

**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**

**Addendum – CVS Health Database Results**

July 28, 2022

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### Version Control

<b>Editors</b>	<b>Date</b>	<b>Version</b>	<b>Description</b>
Acumen, LLC	April 29, 2022	1.0	First Draft
Acumen, LLC, CVS, FDA	May 20, 2022	2.0	Second Draft
Acumen, LLC, CVS, FDA	July 8, 2022	3.0	Third Draft
Acumen, LLC, CVS, FDA	July 28, 2022	4.0	Final Draft

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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
CDM	Common Data Model
CI	Confidence interval
COVID-19	2019 novel coronavirus disease
CVS CTS	CVS Health Clinical Trial Services
FDA	Food and Drug Administration
NH	Nursing home
<b>Health Event Abbreviations</b>	
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
TTP	Thrombosis with thrombocytopenia syndrome
TM	Transverse myelitis
WCV	Well-child and well-care visits

# 1 Overview

As part of a near real-time safety monitoring of COVID-19 vaccines, the FDA Biologics Effectiveness and Safety (BEST) Initiative estimated the background rates of pre-specified adverse event(s) of special interest (AESI) in its databases to serve as the comparator for the observed rates. These historical background rates of adverse events can be used as a comparator to quickly identify potential increased risk of adverse events post-vaccination. The primary report titled *Background Rates of Adverse Events of Special Interest for COVID-19 Vaccine Safety Monitoring* (i.e., “primary report”) describing these background rates is available online [1, 2]. The primary report describes results from five different U.S. administrative claims data sources, with a review of the post-market surveillance of the potential AESI and six negative control events in Table 1. This addendum supplements the primary report by describing the monthly and annual background rates observed between 2019 and 2020 in a sixth data source: CVS Health Aetna commercial claims (CVS Health).

## 2 Methods

### 2.1 Data Source

The administrative claims database CVS Health Clinical Trial Services (CVS CTS) transforms enrollment, demographic, and medical and drug claims data, for individuals enrolled from January 2018 forward in Aetna commercial and Medicare Advantage health plans into a patient-centered, comprehensive Common Data Model (CDM). The CDM contains over 39 million individuals in total and on average about 22 million individuals annually. CVS CTS updates monthly with a data lag of approximately 1 week for drug claims, 6 weeks for outpatient, and 12 weeks for inpatient claims for over 80% of claims. Data are updated monthly with a lag of approximately 2.5 months from the most recent service date for 80% of inpatient claims.

### 2.2 Study Period

The full study period spanned from January 1, 2017 through December 11, 2020; however, results from the CVS Health database were generated using a study period from 2018-2019, meaning that background rates are available for all AESI from 2019-2020. The pre-COVID-19 and peri-COVID-19 time period definitions used for evaluating CVS Health rates were consistent with the analyses described in the primary report: The pre-COVID-19 period extended from the study period start through February 29, 2020 and the peri-COVID-19/pre-vaccine period was defined as March 1, 2020 through study end date.

### 2.3 Study Population

The study population was comprised of an annual cohort with a population that 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 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 incidence 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 1. Specifications for each negative control event are provided in Table 2. Individuals were included in more than one AESI or negative control event-specific cohort if they met all the inclusion criteria.<sup>1</sup> Individuals with an influenza vaccination in the calendar year prior to cohort entry were defined as a subpopulation of special interest.<sup>2</sup>

## 2.4 Health Events: AESI and Negative Control Events

AESI and negative control events are collectively referred to as ‘health events’ in this addendum. 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 [3-5]. The AESI are listed in Table 1, and considerations in the selection of these potential AESI are listed in section 3.5.1 of the primary report. 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.

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. The selected negative control events<sup>3</sup> are listed in Table 2.

## 2.5 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. Exact Poisson 95% confidence intervals (CI) were calculated for each incidence rate.<sup>4</sup>

Within the CVS Health cohort, age-based subpopulations were defined for the pediatric population (ages 0–17 years) and the adult population under 65 years (ages 18–64 years). The rates were stratified by demographic characteristics including age, sex, and history of healthcare-seeking behavior as indicated by prior receipt of influenza vaccination.

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.

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<sup>1</sup> More information on the clean period specifications for each AESI and negative control events and cohort entry requirements are located in section 3.3 of the primary report.

<sup>2</sup> More information on the requirement for the population is found in the 3.4 of the primary report.

<sup>3</sup> More information on the selection and definition of the negative control events is found in section 3.5.2 of the primary report.

<sup>4</sup> More information on the analysis of incident rates is found in section 3.6 of the primary report.



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.

### 3 Results

Across the 17 AESI analyzed, background rates varied considerably over time as well as across subpopulations and demographic strata. The following sections describe temporal, demographic, and subpopulation trends for the adult and pediatric populations.

#### 3.1 Pre-COVID-19

The year 2019 was used to measure pre-COVID-19 incidence rates in the CVS Health data source. The adult population for CVS Health contained between ten to 15 million beneficiaries for AESI and three to ten million beneficiaries for the negative control events. Annual 2019 cohort sizes by event in CVS Health are provided in Table 5, and a summary of 2019 annual incidence rates per 100,000 person-years across all data sources is provided in Table 6.

For most incidence rates and negative control events in the adult and pediatric populations for CVS Health, the pre-COVID-19 rates were similar to the other data sources. For the adult population, the highest incidence rates were AMI, appendicitis, DVT, and PE, and the lowest incidence rates were ENC, GBS, TM, and unusual site TTP. In the pediatric population, appendicitis was the highest AESI at 116.48 (95% Confidence Interval [CI]: [112.20, 120.89]) per 100,000 person-years. AMI, GBS, TM, and unusual site TTP were all below 1 per 100,000 person-years in the pediatric population.

Seasonal trends were observed in anaphylaxis and Bell's palsy in both the adult and pediatric populations (Figure 2C). Anaphylaxis incidence rates increased between February and August and decreased from August to November. Bell's palsy incidence rates increased from May to July and then steadily declined through the end of the year.

#### 3.2 Peri-COVID-19

The peri-COVID-19 period was defined within CVS Health as beginning on March 1, 2020 and ending on December 11, 2020. CVS Health incidence rates were consistent with other data sources' incidence rates in both the pre-COVID-19 and peri-COVID-19. Like the other data sources, many incidence rates decreased from the pre-COVID-19 to peri-COVID-19 period. Further, the monthly incidence rates were the lowest between March and May 2020, but they generally returned to 2019 rates over the remainder of the year.

Within the CVS Health adult population, appendicitis, DVT, and PE had the highest incidence rates per 100,000 person-years, while encephalitis/encephalomyelitis, GBS, TM, and unusual site TTP had incidence rates below 3 per 100,000 person-years. For the CVS Health pediatric population, appendicitis had the highest incidence rate at 100.42 (95% CI: [96.09, 104.90]).

Compared to other data sources, the CVS Health pediatric incidence rates for hemorrhagic stroke 1.59 (95% CI: [1.12, 2.18]), ITP 10.74 (95% CI: [9.46, 12.13]), and non-hemorrhagic stroke 2.34 (95% CI: [1.77, 3.04]) were slightly lower than the rates for the same AESI in other data sources.

In the CVS Health adult population, the greatest decrease in incidence rates from the pre-COVID-19 to peri-COVID-19 period was for GBS, where rates decreased approximately 59%. DIC and common site TTP slightly increased approximately 13% (5.75 to 6.52 events per 100,000 person-years) and 4% (28.25 to 29.24 events per 100,000 person-years), respectively, during the same period.

In the pediatric population, appendicitis had the highest incidence rates at 116.48 (95% CI: [112.20, 120.89]) in the pre-COVID-19 period and 100.42 (95% CI: [96.09, 104.90]) in the peri-COVID-19 period. The largest decrease between periods was in PE at approximately 86%. Between the period, DVT, DIC, hemorrhagic stroke, PE, and unusual site TTP increased between 4% and 33%. The CVS Health adult and pediatric populations' incidence rates for all AESI and control events are available in Table 7C.

Across all data sources, including CVS Health, the negative control event rates decreased in March and April 2020. In the CVS Health adult population, the negative control rates recovered to rates at or above the 2019 rates by December 2020. For the CVS Health pediatric population, only hypertension and well-care visit were included as negative control events. Notably, during the peri-COVID-19 period, the pediatric population's well-care visit incidence rates dropped by more than 100% below the April 2019 rates, but then recovered to similar levels as 2019 by June 2020 (Figure 4D).

### 3.3 Incidence Rates Stratified by Demographic Characteristic

Incidence rates of AESI within the CVS Health population were stratified by age and sex. Similar patterns were observed within the CVS Health population as in the other databases: older age groups and male beneficiaries generally had higher incidence rates of AESI compared to younger age groups and female beneficiaries.

Within the CVS Health adult population, incidence rates for AESI and negative control events generally increased with age. Rates for anaphylaxis, appendicitis, narcolepsy, and TM were highest within the oldest adult age group (age 56–64 years). The CVS Health incidence rates stratified by age are available in Table 9C.

Incidence rates stratified by sex are available in Table 10C. In the adult population, incidence rates for all AESI were higher among males than females other than for anaphylaxis, Bell's palsy, DIC, ITP, narcolepsy, PE, and TM, which were higher among females. Incidence rates for the negative control well-care visits were also higher among the female population than for the male population. Within the pediatric population, all AESI aside from DVT, ITP, PE, and common site TTP were higher among males than among females.

### 3.4 Influenza Vaccinated Subpopulation

In CVS Health adult population, the incidence rates of all AESI and negative control events were higher within the influenza-vaccinated population compared to the general population. AESI rates in the influenza-vaccinated population were approximately 15–80% higher than in the general population, and the negative controls were approximately 31-69%. DVT had the highest incident rate in the influenza vaccinated subpopulation (348.68 [95% CI: [339.63, 357.90]).

Influenza-vaccination stratifications were not available within the pediatric CVS Health population.

## 4 Discussion and Conclusion

Overall, the incidence rates estimated using the CVS Health data source were similar or slightly lower to the other data sources with slight variations among subpopulations. Like the other data sources, the CVS Health data source observed a significant change in rates during the peri-COVID-19 period, seasonality was noted in anaphylaxis and Bell's palsy, and the influenza-vaccinated subpopulation incidence rates were higher than the general population for both AESI and negative control events. While male beneficiaries still maintained the two highest AESI incidence rates (DVT and AMI) within the CVS Health data source, the difference between sexes was less pronounced than in other data sources.

Incidence rates of AESIs 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 addendum 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 (i.e., Medicare) and commercially insured populations, and thus afford contextualization of rates observed after receipt of COVID-19 vaccines in passive surveillance systems.

Please refer to the primary report for additional details as well as a discussion on the strengths and limitations of the study [1].

## 5 References

1. 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, 2021 December 2021. <https://bestinitiative.org/wp-content/uploads/2022/01/C19-Vax-Safety-AESI-Bkgd-Rate-Final-Report-2021.pdf>
2. Center for Biologics Evaluation and Research Office of Biostatistics and Epidemiology Supplemental File: Biologics Effectiveness and Safety (BEST) Initiative: Background Rates of Adverse Events of Special Interest for COVID-19 Vaccine Safety Monitoring, 2021 December 2021. <https://www.bestinitiative.org/wp-content/uploads/2021/02/C-19-Vaccine-Safety-AESI-Background-Rate-Supplemental-2021.xlsx>
3. Center for Biologics Evaluation and Research Office of Biostatistics and Epidemiology Background Rates of Adverse Events of Special Interest for COVID-19 Vaccine Safety Monitoring Protocol, 2021 January 12, 2021. <https://bestinitiative.org/wp-content/uploads/2021/02/C19-Vaccine-Safety-Protocol-2021.pdf>
4. Center for Biologics Evaluation and Research Office of Biostatistics and Epidemiology Supplemental File: Background Rates of Adverse Events of Special Interest for COVID-19 Vaccine Safety Monitoring, 2021. <https://bestinitiative.org/wp-content/uploads/2022/01/C19-Vax-Safety-AESI-Bkgd-Rate-Est-Protocol-Suppl.xlsx>
5. Center for Biologics Evaluation and Research Office of Biostatistics and Epidemiology Background Rates of Adverse Events of Special Interest for COVID-19 Vaccine Safety Monitoring: Protocol Addendum, 2021 December 29, 2021. <https://bestinitiative.org/wp-content/uploads/2022/01/C19-Vax-Safety-AESI-Bkgd-Rate-Protocol-Addendum-2021.pdf>

## 6 Tables and Figures

Please see *Background-Rate-Report-Tables-and-Figures.xlsx* for full presentation of all relevant tables and figures.

**Table 1. List of Adverse Events of Special Interest (AESI)**

Safety AESI	Age Group of Interest	Setting	Clean Window*
<b>General Population Health Events</b>			
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 <sup>£</sup> 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*

**Table 2. 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 8C. Incidence Rates for Pediatric and Adult Populations in CVS Health in pre-COVID and peri-COVID time**

AESI or Negative Control	Incidence Rate (per 100,000 person-years) (95% CI)			
	CVS Health Pediatric Population (age 0-17)		CVS Health Adult Population (age 18-64)	
	Pre-COVID-19 (2019)	Peri-COVID-19 (Mar-Dec 2020)	Pre-COVID-19 (2019)	Peri-COVID-19 (Mar-Dec 2020)
<b>Adverse Events</b>				
Acute myocardial infarction	0.08 (0.01, 0.30)	0.05 (0.00, 0.28)	110.48 (108.31, 112.69)	99.51 (97.21, 101.84)
Anaphylaxis	26.28 (24.60, 28.03)	17.27 (15.75, 18.90)	12.46 (11.86, 13.09)	10.72 (10.08, 11.40)
Appendicitis	116.48 (112.20, 120.89)	100.42 (96.09, 104.90)	117.15 (114.91, 119.43)	105.93 (103.57, 108.34)
Bell's Palsy	21.06 (19.43, 22.79)	21.51 (19.70, 23.45)	97.84 (95.98, 99.72)	89.14 (87.15, 91.17)
Deep vein thrombosis	7.23 (6.19, 8.39)	7.75 (6.58, 9.06)	232.20 (229.03, 235.39)	213.22 (209.86, 216.63)
Disseminated intravascular coagulation	1.59 (1.12, 2.18)	2.09 (1.50, 2.82)	5.75 (5.26, 6.27)	6.52 (5.94, 7.13)
Encephalitis/Encephalomyelitis	2.52 (1.98, 3.16)	1.91 (1.40, 2.55)	2.11 (1.84, 2.40)	2.11 (1.82, 2.45)
Guillain-Barré syndrome	0.54 (0.29, 0.93)	0.40 (0.17, 0.78)	2.23 (1.93, 2.56)	1.35 (1.09, 1.64)
Hemorrhagic stroke	1.59 (1.12, 2.18)	2.04 (1.46, 2.76)	18.49 (17.60, 19.40)	17.76 (16.80, 18.76)
Immune thrombocytopenia	10.74 (9.46, 12.13)	6.36 (5.30, 7.56)	27.40 (26.32, 28.51)	24.90 (23.76, 26.08)
Myocarditis/pericarditis	6.27 (5.30, 7.35)	5.22 (4.27, 6.31)	33.75 (32.55, 34.98)	32.87 (31.56, 34.22)
Narcolepsy	9.06 (7.90, 10.35)	6.16 (5.12, 7.34)	41.17 (39.85, 42.53)	31.02 (29.75, 32.34)
Non-hemorrhagic stroke	1.96 (1.44, 2.61)	1.29 (0.84, 1.89)	59.93 (58.33, 61.56)	54.41 (52.72, 56.14)
Pulmonary embolism	2.34 (1.77, 3.04)	2.38 (1.76, 3.16)	139.95 (137.50, 142.44)	145.04 (142.27, 147.85)
Transverse myelitis	0.58 (0.32, 0.98)	0.35 (0.14, 0.72)	1.41 (1.17, 1.68)	1.11 (0.88, 1.38)
Thrombosis with Thrombocytopenia (Unusual Site)	0.33 (0.14, 0.66)	0.35 (0.14, 0.72)	3.04 (2.69, 3.42)	2.68 (2.32, 3.09)
Thrombosis with Thrombocytopenia (Common Site)	1.38 (0.95, 1.94)	1.39 (0.92, 2.01)	28.25 (27.15, 29.38)	29.24 (28.00, 30.52)
<b>Negative Control Events</b>				
Cervical cancer screening	N/A	N/A	3,551.51 (3,533.84, 3,569.25)	2,921.44 (2,903.64, 2,939.33)
Colonic diverticulitis	3.76 (3.02, 4.62)	3.08 (2.36, 3.95)	2,076.68 (2,067.11, 2,086.28)	1,558.47 (1,549.28, 1,567.71)
Colonoscopy	N/A	N/A	8,445.15 (8,416.90, 8,473.49)	5,843.06 (5,816.72, 5,869.49)
Hypertension	167.71 (162.56, 172.98)	122.07 (117.29, 127.00)	7,798.82 (7,778.71, 7,818.97)	6,751.34 (6,730.71, 6,772.02)
Mammogram	N/A	N/A	49,694.43 (49,609.29, 49,779.68)	38,998.48 (38,914.15, 39,082.95)
Well-care visit	77,997.65 (77,885.92, 78,109.50)	70,192.70 (70,077.11, 70,308.43)	50,233.75 (50,187.18, 50,280.35)	40,953.61 (40,906.89, 41,000.37)

**Table 9C. 2019 AESI Annual Incidence Rates by Age Group in CVS Health**

AESI or Negative Control	CVS Health 2019 Incidence Rate (per 100,000 person-years) (95% CI)					
	Age 0 - 17	Age 18 - 25	Age 26 - 35	Age 36 - 45	Age 46 - 55	Age 56 - 64
<b>Adverse Events</b>						
Acute myocardial infarction	0.08 (0.01, 0.30)	3.88 (2.95, 5.01)	10.99 (9.44, 12.71)	52.05 (48.81, 55.44)	152.85 (147.49, 158.36)	298.14 (290.33, 306.10)
Anaphylaxis	26.28 (24.60, 28.03)	16.07 (14.48, 17.79)	11.31 (10.05, 12.68)	12.56 (11.23, 14.00)	12.87 (11.55, 14.28)	9.76 (8.58, 11.07)
Appendicitis	116.48 (112.20, 120.89)	148.26 (142.20, 154.51)	128.19 (122.77, 133.80)	118.75 (113.84, 123.82)	108.13 (103.63, 112.78)	90.19 (85.93, 94.62)
Bell's Palsy	21.06 (19.43, 22.79)	36.65 (33.99, 39.47)	68.77 (65.27, 72.40)	97.86 (93.79, 102.06)	129.76 (125.21, 134.42)	144.45 (139.46, 149.57)
Deep vein thrombosis	7.23 (6.19, 8.39)	39.74 (36.64, 43.04)	89.57 (85.04, 94.27)	176.55 (170.54, 182.71)	317.13 (309.37, 325.02)	480.29 (470.35, 490.38)
Disseminated intravascular coagulation	1.59 (1.12, 2.18)	1.97 (1.33, 2.82)	3.05 (2.26, 4.02)	4.86 (3.91, 5.97)	6.66 (5.58, 7.89)	11.12 (9.66, 12.75)
Encephalitis/Encephalomyelitis	2.52 (1.98, 3.16)	1.21 (0.76, 1.81)	1.90 (1.36, 2.58)	1.71 (1.21, 2.35)	2.19 (1.63, 2.87)	3.42 (2.69, 4.29)
Guillain-Barré syndrome	0.54 (0.29, 0.93)	1.25 (0.75, 1.95)	1.46 (0.94, 2.18)	2.10 (1.50, 2.88)	2.98 (2.28, 3.84)	3.01 (2.27, 3.91)
Hemorrhagic stroke	1.59 (1.12, 2.18)	2.83 (2.05, 3.81)	5.25 (4.20, 6.48)	10.58 (9.15, 12.17)	23.48 (21.41, 25.70)	45.42 (42.41, 48.59)
Immune thrombocytopenia	10.74 (9.46, 12.13)	13.03 (11.27, 14.97)	24.42 (22.09, 26.94)	26.02 (23.75, 28.45)	29.06 (26.75, 31.51)	41.36 (38.49, 44.39)
Myocarditis/pericarditis	6.27 (5.30, 7.35)	25.85 (23.36, 28.54)	23.93 (21.62, 26.42)	30.83 (28.35, 33.46)	38.71 (36.04, 41.53)	46.40 (43.36, 49.60)
Narcolepsy	9.06 (7.90, 10.35)	41.46 (38.29, 44.83)	42.14 (39.06, 45.41)	43.86 (40.89, 46.98)	41.36 (38.60, 44.27)	37.21 (34.49, 40.09)
Non-hemorrhagic stroke	1.96 (1.44, 2.61)	3.42 (2.55, 4.49)	11.17 (9.61, 12.91)	32.01 (29.49, 34.69)	73.45 (69.75, 77.30)	162.35 (156.60, 168.24)
Pulmonary embolism	2.34 (1.77, 3.04)	29.41 (26.75, 32.27)	58.20 (54.57, 62.02)	111.83 (107.06, 116.75)	186.41 (180.48, 192.48)	280.65 (273.08, 288.38)
Transverse myelitis	0.58 (0.32, 0.98)	0.59 (0.27, 1.12)	1.46 (0.94, 2.18)	1.13 (0.70, 1.73)	1.94 (1.38, 2.65)	1.72 (1.18, 2.43)
Thrombosis with Thrombocytopenia (Unusual Site)	0.33 (0.14, 0.66)	0.79 (0.41, 1.38)	0.43 (0.17, 0.88)	1.35 (0.87, 1.99)	3.98 (3.15, 4.95)	7.85 (6.63, 9.23)
Thrombosis with Thrombocytopenia (Common Site)	1.38 (0.95, 1.94)	3.95 (3.01, 5.08)	7.75 (6.46, 9.22)	14.14 (12.48, 15.96)	34.62 (32.10, 37.30)	73.34 (69.50, 77.34)
<b>Negative Control Event</b>						
Cervical cancer screening	N/A	3,305.07 (3,253.59, 3,357.16)	3,626.86 (3,586.67, 3,667.39)	3,398.78 (3,362.31, 3,435.56)	3,472.13 (3,436.75, 3,507.79)	3,840.12 (3,801.62, 3,878.92)
Colonic diverticulitis	3.76 (3.02, 4.62)	58.17 (54.40, 62.14)	219.28 (212.16, 226.58)	735.70 (723.35, 748.20)	3,260.47 (3,235.15, 3,285.95)	5,649.41 (5,614.29, 5,684.69)
Colonoscopy	N/A	N/A	N/A	3,175.14 (3,093.88, 3,258.00)	7,979.75 (7,940.76, 8,018.89)	9,464.33 (9,420.19, 9,508.64)
Hypertension	167.71 (162.56, 172.98)	940.15 (924.71, 955.79)	2,767.91 (2,741.93, 2,794.07)	6,330.10 (6,291.62, 6,368.75)	12,566.39 (12,510.16, 12,622.81)	19,249.31 (19,169.72, 19,329.15)
Mammogram	N/A	N/A	N/A	44,283.53 (44,112.24, 44,455.32)	50,233.63 (50,098.86, 50,368.67)	52,275.88 (52,133.65, 52,418.40)
Well-care visit	77,997.65 (77,885.92, 78,109.50)	35,257.95 (35,163.67, 35,352.42)	43,996.82 (43,895.37, 44,098.44)	51,934.09 (51,830.45, 52,037.89)	57,327.14 (57,222.61, 57,431.81)	58,594.44 (58,484.60, 58,704.44)



**Table 10C. 2019 AESI Annual Incidence Rates by Sex in CVS Health**

AESI or Negative Control	Incidence Rate (per 100,000 person-years) (95% CI)			
	CVS Health Pediatric Population (age 0-17)		CVS Health Adult Population (age 18-64)	
	Male	Female	Male	Female
<b>Adverse Events</b>				
Acute myocardial infarction	N/A	0.17 (0.02, 0.62)	158.24 (154.47, 162.09)	67.17 (64.83, 69.57)
Anaphylaxis	28.96 (26.51, 31.58)	23.43 (21.19, 25.85)	9.91 (9.13, 10.73)	14.69 (13.78, 15.65)
Appendicitis	137.26 (130.75, 144.01)	94.55 (89.05, 100.30)	121.67 (118.36, 125.05)	113.00 (109.95, 116.10)
Bell's Palsy	21.70 (19.40, 24.19)	20.53 (18.25, 23.01)	90.46 (87.88, 93.10)	104.49 (101.83, 107.19)
Deep vein thrombosis	6.74 (5.36, 8.37)	7.80 (6.28, 9.58)	242.97 (238.27, 247.72)	222.19 (217.91, 226.53)
Disseminated intravascular coagulation	1.73 (1.07, 2.64)	1.46 (0.85, 2.33)	5.24 (4.57, 5.98)	6.27 (5.57, 7.03)
Encephalitis/Encephalomyelitis	3.08 (2.26, 4.11)	1.95 (1.30, 2.82)	2.14 (1.76, 2.58)	2.06 (1.71, 2.48)
Guillain-Barré syndrome	0.66 (0.28, 1.30)	0.34 (0.09, 0.88)	2.51 (2.06, 3.04)	1.95 (1.56, 2.39)
Hemorrhagic stroke	1.81 (1.13, 2.74)	1.37 (0.78, 2.23)	21.40 (20.03, 22.84)	15.91 (14.78, 17.11)
Immune thrombocytopenia	10.27 (8.55, 12.24)	11.32 (9.47, 13.42)	21.48 (20.10, 22.92)	32.84 (31.21, 34.53)
Myocarditis/pericarditis	7.23 (5.80, 8.91)	5.14 (3.93, 6.62)	41.44 (39.52, 43.43)	26.73 (25.26, 28.26)
Narcolepsy	9.12 (7.51, 10.99)	9.00 (7.36, 10.90)	33.49 (31.77, 35.29)	48.24 (46.25, 50.28)
Non-hemorrhagic stroke	2.22 (1.46, 3.23)	1.71 (1.05, 2.65)	70.50 (67.99, 73.08)	50.29 (48.26, 52.37)
Pulmonary embolism	1.89 (1.20, 2.84)	2.83 (1.95, 3.97)	137.06 (133.54, 140.64)	142.45 (139.03, 145.94)
Transverse myelitis	0.66 (0.28, 1.30)	0.51 (0.19, 1.12)	1.19 (0.88, 1.56)	1.62 (1.28, 2.03)
Thrombosis with Thrombocytopenia (Unusual Site)	0.33 (0.09, 0.84)	0.34 (0.09, 0.88)	3.68 (3.12, 4.30)	2.46 (2.03, 2.96)
Thrombosis with Thrombocytopenia (Common Site)	1.07 (0.57, 1.83)	1.71 (1.05, 2.65)	32.91 (31.20, 34.69)	24.09 (22.69, 25.55)
<b>Negative Control Events</b>				
Cervical cancer screening	N/A	N/A	N/A	3,551.51 (3,533.84, 3,569.25)
Colonic diverticulitis	4.03 (2.98, 5.32)	3.51 (2.52, 4.77)	2,160.23 (2,146.06, 2,174.46)	2,000.02 (1,987.01, 2,013.09)
Colonoscopy	N/A	N/A	8,381.51 (8,340.30, 8,422.87)	8,493.49 (8,454.54, 8,532.57)
Hypertension	198.34 (190.50, 206.42)	135.99 (129.38, 142.86)	8,633.88 (8,602.91, 8,664.93)	7,063.81 (7,037.49, 7,090.21)
Mammogram	N/A	N/A	N/A	49,694.43 (49,609.29, 49,779.68)
Well-care visit	77,527.38 (77,371.15, 77,683.85)	78,436.80 (78,276.30, 78,597.55)	32,364.14 (32,309.87, 32,418.47)	66,431.47 (66,357.27, 66,505.73)