

# Guillain-Barré Syndrome Outbreak in Peru 2019 Associated With *Campylobacter jejuni* Infection

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## Abstract

### Objective

To identify the clinical phenotypes and infectious triggers in the 2019 Peruvian Guillain-Barré syndrome (GBS) outbreak.

### Methods

We prospectively collected clinical and neurophysiologic data of patients with GBS admitted to a tertiary hospital in Lima, Peru, between May and August 2019. Molecular, immunologic, and microbiological methods were used to identify causative infectious agents. Sera from 41 controls were compared with cases for antibodies to *Campylobacter jejuni* and gangliosides. Genomic analysis was performed on 4 *C jejuni* isolates.

### Results

The 49 included patients had a median age of 44 years (interquartile range [IQR] 30–54 years), and 28 (57%) were male. Thirty-two (65%) had symptoms of a preceding infection: 24 (49%) diarrhea and 13 (27%) upper respiratory tract infection. The median time between infectious to neurologic symptoms was 3 days (IQR 2–9 days). Eighty percent had a pure motor form of GBS, 21 (43%) had the axonal electrophysiologic subtype, and 18% the demyelinating subtype. Evidence of recent *C jejuni* infection was found in 28/43 (65%). No evidence of recent arbovirus infection was found. Twenty-three cases vs 11 controls (OR 3.3, confidence interval [CI] 95% 1.2–9.2,  $p < 0.01$ ) had IgM and/or IgA antibodies against *C jejuni*. Anti-GM1: phosphatidylserine and/or anti-GT1a:GM1 heteromeric complex antibodies were strongly positive in cases (92.9% sensitivity and 68.3% specificity). Genomic analysis showed that the *C jejuni* strains were closely related and had the Asn51 polymorphism at  *cstII* gene.

### Conclusions

Our study indicates that the 2019 Peruvian GBS outbreak was associated with *C jejuni* infection and that the *C jejuni* strains linked to GBS circulate widely in different parts of the world.

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## Glossary

**CHIKV** = chikungunya virus; **DENV** = dengue virus; **EGRIS** = Erasmus GBS Respiratory Insufficiency Score; **GBS** = Guillain-Barré syndrome; **GBSDS** = Guillain-Barré syndrome Disability Score; **HC** = healthy control; **HCH** = Hospital Cayetano Heredia; **IQR** = interquartile range; **LOS** = lipo-oligosaccharide; **mEGOS** = modified Erasmus GBS Outcome Score; **MRC** = Medical Research Council; **mRS** = modified Rankin Scale; **NCBI** = National Center for Biotechnology Information; **NCS** = nerve conduction study; **PS** = phosphatidylserine; **ROC** = receiver operating characteristic; **ST** = sequence type; **ZIKV** = Zika virus.

Guillain-Barré syndrome (GBS) is an immune-mediated disorder frequently triggered by infections, characterized by an acute flaccid paralysis, accompanied by sensory symptoms and cranial nerve deficits.<sup>1</sup> In recent years, several outbreaks of GBS have been observed globally, including the large outbreaks in Latin America during the Zika virus (ZIKV) epidemic,<sup>2–4</sup> and the possibility of an association between severe acute respiratory syndrome coronavirus 2 infection and GBS has been raised.<sup>5</sup> As the ZIKV epidemic transitioned to an endemic phase in the Americas in 2017, 2 major outbreaks of GBS occurred in Peru in 2018 and 2019. The number of reported GBS cases increased from 59 in 2017 (incidence: 0.19/100,000) to 262 in 2018 (incidence: 0.81/100,000) and 1,120 in 2019 (incidence: 3.44/100,000).<sup>6</sup> During these outbreaks, the increases in GBS cases were also reported in areas where there is no potential arboviral transmission, such as the highlands of Peru. The outbreaks had a seasonal pattern with the major peaks occurring between April and July in both years (figure 1A).<sup>6,7</sup> We investigated the causality of these outbreaks, by performing an observational clinical cohort study of adult patients with GBS evaluated at a tertiary university hospital in Lima during the 2019 outbreak.

## Methods

### Study Population and Design

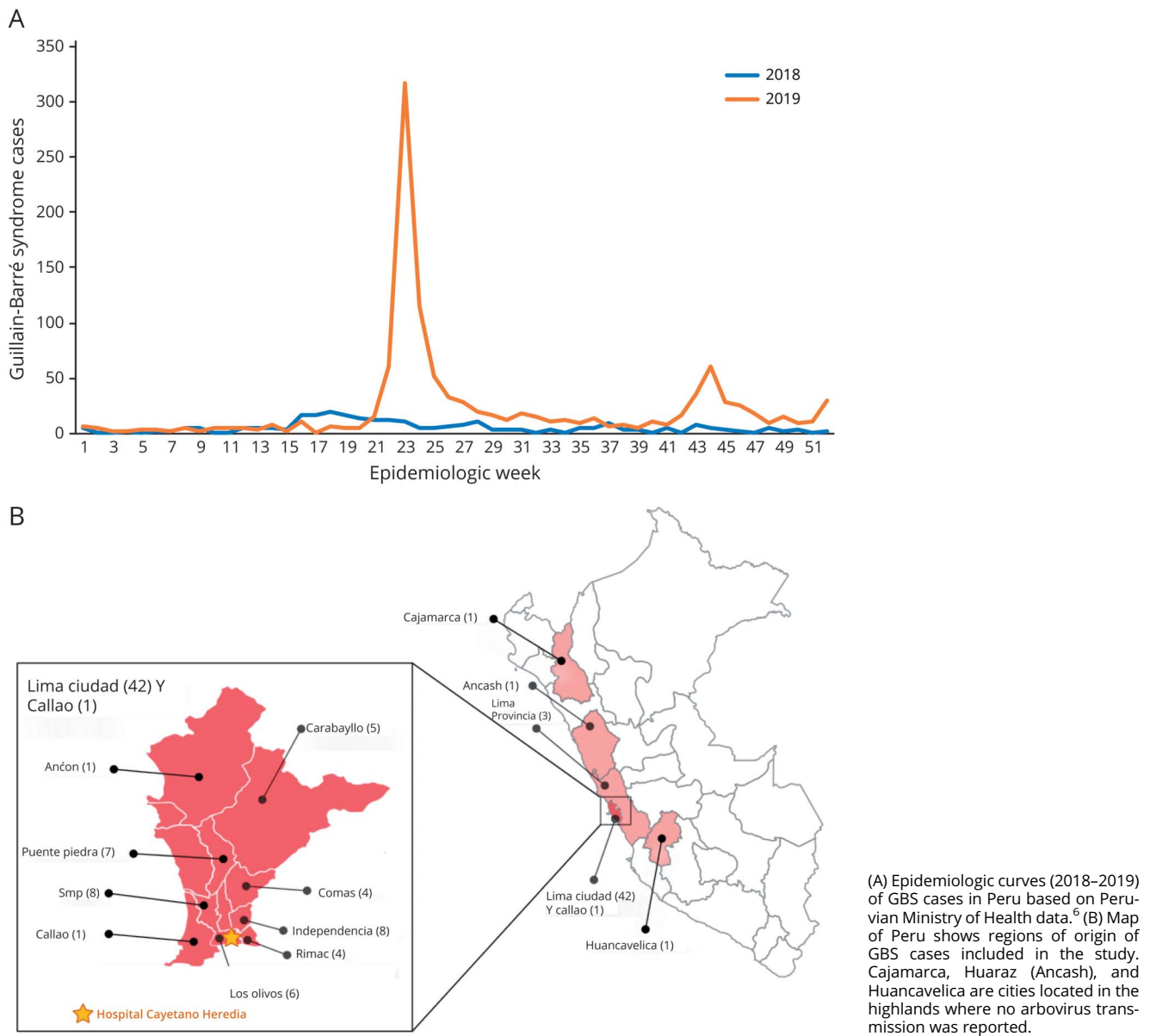
We prospectively evaluated the clinical and laboratory features of patients suspected of GBS at the Hospital Cayetano Heredia (HCH), a university-based tertiary care hospital in Lima, Peru, during the 2019 GBS outbreak (May–August) in Peru. We included all patients who were evaluated by a neurologist and fulfilled the Brighton Collaboration Working Group criteria for diagnosis of GBS with a classification level 1, 2, or 3.<sup>8</sup> Included patients underwent neurologic evaluation during the acute and convalescent phase of their illness and were followed up to 6 months after discharge. Patients with alternative diagnoses or insufficient data were excluded. Blood, CSF, respiratory, and stool samples were obtained during the acute phase as part of the standard of care to identify potential infectious etiologies. Nerve conduction studies (NCSs) and EMG were performed and classified according to the criteria of Hadden et al.<sup>9,10</sup> The clinical and laboratory information was documented using standardized questionnaires of the Neuroviruses Emerging in the Americas Study forms adapted from the International GBS Outcome Study.<sup>3,11</sup>

The onset of GBS and disease nadir were defined as the first day of neurologic symptoms and the most severe clinical weakness, respectively. Pure motor GBS was defined as limb weakness in the absence of sensory deficits at neurologic examination, and sensorimotor GBS was defined as presence of both limb weakness and sensory deficits. Limb muscle strength was evaluated using the Medical Research Council (MRC) sum score.<sup>12</sup> Severity was assessed according to the modified Rankin Scale (mRS),<sup>13</sup> the GBS Disability Score (GBSDS),<sup>14</sup> the modified Erasmus GBS Outcome Score (mEGOS),<sup>15</sup> and the Erasmus GBS Respiratory Insufficiency Score at admission (EGRIS).<sup>16</sup>

### Laboratory Testing

Hematologic and comprehensive metabolic assessments, including among others sodium and potassium levels, liver and kidney function tests, and HIV serology, were performed in all patients at admission. For the investigation of infectious agents, blood, CSF, oropharyngeal swabs, and stool samples were tested at the Naval Medical Research Unit 6 in Lima, Peru. Blood samples were assessed for arboviral infections including ZIKV, dengue virus (DENV), and chikungunya virus (CHIKV) using quantitative real time-PCR.<sup>17</sup> Oropharyngeal swabs were tested for 20 respiratory pathogens using a multiplexed PCR assay (BioFire Diagnostics, Salt Lake City, UT). Stool swabs in Cary Blair medium were analyzed using a multiplexed PCR assay for gastrointestinal pathogens (BioFire Diagnostics), which included 22 pathogens associated with gastroenteritis, such as *Campylobacter* species (*jejuni*, *coli*, and *upsaliensis*), and *Escherichia coli*. Stool samples were cultured for identification and characterization of *E coli* and *C jejuni*.<sup>18</sup> Positive culture samples were further characterized using multiplexed PCR assays for identification of *C jejuni*<sup>19</sup> and Penner types.<sup>19,20</sup> *C jejuni* isolates from stool cultures were sequenced using next-generation sequencing techniques, and the genomic assemblies underwent genomic and phylogenetic analysis based on the hypervariable lipo-oligosaccharide (LOS) region. Phylogenetic analysis was based on 83 *C jejuni* genome assemblies from the National Center for Biotechnology Information (NCBI), which included all 16 genomes reported to be associated with GBS in the NCBI metadata and 67 additional genomes selected to represent a wide range of the collection locations, dates, and studies available (appendix e-1, [links.lww.com/NXI/A403](https://links.lww.com/NXI/A403)). These 83 genomes, the *C jejuni* reference genome (NCTC11168),<sup>21,22</sup> and the 4 genomes of 4 *C jejuni* isolates assembled from the present study were used to construct a phylogenetic tree from the sequence of the

**Figure 1** Epidemiologic Profile of 2018–2019 Guillain-Barré Syndrome (GBS) Outbreaks in Peru



hypervariable LOS biosynthesis gene locus using the Nextstrain-Augur pipeline.<sup>23</sup>

To evaluate the association between *C jejuni* infection and GBS, serum samples from 42 GBS cases were compared with serum samples of 41 controls for the presence of anti-*C jejuni* IgA, IgM, and IgG antibodies by ELISA following a case-control methodology.<sup>24</sup> Control samples were obtained from subjects from the same or neighboring households of the patients with GBS. The controls were evaluated by a neurologist to exclude a history of weakness within the previous year and to document normal neurologic status. The presence of anti-*C jejuni* antibodies was expressed as a ratio of optical density between a test sample and the cutoff serum sample. A ratio > 1.0 for IgM or IgA was considered evidence of a recent

*C jejuni* infection. Concomitant *C jejuni* infection was defined as a positive *Campylobacter* PCR in a stool sample or by stool culture.

Case-control methodology was also used to study anti-ganglioside immunity using a multiplexed array panel to identify specific antiganglioside IgG antibodies. Patient and control sera were screened on microarrays.<sup>25</sup> Glycolipid microarrays consisted of a panel of 16 single glycolipids, the majority of which are gangliosides (GM1, GM2, phosphatidylserine [PS], GM4, GA1, GD1a, GD1b, GT1a, GT1b, GQ1b, GD3, SGPG, LM1, GalNAc-GD1a, GalC, and sulfatide) and 120 heteromeric 1:1 (v:v) complexes printed in duplicate. The presence of antiglycolipid antibodies was determined using human IgG isotype-specific, fluorescent-

conjugated secondary antibodies, and its intensity was measured on a scale of 0–65,535 using a Genepix 4300A (Molecular Devices, San Jose, CA) microarray scanner. Antibody intensity values were reported as the average of duplicate median fluorescent intensity values per sample. Results were graphically displayed as heat maps using Pearson correlation hierarchical clustering (MeV software). The optimal cutoff value for antiglycolipid IgG antibodies, above baseline levels, was calculated from receiver operating characteristic (ROC) curves using Youden index.

### Statistical Analysis

The clinical and laboratory findings were described using absolute and relative frequencies. Median and interquartile ranges (IQRs) were reported for quantitative variables. The  $\chi^2$  or Fisher exact test, OR, and 95% CIs were used to determine differences between the groups. A *p* value <0.05 was considered significant. Area under the curve was calculated for each antiglycolipid antibody combination in ROC analysis. Statistical analyses were performed using Stata software, V15.0 (College-Station, TX).

### Ethical Considerations

This study was reviewed and approved by the HCH Institutional Review Board. All patients (or relatives when patients were incapacitated) and healthy controls (HCs) provided written informed consent.

### Data Availability

All data reported within the article are available anonymized on reasonable request by qualified investigators.

## Results

### Clinical Features

Fifty-nine patients suspected of GBS were seen between May and August 2019. Ten were excluded: 8 had insufficient data due to transfer to other hospitals during the outbreak, 1 patient had a recent infection with HIV, syphilis and tuberculosis, and 1 patient had only cranial nerve involvement. Of the 49 included patients, 43 were from Lima city and 6 from Northern area and highlands of Peru (figure 1B). The demographic and clinical characteristics of the 49 patients are described in table 1. All patients fulfilled Brighton criteria level 1 (84%) or level 2 (16%). The median age was 44 years (IQR 30–54 years), and 28 (57%) were male. Thirty-two patients (65%) had symptoms of an infection 6 weeks preceding the onset of GBS: 24 (49%) diarrhea and 13 (27%) upper respiratory tract symptoms, and 2 patients (4%) received an influenza vaccine. The median time from onset of infectious to neurologic symptoms was 3 days (IQR 2–9 days), and the time from onset of neurologic symptoms to nadir was 6 days (IQR 3–7 days). At admission, all patients reported limb weakness. Quadriparesis evolving in less than 24 hours from neurologic symptom onset was observed in 5 patients (10%). The median GBSDS at admission was 4 (IQR 3–4), and EGRIS was 3 (IQR 2–4). Fifteen

patients (31%) had cranial neuropathy, with the facial nerve most commonly involved. The median MRC sum score was 42 (IQR 26–50). Most patients (80%) were classified clinically as pure motor GBS. Neurologic examination, treatment, and outcome at nadir and at 6-month follow-up are detailed in table e-1 ([links.lww.com/NXI/A406](https://links.lww.com/NXI/A406)).

NCSs/EMG studies were performed in all patients at a median of 16 days after onset of neurologic symptoms (IQR 10–23 days). Twenty-one patients (43%) had axonal neuropathy (acute motor axonal neuropathy), 9 (18%) demyelinating neuropathy (acute inflammatory demyelinating polyneuropathy), 8 (16%) equivocal, 5 (10%) inexcitable, and 6 (12%) had normal studies.

Forty-seven patients (96%) received treatment with IVIg (51%), plasmapheresis (18%), or both (27%). The standard treatment was 5 sessions of plasmapheresis or 0.4 mg/kg/d IVIg for 5 days. IVIg treatment was stopped in 1 patient who developed angioedema during their second session and who died before starting plasmapheresis. Two patients did not receive treatment, 1 because of lack of treatment availability on admission and 1 due to initial misdiagnosis. Both patients improved without treatment. Thirteen patients (27%) were admitted to the intensive care unit, 12 (24%) required ventilatory support, and 6 (12%) had cardiac dysautonomia. The median hospitalization time was 14 days (IQR 9–23 days).

One week after admission, the median mEGOS was 5 (IQR 2–9). Most patients improved as indicated by mRS score at 6-month follow-up (median 2, IQR 1–2) compared with nadir (median 4, IQR 4–5). Four patients (8%) died. The most common sequela after 6 months was neuropathic pain (69%) (table e-1, [links.lww.com/NXI/A406](https://links.lww.com/NXI/A406)).

### Laboratory Testing

Hematologic and biochemical testing at admission were normal in all cases. CSF examination was performed in 48/49 patients at a median of 5 days (IQR 4–7 days) after start of neurologic symptoms. All patients had normal cell counts (median 0, IQR 0–1), and 14 (29%) had an increased protein level (>52 mg/dL) (table 1).

Laboratory results for infectious agents and antiganglioside profiles are described in table 2. One patient with known HIV infection was HIV positive. Twenty (41%) patients underwent testing for ZIKV, 26 (53%) for DENV, and 22 (45%) for CHIKV, and all were negative. Nineteen patients (39%) underwent testing by Film Array respiratory panel, and 5 (26%) were positive for common respiratory viruses not known to be associated with GBS (table 2).

In 43 patients (88%), biosamples were available for *C jejuni* infection testing with either molecular or serologic assays or stool cultures (table e-2, [links.lww.com/NXI/A407](https://links.lww.com/NXI/A407)). In 23/42 (55%) patients, anti-*C jejuni* IgM and/or IgA antibodies were found, of whom 9 also tested positive for *Campylobacter* sp PCR in stool. In contrast, only 11/41 (27%) controls had

**Table 1** Demographic and Clinical Characteristics of Patients With GBS

Characteristics	N = 49
Age, y	44 (30–54)
Male sex	28 (57)
General symptoms before the onset of the GBS (last 6 wk)	32 (65)
Diarrhea <sup>a</sup>	24 (49)
Upper respiratory symptoms <sup>a</sup>	13 (27)
Fever	5 (10)
Headache	3 (6)
Arthralgia	4 (8)
None	17 (35)
Time from onset of infectious symptoms to admission, d <sup>b</sup>	7 (7–14)
Time from onset of infectious symptoms to GBS onset, d <sup>b</sup>	3 (2–9)
Time from onset of GBS symptoms to admission, d	4 (3–6)
Time from onset of GBS symptoms to nadir, d	6 (3–7)
GBS Disability Score at admission	4 (3–4)
Erasmus GBS Respiratory Insufficiency Score at admission	3 (2–4)
Admission to ICU	13 (27)
Mechanical ventilation	12 (24)
Autonomic dysfunction	6 (12)
Duration of hospitalization, d	14 (9–23)
Brighton criteria for GBS diagnosis	
Level 1	41 (84)
Level 2	8 (16)
GBS clinical variant	
Pure motor	39 (80)
Sensorimotor	6 (12)
Pharyngeal-cervical-brachial	2 (4)
Miller Fisher syndrome	1 (2)
Bickerstaff brainstem encephalitis	1 (2)
CSF analysis	48 (98)
Time from onset neurologic symptoms to CSF sampling, d	5 (4–7)
White cell count, cells/mm <sup>3</sup>	0 (0–1)
Total protein, mg/dL	33 (16–58)
Increased protein level <sup>c</sup>	14 (29)
Time from GBS symptom onset to EMG, d	16 (10–23)

**Table 1** Demographic and Clinical Characteristics of Patients With GBS (*continued*)

Characteristics	N = 49
<b>NCS/EMG results and subtype</b>	
AMAN	21 (43)
AIDP	9 (18)
Inexcitable	5 (10)
Equivocal	8 (16)
Normal	6 (12)

Abbreviations: AIDP = acute inflammatory demyelinating polyneuropathy; AMAN = acute motor axonal neuropathy; GBS = Guillain-Barré syndrome; ICU = intensive care unit; NCS = nerve conduction study.

Data are presented as n/N (%) or median (interquartile range).

<sup>a</sup> Six patients had both diarrhea and upper respiratory symptoms.

<sup>b</sup> Based on 32 patients with a history of preceding general symptoms.

<sup>c</sup> Increased protein level is defined as >52 mg/dL. The percentage is based on 48 CSF samples.

evidence of anti-*C jejuni* IgM or IgA (OR: 3.3, CI 95% 1.2–9.2,  $p < 0.01$ ) (table 2).

The PCR-based gastrointestinal panel showed that 14/37 (38%) patients had evidence of *Campylobacter sp* genome. Stool cultures from 4 of these patients grew bacteria, which were confirmed as *C jejuni* by immunologic and molecular assays (table 2, table e-2, [links.lww.com/NXI/A407](https://links.lww.com/NXI/A407)). Penner molecular typing indicated that these isolates were all HS41 capsule type. Genomic analysis showed that these strains were clonal, sequence type (ST) ST2993, with class A LOS biosynthesis locus, a pathogenicity island that contains genes with the potential to generate LOS that mimic human gangliosides. Phylogenetic analysis showed that of the 20 GBS-associated *C jejuni* genomes, 15, including the 4 isolates from this study, have LOS regions fairly closely related to one another and to other strains of *C jejuni* associated with GBS isolated in China and Africa (figures 2 and 3). Sample collection regions do not appear to define clades, with strains from countries with numerous samples spread throughout the tree. All 4 *C jejuni* isolates from our study had the Asn51 polymorphism at *csIII* gene (figure e-1, [links.lww.com/NXI/A404](https://links.lww.com/NXI/A404)) based on the alignments to ICDCCJ07001 indicating the capability to synthesize both alpha 2–3 and alpha 2–8 sialic acid linkages on their LOS core oligosaccharide.<sup>26,27</sup> The genomes of these 4 *C jejuni* isolates were deposited at NCBI within BioProject PRJNA643291 (accession numbers SAMN15508151, SAMN15508152, SAMN15508153, and SAMN15508154, [ncbi.nlm.nih.gov/bioproject/PRJNA643291](https://ncbi.nlm.nih.gov/bioproject/PRJNA643291)).

Combining serologic assay and stool PCR, 28/43 patients (65%) had evidence of recent *C jejuni* infection (table 2, table e-2, [links.lww.com/NXI/A407](https://links.lww.com/NXI/A407)). Of interest, these 28 patients did not significantly differ in the time to nadir, clinical variants, or electrophysiologic subtypes to the 15 patients without evidence of a recent *C jejuni* infection (table e-2). Patients

**Table 2** Laboratory Studies

A. Investigation of Infectious Agents in GBS Cases			
Test/Target	n/N (%)		
<b>qRT-PCR (serum)</b>			
ZIKV	0/20 (0)		
DENV <sup>a</sup>	0/26 (0)		
CHIKV	0/22 (0)		
HIV (ELISA)	1/49 (2)		
<b>Respiratory FilmArray (oropharyngeal swab)<sup>b</sup></b>			
Rhinovirus/enterovirus	3/19 (16)		
Respiratory syncytial virus	1/19 (5)		
Coronavirus OC43	1/19 (5)		
<b>Gastrointestinal FilmArray (stool)<sup>c</sup></b>			
<i>Campylobacter sp</i> <sup>e</sup>	14/37 (38)		
<i>Escherichia coli</i>	16/37 (43)		
<b>Stool culture</b>			
<i>Campylobacter jejuni</i> HS41	4/37 (11)		
<i>E coli</i>	10/37 (27)		
B. Serologic Case-Control Studies			
	GBS, no. (%)	Controls, no. (%)	OR (p)
<b><i>Campylobacter jejuni</i> serology</b>			
Patients tested, no. (%)	42 (100)	41 (100)	—
Anti- <i>C jejuni</i> IgG	42(100)	41 (100)	—
Anti- <i>C jejuni</i> IgM or IgA	23 (55)	11 (27)	<b>3.3 (0.01)</b>
Anti- <i>C jejuni</i> IgM	19 (45)	11 (27)	2.3 (0.081)
Anti- <i>C jejuni</i> IgA	12 (29)	0	—
<b>Antiganglioside profile</b>			
Patients tested, no. (%)	42 (100)	41 (100)	—
GalNAc-GD1a-GBS cases	3 (7)	4 (10)	0.7 (0.668)
GM1-GBS cases	4 (10)	1 (2)	4.2 (0.175)
GM1:GT1a-GBS cases	14 (33)	4 (10)	<b>4.6 (0.009)</b>
GM1:PS-GBS cases	17 (40)	8 (20)	<b>2.8 (0.037)</b>
GT1a-GBS cases	4 (9)	1 (2)	4.2 (0.175)

Abbreviations: CHIKV = chikungunya virus; GBS = Guillain-Barré syndrome; DENV = dengue virus; PS = phosphatidylserine; qRT = quantitative real time; ZIKV = Zika virus. Bold values in OR (p) column indicate statistical significance ( $p < 0.05$ ).

<sup>a</sup> All samples were tested for DENV-1, DENV-2, DENV-3, and DENV-4.

<sup>b</sup> In addition to the listed pathogens detected by the respiratory array assay, other pathogens tested were found negative and those included *Mycoplasma pneumoniae*, adenovirus, coronavirus HKU1, NL63, 229E, and OC43, human metapneumovirus, influenza A, A/H1, A/H3, and A/H1-2009, influenza B, parainfluenza virus 1, 2, 3, and 4, *Bordetella pertussis*, and *Chlamydia pneumoniae*.

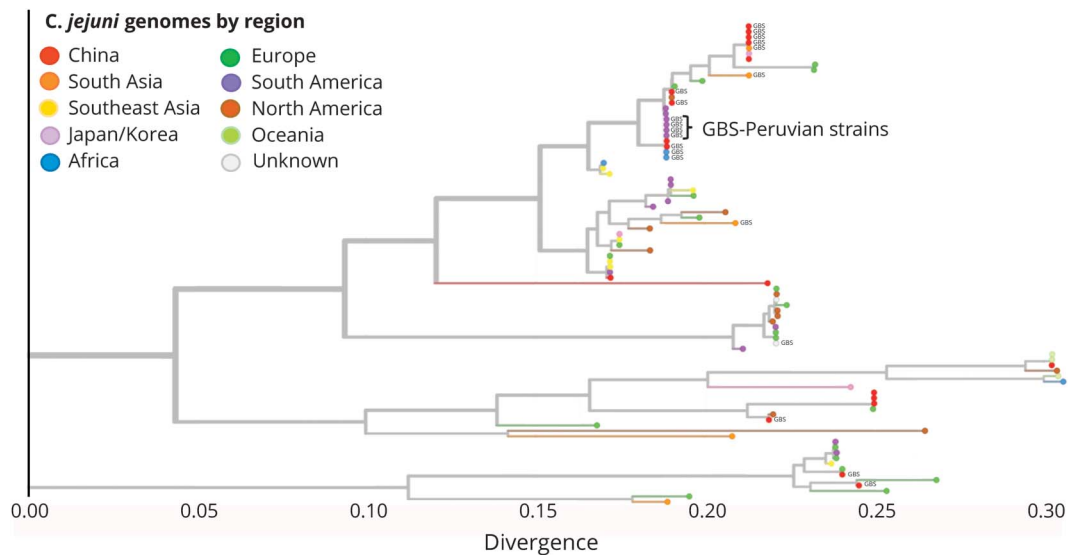
<sup>c</sup> In addition to the *C jejuni* and *E coli* detected, testing for other bacteria, parasite, and viruses included in the assay were negative, which included bacteria: *Clostridium difficile* (toxin A/B), *Plesiomonas shigelloides*, *Salmonella*, *Yersinia enterocolitica*, *Vibrio* (parahaemolyticus, vulnificus, and cholerae), *Vibrio cholerae*, diarrheagenic *E coli/Shigella*, enteroaggregative *E coli* (EAEC), enteropathogenic *E coli* (EPEC), enterotoxigenic *E coli* (ETEC), Shiga-like toxin-producing *E coli* (STEC), *E coli* O157, and *Shigella/enteroinvasive E coli* (EIEC). Parasites: cryptosporidium, *Cyclospora cayetanensis*, *Entamoeba histolytica*, and *Giardia lamblia*. Viruses: adenovirus F 40/41, astrovirus, norovirus GI/GII, rotavirus A, and sapovirus (I, II, IV, and V).

<sup>d</sup> Six patients had coinfection of both *Campylobacter sp* and *E coli*.

<sup>e</sup> *Campylobacter* (*jejuni*, *coli*, and *upsaliensis*).

<sup>f</sup> Three patients had positive culture for both *C jejuni* HS41 and *E coli*.

**Figure 2** Phylogenetic Tree of *Campylobacter jejuni* Isolates in GBS



Phylogenetic tree built from the lipo-oligosaccharide region of 88 *C. jejuni* species using the Nextstrain pipeline, colored by region. The 4 Peruvian strain assemblies are indicated. The tree was built via alignment to the ICDCJ07001 strain and then rooted by inferring ancestral states. GBS = Guillain-Barré syndrome.

with evidence of a recent *C. jejuni* infection had a higher percentage of preceding gastrointestinal symptoms, although this was not significant (43% vs 27%,  $p = 0.69$ ). Other preceding infectious symptoms were also not significantly different.

Antiganglioside IgG antibodies of differing specificities were detected in a high proportion of cases compared with HCs (figure e-2, [links.lww.com/NXI/A405](https://links.lww.com/NXI/A405)). Summarizing this

overview heatmap, 2 broad populations of IgG antibodies were dominantly present in this cohort: those reactive with GM1 alone or in complexes and those reactive with GT1a, alone or in complexes (table 2, figure 4). A smaller number of samples contained antibodies to GalNAc-GD1a alone or in complexes. Antibodies to other gangliosides including GM2, GD1b, GD1a, and GT1b and to myelin glycolipids including SGPG, LM1 and GalC were either very infrequently or not observed. Ganglioside antigens were probed as single

**Figure 3** Phylogenetic Map of *Campylobacter jejuni* Isolates in Guillain-Barré Syndrome (GBS)



Map distribution of strains depicted in the phylogenetic tree. Strains are colored by region of collection, which was available for all but 2 genomes, the *C. jejuni* reference, NCTC11168, and 1 GBS-associated strain, G1, which had no listed collection location. The size of the circles within countries on the associated world map is proportional to how many samples are included from that country.

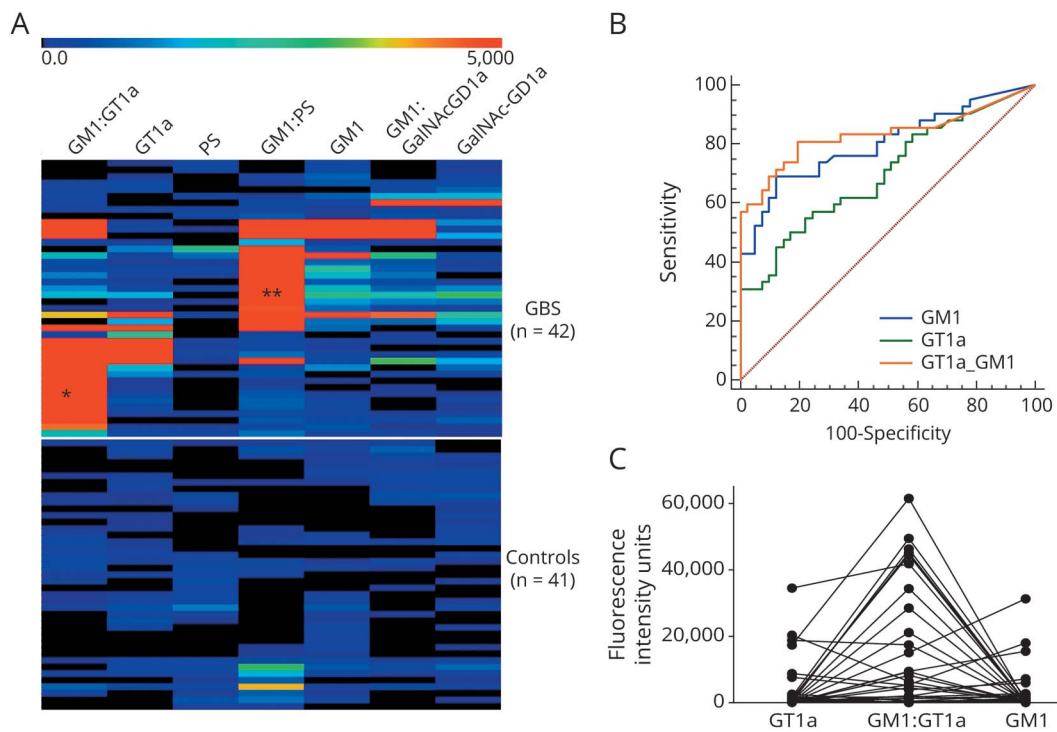
molecules and when in heteromeric complex (1:1 ratio) with one other ganglioside or lipid. This use of complexes is known to enhance antiganglioside antibody signals in a proportion of serum samples.<sup>28</sup> To identify the enhanced binding intensities resulting from complexes, samples were probed against GM1 and GT1a in complex with other lipids (figure 4A). Results were then analyzed and displayed using ROC curve analysis in which the true and false-positive rates are calculated at various threshold settings to generate sensitivity and specificity data for the assay. ROC data for the major targets are shown in figure 4, B and C and figure e-2B and C. Using this approach, GM1 ganglioside in a 1:1 heteromeric complex ratio with PS or GT1a ganglioside proved to be the most significant diagnostic marker. When GM1 was in complex with PS, antibodies to the GM1:PS complex returned a sensitivity 78.6% and a specificity of 78.0% for GBS (figure e-2B). When GM1 was in complex with GT1a, antibodies to the GM1:GT1a complex returned a sensitivity of 81.0% and a specificity of 80.5% for GBS (figure 4B). The enhancing effect, as manifested by an increase in fluorescence intensity units, of GM1 in complex with GT1a vs either antigen alone is shown in figure 4C. In contrast, the GM1:GalNAc-GD1a complex did

not enhance reactivity with either glycolipid alone (figure e-2C). When selecting the GM1:PS and GT1a:GM1 complex antigen targets as biomarkers of GBS, 92.9% of patients had IgG antibodies to one or both of these glycolipid complexes compared with 31.7% of HCs.

## Discussion

In the aftermath of the ZIKV epidemic in Latin America, that was associated with significant increases in the incidence of GBS, 2 large seasonal outbreaks of GBS occurred in Peru in 2018 and 2019.<sup>6,29</sup> Our study, describing a large cohort of patients and controls during the 2019 GBS outbreak in Lima, Peru, demonstrates that this outbreak was associated with *C jejuni* infection, a diarrheal bacterium that is the most common trigger of GBS worldwide. As the outbreak of GBS in 2018 occurred in the same season and regions of the country (figure 1B), this outbreak was likely related to *C jejuni* as well. Because stricter public health measures were instituted in Peru, after the first COVID-19 case in March 2020, GBS incidence decreased to less than 0.27/100,000.<sup>6</sup>

**Figure 4** Antiganglioside Antibody Binding Profile in Peruvian GBS Cases



Graphical displays of GBS and healthy control (HC) serum IgG antiganglioside antibody binding. (A) Heat maps illustrating the IgG binding intensity to 3 single glycolipids and 4 heteromeric complex antigen targets in GBS cases (upper map, n = 42) and HC sera (lower map, n = 41). Each horizontal row refers to the IgG binding reactivity of an individual GBS or HC serum sample, and each vertical row refers to each of the 7 targets displayed. The rainbow bar denotes the intensity scale of IgG binding from low (blue) to high (red) intensity. Two patterns of reactivity are greatly amplified by presenting glycolipids/lipids targets as heteromeric complexes compared with binding to each target alone: GM1:GT1a complex (first column \*) and GM1:PS complex (fourth column \*\*). Note that these 2 patterns of heteromeric complex reactivity do not substantially overlap within any 1 patient, being mutually exclusive. (B) An illustrative receiver operating characteristic (ROC) curve comparing the sensitivity and specificity of GT1a and GM1 as single glycolipids with the GT1a:GM1 heteromeric complex. The highest sensitivity (81%) and specificity (80.5%) are seen with the GM1:GT1a complex. (C) IgG reactivity values of each individual patient are plotted for the same 3 antigen targets (GM1, GT1a, and GM1:GT1a complex) subjected to ROC analysis in panel B. Greatly enhanced binding intensity to the GT1a:GM1 heteromeric complex compared with the sum of the single glycolipid antigens is present in most samples. GBS = Guillain-Barré syndrome; PS = phosphatidylserine.



We found evidence of recent *C jejuni* infection in 28/43 patients (65%), of whom 9 were positive for *Campylobacter* sp PCR in stool. Other preceding infections previously associated with GBS, including *Mycoplasma pneumoniae*, DENV, CHIKV, and ZIKV, were negative in all tested cases. Recent *C jejuni* infection was significantly more likely to occur in GBS cases (23/42, 55%) compared with controls (11/41, 27%, OR: 3.3,  $p < 0.01$ ). Of interest, the proportion of controls with a recent *C jejuni* infection was high (27%), which may be indicative of an ongoing outbreak of *C jejuni*, although our study was not designed to investigate this. This high percentage may also be in part due to overmatching of cases and controls or a high prevalence of *C jejuni* in Peru, as has been indicated by previous serosurveillance studies.<sup>30,31</sup> Notably, the vast majority of *C jejuni* infections, even when bearing ganglioside mimics in their LOS, manifest as uncomplicated enteritis and are not associated with the development of GBS. Genomic analysis of *C jejuni* isolates showed that they have closely related LOS regions to one another and to previously described GBS-associated *C jejuni* genomes from China and Africa reported in the past 2 decades, suggesting that these strains were introduced or reemergent infections from an endemic reservoir rather than being new emergent strains.<sup>32–34</sup>

Besides the laboratory evidence, the clinical and electrophysiologic profile is typical for *C jejuni*-associated GBS as described in previous studies.<sup>9,35,36</sup> The majority of cases had a preceding diarrheal illness, followed by an early-onset, rapidly progressive pure motor axonal GBS. This profile is in contrast to the clinical profile that has been reported in association with ZIKV or COVID-19, where most patients have facial palsy, sensory and motor deficits, and a demyelinating electrophysiologic subtype.<sup>37,38</sup>

However, there was not a uniform relationship between *C jejuni* serotype and clinical, electrodiagnostic, and anti-ganglioside profile. This may be due to methodological factors that prevent unambiguous case definition and ascertainment. For example, CSF examination and electrodiagnostic studies are not always sensitive diagnostic tools in GBS, especially when done early in the disease course. This may have resulted in only 29% of patients having an increased protein level in CSF, or inaccurate classification of electrophysiologic studies as axonal or demyelinating.<sup>8,39</sup> The time between onset of systemic and neurologic symptoms (median 3 days, IQR 2–9 days) was also shorter than expected based on previous studies, which may be due to the wide range of the incubation period of *C jejuni* (1–10 days); patients only reporting symptoms when they become severe; or the presence of a parainfectious rather than postinfectious mechanism, as previously reported in ZIKV-related GBS.<sup>3,40</sup> Another surprising finding was the high percentage (27%) of cases with diarrhea in the group without evidence of a recent *C jejuni* infection. This may be due to the presence of other infections able to trigger GBS that may lead to gastrointestinal symptoms or low sensitivity of the standard serologic testing method for recent *C jejuni* infection (presence of IgM antibody) in a population

where the incidence of infection, as indicated by the universally positive IgG serology, is very high. Notwithstanding previous studies that show diarrhea has been associated with a poor prognosis, the percentage of our patients able to walk at 6 months was high (82%), although we did find that diarrhea was more frequent (67% vs 45%) in patients with worse outcome, as defined by mRS score  $\geq 4$  at 6 months.<sup>35,41</sup>

The antiganglioside antibody profile, with strong positivity for GM1 and anti-GT1a, as single antigens or in complex, is similar to what has previously been found in post-*C jejuni* GBS in other parts of the world and lends strong support that these patients represent the typical immune phenotype seen in *C jejuni*-associated GBS.<sup>42–44</sup> The use of complexes of GM1 and GT1a with each other or other lipids (herein PS) greatly enhanced the sensitivity of antibody detection in this cohort. The significant presence and high frequency of antiganglioside antibodies lends strong evidence to the conclusion that molecular mimicry between *Campylobacter* LOS and gangliosides is the immunopathologic driver of this form of GBS in Peru. The high prevalence of anti-GT1a antibodies in this group is consistent with the *csfII* polymorphism (Asn51) seen in this study and similar to that observed in a GBS outbreak in China.<sup>45</sup>

The main limitation of our study is that we were not able to perform complete laboratory studies in all patients and controls as the study was conducted in the context of an emerging outbreak. We were able to exclude other preceding infections, including arboviruses, in 53% of cases and completed the serologic case-control study in 86% of cases. It is unlikely that different results would have been obtained had all subjects been tested.

In conclusion, we showed that *C jejuni*, and not ZIKV as was initially thought, was the infectious driver of the 2019 GBS outbreak in Peru, and the clinical, electrophysiologic, and immunologic profile was consistent with *C jejuni*-related GBS. The *C jejuni* strains were likely introduced or reemergent infections from an endemic reservoir and not new emergent strains. This finding has global relevance as it indicates that the *C jejuni* strains linked to GBS circulate widely in different parts of the world. This shows that researchers should remain aware of *C jejuni* as a trigger for GBS when investigating the association between other infections, including COVID-19, and GBS. Reinforcing public health measures, including setting up campylobacteriosis and GBS surveillance, to rapidly identify new epidemics, pathologic strains, and sources of transmission should be encouraged to prevent future outbreaks.<sup>30,31,46</sup>

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## Disclosure

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Name	Location	Contribution
<b>Ana P. Ramos, MD</b>	Hospital Cayetano Heredia, Lima, Perú	Designed and conceptualized the study; acquired, analyzed, and interpreted the overall data; and drafted the manuscript for intellectual content

## Appendix (continued)

Name	Location	Contribution
<b>Sonja E. Leonhard, MD</b>	Erasmus MC, University Medical Center Rotterdam, Netherlands	Analyzed <i>C jejuni</i> serology, analyzed and interpreted data, and drafted the manuscript for intellectual content
<b>Susan K. Halstead, PhD</b>	University of Glasgow, Glasgow, United Kingdom	Performed antiganglioside antibody analysis and revised the manuscript for intellectual content
<b>Mireya A. Cuba, MD</b>	Hospital Cayetano Heredia, Lima, Perú	Acquired clinical data and revised the manuscript for intellectual content
<b>Carlos C. Castañeda, MD</b>	Hospital Cayetano Heredia, Lima, Perú	Acquired and analyzed electrophysiology data and revised the manuscript for intellectual content
<b>Jose A. Dioses, MD</b>	Hospital Cayetano Heredia, Lima, Perú	Acquired and analyzed electrophysiology data and revised the manuscript for intellectual content
<b>Martin A. Tipismana, MD</b>	Hospital Cayetano Heredia, Lima, Perú	Acquired clinical data and revised the manuscript for intellectual content
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<b>Alejandro Llanos, MD, PhD</b>	Hospital Cayetano Heredia, Lima, Perú	Analyzed laboratory data and revised the manuscript for intellectual content
<b>Dawn Gourlay, BSc, MSc</b>	University of Glasgow, United Kingdom	Performed antiganglioside antibody analysis and revised the manuscript for intellectual content
<b>Max Grogl, PhD</b>	U.S. Naval Medical Research Unit-6, Lima, Peru	Interpreted bacteriology and virology data and revised the manuscript for intellectual content
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## Appendix (continued)

Name	Location	Contribution
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<b>Steven L. Salzberg, PhD</b>	Johns Hopkins University, Baltimore, MD	Analyzed <i>C jejuni</i> genomic studies and revised the manuscript for intellectual content
<b>Patricia J. Simner, PhD</b>	Johns Hopkins University, Baltimore, MD	Recultured <i>C jejuni</i> isolates, performed DNA sequencing, and revised the manuscript for intellectual content
<b>Hugh J. Willison, MBBS</b>	University of Glasgow, United Kingdom	Performed antiganglioside antibody analysis, analyzed and interpreted data, and drafted the manuscript for intellectual content
<b>Bart C. Jacobs, MD</b>	Erasmus MC, University Medical Center Rotterdam, Netherlands	Performed and analyzed <i>C jejuni</i> serology and revised the manuscript for intellectual content
<b>David R. Cornblath, MD</b>	Johns Hopkins University, Baltimore, MD	Analyzed electrophysiology data and revised the manuscript for intellectual content
<b>Hugo F. Umeres, MD</b>	Hospital Cayetano Heredia, Lima, Perú	Supervised the study and revised the manuscript for intellectual content
<b>Carlos A. Pardo, MD</b>	Johns Hopkins University, Baltimore, MD	Analyzed and interpreted overall data, analyzed <i>C jejuni</i> genomic studies, and drafted the manuscript for intellectual content

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