



Published in final edited form as:

Neurol Sci. 2020 April ; 41(4): 885–891. doi:10.1007/s10072-019-04156-z.

Guillain-Barré syndrome and antecedent cytomegalovirus infection, United States 2009–2015

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Abstract

Objective: To describe incidence and clinical characteristics of cases of Guillain-Barré Syndrome (GBS) in the United States during 2009–2015, and characteristics of GBS cases with antecedent cytomegalovirus (CMV) infection among persons with employer-sponsored insurance.

Methods: We analyzed medical claims from IBM Watson MarketScan® databases. GBS patients were defined as enrollees with an inpatient claim with GBS as the principal diagnosis code, based on ICD-9 or ICD-10, and ≥ 1 claim for lumbar puncture or EMG/nerve conduction study. We assessed intensive care unit (ICU) hospitalization, intubation, dysautonomia, and death. We also assessed selected infectious illness within 60 days prior to first GBS-coded inpatient claim.

Results: We identified 3,486 GBS patients; annual incidence of 1.0–1.2/100,000 persons during 2009–2015. GBS incidence was higher in males (1.2/100,000) than females (0.9/100,000) ($p=0.006$) and increased with age, from 0.4/100,000 in persons 0–17 years old to 2.1/100,000 in persons ≥ 65 years old ($p<0.001$). Half of GBS patients were hospitalized in the ICU, 8% were intubated, 2% developed dysautonomia, and 1% died. Half had a claim for antecedent illness, but only 125 (3.5%) had a claim for specific infectious pathogens. The mean age among 18 GBS patients with antecedent CMV infection was 39 years versus 47 years among those without antecedent CMV infection ($p=0.038$).

Conclusions: Incidence of GBS using a large national claims database was comparable to that reported in the literature, but cases appeared to be less severe. Half of GBS patients reported prior infectious illness, but only a minority had a specific pathogen identified.

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Disclosure Statement: The authors have no potential conflicts of interest to report. Ms. Leung, Dr. Sejvar, Dr. Soares, and Dr. Lanzieri report no disclosures.

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Keywords

GBS, Guillain-Barré Syndrome; Cytomegalovirus; CMV; Healthcare data

Introduction

Guillain-Barré syndrome (GBS) is clinically characterized by acute onset of areflexia or hyporeflexia and bilateral progressive limb weakness, with or without sensory involvement. GBS patients may present with autonomic disturbances, such as tachycardia, bradycardia, hypertension, hypotension, excessive or no sweating, and urinary retention. Clinical nadir occurs in 2–4 weeks, and up to 20–30% of GBS patients present with respiratory failure requiring ventilatory support during their acute illness.^{1, 2} Up to 15% die from acute complications. Although most patients with GBS recover over weeks or months, 20% have residual motor deficits after 1 year.^{1, 2}

GBS is an immune-mediated disease of the peripheral nerves, triggered by antecedent antigenic stimuli such as infections.^{1, 2} Antibodies and inflammatory cells produced in response to infections cross-react with epitopes on peripheral nerves and roots, leading to demyelination and/or axonal damage.³ *Campylobacter jejuni* and cytomegalovirus (CMV) are the most commonly isolated pathogens in GBS. More recently, Zika virus infection has also been identified as a potential trigger of GBS.⁴

In the United States, annual incidence of GBS was 1–2/100,000 persons in the 1970s and early 1980s.^{3, 5–7} A recent study estimated that 8–12% of GBS cases in the U.S. during 2009–2010 were due to *Campylobacter* infections.⁸ However, data on GBS with antecedent CMV infection in the United States are lacking. One study in France estimated GBS incidence of 0.6 to 2.2 cases per 1,000 cases of primary CMV infection, which is similar or greater than incidence among cases with *C. jejuni* infection (0.3 to 0.6 per 1,000).⁹ In this study, we describe incidence and clinical characteristics of GBS cases in the United States during 2009–2015 among persons with employer-sponsored insurance using a large administrative claims database. We also assessed characteristics of GBS cases with antecedent CMV and non-CMV infections.

Methods

Data source

We used the 2009–2015 Truven Health MarketScan® Commercial Claims and Encounters Database (MarketScan Databases, IBM Watson Health, Ann Arbor, MI).^{10, 11} This database includes employer-sponsored insurance healthcare claims for employees and their beneficiaries (defined as MarketScan enrollees) from all US states. The MarketScan databases contain data for over 200 million patients since 1995 and are large enough to allow creation of a nationally representative data sample of Americans with employer-sponsored health insurance, which represents approximately 50% of the US population¹². MarketScan enrollees are assigned a unique number that allows linkage of claims for each patient over time, but cannot be linked back to the patient. Information on enrollment

duration in the MarketScan databases is used to establish periods of continuous enrollment and ensure all healthcare claims data are captured during the observation period. During 2009–2015, the number of enrollees per year ranged from 31 to 57 million, including 2–4 million persons aged ≥ 65 years. The MarketScan databases contain demographic data, inpatient and outpatient diagnostic codes and medical procedures, and outpatient prescription fills. This analysis only included deidentified data; it was therefore deemed by the Centers for Disease Control and Prevention (CDC) not to be human subjects research and it did not require CDC's Institutional Review Board approval.

Case definitions

We defined a GBS patient as an enrollee with (1) an inpatient claim with GBS as the principal diagnosis code, based on the International Classification of Disease, 9th or 10th Revisions, Clinical Modification (ICD-9-CM code 357.0 or ICD-10-CM code G61.0)^{13–15} and (2) at least 1 inpatient claim for any of the following procedures: lumbar puncture, an EMG or nerve conduction study (NCS) within 45 days of the GBS onset date, which are typically part of the diagnostic procedures for patients with GBS [Appendix Table 1]. Data on drugs administered during hospitalization were not available and therefore we were unable to examine use of plasmapheresis and intravenous immunoglobulin (IVIG) among cases. GBS patients had to be enrolled continuously for 60 days prior to their first date of a GBS-coded inpatient claim, which we defined as the GBS onset date.

We assessed the following outcomes among GBS patients: duration of hospitalization, hospitalization in the intensive care unit (ICU), intubation, dysautonomia (diagnostic codes 337.9, G90.9), and death in the hospital [Appendix Table 1]. We also examined the proportion of GBS patients who had dysautonomia beyond the hospitalization in the subset of patients with continuous enrollment in the MarketScan databases 365 days after their GBS onset date. We also assessed antecedent infectious illnesses in the 60 days prior to the GBS onset date using ICD-9-CM or ICD-10-CM diagnostic codes from inpatient and outpatient claims; these included respiratory illness, pneumonia, gastrointestinal illness, and illnesses with any of the following 6 specific pathogens that have been shown to be temporally associated with GBS: *Campylobacter*, CMV, Epstein-Barr virus (EBV), hepatitis E, influenza, and *Mycoplasma pneumoniae* [Appendix Table 1]. Previous studies have looked at antecedent illness within 4–6 weeks prior to GBS onset;^{13, 15} to ensure we captured all antecedent infections, we extended this window to 60 days.

Analysis

We calculated annual GBS incidence as the number of GBS cases divided by the number of enrollees by year and used the Cochrane Armitage trend test to assess annual trends in incidence. To compare incidence by sex and age group, we used a log-linked Poisson binomial model. We compared selected characteristics by age group (<18 and ≥ 18 years) and by antecedent infectious illnesses (CMV and non-CMV infections) using Pearson χ^2 square or Fisher's exact test for categorical variables and *t*-test for continuous variables, and considered results with a *p*-value <0.05 as statistically significant. We performed all analyses using SAS version 9.4 (SAS Institute, Cary, North Carolina).

Results

Overall GBS incidence

We identified 4,612 enrollees with an inpatient claim with GBS as the principal diagnosis code, among whom 3,486 (75.6%) met our study criteria (i.e., ≥ 1 claim for GBS-related procedures and fulfilled enrollment criteria). GBS incidence was 1.2/100,000 persons in 2009 and 1.3/100,000 persons in 2015, with no significant annual trend ($p = 0.155$ [Figure 1]. Among 3,486 GBS patients, 1,932 (55.4%) were males and 3,198 (91.7%) were ≥ 18 years old [Table 1]. The average annual GBS incidence was higher in males (1.2/100,000) than females (0.9/100,000) ($p = 0.007$) and increased with age, from 0.4/100,000 in persons 0–17 years old to 2.0 in persons ≥ 65 years old ($p < 0.001$) [Table 1].

A total of 2,748 (78.8%) GBS patients had a claim for lumbar puncture; 2,286 (65.6%) for EMG, NCS or both. A higher proportion of GBS patients aged ≥ 18 years compared to those aged < 18 years had EMG or NCS (66.6% versus 53.8%; $p < 0.001$). The median length of hospital stay was 6 days (range, 0–106 days). Nearly half of GBS patients (1,701, 48.8%) were admitted to the ICU, 279 (8.0%) were intubated, and 41 (1.2%) died in the hospital. A higher proportion of GBS patients aged ≥ 18 years were intubated compared to those aged < 18 years (8.5% versus 3.8%; $p = 0.006$), but there were no differences for average duration of hospitalization, proportion with ICU admission, or death by age group. A higher proportion of deaths occurred among GBS patients with versus without ICU admission (1.9% versus 0.5%, $p < 0.001$), and patients who were intubated compared to those who were not (6.0% versus 0.8%; $p < 0.001$). The median hospital duration was longer for those who died in the hospital compared to the GBS patients who were discharged (12 days versus 6 days; $p = 0.001$). Only 71 (2.0%) GBS patients had dysautonomia with a higher proportion of GBS patients aged < 18 years with dysautonomia compared to those aged ≥ 18 years (6.1% versus 3.1%; $p = 0.025$). In the subset of GBS patients enrolled for 365 days after GBS onset, 1.8% (38/2,077) had dysautonomia, 18 (47.4%) with onset during hospitalization and 20 (52.6%) with onset after hospitalization. For 18 patients with more than one claim for dysautonomia, the median interval between the first and last claim coded for dysautonomia was 11 days (range, 1–291 days).

Nearly half of GBS patients (1,731, 48.8%) had a claim for an antecedent infectious illness, with a statistically significant higher proportion among those aged < 18 years compared to those ≥ 18 years (59.7% versus 49.6%, $p < 0.001$); almost half of these illnesses were coded as respiratory illnesses [Table 2]. Only 125 (3.6%) of all 3,486 GBS patients had a specific pathogen identified: 55 (44.0%) of 125 had influenza, 33 (26.4%) EBV, 18 (14.4%) CMV, 15 (12.0%) *Campylobacter*, and 9 (7.2%) *M. pneumoniae*; 2 out of the 125 GBS cases had infections with both CMV and EBV and an additional 4 had 2 non-CMV pathogens each [Table 2]. There was a statistically higher proportion of GBS patients aged < 18 years with EBV and *M. pneumoniae* infection compared to GBS patients aged ≥ 18 years [Table 2].

GBS and antecedent CMV infection

GBS patients with antecedent CMV infection tended to be younger than GBS patients without CMV antecedent infection (mean age of 39 years versus 47 years, $p = 0.038$). We

looked at the 125 GBS patients with a specific pathogen identified among patients with an antecedent infectious illness to assess differences between antecedent CMV infection (n = 18) versus other non-CMV pathogens (n = 107). After excluding the 2 with both CMV and EBV, the mean age among 16 GBS patients with antecedent CMV infection was 41 years versus 37 years among 107 GBS patients with other non-CMV antecedent infections ($p=0.3610$), with no other differences found [Table 3]. We identified one 37 year-old GBS patient with an antecedent CMV infection who died 26 days after being hospitalized for GBS; information on cause of death was not available. No deaths were identified in the GBS patients with other antecedent infections.

Discussion

Recent national estimates of GBS incidence in the United States are lacking. Using a national claims database, we found that GBS incidence in the United States during 2009–2015 was 1.1 to 1.3/100,000 persons, which is within the range reported in other studies in North America and Europe.^{3, 7, 15, 16} Additionally, we analyzed data on >3,000 GBS cases. As described in a systematic review of 13 studies GBS, the number of GBS cases per study was smaller, with a range of 33 to 418 GBS cases per study.³ GBS cases in our study appeared to be less severe than those reported in the literature. The median length of hospital stay in our study was 6 days, shorter than that reported in other studies (10–30 days).^{15, 17} In our study, only a small proportion required intubation (8%) or died (1%). Other studies reported respiratory failure requiring intubation in 13% to 25% of GBS cases, and deaths in 3% to 15%.^{1, 2, 7, 15, 17–19} Nearly 50% of our cases, however, required ICU stay during hospitalization. It is possible that our study captured GBS cases that were hospitalized for close monitoring due to the potentially rapid progression of disease, but had milder clinical presentation. A population-based study from Denmark which included diagnostic validation through review of medical records found that 35% of GBS patients were mildly affected defined by a disability score <3.¹⁸

Our findings of increasing GBS incidence with increasing age and slightly higher incidence in males than females are consistent with most other studies.^{2, 3, 7, 16, 20, 21} The age-specific incidence of GBS was lower than reported previously in the United States—1.5/100,000 in persons <15 years old, and 6.1 and 8.6/100,000 in persons 60–69 and 70–79 years old, respectively.²² It is possible that current rates in the United States are lower. Data from Europe up to 2014–2015 show rates of 2–3/100,000 in 60–69 year-olds, which is similar to the rate found in this study.^{17, 18, 21} The difference in current and previously published rates in the United States could be related, in part, to a large proportion of persons aged ≥65 years transitioning to Medicare insurance. The 2–4 million persons aged ≥65 years who remain in MarketScan are a subset of the Medicare-insured population with both employer-sponsored and Medicare insurance. Data from the 2016 Medicare expenditure panel survey show that 54% of Medicare beneficiaries have private insurance. We may have missed GBS-coded hospitalizations in persons aged ≥65 years if their claim was completely paid by Medicare insurance.

We found that 2% of the GBS patients developed dysautonomia, lower than the 16% reported in a study from Denmark.¹⁸ It is possible that we underestimated the proportion

with dysautonomia because we did not capture specific autonomic disturbances, such as cardiac arrhythmias and blood pressure fluctuations. Although the consequences of autonomic system involvement in GBS are generally minor, life-threatening cardiovascular complications may occur in the absence of severe motor impairment or respiratory failure. Among patients with severe GBS who required ICU admission or mechanical ventilation, 7–34% of patients presented with potentially serious bradyarrhythmias.^{23–25}

In published literature, approximately 40–70% of GBS patients report an antecedent infectious illness,^{1, 7, 15, 16, 20} consistent with that found in our study. The range in estimates might be due to different methods in ascertaining and defining GBS cases, and different populations. Other studies have used a 4–6 week window to examine antecedent infections; the proportion with an antecedent infection were similar using a 45-day versus 60-day window (49% versus 50%). Only a minority (7.1%) of the 1,758 with an antecedent illness had a specific pathogen identified. GBS patients <18 years old were more likely than those ≥18 years old to have an antecedent illness, particularly EBV, which was one of the most common pathogens identified.

CMV infection is considered the second most common infection preceding GBS.²⁶ One population-based study from Iceland found 23% of GBS cases tested for CMV had confirmed infection, and 33% tested had *C. jejuni* infection.¹⁷ Although the number of GBS patients with antecedent CMV infection in our study was small, those tended to be younger than GBS patients without CMV antecedent infections, as reported in two studies from Europe.^{9, 27} Studies from Europe and North America have described more severe acute disease for GBS cases with antecedent CMV infection,^{20, 26, 27} and in our study the proportion of GBS patients requiring intubation was higher among those with antecedent CMV infection than other infections, although the difference was not statistically significant. With only 125 with a specific pathogen identified, and 18 with antecedent CMV infection; additional studies are needed to understand GBS and antecedent infectious illnesses. Since CMV infection in immunocompetent persons is often asymptomatic or present with non-specific symptoms, these cases may be missed²⁸.

Our study had a number of limitations. We relied on diagnostic and procedural codes from an administrative database and did not have access to medical records, laboratory testing and results, or drugs administered during hospitalization. Prior studies have found that the sensitivity for identifying diagnostic codes for GBS ranged from 79–90% and the positive predictive value ranged from 55–71%, depending on the data source.^{18, 29, 30} We were unable to abstract clinical characteristics to further confirm GBS diagnoses based on standard criteria.³¹ Since we did not have medical records, we did not have exact dates of onset of GBS and antecedent illnesses. Additionally, without the results of the lumbar puncture, EMG, or NCS, it is possible that some of these persons may have had clinical diagnoses other than GBS, such as porphyria, HIV, botulinum, and paraneoplastic syndrome. It is also possible that the GBS cases were milder than cases published in other studies. We were unable to capture deaths that occurred outside of the hospital. Lastly, our data are from a convenience sample of persons with private employer-sponsored insurance and may not be generalizable to other populations, such as persons with publicly-funded insurance or no

insurance and data may have been missed in healthcare visits that were not submitted for insurance reimbursement.

Conclusions

This study used data from a large national healthcare claims database to provide the most current data on incidence of GBS in the United States. GBS incidence remained stable at about 1/100,000 persons during 2009–2015. Although half of GBS patients had a prior illness, only a minority had a specific pathogen identified. Larger datasets with more robust laboratory diagnostic testing may be able to discern features of CMV-associated GBS. Further studies utilizing electronic medical records would be useful to provide more information on antecedent illnesses including specific pathogens as well as in-depth description of the clinical spectrum of GBS, including manifestations during the acute phase of the disease, GBS subtypes, long-term residual deficits, and impact on quality of life.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We thank Mary Ann Hall for her editorial assistance and thoughtful review of the paper.

Financial Support: This project did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

1. Hughes RA, Cornblath DR. Guillain-Barre syndrome. *Lancet* (London, England) 2005;366:1653–1666.
2. Willison HJ, Jacobs BC, van Doorn PA. Guillain-Barre syndrome. *Lancet* (London, England) 2016;388:717–727.
3. Sejvar JJ, Baughman AL, Wise M, Morgan OW. Population incidence of Guillain-Barre syndrome: a systematic review and meta-analysis. *Neuroepidemiology* 2011;36:123–133. [PubMed: 21422765]
4. Counotte MJ, Egli-Gany D, Riesen M, et al. Zika virus infection as a cause of congenital brain abnormalities and Guillain-Barre syndrome: From systematic review to living systematic review. *F1000Research* 2018;7:196. [PubMed: 30631437]
5. Beghi E, Kurland LT, Mulder DW, Wiederholt WC. Guillain-Barre syndrome. Clinicoepidemiologic features and effect of influenza vaccine. *Archives of neurology* 1985;42:1053–1057. [PubMed: 4051833]
6. Kaplan JE, Schonberger LB, Hurwitz ES, Katona P. Guillain-Barre syndrome in the United States, 1978–1981: additional observations from the national surveillance system. *Neurology* 1983;33:633–637. [PubMed: 6682501]
7. Shui IM, Rett MD, Weintraub E, et al. Guillain-Barre syndrome incidence in a large United States cohort (2000–2009). *Neuroepidemiology* 2012;39:109–115. [PubMed: 22846726]
8. Halpin AL, Gu W, Wise ME, Sejvar JJ, Hoekstra RM, Mahon BE. Post-Campylobacter Guillain Barre Syndrome in the USA: secondary analysis of surveillance data collected during the 2009–2010 novel Influenza A (H1N1) vaccination campaign. *Epidemiology and infection* 2018;146:1740–1745. [PubMed: 29986777]
9. Orlikowski D, Porcher R, Sivadon-Tardy V, et al. Guillain-Barre syndrome following primary cytomegalovirus infection: a prospective cohort study. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2011;52:837–844. [PubMed: 21427390]

10. Quint JB. Health Research Data for the Real World: The MarketScan Databases. Truven Health Analytics White Paper. [online]. Available at: <https://marketscan.truvenhealth.com/marketscanuniversity/publications/2015%20MarketScan%20white%20paper.pdf>. Accessed Feb 7, 2017.
11. Shoffstall AJ, Gaebler JA, Kreher NC, et al. The high direct medical costs of Prader-Willi syndrome. *The Journal of pediatrics* 2016;175:137–143. [PubMed: 27283463]
12. Quint JB. Health Research Data for the Real World: The MarketScan Databases. Truven Health Analytics White Paper [online]. Available at: <https://marketscan.truvenhealth.com/marketscanuniversity/publications/2015%20MarketScan%20white%20paper.pdf>. Accessed Feb 7, 2017.
13. Burwen DR, Sandhu SK, MaCurdy TE, et al. Surveillance for Guillain-Barre syndrome after influenza vaccination among the Medicare population, 2009–2010. *American journal of public health* 2012;102:1921–1927. [PubMed: 22970693]
14. Inokuchi H, Yasunaga H, Nakahara Y, et al. Effect of rehabilitation on mortality of patients with Guillain-Barre Syndrome: a propensity-matched analysis using nationwide database. *European journal of physical and rehabilitation medicine* 2014;50:439–446. [PubMed: 24651152]
15. Salinas JL, Major CG, Pastula DM, et al. Incidence and clinical characteristics of Guillain-Barre syndrome before the introduction of Zika virus in Puerto Rico. *Journal of the neurological sciences* 2017;377:102–106. [PubMed: 28477675]
16. McGrogan A, Madle GC, Seaman HE, de Vries CS. The epidemiology of Guillain-Barre syndrome worldwide. A systematic literature review. *Neuroepidemiology* 2009;32:150–163. [PubMed: 19088488]
17. Hafsteinsdottir B, Olafsson E, Jakobsson F. Incidence and outcome of Guillain-Barre syndrome in Iceland: A population-based study. *Acta neurologica Scandinavica* 2018;138:454–458. [PubMed: 30019469]
18. Al-Hakem H, Sindrup SH, Andersen H, et al. Guillain-Barre syndrome in Denmark: a population-based study on epidemiology, diagnosis and clinical severity. *Journal of neurology* 2018.
19. Styczynski AR, Malta J, Krow-Lucal ER, et al. Increased rates of Guillain-Barre syndrome associated with Zika virus outbreak in the Salvador metropolitan area, Brazil. *PLoS neglected tropical diseases* 2017;11:e0005869. [PubMed: 28854206]
20. Hughes RA, Rees JH. Clinical and epidemiologic features of Guillain-Barre syndrome. *The Journal of infectious diseases* 1997;176 Suppl 2:S92–98. [PubMed: 9396689]
21. Granieri E, Andreasi NG, De Martin P, et al. Incidence study of Guillain-Barre syndrome in the province of Ferrara, Northern Italy, between 2003 and 2017. A 40-year follow-up. *Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology* 2019;40:603–609.
22. Prevots DR, Sutter RW. Assessment of Guillain-Barre syndrome mortality and morbidity in the United States: implications for acute flaccid paralysis surveillance. *The Journal of infectious diseases* 1997;175 Suppl 1:S151–155. [PubMed: 9203708]
23. Flachenecker P. Autonomic dysfunction in Guillain-Barre syndrome and multiple sclerosis. *Journal of neurology* 2007;254 Suppl 2:ii96–101. [PubMed: 17503142]
24. Pfeiffer G, Schiller B, Kruse J, Netzer J. Indicators of dysautonomia in severe Guillain-Barre syndrome. *Journal of neurology* 1999;246:1015–1022. [PubMed: 10631632]
25. Winer JB, Hughes RA, Anderson MJ, Jones DM, Kangro H, Watkins RP. A prospective study of acute idiopathic neuropathy. II. Antecedent events. *Journal of neurology, neurosurgery, and psychiatry* 1988;51:613–618.
26. Hughes RA, Hadden RD, Gregson NA, Smith KJ. Pathogenesis of Guillain-Barre syndrome. *Journal of neuroimmunology* 1999;100:74–97. [PubMed: 10695718]
27. Visser LH, van der Meche FG, Meulstee J, et al. Cytomegalovirus infection and Guillain-Barre syndrome: the clinical, electrophysiologic, and prognostic features. *Dutch Guillain-Barre Study Group. Neurology* 1996;47:668–673. [PubMed: 8797462]
28. Stagno SBW. Cytomegalovirus In: Remington JSKJ, Wilson CB, Baker CJ, ed. *Infectious Disease of the Fetus and Newborn Infant*. Philadelphia, PA: Wb Saunders Co, 2006: 389–424.

29. Bogliun G, Beghi E. Validity of hospital discharge diagnoses for public health surveillance of the Guillain-Barre syndrome. *Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology* 2002;23:113–117.
30. Koobatian TJ, Birkhead GS, Schramm MM, Vogt RL. The use of hospital discharge data for public health surveillance of Guillain-Barre syndrome. *Annals of neurology* 1991;30:618–621. [PubMed: 1789689]
31. Sejvar JJ, Kohl KS, Gidudu J, et al. Guillain-Barre syndrome and Fisher syndrome: case definitions and guidelines for collection, analysis, and presentation of immunization safety data. *Vaccine* 2011;29:599–612. [PubMed: 20600491]

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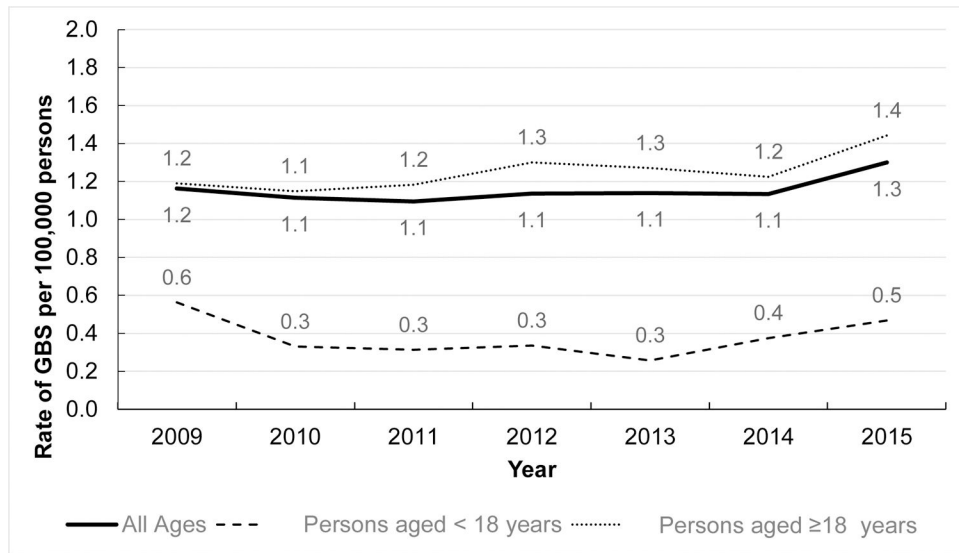


Figure 1.
Incidence of Guillain-Barré Syndrome (GBS) per 100,000 persons, MarketScan 2009–2015

Table 1.

Characteristics of Guillain-Barré Syndrome (GBS) patients and average annual GBS incidence by age and sex, 2009–2015

	GBS Patients, 2009–2015 N = 3,486 n (%)	Average Annual GBS Incidence per 100,000, 2009–2015
Sex		
Male	1,932 (55%)	1.2
Female	1,554 (45%)	0.9
Age Group (years)		
0–17	288 (8%)	0.4
18–34	539 (15%)	0.7
35–44	518 (15%)	1.0
45–54	691 (20%)	1.3
55–64	954 (27%)	2.0
≥65	496 (14%)	2.0

Table 2.

Frequency of Guillain-Barré Syndrome (GBS)-related procedures, GBS severity and outcomes, and infections and vaccinations within 60 days prior to GBS onset, MarketScan 2009–2015 (N = 3,532)

	All Ages N = 3,486		0–17 years N = 288		≥18 years N = 3,198		p-value by age group
Variable	#	%	#	%	#	%	
GBS-related procedures ^a							
Lumbar puncture	2748	78.8%	220	76.4%	2528	79.0%	0.299
EMG or NCS	2286	65.6%	155	53.8%	2131	66.6%	<.001
GBS Severity/Outcomes							
ICU Hospitalization	1701	48.8%	139	48.3%	1588	49.7%	0.851
Intubation	279	8.0%	11	3.8%	273	8.5%	0.006
Died	41	1.2%	1	0.3%	41	1.3%	0.253 *
Dysautonomia	71	2.0%	11	6.1%	60	3.1%	0.025
Infection 60 days before GBS Onset	1731	49.7%	172	59.7%	1586	49.6%	<.001
Respiratory	1598	45.8%	160	55.6%	1462	45.7%	<.001
Pneumonia	295	8.5%	20	6.9%	284	8.9%	0.334
Gastrointestinal Infection	241	6.9%	21	7.3%	225	7.0%	0.792
Specific Pathogen ^b	125	3.6%	23	8.0%	102	3.2%	<.001
CMV	18	0.5%	2	0.7%	16	0.5%	0.656 *
Non-CMV	109	3.1%	22	7.6%	87	2.7%	<.001
Campylobacter	15	0.4%	1	0.3%	14	0.4%	1.000 *
EBV	33	0.9%	10	3.5%	23	0.7%	<.001 *
Hepatitis E	1	0.0%	0	0.0%	1	0.0%	1.000 *
Influenza	55	1.6%	8	2.8%	47	1.4%	0.130 *
Mycoplasma pneumonia	9	0.3%	5	1.7%	4	0.1%	<.001 *

* Fisher's exact test used.

^a GBS-related procedures that occurred 45 before through 45 days after GBS onset date.

^b There were a total of 125 GBS cases with an antecedent illness with a specific pathogen identified. Two of the 125 GBS cases had claims for both CMV and EBV. An additional 4 GBS cases had 2 non-CMV related illnesses each.

Table 3.

Characteristics of Guillain-Barré Syndrome (GBS) patients with antecedent CMV infection (N = 18) and non-CMV infections (N = 107), MarketScan 2009–2015^a

Variable	Persons with GBS and CMV N=18		Persons with GBS and non-CMV Infections (Campylobacter, Epstein-Barr virus, hepatitis E, influenza, <i>Mycoplasma pneumoniae</i>) N=107		p-value ^d
	#	%	#	%	
Year					
2009	2	11.1%	22	20.6%	
2010	1	5.6%	9	8.4%	
2011	4	22.2%	17	15.9%	
2012	4	22.2%	14	13.1%	
2013	5	27.8%	11	10.3%	
2014	1	5.6%	15	14.0%	
2015	1	5.6%	19	17.8%	
Age group (years)					
0–17	2	11.1%	21	19.6%	
18–34	5	27.8%	28	26.2%	
35–44	5	27.8%	16	15.0%	
45–54	1	5.6%	13	12.1%	
55–64	4	22.2%	21	19.6%	
≥65	1	5.6%	8	7.5%	
Gender					1.0000
Female	10	55.6%	54	50.5%	
GBS-related procedures^b					
Lumbar puncture	15	83.3%	91	85.0%	0.713
EMG or NCS	13	72.2%	63	58.9%	0.278
GBS Severity/Outcomes					
Dysautonomia ^c	1	5.6%	3	2.8%	1.000
ICU Hospitalization	9	50.0%	58	54.2%	0.793
Intubation	5	27.8%	17	15.9%	0.473
Died	1	5.6%	0	0.0%	0.130
Median Duration of Hospitalization (range), in days	7 (1–38 days)		7 (0–34 days)		0.811

^aThere were a total of 125 GBS cases with an antecedent infection with a specific pathogen identified. Two of the 125 GBS cases had claims for both CMV and EBV and are included in the frequencies of persons with GBS and CMV.

^bGBS-related procedures that occurred within –45 to 45 days of GBS onset date.

^cProportion of persons with dysautonomia among persons enrolled over the 14-month interval ranging from 2 months before through 12 months after GBS onset date (N = 2,105, 180 in persons aged <18 years and 1,925 in persons aged ≥18 years).

^dStatistical analysis excludes the 2 GBS cases with both CMV and EBV from the comparison of GBS patients with and without CMV.