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Implementation and Evaluation of Guillain-Barré Syndrome Surveillance in Puerto Rico during the 2016 Zika Virus Epidemic

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Abstract

Objective: Guillain-Barré syndrome (GBS) is an uncommon autoimmune disorder that follows infection or vaccination, and increased incidence has been reported during Zika virus (ZIKV) transmission. During the 2016 ZIKV epidemic, the Puerto Rico Department of Health (PRDH) implemented the Enhanced GBS Surveillance System (EGBSSS). Here, we describe EGBSSS implementation and evaluate completeness, validity, and timeliness.

Methods: GBS cases were identified using passive surveillance and discharge diagnostic code for GBS. Completeness was evaluated by capture-recapture methods. Sensitivity and positive predictive value (PPV) for confirmed GBS cases were calculated for both case identification methods. Median time to completion of key time steps were compared by quarter (Q1–4) and hospital size.

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Results: A total of 122 confirmed GBS cases with onset of neurologic illness in 2016 were identified. Capture-recapture methodology estimated that four confirmed GBS cases were missed by both identification methods. Identification of cases by diagnostic code had a higher sensitivity than passive surveillance (89% vs. 80%), but a lower PPV (60% vs. 72%). There was a significant decrease from Q1 to Q3 in median time from hospital admission to case reporting (11 days vs. 2 days, $p = 0.032$) and from Q2 to Q3 in median time from specimen receipt to arbovirus laboratory test reporting (35 days vs. 26 days, $p = 0.004$).

Conclusion: EGBSSS provided complete, valid, and increasingly timely surveillance data, which guided public health action and supported healthcare providers during the ZIKV epidemic. This evaluation provides programmatic lessons for GBS surveillance and emergency response surveillance. [*PR Health Sci J* 2018;37(Special Issue):S85-S92]

Keywords

Guillain-Barré syndrome; Surveillance; Puerto Rico; Zika virus

Guillain-Barré syndrome (GBS) is an autoimmune condition resulting from damage to the peripheral nervous system following an acute infection or less frequently vaccination. Clinically, GBS is generally characterized by monophasic progression of bilateral weakness and hypo- or areflexia (1). Global annual incidence of GBS is estimated at 1.1–1.8 cases per 100,000 population, varying by age group, sex, and geographic region (2, 3). GBS has been associated with infection with various infectious agents (e.g., *Campylobacter jejuni*, cytomegalovirus, Epstein-Barr virus, and *Mycoplasma pneumoniae*), including arthropod-borne viruses (arboviruses) such as dengue virus (DENV) and chikungunya virus (CHIKV) (4–7).

Since 2013, increased GBS incidence has been reported by countries affected by Zika virus (ZIKV), a flavivirus transmitted primarily by *Aedes* species mosquitoes (8, 9). Although most persons infected with ZIKV report no or mild symptoms (i.e., rash, fever, headache), ZIKV outbreaks have coincided with increased incidence of congenital anomalies and of GBS and other neurologic and autoimmune syndromes among adults (10). As a result, on December 1, 2015, the World Health Organization (WHO) and Pan American Health Organization (PAHO) issued an epidemiologic alert urging Member States to prepare and respond to the emergent public health threat (11). Further, on February 1, 2016, WHO declared ZIKV-related microcephaly clusters and other neurologic disorders a Public Health Emergency of International Concern (12).

On December 31, 2015, the Puerto Rico Department of Health (PRDH) reported the first locally acquired case of ZIKV disease in the United States (13). On February 5, 2016, the governor of Puerto Rico signed an executive order declaring ZIKV a Public Health Emergency. Thereafter, PRDH, with assistance from the US Centers for Disease Control and Prevention (CDC) and other partners, implemented an incident management system to coordinate the local public health emergency response (13–15).

As part of the response, in February 2016 PRDH and CDC with collaboration from the University of Puerto Rico established the Enhanced Guillain-Barré Syndrome Surveillance

System (EGBSSS) to: 1) prospectively identify cases of GBS and other neurologic disorders, 2) provide healthcare providers with arbovirus diagnostic testing results (i.e., infection with ZIKV, DENV, and CHIKV), and 3) compare 2016 GBS epidemiologic trends with prior years in Puerto Rico and to other countries affected by ZIKV. In this report, we describe the methods of EGBSSS implementation and associated activities, and evaluate EGBSSS with respect to its completeness, validity, representativeness, and timeliness.

Materials and Methods

Passive surveillance and Specimen submission

To make healthcare providers in Puerto Rico aware of EGBSSS, outreach was conducted using a phased approach focusing first on tertiary hospitals located in municipalities with known cases of ZIKV disease (February-April), later expanding to reference hospitals throughout the island (May-June), and ultimately reaching primary and secondary healthcare centers (July-October). Initial outreach was conducted through telephone calls and expanded by offering site visits and presentations to hospitals and various other health care centers and professional associations. Outreach material was developed in Spanish and English, including: fact sheets, palm cards, posters, and frequently asked questions. Materials were distributed at presentations, conferences, and other activities, and were also available online (available at: salud.gov.pr/Sobre-tu-Salud/Pages/Educacion.aspx). In total, 68 on-site orientations were performed during 2016.

Healthcare providers were requested to report patients with any suspicion of GBS using the “Guillain-Barré Syndrome Case Report Form” (available at: salud.gov.pr/Sobre-tu-Salud/Pages/Educacion.aspx) (Figure 1). Healthcare providers were also requested to submit patient serum specimens for arbovirus diagnostic testing; urine, cerebrospinal fluid (CSF), and saliva could also be submitted. Healthcare providers were instructed to report patients prior to clinical confirmation of GBS to reduce reporting time, improve case identification, and increase the likelihood of laboratory confirmation of infection with ZIKV or another arbovirus. Whenever feasible, the EGBSSS team facilitated specimen transport. Specimens were tested at the PRDH Biological and Chemical Emergencies Laboratory (BCEL) and CDC Dengue Branch (DB).

All specimens were tested for ZIKV DENV, and CHIKV by Trioplex real-time reverse transcriptase polymerase chain reaction (RT-PCR) (16). Serum and CSF specimens were also tested for the three arboviruses by immunoglobulin M enzyme-linked immunosorbent assay (IgM ELISA) (17). Upon completion of diagnostic testing, laboratory reports were sent to providers.

In October 2016, PRDH passed Administrative Order 358 rendering notification of suspected GBS cases compulsory; cases with a clinical suspicion of GBS were to be reported within 72 hours and fatal cases within 24 hours. Where possible, investigation of fatal cases (e.g., collection and analysis of proximal and distal peripheral nerve specimens) were incorporated into established surveillance mechanisms (18). All surveillance activities were reviewed by CDC institutional review board and were determined to be non-research public health activities.

During June-December 2016, a biweekly epidemiologic report summarizing the number and characteristics of GBS patients identified by EGBSSS was published online (available at: [salud.gov.pr/Estadisticas-Registros-y-Publicaciones/Pages/InformedeCasosdelS%
%c3%adndromedeGuillain-Barr%c3%a9.aspx](http://salud.gov.pr/Estadisticas-Registros-y-Publicaciones/Pages/InformedeCasosdelS%c3%adndromedeGuillain-Barr%c3%a9.aspx)) and disseminated to healthcare providers by email.

Case identification using diagnostic code for GBS

During February-April 2017, an end-of-year assessment was conducted using the discharge diagnostic code for GBS to identify additional cases. Hospitals in Puerto Rico were requested to provide a list of patients with hospital admission and ICD-10 code for GBS (G61.0) in 2016. All 57 nonspecialized Puerto Rico hospitals and two major rehabilitative in-patient care centers participated. Specialized health centers unlikely to treat acute-phase GBS patients (i.e., psychiatric, oncologic, and cardiovascular centers) were excluded. Data provided by hospitals included patient name, sex, date of birth, municipality of residence, hospital admission date, hospital date, final diagnoses, total cost of hospitalization, and medical insurance type.

Follow-up by medical record review was conducted for patients not previously reported to EGBSSS if they had a hospitalization of at least 3 days and no alternative diagnosis of neurologic illness. Cases with a confirmed GBS diagnosis were included in cumulative case counts, and the database of the Passive Arbovirus Disease Surveillance System (PADSS), the surveillance system for ZIKV, DENY and CHIKV infections in Puerto Rico, was queried for laboratory results.

Data collection and Case confirmation

For all potential GBS cases identified through passive surveillance and diagnostic code, medical record review using a standardized abstraction tool was conducted. Records were reviewed following hospital discharge, >28 days after onset of neurologic signs for persons who remained hospitalized, or death. GBS neurologic diagnosis was ascertained using the Brighton Collaboration Criteria (BCC), a set of standardized criteria to assess diagnostic certainty of GBS based on clinical presentation, cerebrospinal fluid (CSF) analysis, and electrophysiological findings (19). Confirmed GBS cases were patients that met BCC levels 1–3; suspected GBS cases (BCC level 4) did not meet minimum criteria and had no alternative diagnosis. Patients with an alternative diagnosis (BCC level 5) were considered non-cases of GBS. Other data collected included patient demographics, treatment, outcomes, antecedent illness, and results of in-hospital infectious disease testing.

Data management

Data collected from the GBS case report form, arbovirus test results, chart abstraction form, and disability follow-up interview were stored in a dedicated Research Electronic Data Capture (REDCap) database. The CDC Dengue Laboratory Samples Database System (DLSDB) was used to manage laboratory testing and distribution of results to healthcare providers. Updated case data were summarized and distributed to the emergency response epidemiologic surveillance team at least once per week.

Surveillance evaluation

Frequencies of cases by case definition and identification method (i.e., passive surveillance vs. diagnostic code) were calculated. Completeness of surveillance was evaluated by two-source, capture-recapture methods using the Chapman estimator to assess the number of missed cases and overall sensitivity of EGBSSS for 2016 (20, 21). Sensitivity for detection of confirmed GBS cases was calculated for both case identification methods, compared to total number of confirmed GBS cases identified. Positive predictive value (PPV) for detection of confirmed GBS cases was also calculated for both passive surveillance and diagnostic code-based identification. PPV of cases identified through passive surveillance were compared by hospital size: (large = 200 beds; medium = 100–199 beds; small < 100 beds) using Pearson chi-square and chi-square partitioning.

Representativeness of passive surveillance was evaluated among hospitals and by hospital size and region, which was defined by PRDH health region of hospital location (i.e., Aguadilla, Arecibo, Bayamón, Caguas, Fajardo, Mayaguez, Metro, and Ponce). To assess potential biases in passive surveillance, confirmed GBS cases identified exclusively by diagnostic code were compared to those identified through passive surveillance by quarter of hospital admission, hospital size, and BCC level using Pearson chi-square, Fisher exact tests, and chi-square partitioning.

For confirmed GBS cases identified through passive surveillance, timeliness of three key time steps was analyzed: 1) case reporting (date of hospital admission to date case was reported to PRDH), 2) specimen receipt (date of specimen collection to date of receipt at the laboratory), and 3) arbovirus laboratory test reporting (date of receipt of specimen at the laboratory to date that the report of diagnostic test results was printed). Using Kruskal-Wallis tests and Dwass-Steel-Critchlow-Fligner multiple comparison analyses, median times for passive case reporting and specimen receipt were compared by quarter (Quarter 1 [Q1] = January-March; Q2 = April-June; Q3 = July-September; Q4 = October-December) and hospital size, and median time for arbovirus laboratory test reporting was compared by quarter.

Data cleaning and analyses were performed using Microsoft Excel 2016 (Microsoft, Redmond, WA, USA) and SAS software, version 9.3 (SAS Institute, Cary, NC).

Results

Case identification

During 2016, healthcare providers reported a total of 134 cases with a suspicion of GBS through passive surveillance. Of these, 97 (72%) were confirmed GBS cases, eight (6%) were suspected GBS cases, and 29 (22%) were non-cases (Figure 2). An additional confirmed GBS case in a Puerto Rico resident was reported, but excluded from these analyses because the patient sought care outside of Puerto Rico. Among confirmed cases, ten (10%) had hospital admission during Q1, 22 (27%) during Q2, 46 (47%) during Q3, and 19 (19%) during Q4 (Table 1; Figure 3). Almost all (99%) confirmed GBS cases had at least one specimen received for diagnostic testing for arbovirus infection.

From the review of patient discharge diagnostic codes in 2016, 181 individual patients with an ICD-10 code for GBS were identified (Figure 2). Of these, 100 (55%) had been identified through passive surveillance; nine (5%) did not meet criteria for follow-up. Medical records for the remaining 72 patients were reviewed, of which 25 (35%) were confirmed GBS cases, four (6%) were suspected GBS cases, and 43 (60%) were non-cases. Arbovirus laboratory test results were available for ten (40%) confirmed cases.

Combining cases identified through passive surveillance and by using the discharge diagnostic code for GBS, a total of 122 confirmed and 13 suspected GBS cases were identified with hospitalization during 2016.

Completeness, sensitivity, and positive predictive value

Using Chapman capture- recapture estimate, four confirmed GBS cases may have been missed through passive surveillance and by using the discharge diagnostic code for GBS (Chapman population estimate: 126, 95% CI: 123–129), indicating that EGBSSS captured approximately 97% (122/126) of 2016 GBS cases. For confirmed GBS cases, sensitivity for diagnostic codebased identification (108/122 [89%]) was higher than that of passive surveillance (97/122 [80%]). For confirmed GBS cases, PPV for passive surveillance (97/134 [72%]) was higher than that of diagnostic code-based identification (108/181 [60%]), which identified a larger population of potential cases, including 23 (13%) patients with a history of GBS before 2016. The PPV of passive surveillance for confirmed GBS cases was significantly lower for medium hospitals (21/39 [54%]) compared to hospitals of other sizes ($p = 0.002$).

Representativeness

Cases were reported from 38 of 59 (64%) non-specialized hospitals and rehabilitative centers on the island, including all 19 large, 14 of 24 (58%) medium, and five of 16 (31%) small hospitals. Large hospitals reported the highest proportion of confirmed GBS cases identified through passive surveillance (69/97 [71%]), particularly those at the highest levels of clinical confirmation: 15/19 (79%) cases confirmed as BCC level 1 and 46/61 (75%) cases confirmed as BCC level 2 (Table 1).

Of the 59 health centers that participated in the discharge diagnostic code review, 14 (24%) hospitals reported no patients found using diagnostic code for GBS. There were 25 confirmed GBS cases not identified through passive surveillance, 24 (96%) of which were from hospitals that reported at least one other case. Compared to confirmed GBS cases identified through passive surveillance, those identified exclusively by using the discharge diagnostic code for GBS were hospitalized in the same seven of eight regions (Figure 4), and did not differ by hospital size or BCC level (Table 1). Confirmed cases identified exclusively by diagnostic code differed significantly from those identified by passive surveillance by quarter of hospital admission ($p < 0.001$): confirmed GBS cases identified exclusively by diagnostic code were more likely to have hospital admissions in Q1 compared to those identified through passive surveillance (10/25 [40%] vs. 11/97 [11%]; $p = 0.002$).

Timeliness

Median time from hospital admission to case reporting to EGBSSS was 3 days (range = 0–204 days), and differed significantly both by quarter of hospital admission ($p = 0.024$) and hospital size ($p = 0.015$) (Table 2). Median time to case reporting decreased significantly between Q1 and Q3 (11 days vs. 2 days; $p = 0.032$). Small hospitals had longer median time to case reporting (18 days) than medium (3 days) and large (4 days) hospitals ($p = 0.013$ and $p = 0.037$, respectively).

Median time from specimen collection to receipt at the laboratory was 4 days (range = 0–74 days) and was significantly different by hospital size ($p = 0.078$), but not quarter of specimen collection. Median time to specimen receipt was longer for medium than for large hospitals (5 days vs. 4 days, $p < 0.001$).

Median time from specimen receipt to arbovirus laboratory result reporting was 28 days (range = 5–323 days), and differed significantly by quarter of specimen receipt ($p < 0.001$). Median time to arbovirus laboratory result reporting decreased significantly between Q2 and Q3 (35 days vs. 26 days; $p = 0.004$), despite a significantly smaller proportion of the total number of specimens received during Q2 in comparison to Q3 (45/344 [13%] vs. 141/344 [41%]; $p < 0.001$). Median time to arbovirus laboratory result reporting was also significantly lower between Q1 and Q4 (29 days vs. 22 days; $p = 0.014$), and between Q2 and Q4 (35 days vs. 22 days; $p < 0.001$).

Discussion

Puerto Rico public health officials and healthcare providers responded quickly to the introduction of ZIKV and expected increased GBS incidence by implementing an island-wide GBS surveillance system (13–15, 22). EGBSSS provided complete, valid, and increasingly timely surveillance data, which guided public health action and supported healthcare providers during the 2016 ZIKV epidemic.

Several additional public health activities supplemented passive surveillance. Early in the emergency response, the annual incidence of GBS in Puerto Rico prior to the introduction of ZIKV was estimated, which allowed public health officials to assess increases above historic levels (23). To assist with public health preparedness activities, the number of expected GBS patients during the ZIKV epidemic and associated healthcare needs was also estimated (24). Telephone-based follow-up interviews were conducted with patients at six-month intervals after neurologic illness onset to assess patient long-term disability.

To our knowledge, EGBSSS is the first jurisdiction-wide GBS surveillance system, though hospital-based GBS surveillance systems have been implemented elsewhere (25–28), including during ZIKV epidemics (9, 29–31). Validity and timeliness of EGBSSS was comparable to other GBS surveillance systems in the United States and Europe (25–28). However, EGBSSS passive surveillance sensitivity was greater and PPV was lower compared to those of similar surveillance systems that combined passive surveillance and diagnostic code-based case identification (25, 26, 28). This was likely due to the programmatic priority for rapid case reporting without waiting for diagnostic confirmation.

Compared to a GBS surveillance system established in New York during the 2009 national influenza vaccination campaign, EGBSSS overall estimated completeness of case identification was similar; however, median time to case reporting by providers was 75% shorter (28).

The EGBSSS evaluation highlights several key lessons. First, passive GBS surveillance through healthcare provider reporting provided crucial epidemiologic data throughout the epidemic. Successful implementation was aided by incorporating EGBSSS into existing passive surveillance for arboviral diseases, lowering reporting burden for healthcare providers, and continual, sustained healthcare provider engagement. The sensitivity of passive surveillance was likely lowered by delayed EGBSSS implementation, which began in late Q1.

Second, using two case identification methods maximized overall GBS case identification, with an estimated 97% of confirmed GBS cases having been identified. Individually, each method had relative advantages and disadvantages. Compared to cases identified through review of hospital discharge diagnoses, passive surveillance was more accurate, encouraged a higher rate of specimen submission, and allowed for more timely case identification. Compared to passive surveillance, diagnostic code-based case identification was more sensitive, supporting its utility for estimating GBS incidence when combined with chart review to eliminate coding errors and patients with a history of GBS (23, 25–28, 32).

Finally, island-wide outreach and surveillance were warranted given that, unexpectedly, GBS cases sought care and were managed at large, medium, and small healthcare centers throughout the island. Although the majority of confirmed GBS patients were treated at large hospitals, 32% of patients who were identified at medium or small hospitals may have been missed with less comprehensive outreach and diagnostic code review methods. Moreover, comprehensive outreach helped alert healthcare providers at all levels to the risk of ZIKV and EGBSSS activities.

We note several limitations to EGBSSS and this evaluation. First, due to the timing of EGBSSS implementation, some cases may have been missed, particularly during Q1. Second, additional GBS cases may have been missed, including patients who may not have sought medical attention and mild cases for which GBS was not suspected, as well as fatal cases without clinical suspicion of GBS. However, data completeness was enhanced by assessment activities, and capture-recapture analysis suggests that few cases were missed overall. Finally, medical records could have been incomplete or improperly coded, affecting identification and confirmation of cases.

Despite these limitations, a novel and effective GBS surveillance system was rapidly implemented during the emergency response to the ZIKV epidemic in Puerto Rico. Through a strong collaboration between public health officials and healthcare providers, EGBSSS identified cases, provided arbovirus diagnostic testing, and yielded epidemiologic data with which to compare trends in Puerto Rico and elsewhere. More generally, the evaluation provided programmatic lessons for both GBS surveillance and emergency response surveillance, including facilitating a new surveillance priority by incorporation into an

existing system and maximizing case identification by conducting island-wide outreach and hospital diagnostic code review.

Resumen

Objetivo:

El síndrome de Guillain-Barré (SGB) es un desorden inmunológico, poco común, que se desarrolla luego de una infección o vacunación. Se ha observado un aumento durante brotes del virus de Zika (VZIK). Durante la epidemia del VZIK en 2016, el Departamento de Salud de Puerto Rico (DSPR) implementó el Sistema de Vigilancia Reforzado del SGB (SVRSGB). A continuación, se describe la implementación del SVRSGB y se evalúa su precisión, validez, y puntualidad. Métodos: Casos del SGB fueron identificados utilizando vigilancia pasiva y codificación de alta. Análisis captura-recaptura evaluó la precisión. La validez y el valor positivo predictivo (VPP) se calculó para ambos métodos de identificación de casos. Tiempo para finalizar pasos claves se comparó por trimestres (T1–4) y tamaño de hospital. Resultados: Un total de 122 casos del SGB fueron identificados con inicio de síntomas neurológicos durante el 2016. Se estimó que ambos métodos de identificación fallaron cuatro casos confirmados. La identificación de casos por codificación de alta tuvo mayor sensibilidad que el reporte por vigilancia pasiva (89% vs. 80%), pero un VPP menor (60% vs. 72%). Entre T1 al T3, el tiempo entre admisión al hospital y reporte de caso disminuyó (11 vs. 2 días, $p = 0.032$). Entre T2 al T3, el tiempo entre recibo de muestras y producción del reporte de laboratorio disminuyó (35 vs. 26 días, $p = 0.004$). Conclusión: El SVRSGB proveyó data completa, validada, y en tiempo real, que ayudo a dirigir la respuesta de salud pública y brindo apoyo a los proveedores. Esta evaluación proveyó lecciones pragmáticas para la vigilancia del SGB y durante una respuesta de emergencia.

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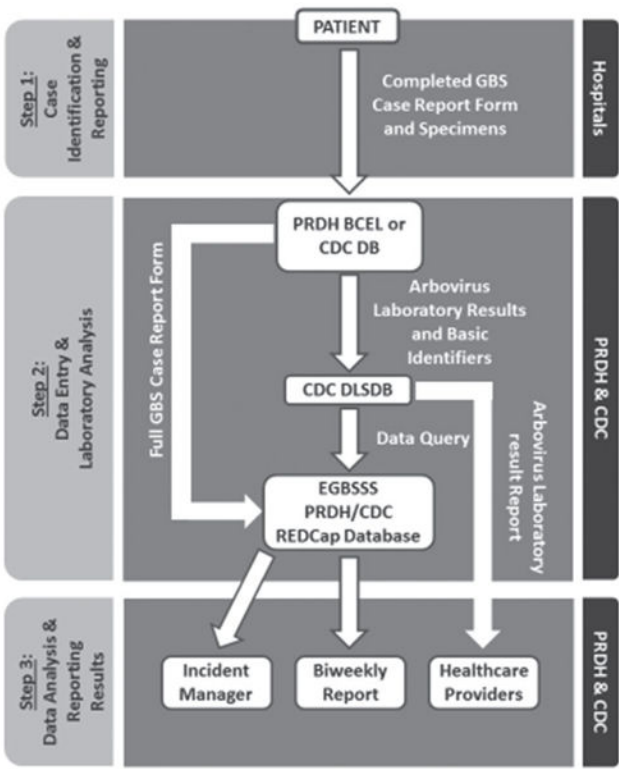


Figure 1. Flow of case reporting, arboviral disease laboratory diagnostic testing, data management, and reporting of test results for the Enhanced Guillain-Barré Syndrome Surveillance System (EGBSSS) - Puerto Rico, 2016.

Abbreviations: GBS = Guillain-Barré syndrome; PRDH = Puerto Rico Department of Health; BCEL = Biological and Chemical Emergencies Laboratory; CDC = Centers for Disease Control and Prevention; DB = Dengue Branch; DLSDB = Dengue Laboratory Samples Database; EGBSSS = Enhanced GBS Surveillance System; REDCap = Research Electronic Data Capture.

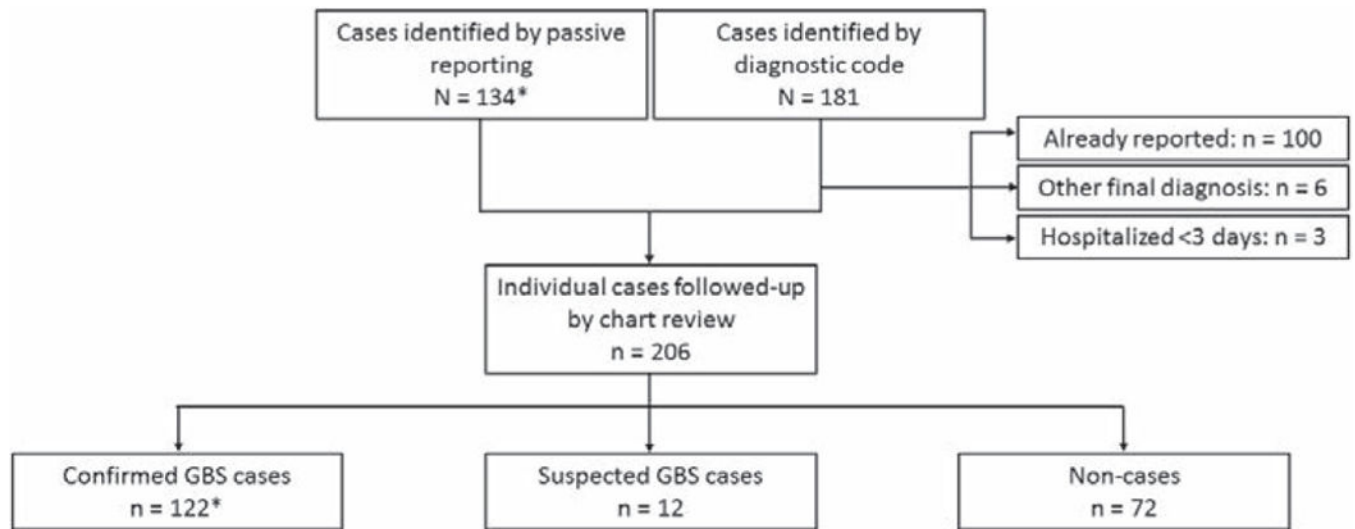


Figure 2. Identification of Guillain-Barré syndrome cases by method of case identification and status of clinical confirmation — Puerto Rico, 2016.

*Does not include confirmed GBS case reported in a Puerto Rico resident who sought care outside of Puerto Rico.

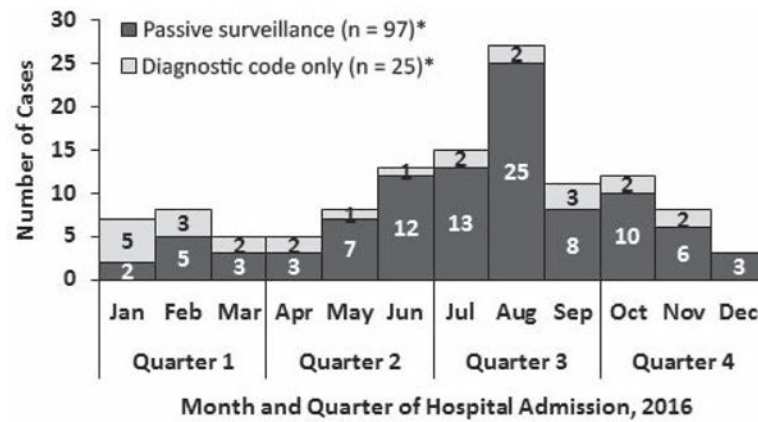


Figure 3. Confirmed Guillain-Barré syndrome cases by method of identification and month of hospital admission — Puerto Rico, 2016 (N = 122).*

*Does not include confirmed GBS case reported in a Puerto Rico resident who sought care outside of Puerto Rico.

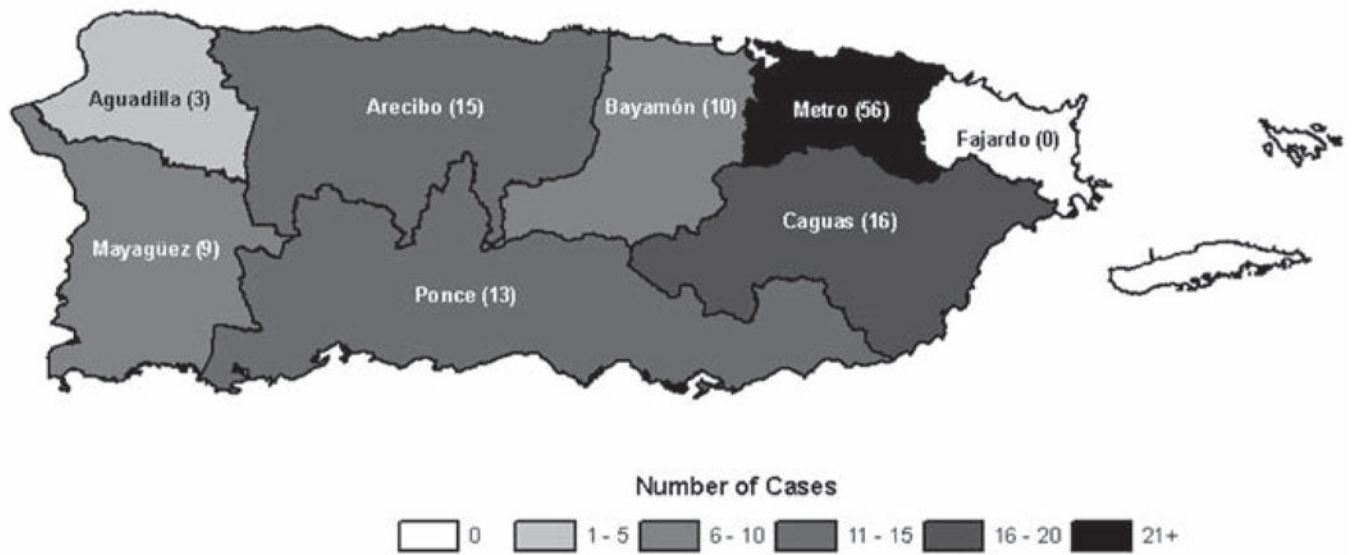


Figure 4. Number of confirmed GBS cases identified by the Enhanced Guillain-Barré Syndrome Surveillance System (EGBSSS) by hospital region — Puerto Rico, 2016 (N = 122).*

*Does not include confirmed GBS case reported in a Puerto Rico resident who sought care outside of Puerto Rico.

Table 1.

Characteristics of confirmed GBS cases identified through passive surveillance and review of hospital discharge diagnostic codes — Puerto Rico, 2016 (N = 122).^{*}

	Passive surveillance (n = 97) [*] n (%)	Diagnostic code only (n = 25) n (%)	P-value
Quarter of hospital admission [†]			<0.001
Quarter 1	10 (10)	10 (40)	
Quarter 2	22 (23)	4 (16)	
Quarter 3	46 (47)	7 (28)	
Quarter 4	19 (20)	4 (16)	
Hospital size [‡]			0.257
Large	69 (71)	14 (56)	
Medium	21 (22)	7 (28)	
Small	7 (7)	4 (16)	
Brighton Collaboration Criteria			0.132
Level 1	19 (20)	4 (16)	
Level 2	61 (63)	12 (48)	
Level 3	17 (18)	9 (36)	

^{*} Does not include confirmed GBS case reported in a Puerto Rico resident who sought care outside of Puerto Rico.

[†] Quarter 1 = January-March; Quarter 2 = April-June; Quarter 3 = July-September; Quarter 4 = October-December.

[‡] Large = 200 beds; Medium = 100–199 beds; Small < 100 beds.

Table 2.

Timeliness in days of case reporting, specimen receipt, and diagnostic testing for cases of Guillain-Barre syndrome or neurologic illness identified through passive surveillance — Puerto Rico, 2016 (N = 134).^{*}

	Mean	Median	Range	P-value
Days from hospital admission to case reporting (n = 134)	11	3	0–204	
Quarter of hospital admission [†]				0.024
Quarter 1 (n = 14)	20	11	0–63	
Quarter 2 (n = 30)	15	6	0–126	
Quarter 3 (n = 57)	9	2	0–204	
Quarter 4 (n = 33)	9	3	0–63	
Hospital size [‡]				0.015
Large (n = 87)	10	4	0–126	
Medium (n = 39)	7	3	0–63	
Small (n = 8)	43	18	1–204	
Days from specimen collection to laboratory receipt (n = 344) [§]	6	4	0–74	
Quarter of specimen collection [†]				0.326
Quarter 1 (n = 22)	6	5	1–18	
Quarter 2 (n = 54)	6	5	0–24	
Quarter 3 (n = 166)	7	4	0–74	
Quarter 4 (n = 102)	5	4	0–22	
Hospital size [‡]				0.022
Large (n = 216)	5	4	0–35	
Medium (n = 113)	9	5	0–74	
Small (n = 15)	4	4	1–11	
Days from specimen laboratory receipt to generation of healthcare provider report of arbovirus test results (n = 307) [¶]	41	26	5–323	
Quarter of specimen receipt [†]				<0.001
Quarter 1 (n = 25)	33	29	5–64	
Quarter 2 (n = 45)	47	35	17–169	
Quarter 3 (n = 141)	40	26	7–323	
Quarter 4 (n = 96)	43	22	9–261	

^{*} Does not include confirmed GBS case reported in a Puerto Rico resident who sought care outside of Puerto Rico.

[†] Quarter 1 = January–March; Quarter 2 = April–June; Quarter 3 = July–September; Quarter 4 = October–December.

[‡] Large = 200 beds; Medium = 100–199 beds; Small < 100 beds.

[§] Specimens from 129 reported cases; does not include specimens from the three cases tested for ZIKV at non-CDC and PRDH facilities and two cases with no specimens received.

[¶] Does not include 37 of the 344 received specimens with no arbovirus test report date.