Background Rates of Adverse Events of Special Interest for COVID-19 Vaccine Safety Monitoring in the United States, 2019–2020

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Target journal: Vaccine – abstract word limit: 300; manuscript word limit: 5,000; up to 10 tables/figures

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HIGHLIGHTS (3–5 bullets, 85 characters each, including spaces)

- Assessed background incidence rate of 17 AESI in 6 administrative claims databases. (84)
- Background rates varied by database and demographic characteristics. (70)
- Rates of most AESI increased with age and were higher among males. (68)
- AMI (Medicare) and anaphylaxis (all databases) rates showed seasonality. (74)
- AESI rates fluctuated in 2020, but most returned to 2019 levels after May 2020. (81)

ABSTRACT (300/300)

Background: The U.S. Food and Drug Administration (FDA) Biologics Effectiveness and Safety (BEST) Initiative conducts active surveillance of adverse events of special interest (AESI) after COVID-19 vaccination. Historical incidence rates (IRs) of AESI are comparators to evaluate safety.

Methods: We estimated IRs of 17 AESI in six administrative claims databases from January 1, 2019, to December 11, 2020: Medicare claims for adults ≥65 years and commercial claims (Blue Health Intelligence®, CVS Health, HealthCore Integrated Research Database, IBM® MarketScan® Commercial Database, Optum pre-adjudicated claims) for adults <65 years. IRs were estimated by sex, age, race/ethnicity (Medicare), and nursing home residency (Medicare) in 2019 and for specific periods in 2020.

Results: The study included >100 million enrollees annually. In 2019, rates of most AESI increased with age. However, compared with commercially insured adults, Medicare enrollees had lower IRs of anaphylaxis (11 vs. 12–19 per 100,000 person-years), appendicitis (80 vs. 117–155), and narcolepsy (38 vs. 41–53). Rates were higher in males than females for most AESI across databases and varied by race/ethnicity and nursing home status (Medicare). Acute myocardial infarction (Medicare) and anaphylaxis (all databases) IRs varied by season. IRs of most AESI were lower during March–May 2020 compared with March–May 2019 but returned to pre-pandemic levels after May 2020. However, rates of Bell's palsy, Guillain-Barré syndrome, narcolepsy, and hemorrhagic/non-hemorrhagic stroke remained lower in multiple databases after May 2020, whereas some AESI (e.g., disseminated intravascular coagulation) exhibited higher rates after May 2020 compared with 2019.

Conclusion: AESI background rates varied by database and demographics and fluctuated in March–December 2020, but most returned to pre-pandemic levels after May 2020. It is critical to standardize demographics and consider seasonal and other trends when comparing historical rates with post-vaccination AESI rates in the same database to evaluate COVID-19 vaccine safety.

Keywords

background rates, vaccine safety surveillance, COVID-19, adverse events

Abbreviations

AESI, Adverse Event of Special Interest

AMI, Acute Myocardial Infarction

BEST, CBER Biologics Effectiveness and Safety

BHI, Blue Health Intelligence

CBER, Center for Biologics Evaluation and Research

CDC, Centers for Disease Control and Prevention

CMS, Centers for Medicare & Medicaid Services

DIC, Disseminated Intravascular Coagulation

EUA, Emergency Use Authorization

DVT, Deep Vein Thrombosis

FDA, Food and Drug Administration

GBS, Guillain-Barré Syndrome

HCPCS, Healthcare Common Procedure Coding System

ICD-10-CM/PCS, International Classification of Diseases, Tenth Revision, Clinical Modification/Procedure Coding System

IR, Incidence Rate

IRR, Incidence Rate Ratio

79 ITP, Immune Thrombocytopenia

80 PE, Pulmonary Embolism

81 SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2

82 TTS, Thrombosis with Thrombocytopenia Syndrome

1. Introduction

Coronavirus disease 2019 (COVID-19) is a contagious respiratory illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). On January 30, 2020, the World Health Organization declared that the COVID-19 outbreak constituted a global public health emergency [1]. As of June 2022, there have been more than 530 million confirmed cases and more than 6 million deaths worldwide—the largest contributor is the United States [2]. Since December 2020, Pfizer-BioNTech, Moderna, Janssen, and Novavax COVID-19 vaccines have been available under emergency use authorization (EUA) or full licensure (Pfizer-BioNTech for individuals aged ≥16 years and Moderna for individuals ≥18 years) by the U.S. Food and Drug Administration (FDA). Additional COVID-19 vaccine candidates are under study in pre-licensure clinical trials [3].

As with all authorized or licensed medical products, clinical trials evaluating COVID-19 vaccine safety can have limitations. Even large phase III trials may have limited statistical power to detect rare adverse events [4]. Post-market surveillance of potential adverse events of special interest (AESI) is needed to continue monitoring the safety of authorized or approved COVID-19 vaccines once they are administered more broadly. An AESI is an untoward occurrence of medical concern that follows immunization but does not necessarily have a causal relationship with vaccination [5]. The FDA Center for Biologics Evaluation and Research (CBER) is monitoring the safety of authorized or approved COVID-19 vaccines using passive and active surveillance systems, in collaboration with other agencies [6]. The FDA Biologics Effectiveness and Safety (BEST) Initiative uses a broad network of large-scale data sources to rapidly monitor vaccine safety where rates of AESI in historical controls serve as comparator (expected) rates.

The background rate is the AESI's incidence rate (IR) estimated from historical cohorts. Background rates of AESI are important in vaccine safety monitoring because they may serve as one comparator to contextualize the observed IRs of the same AESI following vaccination in a similar

population. In addition, stratified AESI background IRs may provide more appropriate comparators than overall IRs for the respective stratum of vaccinated individuals. At the time of this study, published background rates of AESI in the U.S. population using multiple data sources and including both pre-COVID-19 (before 2020) and peri-COVID-19 (after March 2020) periods were limited [7]. Furthermore, the COVID-19 pandemic presented unprecedented challenges to the healthcare system and may have altered patients' care-seeking patterns and rates of reported AESI outcomes. Studies have reported that healthcare service utilization decreased in 2020 [8–10] but returned to near pre-pandemic rates in late 2020 [11].

Using administrative claims data sources in the BEST Initiative, this study estimated background rates of 17 AESI, overall and stratified by population characteristics in six data sources. We carefully evaluated monthly trends in IRs during 2019 and 2020 to better understand how the pandemic may have affected utilization patterns and AESI rates. In addition to AESI background rates, we estimated rates of a few negative control events during 2019 and 2020, which are considered unrelated to vaccination but may reflect changes in healthcare utilization over time.

2. Methods

2.1 Data sources

We used six administrative claims databases from the United States. Individuals aged ≥65 years with Medicare coverage were identified from Centers for Medicare & Medicaid Services (CMS) Medicare fee-for-service claims for beneficiaries enrolled in Medicare Parts A/B. We identified data on commercially insured adults aged <65 years and children aged <18 years from Blue Health Intelligence® (BHI) commercial claims, CVS Health (Aetna) commercial claims, the HealthCore Integrated Research Database®, the IBM® MarketScan® Commercial Database, and Optum pre-adjudicated commercial claims. BHI data were limited to claims for enrollees who received a biologic product, were pregnant, or were born after October 1, 2015. Appendix A herein includes descriptions of the data sources.

The study involved no personally identifiable information and the data used in this study were deidentified and anonymized before use. This study was conducted as a public health mandate and not as a research activity. Our study practices were performed in accordance with the Declaration of Helsinki guidelines.

2.2 Study period

The study period was from January 1, 2019, through December 11, 2020, when FDA issued the first EUA for a vaccine to prevent COVID-19. The observation period started January 1, 2018, to evaluate the clean period requirement (described in Section 2.4). For analysis of the MarketScan data, the study period ended October 31, 2020, to ensure data included in the study were at least 80% complete.

We divided the study period into the pre-COVID-19 period (calendar year 2019) and peri-COVID-19 period (March–October 2020 [MarketScan] and March–December 2020 [all other databases]). January and February 2020 were excluded. We further classified the peri-COVID-19 period into an initial period (March–May 2020) and a later period (June–October 2020 [MarketScan] and June–December 2020 [all other databases]). We chose these subperiods after observing that the rates of negative control events decreased during March–May 2020 but returned to pre-pandemic levels by June 2020.

2.3 AESI and negative control events

In selecting AESI, we considered serious events that have been studied in other vaccines, events that are suspected as possibly related to novel vaccine platforms or adjuvants, and events related to COVID-19 severity that may potentially relate to vaccine failure/immunogenicity (enhanced disease). Other considerations included recommendations from other surveillance research networks such as the Brighton Collaboration [12] and events specific to certain populations of interest such as pregnant or immunocompromised individuals [4, 13, 14]. During AESI selection, none of these events were observed in pre-authorization or pre-licensure studies. Some were seen in post-market data, but that was after our selection.

AESI were identified using International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) diagnosis codes. Development of administrative claims-based AESI algorithms was based on literature reviews and consultations with clinical experts. Claims data came from inpatient facilities, emergency departments, and/or other outpatient facilities and individual healthcare providers or professionals. The healthcare settings in which AESI and negative control events were captured differed by the event (see Supplemental Table 1). We evaluated 17 AESI (acute myocardial infarction [AMI], anaphylaxis, appendicitis, Bell's palsy, deep vein thrombosis [DVT], disseminated intravascular coagulation [DIC], encephalitis/encephalomyelitis, Guillain-Barré syndrome [GBS], hemorrhagic stroke, immune thrombocytopenia [ITP], myocarditis/pericarditis, narcolepsy, non-hemorrhagic stroke, pulmonary embolism [PE], transverse myelitis, unusual site thrombosis with thrombocytopenia [TTS], common site TTS) and three negative control events (colonic diverticulitis, hypertension, well-care visits) (Supplemental Table 1). The publicly posted study protocol includes further details of AESI algorithms [15]. Appendix B herein presents ICD-10-CM diagnosis codes used to identify AESI.

2.4 Study cohort construction

Within each data source, we constructed cohorts for each AESI and negative control event. The general study population included any individual who was enrolled in a medical plan for at least 1 day during the study period, who met age requirements at cohort entry (≥65 years for Medicare, 18–64 years for commercially insured adults, <18 years for commercially insured children [Supplemental Table 1]), and who met a clean period requirement before cohort entry. The clean period requirement was defined as having continuous enrollment for the entire pre-specified clean period and no observed AESI or negative control events (colonic diverticulitis and hypertension only) during the clean period. Clean periods were specific, and some differed for each AESI and negative control event (Supplemental Table 1).

2.5 Statistical analysis

Person-time at risk was calculated as the number of days between cohort entry and the end of follow-up. Individuals in the study population entered the cohort beginning January 1, 2019, or the date the clean period requirement was met (specific to each AESI or negative control event), whichever occurred later. Infants who were born before January 1, 2019 and were continuously enrolled from birth but had not reached the full length of the clean period on January 1 were assigned a cohort entry date of January 1, 2019, provided no AESI occurred during the shortened clean period before entry. For infants who were born during the study period and started enrollment within 31 days of birth, the cohort entry date was the date of birth. Individuals were followed until the earliest date of AESI/negative control event occurrence or censoring due to death, disenrollment, exceeding specified age range (e.g., AESI-specific age criteria, commercially insured population reaching 65 years), or the study period's end. After censoring, individuals could re-enter the same or a different AESI/negative control event cohort if they met another clean period requirement during the study period. Negative control event rates were not estimated in Optum data. Supplemental Figure 1 illustrates the accumulation of person-time at risk with several examples.

We calculated annual 2019, peri-COVID-19 (overall, initial, and later periods), and monthly 2019–2020 IRs for each AESI and negative control event within each data source by dividing the count of incident events during the time at risk in a specified period by the total person-time at risk during the same period. For example, we calculated the annual 2019 rate for a given AESI by dividing the number of incident events that occurred in 2019 by the total person-time at risk in 2019 within the AESI cohort, and we calculated the monthly rate of an AESI by dividing the number of incident events that occurred in a given month by the total person-time at risk in that month. Additionally, 2019 annual IRs were stratified by age and sex (all data sources), as well as race/ethnicity and nursing home residency status (Medicare only). The commercial databases did not have sufficient valid data on race/ethnicity.

IRs are presented as event counts per 100,000 person-years. In descriptive analyses, we calculated incident rate ratios (IRRs) to compare unadjusted IRs between subpopulation strata as well as between 2019 and the peri-COVID-19 periods (initial and later). Exact Poisson 95% confidence intervals (CIs) were calculated for each IR and IRR. Differences were considered when the 95% CI of the IRR did not overlap 1 or when the 95% CIs of IRs for two populations did not overlap. The main results focus on the Medicare population aged ≥65 years and adults aged 18–64 years. Findings among children (0–17 years) are presented briefly in Section 3.1.4 and in the supplemental materials.

2.6 Additional analysis

A report with more extensive results of this study, along with the results of additional analyses not included in this article, is on the BEST Initiative website [16]. The report presents results from an extended study period (2017–2020) and describes background rates of additional AESI and negative control events. The report also presents rates of AESI and negative control events in other subpopulations of interest (e.g., population with recent influenza vaccine). This article does not include those results due to limited space.

3. Results

3.1 Incidence rates of AESI and negative control events, pre- and peri-COVID-19 periods

The total number of eligible adults included in the 2019 analysis from all data sources ranged from approximately 55.5 million (for hypertension) to 110.2 million (for anaphylaxis), while for children, the number ranged from approximately 17.0 million (well-care visits) to 27.0 million (anaphylaxis) (Supplemental Table 2).

3.1.1. Incidence rates of AESI, pre-COVID-19 (2019)

For adults aged ≥65 years in Medicare, the top two AESI with the highest IRs per 100,000 person-years in the pre-COVID-19 period were DVT (1,331.0; 95% CI: 1,326.4–1,355.6) and AMI (1,297.5;

95% CI: 1,293.0–1,302.0), followed by non-hemorrhagic stroke (842.8; 95% CI: 839.2–846.4), PE (755.1; 95% CI: 751.7–758.5), common site TTS (362.3; 95% CI: 360.0–364.7), Bell's palsy (215.4; 95% CI: 213.6–217.2), and hemorrhagic stroke (205.3; 95% CI: 203.5–207.0) (Figure 1, Supplemental Table 3). All other AESI had pre-pandemic IRs under 100 per 100,000 person-years. The rarest events were transverse myelitis (3.4 per 100,000 person-years; 95% CI: 3.2–3.6), GBS (4.6; 95% CI: 4.4–4.9), and encephalitis/encephalomyelitis (9.8; 95% CI: 9.4–10.2).

In the commercially insured population aged 18–64 years, AMI, appendicitis, Bell's palsy, DVT, and PE had IRs of approximately 100 per 100,000 person-years or greater across data sources. IRs were highest for DVT (ranging from 226.5 in Optum to 285.5 in BHI). DIC, encephalitis/encephalomyelitis, GBS, transverse myelitis, and unusual site TTS had a rate below 10 per 100,000 person-years across the commercial insurance data sources. IRs were lowest for transverse myelitis (ranging from 1.3 in MarketScan to 2.0 in BHI).

3.1.2. Heterogeneity in AESI IRs across data sources, pre-COVID-19 (2019)

In 2019, adults aged ≥65 years in Medicare had lower IRs of anaphylaxis, appendicitis, narcolepsy, and well-care visits and higher IRs of all other AESI and negative control events compared with commercially insured adults aged 18–64 years (Figure 1, Supplemental Table 3).

There was also heterogeneity in the IRs of most AESI across the commercial insurance data sources. Rates were higher in BHI and Optum (and CIs did not overlap) than in the other commercial databases for 9 of the 17 AESI: AMI, anaphylaxis, appendicitis, Bell's palsy, ITP, myocarditis/pericarditis, narcolepsy, non-hemorrhagic stroke, and PE (Figure 1, Supplemental Table 3). The rates of DVT, DIC, hemorrhagic stroke, and TTS (unusual and common sites) were higher in BHI than in CVS Health, HealthCore, MarketScan, and Optum. Rates of colonic diverticulitis, hypertension, and well-care visits also were higher in BHI than in CVS Health, HealthCore, and MarketScan.

3.1.3. Variability of incidence rates during the pre- and peri-COVID-19 periods

Six AESI (AMI, appendicitis, Bell's palsy, DVT, GBS, narcolepsy) and all three negative control events had lower IRs across all six data sources during the peri-COVID-19 period than during 2019 (IRR<1 and 95% CI does not include 1) (Figure 1, Supplemental Table 3). IRs decreased during the peri-COVID-19 period in some data sources for anaphylaxis (BHI, CVS Health, HealthCore, MarketScan, Optum), hemorrhagic stroke (Medicare, MarketScan), ITP (Medicare, BHI, CVS Health, MarketScan, Optum), myocarditis/pericarditis (Medicare, MarketScan), non-hemorrhagic stroke (Medicare, BHI, CVS Health, HealthCore, MarketScan), transverse myelitis (BHI, HealthCore), and unusual site TTS (Medicare, MarketScan). Several AESI exhibited elevated IRs during the peri-COVID-19 period among some data sources, including DIC (Medicare, BHI, HealthCore), PE (BHI, CVS Health, HealthCore, Optum), and common site TTS (HealthCore). Rates of encephalitis/encephalomyelitis were similar in the peri-COVID-19 period and 2019 across all six data sources.

3.1.4. Incidence rates among children during the pre- and peri-COVID-19 periods

In 2019, most AESI among children showed low IRs at <10 per 100,000 person-years across all commercial data sources, except for anaphylaxis (24.5–31.3 per 100,000 person-years), appendicitis (106.6–127.5), Bell's palsy (21.1–24.9), and ITP (10.7–12.8) (Supplemental Figure 2 and Supplemental Table 4).

3.2 Monthly incidence rates of AESI, 2019 and 2020

3.2.1. Decrease of incidence rates in 2020 and return to pre-pandemic levels

Figures 2–7 display monthly rates of the AESI and negative control events for each data source. Across all data sources, monthly rates of negative control events showed a marked reduction during the initial peri-COVID-19 period, reaching the lowest value in April 2020. This reduction was followed by a return to similar 2019 levels after May 2020 (Figures 2–7). For adults aged ≥65 years in Medicare (Figure 2), IRs of most AESI reached their lowest value in April 2020, but exceptions included DIC, GBS,

myocarditis/pericarditis, transverse myelitis, and unusual site TTS. For commercially insured adults aged 18–64 years (Figures 3–7), IRs of five AESI also reached their lowest level in April 2020 (AMI, anaphylaxis, appendicitis, DVT, ITP) consistently across data sources.

Compared with 2019 annual IRs, rates during the initial peri-COVID-19 period were lower by more than 10% for most AESI across all data sources (IRR ranging from 0.5 to below 0.9 and 95% CI not including 1) (Supplemental Table 5). There were several exceptions with a higher rate in the initial peri-COVID-19 period or inconsistent trends across data sources. Specifically, DIC rates were elevated during the initial peri-COVID-19 period in BHI, HealthCore, and MarketScan. The IRs for nine AESI decreased 10% or more in the initial peri-COVID-19 period compared with 2019 in some data sources: AMI (Medicare, CVS Health, BHI, MarketScan), encephalitis/encephalomyelitis (Medicare, HealthCore, MarketScan), GBS (Medicare, BHI, CVS Health, MarketScan, Optum), hemorrhagic stroke (Medicare, MarketScan), non-hemorrhagic stroke (Medicare, BHI, CVS Health, HealthCore, MarketScan), PE (Medicare, BHI, CVS Health, HealthCore, MarketScan), transverse myelitis (BHI), common site TTS (Medicare, Optum), and unusual site TTS (Medicare, BHI, HealthCore, MarketScan, Optum).

During the later period of 2020 (June–October 2020 for MarketScan; June–December 2020 for all other data sources), rates of most AESI returned to levels similar to 2019 annual rates (IRR between 0.9 and 1.1 or the 95% CI for IRR including 1), although IRs of GBS were still low after May 2020 across all data sources (IRR ranging from 0.6–0.8). Five AESI remained lower than 90% of 2019 annual rates, with an IRR <0.9 in certain data sources: Bell's palsy (Medicare), narcolepsy (Medicare, CVS Health), hemorrhagic stroke and non-hemorrhagic stroke (MarketScan), and transverse myelitis (BHI). Six AESI exhibited an IR more than 10% higher than the corresponding 2019 annual rate in certain data sources: anaphylaxis (Medicare), DIC (Medicare, HealthCore), myocarditis/pericarditis (BHI), PE (BHI, CVS Health, HealthCore, Optum), and common and unusual site TTS (HealthCore).

3.2.2. Seasonality

For adults aged ≥65 years in 2019 Medicare data, IRs of anaphylaxis were lowest during the winter months (February: 6.6 per 100,000 person-years) and highest during the summer months (July: 16.9) (Figure 2). AMI had a peak IR of 1,408.8 per 100,000 person-years in March and a minimum IR of 1,178.8 per 100,000 person-years in August (data not shown). We observed similar seasonal trends in anaphylaxis in the commercial insurance data sources (Figures 3–7), with the lowest rates in April 2020 at 5.3 to 6.9 per 100,000 person-years and highest rates in August 2020 at 16.3 to 27.2 per 100,000 person-years.

3.3 Incidence rates by population characteristics, 2019

3.3.1. Sex

Table 1 compares 2019 IRs of the AESI between male and female adults via IRRs in each data source. IRs of six AESI (AMI, DVT, hemorrhagic stroke, myocarditis/pericarditis, non-hemorrhagic stroke, common site TTS) were higher for males in all data sources, ranging from 3% higher risk among males compared with females for DVT (IRR=1.03; 95% CI: 1.02–1.03) and non-hemorrhagic stroke (IRR=1.03; 95% CI: 1.02–1.04) in Medicare to more than threefold higher risk among males for AMI in Optum (IRR=3.08; 95% CI: 2.96–3.22). Additionally, six other AESI (appendicitis, DIC, encephalitis/encephalomyelitis, GBS, PE, unusual site TTS) had higher incidence rates for males than females across multiple data sources. Other AESI rates were lower for males than females across multiple data sources, including anaphylaxis (BHI, CVS Health, HealthCore, MarketScan), Bell's palsy (Medicare, BHI, CVS Health, HealthCore, MarketScan), and transverse myelitis (BHI, HealthCore, MarketScan). Additionally, rates of ITP and narcolepsy were lower in males than females across all the commercial insurance data sources but higher among males aged ≥65 years in Medicare.

3.3.2. Age group

Among commercially insured adults aged <65 years, 12 of the 17 AESI had higher IRs in older age groups than among individuals aged 18–25 years (reference group) across all five data sources in 2019

(Table 2). Rates of transverse myelitis were higher in some older age groups than in the reference group in all data sources except Optum. Rates of anaphylaxis, appendicitis, and narcolepsy in older age groups were lower than or similar to the corresponding rates in those aged 18–25 years. Compared with individuals aged 18–25 years, rates of encephalitis/encephalomyelitis were generally similar or lower for those aged 26–55 years but higher for those aged 56–64 years.

Among Medicare beneficiaries aged ≥65 years, rates of AESI also varied by age (Supplemental Table 6). Compared with individuals aged 65–74 years, 10 AESI (AMI, Bell's palsy, DVT, DIC, hemorrhagic and non-hemorrhagic stroke, ITP, myocarditis/pericarditis, PE, common site TTS) had higher rates among those aged ≥75 years, while rates of anaphylaxis, appendicitis, and unusual site TTS were lower among individuals aged ≥75 years.

3.3.3. Nursing home residency status (Medicare only)

Among adults aged ≥65 years in Medicare in 2019, nursing home residents had higher rates for 13 of the 17 AESI, ranging from 35% higher than rates among non-nursing home residents for Bell's palsy (IRR=1.35; 95% CI: 1.29–1.42) to almost threefold higher for DIC (IRR=2.93; 95% CI: 2.69–3.18) (Table 3). Additional AESI with higher rates among nursing home residents included AMI, DVT, encephalitis/encephalomyelitis, hemorrhagic stroke, ITP, myopericarditis/pericarditis, narcolepsy, non-hemorrhagic stroke, PE, transverse myelitis, and common site TTS. Rates of anaphylaxis, appendicitis, and GBS were lower for Medicare nursing home residents than non-residents, and rates of unusual site TTS did not differ by nursing home residency status.

3.3.4. Race/ethnicity (Medicare only)

For adults aged ≥65 years in Medicare, two AESI had higher IRs among people of color than their White counterparts (Supplemental Table 7). Compared with rates for White beneficiaries, rates of DIC were 92% higher for Asian (IRR=1.92; 95% CI: 1.71–2.15), more than twofold higher for Black (IRR=2.34; 95% CI: 2.21–2.48), 61% higher for Hispanic (IRR=1.61; 95% CI: 1.39–1.85), and 69% higher for North

American Native (IRR=1.69; 95% CI: 1.31–2.15) beneficiaries. Rates of hemorrhagic stroke were 48% higher for Asian (IRR=1.48; 95% CI: 1.41–1.56), 56% higher for Black (IRR=1.56; 95% CI: 1.51–1.60), 25% higher for Hispanic (IRR=1.25; 95% CI: 1.17–1.33), and 26% higher for North American Native (IRR=1.26; 95% CI: 1.12–1.42) beneficiaries. Rates of other AESI also displayed disparities that vary across race/ethnicity groups.

4. Discussion

The FDA BEST Initiative comprises large administrative claims data, electronic health records (EHRs), and linked claims-EHR databases. This study used six administrative claims databases in the BEST Initiative and included tens of millions of individuals to conduct one of the first large-scale assessments of AESI background rates in the United States using a common protocol, definitions, and analyses across databases. This study reports the background IRs of 17 AESI and three negative control events. The background rates are used to produce expected rates of AESI for comparison to the observed rates in populations post-COVID-19 vaccination in active surveillance studies to identify increased risks or safety concerns. Considerations in active surveillance monitoring include confounding, generalizability, and the COVID-19 pandemic's effect on AESI incidence, which this study may inform.

We found heterogeneity in the IRs of AESI among different data sources. For commercially insured adults younger than 65 years, we observed variability in AESI rates across the five commercial insurance data sources evaluated in this study. Insurance companies have more or less the same function and serve the same sector of the U.S. population (employees and their families insured through their employers) but may cover different geographic locations. All 17 AESI showed at least a 20% difference in rates among some commercial data sources (data not shown). For most AESI examined, IRs tended to be higher in BHI and Optum than in CVS Health, HealthCore, and MarketScan. The population represented in the BHI data may differ from other commercially insured populations in this study in that the BHI data were limited to individuals who received a biologic product, were pregnant, or were born

after October 1, 2015; the other commercially insured populations included all enrollees. For instance, individuals represented in the BHI data may be more likely to seek care, resulting in higher IRs. Other factors contributing to the heterogeneity across commercial insurance data may be differences in the populations that insurers serve, formulary and care management rules, and data processing systems. This highlights the need for cross-data source active surveillance to account for the differences in background rates observed among the data sources.

Within each data source evaluated, IRs varied by age group and sex and, among the Medicare population, by nursing home residency status and race/ethnicity. Background rates by population characteristics may inform the selection of appropriate comparators in active safety surveillance. Most AESI had higher rates for males than females, increased with age, were higher among Medicare beneficiaries residing in nursing homes, and displayed racial/ethnic differences, with the highest IRs generally among Black beneficiaries (Medicare); however, there were some exceptions to these general observations. Many patterns observed in this study are generally consistent with recent research conducted in the United States [7, 17] and in other countries [7, 18–21], with the exception of narcolepsy and transverse myelitis, for which much lower rates were observed in non-U.S. EHR and claims data [7, 18].

Anaphylaxis and AMI demonstrated seasonality patterns by visual inspection of monthly rates. In both Medicare and the commercial insurance data sources, rates of anaphylaxis were highest during the summer and lowest during the winter months. Additionally, in Medicare, rates of AMI were highest in March and lowest in August. For these AESI, active surveillance may need to account for seasonality when comparing observed rates with expected rates or use different approaches (e.g., concurrent comparator) for appropriate comparisons.

COVID-19 affected healthcare utilization in 2020. This finding is consistent with existing reports [18, 22] and is evidenced by lower rates in 2020 for the negative control events that are acute (colonic

diverticulitis) and chronic (hypertension), as well as for the indicator of time-insensitive preventive care (well-care visits) included in this study. Although many AESI rates returned to pre-COVID-19 levels by the end of 2020, some remained low during the peri-COVID-19 period compared with their 2019 annual rates. The patterns may inform the choice of the appropriate comparator background rates, which may vary by AESI and data source. For instance, using 2019 annual rates as the background rates for AESI that decreased in the peri-COVID-19 period may lead to overestimated expected rates and bias toward the null and may miss a potential safety signal.

We also observed elevated rates of some AESI during the peri-COVID-19 period that may be associated with COVID-19 disease (e.g., DIC in Medicare and HealthCore) [23]. Previous research has shown that coagulopathy is common in severe COVID-19 cases [23–31] and that the risk of myocarditis is elevated among patients with COVID-19 [31]. Related to coagulopathy and myocarditis, we measured the IRs of DIC, DVT, ITP, myocarditis/pericarditis, PE, stroke, and common and unusual site TTS. During June 2020–December 2020, rates of DIC, myocarditis/pericarditis, PE, and common and unusual site TTS were elevated by more than 10% compared with their pre-pandemic rates in at least one data source, while rates of DVT and ITP also showed an increase to a lesser extent (2–7 %) in at least two data sources. Information on the decrease and elevation of rates during the pandemic period is important when conducting active surveillance.

This study has several strengths. It is a large population-based study consisting of more than 100 million individuals across six administrative claims data sources. The large cohort size enables the robust estimation of IRs, particularly for rare AESI. Additionally, the use of pre-adjudicated claims, where available, enabled accumulation of more current data with less delay and allowed for calculation of IR estimates through December 11, 2020, for a broad range of AESI and negative control events. To our knowledge, there has not yet been any prior large-scale study comparing pre- and peri-COVID-19 IRs of AESI, including pandemic-related fluctuations, in the United States. One European study, the vACCine COVID-19 monitoring readinESS (ACCESS) project, funded by the European Medicines Agency, evaluated

the potential impact of the pandemic on AESI background rates [18]. Most prior studies on AESI background rates stratified the rates by demographic characteristics such as age and sex only [7, 18–21]. In addition to age and sex, our study stratified the rates by race/ethnicity and nursing home residence status, where available, and revealed additional heterogeneity in rates by these population characteristics.

Our study also has several limitations. The data reflect only Medicare fee-for-service and certain commercially insured populations. Given the observed variability in rates across data sources, our findings are unlikely to be generalizable to uninsured or other publicly insured (i.e., Medicaid, Medicare Advantage) populations. Although claims data are valuable for efficiently examining health events, all claims databases have certain inherent limitations because claims are collected for payment and not clinical management or research purposes. To provide a timely pandemic response, we generated the AESI claims-based algorithms and risk and clean periods used in this study by reviewing published literature with prioritization of validation studies, communicating with other agencies, and consulting clinical subject matter experts. However, not all AESI definitions had been validated, nor was literature available to determine the clean period for all AESI. The presence of a diagnosis code on a medical claim may represent a rule-out or miscoding; therefore, it may not necessarily reflect the presence of a disease. Although unlikely, potential selection of mis-specified clean periods may have led to the capture of a combination of prevalent and incident events. Finally, the presented comparisons were unadjusted for other variables, and the study did not account for multiple comparisons.

5. Conclusion

This study presents IRs of 17 AESI using a large U.S. population. The estimated rates can serve as historical control rates in any observational study evaluating the safety of medical products when it is not feasible to use concurrent controls (e.g., a comparator group from the same source population as the exposed group followed during the same study period).

A current example of a study in which concurrent controls may not be feasible is initial safety surveillance of COVID-19 vaccines. The authors have used these rates as historical control rates to evaluate the safety of COVID-19 vaccines, applying rapid-cycle analysis or sequential testing soon after each COVID-19 vaccine received EUA from FDA. Although AESI rates varied across data sources and demographic strata in different study periods, the rates were generated in large populations, and the variation likely reflects heterogeneity in the populations as well as some of the unexpected events the population and the healthcare system were experiencing during the study period. Because the AESI rates cover all age groups in the U.S. population and are stratified by certain demographics, they provide more granular comparator estimates and can be used in more diverse studies.

Large population-based data, like the BEST Initiative, may be useful in generating historical comparators used to identify potential increases in observed rates of AESI that may represent a safety concern requiring further evaluation and mitigation.

Funding

This work was supported by the U.S. Food and Drug Administration through the Department of Health and Human Services (HHS) Contract number HHSF223201810022I Task Order 75F40120F19003.

Declaration of competing interest

The authors have no competing interests to declare.

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460

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469 SM, KE, SB, TM, CW, DAD, KA, RO, JS, HLW, CKZ, SA, RF, PL, DT, RD, JO, AS, JK, CR, DB, AMS

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471 YC, JB, PSH, SM, KE, SB, CW, DAD, KA, RO, JS, HLW, CKZ, SA, RF, PL, DT, RD, JO, AS, CR, DB, AMS, TM

472 **Acknowledgments**

473 We thank the following individuals for their support: Lisa S. Kowarski, Veronica Hernandez-Medina, Yu

474 Sun, Molly Bailey, Mary Beth Schaefer, Nasim Lari, Cameron Joyce, Sandia Akhtar, Yixin Jiao, Kathryn

475 Matuska, Jennifer Song, Ron Parambi, Yiyu Fang, Robin Clifford, Katie Reed, Vivian Wilt, Lisa Weatherby,

476 Mike Kirksey, Charlalynn Harris, Jennifer Pigoga, Anne Marie Kline, Nancy Sheffield, Kristin A Sepúlveda,

477 and Tainya C Clarke.

Disclaimer: The opinions expressed are those of the authors and do not necessarily represent the opinions of their respective organizations.

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