

## Epidemiological and cohort study finds no association between COVID-19 and Guillain-Barré syndrome

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Complete List of Authors:	<p>Keddie, Stephen; University College London, Department of neuromuscular diseases; University College London Hospitals NHS Foundation Trust National Hospital for Neurology and Neurosurgery, Centre for Neuromuscular Diseases</p> <p>Pakpoor, Julia; Oxford University Hospitals NHS Foundation Trust National Hospital for Neurology and Neurosurgery, Centre for Neuromuscular Diseases</p> <p>Mousele, Christina; University College London Hospitals NHS Foundation Trust National Hospital for Neurology and Neurosurgery, Centre for Neuromuscular Diseases</p> <p>Pipis, Menelaos; University College London, Department of neuromuscular diseases; University College London Hospitals NHS Foundation Trust National Hospital for Neurology and Neurosurgery, Centre for Neuromuscular Diseases</p> <p>Machado, Pedro; University College London, Department of Neuromuscular Diseases; University College London Hospitals NHS Foundation Trust National Hospital for Neurology and Neurosurgery, Centre for Neuromuscular Diseases</p> <p>Foster, Mark; University College London Hospitals NHS Foundation Trust National Hospital for Neurology and Neurosurgery, Centre for Neuromuscular Diseases</p> <p>Record, Christopher; St George's University Hospitals NHS Foundation Trust</p> <p>Keh, Ryan; Salford Royal NHS Foundation Trust, Department of Neurology</p> <p>Fehmi, Janev; University of Oxford Nuffield Department of Clinical Neurosciences</p> <p>Paterson, Ross; University College London Hospitals NHS Foundation Trust National Hospital for Neurology and Neurosurgery</p> <p>Bharambe, Viraj; The Walton Centre NHS Foundation Trust, Clinical Neurosciences, Clinical and Experimental Sciences</p> <p>Clayton, Lisa; Barts and The London NHS Trust, Neurology</p> <p>Allen, Claire; Poole Hospital NHS Foundation Trust</p> <p>Price, Olivia; Basildon and Thurrock University Hospitals NHS Foundation Trust</p> <p>Wall, Jasmine; Lancashire Teaching Hospitals NHS Foundation Trust</p> <p>Kiss-csenki, Annamaria; Hampshire Hospitals NHS Foundation Trust</p> <p>Rathnasabapathi, Dipa; University Hospital Southampton NHS Foundation Trust</p> <p>Geraldes, Ruth; University of Oxford Nuffield Department of Clinical Neurosciences</p>

	<p>Yermakova, Tatyana; Leeds Teaching Hospitals NHS Trust King-Robson, Joshua; King's College London, Neurology Zosmer, Maya; North Middlesex University Hospital Rajakulendran, Sanjeev; University College London Hospitals NHS Foundation Trust National Hospital for Neurology and Neurosurgery, Centre for Neuromuscular Diseases Sumaria, Sheetal; University College London Hospitals NHS Foundation Trust National Hospital for Neurology and Neurosurgery, Centre for Neuromuscular Diseases Farmer, Simon; University College London Hospitals NHS Foundation Trust National Hospital for Neurology and Neurosurgery Nortley, Ross; UCL, Queen Square Institute of Neurology; Wexham Park Hospital Marshall, Charles; Barts and The London NHS Trust, Neurology Newman, Edward J.; Queen Elizabeth University Hospital, Neurology Nirmalananthan, Niranjana ; St George's University Hospitals NHS Foundation Trust Kumar, Guru; Darent Valley Hospital Pinto, Aswin; University Hospital Southampton NHS Foundation Trust Holt, James; The Walton Centre NHS Foundation Trust, Clinical Neurosciences, Clinical and Experimental Sciences Lavin, Tim; Salford Royal NHS Foundation Trust, Department of Neurology Brennan, Kathryn; Queen Elizabeth University Hospital, Neurology Zandi, Michael; UCL, Queen Square Institute of Neurology Jayaseelan, Dipa; UCL, Queen Square Institute of Neurology; Watford General Hospital Pritchard, Jane; Imperial College Healthcare NHS Trust Hadden, Robert; King's College London, Neurology Manji, Hadi; University College London Hospitals NHS Foundation Trust National Hospital for Neurology and Neurosurgery, Centre for Neuromuscular Diseases Willison, Hugh; Queen Elizabeth University Hospital, Neurology Rinaldi, Simon; University of Oxford Nuffield Department of Clinical Neurosciences Carr, Aisling; University College London Hospitals NHS Foundation Trust National Hospital for Neurology and Neurosurgery, Centre for Neuromuscular Disease Lunn, Michael; University College London, Department of neuromuscular diseases; University College London Hospitals NHS Foundation Trust National Hospital for Neurology and Neurosurgery, Centre for Neuromuscular Diseases</p>
Methodology:	
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# Epidemiological and cohort study finds no association between COVID-19 and Guillain-Barré syndrome

**Running title; No association between COVID-19 and GBS**

## Authors and affiliations

Keddie S<sup>1,2</sup>, Pakpoor J<sup>3</sup>, Mousele C<sup>2</sup>, Pipis M<sup>1,2</sup>, Machado PM<sup>1,2</sup>, Foster M<sup>2</sup>, Record CJ<sup>4</sup>, Keh YS<sup>5</sup>, Fehmi J<sup>6</sup>, Paterson RW<sup>2,7</sup>, Bharambe V<sup>8</sup>, Clayton LM<sup>9</sup>, Allen C<sup>10</sup>, Price O<sup>11</sup>, Wall J<sup>5</sup>, Kiss-Csenki A<sup>12</sup>, Rathnasabapathi DP<sup>13</sup>, Geraldine R<sup>6,14</sup>, Yermakova T<sup>15</sup>, King-Robson J<sup>16</sup>, Zosmer M<sup>17</sup>, Rajakulendran S<sup>2,17</sup>, Sumaria S<sup>2</sup>, Farmer SF<sup>2</sup>, Nortley R<sup>2,14</sup>, Marshall CR<sup>9</sup>, Newman E<sup>18</sup>, Nirmalananthan N<sup>4</sup>, Kumar G<sup>7</sup>, Pinto AA<sup>13</sup>, Holt J<sup>8</sup>, Lavin TM<sup>8</sup>, Brennan KM<sup>18</sup>, Zandi M<sup>2</sup>, Jayaseelan DL<sup>2,20</sup>, Pritchard J<sup>21</sup>, Hadden RDM<sup>16</sup>, Manji H<sup>1,2</sup>, Willison HJ<sup>18</sup>, Rinaldi S<sup>3,6</sup>, Carr AS<sup>2</sup>, Lunn MP<sup>1,2</sup>.

1. Department of Neuromuscular Diseases, University College London, London, UK
2. National Hospital for Neurology and Neurosurgery, University College London Hospitals NHS Foundation Trust, London, UK
3. Oxford School of Public Health, Oxford, UK
4. St George's University Hospitals NHS Foundation Trust, London, UK
5. Lancashire Teaching Hospitals NHS Foundation Trust, UK
6. Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK
7. Darent Valley Hospital, Dartford, UK
8. The Walton Centre National Health Service (NHS) Foundation Trust, Liverpool, UK.

9. Barts Health NHS Trust, London, UK
10. Poole Hospital NHS Foundation Trust, Poole, UK
11. Basildon and Thurrock University Hospital Trust, Basildon, UK
12. Hampshire Hospitals NHS Foundation Trust, Hampshire, UK
13. Wessex Neurological Centre, University Hospital Southampton NHS Foundation Trust, Southampton, UK
14. Wexham Park Hospital, Frimley Health Foundation Trust, Berkshire, UK
15. Leeds Teaching Hospitals NHS Trust, Leeds, UK
16. Kings College Hospital NHS Foundation Trust, London, UK
17. North Middlesex University Hospital NHS Trust, London, UK
18. Queen Elizabeth University Hospital, Glasgow, UK
19. Manchester Centre for Clinical Neuroscience, Salford Royal Hospital NHS Foundation Trust, Manchester, UK
20. West Hertfordshire Hospitals NHS Trust, Watford, UK
21. Imperial College Healthcare NHS trust, London, UK

**Corresponding author:**

Professor Michael P Lunn

Centre for Neuromuscular Disease, National Hospital for Neurology and Neurosurgery,  
Queen Square, London, WC1N 3BG

Phone 1: +44 (0)203 448 3812

Fax 1: +44 (0)203 448 3797

Email: [michaellunn@nhs.net](mailto:michaellunn@nhs.net)

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## Abstract

### Background

Reports of Guillain-Barré Syndrome (GBS) have emerged during the Coronavirus Disease 2019 (COVID-19) pandemic. This epidemiological and cohort study sought to investigate any causative association between COVID-19 infection and GBS.

### Methods

The epidemiology of GBS cases reported to the UK National IVIg Database was studied from 2016-2019 and compared to cases reported during the COVID-19 pandemic. Data were stratified by hospital trust and region, with numbers of reported cases per month. UK population data for COVID-19 infection were collated from UK public health bodies. In parallel, but separately, members of the British Peripheral Nerve Society prospectively reported incident cases of GBS during the pandemic at their hospitals to a central register. The clinical features, investigation findings and outcomes of COVID-19 (definite or probable) and non-COVID-19 associated GBS cases in his cohort were compared.

### Results

The incidence of GBS treated in UK hospitals from 2016-2019 was 1.65-1.88 per 100,000 people per year. In 2020, GBS and COVID-19 incidences varied between regions and did not correlate with one another ( $r = 0.06$ , 95% CI -0.56 to 0.63,  $p=0.86$ ). GBS incidence fell between March and May 2020 compared to the same months of 2016-2019. In an independent cohort study, forty-seven GBS cases were reported (COVID-19 status - 13 definite, 12 probable, 22 non-COVID-19). There were no significant differences in the

pattern of weakness, time to nadir, neurophysiology, CSF findings or outcome between these groups. Intubation was more frequent in the COVID-19 affected cohort (7/13, 54% vs 5/22, 23% in COVID negative) likely related to COVID-19 pulmonary involvement.

## Conclusions

Although it is not possible to entirely rule out the possibility of a link this study finds no epidemiological or phenotypic clues of SARS-CoV-2 being causative of GBS. GBS incidence has fallen during the pandemic which may be the influence of lockdown measures reducing transmission of GBS inducing pathogens such as *Campylobacter jejuni* and respiratory viruses.

## Introduction

The first cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were reported to the World Health Organisation in late 2019, and by March 2020 COVID-19 was pandemic.(WHO, 2020) SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV) were associated with neurological sequelae.(Li *et al.*, 2020) Early reports identified neurological symptoms of COVID-19 infection as fever, headache, anosmia and dysgeusia.(Mao *et al.*, 2020) Subsequently COVID-19 infection has been associated with stroke, meningoencephalitis, acute disseminated encephalomyelitis and Guillain-Barré syndrome (GBS).(Ghannam *et al.*, 2020; Paterson *et al.*, 2020; Varatharaj *et al.*, 2020) The first reported case of GBS questioned a possible link with COVID-19 and occurred in late January 2020 in a COVID-19 asymptomatic patient who developed COVID-19 symptoms at Day 8 of GBS. (Zhao *et al.*, 2020) The first series of five patients with GBS following SARS-CoV-2 infection was reported in April 2020,(Toscano *et al.*, 2020) followed by case reports, case series and collective reviews..

GBS is an acute, post-infectious immune mediated polyradiculoneuropathy typically arising a few days to 6 weeks after bacterial or viral infections including *Campylobacter jejuni*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, influenza, Epstein-Barr virus, cytomegalovirus, and more recently, Zika virus.(Tam *et al.*, 2007; Lehmann *et al.*, 2010; Cao-Lormeau *et al.*, 2016) The pathogenesis of GBS following the majority of presumed causative infectious is unknown, although humoral molecular mimicry is definitively established for *C. jejuni* associated GBS, and may play a role in many or most cases of GBS. (Willison and Yuki, 2002; Loshaj-Shala *et al.*, 2015) The pathological initiating event of *C. jejuni* GBS is the manufacture of antibodies to lipo-oligosaccharide surface epitopes of *C*



*jejuni* that which cross-react with peripheral nerve glycolipids, resulting in complement fixation, macrophage attraction and resultant peripheral axon or myelin nerve damage. (Yuki and Hartung, 2012) This mechanism may also occur with other bacterial and viral pathogens since anti-ganglioside antibodies are found in up to 60% of GBS cases, (Kaida *et al.*, 2009) including those associated with viral infections; for example, anti-GM2 antibodies occur in CMV-associated GBS. GBS associated with ganglioside complexes increases the frequency of potential ganglioside related molecular mimicry, and the presence of antibodies to paranodal and juxtaparanodal antigens suggests an unproven post-infectious link to protein epitopes. (Devaux *et al.*, 2012; Rinaldi *et al.*, 2013) Zika-associated GBS has such a close association to seroconversion that some cases may be due to direct but unproven neurotropic damage.

SARS CoV-2 is a single-stranded RNA enveloped virus. Open reading frames (ORF) encode for replicase proteins and the structural proteins which are the spike (S), nucleocapsid (N), envelope (E) and membrane (M) proteins. (Liu *et al.*, 2014) To date we know of no homology between SARS-CoV-2 surface epitopes and peripheral nerve tissue. Reports of varied anti-ganglioside antibodies in association with COVID-19 GBS suggest that a uniform CMV-like immune mediated hypothesis is unsupported. More comprehensive epidemiological characterisation is crucial to understanding any causal link. With over 33 million cases of COVID-19 infection worldwide by 29<sup>th</sup> September, (European Centre for Disease Prevention and Control, 2020) the question of whether COVID-19 infection is a cause of GBS or a coincidental finding remains to be answered.

This study aimed to investigate whether a causal relationship could be determined between COVID-19 and GBS, and was performed in three parts. Firstly, we retrospectively explored UK population-based epidemiological datasets of cases with confirmed COVID-19 and compared that to patients hospitalised with GBS. Separately, but in parallel, we characterised a large cohort of the incident UK GBS cases presenting both with, and without, COVID-19 to explore timing of onset, and any identifying phenotypic characteristics that might hint at a specific mechanistic link (as for example in sensory GBS associated with CMV). Finally, we explored any homology between SARS-CoV-2 and the human genome and proteome which would support a molecular mimicry mechanism.

## Methods

### Epidemiological case reporting

Incident hospitalised cases of GBS were retrospectively ascertained from the UK National Immunoglobulin Database from the 1<sup>st</sup> January to the 31<sup>st</sup> May 2020, demonstrating the frequency of GBS cases across the year, pre and during the COVID-19 pandemic. NHS England (NHSE) procures the total intravenous immunoglobulin (IVIg) supply for England, Scotland and Northern Ireland. NHSE mandates that every IVIg prescription is approved by a clinical panel and is reported onto the database within 90 days. Recording compliance is almost 100% as hospital trusts are only reimbursed once records of dispensed volumes are submitted; these are retrospectively cross-checked against supply and returned stocks. (Foster, 2017) To ensure complete reporting of cases, NHSE specifically mandated all users of the National Immunoglobulin database to log any outstanding GBS cases by 30<sup>th</sup> June 2020 by email on the 9<sup>th</sup> June 2020. Data retrieval was then performed on the 7<sup>th</sup> July 2020 to allow time for reporting delay.

Current UK guidance for GBS treatment indicates IVIg or plasma exchange (PLEX) as first line therapy, (Department of Health, 2011) but IVIg is, in practice, first line in most UK hospitals as PLEX is normally not as available. IVIG is also only authorised in the UK for patients with Hughes Grade  $\geq 4$ , progressing towards intubation and ventilation, with a high likelihood of respiratory support (mEGRIS score  $\geq 3$ ) or a predicted poor prognosis (mEGOS  $\geq 4$ ). The patients usually treated with IVIG in the UK are those who require admission, and although this under-ascertains the true incidence of GBS, it reduces the effects of attendance bias in a pandemic. IVIG is given to nearly all presenting GBS patients in Europe as illustrated by 86% (612/715) of European cases treated with IVIg in the International GBS Outcome Study (IGOS), (Doets *et al.*, 2018) and 88% (37/42) of 'COVID-19 GBS' in the literature until July. (Uncini *et al.*, 2020)

We also searched the NHSE IVIg database for GBS cases from 1<sup>st</sup> January to the 31<sup>st</sup> May in each of the years 2016 to 2019 ) to determine the incidence of non-COVID-19 reported cases of GBS to compare to the 2020 pandemic data. Data were stratified by hospital trust and region. UK population data for COVID-19 PCR confirmed infection were collated from Public Health England, Health Protection Scotland and the Public Health Agency of Northern Ireland. Because of the lack of testing available testing early in the pandemic, COVID-19 PCR confirmed cases were significantly fewer than the true incidence of infection across the UK. (Connors and Sutherland, 2020) Thus in addition, we obtained data from the NHS Blood Transfusion Service (NHSBT) (Public Health England, 2020a) of antibody seroprevalence across the UK to SARS-CoV-2, and used the London data to study the number of GBS cases

that occurred compared both to the number of PCR confirmed cases and the number of seroconverted COVID-19 cases during the pandemic months.

### Cohort study

In parallel to the epidemiological study, we conducted a prospective cohort study to compare the demographic, phenotypic and infective associations of COVID-19 associated GBS (definite and probable) to COVID-19 negative GBS reported during the same study period.

Reports of GBS were submitted by members of the British Peripheral Nerve Society, who cover 81 different UK sites. Members were emailed on a weekly basis to collect information on hospital presentations of GBS from the 1st March to the 31<sup>st</sup> May, 2020. Reporting was restricted to BPNS members to achieve a comprehensively characterised representative sample of incident cases diagnosed by peripheral nerve experts. Data were entered to the International Neuromuscular COVID-19 database ([www.ucl.ac.uk/centre-for-neuromuscular-diseases/news/2020/may/international-neuromuscular-covid-19-database](http://www.ucl.ac.uk/centre-for-neuromuscular-diseases/news/2020/may/international-neuromuscular-covid-19-database)), at the Centre for Neuromuscular Disease. Cohort study data collection ended on July 1<sup>st</sup> 2020 to allow time for retrospective case reporting. Anonymised clinical data of demographics and medical history, COVID-19 infection, symptoms and management were collected. Precipitating illness, clinical features of GBS, investigation findings including cerebrospinal fluid (CSF) and electrophysiology, management and outcomes were also collated.

Data collected from the cohort study were compared to the phenotypic characteristics of the published European International GBS Outcome Study cases to see whether pandemic presentations differed from a comparable cohort of non-pandemic phenotypes.(Doets *et al.*, 2018)

## Evidence of COVID-19

GBS cases were stratified into three groups; definite COVID-19, probable COVID-19 and non-COVID-19. Definite cases had either a positive nasal or throat swab PCR for viral RNA or a subsequent positive serological test for anti-SARS-CoV-2 IgM or IgG irrespective of clinical signs and symptoms. Probable cases were defined by the presence of clinical symptoms consistent with COVID-19 infection as per the European Centre for Disease Prevention and Control case definitions, (European Center for Disease Prevention and Control, 2020) or pulmonary imaging (CXR or CT) highly suggestive of COVID-19 (airway opacification typically bilateral, peripheral and basal in distribution) where PCR analysis was negative. Occurrence of GBS within 6 weeks of acute COVID-19 infection (clinically or on confirmed laboratory findings) was considered necessary to confirm a definite link, with longer timeframes accepted but recorded in the data and classified as probable. (Ellul *et al.*, 2020)

## Search for homology between SARS CoV-2 and human genome and proteome

At the time of this study relatively little is known of the epitope presentation and immunobiology of SARS CoV-2. We searched for evidence of molecular mimicry between any SARS CoV2 proteins and human nerve axonal or myelin proteins and glycoproteins, recognising that epitopes are not all protein and not necessarily all linear. We searched for human homologs of proteins encoded by the SARS CoV-2 genome using the National Centre for Biotechnology Information (NCBI's) Basic Local Alignment Search Tool (BLAST) to identify common amino acid sequences in the human Reference Sequence Database

(refseq\_protein). The NCBI BLAST was also used to query the SARS CoV-2 genome against the human genome for any significant alignments at specific genomic loci.

The expect value (E-value) quantifies the number of times a specific alignment can be 'expected' to occur in a database by chance. As the E-value decreases the significance of the alignment in the specified database increases. Any alignment with an E-value of  $\leq 1 \times 10^{-4}$  was considered homologous to a human protein (error rate  $< 0.01\%$ ).

### Statistical analysis

The incidence rates of GBS and COVID-19 (95% confidence intervals by Byar's approximation method)(Breslow and Day, 1987) were calculated by dividing regional cases and time period by the relevant mid-year population estimate. Mid-year population estimates at both regional and national level were obtained from the UK Office for National Statistics. (Office for National Statistics, 2019) We explored any association between the incidence of GBS and the incidence of COVID-19 in UK regions in 2020 (January to May) using Pearson's correlation coefficient. The Shapiro-Wilk test was used to determine suitability of parametric tests.

COVID-19 definite and probable cases in the cohort were statistically compared against non-COVID-19 associated GBS. In addition, to determine whether characteristics differed between pandemic and non-pandemic GBS phenotypes, clinical characteristics of our study cohort were also compared to published IGOS study participants. We used Mann-Whitney U to test non-parametric continuous data, and the  $\chi^2$  or Fisher's exact test to compare proportions. IGOS data stratified to European/American cases (n=715) were used in

preference to the entire IGOS cohort (n=925) where available.(Doets *et al.*, 2018) R (4.0.0) and GraphPad prism (8.1.2) were used for analysis and figures.

## Ethics

The UK Health Research Authority was consulted and advised the study did not require review by an NHS Research Ethics Committee as an analysis of previously collected non-identifiable information. The project was submitted as a “Service Evaluation” to the Clinical Audit and Quality Improvement Subcommittee (CAQISC).

## Data availability

Data is available upon the request to the corresponding author.

## Results

### Epidemiological study

The NHSE IVIg Database reported a mean of 1098 (range 1021-1155) GBS cases per year in the UK (excluding Scotland) between 2016-2019 (monthly range 83 to 170 cases). This represents the UK GBS population who are admitted to hospital with GBS and can be treated. As PLEX is seldom used and only patients with significant GBS are treated, IVIg treatments represent the vast majority of UK cases. Annual UK GBS incidence requiring treatment was therefore a minimum of 1.65-1.88 per 100,000 people each year across this period, consistent with the incidence of GBS in Europe and North America from a previous meta-analysis of 1,643 GBS cases (range 0.81 to 1.89 cases per 100,000). (Sejvar *et al.*, 2011a) These

comparative figures along with the mandatory reporting supports the NHSE IVIg database as the most comprehensive, complete and accurate resource for epidemiological analysis of GBS in the UK.

Although COVID-19 was first reported in the UK on January 31<sup>st</sup> 2020, significant numbers of daily new infections in the first wave (>1000 per day) did not occur until March, with the highest recorded daily count of 6,201 confirmed cases prior to this report on 1st May.(Public Health England, 2020b) Through April and May there were between 4000 and 6000 COVID-19 cases per day. If a strong causative and temporal association existed, COVID-19 GBS cases would be expected to rise in subsequent weeks (see Figure 1). However, even accounting for the consistent summer dip in GBS cases seen in 2016-2019, GBS cases in March (93), April (70) and May (56) of 2020 were significantly fewer than years 2016 to 2019 (mean 132 (March), 116 (April) and 113 (May)) (Figure 2). GBS and COVID-19 incidences varied across UK regions with no correlation between COVID-19 and GBS at a regional level ( $r = 0.060$  95% CI -0.56 to 0.63,  $P = 0.86$ ) (See Figure 3 and supplementary table 1).

By the 1<sup>st</sup> March 2020 there were only 17 PCR +ve confirmed COVID-19 cases in London which increased to 26,798 by the 27<sup>th</sup> April 2020.(Public Health England, 2020b) In London there were 25 cases of GBS registered to the NHSE IVIG database during this time (138 in the rest of the UK). Using these figures for this period, the estimated occurrence rate is 0.82 GBS cases per 1000 COVID-19 infections. However, serological data from London blood donors on the 27<sup>th</sup> April 2020 reported the prevalence of prior SARS-CoV-2 infection in London as 17.5%, (Public Health England, 2020a) equivalent to 1,571,850 people having



made a serological response to COVID-19. This is more likely to give the true estimate of COVID-19 infections in the community. Using 1 571 850 as the denominator for infection, the occurrence rate of GBS is more likely to be 0.016 cases per 1000 COVID-19 infections.

### Cohort study

Forty-seven cases of GBS were reported to the cohort by BPNS members over a 12-week collection period. Patients were classified according to the Brighton Criteria ranging from high to low of diagnostic certainty. (Sejvar *et al.*, 2011b) 22 were level 1 (46%) and 15/47 (32%) level 2 with four level 3 and six (13%) level 4, similar to previously reported large GBS cohorts. (Fokke *et al.*, 2014) Of the 47 cases, 13 had definite COVID-19 infection, 12 were probable, and 22 had GBS with no evidence of COVID-19. Median age was 57 years (IQR 19-88), 33 were men (70%) and 29 (66%) were Caucasian. The male:female ratio in the COVID-19 patients was 5.5 compared to 1.4 in the non-COVID and IGOS study. Men are more likely to be significantly unwell and hospitalised with COVID-19 infection which may partially or completely explain this difference. (Docherty *et al.*, 2020; Williamson *et al.*, 2020)

The clinical characteristics of the patients with GBS are shown in Table 1. For patients with COVID-19 infection, the median time between onset of infective symptoms and neurological weakness was 12 days for definite COVID-19 and 5 days for probable cases; however the range of time intervals was very broad, ranging from 0 to 37 days in definite and -14 to 52 days in probable cases, with only one case in which GBS developed over 6 weeks following COVID-19 onset. Three probable cases developed symptoms of GBS without any clear COVID-19 symptoms, and had incidental imaging evidence of COVID-19 suggesting recent

mild or asymptomatic infection. Numbers of non-COVID-19 GBS cases with symptoms of a precipitating illnesses, particularly gastroenteritis, were significantly fewer than that compared to the IGOS cohort (1/22, 5% in non-COVID-19 cases compared to 163/652 (25%) in the IGOS cohort,  $p < 0.000$ ). This may be an effect of lock down with improved hand hygiene reducing numbers of faecal-oral pathogen transmissions. The pattern of weakness and time to nadir were no different between COVID-19 associated GBS and non-COVID-19 GBS. Cranial nerve involvement was the only finding more frequent in the IGOS study compared to our cohort. Although not statistically significant, electrophysiological studies found a higher proportion of axonal GBS in the non-COVID-19 patients (four Acute Motor and Sensory Axonal Neuropathy (AMSAN) and one Acute Motor Axonal Neuropathy (AMAN), 23%), compared to one with AMSAN only from the COVID-19 positive group.

The use of ventilation did not differ significantly between COVID-19 (definite and probable) cases versus non-COVID-19 GBS. However, the number of COVID-19 definite GBS cases ventilated was higher than all other groups (7/13, 54% compared to 0/12 probable and 5/22, 22% non-COVID-19). Despite this, the GBS disability score at four weeks was no different between all groups, suggesting the requirement for initial ventilation was secondary to active COVID-19 pulmonary involvement rather than neuromuscular weakness in PCR positive, definite COVID-19 cases.

There were no differences in the treatment of GBS subgroups. IVIg was the first therapy in 83% cases, and only one patient received plasma exchange as second line therapy. One patient received more than one course of IVIg. One patient (COVID-19 definite) died. Death was attributed to pulmonary complications rather than neuromuscular weakness.

### Comparison between SARS-CoV-2 and human genome and proteome

When we examined the entire SARS CoV-2 genome (29903 bases, b; NC\_045512.2) as well as overlapping fragments of 1000b ( $\pm$  500b) and compared this to the human genome, we found no significant similarity.

We also explored individual proteins encoded by the SARS-CoV-2 genome comparing these against all referenced human proteins. Only the replicase ORF1ab/ORF1a polyprotein (7096 amino acids) produced a match with the human mono-ADP-ribosyltransferase (PARP14) protein. PARP14 belongs to an enzyme superfamily involved in histone modification during DNA damage and is ubiquitously expressed making it unlikely as a mimotope. These two proteins are 32% identical (E-value  $3 \times 10^{-6}$ ) but have only 1 contiguous identical sequence of 5 or more amino acids (Val-Val-Val-Asn-Ala) that might act as a cross reactive linear peptide epitope. The remaining SARS-CoV-2 proteins including the spike/surface, envelope, membrane and nucleocapsid phosphoprotein have no significant similarity with any referenced human protein.

### Discussion

Although it is profoundly difficult to prove no link in a rare disease, this retrospective epidemiological and prospective cohort study does not support any significant causal link between COVID-19 infection and GBS. (Lucas and McMichael, 2005) We have used several reliable sources of data to collate the best evidence from each to demonstrate the lack of likelihood of a significant causative link. The population-based data find no plausible temporal relationship between COVID-19 and GBS (figure 1), a reduction in cases of GBS in

comparison to preceding years (figure 2) and no correlation between COVID and GBS incidence at regional level (figure 3). There are in addition no identifiable COVID-19 associated GBS features that differentiate it from GBS in non-pandemic circumstances, in this, the largest cohort reported to date. There are also no scientific data to support a molecular mimicry link of SARS-CoV-2 to GBS at the nucleic acid or protein level, other than a presumptive analogy to other known bacterial and viral GBS-causing pathogens. The lack of even a short, linear homology between the SARS-CoV-2 structure proteins and any axonal or myelin surface proteins reduces the likelihood that molecular mimicry with SARS-CoV-2 might be a putative mechanistic link of SARS-CoV2 to GBS.

The UK has a single highly regulated IVIG supply. IVIG is routinely available for all patients with GBS, but every vial given for GBS is logged under a mandatory NHS-based system linked directly to clinicians and to subsequent payment. The mandatory reporting to the NHSE National Immunoglobulin database correlated with audits and clinical data showing that nearly all GBS patients receive IVIG, as well as incidence figures from this data source which correspond exactly with reported incidence rates from multinational population based epidemiological studies supports the Database as an appropriate repository for epidemiological analysis. Using this almost unique source we identified significantly fewer cases of GBS during the COVID-19 pandemic compared to previous years. This could represent an under-ascertainment of cases during lock down for a number of reasons including incomplete IVIg prescription recording or patients avoiding hospital attendance.

UK Hospital Trusts are mandated to report all IVIG treatments to the Database within 90 days and previous database analyses have shown 95% of cases were recorded within 30 days

of treatment, and 98% within 90 days. We collected data from 1<sup>st</sup> January to 31<sup>st</sup> May 2020 on July the 7<sup>th</sup> allowing sufficient time to capture the majority of reported cases. A subsequent direct check of complete IVIG reporting, specific requests for clinicians to document cases and a cross check between clinical reports and IVIg prescribing data ensured we have as complete a dataset as possible.

Mildly symptomatic patients may have decided not to visit hospital for fear of contracting COVID-19. This issue was recognised in stroke and emergency medicine with declines in overall admissions worldwide. (Aguiar de Sousa *et al.*, 2020; Markus and Brainin, 2020; Perry *et al.*, 2020; Public Health England, 2020c). Physicians' prescribing behaviour could also have changed during the pandemic, being more selective in patients treated, including with IVIg. However, the National Immunoglobulin Database only records GBS cases meeting criteria for treatment. The indication for IVIg treatment in GBS is for non-ambulant patients, and therefore it is unlikely such patients remained at home or would not be admitted to hospital. Even in 2016-19 only cases with significant disability and meeting criteria for treatment were recorded. This significantly reduces the likelihood of a disparity resulting from mild disease attendance bias, as a result of COVID-19 explaining the decline.

Furthermore, within our cohort study 83% of cases were treated with IVIG, providing cross validation of high treatment rates, but also the fact that milder patients continued to attend to some extent.

We hypothesise that the lockdown measures introduced to prevent COVID-19 transmission have had secondary effects of reducing other common transmissible infective GBS triggers such as upper respiratory tract infections through social distancing and mask wearing, and

gastrointestinal illnesses as fewer people dined out and stricter hand hygiene was adhered to. In our cohort of 47, only 1/47 (2%) reported diarrhoea preceding their GBS, significantly fewer than in the European IGOS patients at 25%. (Doets *et al.*, 2018) This is speculative but consistent with our hypothesis. Other studies have reported significant reductions in airborne or faeco-oral transmissible infectious diseases during lockdown, supporting this assertion.(Angoulvant *et al.*, 2020) Although the true impact of hygiene measures is unknown, the avoidance of *C. jejuni* and respiratory pathogens could conceivably reduce the incidence of GBS, and may explain the pandemic related reduction of GBS cases. Successful interventions to lower *Campylobacter* contamination of fresh poultry meat have previously been reported to reduce hospitalisations for GBS by 13%, (Baker *et al.*, 2012) and so this assertion is not impossible.

The true COVID-19 incidence in the UK is known to have been significantly under-reported. Until the end of March 2020, only patients admitted to hospital were tested for COVID-19 by PCR, and after this time it took two months for community testing to record symptomatic cases elsewhere. Only PCR confirmed cases were reported in the published data. Where a known link of GBS to an infectious agent exists, rates of occurrence have been published and are in the range of 0.2 to 2.2 cases per 1000 infections; for example GBS occurs at 0.25-0.65 per 1000 cases of *C. jejuni*, 0.6-2.2 per 1000 cases of primary cytomegalovirus, and 0.24 per 1000 Zika virus infections.(Orlikowski *et al.*, 2011; Yuki and Hartung, 2012; Cao-Lormeau *et al.*, 2016) Utilising PCR confirmed cases as a denominator to calculate the rate of GBS COVID occurrence suggests 0.82 cases per 1000 COVID-19 infections. As COVID-19 is a novel infection with no pre-existing seropositivity, it provides a unique opportunity to assess infection relationship rates. The true community infection rates of COVID were nearly 60-times higher than the published PCR rate from the measured seroprevalence; furthermore

serological data may even still under-report the true COVID-19 infection rates as antibody responses are not detectable in all post COVID-19 infected cases, in which SARS-CoV-2 specific T cell immune responses may occur.(Sekine *et al.*, 2020) The COVID-19 seroprevalence estimated GBS incidence is 0.016 per 1000 COVID-19 infections (1.6 per 100000, and equivalent to the usual incidence of GBS). Although it is very difficult to entirely rule out a causative link, these data provide further evidence for a lack of strong relationship between COVID-19 and GBS compared to other recognised GBS-associated infective pathogens, and potential over-reporting of an association when using PCR confirmed cases only.

Whilst at an epidemiological level we found no increase in GBS linked to the COVID-19 epidemic, our data do not exclude the possibility that SARS-Cov-2 might be a driver of GBS in very rare cases, or that a significant reduction in non-COVID-19 GBS could mask a smaller spike of COVID GBS cases. However, other infective causes of GBS have been identified through demonstrating a peak in incidence temporally related to rises in the causative infective pathogen. With SARS-CoV-2 being one of the most prevalent infective pathogens in the last century, it is more conceivable that the absence of any increase in GBS cases during the pandemic is more likely due to a lack of causation between COVID-19 and GBS. We have also shown that there is no significant homology between any SARS-CoV-2 genetic or linear protein structure and human linear protein structures, making a molecular mimicry causation less likely. The lack of homology does not exclude immunological similarity entirely as antibody epitopes are often non-linear. Furthermore, post-translational modification of viral proteins by their host cells can occur, which theoretically could result in the generation of immunogenic surface glycomolecules so far unknown.(Mary *et al.*, 2019) Although molecular mimicry is the only fully proven pathogenic GBS mechanism, we

acknowledge others could exist. More research is required to determine whether a causal relationship exists between SARS-CoV-2 and GBS.

Some small early series of COVID-19 associated GBS have been reported. (Gigli *et al.*, 2020; Toscano *et al.*, 2020) The series of Gigli *et al.* reported eight patients, all of whom were swab negative, one seropositive only and only 4 with COVID symptoms. Another small cohort of five reported specific disease characteristics suggesting differences from typical AIDP. (Toscano *et al.*, 2020) Our prospective cohort study compared 47 cases of GBS, 13 with definite COVID-19 infection, 12 probable, and 22 with no evidence of COVID-19. Although over half of cases in our clinical cohort of GBS had evidence of COVID-19 infection, reporting bias could have influenced these proportions. A similar effect will have influenced the medical literature with over-reporting of COVID-19 GBS cases in small studies creating an impression of significant co-existence of the two conditions. The purpose of our cohort was only to compare clinical characteristics of COVID-19 and non COVID-19 associated GBS.. Our cohort revealed no differences in the clinical and neurophysiological features, disease severity and outcomes of COVID-19 and non-COVID-19 associated GBS.. A larger proportion of COVID-19 PCR positive GBS cases required mechanical intervention compared to all other groups. The similar rate of neurological recovery across all groups suggests ventilation was more related to COVID-19 associated pulmonary involvement rather than neuromuscular deficit at nadir.

This population based epidemiological study was not fully prospective but has been able to demonstrate no relationship between GBS and COVID-19 infections across the UK through the interrogation of several complementary data sources. As we explore potential COVID-19



associated neurological disease, a measured analysis of the statistical probability of rare disease occurrence in the context of a pandemic is required to investigate causation appropriately, and continue to manage non-COVID-19 neurology with the associated challenges on healthcare resources. This epidemiological and cohort study contradicts a growing number of reports postulating causation between SARS-CoV-2 and GBS, and indeed demonstrates a reduction of GBS cases. This paper alone cannot be considered definitive in ruling out SARS-CoV-2 as a cause of GBS, but further prospective data collection of COVID-19 associated GBS cases and laboratory research are required. Although prompt reporting of disease manifestations and potential associations of COVID-19 is important to inform public health decisions, robust scientific assessment to establish causality versus association is essential to evolve our understanding of this novel viral pathogen and its sequelae.

#### Competing interests

The authors report no competing interests

## References

Aguiar de Sousa D, Sandset EC, Elkind MS V. The Curious Case of the Missing Strokes During the COVID-19 Pandemic. *Stroke* 2020; 51: 1921–1923.

Angoulvant F, Ouldali N, Yang DD, Filser M, Gajdos V, Rybak A, et al. COVID-19 pandemic: Impact caused by school closure and national lockdown on pediatric visits and admissions for viral and non-viral infections, a time series analysis. *Clin. Infect. Dis.* 2020

Baker MG, Kvalsvig A, Zhang J, Lake R, Sears A, Wilson N. Declining Guillain-Barré syndrome after campylobacteriosis control, New Zealand, 1988-2010. *Emerg. Infect. Dis.* 2012; 18: 226–233.

Breslow NE, Day NE. Statistical methods in cancer research. Volume II--The design and analysis of cohort studies. IARC Sci. Publ. 1987: 1–406.

Cao-Lormeau VM, Blake A, Mons S, Lastère S, Roche C, Vanhomwegen J, et al. Guillain-Barré Syndrome outbreak associated with Zika virus infection in French Polynesia: A case-control study. *Lancet* 2016; 387: 1531–1539.

Connors E, Sutherland E. Coronavirus (COVID-19) Infection Survey - Office for National Statistics [Internet]. Off. Natl. Stat. 2020[cited 2020 Sep 15] Available from: <https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/coronaviruscovid19infectionsurveypilot/latest>

Department of Health. Clinical guidelines for immunoglobulin use: update to second edition. London: 2011.

Devaux JJ, Odaka M, Yuki N. Nodal proteins are target antigens in Guillain-Barré syndrome. *J. Peripher. Nerv. Syst.* 2012; 17: 62–71.

Docherty AB, Harrison EM, Green CA, Hardwick HE, Pius R, Norman L, et al. Features of

16,749 hospitalised UK patients with COVID-19 using the ISARIC WHO Clinical Characterisation Protocol. medRxiv 2020; 10: 2020.04.23.20076042.

Doets A, Verboon C, Berg B Van Den, Brain TH-, 2018 U. Regional variation of Guillain-Barré syndrome. Brain 2018; 141: 2866–2877.

Ellul MA, Benjamin L, Singh B, Lant S, Michael BD, Easton A, et al. Neurological associations of COVID-19. Lancet Neurol. 2020; 19: 767–783.

European center for disease prevention and control. Case definition for coronavirus disease 2019 (COVID-19), as of 29 May 2020. 2020.

European Centre for Disease Prevention and Control. COVID-19 situation update worldwide, as of 29th September 2020. 2020.

Fokke C, Van Den Berg B, Drenthen J, Walgaard C, Van Doorn PA, Jacobs BC. Diagnosis of Guillain-Barré syndrome and validation of Brighton criteria. Brain 2014; 137: 33–43.

Foster M. Immunoglobulin Database Annual Report 2017/18. 2017.

Ghannam M, Alshaer Q, Al-Chalabi M, Zakarna L, Robertson J, Manousakis G. Neurological involvement of coronavirus disease 2019: a systematic review. J. Neurol. 2020: 1.

Gigli GL, Bax F, Marini A, Pellitteri G, Scalise A, Surcinelli A, et al. Guillain-Barré syndrome in the COVID-19 era: just an occasional cluster? J. Neurol. 2020

Kaida K, Ariga T, Yu RK. Antiganglioside antibodies and their pathophysiological effects on Guillain-Barré syndrome and related disorders - A review. Glycobiology 2009; 19: 676–692.

Lehmann HC, Hartung HP, Kieseier BC, Hughes RAC. Guillain-Barré syndrome after exposure to influenza virus. Lancet Infect. Dis. 2010; 10: 643–651.

Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role

in the respiratory failure of COVID-19 patients. *J. Med. Virol.* 2020; 92: 552–555.

Liu DX, Fung TS, Chong KKL, Shukla A, Hilgenfeld R. Accessory proteins of SARS-CoV and other coronaviruses. *Antiviral Res.* 2014; 109: 97–109.

Loshaj-Shala A, Regazzoni L, Daci A, Orioli M, Brezovska K, Panovska AP, et al. Guillain Barré syndrome (GBS): New insights in the molecular mimicry between *C. jejuni* and human peripheral nerve (HPN) proteins. *J. Neuroimmunol.* 2015; 289: 168–176.

Lucas RM, McMichael AJ. Public Health Classics Association or causation: evaluating links between ‘environment and disease’. 2005.

Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic Manifestations of Hospitalized Patients with Coronavirus Disease 2019 in Wuhan, China. *JAMA Neurol.* 2020; 77: 683–690.

Markus HS, Brainin M. COVID-19 and stroke—A global World Stroke Organization perspective. *Int. J. Stroke* 2020; 15: 361–364.

Mary B, Maurya S, Arumugam S, Kumar V, Jayandharan GR. Post-translational modifications in capsid proteins of recombinant adeno-associated virus (AAV) 1-rh10 serotypes. *FEBS J.* 2019; 286: 4964–4981.

Office for National Statistics. Estimates of the population for the UK, England and Wales, Scotland and Northern Ireland - Office for National Statistics [Internet]. 2019[cited 2020 Jul 16] Available from:

<https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/datasets/populationestimatesforukenglandandwalesScotlandandnorthernireland>

Orlikowski D, Porcher R, Sivadon-Tardy V, Quincampoix JC, Raphaël JC, Durand MC, et al. Guillain-barré syndrome following primary cytomegalovirus infection: A prospective cohort

study. Clin. Infect. Dis. 2011; 52: 837–844.

Paterson RW, Brown RL, Benjamin L, Nortley R, Wiethoff S, Bharucha T, et al. The emerging spectrum of COVID-19 neurology: clinical, radiological and laboratory findings. Brain 2020

Perry R, Banaras A, Werring DJ, Simister R. What has caused the fall in stroke admissions during the COVID-19 pandemic? J. Neurol. 2020; 1: 3.

Public Health England. Sero-surveillance of COVID-19 [Internet]. 2020a[cited 2020 Jul 13] Available from: <https://www.gov.uk/government/publications/national-covid-19-surveillance-reports/sero-surveillance-of-covid-19>

Public Health England. Coronavirus (COVID-19) in the UK [Internet]. 2020b[cited 2020 Jul 11] Available from: <https://coronavirus-staging.data.gov.uk/cases>

Public Health England. Emergency Department Syndromic Surveillance System Week 23 [Internet]. 2020c Available from: [https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment\\_data/file/891440/EDSSSBulletin2020wk23.pdf](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/891440/EDSSSBulletin2020wk23.pdf).

Rinaldi S, Brennan KM, Kalna G, Walgaard C, van Doorn P, Jacobs BC, et al. Antibodies to heteromeric glycolipid complexes in Guillain-Barré syndrome. PLoS One 2013; 8: e82337.

Sejvar JJ, Baughman AL, Wise M, Morgan OW. Population incidence of Guillain-Barré syndrome: A systematic review and meta-analysis. Neuroepidemiology 2011a; 36: 123–133.

Sejvar JJ, Kohl KS, Gidudu J, Amato A, Bakshi N, Baxter R, et al. Guillain-Barré syndrome and Fisher syndrome: Case definitions and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine 2011b; 29: 599–612.

Sekine T, Perez-Potti A, Rivera-Ballesteros O, Straling K, Gorin J-B, Olsson A, et al. Robust

T cell immunity in convalescent individuals with asymptomatic or mild COVID-19. *bioRxiv* 2020: 2020.06.29.174888.

Tam CC, O'Brien SJ, Petersen I, Islam A, Hayward A, Rodriguez LC. Guillain-Barré syndrome and preceding infection with *Campylobacter*, influenza and Epstein-Barr virus in the General Practice Research Database. *PLoS One* 2007; 2

Toscano G, Palmerini F, Ravaglia S, Ruiz L, Invernizzi P, Cuzzoni MG, et al. Guillain-Barré Syndrome Associated with SARS-CoV-2. *N. Engl. J. Med.* 2020

Uncini A, Vallat J-M, Jacobs BC. Guillain-Barré syndrome in SARS-CoV-2 infection: an instant systematic review of the first six months of pandemic. *J. Neurol. Neurosurg. Psychiatry* 2020; 0: 1–6.

Varatharaj A, Thomas N, Ellul MA, Davies NWS, Pollak TA, Tenorio EL, et al. Neurological and neuropsychiatric complications of COVID-19 in 153 patients: a UK-wide surveillance study. *The Lancet Psychiatry* 2020

WHO. Timeline of WHO's response to COVID-19. *World Heal. Organ.* 2020: 1–27.

Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, et al. OpenSAFELY: factors associated with COVID-19 death in 17 million patients. *Nature* 2020

Willison H, Yuki N. Peripheral neuropathies and anti-glycolipid antibodies. *Brain* 2002; 125: 2591–625.

Yuki N, Hartung H-P. Guillain-Barré Syndrome. *N. Engl. J. Med.* 2012; 366: 2294–2304.

Zhao H, Shen D, Zhou H, Liu J, Chen S. Guillain-Barré syndrome associated with SARS-CoV-2 infection: causality or coincidence? *Lancet Neurol.* 2020; 19: 383–384.

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Table 1: Cohort study data demonstrating clinical characteristics of Guillain-Barré Syndrome with definite, probable and without COVID-19 infection.

GBS features	COVID-19 Definite	COVID-19 Probable	Non COVID-19	P Value
<b>Number</b>	13/47 (28)	12/47 (26)	22/47 (47)	
<b>Age, years (IQR)</b>	60 (57 - 66)	57 (50 - 60)	54.5 (34-66)	0.528
<b>Sex, male:female (ratio)</b>	11:2 (5.5)	9:3 (3.0)	13:9 (1.4)	0.200
<b>Ethnicity/ Origin (%)</b>				
White	8 (62)	6 (50)	15 (68)	0.548
Black, Asian and minority ethnic	3 (23)	2 (17)	5 (23)	
Unknown	2 (15)	2 (17)	2 (9)	
<b>Comorbidities (%)</b>				
Hypertension	3 (23)	1 (8)	4 (18)	>0.999
Diabetes	1 (8)	1 (8)	3 (14)	>0.999
Hypercholesterolaemia	2 (15)	3 (25)	1 (5)	0.194
Cerebrovascular Disease	1 (8)	0 (0)	1 (5)	>0.999
COPD/ Asthma	2 (15)	0 (0)	0 (0)	0.491
<b>Severity and Distribution of weakness (%)</b>				
Tetraparesis	9 (69)	8 (67)	13 (59)	0.558
Weakness lower limbs only	2 (15)	3 (25)	5 (23)	>0.999
Weakness upper limbs only	0 (0)	0 (0)	0 (0)	>0.999
Unilateral limb weakness	1 (8)	0 (0)	0 (0)	>0.999
No limb weakness	1 (8)	1 (8)	2 (9)	>0.999
Other	0 (0)	0 (0)	2 (9)	0.213
<b>GBS syndrome (%)</b>				
Normal Neurophysiology	0 (0)	1 (8)	1 (5)	0.084
AIDP	7 (54)	2(17)	12 (55)	0.248
Axonal (AMAN/ AMSAN)	0 (0)	1 (8)	5 (23)	0.084
Miller Fisher	1 (8)	0 (0)	0 (0)	>0.999
Neurophysiology not assessed	5 (38)	8 (67)	4 (18)	<b>0.031</b>
<b>Preceding illness (%)</b>				
Upper respiratory tract infection	10 (77)	2(17)	6 (27)	0.229
Gastrointestinal infection	0 (0)	0 (0)	1 (5)	0.468
Other	0 (0)	0 (0)	2 (9)	0.214
<b>Presence of sensory deficit (%)</b>	6 (46)	7 (58)	11 (50)	>0.999
<b>Cranial nerve involvement (%)</b>	3 (23)	6 (50)	6 (27)	0.550
<b>CSF results</b>				
<b>Protein, g/l (IQR)</b>	0.78 (0.50–0.99)	1.08 (0.69-1.66)	0.49 (0.33-1.23)	0.172
<0.4 g/l	0/11 (0)	2/10 (20)	7/19 (37)	
0.4-1 g/l	8/11 (73)	3/10 (30)	6/19 (32)	
>1 g/l	3/11 (27)	5/10 (50)	6/19 (32)	



<b>White Cell Count, cells/ul (IQR)</b>	<b>2 (0 - 5)</b>	<b>2 (0 - 13)</b>	<b>2 (0 - 38)</b>	<b>0.762</b>
<5	10/10 (100)	8/10 (80)	16/19 (84)	
5 to 10	0/10 (0)	0/10 (0)	2/19 (11)	
>10	0/10 (0)	2/10 (20)	1/19 (5)	
<b>Positive Gangliosides (%)</b>	<b>0 (0)</b>	<b>0 (0)</b>	<b>5 (10)</b>	<b>0.017</b>
<b>Time from COVID-19 symptoms to weakness, days (IQR)</b>	<b>12 (4 - 21)</b>	<b>5 (-7 - 19)</b>	<b>NA</b>	
<b>Time weakness to admission, days (IQR)</b>	<b>2 (-1 - 4)</b>	<b>10 (4 - 14)</b>	<b>4 (1 - 5)</b>	<b>0.534</b>
<b>Time from weakness onset to nadir, days (IQR)</b>	<b>7 (4 - 11)</b>	<b>11 (5 - 17)</b>	<b>6 (4 - 9)</b>	<b>0.311</b>
<b>Invasive mechanical ventilation during illness (%)</b>	<b>7 (54)</b>	<b>0 (0)</b>	<b>5 (23)</b>	<b>0.747</b>
<b>ITU as the maximum level of care required (%)</b>	<b>7 (54)</b>	<b>1 (8)</b>	<b>9 (41)</b>	<b>0.558</b>
<b>HDU as the maximum level of care required (%)</b>	<b>3 (23)</b>	<b>0 (0)</b>	<b>1 (5)</b>	<b>0.611</b>
<b>GBS disability score at 4 weeks from admission, (IQR)</b>	<b>3 (2-4)</b>	<b>2.5 (1.75 - 3)</b>	<b>3.5 (2 - 4)</b>	<b>0.990</b>
Healthy - 0	0 (0)	2 (17)	1 (5)	
Minor symptoms and capable of running - 1	1 (8)	1 (8)	2 (9)	
Able to walk 10 m without assistance but unable to run - 2	2 (15)	3 (25)	4 (18)	
Able to walk 10 m across an open space with help - 3	3 (23)	4 (33)	3 (14)	
Bedridden or chair bound - 4	4 (31)	2 (17)	8 (36)	
Requiring assisted ventilation for at least part of the day - 5	1 (8)	0 (0)	3 (14)	
Dead - 6	1 (8)	0 (0)	0 (0)	
<b>GBS disability score on discharge, (IQR)</b>	<b>3 (2 - 4)</b>	<b>2 (1.75 - 3)</b>	<b>3 (2 - 4)</b>	<b>0.658</b>
Healthy - 0	1 (8)	1 (8)	1 (5)	
Minor symptoms and capable of running - 1	1 (8)	1 (8)	2 (9)	
Able to walk 10 m without assistance but unable to run - 2	2 (15)	4 (33)	5 (23)	
Able to walk 10 m across an open space with help - 3	3 (23)	3 (25)	4 (18)	
Bedridden or chair bound - 4	2 (15)	1 (8)	4 (18)	
Requiring assisted ventilation for at least part of the day - 5	1 (8)	0 (0)	0 (0)	
Dead - 6	1 (8)	0 (0)	0 (0)	
<b>Initial Treatment Type (%)</b>				
IVIg	9 (69)	9 (75)	21(95)	0.052
PLEX	0 (0)	0 (0)	0 (0)	
Nil	4 (31)	3 (25)	1 (5)	0.052
<b>Mortality (%)</b>	<b>1 (8)</b>	<b>0 (0)</b>	<b>0 (0)</b>	<b>&gt;0.999</b>

Data are presented as *n* (%) or median (IQR). *P*-values represent a comparison between COVID-19 definite and COVID-19 probable to non-COVID-19 GBS. *P*-values below 0.05 are highlighted in bold.

Table 2: Clinical characteristics of COVID-19 pandemic Guillain-Barré Syndrome compared to IGOS cohort.

GBS features	Overall	IGOS Cohort 2018	P Value
<b>Number</b>	47	<b>925</b>	
<b>Age, years (IQR)</b>	57 (19 - 88)	55 (37-67)	
<b>Sex, male:female (ratio)</b>	33:14 (2.36)	418:297 (1.41)	0.127
<b>Severity and Distribution of weakness</b>			
Tetraparesis	30/47 (64)	677/924 (73)	0.178
Weakness lower limbs only	10/47 (21)	105/924 (11)	0.059
Weakness upper limbs only	0/47 (0)	19/924 (2)	>0.999
Unilateral limb weakness	1/47 (2)	10/924 (1)	0.422
No limb weakness	4/47 (9)	15/924 (2)	<b>0.010</b>
<b>GBS syndrome</b>			
Normal Neurophysiology	2/47 (4)	36/573 (6)	0.758
AIDP	21/47 (45)	312/573 (55)	0.224
Axonal (AMAN/ AMSAN)	6/47 (12)	33/573 (6)	0.107
<b>Preceding illness</b>			
Upper respiratory tract infection	18/47 (38)	248/652 (38)	>0.999
Gastrointestinal infection	1/47 (2)	163/652 (25)	<b>&lt;0.000</b>
<b>Presence of sensory deficit</b>	26/47 (55)	408/588 (69)	0.051
<b>Cranial nerve involvement</b>	15/47 (32)	304/620(49)	<b>0.033</b>
<b>CSF results</b>			
<b>Protein g/l, median (IQR)</b>	0.695 (0.24 - 4.16))	0.98 (0.59-1.84)	
<0.4 g/l	16/39 (41)	262/823 (32)	0.144
>0.4 g/l	23/39 (59)	561/823 (68)	0.225
<b>White Cell Count (median)</b>	2 (0 - 38)		
<5	30/35 (86)	641/823 (80)	0.401
5 to 50	5/35 (14)	149/823 (19)	0.659
>50	0/35 (0)	14/823 (2)	>0.999
<b>Time of weakness to admission, days (IQR)</b>	4 (-13 - 27)	3 (2 - 6)	
<b>Number of patients requiring invasive mechanical ventilation during illness</b>	12/47 (26)	121/715 (17)	0.162
<b>Initial Treatment Type</b>			
IVIg	39/47 (83)	612/715 (86)	0.668
PLEX	0/47 (0)	43/715 (6)	0.101
<b>Mortality</b>	1/47 (2)	44/659 (7)	0.352

Data are presented as *n* (%) or median (IQR). *P*-values represent a comparison between the COVID-19 cohort (definite, probable and non-COVID-19) GBS compared to that of the IGOS study cohort. Note that IGOS denominator values reflect worldwide cases reported (*n*=925) or once stratified for 'Europe/ American' cases (*n*=715) if available.

Figure 1: Numbers of new daily COVID-19 infections from February to May inclusive, 2020 (red line) compared to Guillain-Barré syndrome cases in the UK between February to May inclusive from 2016 to 2020 (years depicted by colours in figure legend).

Figure 2: Monthly incidence of Guillain-Barré syndrome per 100,000 people treated with IVIg in the UK between January and May inclusive for 2016-2020.

Figure 3: Heatmap of regional incidences of Guillain-Barré syndrome and COVID-19 infections per 100,000 across the UK from January to May inclusive, 2020.

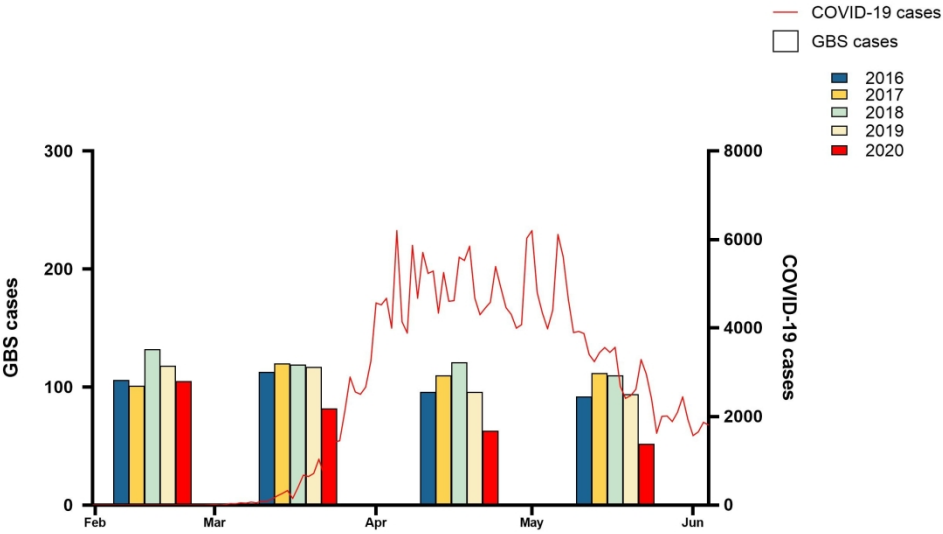


Figure 1: Numbers of new daily COVID-19 infections from February to May inclusive, 2020 (red line) compared to Guillain-Barré syndrome cases in the UK between February to May inclusive from 2016 to 2020 (years depicted by colours in figure legend).

219x124mm (300 x 300 DPI)

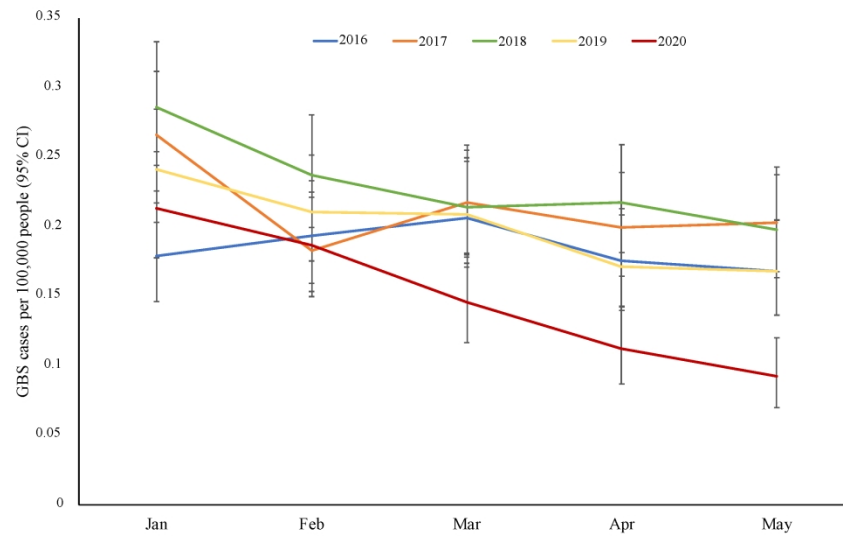


Figure 2: Monthly incidence of Guillain-Barré syndrome per 100,000 people treated with IVIg in the UK between January and May inclusive for 2016-2020.

297x209mm (300 x 300 DPI)

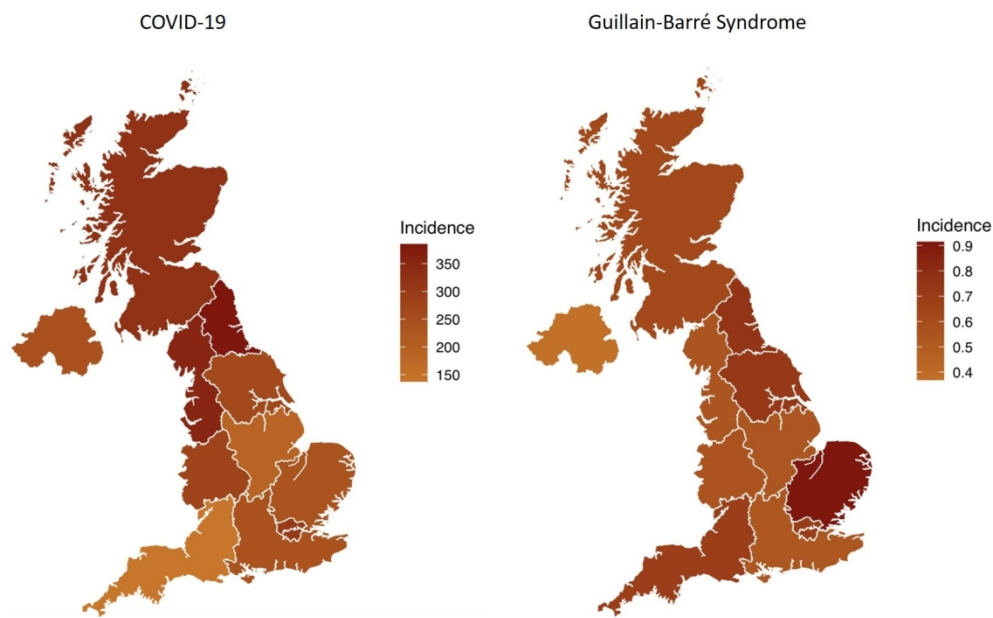


Figure 3: Heatmap of regional incidences of Guillain-Barré syndrome and COVID-19 infections per 100,000 across the UK from January to May inclusive, 2020.

451x277mm (96 x 96 DPI)

## Supplementary material

Table 1: Incidence rate per 100,000 people (95% confidence interval) for Guillain-Barré Syndrome Jan-May 2020

Guillain-Barré Syndrome					COVID-19			
Region	No. Cases	Incidence rate	Lower 95%CI	Upper 95%CI	Incidence rate	No. Cases	Lower 95%CI	Upper 95%CI
Scotland	34	0.62	0.43	0.87	323.54	17676	318.80	328.34
Northern Ireland	7	0.37	0.15	0.76	241.33	4570	234.41	248.40
North East	20	0.75	0.46	1.16	385.06	10281	377.68	392.56
North West	40	0.54	0.39	0.74	352.64	25888	348.36	356.96
Yorkshire and the Humber	40	0.73	0.52	0.99	262.31	14435	258.06	266.62
East Midlands	26	0.54	0.35	0.79	191.05	9239	187.18	194.97
West Midlands	33	0.56	0.38	0.78	274.08	16264	269.89	278.32
East of England	57	0.91	0.69	1.18	231.62	14444	227.87	235.42
London	63	0.70	0.54	0.90	302.34	27096	298.76	305.96
South East	49	0.53	0.39	0.71	237.52	21805	234.39	240.69
South West	39	0.69	0.49	0.95	137.63	7741	134.59	140.72

For Peer Review



## Supplementary material

**Table 1: Reports of Guillain-Barré Syndrome and variants associated with COVID-19 infection.**

First author, county	Cases	Age, sex	Presentation	COVID-19 diagnosis	Time from COVID-19 symptoms to weakness onset	Tests for infection	Anti-ganglioside antibodies	Radiology	Neuroradiology	Neurophysiology	CSF	Management	Outcome
Abdelnoor, UK <sup>1</sup>	1	69, f	Three-day history of lower limb weakness. Numbness in lower legs lasting for hours. No arm, cranial nerve symptoms. Developed temperature and confusion day four of admission	Nasopharyngeal swab-PCR positive on admission	Asymptomatic. Positive swab three days following onset of weakness	NR		CXR-right lower-lobe consolidation	MRI-head and-whole spine showing old infarcts in left frontal, parietal, occipital lobes	NR	NR	No treatment	Spontaneous recovery of power and gait. Discharged home at 18 days
Alberti, Italy <sup>2</sup>	1	71, m	Subacute weakness of paraesthesia in hands and feet, with rapid evolution to severe flaccid tetraparesis over three	Nasopharyngeal swab-PCR positive on admission, three days post neurological onset	The week before neurological symptoms had fever, and during admission	NR		CT-chest ground glass opacities	CT-head normal	Severe acute inflammatory demyelinating polyneuropathy	WCC-9 x10 <sup>6</sup> /L Protein 54mg/dL	Ventilation Proning Lopinavir Ritonavir Hydroxychloroquine IVIg 0.4g/kg/day for five days	Died on day two

			days- Dysautonomia		was hypoxic								
Camdes sanche, France <sup>3</sup>	1	64, m	Admitted following a fall with cough and fever. Day nine developed paraesthesia in hands and feet and progressive quadriparesis with areflexia. Developed dysphagia and respiratory compromise requiring intubation	Nasophar yngeal swab-PCR positive on admission	11-days before weakness	Campyloba cter, mycoplasm a, salmonella, CMV, EMV, HSV1 & 2, VZV, influenza, HIV, hepatitis-E all-negative	Negative	CT-chest ground glass opacities	NR	WCC-normal Protein-166mg/dL	Evidenc e-of prolong ed DMLs, slow conducti on velocity and conducti on block-F wave prolong ation. Diagnos ed-AIDP.	Oxygen Lopinavir Ritonavir IVIg-0.4g/kg/day for five days	No outcome reported
Coen, Switzerl and <sup>4</sup>	1	70's, m	Symmetrical flaccid areflexic paraparesis, allodynia, difficulties in voiding. No sensory impairment	Nasophar yngeal swab-PCR positive five-days before admission	10-days before neurologic al-onset had myalgia, dry-cough, fever	Anti-SARS- CoV-2-IgA and-IgG +ve	Negative	CXR normal	Contrast- enhanced MRI-no myelopat hy	Sensorimotor demyelinating polyneuropathy with sural-sparing. Decreased or absent F-waves. AIDP	Albumin ocytolog ic dissocia tion. Negativ e-for meningi tis/ence phalitis panel testing (Biofire Diagnos tics, UT) SARS- CoV-2 PCR negative	IVIg-0.4g/kg/day for five days	Rapid improveme nt-by day 11

Dinkin, USA <sup>5</sup>	1	36, m	Ophthalmoplegia with right oculomotor palsy and bilateral abducens palsies. Reduced lower-limb reflexes. Bilateral distal lower-limb paraesthesia and sensation. Ataxic gait	Nasopharyngeal swab-PCR on admission	Four days before neurological presentation had fever, cough, myalgia	NR	Negative	CXR normal	MRI brain hyperintensity and enlargement of left oculomotor nerve	NR	NR	Hydroxychloroquine IVIG 0.4g/kg/day for five days	Partial response, discharged at three days
EL-Otmani, Morocco <sup>6</sup>	1	70, f	Rapid-onset progressive bilateral weakness in all four limbs with paraesthesia and areflexia	Nasopharyngeal swab-PCR positive 10 days into admission	Three days before neurological onset developed dry cough lasting 48 hours	NR	NR	CT-chest ground glass opacities	NR	Marked reduction or absence of potentials in both motor and sensory nerves in all four limbs. No abnormalities in conduction velocities and latencies. EMG found diffuse and abundant fibrillation potentials at rest. Diagnosis of AMSAN	WCC normal Protein 100mg/dL SARS-CoV-2 PCR negative	Hydroxychloroquine Azithromycin IVIG 0.4g/kg/day for five days	Outcome at one week no improvement
Guijarro-Castro, Spain <sup>7</sup>	1	70, m	Subacute weakness in all limbs with areflexia over five days	Nasopharyngeal swab-PCR positive three weeks prior to weakness	Experienced COVID-19 pneumonia 3 weeks prior	NR	NR	CT-chest ground glass opacities	NR	Delayed DMLs, absent F waves, symmetrical acute motor and sensory polyradiculoneuropathy. EMG showed	WCC $0 \times 10^6/L$ Protein 49mg/dL	Oxygen Hydroxychloroquine Azithromycin Ceftriaxone Dexamethasone IVIG 0.4g/kg/day for five days	Clinical improvement on the third day of therapy. By day 14 mild weakness

										neurogenic involvement without denervation			in dorsal interossei; ankle dorsiflexion and areflexia
Gutiérrez-Ortiz, Spain <sup>8</sup>	1	50, m	Right internuclear ophthalmoparesis with right oculomotor palsy, ataxia and areflexia	Nasopharyngeal swab-PCR positive on admission	5 days before history of cough, fever, malaise, headache, anosmia, ageusia.	NR	Anti-GD1b-IgG detected in serum	CXR normal	CT head normal	WCC normal Protein 80mg/dL Normal glucose  CSF cytology, cultures and infectious pathogens negative	NR	IVIg 0.4g/kg/day for five days	Complete recovery at two weeks other than anosmia and ageusia
Marta-Enguita, Spain <sup>9</sup>	1	76, f	10-day history lower back ache radiating down legs. Paraesthesia distally in all limbs, followed by progressive weakness, proximal worse to distal. Areflexia. Reduced sensation below knee. Once admitted rapid development of dysphagia, onset of respiratory failure.	Nasopharyngeal swab-PCR positive one day before onset of neurological symptoms	8 days before back pain onset had cough, fatigue, fever	NR	NR	CT chest ground glass opacities	CT head normal. CT C and T-spine showed degeneration only	NR	NR	Co-amoxiclav Azithromycin Analgesia High flow oxygen	Died within 24 hours of admission

Padroni, Italy <sup>10</sup>	1	70, f	Hand and feet paraesthesia and progressive distal weakness in all limbs. Areflexia. On IVIG developed respiratory insufficiency and intubated	Nasopharyngeal swab-PCR positive 23 days before neurological weakness	24 days before weakness had fever, dry cough resolved in days	Mycoplasma, CMV negative. Urine negative antigen test for legionella and streptococcal pneumoniae	NR	CT chest ground glass opacities	NR	WCC normal Protein 48mg/dL  Negative for HSV, VZV, CMV, EBV, HIV, borrelia antibodies.	Prolonged DMLs, reduced conduction velocities and prolonged F waves. AIDP diagnosed.	IVIG 0.4g/kg/day for five days	No update on outcome from ventilated status
Scheidt, Germany <sup>11</sup>	1	54, f	Acute proximal moderate paraparesis with areflexia and sensory. Two days following complained of dysphagia	Nasopharyngeal swab-PCR positive three weeks before neurological symptoms	Three weeks	Borrelia, Campylobacter, HIV negative	NR			Prolonged DMLs and temporal dispersion of CMAP of common peroneal. Normal F waves with complex A waves on both tibial nerves. Motor conduction velocities normal. EMG no denervation. AIDP diagnosed	WCC normal Protein 140mg/dL	IVIG 0.4g/kg/day for five days	Day 14 almost complete recovery
Sedaghat, Iran <sup>12</sup>	1	65, m	Acute progressive ascending symmetric quadriparesis over five days. Facial paresis. Areflexia	Nasopharyngeal swab-PCR positive 2 weeks before neurological onset	Two weeks	NR	NR	CT chest ground glass opacities and pleural effusion	MRI brain and C-spine mild disc herniation	Decreased amplitude at compound muscle action potential and no response at sensory nerve action potential. Electromyography showed decreased recruitment.	NR	Lopinavir Ritonavir Hydroxychloroquine Azithromycin IVIG 0.4g/kg/day for five days	NR

										AMSAN-variant diagnosed			
Velayos Galan, Spain <sup>13</sup>	1	43,m	Symmetrical weakness involving all limbs leading to inability to walk. Sensory alterations in distal limbs. Areflexia. Two days in developed bilateral facial palsy, dysphagia	Nasopharyngeal swab-PCR positive on admission	10-days before neurological onset experienced diarrhoea and upper respiratory tract symptoms	NR	NR	CXR suggestive of COVID-19	NR	Increased distal motor latency and decreased sensory nerve conduction velocity in the nerves evaluated. Increased minimal F-wave latency in the right L5 and S1 spinal nerve roots. AIDP diagnosed	NR	Oxygen Lopinavir Ritonavir Hydroxychloroquine Amoxicillin Corticosteroids IVIg 0.4g/kg/day for five days	Neurological symptoms progressed favourably
Virani, USA <sup>14</sup>	1	54, m	Progressive weakness in lower then upper limbs. Areflexia. Developed dyspnoea and weakness progress to involve trunk. Urine retention. Ventilated	Nasopharyngeal swab-PCR positive two days following onset of neurological symptoms - Rhinovirus also positive	10-days before weakness developed fever	NR	NR	MRI spine incidental discovery of ground glass opacities in lungs	MRI spine normal	NR	NR	IVIg 0.4g/kg/day for five days	Following four days IVIG off ventilator. ON discharge upper limb weakness resolved, lower limbs remain weak
Webb, UK <sup>15</sup>	1	57, m	One-day history progressive limb weakness and foot dysesthesia. Progressed over 48 hours unable to	Nasopharyngeal swab-PCR positive on admission	One-week before weakness, history of cough and headache, myalgia and malaise	HIV, hepatitis, syphilis negative	Negative	CXR normal. CT chest ground glass opacification	NR	reduced conduction velocity and prolonged DMLs in motor and sensory nerves in the upper and lower limbs. Dispersion in MUAPs. F-waves	WCC normal Protein 51mg/dL Viral PCR negative for SARS-	Ventilation Co-amoxiclav IVIg 0.4g/kg/day for five days	Tracheostomy day 6, is improving and being weaned off ventilation

			stand-with flaccid symmetrical sensory and motor neuropathy. Areflexia. Day three progressed with dysphagia and respiratory compromise requiring intubation							absent. Sensory nerves showed reduced conduction velocities. AIDP diagnosed	CoV-2 RNA		
Zhao, China <sup>16</sup>	1	61, f	Progressive symmetric weakness in legs then the arms over four days with reduced sensation to distal limbs. Day eight developed dry cough and fever	Nasopharyngeal swab-PCR positive at day eight	COVID symptoms day eight following weakness onset	NR	NR	CT chest ground glass opacities	NR	Distal latencies and absent F waves. AIDP diagnosed	WCC $5 \times 10^6/L$ Protein $124 \text{ mg/dL}$	Arbidol Lopinavir Ritonavir IVIg 0.4g/kg/day for five days	Normal power and reflexes on discharge day 30
Gigli, Italy <sup>17</sup>	8	76, m 70, m 80, m 59, m 59, f 82, m 53, m 59, f	Paraparesis in three, tetraparesis in three, facial weakness in one, dysarthria in two. Paraesthesia in six	Negative in all	COVID symptoms in 4, no time frame included	1: Negative serology for Borrelia and West Nile. 2-4: Negative for Borrelia and TBE 5+6: NR	Taken in six, positive in one (GD1a, GT1b, sulfatide)	Chest changes (CXR or CT) in four.	NR	CSF leucocytes taken in 7, all normal. Protein raised in 5 (range 216-1928 mg/L)  PCR for EBV, CMV, Enterovirus, HSV-1, HSV-2,	AIDP in six, AMSAN in one, MFS in one	All treated with IVIg 0.4g/kg/day (information provided through personal communications, not reported in manuscript)	NR

						7: Negative PCR for influenza A and B. Negative for Borrelia and TBE 8: NR  SARS-CoV-2 serology taken from 6, positive for IgM and IgG in one				HHV-6, Hepatitis e, VZV taken in four, all negative			
Tatu, France <sup>18</sup>	7	79, f 74, f 75, m 48, f 71, m 77, f	Paraparesis in four, tetraparesis in two. Facial weakness in one, ataxia in four. Paraesthesia in six	Negative in all	No COVID symptoms documented	Negative for Borrelia, HIV, EBV, CMV, Campylobacter Jejuni in cases 1-5. Hepatitis E positive serology in case 3.  SARS-CoV-2 serology negative in all	Taken in all six, positive in one (GM1, GM2, sulfatide)	NR	NR	CSF leucocytes raised in one (7/mm <sup>3</sup> ). Protein raised in five of six cases, (range 210-2870mg/dL)	AIDP in six, AMSAN in one	All treated with IVIG 0.4g/kg/day	Three admitted to ICU. Favourable in five. Two relapsed, one died
Toscana <sup>19</sup> , Italy	5	77, f 23, m 55, m 76, m 61, m	Lower limb weakness and paraesthesia in four, facial diplegia and ataxia in one.	Nasopharyngeal swab PCR positive on admission	Ranged from five to 10 days	One negative for Campylobacter Jejuni, EBV, CMV,	Three tested, all negative	1: CT chest bilateral pneumonia 2: NR 3: CT chest ground	MRI enhancement of caudal roots in two, facial	WCC normal in all. Protein 101mg/dL, 123mg/dL, 193mg/dL,	AMSAN in two, AMAN in one, demyelination	All treated with IVIG 0.4g/kg/day for 5 days, two treated with two infusions. One plasma exchange.	3 required intubation. At four weeks two remain ventilated,



			Generalised flaccid tetraparesis over 36 hours – four days in four patients, three required ventilation	in four, negative in one but antibody positive		HSV, influenza and HIV		glass opacities 4: negative chest imaging 5: CXR and CT interstitial pneumonia	nerve in one, no change in two	normal and 40mg/dL All negative viral PCR for SARS-CoV-2 RNA	nating in two		two receiving physiotherapy with flaccid paraplegia and minimal upper limb movement and one discharged walking independently
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AIDP= acute inflammatory demyelinating polyradiculoneuropathy, AMAN= acute motor axonal neuropathy, AMSAN= acute motor sensory axonal neuropathy, MFS= Miller Fisher syndrome, CSF= cerebrospinal fluid, PCR= polymerase chain reaction, NR= not recorded, CXR= chest X ray, CT= computerised tomography, MRI= magnetic resonance imaging, EMG= electromyography, DML= distal motor latency, CMAP= compound motor action potential, MUAP= motor unit action potential, WCC= white cell count, CMV= cytomegalovirus, EBV= Epstein-Barr virus, HSV= herpes simplex virus, HIV= human immunodeficiency virus, VZV= Varicella Zoster virus, TBE= tick bite encephalitis.

Table 12: Incidence rate per 100,000 people (95% confidence interval) for Guillain-Barré Syndrome Jan-May 2020

Guillain-Barré Syndrome					COVID-19			
Region	No. Cases	Incidence rate	Lower 95%CI	Upper 95%CI	Incidence rate	No. Cases	Lower 95%CI	Upper 95%CI
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## References

- 1.—— Abdelnour L, Eltahir Abdalla M, Babiker S. COVID-19 infection presenting as motor peripheral neuropathy. *J Formos Med Assoc.* 2020;119(6):1119-1120.
- 2.—— Alberti P, Beretta S, Piatti M, et al. Guillain-Barré syndrome related to COVID-19 infection. *Neurol Neuroimmunol NeuroInflammation.* 2020;7(4).
- 3.—— Camdessanche JP, Morel J, Pozzetto B, Paul S, Tholance Y, Botelho-Nevers E. COVID-19 may induce Guillain-Barré syndrome. *Rev Neurol (Paris).* 2020;176(6):516.
- 4.—— Coen M, Jeanson G, Culebras Almeida LA, et al. Guillain-Barré syndrome as a complication of SARS-CoV-2 infection. *Brain Behav Immun.* 2020;87:111.
- 5.—— Dinkin M, Gao V, Kahan J, et al. COVID-19 presenting with ophthalmoparesis from cranial nerve palsy. *Neurology.* May 2020;10.1212/WNL.0000000000009700.
- 6.—— El Otmani H, El Moutawakil B, Rafai MA, et al. Covid-19 and Guillain-Barré syndrome: More than a coincidence! *Rev Neurol (Paris).* 2020;176(6):518.
- 7.—— Guijarro-Castro C, Rosón-González M, Abreu A, García-Arratibel A, Ochoa-Mulas M. Guillain-Barré síndrome associated with SARS-CoV-2 infection. Comments after 16 published cases. *Neurología.* June 2020.
- 8.—— Gutiérrez-Ortiz C, Méndez A, Rodrigo-Rey S, et al. Miller Fisher Syndrome and polyneuritis cranialis in COVID-19. *Neurology.* April 2020;10.1212/WNL.0000000000009619.
- 9.—— Marta-Enguita J, Rubio-Baines I, Gastón-Zubimendi I. Fatal Guillain-Barre syndrome after infection with SARS-CoV-2. *Neurol (English Ed).* 2020;35(4):265-267.
- 10.—— Padroni M, Mastrangelo V, Asioli GM, et al. Guillain-Barré syndrome following COVID-19: new infection, old complication? *J Neurol.* 2020;1:1.
- 11.—— Scheidl E, Canseco DD, Hadji-Naumov A, Bereznai B. Guillain-Barre syndrome during SARS-CoV-2 pandemic: a case report and review of recent literature. *J Peripher Nerv Syst.* June 2020.
- 12.—— Sedaghat Z, Karimi N. Guillain-Barre syndrome associated with COVID-19 infection: A case report. *J Clin Neurosci.* 2020;76:233.

13. — Velayos Galán A, del Saz Saucedo P, Peinado Postigo F, Botia Paniagua E. Guillain-Barré syndrome associated with SARS-CoV-2 infection. *Neurol (English Ed)*. 2020;35(4):268-269.

14. — Virani A, Rabold E, Hanson T, et al. Guillain-Barré Syndrome associated with SARS-CoV-2 infection. *IDCases*. 2020;20:e00771.

15. — Webb S, Wallace VC, Martin-Lopez D, Yogarajah M. Guillain-Barré syndrome following COVID-19: a newly emerging post-infectious complication. *BMJ Case Rep*. 2020;13(6):236182.

16. — Zhao H, Shen D, Zhou H, Liu J, Chen S. Guillain-Barré syndrome associated with SARS-CoV-2 infection: causality or coincidence? *Lancet Neurol*. 2020;19(5):383-384.

17. — Gigli GL, Bax F, Marini A, et al. Guillain-Barré syndrome in the COVID-19 era: just an occasional cluster? *J Neurol*. 2020.

18. — Tatu L, Nono S, Grácio S, Koçer S. Guillain-Barré syndrome in the COVID-19 era: another occasional cluster? *J Neurol*. June 2020:1.

19. — Toscano G, Palmerini F, Ravaglia S, et al. Guillain-Barré Syndrome Associated with SARS-CoV-2. *N Engl J Med*. April 2020.

## STROBE statement: Reporting guidelines checklist for cohort, case-control and cross-sectional studies

SECTION	ITEM NUMBER	CHECKLIST ITEM	REPORTED ON PAGE NUMBER:
<b>TITLE AND ABSTRACT</b>			
	1a	Indicate the study's design with a commonly used term in the title or the abstract	1
	1b	Provide in the abstract an informative and balanced summary of what was done and what was found	4
<b>INTRODUCTION</b>			
Background and objectives	2	Explain the scientific background and rationale for the investigation being reported	6
	3	State specific objectives, including any pre-specified hypotheses	7
<b>METHODS</b>			
Study design	4	Present key elements of study design early in the paper	7-10
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-10
Participants	6a	Cohort study—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	7-10
	6b	Cohort study—For matched studies, give matching criteria and number of exposed and unexposed Case-control study—For matched studies, give matching criteria and the number of controls per case Variables	11 + table
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8
Data sources/measurements	8*	For each variable of interest, give sources of data and details of methods of assessment	7

SECTION	ITEM NUMBER	CHECKLIST ITEM	REPORTED ON PAGE NUMBER:
		(measurement). Describe comparability of assessment methods if there is more than one group.	
Bias	9	Describe any efforts to address potential sources of bias.	15
Study size	10	Explain how the study size was arrived at	7-8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why.	8
Statistical methods	12a	Describe all statistical methods, including those used to control for confounding	9
	12b	Describe any methods used to examine subgroups and interactions	10
	12c	Explain how missing data were addressed	nd
	12d	Cohort study—If applicable, explain how loss to follow-up was addressed Case-control study—If applicable, explain how matching of cases and controls was addressed Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	na
	12e	Describe any sensitivity analyses	na
RESULTS			
Participants	13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	11-12
	13b	Give reasons for non-participation at each stage	na
	13c	Consider use of a flow diagram	na
Descriptive Data	14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11-12
	14b	Indicate number of participants with missing data for each variable of interest	Table
	14c	Cohort study—Summarise follow-up time (eg, average and total amount)	11-12
Outcome Data	15*	Cohort study—Report numbers of outcome events or summary measures over time Case-control study—Report numbers in each exposure category, or summary measures of exposure Cross-sectional study—Report numbers of outcome events or summary measures	11-13

SECTION	ITEM NUMBER	CHECKLIST ITEM	REPORTED ON PAGE NUMBER:
Main Results	16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g. 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-13
	16b	Report category boundaries when continuous variables were categorized	11-13
	16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Na
	16d	Report results of any adjustments for multiple comparisons	Na
Other Analyses	17a	Report other analyses done—e.g. analyses of subgroups and interactions, and sensitivity analyses	14
	17b	If numerous genetic exposures (genetic variants) were examined, summarize results from all analyses undertaken	Na
	17c	If detailed results are available elsewhere, state how they can be accessed	6,8
<b>DISCUSSION</b>			
Key Results	18	Summarise key results with reference to study objectives	15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16-18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16-19
Generalisability	21	Discuss the generalisability (external validity) of the study results Other information	19
<b>FUNDING</b>			
	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	3

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.