, prevalence, aetiology, and control measures (56-60), no current literature indicates if there is an immunological benefit conferred to individuals following infection with either SARS-CoV, or MERS-CoV, and is a potential source of future research. COVID-19-associated encephalitis is a rare secondary infection following SARS-CoV-2 infection. It presents with encephalopathy and encephalitis, and requires a combinational diagnostic approach as there are a range of differential diagnoses that complicate diagnosis and subsequent treatment. Transmission and available preventative and treatment options have also been explored. Current research and literature has been provided in this watching brief, but a variety of key questions have been identified as well, forming the basis of intensive future research.
Key Questions	1. Is there an association between subvariants of SARS-CoV-2 and encephalitis? 2. Does previous infection with SARS-CoV or MERS-CoV confer any immunological benefit?

	3. Can reinfection with SARS-CoV-2 lead to a re-emergence of encephalitis? If so, is onset time truncated? If so, is there a reduction in encephalitis' intensity or duration? Is there an immunological protective factor? 4. How effective are various vaccines on variants of interest and variants of concern and their associated risk for developing COVID-19-associated encephalitis? Does waning immunity increase risk of developing COVID-19 associated-encephalitis? 5. Can pharmacological RIKP 3 be incorporated into future vaccines to protect against encephalitis? 6. What is the lifetime risk of developing neurological disorders in non-hospitalised individuals with neurological manifestations? What long term neuronal damage occurs following infection? 7. What mitigation strategies are available and most effective in preventing COVID-19 associated encephalitis from developing? For how long should these strategies be implemented for? 8. What alternatives exist for rapid diagnosis and treatment in resource constrained or overwhelmed health systems? 9. Why are PCR tests negative in 50% of cases – is there a specific underlying and currently unknown biological reason? 10. What is the underlying biological mechanism for the difference in onset of COVID-19-associated encephalitis between males and females?

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