Clinical Infectious Diseases

MAJOR ARTICLE

Estimating Risk of Guillain-Barré Syndrome in US Medicare-Enrolled Older Adults Following Medically Attended Respiratory Syncytial Virus Disease: A Self-Controlled Case Series Analysis

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Background: Guillain-Barré syndrome (GBS) is considered a rare complication of viral respiratory infections (e.g., influenza and SARS-CoV-2), however its association with RSV infection has not been studied. We performed a self-controlled case series analysis to estimate GBS risk following medically attended RSV disease among older adults.

Methods: We identified adults aged ≥65 years with medically attended RSV disease and incident inpatient GBS using specific ICD codes, excluding those with prior GBS, from the US Medicare claims data (2011–2024). Risk period was 1 to 42 days post-RSV disease index date; the control period encompassed −180 to −22 days and 43 to 180 days of RSV disease index date. Conditional Poisson regression estimated RSV-related GBS incidence rate ratios (IRRs), adjusting for seasonality and viral activities. Medicare data policies prohibit cell case counts <11 from being displayed.

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Results: Among 452,471 eligible patients with RSV disease, <11 incident GBS cases occurred in the risk period and 34 during the control period. The adjusted IRR for GBS post RSV disease was 2.11 (95% CI: 1.01–4.37), consistent across sensitivity analyses of alternative risk/control periods and after excluding coinfections. The IRR increased to 2.59 (1.17–5.73) after ICD-10 code adoption, with a marked rise among patients aged ≥75 years (3.98 [1.45–10.91]).

Conclusion: GBS risk increases after RSV disease compared to control periods not temporally adjacent to RSV disease, with an effect particularly evident among patients aged ≥75 years. RSV should be recognized as one of the pathogens that may rarely lead to GBS.

Keywords: Guillain-Barré syndrome; incidence rate ratios; older adults; RSV

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INTRODUCTION

Guillain-Barré syndrome (GBS) is a rare neurological disorder involving autoimmune-mediated destruction of peripheral nerves leading to acute neuromuscular paralysis [1, 2]. Globally, the burden of GBS has been increasing, with a 6.4% rise in age-standardized prevalence between 1990 and 2019 [3] and a 3.8% change annually in age-adjusted mortality between 2014 and 2020 [4]. The age-specific GBS rate also increases with age, rising from 0.62 cases per 100,000 person-years among persons <9 years of age to 2.66 cases per 100,000 person-years among those aged 80–89 years [5]. In 2019, GBS incidence among US Medicare-enrolled adults aged ≥65 years was 4.6 cases per 100,000 person-years [6]. The estimated annual economic burden of GBS in the US is $1.7 billion, highlighting the substantial lifetime health and financial impact of the disease [7].

GBS may be triggered by bacterial or viral infections, most commonly respiratory or gastrointestinal infections [2]. The most frequent infectious GBS trigger is *Campylobacter jejuni,* a cause of acute gastroenteritis [1, 2]. Other implicated pathogens include cytomegalovirus, Epstein-Barr virus, human immunodeficiency virus, chikungunya virus, Zika virus [8], SARS-CoV-2 [9], varicella-zoster virus [10], influenza, and *Mycoplasma pneumoniae* [11]. GBS may very rarely develop in the days or weeks after certain vaccinations, such as influenza [12], adenovirus-vector SARS-CoV-2 vaccines (ChAdOx1-S and Ad.26.COV2.S) [13-15], and recombinant zoster vaccine [16]. Also, recently, GBS has been identified as a potential safety concern for RSV protein subunit vaccines among older adults [17].

While a few case reports have suggested a potential relationship between GBS and RSV disease in both pediatric [18, 19] and adult [20, 21] populations, the population-based risk of GBS following RSV infection in adults has not been studied yet. Studying such an association is challenging primarily due to infrequent RSV testing rates among adults [22] and the rarity of GBS. Although standard-of-care diagnosis is infrequent, based on prospective studies, the US RSV

disease burden is considerable, with an estimated 159,000 RSV-related hospitalizations and 9,500–12,700 deaths annually among adults aged ≥65 years [23, 24]. We performed a retrospective, self-controlled case series (SCCS) analysis to estimate the risk of incident GBS in older adults following medically attended RSV disease.

METHODS

Data source

In this SCCS analysis, we utilized US Centers for Medicare and Medicaid Services (CMS) administrative claims databases to assess the GBS risk following medically attended RSV disease among beneficiaries enrolled in Medicare Fee-for-Service (FFS; Parts A and B; data available from 01 January 2010 through 31 December 2024) and Medicare Advantage (Part C; data available from 01 January 2017 to 31 December 2022). The database contained enrollment information and adjudicated claims, and all available claim files were assessed including inpatient care, skilled nursing facility care, hospice care, home health, hospital outpatient services, durable medical equipment (DME), physician services, and other non-institutional services. The RESearch Data Assistance Center reports that Medicare covers ~96% of all US citizens aged ≥65 years [25]. All Medicare claims structured data were stored within the Chronic Conditions Warehouse Virtual Research Data Center; a secure research environment only accessible to approved users. The databases were de-identified and certified by an independent third party to comply with the Health Insurance Portability and Accountability Act (HIPAA) of 1996. Furthermore, these data were exempted from privacy laws and the need for informed consent. The study adhered to all legal and regulatory requirements.

Study Design, Setting, and Population

Patient identification for the primary SCCS analysis is outlined in Figure 1. The primary SCCS analysis included US Medicare beneficiaries (a) enrolled in Medicare FFS Parts A and B between 01 January 2011 through 31 December 2024 or Medicare Advantage/Part C between 2017 to 2022, (b) aged ≥65 years, (c) with both RSV disease and a GBS outcome during the study period, considering only the first RSV disease episode in the observation period, and (d) with continuous enrollment applied as 12 months prior to GBS index date, and 6 months post RSV index date.

RSV disease was identified using RSV-specific International Classification of Diseases (ICD) diagnosis codes (Supplemental Table 1), i.e., administrative claims with a primary or secondary RSV diagnosis code from any care settings, including outpatient visits, inpatient visits, home health, hospice, skilled nursing facility, DME, and carrier claims (which included non-institutional providers). The RSV identification period was from 01 July 2011 through 30 June 2024 for Medicare FFS and from 01 July 2017 through 30 June 2022 for Medical Advantage. RSV index date was the earliest date of the RSV diagnosis during the identification period.

GBS events were identified by a GBS ICD code (Supplemental Table 1) in the primary diagnosis position for a hospitalization event or in any position or any care setting with a hospitalization within 7 days. Patients with a prior history of a diagnosis for GBS or chronic inflammatory demyelinating polyneuritis in any setting within the preceding 12 months were excluded to ensure only new GBS cases were included. GBS event identification period was from 01 January 2011 to 31 December 2024.

A schematic for this SCCS study is presented in Figure 2. The primary risk period was defined as 1 to 42 days following the RSV index date, with a predefined buffer period of 21 days preceding the RSV index date (to account for potential delays in testing/diagnosis). The primary control period encompassed the remaining time within the one-year observation period (i.e., –180 to –22 days before and 43 to 180 days after the RSV index date).

Data collection

Patient demographics (such as age, sex, race, US geographic region) at the RSV index date and clinical characteristics (e.g., Charlson comorbidity index [CCI] and comorbid conditions) during the 6 months prior to the RSV index date were measured.

Statistical analyses

Baseline patient demographics and clinical characteristics were analyzed descriptively. For categorical variables, numbers and percentages were provided. For continuous variables, means and standard deviations were reported. Conditional Poisson regression was used to estimate the incidence rate ratios (IRRs) of GBS following medically attended RSV disease by comparing GBS incidence in the risk period with the control periods. Adjustments for seasonality (calendar-quarter months), and COVID-19/influenza activity as time-varying covariates were performed. Individuals were censored on the date of death, at disenrollment, or at end of study period, whichever came first. A range of sensitivity analyses were conducted to evaluate the robustness of the estimates: (a) restricting to the period after ICD-10 introduction (starting from 01 October 2015) to ensure consistent diagnostic coding, (b) using a post-infection only control period (43 to 180 days after the RSV index date) to avoid the inclusion of pre-infection time, which may be confounded by prodromal symptoms or delays in RSV diagnosis, (c) using a pre-infection only control period (−180 to −22 days before the RSV index date) to avoid including time that may overlap with a potential risk window, particularly if GBS onset occurs beyond the conventional 42-day post-infection period, (d) using a risk period of 1 to 21 days after the RSV index date to align with the biologically plausible window for GBS onset following viral infections, while accounting for potential delays in RSV diagnosis, (e) removing patients with coinfection of RSV and influenza/COVID-19 (defined within a two-week window) to reduce confounding and ensure that GBS risk is attributable to RSV infection alone, (f) removing patients who died within 30 days of GBS to evaluate the potential violation of assumption with the event-dependent observation period, and (g) further adjusting for the history of influenza, COVID-19, and Shingrix vaccination

in the primary analysis. We also stratified the primary analysis by age group (65–74 vs ≥75 years) to assess potential effect modification by age. Data were analyzed using SAS 9.4 (SAS Institute, Cary NC). Medicare data policies prohibit cell case counts <11 from being displayed, but these counts were available for use in calculations.

RESULTS

In the primary analysis spanning 01 January 2011 to 31 December 2024, a total of 452,471 eligible patients with medically attended RSV disease were identified across Medicare FFS Parts A and B and Medicare Advantage Part C claims data. Among these eligible patients, <11 incident GBS cases were observed in the risk period of 1 to 42 days after the RSV index date, and 34 incident GBS cases in the primary control period (i.e., –180 to –22 days before and 43 to 180 days after the RSV index date). When the control period was limited to the post-infection period (43 to 180 days after the RSV index date), 15 incident GBS cases were identified. Among all incident GBS cases, 44.6% (25) were male, 39.3% (22) were aged 65–74 years, and majority were White (Table 1). Over half (62.5%) of the RSV index dates occurred between October and March. The mean (SD) for CCI was 4.33 (2.48).

The unadjusted and adjusted IRR of GBS following medically attended RSV disease are shown in Figure 3, using various risk and control periods. Overall, the adjusted IRR of GBS following medically attended RSV disease was 2.11 (95% CI: 1.01–4.37) when using the primary control period. The IRR estimates remained consistent when a post-infection only control period (aIRR=2.16; 95% CI: 0.92–5.04) or a pre-infection only control period (aIRR=2.21; 95% CI: 0.98–4.95) was applied. Similarly, the adjusted IRR remained consistent with a risk period of 1 to 21 days and the primary control period (aIRR=2.35; 95% CI: 0.97–5.71). When the analysis was restricted to the period after ICD-10 code introduction, the IRR estimate increased slightly (aIRR=2.59; 95% CI: 1.17–5.73).

In the sensitivity analysis limited to patients without coinfections of RSV with influenza/COVID-19, the adjusted IRR was 2.33 (95% CI: 1.12–4.87) (Figure 4). When patients who died within 30 days of GBS were excluded, the aIRR estimate was 2.05 (0.96– 4.39). Further adjustment for vaccination history (influenza, COVID-19, and Shingrix) yielded consistent estimates with the primary findings (Supplemental Table 2). In the age-stratified analysis, the IRR estimate was higher among patients aged ≥75 years (aIRR=2.46; 95% CI: 0.99–6.15) compared to those aged 65 to 74 years (aIRR=1.55; 95% CI: 0.43–5.60). After ICD-10 code introduction, this elevation was more evident in patients aged ≥75 years (aIRR=3.98; 95% CI: 1.45–10.91) compared to those aged 65 to 74 years (aIRR=1.31; 95% CI: 0.28–6.12).

DISCUSSION

We leveraged this large nationwide database to conduct the first study to investigate GBS risk following medically attended RSV disease. In our SCCS analysis of US Medicare beneficiaries aged ≥65 years, we identified a 2–2.5 fold overall increased risk of GBS in the 42 days following medically attended RSV disease compared to control periods not temporally adjacent to RSV disease (i.e., well before or after the risk period). GBS risk following RSV disease was elevated in both the primary analyses and sensitivity analyses, with the highest risk point estimate observed among those ≥75 years (2.5–4 fold increase).

These findings are consistent with the known ability of other respiratory viruses, such as influenza [26] and SARS-CoV-2 [27-29], to rarely provoke GBS events. A SCCS study reported an increased risk of GBS in the 1–28 days following a SARS-CoV-2-positive test (IRR=5.25; 95% CI: 3.00–9.18) [9]. Furthermore, a SCCS study [30] and systematic literature reviews [31, 32] have highlighted a potential correlation between the development of GBS and COVID-19. Similarly, a UK SCCS study found an increased incidence of GBS within 30 days (IRR=16.64; 95% CI: 9.37–29.54) and 90 days following a consultation for influenza-like illness (IRR=7.35; 95% CI: 4.36–12.38) [33]. No laboratory confirmation was included so respiratory viruses other than influenza may have contributed to the estimate. A study from Norway during the 2009 H1N1 influenza pandemic reported a hazard ratio of 4.89 (95% CI: 1.17–20.36) for GBS among patients within 42 days of a diagnosis of pandemic influenza [34]. RSV is known to have a similar post-infectious sequelae profile to influenza and COVID-19—including cardiac complications, increased risk of hospital readmission, and decline in pulmonary function and functional status [35]—and GBS may now be considered among these potential sequelae.

Additionally, our age-stratified analysis found a higher GBS risk following RSV disease in individuals aged ≥75 years (2.5–4 fold increase). This aligns with broader epidemiological data showing that GBS incidence increases with age—from 1.85 cases per 100,000 person-years in those aged 60–69 years to 2.66 cases per 100,000 person-years in those aged ≥80 years [5]. These findings underscore the increased vulnerability of older adults to post-infectious neurological complications. Multiple RSV vaccination programs specifically target those ≥75 years due to their high risk for severe RSV disease. For example, the UK National Health Services (NHS) recommends RSV vaccine for adults aged 75–79 years [36] and the US ACIP recommends universal vaccination for adults ≥75 years [37]. Our findings suggest that, in addition to preventing severe RSV disease in this population [38, 39], these programs may avert some GBS events that occur as a sequela of RSV disease.

GBS following respiratory infection is thought to result from an autoimmune response triggered by molecular mimicry, where the immune system mistakenly attacks peripheral nerves [1]. Additional mechanisms such as systemic inflammation and immune dysregulation may also contribute [1]. The observed 2–2.5 fold increase in incident GBS risk following medically attended RSV disease was lower than that observed with some other infections [33]. One potential

methodological reason for this was that the specific onset date for the RSV infections were uncertain, because RSV positivity was determined based on the timing of the associated medical visits or hospital admission rather than symptom onset or RSV test date. The imprecision in the available RSV infection timing may have attenuated our point estimates, making them conservative. One partial mitigation that was implemented was to incorporate a buffer period prior to the RSV-related medical visits or hospital admission to minimize inadvertent inclusion of RSV-exposed time in the control period, but less precise data on infection timing may have biased our IRR towards the null. Replication of this study in setting with linkage to RSV testing data, ideally of a high frequency, would allow for more precision in estimating the actual relative risk of GBS following RSV disease.

Although rare, some vaccines, such as those for herpes zoster [16] and certain influenza viruses [12], can trigger GBS, especially if the pathogen itself is linked to this condition. Also, recently, GBS has been identified as a potential risk for RSV protein subunit vaccines (i.e., bivalent RSVpreF and adjuvanted RSVpreF3) among older adults; a SCCS analysis by the US FDA estimated a 2 to 2.5 fold increase risk of GBS in the 42 days after RSV vaccination, respectively [17]. However, the related text in the FDA product labels note "available evidence is insufficient to establish a causal relationship" [40]. In another more recent US SCCS analysis, RSV subunit vaccines were associated with an elevated GBS risk [41], however, this study does not include medical chart validation of GBS diagnosis, seasonality adjustment, and event-dependent observation period (i.e., Farrington adjustment), which were all included in FDA's study, which may have biased the risk estimates.

Notably, the benefits of vaccination in preventing serious diseases have been agreed to substantially outweigh this risk, and vaccination has been documented to not increase risk of GBS relapse [16, 42]. For pathogens where the GBS IRR is greater for infection than vaccine [33], and where infection is common (e.g., RSV, influenza, and SARS-CoV-2), it is possible that the overall risk of GBS may be lower or equivalent among vaccinated versus unvaccinated populations, although this should be evaluated quantitatively. A simulation study that modelled the joint risk of GBS if influenza illness occurred in individuals who had been vaccinated suggested that, under many circumstances, vaccination is more likely to decrease rather than increase an individual's overall risk of acquiring GBS [43]. A similar analysis is warranted for RSV as more data emerges.

While we have identified an increased risk for GBS following RSV disease, as mentioned above, the magnitude may be underestimated due to the lack of precise timing on RSV infection date or RSV testing data, and so further research to more precisely estimate the IRR is needed to ensure such assessments are accurate. Additionally, overall vaccine risk-benefit profiles should consider all benefits and risks, not just those for a particular outcome, and should balance the potential increased risk of GBS from a given vaccine with the risk reduction it provides by preventing disease.

This study has several notable strengths. First, the SCCS design inherently accounts for potential time-invariant confounders, such as sex, race/ethnicity, geography, and underlying conditions, as comparisons are made between risk and control periods for the same individual instead of between individuals. This also allows for control of unmeasured confounders such as lifestyle factors. Second, we had access to a large national database of Medicare beneficiaries, providing reliable and generalizable estimates of GBS risk for older US adults. Third, adjusting for seasonality and various robust sensitivity analyses further enhanced the validity and reliability of the study results.

This study should be considered in the context of its limitations. First, all patients included in this study were enrolled in Medicare health plans (FFS Parts A and B or Medicare Advantage Part C) during the study period; thus, findings from this study may not be generalizable to uninsured populations, patients with health plans not represented in the database (such as those with employer-sponsored health insurance, or other government insurance), and those aged <65 years. Second, because medical and pharmaceutical claims are collected for the purpose of payment, there are inherent limitations to the use of claims databases for research. Coding errors may result in inaccurate or incomplete data, leading to potential exposure and outcome misclassification as discussed above. Despite these limitations, claims data remain a robust and valuable resource for examining healthcare outcomes in real-world settings, including rare conditions, such as GBS. It offers a comprehensive view of patient interactions across various healthcare systems, enabling the monitoring and identification of rare event outcomes. Third, SCCS studies do not necessarily eliminate potential for residual confounding from effects that are time varying [44], but we have accounted for several time-varying confounders in our adjusted analyses. Fourth, due to the unavailability of RSV testing data, RSV status was inferred using RSV-specific ICD codes. The specificity of these codes has been found to be almost perfect (99.8% to 100%), and so is unlikely to lead to misclassification of identified RSV disease [45, 46]. However, the poor sensitivity of these codes among older adults (2% to 6%) would lead to the exclusion of some RSV disease cases where GBS develops [45, 46]. Although this does not impact the validity of the findings, it affects the statistical power of the study.

Finally, GBS cases were identified based on the ICD 10 code diagnosis without confirmation by chart review, which is the approach used by many GBS SCCS studies. Studies have investigated the validity of such codes and found that a GBS code in the primary position for hospitalization (our case definition) had a ~70% positive predictive value (PPV) [17]. While differential PPVs for risk and control periods have been reported for vaccine studies (i.e., GBS diagnosis less likely to be confirmed in a risk period closer to vaccination) [17], this has not been reported for studies of post-infection GBS and thus IRRs derived from our analysis would not be expected to be impacted by imperfect PPV.

CONCLUSION

Our study found an increased risk of GBS among adults aged ≥65 years following medically attended RSV disease compared to control periods not in proximity to RSV disease, particularly among persons ≥75 years. RSV could be one of the viral respiratory pathogens that can lead to the rare complication of GBS. These data should be considered in risk-benefit analyses for RSV vaccines, particularly vaccines targeting older adults. Additional studies ideally including validation of GBS diagnosis and linked laboratory data for more precise exposure timing, are needed to confirm this relationship.

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Conflict of interest: Caihua Liang, Jennifer Judy, Erica L. Chilson, Scott P. Kelly, Qing Liu, and Elizabeth Begier are employees of Pfizer and may hold stock or stock options. Bradford D. Gessner was employed at Pfizer during this study. Jason D. Maynard and Heidi De Souza report no conflicts of interest.

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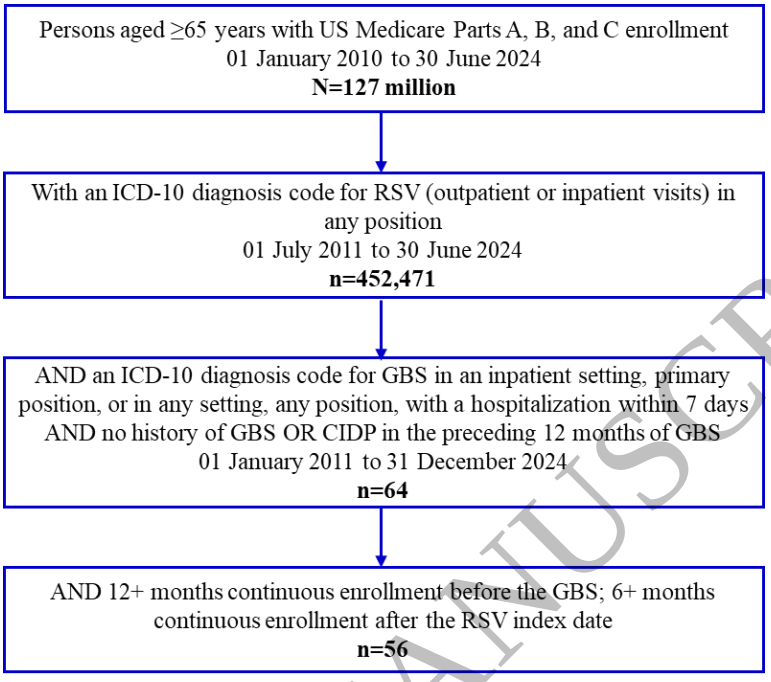
Data availability: All data related to the findings in this manuscript are available as references and will be shared upon request, while maintaining the necessary confidentiality for sensitive data.

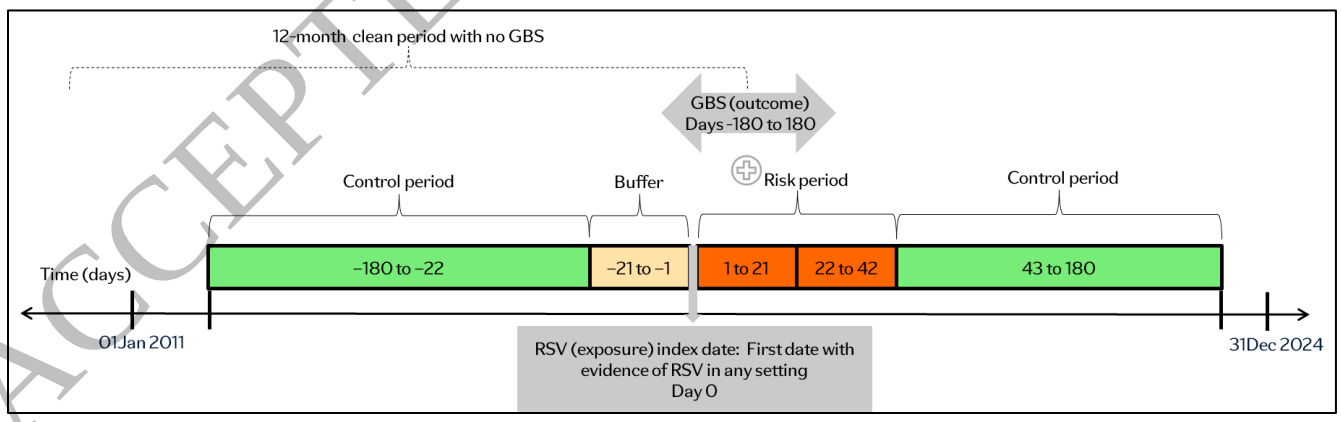
Author Contributions: Authors contributed as CL, JJ, ELC, BDG, EB: conceptualization; CL, QL, JDM, HDS: data curation; CL, JDM, HDS: formal analysis; BDG and EB: funding; CL, JJ, BDG and EB: investigation; CL and EB: methodology; CL, JJ: project administration; ELC, BDG, EB: resources and supervision; JDM and HDS: software and visualization; QL, JDM, HDS: Validation; CL: Writing original draft. All authors contributed to and approved the final version of the manuscript.

Figure 1. Patient identification for the primary SCCS analysis



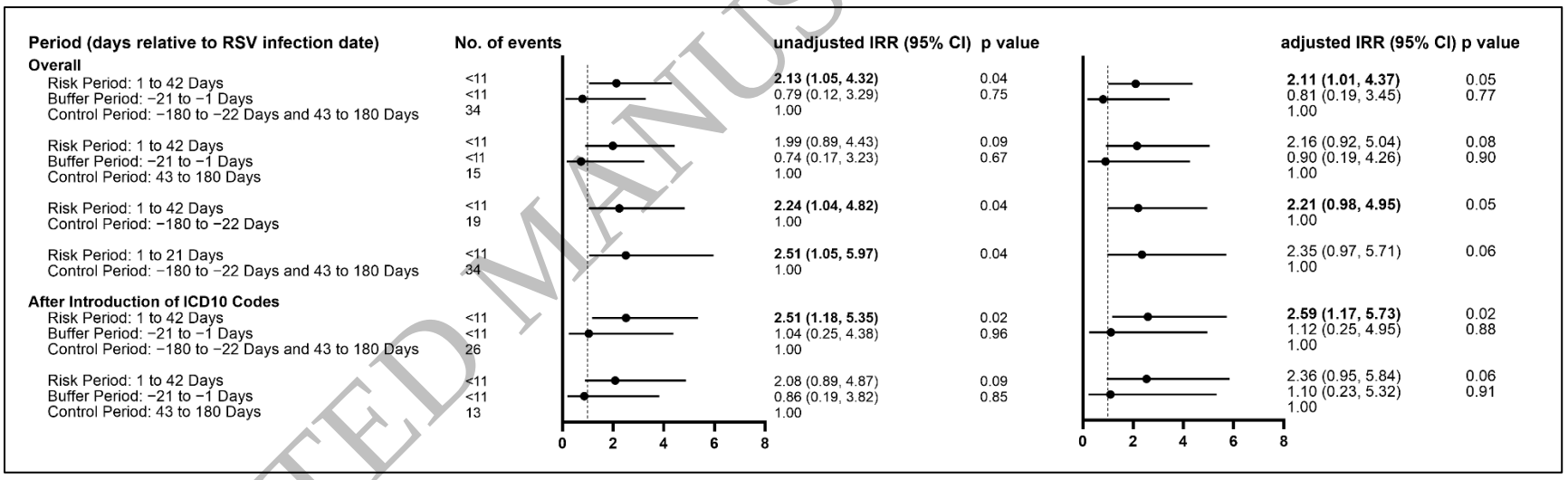
Abbreviations: CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; GBS, Guillain-Barré syndrome; ICD-10, International Classification of Diseases, 10th Revision; RSV, respiratory syncytial virus; SCCS, self-controlled case series; US, United States.

Figure 2. Schematic for the main SCCS analysis, US Medicare data, 01 January 2011–31 December 2024



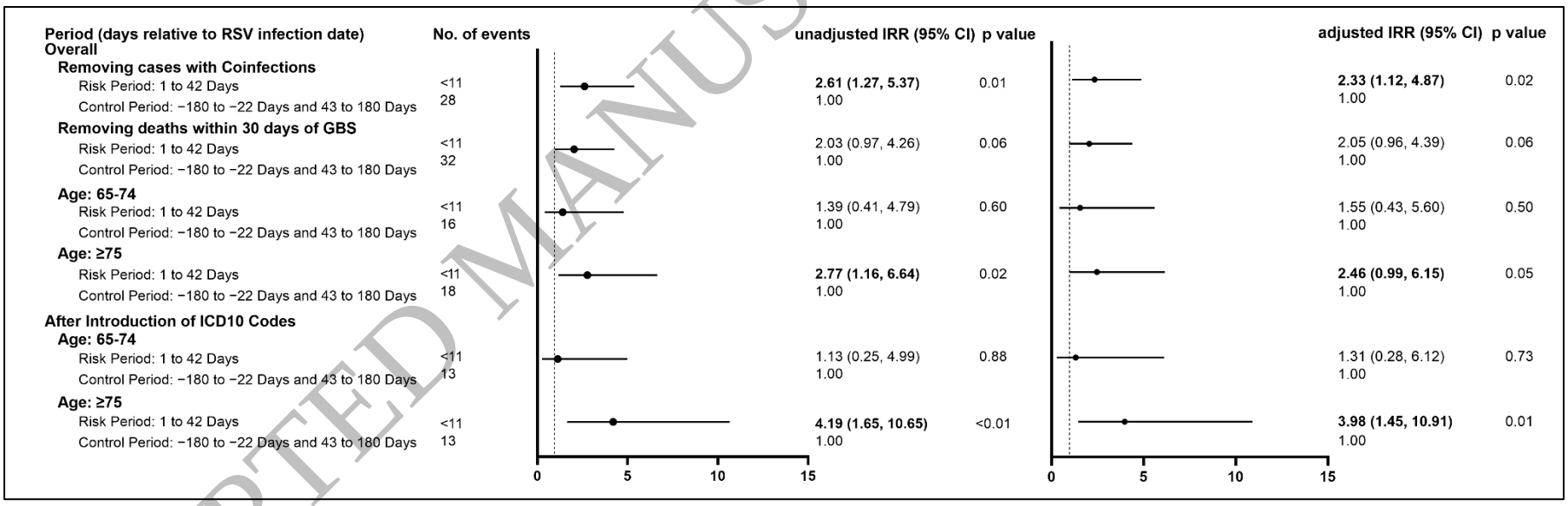
Abbreviations: GBS, Guillain-Barré syndrome; RSV, respiratory syncytial virus.

Figure 3. Unadjusted and adjusted incidence rate ratios of GBS following medically attended RSV disease



The aIRR accounted for time-varying covariates, including seasonality and influenza and COVID-19 activity.
Medicare data policies prohibit cell case counts <11 from being displayed but they may be used for calculations.
Abbreviations: CI, confidence interval; ICD-10, International Classification of Diseases, 10th Revision; IRR, incidence rate ratio

Figure 4. Sensitivity and stratified analyses for IRR estimation



The aIRR accounted for time-varying covariates, including seasonality and influenza and COVID-19 activity.
Medicare data policies prohibit cell case counts <11 from being displayed but they may be used for calculations.
Abbreviations: CI, confidence interval; ICD-10, International Classification of Diseases, 10th Revision; IRR, incidence rate ratio

Table 1. Demographics and clinical characteristics of US Medicare-enrolled patients between 01 January 2011 and 31 December 2024

Characteristics	Combined Medicare Parts A, B, and C
Age group, years, n (%)	
65–74	22 (39.3)
≥75	34 (60.7)
Age (continuous), years, Mean (SD)	77.83 (7.53)
Sex, n (%)	
Male	25 (44.6)
Female	31 (55.4)
Race, n (%)	
White	>40[a]
Non-White	<11
US geographic region, n (%)	
Northeast	22 (39.3)
Midwest	14 (25.0)
South	>11[a]
West	<11
RSV Index Year, n (%)	
ICD-9 (2011–2015)	<11
ICD-10 (2016–2024)	>40[a]
Q1 (Jan-Mar)	18 (32.1)
Q2 (Apr-Jun)	>11[a]
Q3 (Jul-Sep)	<11
Q4 (Oct-Dec)	17 (30.4)
CCI, Mean (SD)	4.33 (2.48)
Comorbidities of interest[b], n (%)	
Cardiovascular	49 (87.5)
Chronic cardiopulmonary	12 (21.4)
Chronic metabolic	<11
Diabetes	20 (35.7)
Frailty	31 (55.4)
Hematologic disorders	17 (30.4)
Immunocompromised	38 (67.9)
Kidney disorders	11 (19.6)
Liver disorders	<11
Lung disease	24 (42.9)
Other neurologic or neuromuscular	37 (66.1)
Obesity	<11
Co-infection, n (%)	

Influenza (within ±14 days of RSV)	<11
COVID-19 (within ±14 days of RSV)	<11

Note: Medicare data policies prohibit cell case counts <11 from being displayed but they may be used for calculations.

[a]Some counts >11 are also blinded per CMS rules to prevent reverse calculation of sensitive data.

[b]Comorbidities were identified during the 6 months prior to RSV disease.

Abbreviations: CCI, Charlson Comorbidity Index; COVID-19, coronavirus disease 2019; ICD-9/10, International Classification of Diseases, 9th or 10th Revision; IQR, interquartile range; RSV, respiratory syncytial virus; SCCS, self-controlled case series; SD, standard deviation.

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Alt text

Figure 1: Flowchart showing patient identification from screening to inclusion. A total of 56 patients were included in the study.

Figure 2: Schematic of the study design, illustrating control, buffer, and risk periods.

Figure 3: Forest plot depicting the unadjusted and adjusted incidence rate ratios (IRRs) during risk and buffer period in comparison to different control periods, for overall population and after introduction of ICD-10 codes.

Figure 4: Forest plot depicting the unadjusted and adjusted incidence rate ratios (IRRs) during risk and buffer period in comparison to different control periods in sensitivity and stratified analyese by removing cases with coinfection, removing deaths within 30 days of GBS for overall population, and by age for overall population and after introduction of ICD-10 codes.