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Original Article

Sensitivity of Guillain-Barre Syndrome Surveillance in the Brazilian Federal District, using the Capture-Recapture Method

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Abstract

Introduction: Guillain-Barre Syndrome (GBS) is an acute immune-mediated polyneuropathy that compromises the peripheral and cranial nerves. It is characterized by rapid-onset paresthesia accompanied by progressive weakness in the lower extremities followed by symmetric ascending paralysis.
Methodology: assessment of sensitivity to detect GBS between March 2017 and May 2019 in a public referral hospital, using the capture-recapture method based on the Chapman estimator and comparing three GBS data sources: the hospital-based sentinel surveillance system (VSBH), Human Immunoglobulin Dispensing Records System (RDIH), and Hospital Information System (SIH).
Results: A total of 259 possible cases were identified (captured). Of these, 58 were confirmed and most resided in the Federal District. The VSBH showed the greatest sensitivity in case identification. The temporal distribution of cases showed periods with no cases identified, and more were registered during the rainy season from October to May, when high temperatures also occur.
Conclusions: Increased circulation of arboviruses and gastrointestinal infections during the rainy season may explain the greater concentration of GBS cases. It is important to note that one-third of the cases identified in the different data sources do not converge, demonstrating that no single surveillance system is 100% effective. The severity and possible increase in cases related to GBS demonstrates the need for an improved surveillance system capable of monitoring and following-up cases involving neurological syndromes, regardless of the event preceding infection.

Key words: Surveillance system; Guillain-Barre Syndrome; arboviruses.

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Introduction

Guillain-Barre Syndrome (GBS) is an acute immune-mediated polyneuropathy that compromises the peripheral and cranial nerves. It is characterized by rapid-onset paresthesia accompanied by progressive weakness in the lower extremities followed by symmetric ascending paralysis [1]. Its etiology has yet to be fully elucidated; however, most cases are preceded by viral, respiratory or gastrointestinal infections, immunization or surgery [2].

The estimated global incidence rate of GBS between 1966 and 2009 was between 0.8 and 1.9 cases per 100,000 person-years [3]. In the Americas, between 0.4 and 2.12 cases were reported per 100,000 people from 2015 to 2018 [4]. Although GBS can affect any age group, it is more likely to occur in older men. Specific treatment for the condition aims to accelerate the recovery process, reducing complications associated with the acute phase and mitigating long-term neurological deficits, and includes the use of plasmapheresis and intravenous immunoglobulin, both of which are available through the Brazilian National Health System (SUS) [5].

With the introduction of new viruses such as Zika (ZIKV) [6] and Chikungunya (CHIKV) [7] in the Americas, including Brazil, there has been an increase in registered cases of neuroinvasive diseases [4]. The high rate of hospitalizations, along with treatment and rehabilitation, incurs a heavy burden, including significant financial costs for those affected and the lifelong sequelae, as well as early death resulting in loss of productivity for individuals and society as a whole [8].

In response to the growing number of cases of GBS and other neurological disorders, the Brazilian Ministry of Health proposed using a hospital-based sentinel surveillance system (VSBH) to monitor these diseases. The system was implemented in all the country's capital cities and investigates the presence of arbovirus infection preceding neurological symptoms. In addition, VSBH aimed to provide a framework for diagnosing, treating and monitoring cases of acute viral encephalitis, acute transverse myelitis, acute disseminated encephalomyelitis and GBS. The surveillance protocol for neuroinvasive diseases includes mandatory reporting and investigation of enteroviruses in the feces for all cases of acute flaccid paralysis (AFP) in individuals under 15 years old and in all health care units nationwide, as a mechanism for global polio surveillance [9, 10].

The ability of VSBH systems to identify the most frequent neuroinvasive diseases, such as GBS, remains unknown. As such, in March 2017, a hospital-based sentinel surveillance system was implemented to monitor GBS (VS-GBS), along with a clinical cohort study to identify and monitor patients hospitalized at a public referral hospital in the Federal District (HPRDF) [8]. Analysis of the VS-GBS sensitivity by comparing different data sources may provide important information on the usefulness of health surveillance systems in detecting cases. As such, the aim of the present study was to estimate the sensitivity of the VS-GBS in the Federal District, comparing three different data sources between 2017 and 2019.

Methodology

Study design

This is a sensitivity analysis for GBS detection between March 2017 and May 2019.

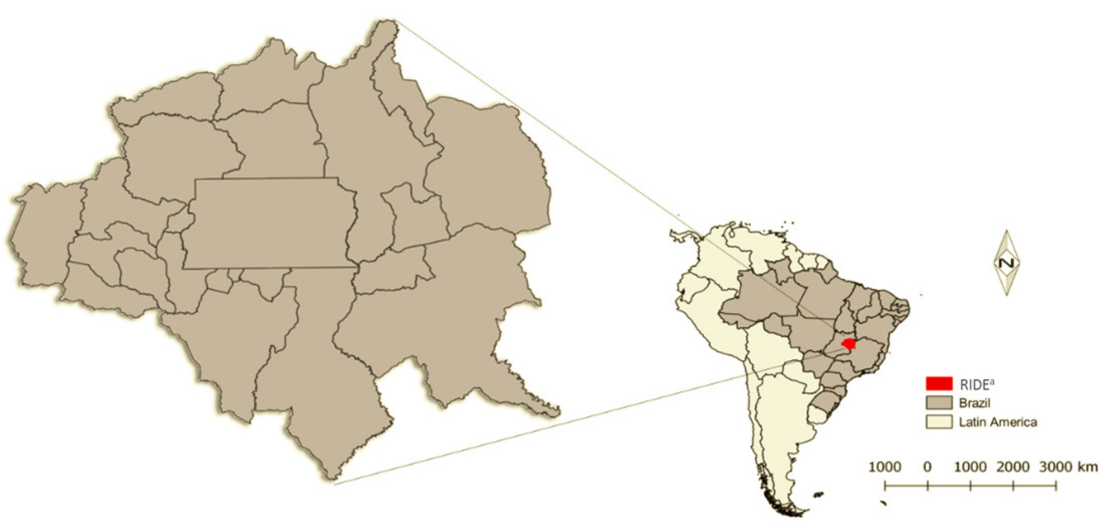
Study site

The study was conducted at a tertiary referral hospital (HPRDF), which became a sentinel surveillance facility in September 2017, when the Ministry of Health proposed a VSBH to monitor neuroinvasive diseases caused by arboviruses [9]. However, it has functioned as a VS-GBS since March 2017, when our study began.

The hospital staff consists of 1,434 phisicians and 4,037 workers from other health fields. The facility is structured to provide treatment across 13 clinical and 14 surgical specialties and has 6 types of intensive care units (ICUs) with a total of 661 beds, 27 of which are allocated to clinical neurology [11].

It serves as a critical care referral center for residents of the Integrated Development Region of the Federal District and Surrounding Areas (RIDE), which consists of the Federal District (DF), and 19 municipalities in the state of Goiás (Midwest Brazil), and two municipalities in Minas Gerais (Southeast Brazil), with a total area of 56,433.53 km² and an estimated 4,118,154 inhabitants in 2014 [12, 13] (Figure 1).

Figure 1. Geographic area of the study site – RIDE[a].



RIDE[a]: Integrated Development Region of the Federal District and Surrounding Areas.

Study population and case definition

The study population consisted of individuals with GBS resident in the RIDE, based on records from three information systems: (i) the hospital-based sentinel surveillance system for monitoring GBS (VS-GBS) described by Peixoto *et al.* 2019 [8]; (ii) the Human Immunoglobulin Dispensing Records System (RDIH) affiliated with the Federal District Department of Health; and (iii) the Hospital Information System (SIH). Cases were recorded under the code G61.0, in accordance with the International Classification of Diseases (ICD-10).

Due to the availability of ICU beds and its specialized neurology department, the HPRDF received suspected cases of GBS who exhibited rapid-onset paresthesia accompanied by progressive weakness in the lower extremities followed by symmetric ascending paralysis, with confirmation based on the Brighton criteria [1,14].

Data collection and case confirmation

In order to establish the study population, data were collected from three sources, with cases registered in the VS-GBS confirmed by a team of neurologists at the HPRDF that registered case admissions and then notified the research team.

Cases identified by the SIH were selected based on the ICD-10: G61.0 code allocated on admission to the HPRDF and individuals registered in the RDIH were initially identified by name, after which their medical charts were located to provide a summary of the case characteristics. Cases that exhibited levels 1, 2 or 3 of diagnostic certainty according to the Brighton criteria were confirmed and those at levels 4 or 5 discarded [14]. Cases identified in the SIH and RDIH were analyzed independently by two trained health professionals. Differences encountered during this classification were discussed individually with experts in order to reach a consensus.

It is important to highlight that the RDIH was selected as an object of study because the specific treatment strategy adopted by the HPRDF for GBS is intravenous immunoglobulin.

Capture and recapture

Following identification of GBS cases in the different data sources, the information was considered concordant when the same records were found in all three sources (VS-GBS, RDIH and SIH). Next, a Venn diagram was constructed to illustrate case distribution.

The capture-recapture method was used to assess the effectiveness and capacity of the data sources in identifying GBS cases, based on the Chapman estimator and considering the following assumptions: studies involving closed cohorts; small sample size found in each source; exclusion of duplicate cases; and two-by-two comparison between data sources. The capture-recapture technique is widely used in ecology research and wildlife surveys, but has also gained ground in epidemiological models, particularly when aimed at validating surveillance systems, since it provides a more precise estimate of incidence than traditional methods, such as passive surveillance [15–17].

Given that GBS is a rare, potentially serious and high-cost disease, the tool is useful in terms of improving surveillance systems created to identify its real pattern of occurrence. As such, the Chapman estimator was used to assess the estimated number of cases and their variance, resulting in an analysis of the overall sensitivity of the VS-GBS compared to the RDIH and SIH.

The following formulas were used to estimate the number of GBS cases identified by each data source and the respective 95% confidence interval (95% IC) [15, 16]: the number of estimated cases (N) was calculated by the sum of the cases identified in the first data source plus one (B+1), multiplied by the sum of the cases identified by the second source plus one (C+1), divided by the number of converged cases in both sources plus one (A+1), and subtracting one (-1) from the result.

$$N\ (estimated) = \frac{(B+1)\ (C+1)}{(A+1)} - 1$$

The variance of N was calculated as follows. Numerator: sum of the cases identified in the first data source plus 1 (B+1), multiplied by the sum of the cases identified in the second source plus 1 (C+1), multiplied by the difference between the total cases identified in the first source and the converged cases of both data sources (B-A), multiplied by the difference between the total cases identified in the second source and the converged cases of both data sources (C-A). Denominator: sum of the converged cases between both sources (A) plus 1 (+1), multiplied by the sum of the converged cases between both sources (A) plus 1 (+1), multiplied by the sum of the converged cases between both sources (A) plus 2 (+2). Finally, the numerator is divided by the denominator.

$$Variance\ (N\ estimated) = \frac{(B+1)\ (C+1)\ (B-A)\ (C-A)}{(A+1)\ (A+1)\ (A+2)}$$

The 95% confidence interval was calculated by adding or subtracting 1.96 from the estimated N value (to determine the maximum and minimum value) and then multiplying the result by the square root of the variance of N.

$$95\%IC = N\ estimated \pm 1.96\sqrt{Variance\ (N\ estimated)}$$

Data processing and analysis

Descriptive analysis was performed using absolute and relative frequency for categorical variables, Microsoft Office Excel 2016® to generate tables and graphs and Qgis version 2.18.9 to create maps.

Ethical considerations

The study was approved by the Research Ethics Committee of the University of Brasília School of Medicine under protocol number 1.989.868, and the Federal District Department of Health (protocol number 1.910.158).

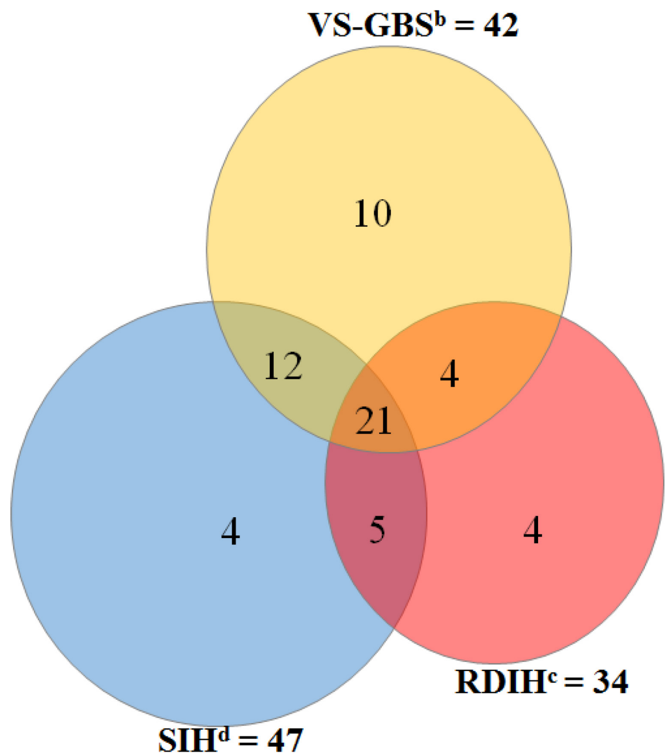
Results

In the process of identifying cases from the three data sources analyzed (Figure 2), 139 possible GBS cases were captured, 123 of which were confirmed. Considering the total number of cased identified in the three data sources (VS-GBS, RDIH and SIH), SIH captured the largest number of GBS cases (47), followed by VS-GBS (42) and RDIH (34), as demonstrated in Figure 3. One-third of the cases were identified in all three sources simultaneously.

The number of identified and confirmed GBS cases per source is described in Figure 2. The VS-GBS confirmed the highest number of cases among those registered, whereas SIH captured the largest number of cases but recorded the greatest variation in case confirmation. The RDIH obtained the lowest number of registered and confirmed cases.

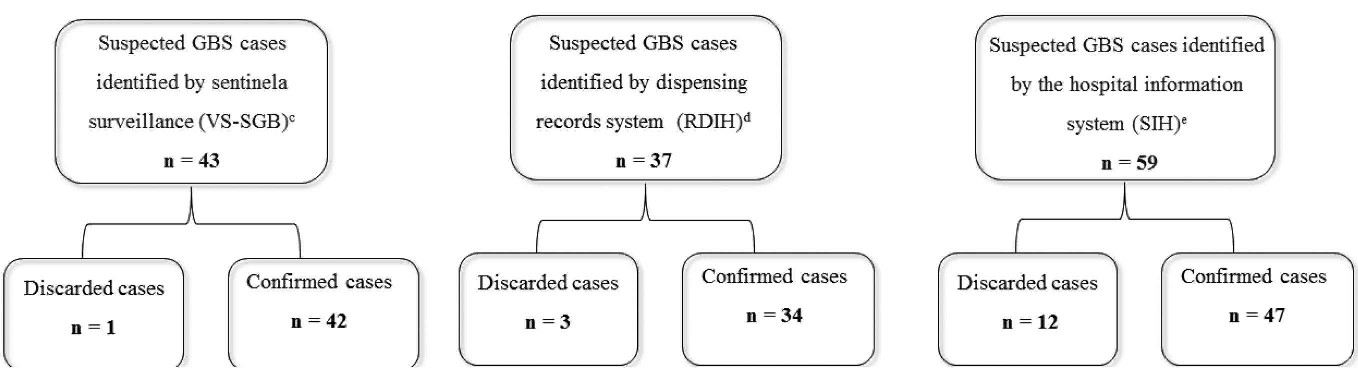
Analysis of case distribution according to month and data source (Figure 4) demonstrated a greater concentration of cases between October 2017 and April 2018, with cases captured by all three sources, albeit at different intensities. Although RDIH registered the fewest cases overall, it was the only source to detect cases in September 2017, as observed for SIH in November 2018. Periods when no cases were registered exhibited similar time profiles. It is important to note

Figure 3. GBS[a] cases confirmed by the VS-GBS[b], RDIH[c] and SIH[d] data sources. RIDE[e], Brazil, 2017-2019.



GBS[a]: Guillain-Barre Syndrome; RIDE[b]: Integrated Development Region of the Federal District and Surrounding Areas; VS-GBS[c]: Sentinel Surveillance for Monitoring GBS Cases; RDIH[d]: Human Immunoglobulin Dispensing Records System; SIH[e]: Hospital Information System.

Figure 2. GBS[a] cases identification by data source and confirmation status. RIDE[b], Brazil, 2017-2019.



GBS[a]: Guillain-Barre Syndrome; RIDE[b]: Integrated Development Region of the Federal District and Surrounding Areas; VS-GBS[c]: Sentinel Surveillance for Monitoring GBS Cases; RDIH[d]: Human Immunoglobulin Dispensing Records System; SIH[e]: Hospital Information System.

that no cases were registered by RDIH after February 2019.

Assessment of geographic distribution by place of residence revealed that most of these individuals reside in the Federal District. The points indicating the homes of GBS cases identified by VS-GBS and SIH are concentrated in similar regions and closer to the HPRDF when compared to the RDIH data source, which exhibits greater dispersion and distance from the HPRDF (Figure 4).

A comparison of common cases between paired sources indicated that the lowest estimate was recorded by VS-GBS x RDIH, while SIH x RDIH registered the largest number of estimated cases and the greatest variance among all the sources analyzed. Considering CI95%, the actual estimated number of cases across the three paired sources varies from 50 to 68 cases (Table 1). The minimum value established by CI95% was still higher than those recorded for all the data sources.

The highest percentage of coverage in GBS case identification was obtained between VS-GBS and SIH (Table 1) and the lowest for the RDIH system. As expected, the SIH sowed the lowest rate of under-reporting and the RDIH the highest.

Discussion

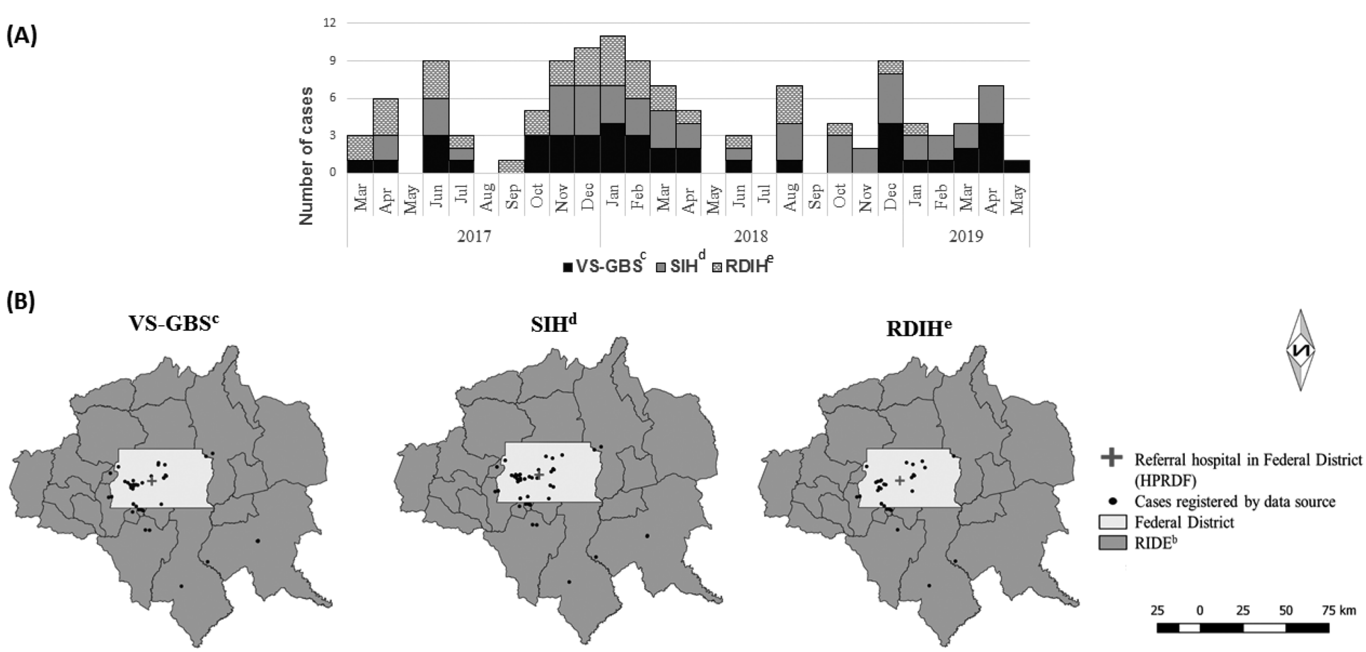
The present study assessed the sensitivity of a VS-GBS system in detecting GBS cases compared to two other data sources, namely the RDIH and SIH, between 2017 and 2019. Comparison of the three data sources demonstrated that the SIH and VS-GBS exhibit greater

Table 1. Observed and estimated cases, coverage and underreporting of GBS[a] by comparing paired data sources. RIDE[b], 2017-2019.

Data sources	Observed N	Estimated N	Variance N	IC 95%	Coverage (%)		Underreporting (%)	
SV-GBS[c] x SIH[d]	33	60	6	55 - 65	SV-SGB 70	HIS 78	SV-SGB 30	HIS 22
SV-GBS[c] x RDIH[e]	25	57	13	50- 64	SV-SGB 74	IDRFDS 60	SV-SGB 26	IDRFDS 40
SIH[d] x RDIH[e]	26	61	14	54 - 68	HIS 77	IDRFDS 56	HIS 23	IDRFDS 44

GBS[a]: Guillain-Barre Syndrome; RIDE[b]: Integrated Development Region of the Federal District and Surrounding Areas; VS-GBS[c]: Sentinel Surveillance for Monitoring GBS; SIH[d]: Hospital Information System; RDIH[e]: Human Immunoglobulin Dispensing Records System.

Figure 4. Number of confirmed GBS[a] cases by place of residence, identification source and month of symptom onset. RIDE[b], Brazil, 2017-2019.



(A) Number of confirmed GBS cases by identification source and month of symptom onset; **(B)** Number of confirmed GBS cases by place of residence; GBS[a]: Guillain-Barre Syndrome; RIDE[b]: Integrated Development Region of the Federal District and Surrounding Areas; VS-GBS[c]: Sentinel Surveillance for Monitoring GBS Cases; SIH[d]: Hospital Information System; RDIH[e]: Human Immunoglobulin Dispensing Records System.

sensitivity in identifying cases, with n = 42 and n = 47, respectively, when compared to the RDIH.

Of the three sources analyzed, the VS-GBS confirmed the largest number or registered cases, whereas SIH identified the highest number but showed the greatest variation for confirmed cases. The HPRDF is a tertiary referral hospital for the RIDE that provides specialized services and has a team of neurology specialists [11]. It is believed that these conditions favor early identification of cases admitted to the hospital exhibiting symptoms compatible with GBS, which are more likely to be detected by the SIH based on the ICD G61.0 code. The SIH is used to register procedures related to all hospital admissions within the Brazilian public health system in order to subsidize hospital billing [18, 19].

Since no surveillance system is 100% effective [20], there are periods in which no cases were identified by the VS-GBS. Although sentinel surveillance systems are a good strategy in monitoring cases, flaws are evident in the case records due to the possibility of intermittent identification depending on the particularities of the healthcare team involved [21]. In the present study, shortcomings in case registration are believed to have occurred during the absence of more experienced healthcare professionals at certain times due to vacations or staff reshuffling.

Cases detected more frequently by the VS-GBS and SIH were those that lived near the HPRDF. Individuals residing further away may have accessed the hospital through the service of Access to Healthcare Regulations (Regulação do Acesso à Assistência), which organizes and qualifies access to health services, albeit without a diagnostic hypothesis for GBS (ICD-10 G61.0). The gateway by which patients entered the different systems may have influenced suspected diagnoses, since multidisciplinary teams in the Federal District may be more sensitive to identifying GBS when compared to those from other Brazilian states, thereby affecting SIH and VS-GBS.

Sentinel surveillance systems in other countries suggest greater coverage when compared to other data sources. In Puerto Rico and New York, sentinel systems for GBS identified more than 90% of estimated and observed cases when compared to another data source [22, 23]. These findings indicate that although the Federal District sentinel system here provides standard coverage, shortcomings are evident and in-depth analysis is needed in order to improve its autonomy. Models based on specialists may be more sensitive in terms of identifying cases than service-based sentinel systems.

The capture-recapture method in conjunction with the Chapman estimator demonstrated that one-third of the cases recorded in the different data sources did not converge. This indicates uncertainty when registering information, particularly in terms of controlling the dispensation of specialty drugs. Although the HPRDF is responsible for 70% of cases registered under ICD-10 G61.0 and treated by the Federal District public health service [18], the magnitude of the problem may be underestimated. On the other hand, the tool used to estimate the number of cases is a mathematical model and therefore subject to its own limitations. As such, it is possible that the number of cases identified represents the real incidence in the population.

Furthermore, it is important to note three possible limitations of this study: i) analysis of secondary data used for the RDIH and hospital admission billing (SIH). Although neither of these systems are epidemiological information systems, they can be used as a proxy to identify GBS cases. The SIH is more reliable given the number of studies that use the system as a data source, and its results are consistent with the literature, further strengthening its relevance [19,24]; ii) analysis of cases registered under ICD-10 G61.0 on admission, which may have underestimated the number of suspected cases, since other possible GBS cases may not have been recorded using this code on admission to the hospital. However, this is not believed to have occurred in many cases since the SIH obtained the highest number of registered cases; iii) analysis of individual medical charts, since some information may not have been recorded. Nevertheless, most of the charts in this study were properly filled out by multidisciplinary teams specialized in caring for neurological disorders.

Although GBS is a rare condition, the emergence of arboviruses prompted an increase in registered cases in different regions of Brazil and other countries demonstrating the severity of the disease and the high costs involved in treating these patients [8]. We believe that an enhanced specialist-centered surveillance system at sentinel hospitals is capable of improving the monitoring and follow-up of cases related to neurological syndromes and not only those involving arboviruses [9] or acute flaccid paralysis (AFP) [10]. Thus, it is possible to identify the actual pattern of occurrence and propose control tools.

Further research is needed to analyze the current surveillance systems for arbovirus-related neuroinvasive diseases and AFP in Brazil. Additionally, we propose the implementation of a system capable of consistently monitoring neuroinvasive diseases regardless of the preceding event, with a focus on the specialist-centered sentinel model as opposed to the sentinel hospital.

Conclusions

Our results are unprecedented in Brazil in terms of assessing records of GBS cases across three independent data sources. The VS-GB and SIH systems identified the highest number of cases and the RDIH the lowest.

Given the possible increase in GBS-related cases and their severity, there is a need for improved surveillance systems capable of monitoring and following-up cases related to neurological syndromes and not only those involving arboviruses [9] or AFP [10]. This will make it possible to identify the actual pattern of occurrence and propose control tools whenever possible.

The incidence of GBS is rising across several regions in the presence of emerging and reemerging infectious diseases, such as arboviruses. This scenario heightens awareness regarding the severity of GBS and the high costs involved in treating these patients [8]. Assessing how close estimates are to the actual number of cases will make it possible to predict the resources needed by the health system.

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Authors' contributions

AFMO, LGG and WNA designed the study. AFMO selected the medical charts, compiled a summary of the clinical information, created the database and the maps available in the manuscript. LMM revised the data extracted from the charts. AFMO, LGG, MMB, PRM, AAA, JMASM, LMM, KKSG and WNA contributed to data analysis and interpretation and helped write the manuscript. All the authors were responsible for revising the manuscript, and read and approved the final version.

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