

**Center for Biologics Evaluation and Research
Office of Biostatistics and Epidemiology**

Biologics Effectiveness and Safety (BEST) Initiative

Background Rates of Adverse Events of Special Interest for COVID-19 Vaccine Safety Monitoring

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List of Acronyms and Abbreviations

Acronym or abbreviation	Definition
AESI	Adverse event(s) of special interest
BEST	Biologics Effectiveness and Safety Initiative
CBER	Center for Biologics Evaluation and Research
CI	Confidence interval
COVID-19	2019 novel coronavirus disease
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
NDC	National Drug Code
NH	Nursing home
RT-PCR	Reverse transcriptase polymerase chain reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
Health Event Abbreviations	
AMI	Acute myocardial infarction
CCS	Cervical cancer screenings
CD	Colonic diverticulitis
DVT	Deep vein thrombosis
DIC	Disseminated intravascular coagulation
ENC	Encephalitis/Encephalomyelitis
GBS	Guillain-Barré syndrome
HS	Hemorrhagic stroke
ITP	Immune thrombocytopenia
NHS	Non-hemorrhagic stroke
PE	Pulmonary embolism
TTS	Thrombosis with thrombocytopenia syndrome
TM	Transverse myelitis
WCV	Well-child and well-care visits

Executive Summary

Background

As of September 10, 2021, three COVID-19 vaccines are available for use in the United States through licensing (Pfizer-BioNTech) or under Emergency Use Authorizations (EUAs; Moderna and Janssen), with numerous other COVID-19 vaccines under study in pre-licensure clinical trials. For all licensed or authorized vaccines, there are limitations in the safety data accrued during clinical trials, including under-representation of special subpopulations, such as pregnant women, or low capture of rare health events.

Post-market surveillance of potential adverse events of special interest (AESI) following vaccination is needed to continue monitoring the safety of available COVID-19 vaccines. As part of a near real-time safety monitoring of COVID-19 vaccines, the US Food and Drug Administration (FDA) Biologics Effectiveness and Safety (BEST) Initiative used historical background rates of adverse events as a comparator to quickly identify potential increased risk of adverse events post-vaccination. FDA BEST estimated the background rates of pre-specified AESI within the specific data sources and populations as appropriate comparator for the observed rates.

Objectives

The primary objective of this report is to provide annual and monthly incidence rates for 17 AESI, and six negative control events between 2017 and 2020 within five different U.S. administrative claims data sources. Rates were stratified by demographic characteristics including age, sex, race/ethnicity (where available), and nursing home status (where available/relevant), as well as by specific subpopulations of interest including older adults aged 65 years or older, adults between the ages of 18 and 64 years, children under the age of 18 years, and individuals with a history of healthcare-seeking behavior as indicated by prior receipt of influenza vaccination.

Results

For the 17 AESI analyzed, incidence rates varied temporally, across demographic strata, subpopulations, and data sources. Incidence rates were stable from 2017 to 2019 for the majority of AESI although continuously increasing or decreasing rates over time were noted for some. A substantial dip in incidence rates was noted for almost all AESI and all negative control events between March and May 2020, corresponding to the period during which the first wave of COVID-19 cases was observed in the United States. Rates returned to historical levels by October 2020 for most AESI, although some did remain depressed, while others showed unusually high increases toward the end of 2020. Most AESI incidence rates were highest in the older adult population and lowest in the pediatric population, and varied widely across different demographic strata including sex, race, age, and nursing home status. Additionally, incidence rates were typically similar or higher in the influenza vaccinated subpopulation compared to the general population.

Conclusions

AESI background rates vary widely across subpopulations, demographic strata, and data sources, and it is crucial to take these factors into account when determining the appropriate background rate to use for surveillance activities. These AESI rates are used as expected (comparator) rates in Food and Drug Administration (FDA) Biologics Effectiveness and Safety (BEST) Initiative's near real-time surveillance of COVID-19 vaccines.

1. Background

The 2019 coronavirus (COVID-19) is a contagious respiratory illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The first COVID-19 case was reported in China in December 2019,¹ and the first non-travel-related U.S. case was confirmed in February 2020, in a California resident.^{2,3} As of September 10, 2021 a total of 223.6 million cases and 4.6 million deaths have been reported worldwide.⁴ The highest number of cases and deaths has been reported from the U.S. (>40.7 million cases and >656,000 deaths).⁵

As of September 10, 2021, the Pfizer-BioNTech COVID-19 vaccine has received full FDA approval, the Moderna and Janssen COVID-19 vaccines have received emergency use authorization (EUA) from the FDA, and multiple other COVID-19 vaccines are under study in pre-licensure clinical trials. As with all licensed or authorized vaccines, there can be limitations in the safety data accrued from the pre-licensure or pre-authorization COVID-19 vaccine clinical studies. Clinical trials may not adequately represent special populations, such as pregnant women, and may not be large enough to capture all potential safety risks, particularly for rare health events.

Post-market surveillance of potential adverse events of special interest (AESI) following vaccination is needed to continue monitoring the safety of approved or authorized COVID-19 vaccines. An AESI is an untoward occurrence of medical concern which follows immunization, but may not necessarily have a causal relationship with vaccination.⁶ When conducting active surveillance, background rates of adverse events estimated from a similar historical cohort can serve as a comparator (or baseline) to identify potential increased risk of adverse events following vaccination when concurrent unvaccinated populations are not feasible or available as a comparator.

The US Food and Drug Administration (FDA) Biologics Effectiveness and Safety (BEST) Initiative is an active surveillance program for biologics in the Center for Biologics Evaluation and Research (CBER). As part of a near real-time safety monitoring of COVID-19 vaccines,⁷ BEST program estimated the background rates of pre-specified AESI in its databases as the comparator for the observed rates. None of the pre-specified AESI has been associated with COVID-19 vaccines based on available pre-licensure or pre-authorization evidence. This report summarizes the annual and monthly incidence rates for 17 AESI, and six negative control outcomes between 2017 and 2020 within five different U.S. administrative claims data sources in the BEST Initiative that informs the near real time surveillance of COVID-19 vaccines.

2. Objectives

This report summarizes the background incidence rates for 17 AESI and six negative control outcomes in historical cohorts using five U.S. administrative claims data sources. Annual and monthly incidence rate trends, rates stratified by demographics, and rates within specific subpopulations of interest are also reported.

3. Methods

3.1 Data Sources

The following five administrative claims databases from the U.S. were used: Centers for Medicare & Medicaid Services (CMS) Medicare Fee-for-Service (FFS) claims, Blue Health Intelligence® (BHI®)^a commercial claims, IBM® MarketScan® Commercial Database, Optum pre-adjudicated commercial claims, and HealthCore commercial claims.^b

CMS Medicare data contain enrollment, demographic, and claims information for all individuals enrolled in Parts A/B (since 1991), Part C (since 2012), and Part D (since 2006). Medicare Parts A/B (FFS) data were used for this study. Medicare FFS currently contains over 100 million beneficiaries in total and about 34 million beneficiaries annually, on average.

BHI data provide HIPAA compliant, de-identified enrollment, demographic, and claims information from Blue Cross® and Blue Shield® commercial health insurance plans in the U.S. for the last ten years. Data available for this study were limited to a cohort of all enrollees who received a biologic product, were pregnant, or were born after October 1, 2015. Pregnant women were identified via codes for prenatal care, gestational age, or pregnancy outcomes. The BHI cohort population for this study contains over 34 million individuals in total and about 17 million enrollees annually, on average.

The IBM® MarketScan® Research Databases capture person-level clinical utilization, expenditures, and enrollment across inpatient, outpatient, prescription drug, and carve-out services since 1995. The MarketScan Commercial Database includes data from over 273 million active employees, early retirees, Consolidated Omnibus Budget Reconciliation Act (COBRA) continuees, and dependents insured by employer-sponsored plans historically. During the study period, over 55 million enrollees were included in the study population, with an annual average of approximately 25 million.

The Optum data includes enrollment, prescription drug and pre-adjudicated hospital and physician health insurance claims. The pre-adjudicated claims database includes claims for privately insured and Medicare Advantage enrollees. Hospital and physician claims undergo initial processing on a daily basis from a large number of providers across the U.S. who accept patients with health insurance. Optum has established an ongoing weekly update schedule to

^a Blue Health Intelligence® (BHI®) is a trade name of Health Intelligence Company, LLC, an independent licensee of the Blue Cross Blue Shield Association. Blue Health Intelligence and BHI are registered trademarks of the Blue Cross Blue Shield Association.

^b Background rates from CVS Health are not included in this report.

incorporate newly processed claims into the pre-adjudicated claims database. This data source was utilized to reduce the delay between the occurrence of healthcare services and their presence in the database. The pre-adjudicated claims have an approximately two-month delay for 90% completeness for inpatient claims and over 70% completeness at one-month for outpatient claims.

Commercial insurance claims data in HealthCore Integrated Research Environment (HIRE) were used for the analyses described in this report. This proprietary research environment combines medical and pharmacy claims, and laboratory results, drawn from nearly 73 million unique individuals with medical coverage, with approximately 55 million also having pharmacy coverage dating back to 2006. The data environment contains office, outpatient, and ER visits, hospital stays, outpatient surgeries, ambulance transportation, skilled nursing facility episodes, as well as durable medical equipment. The data currently contain over 23 million members in 2020 with a data lag of 3 months for complete data and 1–3 months for pharmacy dispensings and early settled outpatient claims.

3.2 Study Period

The study period for each data source is presented in Table 1. For Medicare, BHI, and HealthCore data sources, the study period spanned from January 1, 2017 through December 11, 2020, when the FDA issued the first EUA for a COVID-19 vaccine (Pfizer-BioNTech), the first COVID-19 vaccine available in the U.S. For MarketScan, the study period spanned from January 1, 2017 through October 31, 2020, as this was the latest date through which data were at least 80% complete at the time of analysis. For Optum, the study period spanned from January 1, 2019 through December 11, 2020 due to data unavailability prior to 2018 and the need for a one-year baseline period prior to study start.

Table 1. Data Sources and Study Periods

Data Source	Study Period
Medicare	January 1, 2017 – December 11, 2020
BHI	January 1, 2017 – December 11, 2020
MarketScan	January 1, 2017 – October 31, 2020
Optum	January 1, 2019 – December 11, 2020
HealthCore	January 1, 2017 – December 11, 2020

The study period was categorized into pre-COVID-19 and peri-COVID-19 time periods for exploratory analyses. For all data sources, the pre-COVID-19 period extended from the study period start through February 29, 2020. The peri-COVID-19/pre-vaccine period was defined as March 1, 2020 through study end date. March 1, 2020 was chosen as the start of the peri-COVID period based on preliminary assessments in the data sources showing COVID-19 diagnoses and RT-PCR testing accrual starting on March 1, 2020.

3.3 Study Population

Within each data source, annual cohorts were constructed for calendar years 2017–2020, as data were available. In each annual cohort, the general study population included any

individual enrolled in a medical plan for at least one day during the calendar year and who met the event-specific clean period requirement before cohort entry. The clean period requirement was defined as having (1) continuous enrollment for the length of the pre-specified clean window (i.e., a baseline period specific to each AESI to establish an incident AESI) prior to the cohort entry date and (2) no diagnosis from the specified care setting(s) for the AESI during the clean period. Clean period specifications for each AESI are provided in Table 2. Continuous enrollment for the length of the baseline period was also required for all negative control events, but only some negative control events additionally required a clean period. Negative control events which were preventative care services did not require a clean period. Given that many of these services are recommended annually (e.g., well-care visits), an incident case – defined as the first occurrence – was considered less meaningful in tracking healthcare utilization pattern changes. Specifications for each negative control event are provided in Table 3. Individuals were included in more than one AESI or negative control event-specific cohort if they met all the inclusion criteria.

For each annual cohort, the cohort entry date was defined as January 1 of the given calendar year or the date on which the clean period requirement was met, whichever occurred later. Infants who were born before January 1 and were continuously enrolled from birth, but who had not reached the full length of the clean period on January 1 were assigned a cohort entry date of January 1, provided no AESI occurred during the shortened clean period prior to entry. For those infants who were born in the year and started enrollment within 31 days of birth, the cohort entry date was the date of birth.

The cohort entry requirement was different for negative control events because of the minimum age requirement for some events, and the lack of clean period requirement for others (Table 3). For hypertension and colonic diverticulitis, the cohort entry date was the later date of January 1 of a given calendar year, or the date an individual met the clean period requirement, or the date an individual reached 18 years of age. For preventive care services, the cohort entry date was the later date of January 1 of a given calendar year, or the date an individual had one year of continuous enrollment, or the date the individual reached the specified age range (e.g., 45 years old and older for screening colonoscopy).

Individuals were followed from cohort entry date through health event occurrence, or through censoring due to death, disenrollment, end of calendar year, or the date of the latest data that reached approximately 80% completion (applicable to the later months of 2020 for some data sources at the time of analysis), whichever came first. Individuals who experienced a health event, or who were censored, may re-enter the same annual health event cohort if another clean period requirement was met during the same calendar year. Note that this is only possible among health events with a clean window length of less than 365 days. Individuals who re-entered the cohort were treated as separate observations, and a subsequent occurrence of the health event after the re-entry and during follow-up was treated as an incident case.

Cohorts were constructed for individuals aged 0-64 years at the time of cohort entry within BHI, MarketScan, Optum, and HealthCore data sources. Within these cohorts, age-based

subpopulations were defined for the pediatric population (ages 0–17 years) and the adult population under 65 years (ages 18–64 years). Cohorts were constructed for an older adult population, defined as individuals aged 65 years or older at the time of cohort entry, within Medicare data.

3.4 Influenza Vaccinated Subpopulation Definition

Individuals with an influenza vaccination in the calendar year prior to cohort entry were defined as a subpopulation of special interest. Background rates for the influenza vaccinated population were assessed because influenza vaccination status has been used as a proxy measure for healthcare-seeking behaviors in previous studies.⁸ Individuals with a recent influenza vaccination may have different outcome rates for various conditions of interest. A list of procedure (HCPCS) and National Drug Codes (NDCs) used to identify influenza vaccinations for this analysis can be found in the supplemental materials of the study protocol.⁹ Incidence rates within the influenza vaccinated pediatric population were not calculated in the HealthCore data source.

3.5 Health Events

AESI and negative control events are collectively referred to as ‘health events’ in this report. A list of medical billing codes used to identify health events for this analysis can be found in the supplemental materials of the study protocol.⁹

3.5.1 AESI

The AESI analyzed in this report are listed in Table 2. These AESI have not been associated with COVID-19 vaccination in the pre-authorization data. Considerations in the selection of these potential AESI included serious events that have followed other immunizations, events that are potentially related to novel platforms or adjuvants, events that are related to COVID-19 severity that may potentially relate to vaccine failure/immunogenicity (enhanced disease), or other considerations including recommendations from other surveillance systems and events that are potentially specific to particular populations of interest. Development of the claims-based AESI algorithms was based on literature reviews and consultations with clinical experts.

Two AESI of thrombosis with thrombocytopenia syndrome (TTS), unusual site TTS and common site TTS, are composite health events requiring co-occurrence of two conditions. A composite episode of TTS was defined as a thrombotic event and a thrombocytopenia (TP) event within 13 days of each other, with a total length of ≤ 14 calendar days including the start date of the episode. The TTS composite event date was defined as the start date of the composite episode (the earliest date when either thrombosis or TP event occurs in an episode).

Claims from inpatient facilities (IP), outpatient facilities in the emergency department (OP-ED), and all outpatient facilities and individual providers or professionals (OP/PB) were used to capture AESI.

Table 2. List of Adverse Events of Special Interest (AESI)

Safety AESI	Age Group of Interest	Setting	Clean Window*
General Population Health Events			
Guillain-Barré syndrome (GBS)	All	IP- primary position only	365 days
Bell's palsy	All	IP, OP/PB	183 days
Anaphylaxis	All	IP, OP-ED	30 days
Encephalitis/Encephalomyelitis (ENC)	All	IP	183 days
Narcolepsy	All	IP, OP/PB	365 days
Appendicitis	All	IP, OP-ED	365 days
Non-hemorrhagic stroke (NHS)	All	IP	365 days
Hemorrhagic stroke (HS)	All	IP	365 days
Acute myocardial infarction (AMI)	All	IP	365 days
Myocarditis/pericarditis	All	IP, OP/PB	365 days
Deep vein thrombosis (DVT)	All	IP, OP/PB	365 days
Pulmonary embolism (PE)	All	IP, OP/PB	365 days
Disseminated intravascular coagulation (DIC)	All	IP, OP-ED	365 days
Immune thrombocytopenia (ITP)	All	IP, OP/PB	365 days
Transverse myelitis (TM)	All	IP, OP-ED	365 days
Unusual site thrombosis with thrombocytopenia (Unusual site TTS)	All	IP, OP-ED (unusual site thrombosis); IP, OP/PB (thrombocytopenia)	365 days
Common site thromboses [£] with thrombocytopenia (Common site TTS)	All	Settings specific to each sub-event (common site thromboses); IP, OP/PB (thrombocytopenia)	365 days

Setting Definitions: IP refers to inpatient facility claims. OP-ED refers to a subset of outpatient facility claims occurring in the emergency department. OP/PB refers to all outpatient facility claims, and professional/provider claims except those professional/provider claims with a laboratory place of service.

** Clean window is defined as the time period prior to cohort entry, during which no AESI was observed. References for the duration of these windows could not be located in the literature and are instead based on input from clinicians.*

£Common site thromboses include acute myocardial infarction, deep vein thrombosis, hemorrhagic stroke, non-hemorrhagic stroke, and pulmonary embolism

3.5.2 Negative Control Events

Analysis was additionally conducted for negative control events posited to be unrelated to COVID-19 vaccination, but which may reflect healthcare utilization changes as a result of

lockdowns or altered healthcare-seeking behavior during the pandemic. Incidence rates for these events may be helpful in understanding changes in baseline medical care patterns over time. The selected negative control events are listed in Table 3. Colonic diverticulitis was selected because it is an urgent condition that requires immediate treatment and healthcare utilization for this event should remain stable during the pre-COVID-19 and peri-COVID-19 periods. Hypertension, screenings for well-child and well-care visits, and screenings for breast, cervical, and colon cancer were included as non-urgent conditions that are hypothesized to occur at a lower than usual rate during the peri-COVID-19 period because of delayed healthcare-seeking behavior. Incidence rates for negative control events were not calculated within the Optum data source. Table 4 lists the subpopulations and health events examined in each data source.

Table 3. List of Negative Control Events

Negative Control Event	Age Group of Interest	Setting	Continuous Enrollment or Clean Window
Colonic diverticulitis (CD)	18 years and older	IP, OP/PB	365 days* (clean window)
Hypertension	18 years and older	IP, OP/PB	
Well-child and well-care visits (WCV)	All ages	IP, OP/PB	365 days** (continuous enrollment)
Colonoscopies for colorectal cancer screening	45 years and older	IP, OP/PB	
Mammograms for breast cancer screening	Women, 40 years and older	IP, OP/PB	
Cervical cancer screenings (CCS)	Women, 21 years and older	IP, OP/PB	

Setting Definitions: IP refers to inpatient facility claims. OP/PB refers to all outpatient facility claims, and professional/provider claims except those professional/provider claims with a laboratory place of service.

** References for these windows could not be found in the literature and are instead based on input from clinicians. The clean window is meant to increase comparability of these negative control events to the safety AESI.*

*** A clean window is not implemented for preventive care visits or screenings to not exclude patients who sought preventive care in the previous year.*

Table 4. Health Events and Subpopulations Evaluated by Data Source

Health Event or Subpopulation	Medicare	BHI	MarketScan	Optum	HealthCore
Subpopulations					
Older Adults (age 65+)	X				
Adults (age 18-64)		X	X	X	X
Pediatric (age 0-17)		X	X	X	X
Influenza Vaccinated	X	X	X	X	
Health Events					

Health Event or Subpopulation	Medicare	BHI	MarketScan	Optum	HealthCore
AESI (17 events total)	X	X	X	X	X
Negative Control Events (6 events total)	X	X	X		X

3.6 Statistical Analysis

Annual, cumulative monthly, and monthly incidence rates were calculated for each AESI within each separate data source by dividing the count of incident cases during the time at risk by the total person-time at risk during the specified time period. Person-time at risk for each individual within a given annual cohort was calculated as the time between cohort entry date and end of follow-up (see section 3.3 for details on definition of cohort entry and follow-up). Incidence rates were additionally calculated within strata of age and sex (all data sources), as well as race/ethnicity and nursing home residency status (Medicare only). All characteristics were assessed on the cohort entry date. Rates are presented in this report as event counts per 100,000 person-years. Exact Poisson 95% confidence intervals (CI) were calculated for each incidence rate. Additional details on rate calculation are provided in the publicly posted protocol on the website of the FDA BEST Initiative.¹⁰ Comparative descriptive statistics (e.g., percent changes) between rates were derived from the results in each data source.

AESI can be affected by factors that change through a calendar year and can exhibit seasonal trends. To assess seasonality, we plotted monthly incidence rates within each calendar year in the study period for each data source and visually inspected variations across calendar months. Percent differences between monthly incidence rates in the summer and winter were assessed.

4. Results

Across the 17 AESI analyzed within all data sources, background rates varied considerably over time as well as across subpopulations and demographic strata. The following sections describe temporal, demographic, and subpopulation trends within the older adults aged 65 years and older, adults aged 18–64 years, and pediatric populations (0–17 years). Descriptive comparisons between different populations of interest were made by comparing the point estimates and 95% confidence intervals of incidence rates for a given health event. Incidence rates between two populations were considered *similar* if their 95% confidence intervals overlapped, and *different* otherwise.

4.1 Pre-COVID Incidence Rates

4.1.1 Overview

This section provides an overview of the health event incidence rates observed during the pre-COVID-19 period, defined as all time between study start date and February 29, 2020, for the older adult (age 65 years and over), adult (age 18–64 years), and pediatric (under age 18 years) populations. Within each of these populations, annual incidence rate trends within pre-COVID time were assessed for each AESI and negative control event, as available in each data source.

For assessments listed in this subsection, 2019 annual incidence rates, the only pre-COVID year available for all data sources, were used to provide an overview of rates observed in the pre-COVID time. Annual 2019 cohort sizes by event are provided in Table 5. The older adult population in Medicare contained approximately 27 million beneficiaries. The adult populations in BHI, MarketScan, Optum, and HealthCore contained approximately 15.9 million, 14.4 million, 9.3 million, and 12.9 million individuals, respectively. The pediatric populations in BHI, MarketScan, Optum, and HealthCore contained approximately 6.2, 4.4, 3.2, and 3.8 million individuals, respectively.

A summary of 2019 annual incidence rates per 100,000 person-years across all data sources is provided in Table 6. Among older adults aged 65 years and above (Medicare), the AESI with the highest observed annual incidence rates per 100,000 person-years (95% CI) in 2019 were deep vein thrombosis (DVT) 1,330.99 (1,326.43, 1,335.55), acute myocardial infarction (AMI) 1,297.48 (1,293.01, 1,301.97), and non-hemorrhagic stroke (NHS) 842.83 (839.23, 846.44). The AESI with the lowest observed annual incidence rates were transverse myelitis (TM) 3.38 (3.15, 3.61), Guillain-Barré syndrome (GBS) 4.63 (4.36, 4.90), and encephalitis/encephalomyelitis (ENC) 9.82 (9.44, 10.21) per 100,000 person-years. The older adult population typically had higher AESI incidence rates compared to the adult and pediatric populations, particularly for cardiovascular AESI. However, two AESI (anaphylaxis and appendicitis) showed lower incidence rates in the older adult population compared to the adult or pediatric populations.

Across all commercial claims (i.e., BHI, MarketScan, Optum, and HealthCore) containing the adult population aged 18–64 years, the AESI with the highest annual incidence rate per 100,000 person-years in 2019 were DVT (226.52–285.50 across the four data sources), pulmonary embolism (PE) (139.64–179.46), appendicitis (118.73–155.05), and AMI (110.28–149.45). The least common AESI were TM (1.28–1.96), GBS (2.24–3.11), ENC (2.08–3.34), disseminated intravascular coagulation (DIC) (4.72–8.96), and unusual site TTS (2.02–3.80). Across data sources, Optum and BHI generally had higher rates than MarketScan and HealthCore for most AESI.

Across all commercial claims (BHI, MarketScan, Optum, and HealthCore) that contain the pediatric population aged 0–17 years, the AESI with the highest annual incidence rates per 100,000 person-years in 2019 were appendicitis (106.59–127.48), anaphylaxis (24.54–31.30), and Bell's palsy (21.84–24.91). There were three AESI with incidence rates equal to or lower than 1 per 100,000 person-years: TM, unusual site TTS, and AMI.

4.1.2 Pre-COVID Trends in Adult Population 65 Years and Older

Event incidence rates and 95% CIs for the years 2017, 2018, and 2019 in the Medicare older adult population aged 65 years or older are displayed in Figure 1A and Table 7A. Discrepancies in annual incidence rates across years are discussed only if the rates are *different*.

In the older adult population, four of the 17 AESI appeared to have steady increases. There was a continued increase across all three years for AMI, anaphylaxis, appendicitis, and unusual site TTS. AMI increased approximately 3% each year, and anaphylaxis, appendicitis, and unusual site TTS increased at least 9% each year. Appendicitis saw the largest increase of 26% from

2017 to 2018 and 64% from 2018 to 2019, which was partly attributable to changes in billable appendicitis codes occurring in October 2018 (see Appendix A for details). There was a continued decrease across all three years for DVT, DIC, and immune thrombocytopenia (ITP). ITP saw the largest decrease of approximately 5% each year.

Seasonality trends across the entire pre-COVID period were assessed and identified for two AESI as shown in Figure 2A. For anaphylaxis, there was a substantial decrease during the fall and winter months and a substantial increase during the spring and summer months. In 2019, the minimum incidence rate was 6.57 per 100,000 person-years in February and the peak incidence rate was 16.78 per 100,000 person-years in July. AMI also showed consistent seasonality within 2019, with a peak incidence rate of 1,408.83 per 100,000 person-years in March and a minimum incidence rate of 1,178.82 per 100,000 person-years in August.

4.1.3 Pre-COVID Trends in Adult Population Under 65 Years

The adult population was analyzed separately in BHI, MarketScan, Optum, and HealthCore data. Annual incidence rates for all events during pre-COVID time are displayed in Figure 1B and Tables 7B–7E for BHI, MarketScan, Optum, and HealthCore, respectively. Within Optum data, only 2019 incidence rates are available. Therefore, assessments of trends across pre-COVID years (2017–2019) were restricted to BHI, MarketScan, and HealthCore. Within these three data sources, almost all AESI exhibited similar incidence rates across pre-COVID time. The exceptions were anaphylaxis and appendicitis, which showed increases of at least 10% each year across all three years, and NHS which increased by 9–12% from 2018–2019 within all three data sources. Additionally, from 2018 to 2019, PE incidence rates increased by 3–4% in MarketScan and BHI, and narcolepsy incidence rates increased by 6% in HealthCore and MarketScan.

Seasonality in the adult population was examined in the BHI, MarketScan, Optum, and HealthCore databases as shown in Figures 2B–2E. Monthly rates were derived from an analysis of Optum pre-adjudicated claims data. Similar seasonal patterns were observed for anaphylaxis, with a substantial decrease in fall and winter months and a substantial increase in spring and summer months. In 2019, anaphylaxis incidence rates ranged from approximately 9–14 per 100,000 person-years in January to 21 (HealthCore and MarketScan), 25 (Optum), and 27 (BHI) in August.

4.1.4 Pre-COVID Trends in Pediatric Population

The pediatric population was analyzed separately in BHI, MarketScan, Optum, and HealthCore data. Annual incidence rates in 2019 for all health events during pre-COVID time are displayed in Figure 1C and Tables 7B–7E. As with the adult population, only 2019 incidence rates are available for Optum and assessments of trends across pre-COVID years (2017–2019) are restricted to BHI, MarketScan, and HealthCore. Within all three of these data sources, the incidence rates were similar across years for all AESI except anaphylaxis and appendicitis both of which increased over time.

Between 2017 and 2019, anaphylaxis increased by 33% (BHI), 43% (MarketScan), and 48% (HealthCore). During the same period, the appendicitis incidence increased by 43% (BHI), 50% (MarketScan), and 29% (HealthCore), which may be driven by changes in billable appendicitis codes (see Appendix A for details).

Seasonality was observed for Bell's palsy in BHI and HealthCore but was less evident within MarketScan and Optum. Within BHI and HealthCore, Bell's palsy showed a minimum incidence rate of 17–19 per 100,000 person-years in October and a peak incidence rate in July of approximately 30 (BHI) and 34 (HealthCore) per 100,000 person-years in 2019 (Figures 2B and 2E).

4.2 Peri-COVID Incidence Rates

4.2.1 Overview

This section describes incidence rates of AESI and negative control events within the peri-COVID-19 period, which was defined as beginning on March 1, 2020 and ending on December 11, 2020 for all data sources except MarketScan, where the peri-COVID period end date was October 31, 2020, the latest date through which data were at least 80% complete at the time of analysis. This period was defined to assess the impact of COVID-19 on incidence rates by comparing pre-COVID-19 to peri-COVID-19 rates within the older adult (age 65 and over), adult (age 18–64 years), and pediatric (under age 18) populations. For comparisons listed in this section, 2019 annual incidence rates were used to represent rates in the pre-COVID-19 time. The 2019 calendar year was selected because it is the only pre-COVID-19 year available for all data sources.

Overall, within the older adult population in Medicare and the adult populations in BHI, MarketScan, Optum, and HealthCore, the majority of AESI showed lower rates in the peri-COVID-19 period compared to the pre-COVID-19 period. For the pediatric population, two AESI (anaphylaxis and narcolepsy) exhibited lower rates in the peri-COVID-19 than the pre-COVID-19 period across all databases; in BHI, MarketScan, and HealthCore, ITP rates were also lower in the peri-COVID-19 than the pre-COVID-19 period. The remainder of the AESI either remained the same across time periods or did not show a consistent pattern across databases. All negative control events generally showed lower rates in the peri-COVID-19 period across the older adult, adult, and pediatric populations. Within the peri-COVID-19 period, monthly incidence rates were the lowest between March and May 2020.

4.2.2 Peri-COVID Trends in Adult Population 65 Years and Older

Comparisons in incidence rates between pre-COVID-19 and peri-COVID-19 periods for the older adult population are provided in Figure 3A and Table 8A. Within the Medicare older adult population, anaphylaxis, ENC, and TM were the only AESI that exhibited similar incidence rates between the pre-COVID-19 and peri-COVID-19 periods. All other AESI and negative control event rates decreased in the peri-COVID-19 time, except for DIC, which increased by 8%. The largest decreases from pre-COVID-19 to peri-COVID-19 time occurred in narcolepsy (23%), GBS (21%), and Bell's palsy (20%). DVT, ITP, and NHS also decreased by more than 10%.

Examples of non-cumulative, monthly incidence rate trends in select health events can be seen in Figure 4A. The largest decrease in rates during peri-COVID-19 time was observed between March and May 2020. AESI captured in outpatient and physician office settings in addition to the inpatient setting showed the steepest declines in rates with monthly incidence rates dropping in April 2020 to 19–44% below what was observed in April 2019. The exception was DIC, which increased by 6%. AESI captured exclusively in the inpatient setting dropped in April 2020 to 13–25% below what was observed in April 2019. Monthly rates remained depressed until June 2020 when most rates gradually began increasing back to pre-COVID-19 levels. The majority of AESI returned to within 5% of pre-COVID-19 levels by October 2020. ITP, Bell's palsy, and narcolepsy continued to be 11–31% lower than pre-COVID-19 levels in October 2020 but all recovered by December 2020. PE and DIC increased above levels observed in the pre-COVID-19 time starting in August 2020. Incidence rates were 9% (PE) and 26% (DIC) greater in September 2020, and 43% (PE) and 11% (DIC) greater in December 2020, compared to rates observed in the corresponding months of 2019. Additionally, myocarditis/pericarditis showed an elevated rate in December 2020 that was 28% higher compared to December 2019.

Negative control events also decreased in the peri-COVID-19 period (March to December 2020) by 18% or more compared to the 2019 rates, except for cervical cancer screenings (CCS) and well-care visits (WCV) which decreased by 4% and 5%, respectively. From March to May 2020, non-cumulative monthly rates for all negative control events were substantially lower compared with those in the corresponding months of 2019. For example, in April 2020, rates for all negative control events were at least 50% less than those in April 2019, with the greatest decrease seen in colonoscopies (89%) and mammograms (92%). By June 2020, CCS, mammograms, WCV, and hypertension had returned to near pre-COVID-19 rates, and by December 2020, incidence rates for all negative control events had returned to pre-COVID-19 levels.

4.2.3 Peri-COVID Trends in Adult Population Under 65 Years

The adult population was analyzed separately in the BHI, MarketScan, Optum, and HealthCore data sources. Comparisons in incidence rates between pre-COVID and peri-COVID time are displayed for BHI, MarketScan, Optum, and HealthCore in Figure 3B and Tables 8B–8E, respectively. Across all four data sources, ENC, myocarditis/pericarditis, and unusual site TTS showed similar incidence rates between the pre-COVID and peri-COVID periods. Additionally, anaphylaxis, DIC, HS, ITP, TM, and common site TTS showed similar incidence rates between the two periods within at least two data sources. Appendicitis, Bell's palsy, DVT, GBS, and narcolepsy, showed lower rates in peri-COVID time across all four data sources. Finally, within BHI, Optum, and HealthCore data, incidence rates for PE were higher in peri-COVID time than in pre-COVID time. HealthCore also showed higher rates in peri-COVID time for DIC and common site TTS, but this was not observed in any other data sources. All six negative control events were lower in peri-COVID time compared to pre-COVID time within all data sources.

Examples of monthly trends in peri-COVID time for select events in BHI, MarketScan, Optum, and HealthCore among adult populations are presented in Figures 4B, 4D, 4F, 4H, respectively. The selected events displayed in these figures (i.e., DIC, NHS, PE, and well-care visits) were

chosen to represent a range of care settings (e.g., DIC is defined in the IP, OP-ER settings, NHS is defined in the IP setting, and PE is defined in the IP, OP/PB settings), and a range of observed patterns in the peri-COVID time.

Between March and May 2020, the majority of AESI and negative control events showed a decrease in incidence rates across data sources. As in the older adult population, the main exception to this observation was DIC, which showed similar or higher monthly incidence rates in March through May 2020 compared to March through May 2019 within all four data sources. Although many AESI returned to pre-COVID levels by December, 2020 there were some exceptions. In MarketScan, Optum, and HealthCore, GBS and anaphylaxis continued to have lower monthly incidence rates at the end of 2020 compared to the end of 2019. There were also three AESI that showed markedly higher monthly incidence rates at the end of 2020 compared to the same calendar months in pre-COVID time, across multiple data sources. Within BHI, Optum, and HealthCore, PE showed elevated monthly incidence rates from July 2020 onwards; PE rates in December 2020 were 50–72% higher than they were in December 2019. Myocarditis/pericarditis monthly incidence rates were elevated from September 2020 onwards with rates in December 2020 being 18%, 61%, and 51% higher than in December 2019 within the BHI, Optum, and HealthCore data sources, respectively. Finally, DVT incidence rates were elevated in December 2020 solely and were 25–35% higher than in December 2019 within BHI, Optum, and HealthCore. Note that MarketScan incidence rates only extended through October 2020, and therefore many of the above comparisons could not be made in that data source. Additional data source-specific trends in peri-COVID time are provided below.

In BHI, in April 2020, the monthly incidence rate of most AESI was 16–39% lower than it was in April 2019. Notable exceptions in BHI were HS, which only declined by 9%, anaphylaxis, which had the largest decrease by 55%, and DIC, which increased by 29%. By July 2020, almost all AESI had recovered to within 10% of pre-COVID rates except for GBS and narcolepsy, which both recovered by December 2020. The monthly incidence rate for ITP in December 2020 was observed to be 55% higher than the monthly incidence rate in December 2019. PE, myocarditis/pericarditis, and DVT also showed elevated monthly incidence rates in the latter portion of 2020, as described above.

In MarketScan, in April 2020, the monthly incidence rate of most AESI was 17–41% lower than it was in April 2019. The exceptions were NHS, PE, and TTS (both common and unusual site), which only declined by 15% or less; anaphylaxis, which had the largest decrease at 53%; and DIC, which increased by 41%. By July 2020, fewer AESI in MarketScan compared to BHI had recovered to and remained within 10% of the 2019 incidence rate through October 2020 (the last month of data evaluated in MarketScan); only DVT, ITP, myocarditis/pericarditis, PE, and common site TTS had recovered.

In Optum, in April 2020, the monthly incidence rate of most AESI was 19–35% lower than that in April 2019. The exceptions were HS, NHS, and PE, which declined by less than 10%; anaphylaxis, GBS, ITP, and TM, which declined by over 50%; and DIC, which increased by 25%. By December 2020, incidence rates for most AESI had recovered to within 10% of pre-

COVID rates except for anaphylaxis, GBS, and unusual site TTS, which remained lower, and DVT, myocarditis/pericarditis, and PE, which were noticeably higher.

In HealthCore, in April 2020, the monthly incidence rates of most AESI were 11–29% lower than those in April 2019. The exceptions were common site TTS, which declined by 3%; ENC, narcolepsy, and anaphylaxis, which declined by more than 35%; and DIC, which increased by 38%. By September 2020, the majority of AESI recovered to and remained within 10% of pre-COVID levels through December 2020; the only AESI that did not recover and maintained lower rates were anaphylaxis and GBS. Additionally, several AESI showed higher monthly incidence rates in the latter portion of 2020 compared to 2019. When comparing monthly incidence rates in December 2020 to rates in December 2019, common site TTS, DIC, ITP, narcolepsy, and unusual site TTS were 24%, 41%, 53%, 35%, and 250% higher, respectively. Myocarditis/pericarditis, PE, and DVT were also elevated, as described above.

As seen in the older adult population in Medicare, negative control event rates decreased drastically in March and April 2020. Monthly rates were 30–93% lower in April 2020 compared to April 2019 for all negative control events in BHI, MarketScan, and HealthCore data – negative control event rates were not captured in Optum data. In BHI, hypertension, mammogram, cervical cancer screenings, and well-care visits returned to within 10% of 2019 rates by June 2020 and all negative control event rates recovered to 2019 levels by October 2020. In MarketScan, hypertension, mammograms, and well-care visits returned to 2019 levels by June 2020 and colonic diverticulitis (CD) and colonoscopy rates had recovered to within 10% of 2019 rates by September 2020. Cervical cancer screenings remained depressed by approximately 10% or more through October 2020. In HealthCore, by June 2020, all negative control events except CD and colonoscopies had recovered to within 10% of 2019 rates; by September 2020, all events returned to and remained within 10% of 2019 rates.

4.2.4 Peri-COVID Trends in Pediatric Population

The pediatric population (ages 0–17 years) was analyzed separately in the BHI, MarketScan, Optum, and HealthCore data sources. Comparisons in incidence rates between pre-COVID and peri-COVID time are displayed for BHI, MarketScan, Optum, and HealthCore in Figure 3C and Tables 8B–8E. Across all data sources, the majority of AESI showed similar incidence rates between the pre-COVID and peri-COVID periods. The remainder exhibited lower incidence rates in the peri-COVID period compared to the pre-COVID period. Anaphylaxis and narcolepsy exhibited lower incidence rates in the peri-COVID period compared to the pre-COVID period within all four data sources. Within BHI, MarketScan, and HealthCore, ITP also exhibited lower incidence rates in peri-COVID time. Finally, appendicitis showed lower incidence rates in peri-COVID time within HealthCore data only, while similar rates were observed between pre and peri-COVID time in all other data sources. Incidence rates for most AESI in the pediatric population were much lower than those in the older age groups and were less stable.

In BHI, monthly rates in April 2020 for anaphylaxis, ITP, and narcolepsy were 59%, 52%, and 62% lower than those in April 2019, respectively. Incidence rates for anaphylaxis and

narcolepsy recovered to pre-COVID levels by October 2020, but ITP rates remained depressed through December 2020.

In MarketScan, rates in April 2020 for anaphylaxis, ITP, and narcolepsy were 62%, 70%, and 65% lower than those in April 2019. Although ITP rates returned to within 5% of 2019 rates by July 2020 and generally remained around those levels, they dipped briefly in September 2020. Unlike BHI, narcolepsy and anaphylaxis rates remained 15–41% lower than pre-COVID rates through October 2020.

In Optum, monthly rates in April 2020 for pediatric anaphylaxis and narcolepsy were 64% and 72% lower than monthly rates in April 2019, respectively. By October 2020, the narcolepsy monthly incidence rate recovered to within 10% of 2019 levels, and plateaued through December 2020, while the anaphylaxis monthly incidence rate remained more than 30% lower than 2019 rates during these same calendar months.

In HealthCore, anaphylaxis, appendicitis, ITP, and narcolepsy monthly rates in April 2020 were 21–66% lower than those in April 2019. By May 2020, appendicitis monthly incidence rates recovered to within 10% of 2019 rates and largely remained at this level through December 2020. Narcolepsy monthly incidence rates recovered to 2019 levels in October 2020. Anaphylaxis and ITP rates remained depressed through December 2020.

The only negative control event defined for the pediatric population was well-child visit, which was 60% lower in April 2020 compared to April 2019 in BHI, 47% lower in MarketScan, and 64% lower in HealthCore. Negative control events were not measured in Optum data. Well-child visit rates recovered to pre-COVID levels by June 2020 within BHI, MarketScan, and HealthCore data sources.

4.3 Incidence Rates Stratified by Demographic Characteristic

This section describes incidence rates stratified by age, sex, race/ethnicity (Medicare only), and nursing home residency status (Medicare only) for AESI and negative control events. For comparisons listed in this section, 2019 annual incidence rates were used to represent typical rates because demographic trends were comparable across all years evaluated and because 2019 was the only pre-COVID year for which rates were available in all data sources.

Overall, older age groups, men, racial minority groups, and individuals in nursing homes generally had higher incidence rates compared to other demographic groups.

4.3.1 Demographic Trends in Adult Population 65 Years and Older

Annual incidence rates stratified by age groups within the Medicare population aged 65 years and older are given in Table 9A. Within this population, 10 AESI (AMI, anaphylaxis, appendicitis, DVT, HS, ITP, NHS, PE, unusual site TTS, common site TTS) showed different incidence rates across all three age groups (i.e., ages 65–74, 75–84, 85+). AMI, DVT, HS, ITP, NHS, PE, and common site TTS all exhibited increasing rates with increasing age, with the largest increases observed for NHS (254% increase between the 65–74 and 85+ age groups), HS (198%), and AMI (195% increase). Anaphylaxis, appendicitis, and unusual site TTS decreased with

increasing age, and showed rates that were 60%, 37%, and 55%, respectively, lower in the 85+ age group compared to the 65–74 age group. The remaining seven AESI showed similar incidence rates between two of the age groups. Incidence rates for ENC, GBS, narcolepsy, and TM were similar between the 65–74 and 75–84 age groups. Incidence rates for Bell's palsy, DIC, and myocarditis/pericarditis were similar between the 75–84 and 85+ age groups.

Within sex strata (Table 10A), annual incidence rates were higher in males for all AESI except for anaphylaxis, Bell's palsy, and TM. Bell's palsy was higher (5%) among females, while the other two AESI were similar between males and females. AESI rates that were particularly high among males compared to females included common site TTS (72% higher in males), GBS (68%), unusual site TTS (56%), and AMI (40%).

Within race/ethnicity strata (Table 11), nine AESI were highest among Black beneficiaries (DVT, DIC, ENC, HS, myocarditis/pericarditis, NHS, PE, TM, common site TTS), five were highest among North American Native beneficiaries (AMI, anaphylaxis, Bell's palsy, GBS, unusual site TTS), and two were highest among White beneficiaries (ITP, narcolepsy). Certain AESI rates were noticeably higher for a specific race/ethnicity, where the observed incidence rate was considerably higher compared to the next highest observed rate. For instance, the 2019 annual incidence rate of DVT was 48% higher among Black beneficiaries compared to Hispanic beneficiaries, and PE was 42% higher for Black beneficiaries compared to White beneficiaries. There was a consistent disparity between White and non-White individuals for two AESI (DIC and HS). Incidence rates among White beneficiaries were 38% and 20% lower for DIC and HS, respectively, when compared to the next lowest observed rate.

When stratified by nursing home status (Table 12), only GBS and unusual site TTS showed similar annual incidence rates between individuals who were in a nursing home and those who were not. Among the AESI with different rates, only anaphylaxis and appendicitis were higher among non-nursing home beneficiaries. The annual incidence rates of the remaining 13 AESI were all higher among the nursing home population, and usually by a considerable extent. Most of these 13 AESI had rates that were approximately double in the nursing home population compared to the non-nursing home populations, and others were nearly tripled (e.g., DIC 193% higher, DVT 192% higher, AMI 142% higher).

4.3.2 Demographic Trends in Adult Population Under 65 Years

Within the BHI, MarketScan, Optum, and HealthCore commercial data sources, incidence rates in the adult population generally increased with age, a trend which was also observed in Medicare older adult population. Annual 2019 incidence rates stratified by age group within BHI, MarketScan, Optum, and HealthCore are shown in Tables 9B–9E, respectively. Within BHI, incidence rates for all AESI except for anaphylaxis, appendicitis, narcolepsy, and TM were highest within the oldest age group (ages 56–64), although similar rates for Bell's palsy were observed between the 46–55 and 56–64 age groups. Of note, when comparing the 46–55 and 56–64 age groups, incidence rates were particularly high in the older age group for AMI (84% higher), NHS (84%), common site TTS (77%), HS (63%), unusual site TTS (63%), and DIC (52%).

Similar results were observed within MarketScan, Optum, and HealthCore. Percent increases from the 46–55 to the 56–64 age group stratum were again most stark for AMI (73–87%), NHS (94–109%), common site TTS (102–111%), HS (65–87%), unusual site TTS (76–100%), and DIC (49–104%). These differences were generally larger in MarketScan and HealthCore compared to BHI and Optum. Across adult populations in all commercial data sources, incidence rates for all of the negative control events except for CCS were higher among older age groups.

Annual incidence rates in 2019 stratified by sex within BHI, MarketScan, Optum, and HealthCore are shown in Tables 10B–10E, respectively. Within BHI, incidence rates for all AESI were different between males and females. Within MarketScan, Optum, and HealthCore, however, sex differences in annual rates were less common. Within MarketScan, incidence rates for appendicitis, DIC, ENC, PE, TM, and unusual site TTS were all similar between males and females. Within Optum, anaphylaxis, Bell's palsy, DIC, ENC, and TM were all similar. Within HealthCore, appendicitis, DIC, ENC, GBS, PE, TM, and unusual site TTS were all similar. Two AESI (ITP [37-53%] and narcolepsy [29-73%]) were higher in females in all commercial data sources. Further, anaphylaxis (26-40%) and Bell's palsy (8-17%) were higher in females for BHI, MarketScan, and HealthCore, and TM (47%) was higher for females in BHI. The 2019 annual rates for the remaining AESI in each data source were higher in males than females, with some of the greatest differences between sexes exhibited for AMI (144-208% higher in males), myocarditis/pericarditis (59-84% higher in males) and common site TTS (49-71% higher in males). For the negative control events, incidence rates for CD and hypertension were higher in males compared to females within BHI, MarketScan, and HealthCore. Incidence rates for well-care visits were higher among females than males in each of the three data sources. Colonoscopy rates were higher for females in MarketScan and HealthCore, but lower for females in BHI. Two negative control events were calculated among only females: CCS and mammograms.

4.3.3 Demographic Trends in Pediatric Population

Within the pediatric population, AESI rates were typically much lower than those within older populations, except for anaphylaxis and appendicitis. Age-stratified annual incidence rates are shown for BHI, MarketScan, Optum, and HealthCore in Tables 9B–9E, respectively. Across the commercial data sources, the most common AESI in the pediatric population were appendicitis (106.59 to 127.48 per 100,000 person-years), anaphylaxis (24.54 to 31.30 per 100,000 person-years) and Bell's palsy (21.84 and 24.91 per 100,000 person-years).

Annual incidence rates in 2019 stratified by sex among the pediatric population within BHI, MarketScan, Optum, and HealthCore are shown in Tables 10B–10E, respectively. The majority of AESI incidence rates were similar between pediatric males and females for all commercial data sources, but there was some minor variability. In BHI, rates were higher in males for anaphylaxis (26%), appendicitis (34%), and myocarditis/pericarditis (43%), but lower in males for Bell's palsy (15%). In MarketScan, rates were higher in males for appendicitis (54%) and myocarditis/pericarditis (95%). In Optum, rates were higher in males for anaphylaxis (25%), appendicitis (44%), and myocarditis/pericarditis (81%), but lower in males for narcolepsy (33%).

In HealthCore, rates were higher in males for anaphylaxis (22%), appendicitis (46%), HS (109%), and myocarditis/pericarditis (89%). Well-child visit incidence rates were slightly higher among females than males in the pediatric population across all commercial data sources for which they were measured (BHI, MarketScan, HealthCore).

4.4 Influenza Vaccinated Subpopulation

This section describes incidence rates of AEFI and negative control events within a subpopulation of individuals who received an influenza vaccination in the year prior to cohort entry, and it describes how those rates compare to those within the general study population. This subpopulation was defined to examine incidence rates among individuals who may be more likely to seek healthcare services and preventative care, with prior influenza vaccination serving as a proxy for this healthcare-seeking behavior. For comparisons listed in this section, 2019 annual incidence rates were used to represent rates. The 2019 calendar year was selected because it is the only pre-COVID year available for all data sources.

Overall, for the older adult and adult populations, about half of the AEFI had similar rates within the general study and influenza vaccinated populations, while the other half typically showed higher rates within the influenza vaccinated population. However, results did vary by data source. For the pediatric population, almost all AEFI had similar rates between the general and influenza vaccinated populations. Negative control events typically had higher incidence rates in the influenza vaccinated population. Detailed findings for each age-based population are summarized in the subsections below.

4.4.1 Influenza Vaccinated Adult Population 65 Years or Older

Incidence rates for the general and influenza vaccinated older adult populations in Medicare are displayed in Figure 5A and Table 13A. Eight AEFI showed similar incidence rates between the general and influenza vaccinated populations. Seven of these AEFI were solely defined in the inpatient (AMI, GBS, HS, and ENC) or inpatient and outpatient emergency department (anaphylaxis, DIC, TM) settings, potentially indicating that fewer differences existed between the two populations for severe events requiring emergency or hospital care. Incidence rates were higher in the influenza vaccinated population compared to the general population for eight other AEFI. For six of these eight (appendicitis, Bell's palsy, DVT, narcolepsy, PE, common site TTS), the influenza vaccinated population was 4–6% higher than the general older adult population while for the other two (ITP, myocarditis/pericarditis), the influenza vaccinated population was 12–15% higher than the general older adult population. The only AEFI for which the rate was lower in the influenza vaccinated population relative to the general older adult population was NHS, which was 3% lower among influenza vaccinated individuals. All six negative control events exhibited rates that were 9–21% higher in the influenza vaccinated population compared to the general older adult population.

4.4.2 Influenza Vaccinated Adult Population Under 65 Years

The adult population aged 18–64 years was analyzed separately in BHI, MarketScan, Optum, and HealthCore data sources. Annual incidence rates in 2019 for the general and influenza

vaccinated adult populations within BHI, MarketScan, Optum, and HealthCore are given in Figure 5B and Tables 13B–13E. Four AESI (ENC, GBS, HS, and TM) showed similar rates between the general adult and influenza vaccinated populations across all four data sources. Comparisons between the two populations for the remaining AESI differed between data sources.

In the BHI adult population, similar annual incidence rates between the general and influenza vaccinated adult populations were observed for nine AESI. Five of the remaining eight AESI exhibited higher incidence rates in the influenza vaccinated population compared to the general population (Bell's palsy, DVT, myocarditis/pericarditis, narcolepsy, PE), while the last three exhibited lower incidence rates in the influenza vaccinated population (AMI, appendicitis, DIC). Among the eight AESI with rate differences between the general and influenza vaccinated populations, seven had a difference magnitude of 4–10%. DIC exhibited the largest discrepancy and was 21% lower in the influenza vaccinated population relative to the general population.

In the MarketScan adult population, similar trends were observed but a larger number of AESI showed a substantial elevation in rates in the influenza vaccinated population compared to the general population. Six AESI (appendicitis, ENC, GBS, HS, NHS, and TM) had similar incidence rates between the general and influenza vaccinated populations. The remaining 11 AESI exhibited higher incidence rates in the influenza vaccinated population compared to the general population. The magnitude of the increase was much higher than that seen in the Medicare older adult population or in BHI data. Influenza vaccinated population incidence rates were 74% higher for unusual site TTS, 42% higher for ITP, 37% higher for common site TTS, 35% higher for DIC, and between 10–28% higher for the remaining seven AESI (AMI, anaphylaxis, Bell's palsy, DVT, myocarditis/pericarditis, narcolepsy, PE), when compared to the general adult population.

In the Optum adult population, ten AESI showed similar annual incidence rates between the general and influenza vaccinated population. Six of the remaining AESI (DVT, ITP, narcolepsy, PE, unusual site TTS, common site TTS) showed higher incidence rates in the influenza vaccinated population. As in MarketScan data, the largest differences came from unusual site TTS, common site TTS, and ITP which were 91%, 27%, and 27% higher in the influenza vaccinated population relative to the general population, respectively. Only one AESI (appendicitis) showed a lower rate in the influenza vaccinated population relative to the general adult population.

Finally, in the HealthCore adult population, six AESI (anaphylaxis, appendicitis, ENC, GBS, HS, and TM) showed similar annual incidence rates between the two populations while all of the remaining 11 AESI exhibited higher incidence rates in the influenza vaccinated population compared to the general adult population. Similar to MarketScan and Optum, the AESI with the largest differences were unusual site TTS, common site TTS, DIC, and ITP, which were 70%, 51%, 50%, and 49% higher in the influenza vaccinated population, respectively.

Incidence rates of negative control events were not calculated within Optum data. Within each of the other three data sources, incidence rates for all negative control events (CCS, CD,

colonoscopies, mammograms, hypertension, and WCV) were higher in the influenza vaccinated population compared to the general adult population. The magnitude of the difference was largest within MarketScan and HealthCore, where incidence rates were 12–56% higher in the influenza vaccinated population relative to the general adult population. In BHI, event incidence rates were only 3–23% higher in the influenza vaccinated population.

4.4.3 Influenza Vaccinated Pediatric Population

Annual incidence rates for the general and influenza vaccinated pediatric populations within BHI, MarketScan, and Optum are provided in Figure 5C and Tables 13B, 13C, and 13D, respectively. Incidence rates within the influenza vaccinated pediatric population were not calculated within HealthCore.

Across all three data sources (BHI, MarketScan, and Optum), almost all AESI showed similar incidence rates between the general and influenza vaccinated pediatric populations. Within BHI there was only one exception, appendicitis, which was 17% lower in the influenza vaccinated population compared to the general pediatric population. Within MarketScan and Optum there were three exceptions: anaphylaxis was 19–28% higher in the influenza vaccinated population, appendicitis was 8–16% lower in the influenza vaccinated population, and DVT was 26–30% lower in the influenza vaccinated population relative to the general pediatric population.

Incidence rates for well-child and well-care visits among the pediatric population were only calculated in the BHI and MarketScan data sources. Within MarketScan, incidence rates were 6% lower in the influenza vaccinated population relative to the general pediatric population. However, within BHI, incidence rates were 15% higher in the influenza vaccinated population compared to the general pediatric population.

5. Discussion and Conclusions

This report provides a comprehensive summary of incidence rates for 17 AESI and six negative control events between January 2017 and December 11, 2020 for older adult, adult, and pediatric populations as observed within five different administrative claims databases within the U.S. Incidence rates between 2017 and 2019 tended to be stable over time for most AESI although a few showed continuously increasing or decreasing trends over calendar time. Notably, anaphylaxis and appendicitis showed continuously increasing annual incidence rates between 2017 and 2019 within all three age subpopulations. Within older adults specifically, AMI and unusual site TTS showed increasing trends between 2017 and 2019, while DVT, DIC, and ITP showed decreasing trends. Visual inspection finds obvious seasonality for three AESI, specifically anaphylaxis and AMI among older adults, anaphylaxis among adults, and Bell's palsy among the pediatric population.

Monthly incidence rates for the majority of AESI and all negative control events were substantially impacted by the rise of COVID-19 cases in the U.S. beginning in March 2020. Incidence rates for all AESI, with the exception of DIC, as well as all negative control events showed a decrease in monthly incidence rates between March and May 2020. This was likely related to decreased healthcare utilization during this time^{11,12}, as well as the widespread

implementation of shelter in place orders and other public health policies designed to prevent the spread of COVID-19. Incidence rates for some health events recovered to pre-COVID levels as early as June 2020, while others recovered more gradually. Most health events returned to pre-COVID levels by October 2020, but recovery varied across data sources and there were some AESI, such as anaphylaxis, which remained lower than pre-COVID levels at the end of the study period. This may be expected given that stringent COVID-19 precautionary measures were still in place at the end of 2020, and health events that can result from external exposures may have been curtailed due to shelter in place orders. A few AESI, notably PE and myocarditis/pericarditis, showed an increase in monthly incidence rates in the second half of 2020, particularly in November and December, which were 40–50% higher than the corresponding monthly rates of any of the pre-COVID years. DVT and DIC also showed elevated monthly rates at the end of 2020 in some age-specific subpopulations and data sources. These increases in AESI rates may be partly associated with the spike in COVID-19 cases which occurred between November 2020 and January 2021. Several articles and case reports have indicated an increase in the risk of certain cardiovascular events, including AMI, stroke, and PE, following COVID-19 infection.^{13,14}

Health event incidence rates varied widely across age groups and nursing home residency status, and, to a lesser extent, across sex and race/ethnicity categories. Incidence rates for most AESI increased with age, although a few, including anaphylaxis and appendicitis, showed the opposite trend. Among older adults, and to a lesser extent among adults, AESI incidence rates tended to be higher among males than females. Fewer sex differences were observed within the pediatric population, and sex differences observed in BHI may be partly explained by the oversampled female population. When looking across strata of race/ethnicity within the older adult population (the only group for which race/ethnicity data were available), the highest AESI incidence rates were typically observed among Black or North American Native populations. Among older adults, the nursing home population had higher incidence rates than the non-nursing home population for all AESI except for appendicitis and anaphylaxis. The variations in incidence rates within strata of demographics support standardization when estimating more comparable expected counts in safety surveillance.

Incidence rates also varied based on healthcare seeking behaviors, as approximated by receipt of an influenza vaccination in the year prior to cohort entry. Adults and older adults who had received a prior influenza vaccination typically had similar or higher AESI incidence rates, and exclusively higher negative control event incidence rates, compared to the general population. This general trend of higher negative control event incidence rates within the influenza vaccinated population may reflect a general willingness to receive preventive healthcare services. However, within the pediatric population, few differences in AESI incidence rates and inconsistent differences in negative control event incidence rates were observed between the overall and influenza vaccinated populations. This may be reflective of the general health of the pediatric population, which was shown to exhibit low AESI rates, and the standard frequency of well-child visits (the sole negative control event examined within the pediatric population), which regularly occur independently of influenza vaccination schedules.

Within a given age-defined population (i.e., older adults, adults, pediatric), broad demographic and annual incidence rate trends in health events were largely similar across data sources. Additionally, the incidence rates were of similar magnitude across data sources, although variability did exist. Among the four commercial data sources (BHI, MarketScan, Optum, and HealthCore), incidence rate estimates were notably highest within the BHI data source, followed by Optum. This may in part be due to the nature of the BHI data used in this report, which did not represent the full set of BHI enrollees, but rather a cohort of individuals who had received a biologic product, were pregnant, or were born on or after October 1, 2015. These individuals may be more likely to require healthcare services compared to a broader population of all commercial insurance plan enrollees, contributing to the observed elevated event incidence rates in BHI.

In general, the background rates reported here are consistent with other published reports. However, most of the literature only provided general population estimates that were not stratified by demographic characteristics, and some of the reports were from older data sources that may have been outdated.

A 2021 study published by Gubernot et al. provided a large-scale compilation of CDC, FDA, and medical panel reports summarizing AESI incidence rates within the United States, largely within pre-COVID time periods.¹⁶ Ten of the AESI in that paper overlapped with those in our study, and the incidence rates reported by Gubernot et al. were broadly similar to our pre-COVID rates with a few exceptions. The largest discrepancy was observed for myocarditis/pericarditis, where Gubernot et al. reported an incidence rate of 26 per 100,000 person-years among Medicare beneficiaries, whereas our study found a much higher rate of 88 per 100,000 person-years in Medicare. This may be due to the fact that the algorithm used by Gubernot focused on acute pericarditis hospitalizations, whereas our study used a broader definition that included outpatient care and encompassed myocarditis.

An international study led by researchers at the Observational Health Data Sciences and Informatics (OHDSI) network produced a comprehensive summary of incidence rates for 15 AESI (a subset of the 17 AESI analyzed in our report) between 2017 and 2019 using pooled estimates from electronic health records and claims data sources.¹⁷ The results from that study also line up well with our own; for all AESI there is overlap between the point estimates calculated in our study and the 95% confidence intervals calculated by OHDSI. Among the older adult population, incidence rates tended to be higher in the Medicare population used in our study compared to the commercial populations from Optum, IQVIA, and MarketScan used by OHDSI. This may be due to differences in the underlying data sources – the CMS Medicare data used in this report covers a broader range of the older adult population while the subset of older adults who receive coverage from commercial plans may reflect a healthier subpopulation. Additionally, our data showed some small differences between sex strata for a few AESI that were not apparent in OHDSI, which may partly be due to our larger sample size. Broadly, similar age and sex-based trends were observed in both studies.

Finally, a report published by the European Medicines Agency (EMA)-funded vACCine covid-19 monitoring readinESS (ACCESS) project provided a comprehensive summary of incidence

rates for 42 AESI between 2017 and 2020 calculated from ten data sources originating from seven European countries.¹⁵ Nine of these AESI overlapped within our own. We observed similar rates for five of these AESI: GBS, ITP, NHS, HS, and TM. For the other four, our reported rates were higher than those reported by ACCESS: narcolepsy (2–3 in ACCESS compared to 44–52 per 100,000 person-years in the adult population within our study), myocarditis/pericarditis (11–16 compared to 34–41), DIC (2–3 compared to 4–9), and anaphylaxis (8 compared to 14–19). This may be due to differences in the diagnosis codes, algorithms and care settings used to identify these AESI, as well as differences in the underlying data sources. Similar age trends were seen for all nine AESI between ACCESS and our own study.

This study has several strengths. It represents a large population-based study consisting of over 80 million individuals across five administrative claims data sources in the US. The large cohort sizes enable more precise incidence rate estimates compared to other existing studies. Additionally, the use of pre-adjudicated claims in this study, where available, enabled rapid accumulation of data, and the ability to calculate incidence rate estimates throughout the entirety of 2020 for a broad range of AESI and negative control events. There have not yet been any other broad-population based studies in the US comparing pre and peri-COVID incidence rates to our knowledge, although at least one study making this comparison has been published using European data.¹⁵ Our study also provides a granular set of incidence rate calculations within age, sex, race/ethnicity, and nursing home residency status strata. Other studies in the literature typically lack this granularity.

Our study has several limitations. The data summarized in this report only reflect Medicare and certain commercially insured populations and therefore may not be generalizable to non-insured or other publicly-insured (e.g., Medicaid) populations. While claims data are extremely valuable for the efficient and effective examination of health events, all administrative claims databases have certain inherent limitations because the claims are collected for the purpose of payment and not research. The presence of a diagnosis code on a medical claim may not represent true presence of a disease, as the diagnosis code may be incorrectly coded or included as a diagnosis that was evaluated for rule-out purposes rather than actual disease. Since published literature was not available for all AESI to determine the appropriate length of the baseline clean period, it is possible that some periods were set incorrectly leading some rates to reflect a combination of prevalent and incident cases. Additionally, changes in coding can lead to changes in calculated incidence rates (Appendix A). This was seen for appendicitis, which underwent a coding change in October 2018, causing a substantial discrepancy between 2018 and 2019 annual rates. Any substantial changes in coding guidelines in the future could affect the relevance of the rates reported here moving forward. In order to provide a timely pandemic response, the AESI claims-based algorithms and risk and clean windows used in the report were generated by systematically reviewing published literature with prioritization of validation studies (Appendix B), communicating with other agencies, and consulting clinical subject matter experts.

In summary, AESI background rates vary widely across subpopulations, demographic strata, and data sources, and it is crucial to take these factors into account when determining the appropriate background rate to use for surveillance activities. These AESI rates are used in the selection of expected rates in the BEST Initiative near-real time surveillance of COVID-19 vaccines. Further, the incidence rates of AESI and negative controls events presented in this report are valuable tools for understanding the absolute magnitude of background rates prior to and during the COVID-19 pandemic, as well as the magnitude of background rates stratified by demographic factors. These rates were calculated in large US publicly and commercially insured populations, and thus afford contextualization of rates observed after receipt of COVID-19 vaccines in passive surveillance systems.

Forest Plots

Figure 1A. Forest Plot of 2017–2019 Pre-COVID Annual Incidence Rates for the Older Adult Population (Age 65+) in Medicare

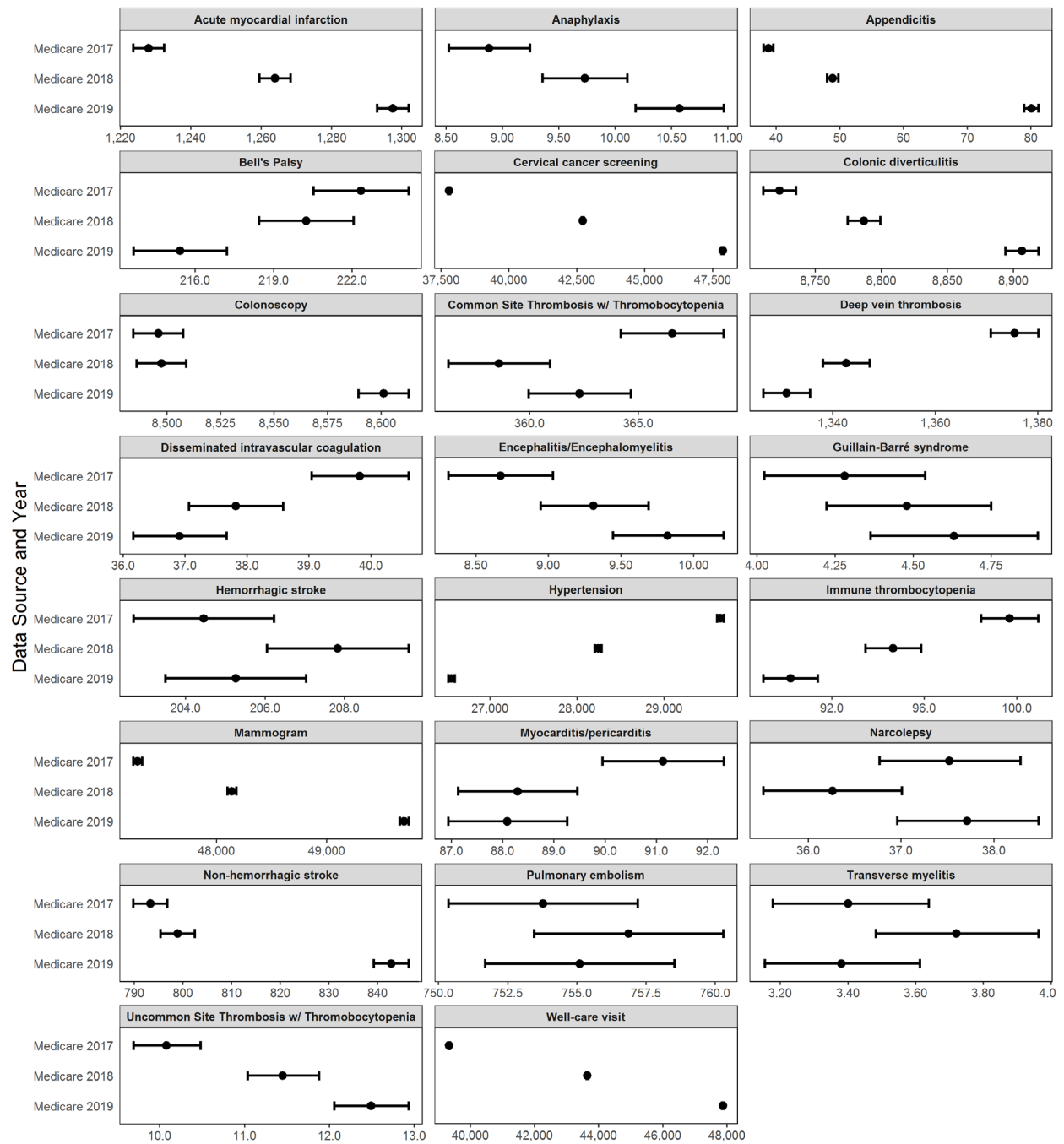


Figure 1B. Forest Plot of 2017–2019 Pre-COVID Annual Incidence Rates for Adult (Age 18–64) Populations in BHI, HealthCore, MarketScan, and Optum

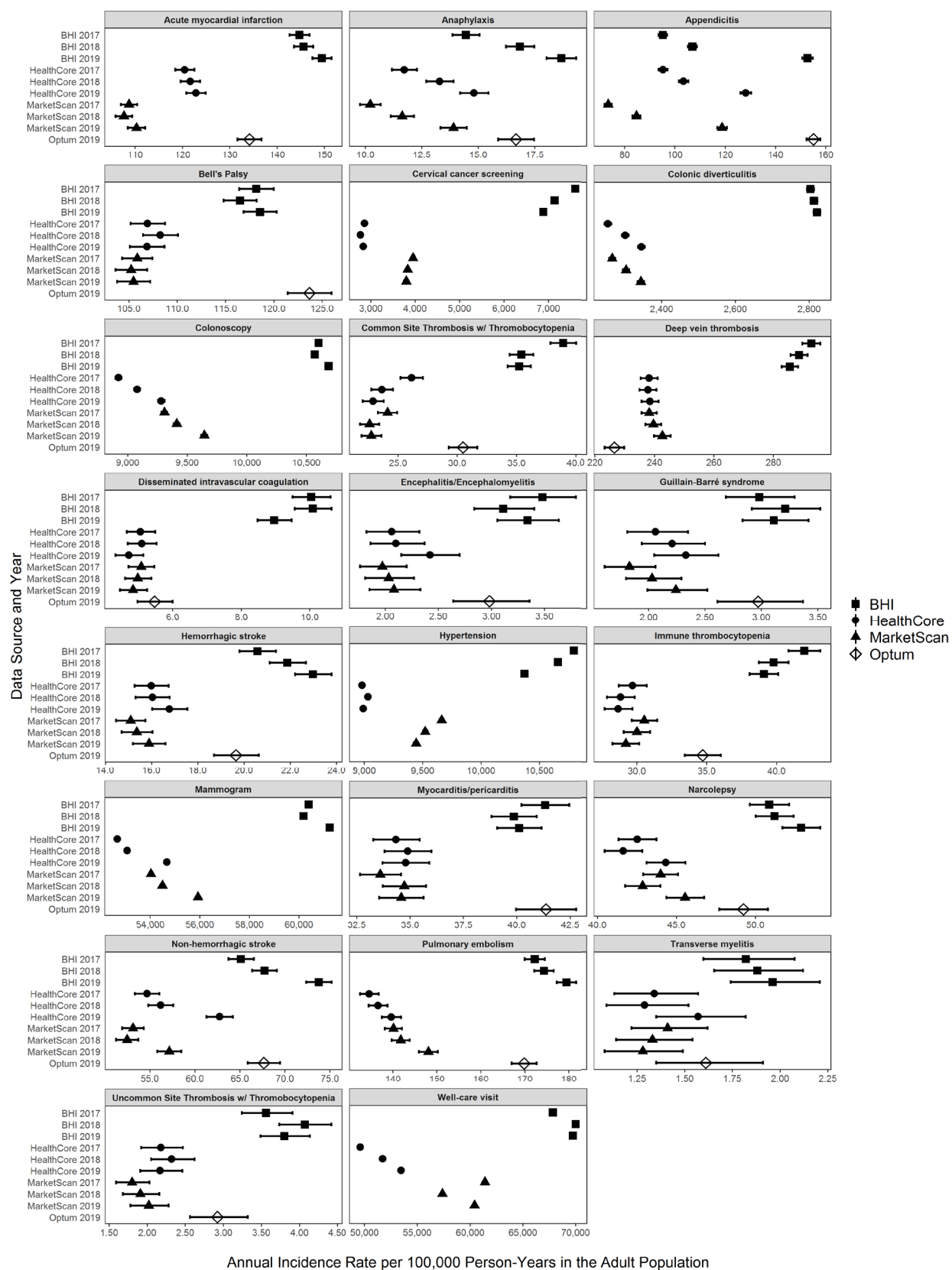


Figure 1C. Forest Plot of 2017–2019 Pre-COVID Annual Incidence Rates for Pediatric (Age 0–17) Populations in BHI, HealthCore, MarketScan, and Optum

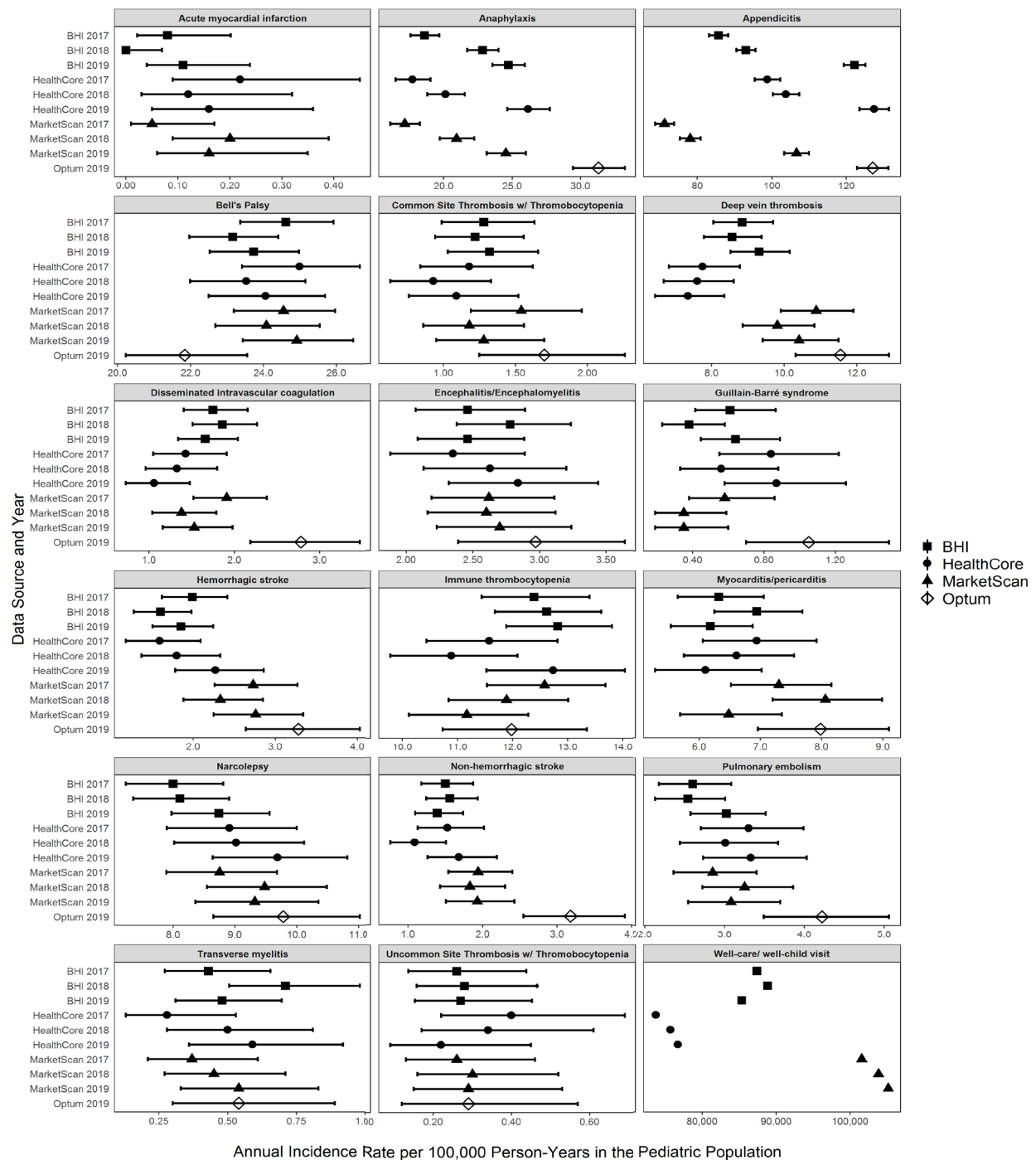
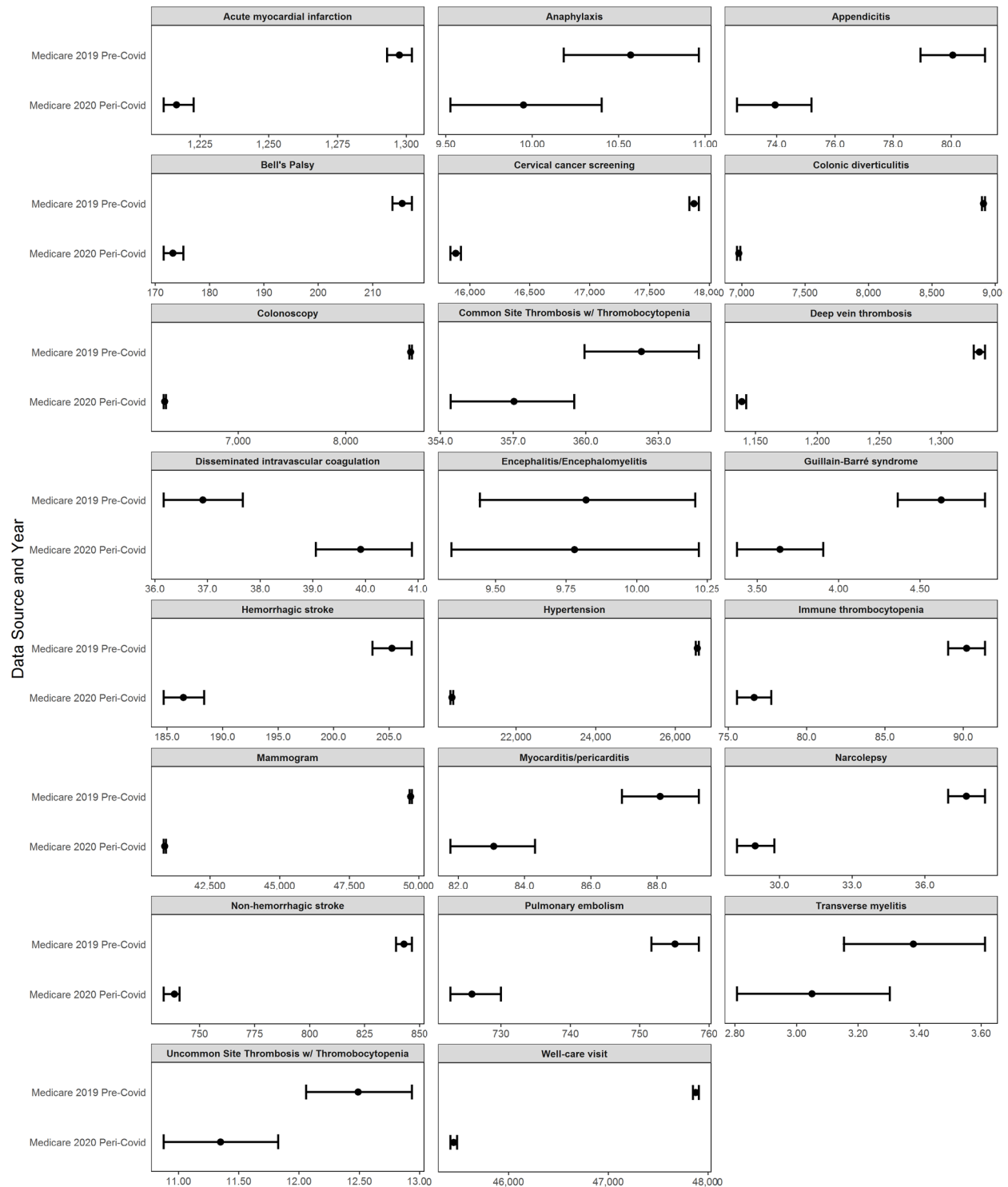
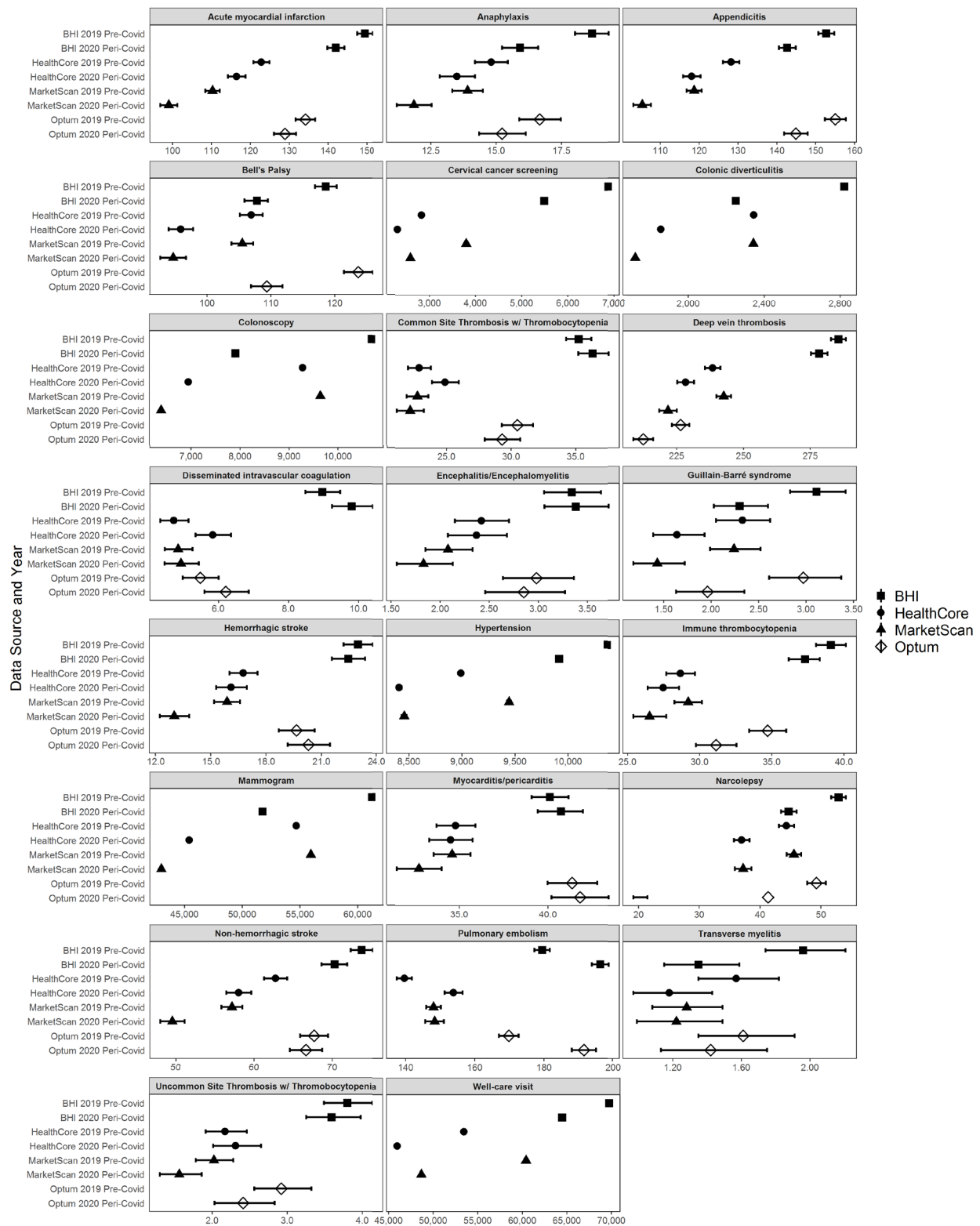


Figure 3A. Forest Plot of Incidence Rates for the Older Adult Population (Age 65+) in Medicare in pre-COVID and peri-COVID time



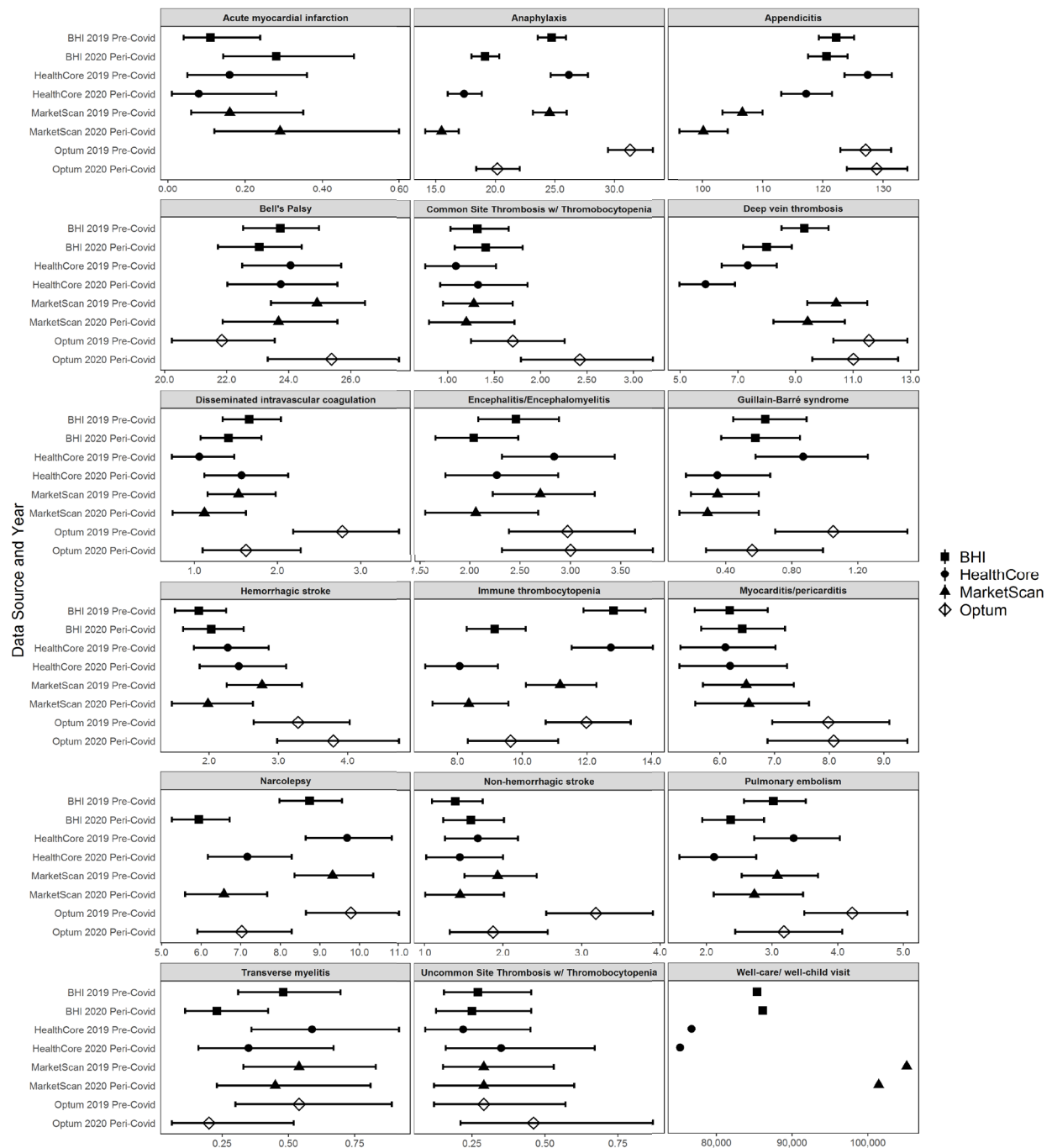
Pre-Covid (2019) and Peri-Covid (2020) Incidence Rate per 100,000 Person-Years in the Older Adult Population

Figure 3B. Forest Plot of Incidence Rates for Adult (Age 18–64) Populations in BHI, HealthCore, MarketScan, and Optum in pre-COVID and peri-COVID time



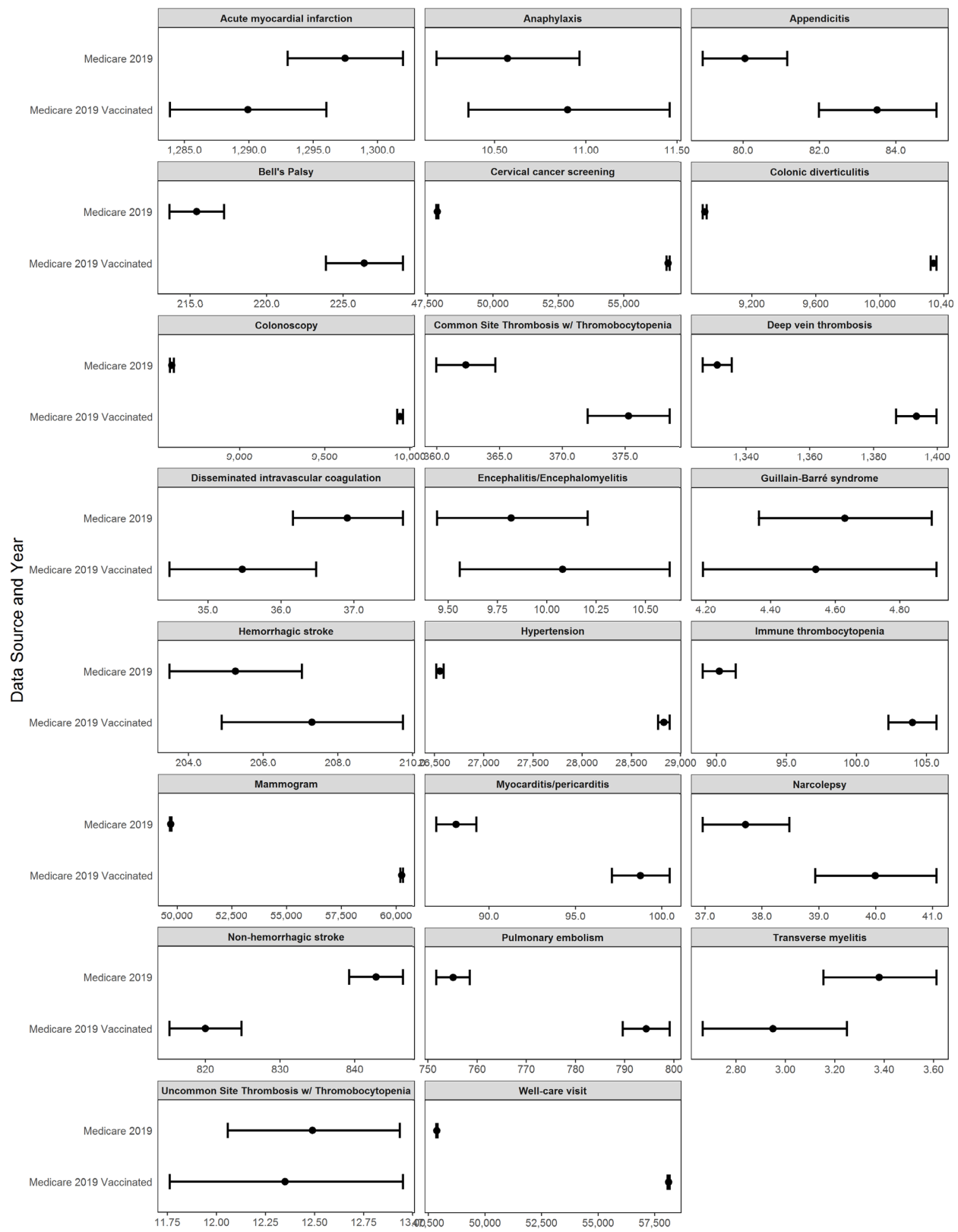
Pre-Covid (2019) and Peri-Covid (2020) Incidence Rate per 100,000 Person-Years in the Adult Population

Figure 3C. Forest Plot of Incidence Rates for Pediatric (Age 0–17) Populations in BHI, HealthCore, MarketScan, and Optum in pre-COVID and peri-COVID time



Pre-Covid (2019) and Peri-Covid (2020) Incidence Rate per 100,000 Person-Years in the Pediatric Population

Figure 5A. Forest Plot of Incidence Rates for Influenza Vaccinated and General Older Adult (Age 65+) Populations in Medicare



2019 Annual and Flu Vaccinated Incidence Rate per 100,000 Person-Years in the Older Adult Population

Figure 5B. Forest Plot of Incidence Rates for Influenza Vaccinated and General Adult (Age 18–64) Populations in BHI, HealthCore, MarketScan, and Optum

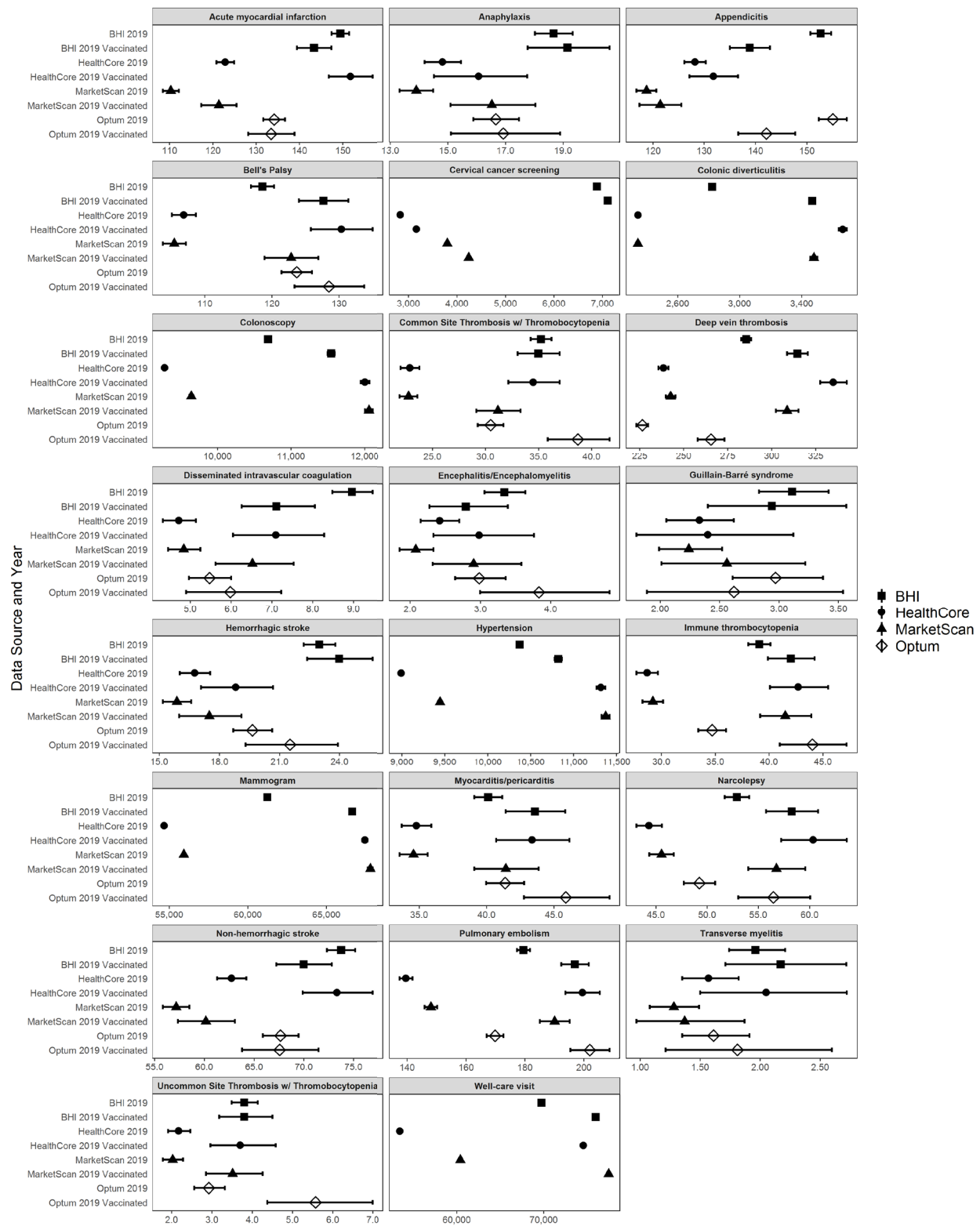
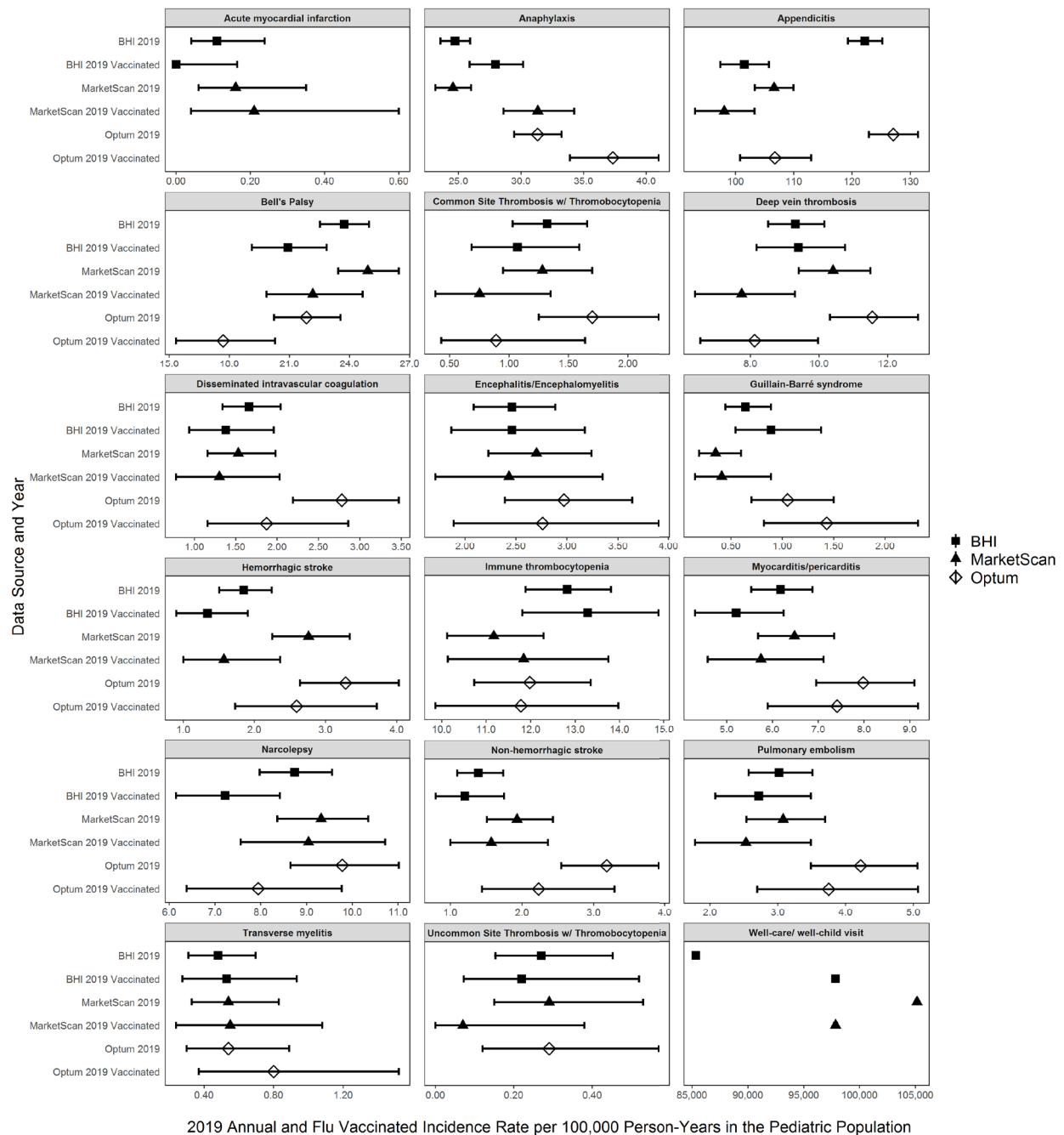


Figure 5C. Forest Plot of Incidence Rates for Influenza Vaccinated and General Pediatric (Age 0–17) Populations in BHI, MarketScan, and Optum



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Appendix A: Changes in Billing Codes over Time

The code lists for all health events were reviewed to determine if the effective date for any of the codes fell between 2017 and 2020. This was found to occur in five health events:

AESI	Code	Description	Effective Date
Acute Myocardial Infarction (AMI)	I219	Acute myocardial infarction, unspecified	10/1/2017
	I21A1	Myocardial infarction type 2	10/1/2017
	I21A9	Other myocardial infarction type	10/1/2017
Appendicitis	K3520	Acute appendicitis with generalized peritonitis without abscess	10/1/2018
	K3521	Acute appendicitis with generalized peritonitis with abscess	10/1/2018
	K3530	Acute appendicitis with localized peritonitis without perforation or gangrene	10/1/2018
	K3531	Acute appendicitis with localized peritonitis and gangrene, without perforation	10/1/2018
	K3532	Acute appendicitis with perforation and localized peritonitis, without abscess	10/1/2018
	K3533	Acute appendicitis with perforation and localized peritonitis, with abscess	10/1/2018
	K35890	Other acute appendicitis without perforation or gangrene	10/1/2018
	K35891	Other acute appendicitis without perforation, with gangrene	10/1/2018
Deep Vein Thrombosis (DVT)	I82451	Acute embolism and thrombosis of right peroneal vein	10/1/2019
	I82452	Acute embolism and thrombosis of left peroneal vein	10/1/2019
	I82453	Acute embolism and thrombosis of peroneal vein, bilateral	10/1/2019
	I82459	Acute embolism and thrombosis of unspecified peroneal vein	10/1/2019
	I82461	Acute embolism and thrombosis of right calf muscular vein	10/1/2019
	I82462	Acute embolism and thrombosis of left calf muscular vein	10/1/2019
	I82463	Acute embolism and thrombosis of calf muscular vein, bilateral	10/1/2019
	I82469	Acute embolism and thrombosis of unspecified calf muscular vein	10/1/2019
Non-Hemorrhagic Stroke (NHS)	I6381	Other cerebral infarction due to occlusion or stenosis of small artery	10/1/2018
	I6389	Other cerebral infarction	10/1/2018
Pulmonary Embolism (PE)	I2693	Single subsegmental pulmonary embolism without acute cor pulmonale	10/1/2019
	I2694	Multiple subsegmental pulmonary emboli without acute cor pulmonale	10/1/2019

Appendix B: AESI Algorithm Validation

AESI	Citation	Algorithm Incidence Rules	ICD Codes	PPV
Guillain-Barré syndrome (GBS)	Arya et al. ¹⁸	Identified GBS claims from the inpatient setting, using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9) code 357.0 until September 30, 2015, and the International Classification of Diseases, Tenth Revision, Clinical modification (ICD-10) code G61.0 afterwards, only the first discharge diagnosis position.	ICD-9: 357.0 ICD-10: G61.0	PPV of an inpatient diagnosis of GBS in ICD-10 of 71.21% (95% CI: 63.49%, 78.94%) for the 2015–16 season
	Perez-Vilar et al. ¹⁹	Identified GBS claims from the inpatient and outpatient settings using the International Classification of Diseases, Ninth Revision, Clinical modification (ICD-9-CM) code 357.0 (until September 30, 2015) and the International Classification of Diseases, Tenth Revision, Clinical modification (ICD-10-CM) code G61.0.	ICD-9: 357.0 ICD-10: G61.0	
	Polakowski et al. ²⁰	International Classification of Diseases, Ninth Revision, Clinical Modification diagnostic code 357.0 as the principal diagnosis or any of 9 possible secondary discharge diagnoses.	ICD-9: 357.0	In identifying chart-confirmed GBS cases was 35.8% overall -68.2% for principal diagnoses -7.8% for secondary diagnoses
	Greene et al. ²¹	Potential GBS cases were identified by searching for ICD-9 code 357.0 (acute infective polyneuritis) in any setting (in- patient, emergency department, or clinic). To restrict the data to new-onset events, we excluded cases if they had another GBS diagnosis recorded in electronic data within the prior year.	ICD-9: 357.0	Positive predictive value of 42.0% (29/69) for ICD-9 code 357.0 The positive predictive value for initial GBS diagnoses in the inpatient setting (20/31 1/4 64.5%) was higher than the positive predictive values in the clinic (8/30 1/4 26.7%) and emergency department (1/8 1/4 12.5%) settings.
Bell's palsy	Brandenbur et al. ²²	In public health department, general medical clinic or an outpatient physical therapy practice	ICD-9-CM: 351.x, 767.5, 053.11	PPV = 81% (221/272) for facial paralysis (95% CI: 76% to 85%)
	Lee et al. ²³	N/A	4 studies used ICD-9-CM 351.0 only; 1 used 351.x; 1 used 351.x, 767.5, 053.11 and H-ICDA 350	84% (95% CI 82–86) for definite/probably (351.0 only) 81% (95% CI 76–85%) for H_ICDA, 351.x, 767.5, and 053.11
	Rowhani-Rahbar et al. ²⁴	Code in any position	ICD-9-CM 351.0	PPV for definite or probable cases = 84% (95% CI 82% to 86%) PPV for definite cases = 20.1%
	Rowhani-Rahbar et al. ²⁵	For each case, the observed immunization status (a dichotomous dependent variable coded 0 or 1) during prespecified risk intervals of 1–14 days (weeks 1–2), 1–28 days (weeks 1–4), and 29–56 days (weeks 5–8) prior to onset was determined.	ICD-9-CM 351.0	87.8%
Encephalitis/ Encephalomyelitis (ENC)	Wiese et al. ²⁶	ICD based primary diagnoses only	ICD-9: 003.21, 036.0, 047.x, 049.x, 053.0, 054.72, 072.1, 091.81, 094.2, 098.82, 100.81, 320.x, 036.1, 054.3, 056.01, 058.21, 058.29, 062.x, 063.x, 064.x, 066.41, 072.2, 094.81, 130.0, 323.x	Meningitis/ encephalitis n=10 PPV 50.0 (95% CI 23.7-76.3)

AESI	Citation	Algorithm Incidence Rules	ICD Codes	PPV
Encephalitis/ Encephalomyelitis (ENC)	Samannodi et al. ²⁷	Admission ICD-10 coding	ICD-10: A17.8 , A50.4, A52.1 , A81.1, A81.9, A82.x, A83.x, A84.x, A85.x, A86, A88.8, A89, A92.3, B00.4, B01.1, B02.0, B10.0, B05.0, B06.0, B20.x, B26.2, B45.1, B57.4, B56.x, B58.2, B60.2, G04.0, G04.2, G04.8, G04.9, G05.x, G93.4, B94.1, B94.8	14%
Appendicitis	Coward et al. ²⁸⁻³⁰	Admitted to hospital with ICD code for appendicitis	ICD-10-CA Non-perforated appendicitis: K35.1, K35.9 Perforated appendicitis: K35.0	All appendicitis: 83.0% (82.2–83.7%) Perforated appendicitis: 52.4% (50.6–54.2%) Non-perforated appendicitis: 92.7 (92.0–93.4%) Pediatric appendicitis: 73.0% (71.3–74.7%) Adult appendicitis: 86.5% (85.7–87.2%)
	Kleif et al. ³¹	Patients with a primary or secondary diagnosis of appendicitis according to the International Classification of Diseases, version 10 (ICD-10 K35–37). As an additional analysis, the validity was calculated for patients having both a diagnosis of appendicitis (ICD-10: k35, k36, and k37) and a registered surgical procedure code for the removal of the appendix in the Danish National Patient Register.	ICD-10: K35, K36, K37	Diagnosis: 76.9% (76.7–77.1%) Diagnosis + Procedure: 89.5% (89.4–89.7%)
Myocarditis/pericarditis	Østergaard et al. ³²	Primary or secondary first-time diagnosis from departments of cardiology, internal medicine, acute medicine and neurology	ICD-10: I40, I41, I090, I514	PPV = 64% for myocarditis
Disseminated intravascular coagulation (DIC)	Friedman et al. ³³	ICD-9-CM or ICD-10-CM diagnosis code for DIC	NR	15% (95% CI 10-22%)
	Jawaid et al. ³⁴	Clinical notes and ICD diagnosis codes	NR	NR
Immune thrombocytopenia (ITP)	Rhee et al. ³⁵	Assessment of medical record for objective clinical marker - Nadir platelet count during hospitalization <50,000/μL and >50 % decrease from baseline*	ICD-9: 287.3; 287.5	Sensitivity (range between 2005 - 2013): 20 - 25% PPV (range between 2005 – 2013): 35 – 47%
	Terrel et al. ³⁶	Review of medical records OUMC for definite diagnosis of ITP by hemotologist/non-hemotologist	ICD-9: 287.3	The PPV for the administrative code for identifying patients with a definite diagnosis of ITP by a hematologist was 0.65 (356/548) overall - PPV children: 72% (215/300) - PPV adults: 69% (97/140)
Transverse myelitis (TM)	Schultz et al. ³⁷	Physician diagnosis of idiopathic or systemic lupus erythematosus-related ATM and MRI/CSF evidence of TM ATM defined as development of sensory, motor or autonomic dysfunction attributable to spinal cord lesions and progressing over hours or up to 3 weeks before admission to hospital	ICD-9: Acute TM: 341.20 Acute TM in conditions classified elsewhere: 341.21 Idiopathic TM: 341.22 Other causes of encephalitis and encephalomyelitis: 323.8 Unspecified causes of encephalitis, myelitis, and encephalomyelitis: 323.9	PPV: 62.1% 95% CI = 51.6–71.5% 54/87 ICD-identified cases were confirmed
	Klein et al. ³⁸	Chart review by neurologist NR	ICD-9: 323.9, written text in diagnosis	PPV: 75.7% (95% CI: 68.5–81.9%). Not generalizable due to use of text write in diagnoses.
Unusual site thrombosis with thrombocytopenia (Unusual site TTS)	Handley and Emsley ³⁹	Used ICD-10-CM codes to identify intracranial venous thrombosis (ICVT) and conducted a validation	ICD-10-CM codes (any position) G08, I67.6, I63.6, O22.5x, and O87.3	Across 65 patient records: PPV of 92.3% (95% CI 82.8–97.1%)

AESI	Citation	Algorithm Incidence Rules	ICD Codes	PPV
Unusual site thrombosis with thrombocytopenia (Unusual site TTS)	Lieberman et al. ⁴⁰	Used ICD-9-CM to identify cerebral venous thrombosis (CVT) and conducted a validation	ICD-9-CM codes (any position) 325.0, 437.6, and 671.5 in the emergency department or following inpatient admission	Any position (n=111): PPV of 75.7% (95% CI 66.9–82.8) Primary position: 83.8% (95% CI 68.5–92.7%)
	Pottegård ⁴¹	Used ICD-10 codes to assess the incidence of cardiovascular and haemostatic events in the first 28 days after vaccination with the Oxford-AstraZeneca vaccine ChAdOx1-S and to compare them with rates observed in the general populations.	ICD-10-based outcome definitions	No validation was conducted
	Prieto-Alhambra and Burn ⁴²	Used routinely-collected healthcare data from databases throughout Europe were used to identify incidence of thromboembolic events and co-occurrence with thrombocytopenia (Thrombosis-thrombocytopenia syndromes (TTS)) in the general population and in persons vaccinated against SARS-CoV-2 at 7, 14, 21, and 28 days Co-occurrence was defined as thrombocytopenia identified/recorded within 10 days before/after the diagnosis of the thrombotic event.	ICD-10-based outcome definitions	No validation was conducted
Common site thromboses with thrombocytopenia (Common site TTS)	Amman et al. ⁴³	Algorithm of ICD-9-CM administrative codes used to identify potential acute venous thromboembolism cases: 415.11 Iatrogenic pulmonary embolism and infarction 415.12 Septic pulmonary embolism 415.13 Saddle embolus of pulmonary artery 415.19 Other pulmonary embolism and infarction 451.11 Phlebitis and thrombophlebitis of femoral vein (deep) (superficial) 451.19 Phlebitis and thrombophlebitis of deep veins of lower extremities, other 451.2 Phlebitis and thrombophlebitis of lower extremities, unspecified 451.9 Phlebitis and thrombophlebitis of unspecified site 453.1 Thrombophlebitis migrans 453.2 Other venous embolism and thrombosis of inferior vena cava 453.40 Acute venous embolism and thrombosis of unspecified deep vessels of lower extremity 453.41 Acute venous embolism and thrombosis of deep vessels of proximal lower extremity 453.42 Acute venous embolism and thrombosis of deep vessels of distal lower extremity 453.9 Other venous embolism and thrombosis of unspecified site		Depends on position of diagnostic code (primary vs unspecified) and whether upper extremity DVTs were viewed as true cases or false positives. PPVs reported for all cases in report and appendix, and range from 26% (PPV for unspecified position) to 93% (PPV for primary position counting all DVTs and PEs as confirmed events)
Common site thromboses with thrombocytopenia (Common site TTS)	Prat et al. ⁴⁴	All ICD-10 codes (see table 1 for label descriptions and number of hospital stays per code) Peripheral arterial thrombosis: I74.0; I74.1; I74.2; I74.3; I74.4; I74.5; I74.8; I74.9 Peripheral vein thrombosis: I80.0; I80.1; I80.2; I80.3; I80.8; I80.9; I81; I82.0; I82.1; I82.3; I82.8; I82.9 Pulmonary embolism: I26.0; I26.9 Cerebral Venous Thrombosis: I63.6; I67.6; O22.5		The PPV of peripheral arterial thrombosis codes was 83.0%, 95% confidence interval (CI): 73.9–89.1, and the PPV of correct location of thrombosis was 81.0%, 95% CI: 72.2–87.5. The PPV of pulmonary embolism was 99.0%, 95% CI: 93.8–99.9. The PPV of peripheral venous thrombosis was 95.0%, 95% CI: 88.2–98.1, and the PPV of correct location of thrombosis was 85.0%, 95% CI: 76.7–90.7.
	Amman et al. ⁴⁵	The endpoint definition used to identify potential AIS cases included the following ICD-9-CM diagnosis codes originating from an inpatient hospital encounter: 433.x1 (occlusion and stenosis of pre-cerebral arteries with		

AESI	Citation	Algorithm Incidence Rules	ICD Codes	PPV
Common site thromboses with thrombocytopenia (Common site TTS)	Chrischilles et al. ⁴⁶	cerebral infarction), 434.xx (occlusion of cerebral arteries), or 436 (acute but ill-defined cerebrovascular disease). Ischemic stroke: 433.1, 434.4, 436 (recommended by Mini-Sentinel Protocol Core) Myocardial infarction: 410.x0, 410.x1 (well-validated) Pulmonary embolism: 415.1x (recommended by Mini-Sentinel Protocol Core) DVT: 451.11, 451.19, 451.2, 451.9, 453.1, 453.2, 453.40, 453.41, 453.42, 453.9, 325.xx, 437.6 (excluding 453.8 code series for upper extremity thrombosis) (recommended by Mini-Sentinel Protocol Core) Other: Individuals of any age New IVIg users (defined) Had chart-confirmed TEE (above) within the relevant risk window maintained health plan enrollment from date of IVIg treatment through the TEE date At least 183 enrollment prior to IVIg initiation Primary or unspecified position diagnosis codes Transient ischemic attacks (TIA) and non-MI coronary syndromes (e.g. unstable angina, ICD-9-CM code 411) were considered but excluded due to subjective validation criteria. Also excluded were a number of less common types of thrombosis, particularly those that are likely related to comorbidities (e.g. portal vein thrombosis is typically related to severe liver disease). Outcomes less specific to thrombosis, such as abdominal ischemia, were excluded. Hemorrhagic stroke was considered because it can be a consequence of cerebral venous occlusion, but ultimately excluded because most hemorrhagic strokes are not related to a cerebral venous occlusion. Most of these outcomes are severe enough that medical attention should be sought if they occur. However, there may be a lag between onset and diagnosis for venous TEE, particularly DVT.		Not specified
	Aboa-Eboule et al. ⁴⁷	An algorithm was applied to select primary diagnoses with one of the following ICD-10 codes: I61, I63, I64, and G46. Exclusion criteria were ICD-10 codes for transient ischemic attacks (G45) and subarachnoid hemorrhage (I60). All hospitalizations with a diagnosis of stroke were considered.		The overall sensitivity and PPV of the FHDDB for the diagnosis of stroke were, respectively, 77.1 % (95 % CI 74.2–80) and 69.2 % (95 % CI 66.1–72.2).
	Cutrona et al. ^{48,49}	Hospitalized patients with 410.x0 or 410.x1 in primary position		A PPV was calculated as the percentage of confirmed cases (definite or probable) of AMI among all hospitalizations identified. Overall, the PPV was 86.0% (95% CI: 79.2%, 91.2%). PPVs ranged from 76.3% to 94.3% across the Data Partners (Table 1). Several different subgroups defined a priori were examined (Table 2), but PPV estimates were imprecise due to the small sample size.
	Cutrona et al. ⁴⁹	Our final algorithm to identify AMI patients identified patients with ICD-9 principal (or first-listed) discharge codes 410.x0 and 410.x1.		Not reported (examined in a subsequent publication)

AESI	Citation	Algorithm Incidence Rules	ICD Codes	PPV
Common site thromboses with thrombocytopenia (Common site TTS)	Tamariz et al. ⁵⁰	The strongest PPV for pulmonary embolism was associated with an algorithm using ICD9 code 415.1, CPT codes 33910 and 33915 (pulmonary embolectomy) and at least two claims of prothombin time (CPT code 85610). The strongest ICD9 codes for DVT combined the 451 (phlebitis and thrombophlebitis) and 453 (vena cava) with the subcodes indicating where in the vein the thrombosis occurred. This led to a PPV of 84%. For non-specific codes (451.2, 453.8 and 453.9), the PPV was 79%. VTE algorithms combining PE and DVT had the highest PPV. When ICD-9 codes and subcodes 451.x, 453.x, and 415.x were used, the reported PPV was 96%. When ICD-9 codes and subcodes 451.x and 415.x were used, the reported PPV was 93%.		PE only: 24-92% (depending on population/algorithm) DVT only: 31-97% (depending on population and algorithm) PE/DVT combined: 93-96% (depending on algorithm).