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Incidence of Guillain-Barré syndrome in the world between 1985 and 2020: a systematic Review

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Abstract

Introduction: Guillain-Barré syndrome (GBS) is an acute inflammatory demyelinating polyradiculoneuropathy that affects the peripheral nervous system. The study aimed to describe the incidence of GBS in the world up to the year 2020. **Methods:** A systematic review was conducted. Searches were done in four databases, PUBMED, EMBASE, EBSCO and *Biblioteca virtual em Saude (BVS)*, and in grey literature and manual search in the reference lists of eligible studies. **Results:** A total of 72 studies were included. The incidence of GBS among the cohort studies varied from 0.30 to 6.08 cases per 100.000 habitants and 0.42 to 6.58 cases per 100.000 person-years. Among the self-controlled studies, the risk incidence ranged from 0.072 to 1 case per 100.000 habitants and 1.73 to 4.30 cases per 100.000 person-years. **Conclusions:** The reported incidence of GBS in the world among the studies included in the review is slightly higher than that reported in previous studies. The highest incidence rates were associated with public health events of international concern.

Keywords: Guillain-Barre Syndrome, Epidemiology, Incidence, Systematic Review.

Introduction

Guillain-Barré syndrome (GBS) is an autoimmune disease that affects the peripheral nervous system. It is characterized by a symmetric ascending paralysis, hyporeflexia or areflexia. It is a monophasic syndrome with severity peak between two to four weeks after onset. It is the most common cause of acute or subacute flaccid weakness in the world after the eradication of poliomyelitis (1–4).

The syndrome onset is associated with antecedent infection in about 70% of the cases (3,5,6). *Campylobacter jejuni* is the most associated infectious trigger of GBS, other infectious agents include *Cytomegalovirus*, Epstein-Barr virus and *Mycoplasma pneumoniae,* arboviral infections like dengue virus, Zika virus, Western Nile virus and Chikungunya virus (4–8). Recently, there has been a temporal association of GBS and SARS-CoV-2 virus (9,10). The non-infectious triggers of GBS include vaccines, surgery, ganglioside administration and conditions that cause immunosuppression (1,4).

There are various subtypes or variants of GBS according to neurophysiologic studies. The most common subtype of GBS is acute inflammatory demyelinating polyneuropathy (AIDP) that is characterized by demyelination of the nerve fiber. The other common variant is the acute motor axonal neuropathy (AMAN) distinguished by axonal motor nerve degeneration. The variant AMAN has a sensorial form, acute motor and sensory neuropathy (AMSAN). Other rare variants include Miller Fisher syndrome (MFS) that is characterized by ophthalmoplegia, areflexia and ataxia, Bickerstaff brainstem encephalitis, pharyngeal-brachial pattern and pure sensory form (3,5,11,12).

Over the past decades, studies have been published showing the incidence of GBS in the world, but none has been published in the recent past (13,14). During the last two decades, two public health events of international concern occurred, the 2009 AH1N1 influenza pandemic, and the ZIKV epidemic in 2015 (15,16). The H1N1 infection as well as the influenza vaccinations were associated with an increase of GBS cases in some countries (17,18). In relation to the ZIKV epidemic, there was an increase in the number of reported GBS cases in countries with confirmed transmission of the virus (19).

The 2009 AH1N1 was first reported in the United States of America (USA) in 2009 and later spread to other parts of the world (15). The vaccines against the virus have been investigated for association with an increase in the number of GBS cases. In the USA for example, a study that analyzed about 23 million vaccinated people with AH1N1 2009 monovalent inactivated vaccines with data obtained from adverse events monitoring systems, a small increased risk of GBS of about 1.6 excess cases per million vaccinated people was found, incidence rate ratio 2.35 (95% Confidence Interval (CI)1.42 – 4.01, p= 0.0003 (17).

Zika virus infection (ZIKV) was initially associated with the development of GBS in French Polynesia in the 2013-2014 ZIKV epidemic. Cao-Lormeau and colleagues reported the occurrence of GBS among ZIKV infected cases attended in a hospital compared with non-febrile cases from the same hospital with an Odds Ratio of 59.7 (CI 95%: 10·4–+∞) (20,21). Later, similar cases were reported in the Americas (21–23). The GBS incidence in the world as result of all factors associated with its development is estimated at 0.6 to 4.0/100.000 habitants (4) and among ZIKV infected cases in Latina America and the Caribbean at 0.32 to 9.35/100.000 habitants (23).

The last epidemiological update of the World Health Organization (WHO) about ZIKV in the world was published in July 2019. According to the report, 87 countries and territories in four of the six WHO regions had reported evidence of autochthonous transmission of ZIKV (African Region, Region of the Americas, South-East Asia region and Western Pacific region). The report also stated that 61 countries in all the six WHO regions had *Aedes aegypti* circulation but had not reported any ZIKV transmission. According to the report, this does not rule out the absence of transmission, there might be a possibility that the cases have not yet been detected or reported (24).

This systematic review aimed to describe the incidence and prevalence rates of GBS in the world up to December 2020 and to identify variations that may have occurred during public health emergency of international concern caused by the H1N1 virus in 2009 and Zika virus in 2015. The updated frequency of GBS in the world can help understand the magnitude of its occurrence and estimate the social and economic impact in different parts of the world especially after the occurrence the above mentioned health events of international concern.

Materials and Methods

This systematic review was conducted as per the study protocol previously elaborated and registered in International Prospective Register of Systematic Reviews (PROSPERO) under registry number: CRD42021242039.The systematic review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) (25).

Sources of information

The following databases were searched for eligible studies: EBSCOhost Reseach Databases (EBSCO); Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Médica dataBASE (EMBASE) e *Biblioteca Virtual em Saúde* (BVS). Additional articles were obtained from manual search in reference lists of identified and selected articles. Gray literature was searched in a catalog of theses and dissertations of the Brazilian Federal Agency for Support and Evaluation of High Level Education (CAPES), Brazilian digital theses and dissertations library (BDTD) and the international gray literature site OpenGrey (26–28).

Research question and search strategy

The research question was formulated using part of the acronym PECOS (population, exposure, outcome and study design). The study question was: What is the incidence/prevalence of Guillain-Barré syndrome cases in different regions of the world?

The search strategy was elaborated by V.W and validated by M.R and H.M. The strategy was at first formulated using MESH terms on PUBMED and adapted to other databases and included common terms like “Guillain-Barré syndrome”, “incidence” and “prevalence” **(Supplementary Material 1:Table 1).**

Eligibility criteria

Studies were included if they met the following eligibility criteria: epidemiological studies published until 2nd December 2020 when the searches were done in the databases, descriptive or analytical studies that reported the frequency of GBS (analytical and descriptive cohorts and cross-sectional studies, self-controlled case series, self-controlled risk interval studies, case cross-over),

they included GBS cases confirmed using internationally accepted criteria or by consensus by specialists, GBS cases in any age group and if published in Portuguese, English, Spanish or French.

Study designs included

The study designs included in this study were descriptive or analytical studies (analytical and descriptive cohorts, self-controlled case series (SCCS), self-controlled risk interval studies (SCRI), case cross -over) because they are ideal studies to report the frequency of events (29–32).

Study selection and data extraction

Two authors (V.W and C.F) working independently screened the titles and summaries of the registries obtained from the databases and grey literature according to the eligibility criteria on Rayyan platform (33). Full text eligibility was also done independently by the same authors and conflicts were resolved by consensus.

Data extraction was done by V.W and R.B and conflicts were solved by either M.R or H.M. Data were extracted on a spreadsheet previously elaborated and validated by all the authors. The following information was extracted: author and year of publication, study execution period, study population, sample size, number of male and female cases, male to female case ratio, age (mean, median, range), etiological factor(s) reported, validation criteria of the etiological factor(s), validation criteria of GBS, GBS variant, gross incidence or prevalence rate in the general population and among male and female population and the adjusted incidence or prevalence rate. For the SCCS and SCRI, the incidence was considered only in the risk period only.

Quality assessment

The methodological quality of the individual studies was done using Joanna Briggs instruments for cohort studies and was adapted to fit the descriptive nature of the studies included (34). The SCCS and SCRI studies were evaluated using an instrument adapted from the NewCastle Ottawa Scale for cohort studies by Wachira and colleagues (7).

Data synthesis and report of the incidence or prevalence outcomes

If the evidence obtained would allow the quantitative combination of the results, a metanalysis would be performed. If not, a qualitative synthesis of the data would be done.

For the report of the outcomes of interest, the World Health Organization (WHO) regions were used. The report of the of the outcomes was done in the following categories : Incidence of GBS in the general population 1985 -2019, Incidence of GBS in the world among age-groups 1985 -2019, Incidence of GBS in the world among male and female populations 1985 -2019, and distribution of GBS variants in the world 1985 – 2019.

Results

A total of 2,424 registries were obtained from the databases, grey literature sites and manual search from the references of eligible studies. After duplicates removal, 1,856 titles and summaries were screened, and 1,702 registries were excluded for not fulfilling the eligibility criteria. For the full text reading phase, 154 registries were eligible of which 82, were excluded for not meeting the eligibility criteria. The list of the include and excluded studies and the motive for exclusion is provided in **Supplementary Material 2: List 1 and 2**. A total of 72 articles were considered for the qualitative synthesis of this systematic review **(Figure 1).** It was not possible to perform a metanalysis due to the methodological heterogeneity of the studies included that was brought about by the different study designs, different study samples and varying possible etiological agents studies. In this regard, a qualitative synthesis of the results was done.

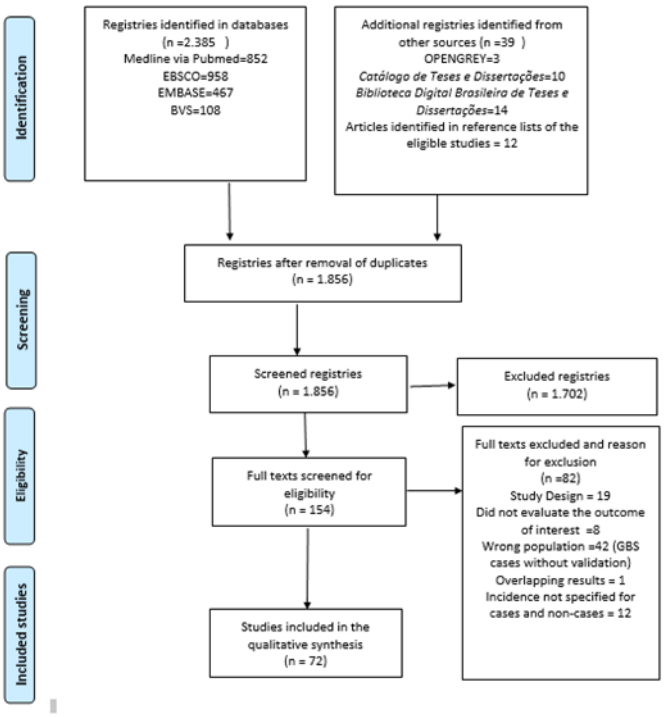

Figure 1: Flow chart of the selection and inclusion of studies**.**

Characteristics of the included studies

The studies included in this review were published between the year 1985 and 2019. There was no eligible study published in the year 2020. For characterization purposes, some of the individual studies were counted more than once because they presented more than one study design or had different study populations for the etiological factors studied and consequently different incidence rates. In this regard, for the characterization of the studies, a total of 80 studies was utilized. The WHO regional criteria was used to describe the geographical distribution of the published studies. Most of the studies investigated populations from the European region (n=35 [43.8%]) and the American region (n= 33 [41.3%]). The other study populations reported in the studies were from the Eastern Mediterranean (n= 5 [6.3%]), West Pacific (n=6 [(7,5%]), mixed regions: Africa and Europe (n=1 [1.3%]). None of the included studies were from Southeast Asia.

In relation to the study design, a majority, 66 (82.5%) studies had a cohort design, 13 (16.3%) were SCCS and 1 (1,3%) was a SCRI study design. The

methodological quality of individual studies was low in 2 cohort studies, moderate in 59 and high in 3 (one of the cohort studies evaluated 3 etiologies of GBS and was evaluated only once). For the SCCS and SCRI, none was evaluated as low quality, 2 had moderate quality and 7 were of high quality (there were 14 studies originally but two evaluated more than one etiological agent but were evaluated only once) **(Supplementary Material 1: Table 2 and 3).**

Guillain-Barré variants were reported in 21 studies. The AIDP variant was the most reported, with a total of 17 (26.2%) of the total reports, followed by AMAN with 12 (18.5%), AMSAN with 10 (15.4%), and Miller Fisher Syndrome with 11 (16.9%) studies. The most used GBS validation criteria were the Brighton Criteria, 29 (36.3%) studies; National Institute of Neurological and Communicative Disorders and Stroke (NINCDS), 23 (28.8%) and Asbury and Cornblath criteria, 12 (15%) (Table 1).

Guillain-Barré etiological factors were reported in 74 (92.5%) of the studies and respiratory, gastrointestinal and other non-specified infections were mostly reported in the studies as well as influenza vaccines (pandemic H1N1, seasonal or non-specified influenza vaccines) **(Table 1).**

The 72 studies eligible in this systematic review represent 44 countries and territories in the world, among them, 23 have had confirmation of the transmission of ZIKV and eight of them have had outbreaks according to the reports of the WHO. These eight countries and territories are Brazil, Martinique, USA, Argentina, Colombia, Honduras, Porto Rico, Aruba and Chile. Other four countries have had confirmation of the presence of Aedes aegypti but no confirmed cases of ZIKV infection; Australia, China, Tanzania and Oman (35,36).

Only the USA had eligible studies before and after the ZIKV epidemic, but ZIKV was not among the etiological factors reported that led to the development of GBS. Most of the studies from the USA reported vaccines as the etiological factors especially the influenza vaccines. In this systematic review, only one study reported ZIKV as the etiological agent causing GBS. Consequently, due to the lack of eligible studies that would allow the comparison of GBS before and from the start of ZIKV epidemic, this comparison was not possible. We therefore only updated the incidence of GBS in the world.

In relation to the studies that evaluated the development of GBS after the administration of the influenza vaccines, most of them were elaborated with data from the H1N1 pandemic period. A majority of the included studies elaborated before this period and that reported influenza vaccines as an etiological agent of GBS, did not specify in the results the frequency of GBS attributed to the influenza vaccinations. One of the studies in the pre-pandemic period reported a GBS incidence of 0.46 cases per million vaccinations after influenza vaccination between 1990 to 2009 in the USA (37). With data from the pandemic period between 2009-2010, Vellozi and colleagues reported a cumulative incidence of GBS cases following the pandemic influenza vaccination of 6.58/100,000 person-years (38). Kim and colleagues reported an incidence of 0.87 (CI 95% 0.49 – 1.26) after the pandemic influenza vaccination in South Korea (39).

Incidence of GBS in the general population 1985 -2019

In the period of study, the GBS incidence rate among the cohort studies in the general population varied from 0.30 in Brazil to 6.08 cases per 100.000 habitants in Martinique (40,41) and 0.42 in Japan to 6.58 cases per 100.000 person-years (CI 95% 5.05 -8.24) in the United States of America (USA) (38,42). In relation to the SCCS and SCRI studies included, the risk incidence varied from 0.072 case in Australia to 1 case per 100.000 habitants in Iran (43,44) and also 1.73 cases in the USA to 4.30 cases 100.000 person-years also in the USA (45,46). **(Table 2).**

Incidence of GBS in the world among age-groups 1985 -2019

In relation to the GBS incidence rate among age groups, not all studies presented this information. For the age group above 50 years, the incidence rate varied from 0.44/100.000 person-years among individuals aged 50 to 59 years in China to 12.97/100.000 (CI 95% 6.55 -20.24) person-years in the US among individuals above 65 years (38,47). In the age group above 80 years, the incidence rate reported in most studies was low compared to other age groups. The rates ranged from 0.29/100.00 habitants in the population above 80 years in Western Balkans to 6.26/100.000 habitants in Spain among individuals within the age range of 80 - 89 years (48,49).

In relation to children and adolescents, the incidence rates reported in some of the studies ranged from 0.25 cases in Italy to 1.57 cases per 100.000 habitants in Spain (50,51) and 0.39 cases in Denmark to 1.21/100.000 person-years in Sweden in the age group of 10 to 19 years (52,53). In the age group of 0 to 10 years, the incidence rate varied from 0.37/100.000 person-years in China to 1.25/100.000 person-years in the Netherlands (54,55) and 0.41 cases in Spain to 4.0 cases per 100.000 children between 0-9 years and 4.7 cases per 100.000 children between 0-4 years in Oman (56,57). **(Table 2).** .

Incidence of GBS in the world among male and female populations 1985 - 2019

The highest ratio between male and female GBS cases was 3.3:1 in Spain (49). A total of 24 studies reported specific incidence rates in the male and female cases studied, among the male cases, the rate varied from 0.53/100.000 (CI 95% 31.12 – 57.92) person-years in Japan to 4.95/100.000 person-years in Norway (42,58) and 1.18/100.000 (CI 95% 0.84 – 1.61) habitants in Spain in 1994 to 3.16/100.000 habitants still in Spain in 2018 (49,51). The incidence rates in the female population ranged from 0.31/100.000 (CI 95% 18.61 – 40.47) person-years in Japan to 3.4 /100.000 person-years in Norway (42,58) and 0,7/100.000 (CI 95% 0.45 – 1.03) habitants in Spain to 1,71/100.000 (CI 95% 0,88 – 2,99) habitants in Italy (51,59). The SCCS and SCRI study designs did not report the incidence rates in terms of age groups **(Table 2).**

Distribution of GBS variants in the world 1985 - 2019

Guillain-Barré variants were reported in only 22 studies. The most reported variant was AIDP in all WHO regions with high proportions of about 95% in Martinique and 96% in Italy (41,50). Other variants reported were AMAN, AMSAN, Pharyngeal-cervical-brachial and MFS but in smaller proportions **(Table 1).**

Discussion

To the best of our knowledge, this is the first systematic review to evaluate the incidence or prevalence rates of GBS over a large period of time and also try to analyze the frequency of GBS after the AH1N1 influenza pandemic in 2009

and the ZIKV epidemic in 2015. In the last decades, two systematic reviews analyzing the GBS incidence in the world have been published (13,14).

In reference to the WHO regions, most of the studies investigated populations from Europe and the Americas. In terms of country of elaboration and the origin of the populations studied, a majority of the studies were from the USA. The assessment of the methodological quality of individual studies was moderate in general. In terms of the criteria of GBS validation, most of the studies reported the use of the Brighton Criteria or NINCDS to validate the GBS cases.

The most reported GBS variant was AIDP. It is the most common variant and is characterized by demyelination of the axons and it is present in about 85% of diagnosed GBS cases. It is more common in North America and Europe (60,61).

The incidence rate of GBS in the world reported in previous studies varies from 0.6 to 4 cases per 100.000 habitants (4,13,14,60). In the present systematic review, the incidence rate in the general population ranged from 0.30 cases to 6.08 per 100.000 habitants and 0.42 cases to 6.58 person-years among the cohort studies (38,40–42). In relation to the SCCS and SCRI study designs, the risk incidence varied from 0.072 cases to 1 case per 100.000 habitants and 1,73 to 4.3 cases per 100.000 habitants (43–46). The rates in the general population reported in the present systematic review are higher than those reported in the previous studies.

GBS occurs in all ages, but it is more common among individuals over the age of 50 years. The estimated incidence as reported in previous studies in this population is 1.7 to 3.3 cases per 100.000 habitants (13,62,63). In relation to the studies in this review that reported GBS incidence among adults from 50 years and above varied from 0.44 person-years in the age group of 50-59 years to 12.97/100.000 person-years in individuals with ≥ 65 years (38,47). The GBS prognosis at this age is poor with reports of long hospital stay, mortality or delayed response to the treatment given (48,64,65). GBS is an autoimmune disease that affects the peripherical nervous system. With age, there are natural alterations of the nerves in terms of the functioning of the immune cells and the decline of their

recovery process. That might be associated with the poor prognosis in this age group (66).

GBS is not as common in children and adolescents as compared to the adult population. In this population, the estimated incidence in the world is of 0.62 cases per 100.000 habitants between 0 and 9 years and 0.75 cases per 100.000 habitants in the age group of 10 to 19 years (67). In this systematic review, the reported incidence in children and adolescents was high in some studies with an incidence of upto to 4.7/100.000 cases per 100.000 children in the age group of 0 to 4 years (57) . GBS is a common cause of flaccid paralysis in children. Acute flaccid paralysis is characterized by damage of the lower motor neurons in the anterior horns of the spinal cord or in the peripheral nerves. This can be caused by a viral infection like polioviruses and other enteroviruses or due to immune mediated conditions like GBS (68,69). Differential diagnosis is thus necessary to distinguish the cause of flaccid paralysis in this population.

It is also worth noting that the high incidence rates were mostly reported in the regions of the Americas and Europe among the adult population (38,49,56) while among children and adolescents, the frequency rates were mostly reported in the Eastern Mediterranean and West Pacific regions (57). This can be explained by the populational age differences in each region. The regions of Europe and the Americas have aged populations and this may explain why most of the cases were adults (70). Another reason could be due to the absence of eligible studies in this systematic review that could help analyze the GBS frequency among different regions and age groups.

Most studies reported the ratio between male and female GBS cases and the highest ratio was 3.3:1 (49). There are reports in scientific literature that GBS is more common in males than females but it is not yet known what causes this difference (6,11,14,60,63).

In this systematic review, the highest frequencies of GBS were associated with the pandemic AH1N1 influenza vaccinations in the USA, 6.58/100.000 person-years (38) and infection by ZIKV in Martinique, 6.08/100.000 habitants (41). Among the eligible studies, most of the reported etiological factors were influenza vaccines, both the pandemic, seasonal and in some studies the

influenza vaccines were not specified. Zika virus infection as a precedent factor in the development of GBS was reported in only one study.

One of the objectives of this systematic review was to compare the incidence of GBS before and after the AH1N1 influenza pandemic in 2009 and the ZIKV epidemic in 2015. In the case of ZIKV epidemic, this was not possible due to the lack of eligible studies in the countries and territories with confirmed transmission cases of ZIKV infection that would allow this comparison. As for the AH1N1 pandemic, most of the eligible studies from the pre-pandemic period also reported other factors associated with the development of GBS and did not stratify the frequency of GBS associated with each of these factors. Consequently, it was impossible to compare the frequency of GBS in the two periods.

Zika virus infection was first associated with the development of GBS in French Polynesia during a ZIKV infection outbreak between 2013 and 2014. A total of 42 cases of GBS were reported which was higher than the expected three to eight cases a year (71). This scenario was also reported in other countries in the Americas especially Brazil between 2015 and 2016 (21). The mechanism between ZIKV infection and GBS development is not yet established. It is believed that the exacerbated response of the immune system after a viral infection can trigger an immunopathogenic process that attacks the peripheral nerves and, in this process, there is the development of GBS (19,72,73).

The burden of ZIKV in the world has been estimated at 44,000 DALYs between 2010 and 2019. In this period, the highest burden of the infection was attributed to the Americas region with a total of 42,690 DALYs (74). In relation to the burden of disease of GBS due to ZIKV infection in Brazil, the estimated DALYs of GBS in 2015 and 2016 during the ZIKV infection epidemic were 6,054.61 and 7,88.49, respectively (75). This shows the impact the ZIKV has on health and economic systems in countries affected by its circulation.

Influenza vaccines were first associated with the development of GBS in the influenza A/New Jersey/1976 vaccination campaigns. An 8-fold increase in the risk of GBS was reported after vaccination with the pick occurring in a period of two to three weeks post vaccination. The estimated attributable risk was of one

additional case per 100,000 doses administered (76,77). Years after the occurrence of this association of the vaccines and rise in GBS cases, various studies have been elaborated to investigate these association of influenza vaccines and the development of GBS. Some have reported increased risk of GBS in the post vaccination period while others have not reported any association (77). A study from the United Kingdom found no increased risk of GBS 6 weeks after the administration of the pandemic influenza vaccination. The relative incidence in the study was 1.05 (CI 0.37- 2.24) (78). Similarly, in another study that aimed to estimate the association between the pandemic influenza vaccination and occurrence of GBS in the Norwegian population, the incidence risk ratio (IRR) 42 days after the administration of the vaccine was not statistically significant, IRR 1.12 (CI 95% 0,55 - 2,26) (18). In the present systematic review, an increased risk of GBS was reported after the pandemic H1N1 vaccination, like in the USA with reports of an accumulated risk incidence of 6.58/100.000 person-years in one of the eligible studies (38).

The burden of the influenza pandemic was estimated at 60.8 million cases in the USA between April 2009 and April 2010. In the same period, 274,304 hospitalizations and 12,469 deaths were reported (79). In Mexico, between April to December 2009, the estimated Years of Life Lost (YLL) were 445,000 (CI 95% 339,000 – 551,000) (80).

The GBS economic burden due to other causes has been estimated in some countries. In South Korea, the median cost of treatment per year between 2010 and 2016 was estimated at 16,428 American dollars (USD). In the US, the estimated direct and indirect costs per patient in the year 2004 was 74.010 USD. Another study elaborated in France with data from the year 1999 and according to the severity of GBS, the estimated cost was 83.707 USD for mild GBS and 123.780 for severe GBS (81,82). In Brazil, the estimated direct and indirect costs of GBS in 2016 was 11,997,225.85 USD (83). It is worth noting that the costs can compromise the household income, which can lead to indebtedness and deepen impoverishment. This shows that GBS has a huge economic impact on patients and health care systems (84).

Guillain-Barré syndrome is reported to have a good prognosis but in 20% of the cases, residual impairment and disability is reported in about six to twelve

months after diagnosis. Some of the residual deficits include reduced muscle force, fatigue and pain and this directly affects the execution of daily activities as well as work related tasks (85,86). Consequently, there are effects on the psychosocial functioning of the patient. Babur and Awan reported in their study that GBS survivors have low confidence and self-esteem, suffer from depression and anxiety and their status affects how they conform to the society (87).

This is the first systematic review to estimate the incidence of GBS in the world over a large period of time. There was no limitation in terms of the year of publication, a comprehensive search of eligible studies was done, and a substantial number of studies were analyzed. Another strength is that one of the eligibility criteria was validation of the cases by internationally accepted criteria, thus only confirmed GBS cases were considered in this review. Also, some of the studies presented the incidence rates by sex or by age group and that helped to analyze these subgroups. As a limitation, it was not possible to do a metanalysis in this systematic review due to the heterogeneity of the studies included in terms of study designs, samples and the lack of stratified incidence rates depending on the etiological agents studied. It was also not possible to compare the frequency of GBS in the world before and from the start of ZIKV epidemic due to lack of studies that would allow this comparison. Also, the studies included did not allow the comparison of the frequency of GBS before and after the A/H1N1 pandemic. The incidence rate of GBS was a bit higher than that reported in previous studies.

Supplementary Material 1: Table 1. Search strategies

Supplementary Material 1: Table 2. Quality evaluation of cohort studies

Supplementary Material 1: Table 3. Quality evaluation of Self-controlled case series studies/Self-controlled risk interval design

Supplementary Material 2: List 1: List of the included studies

Supplementary Material 2: List 2: List of the excluded studies and the motive for exclusion.

Table 1: Characteristics of the included studies,1985-2019.

Table 2: Results: Frequency measures of GBS 1985-2020

Author Contribution:

VW, HP and MO conceived the study and designed the study protocol. CF and RB revised and approved the study protocol. VW and CF carried out the screening. VW and RB extracted data from records. VW drafted the manuscript. CF, RB, HP and MR critically revised the manuscript. All authors read and approved the final manuscript.

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Conflict of interest

The authors do not have no conflicts of interest to declare that are relevant to the content of this article.

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