



Review

U.S. Population-Based background incidence rates of medical conditions for use in safety assessment of COVID-19 vaccines



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ABSTRACT

The Coronavirus Disease 2019 (COVID-19) pandemic has had a devastating impact on global health, and has resulted in an unprecedented, international collaborative effort to develop vaccines to control the outbreak, protect human lives, and avoid further social and economic disruption. Mass vaccination campaigns are underway in multiple countries and are expected worldwide once more vaccine becomes available. Some early candidate vaccines use novel platforms, such as mRNA encapsulated in lipid nanoparticles, and relatively new platforms, such as replication-deficient viral vectors. While these new vaccine platforms hold promise, limited safety data in humans are available. Serious health outcomes linked to vaccinations are rare, and some outcomes may occur incidentally in the vaccinated population. Knowledge of background incidence rates of these medical conditions is a critical component of vaccine safety monitoring to aid in the assessment of adverse events temporally associated with vaccination and to put these events into context with what would be expected due to chance alone. A list of 22 potential adverse events of special interest (AESI), including neurologic, autoimmune, and cardiovascular disorders, was compiled by subject matter experts at the U.S. Food and Drug Administration and the Centers for Disease Control and Prevention. The most recently available U.S. background rates for these medical conditions, overall and by age, sex, and race/ethnicity (when available), were sourced from reported statistics (data published by medical panels/ associations or federal government reports), and literature reviews in PubMed. This review provides estimates of background incidence rates for medical conditions that may be monitored or studied as AESI during safety surveillance and research for COVID-19 vaccines and other new vaccines.

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1. Introduction

The novel Coronavirus Disease 2019 (COVID-19) outbreak was first detected in Wuhan, China, in December 2019 and quickly spread to other countries; the World Health Organization declared a global public health emergency on January 30, 2020 [1]. This pandemic is estimated to have caused over 2.5 million deaths worldwide as of March 1, 2021 [2], and spurred unparalleled collaborative efforts to control and prevent COVID-19, including expedited vaccine development. Some early candidate vaccines use novel platforms, such as mRNA encapsulated in lipid nanoparticles, and relatively new platforms, such as replication-deficient viral vectors. In mid-December 2020, two mRNA COVID-19 vaccines received emergency use authorizations by the United States (U.S.) Food and Drug Administration (FDA), and many other candidate vaccines are under development [3]. Vaccination programs are expected to play an important role in preventing further COVID-19 spread, which is necessary to safeguard human lives, avoid overwhelming health systems, and avert further social and economic disruption.

Although mild to moderate local or systemic adverse events may occur after vaccination, serious health outcomes linked to vaccination are rare [4]. The findings from early post-authorization safety monitoring of COVID-19 vaccines in the U.S. are reassuring. Anaphylaxis cases have been detected following both authorized mRNA vaccines, though rarely. No safety signals have been detected for any other clinically important adverse events [5]. However, public concern about vaccine safety persists because of the unprecedented speed with which COVID-19 vaccines were developed and deployed. These perceptions may contribute to vaccine hesitancy [6]. Additionally, when events are rare, determining whether adverse events following vaccination are vaccine-related is critical, but difficult.

In the U.S., COVID-19 vaccine safety is closely monitored by the FDA and the Centers for Disease Control and Prevention (CDC) through both passive and active safety surveillance systems in collaboration with the Center for Medicare and Medicaid Services, the Department of Veterans Affairs, and other academic and large non-government healthcare data systems.

For example, the Vaccine Adverse Event Reporting System (VAERS) is a national spontaneous reporting (passive surveillance) system designed to detect unusual and unexpected patterns of adverse event reporting that might indicate a vaccine safety problem [7]. VAERS is not designed to assess causality. Additionally, incidence rates of post-vaccination adverse events of special interest (AESI) may be obtained from epidemiological studies assessing population-based data and active surveillance systems that are used to detect and confirm adverse events, including those signaled and followed up in VAERS [8]. State-of-the-art technologies are implemented for a coordinated and overlapping approach to monitor the safety of the COVID-19 vaccines. (<https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/covid-19-vaccine-safety-surveillance>).

Background incidence rates of medical conditions that are potential AESI for vaccine safety monitoring are important for contextualizing rates from vaccine safety surveillance data by allowing the comparison of expected rates of these conditions in the general population with observed event rates following vaccination. Published background rates of various diseases facilitated safety monitoring of AESI during pandemic H1N1 influenza vaccination in 2009–2010 [9].

Robust incidence data are available for many medical conditions that present as potential AESI. Knowledge of the most recent background rates of potential AESI in the U.S. population, and data on known vaccine-associated AESI, will support COVID-19 vaccine

safety surveillance and research and inform product-specific vaccine benefit-risk analyses and public health communication. The objective of this review is to present estimated background incidence rates of medical conditions based on existing literature that may also present as AESIs following COVID-19 vaccination.

2. Methods

A list of AESI was compiled by subject matter experts at the FDA and CDC (Table 1). The list is not exhaustive but reflects serious conditions that have been designated as AESI with respect to vaccination based on historical interest, general interest, known

association with natural SARS-CoV-2 infection, or known causal association with vaccination.

Sources of reported statistics for AESI included publicly available data on CDC or other U.S. government web pages and data published by medical panels or associations. Literature reviews were completed in PubMed (<https://pubmed.ncbi.nlm.nih.gov/>) for AESI lacking reported statistics, or where statistics did not address rates by age group or sex or following vaccination. In consultation with an FDA librarian, a PubMed search string was developed to identify published papers using a combination of search terms, including epidemiology, epidemiol*, incidence, background rate*, and medical subject headings related to the AESI (<https://www.ncbi.nlm.nih.gov/mesh>). Searches were completed by

Table 1

Conditions of interest and methodology for determining background rates in the US or other relevant populations.

Condition	ICD-9 Codes ¹	ICD-10 Codes ¹	Reported Statistics	Literature Review	Other
Neurologic conditions					
Guillain-Barré syndrome (GBS)	357.0	G61.0		X	
Multiple sclerosis (MS)	323.61; 323.81; 340.0; 341.0; 341.1; 341.20; 341.22; 341.8; 341.9; 377.30; 377.32; 377.39	G35.0; G36; G37		X	
Transverse myelitis (TM)	341.2; 323.9	G36.0; G37.0; G37.8; G37.9; G37.3		X	
Optic neuritis (ON)	377.32	H46.0		X	
Chronic inflammatory demyelinating polyneuropathy (CIDP)	N/A	N/A		X	
Acute disseminated encephalomyelitis (ADEM)	052.0; 055.0; 136.9; 323.5; 323.6; 323.61; 323.8; 323.9	N/A		X	
Meningitis, aseptic (AM)	045.2, 047.X, 048, 049.X, 072.1, 321; 322.X	N/A		X	
Encephalitis	323.5; 323.6; 323.61; 323.62; 323.9	N/A		X	
Seizures	345.xx; 333.2; 779.0; 780.3; 780.39 780.2; 780.31	N/A		X	
Cerebrovascular accident (stroke), ischemic and hemorrhagic	430–438	G45.X; I60.X; I61.X; I62.X; I63.X; I65.X; I66.X; I67.X	X	X	
Narcolepsy and cataplexy	N/A	N/A		X	
Cardiovascular conditions					
Myocarditis and pericarditis	420.90; 420.91; 420.90; 420.91; 420.99; 420.00; 422.0; 422.90; 422.91; 422.99; 423.9; 429.0; 391.0	N/A		X	
Venous thromboembolism (VTE)	451.1; 451.2; 451.8; 451.8; 451.9; 453.1; 453.2; 453.8; 453.9; 634.6; 635.6; 636.6; 637.6; 638.6; 639.6; 671.3; 671.4; 671.9; 673.2; 673.2; 996.7; 996.7; 997.2; 999.2	N/A	X	X	
Myocardial infarction, acute (MI)	410.xx; 411.xx	I21.9	X	X	
Mortality					
All cause, cause-specific, and sudden death	N/A	N/A ²	X	X	
Pregnancy loss, including spontaneous abortion (SAB)	634.x; 637.x	N/A	X	X	
Fetal deaths, gestational age ≥ 20 weeks	N/A	P95; P02; P01; Q00-Q99; P00	X		
Other					
Kawasaki disease (KD)	446.1	M30.3		X	
Multisystem inflammatory syndrome, children (MIS-C) ³	N/A	N/A		X	X ³
Anaphylaxis	989.5; 995.0; 995.20; 995.21; 995.27; 995.60–995.69; 995.7; 999.4; 999.41; 999.42; 999.49; 999.50; E9480–E948.9; E949.0–E949.9	T78.0; T78.2; T80.5; T88.6		X	
Idiopathic or immune thrombocytopenic purpura (ITP)	287.0–287.9	D69.3		X	
Vaccine-mediated enhanced disease (VMED) ³	N/A	N/A			

N/A = ICD codes not reported in the studies, use of a different case ascertainment, or no studies within timeframe of 9th or 10th revision.

1 - International Classification of Diseases (ICD) 9th/10th Revision codes used in the referenced studies or reported statistics, when available. Numerous ICD-9 and ICD-10 codes were used in various studies; all codes are not listed here. Refer to each study for specific codes utilized.

2 - ICD-10 codes generally listed by code groupings in available mortality studies, which are too extensive to list here. Refer to related studies for specific codes utilized.

3 - Published rates were limited for MIS-C and absent for MIS in adults and VMED. Sources reporting numbers of known cases and published cases series were reviewed for MIS-C.

November 6, 2020 (data lock point for references used for multi-system inflammatory syndrome was December 4, 2020), restricted to English language papers, and prioritized the most recent background rates, excluding literature older than 1970. Titles and abstracts were reviewed for inclusion; in some cases, full text papers were reviewed for inclusion if the abstract did not include rates or populations studied. Additional published literature not found in the PubMed search was included after review of reference lists or through consultation with subject matter experts.

Investigators were assigned as primary or secondary reviewers for one or more AESI. For each AESI, primary reviewers extracted background rates in the general U.S. population and, where available, rates by age, sex, and race/ethnicity, and following vaccination. If review of U.S. literature failed to identify published background rates in the general population or following vaccination or COVID-19 disease, the international literature was reviewed for inclusion.

The secondary reviewer verified abstracted data sources and tables as a quality check on the initial abstraction.

3. Results/Discussion

Among the 22 AESI, background rates were derived most frequently from literature review ($N = 20$ conditions, 87%) and/or from reported statistics ($N = 6$ conditions, 26%) (Table 1). The results for each AESI are summarized in the text below and in Table 2; additional information about the specific studies, including sub-populations can be found in Supplemental Tables 1–21.

3.1. Neurological conditions

3.1.1. Guillain-Barré syndrome (GBS)

Overall incidence of GBS, a heterogeneous condition with several variant forms, is estimated to be 1–2/100,000 per year [10] (Supplemental Table 1). A meta-analysis of GBS incidence (1966–2009) reported a crude incidence of 0.81–1.89 (median 1.11) cases/100,000 person-years (PY), increased risk among males, and a 20% increase per 10-year increase in age (age-specific rates increased from 0.62 cases/100,000 PY among those aged 0–9 years[y] to 2.66 cases/100,000 PY among those 80–89y) [11]. A large U.S. cohort study (2000–2009) reported an overall age-standardized incidence of 1.72/100,000 PY, with rates of 1.45 and 2.04 for females and males, respectively, and increases in incidence by 50% per 10-year increase in age [12]. A California study reported overall incidence of 2.4/100,000 PY in people aged 10–62y, with peaks in the lowest and oldest age groups and higher rates among males than females for all age groups [13]. The slightly higher incidence in this study compared with others may result from inclusion of GBS variants (e.g., Miller Fisher Syndrome). Additionally, an analysis of the Nationwide Inpatient Sample (NIS) database determined GBS hospitalizations incidence in adults ≥ 18 y to be 1.65–1.79/100,000 in 2000–2004 [14]. Additional population-based studies may be found in Supplemental Table 1 [15–16].

Population-based surveillance for GBS in 44.9 million U.S. residents enrolled in the Emerging Infections Program (EIP) during the 2009–2010 H1N1 influenza vaccination campaign (October 2009–May 2010) found a rate of 1.85/100,000 PY in persons who received the H1N1 vaccine within the 42-day GBS risk period. Compared to unvaccinated people, GBS incidence immediately following H1N1 vaccination was higher among vaccinated people (adjusted rate ratio = 1.57) [17]. Of note, over half of GBS cases who received H1N1 vaccine during the 42 days before illness onset also reported other exposures possibly linked to GBS. Slightly elevated risk of GBS after H1N1 vaccination during the 2009–2010 influenza season was also observed in a self-controlled risk interval study that

found an elevated risk of confirmed GBS following receipt of mono-valent inactivated influenza vaccine during the predefined risk period of 1–42 days (relative risk = 4.4) [18], and in a retrospective study of Medicare beneficiaries (attributable risk: 2.47/100,000 PY) [19]. An EIP study reported rates in vaccinated and unvaccinated populations of 1.92/100,000 PY and 1.21/100,000 PY, respectively [20], while other studies found a lower risk or no association between vaccinated and unvaccinated populations [21–22].

A recent study in Italy compared GBS incidence at time periods before and during the COVID-19 pandemic and estimated the rates of GBS at 0.93/100,000 (March–April 2019) and 2.43/100,000 (March–April 2020), indicating a 2.6-fold increase [23]. The study estimated the incidence of GBS in COVID-19 positive patients was 47.9/100,000. When considering

only the COVID-19-positive cases hospitalized in March and April 2020, the incidence of GBS was 236/100,000 cases. GBS may thus be a clinical component of COVID-19 infection, and the association requires further study.

3.1.2. Multiple sclerosis (MS)

MS incidence studies report a range of estimates in the general adult population (5.0–14.2/100,000 PY), yet all demonstrate rates significantly higher in females than males (Supplemental Table 2). A multi-ethnic population-based study in California reported an overall rate of 5.0/100,000 PY in a 2008–2010 cohort, with the highest incidence in Black or African American persons (10.24/100,000 PY), followed by White persons (7.28), Hispanic or Latino persons (2.94) and Asian/Pacific Islander (PI) persons (1.45) [24]. Using the same database, a pediatric population-based study found the incidence to be 0.51/100,000 PY for those ≤ 18 y; most cases were in Hispanic children (56%), followed by Black or African American children (24%), Asian/PI children (12%), and White children (8%) [25]. A study using Rochester Epidemiology Project (REP) data (1985–2000) found an overall incidence of 7.5/100,000 [26], while a California study reported an overall rate of 14.2/100,000 PY [13]. A study of military personnel found an overall unadjusted rate of 14.9/100,000 PY, with a notably higher incidence of 34.4/100,000 PY for females [27].

3.1.3. Transverse myelitis (TM)

Incidence studies for TM are rare and differ by diagnostic criteria utilized; however, all available studies demonstrated a preponderance of female cases. A retrospective analysis of patients of five hospitals in New Mexico (1980–1990) found an overall rate of 4.6/million [28], whereas a 2003–2016 REP study found a rate of 9.49/million PY (7.15 for males and 11.74 for females) [29] (Supplemental Table 3). A California study reported a higher incidence of 3.1/100,000 PY [13], possibly because the study did not distinguish TM cases from those later diagnosed as MS.

3.1.4. Optic neuritis (ON)

There is a paucity of data regarding ON incidence (Supplemental Table 4). A 2000–2018 REP study reported a population-based rate of 3.9/100,000, with 67% occurring in females [30]. An older study (1985–1991) using the same data source found an overall rate of 5.1/100,000 PY (2.6/100,000 PY in males and 7.5/100,000 PY in females) [31].

3.1.5. Chronic inflammatory demyelinating polyneuropathy (CIDP)

One U.S. population-based analysis was found for CIDP (1982–2001), which reported incidence of 1.6/100,000 for persons aged 4–83y (median 58y) [32] (Supplemental Table 5). A 2019 systematic review and meta-analysis reported a pooled crude incidence of 0.33/100,000 PY, with study-based rates ranging from 0.15 to 0.70/100,000 PY (0.51–0.90/100,000 population for males and 0.14–0.48/100,000 for females) [33]. A systematic review of

Table 2
Medical Condition Incidence Rate Ranges Among the US General Population and Vaccinees.

Medical Condition [Supplemental Table number]	Incidence Rate Range, Total, US Population ¹ [Ref]	Study Population with Lowest Rate ¹ [Ref]	Study Population with Highest Rate ¹ [Ref]	Incidence Rate Range Post-vaccination [Ref]
Guillain-Barre' syndrome (GSB) [1]	0.24 – 2.4 per 100,000 PY [10–16]	US Pregnant Women (0.24/100,000 PY) [15]	California, persons 10–62y of age (2.4/100,000 PY) [13]	1.19 – 4.3 per 100,000 PY [17,19–22]
Multiple Sclerosis (MS) [2]	0.51–14.9 per 100,000 PY [13,24–27]	California Children ≤ 18y (0.51/100,000 PY) [25]	US active Military (14.9 per 100,000 PY) [27]	N/A
Transverse myelitis (TM) [3]	4.6 – 8.64 per million population [28–29]	Albuquerque, NM (4.6/million) [28]	Olmstead County Minnesota (8.64/million; 9.49/million PY) [29]	N/A
Optic Neuritis (ON) [4]	3.1 – 9.49 per million PY [13,29] 3.9 per 100,000 population [30] 5.1 per 100,000 PY [31]	California 10–62y of age (3.1/million PY) [13] N/A	N/A	N/A
Chronic inflammatory demyelinating polyneuropathy (CIDP) [5]	1.6 per 100,000 population [32]	N/A	N/A	N/A
Acute disseminated encephalomyelitis (ADEM) [6]	0.4 – 0.5 per 100,000 children [35–36]	San Diego, CA, children < 20y (0.4/100,000) [36]	US children ≤ 18y (0.5/100,000) [35]	0.05 – 0.15 per 1 million doses distributed [37]
Aseptic meningitis (AM) [7]	10.9 – 17.8 per 100,000 PY [38]	Olmsted County, MN, 1950–1981 (10.9/100,000 PY) [38]	Olmsted County, MN, 1976–1981 (17.8/100,000 PY) [38]	16.9 per 100,000 PY, children 12–23 m of age [39]
Encephalitis [8]	6.9 – 7.3 per 100,000 population, all etiologies [40–42] 0.6 – 1.0 per 100,000 PY, specific etiologies [42]	US hospitalizations 1998–2010 (6.9/100,000) [40] Olmsted County, MN, viral etiology (0.6/100,000 PY) [42]	US hospitalizations 2000–2010 (7.3/100,000) [41] Olmsted County, MN, infectious etiology (1.0/100,000 PY) [42]	0.01 – 0.02/100,000 population [41]
Seizures (Epilepsy and first unprovoked seizure) [9]	16.4 – 44 per 100,000 PY, epilepsy [44–46] 41.1 – 61 per 100,000 PY, first unprovoked seizure [44–46]	New York City, low-income, predominantly Hispanic community, epilepsy (16.4/100,000 PY); first unprovoked seizure (41.1/100,000 PY) [45]	Minnesota, Rochester residents, epilepsy (44/100,000 PY); first unprovoked seizure (61/100,000 PY) [44]	N/A
Cerebrovascular accident (all stroke types) [10]	4.6 – 679 per 100,000 PY [47–56]	California, children < 20y of age (4.6/100,000 PY) [55]	US, American Indian or Alaska Native, 45–72y of age (679/100,000 PY) [47]	US children 11 m–17y, varicella vaccine, 1.2/100,000 PY [58]
Narcolepsy and cataplexy [11]	1.37 per 100,000 population [60]	N/A	N/A	N/A
Myocarditis and pericarditis [12]	5.73 – 26 per 100,000 PY, acute pericarditis [62–63] 0.95 – 2.16 per 100,000 population, myopericarditis [64–65]	US, persons ≥ 16y of age, 2003–2012, acute pericarditis (5.73/100,000 PY) [62] US military members, 2004–2008, myocarditis (0.95/100,000) [64] Worcester, MA residents (108/100,000) [69]	US Medicare beneficiaries ≥ 65y of age, acute pericarditis (26/100,000 PY) [63] US military members, 2002–2003, myocarditis (2.16/100,000) [65] US hospitalized patients, 1979–2001 (167/100,000) [72]	0.24 – 55/100,000 vaccinees [65–68]
Venous thromboembolism (VTE) [13]	108 – 167 per 100,000 population [69–72]	N/A	N/A	N/A
Myocardial infarction (MI), acute [14]	0.3 – 15.9 per 1,000 PY [73]	US White females, 35–44y of age (0.3/1,000) [73]	US Black or African American males, 75–84y of age (15.9/1,000) [73]	38.9/1,000 PY [75]
Mortality [15]	863.8 per 100,000 population, all-cause (≥1y of age) [76] 579.2 per 100,000 live births, infant (<1y of age) [77] 384.3 per 100,000 live births, neonatal (<28 days of age) [77]	N/A	N/A	442.5 per 100,000 person-years [79]
Pregnancy loss [16]	17.9 per 1,000 women [81]	N/A	N/A	N/A
Fetal deaths at ≥ 20w gestation [17]	587.8 – 596 per 100,000 live births and fetal deaths [87–88]	34 states and the District of Columbia, 2015–2017, representing 60% of fetal deaths in the U.S. (587.8/100,000 live births and fetal deaths) [87] Buffalo, NY, children < 5y of age (15.8/100,000) [91]	US, 2013 (596/100,000 live births and fetal deaths) [88]	520 per 100,000 live births [89]
Kawasaki's disease or syndrome (KD/KS) [18]	15.9 – 50.4 per 100,000 children < 5y of age [90–95]	N/A	Hawaii children < 5y of age (50.4/100,000) [92]	5.1 per 100,000 children 0–6y of age, verified cases [97]
Multiple system inflammatory syndrome in children (MIS-C) [19]	2.0 per 100,000 persons < 21y of age [100]	N/A	N/A	N/A

Table 2 (continued)

Medical Condition [Supplemental Table number]	Incidence Rate Range, Total, US Population ¹ [Ref]	Study Population with Lowest Rate ¹ [Ref]	Study Population with Highest Rate ¹ [Ref]	Incidence Rate Range Post-vaccination [Ref]
Anaphylaxis [20] ²	Hospitalizations: 21.0–25.1 per million population [101] ED visits: 58.8–71.1 per million population [101]; 42.0 per 100,000 PY [102]; 30.5 – 38 per 100,000 ED visits [104]	N/A	N/A	1.31 per 1 million doses administered [105]
Idiopathic or immune thrombocytopenic purpura (ITP) [21]	2.7 – 8.8 per 100,000 PY [107–110]	US VSD sites, children < 18y of age, 1991–2000 (2.7/100,000 PY) [109]	US children < 18y of age, 2011–2016 (8.8/100,000) [108]	1.9 – 5.89 per 100,000 doses administered (children) [111–113]

N/A = Rates are not available or cannot be summarized; refer to supplemental tables and referenced studies for more information

1 – Total rate ranges, refer to supplemental tables for sub-population rates; studies may use different case definition criteria, source data, date ranges and/or populations.

2- Studies use different denominator data; refer to the Anaphylaxis supplemental table 20.

adults $\geq$ 18y (May 2009–May 2019) reported an incidence of 0.2–1.6/100,000 [34].

3.1.6. Acute disseminated encephalomyelitis (ADEM)

As with other central nervous system demyelinating diseases, there are few data on ADEM incidence—a disorder most common in children—in the literature, primarily due to difficulties in making the diagnosis [35]. A retrospective review of the NIS (2006–2014) reported a pediatric ($\leq$ 18y) hospitalization rate of 0.5/100,000, with no difference between males and females (Supplemental Table 6) [35]. A California study (1991–2000) determined rates by age strata: 0.4/100,000 in children < 20y (0.6/100,000 in children 0–4y and 0.8/100,000 in children 5–9y) [36]. A VAERS study of post-vaccination ADEM estimated a mean incidence of 0.05 cases/million seasonal influenza vaccine doses distributed and a higher rate following H1N1 vaccination (0.15 cases/million doses distributed) [37].

3.1.7. Aseptic meningitis (AM)

Available studies of AM incidence were limited (Supplemental Table 7). One study reported rates of 10.9/100,000 PY for 1950–1981 and 17.8/100,000 PY for 1976–1981 [38]. Rates were significantly higher among those < 1y (82.4/100,000 PY) and higher for males (13.1/100,000 PY) than females (8.7/100,000 PY). A 1997 case-control Vaccine Safety Datalink (VSD) study of children 12–23 months(m) vaccinated for measles, mumps, and rubella (MMR) found a rate of 16.9/100,000 PY within the predefined risk windows of 8–14 and < 30 days [39].

3.1.8. Encephalitis

Encephalitis might be caused by viral or bacterial infections, autoimmune disorders, or noninfectious inflammatory conditions. Difference in etiologies and case ascertainment might account for variation in rates reported in population-based studies (Supplemental Table 8). A study using the NIS (1998–2010) estimated the average annual age-adjusted rate of encephalitis-associated hospitalizations to be 6.9/100,000, of which viral etiologies—herpesvirus in particular—were the predominant cause [40]. A 2000–2010 retrospective observational analysis of NIS data reported an incidence of 7.3 hospitalizations/100,000, with the highest rates among females (7.6/100,000) and those < 1y and $\geq$ 65y (13.5/100,000, 14.1/100,000, respectively) [41]. Among patients with an identified etiology, viral causes were the most common (25.6%). An RFP study (1995–2015) reported the incidence of autoimmune and infectious encephalitis as 0.8/100,000 PY and 1.0/100,000 PY, respectively [42]. Autoimmune encephalitis incidence increased from 0.4/100,000 PY (1995–2005) to 1.2/100,000 PY (2006–2015); this increase was attributed to improved detection of autoantibody-positive cases. Incidence of autoimmune encephalitis was higher among Black or African American persons (2.8/100,000 PY) than White persons (0.7/100,000 PY); however, there was no racial difference seen among incident cases of infectious encephalitis.

A study by the California Encephalitis Project (1998–2008) found no association between childhood immunization and encephalitis and no significant association between vaccination and onset of encephalitis during the predefined risk windows of 21 and 42 days after vaccination [43].

3.1.9. Seizures

Available incidence rates for seizures were extracted from population-based studies using medical records from large integrated healthcare organizations in various states (Supplemental Table 9). Rates were separated into two categories: a first unprovoked seizure and epilepsy (recurrent unprovoked seizures). Rates of first unprovoked seizure ranged from 41.1 to 61/100,000 PY and rates of epilepsy ranged from 16.4 to 44/100,000 PY [44–46]. Rates varied by sex, age, geographic location, and population type.

3.1.10. Cerebrovascular accident (stroke), ischemic and hemorrhagic

Available estimates on incidence of stroke were wide-ranging and varied by type of stroke, sex, race/ethnicity, and age (Supplemental Table 10). A large community-based prospective cohort study (1987–2017) of adults ≥ 45 y estimated the overall rate of stroke was 4.10/1,000 PY; rates were higher among males than females (4.59 vs. 3.74/1,000 PY) and among those ≥ 65 y (5.58 vs. 2.19/1,000 PY for those < 65 y), and increased over the duration of the study period [47–48].

A Healthcare Utilization Project study of adults ≥ 18 y stratified stroke by age group and stroke type (subarachnoid hemorrhage [SAH], intracerebral hemorrhage [ICH], and acute ischemic stroke [AIS]) [49]. AIS occurred most frequently in all age groups. The Greater Cincinnati/Northern Kentucky Stroke Study reported slightly higher rates of stroke among females (198/100,000) than males (192/100,000) [50]. AIS was most common, regardless of sex, followed by ICH and SAH.

A few studies detailed rates among minority subpopulations. A large community-based prospective cohort study noted a higher rate of stroke among Black or African American persons (6.26/1,000 PY) than White persons (3.39/1,000 PY) [47]. Another population-based surveillance study reported a higher rate of ischemic stroke of all types among Black or African American persons (191/100,000) and Hispanic or Latino persons (149/100,000), compared with White persons (88/100,000) [51]. The Brain Attack Surveillance Corpus Christi study determined the average ICH rate among a population of Mexican-American persons (M–A) and non-Hispanic White persons (NHW) adults aged ≥ 45 y to be 4.30/10,000 [52]. Another study of the same population found rates of first ischemic stroke lowest among NHW 45–59y (6.5/10,000) and highest among M–A ≥ 75 y (52.4/10,000) [53]. The longitudinal population-based observational Strong Heart Study of American Indian and Alaska Native persons aged 45–74y found a rate of strokes of 679/100,000 PY, with 86% of strokes being ischemic [54].

Two retrospective studies of pediatric stroke were found, with one study of children < 20 y reporting a rate of ischemic and hemorrhagic stroke of 4.6/100,000 PY [55]. Another study of children 1 m–19y noted a rate of 2.3/100,000 [56].

A study of Behavioral Risk Factors Surveillance System data that assessed risk of stroke following zoster vaccination among individuals aged 50–79y found a higher risk for stroke among those who had not been vaccinated (Hazard ratio: 1.73) [57]. A study of children ages 11 m–17y from the VSD reported ischemic stroke incidence of 1.2/100,000 PY and found varicella vaccination was not associated with ischemic stroke in children within 12 months of vaccination [58].

3.1.11. Narcolepsy and cataplexy

We identified only one relevant study on incidence of narcolepsy and cataplexy, which was based on cases confirmed by medical record review; other studies using diagnosis codes without chart confirmation were excluded because they likely overestimate true incidence [59] (Supplemental Table 11). A population-based study from REP reported a rate of 1.37/100,000 [60]. Rates varied by age and sex, with peak rates in the second decade (3.84/100,000 in those 10–19y) and higher rates among males (1.72 vs. 1.05 females). The rate for the sub-set of narcolepsy with cataplexy was 0.74/100,000.

3.2. Cardiovascular conditions

3.2.1. Myocarditis and pericarditis

The incidences of acute pericarditis and myopericarditis (cases of acute pericarditis that also demonstrate myocarditis) are unknown; however, the incidence of myocarditis is estimated to be 1–10 cases/100,000 persons annually [61] (Supplemental Table 12).

A 2003–2012 NIS study of acute pericarditis hospitalizations among patients ≥ 16 y found an overall hospitalization rate of 57.3/million PY, significantly higher for males than females (incidence rate ratio: 1.56) [62]. Another study (1999–2012) reported a hospitalization rate for acute pericarditis among Medicare beneficiaries ≥ 65 y of 26/100,000 PY, with higher incidence among males [63].

Several studies compared myopericarditis rates in vaccinated and unvaccinated populations, with a focus on smallpox vaccination. One study reported an estimated incidence of 7.4/100,000 for pericarditis and 0.95/100,000 for myocarditis in U.S. military personnel deployed to Iraq and Kuwait during 2004–2008 [64]. In this study, 11 of 79 (14%) cases of pericarditis and myopericarditis received smallpox vaccination 4–30 days prior to diagnosis. Another study reported the incidence of myopericarditis following smallpox vaccination among vaccinia-naïve military personnel was 7.8/100,000 over a 30-day observation window, compared with a background incidence of myopericarditis in all service members on active duty of 2.16/100,000 over any 30-day period (2002) [65]. A similar study of military personnel reported an incidence for myopericarditis following smallpox vaccination (2002–2003) of 16.11/100,000 in primary vaccinees over a 30-day observation window compared to 2.07/100,000 among re-vaccinees [66]. A VAERS study of myocarditis or pericarditis after smallpox vaccination in civilians found a rate of 5.5/10,000 vaccinees [67]. A VSD study of adults ≥ 18 y (1996–2007) found an estimated myopericarditis incidence of 0.24/100,000 for individuals vaccinated with live viral vaccines [68].

3.2.2. Venous thromboembolism (VTE)

Estimates of VTE incidence vary widely (Supplemental Table 13). One small population-based study estimated an overall rate of 108/100,000 and an increase in VTE rates over the 25y study period [69]. Another small population-based study found a rate of 117/100,000, with rates higher among men and increasing by age [70]. An analysis of clinical administrative databases and hospital- and community-based studies estimated a rate of 1–2/1,000 and 10%–30% mortality within 30 days of VTE [71].

A large study of national hospital discharge data estimated an annual VTE diagnosis rate of 113–167/100,000 [72]. Across available estimates, there was heterogeneity of VTE rates by subgroup (e.g., age, sex).

3.2.3. Myocardial infarction, acute (MI)

Estimates of MI incidence are frequently updated and validated by the National Heart, Lung, and Blood Institute (Supplemental Table 14). The most recent incidence estimate is 805,000 events/year among those ≥ 35 y [73]. The average age for first MI is lower among males (65.6y) than females (72.0y). Rates vary by race and sex, with the highest rates among Black or African American males. Rates of MI increase with age, regardless of sex or race.

A California-based cohort study in men 45–69y that assessed the impact of pneumococcal vaccination on MI estimated a rate of 10.73/1,000 PY and found no evidence of association between vaccination and MI [74]. Another study in Washington State of MI survivors receiving serial seasonal influenza vaccinations found a rate of 127/3,267 PY and no association between vaccination and risk of recurrent MI [75].

3.3. Mortality

3.3.1. All-cause and cause-specific mortality

According to the National Vital Statistics System (NVSS), all-cause mortality was estimated to be 836.8/100,000 in 2018 [76]. Rates were higher for males than females in all age groups (Supplemental Table 15). The 10 leading causes of death in descending

order were heart disease, cancer, unintentional injuries, chronic lower respiratory diseases, stroke, Alzheimer's disease, diabetes, influenza and pneumonia, kidney disease, and suicide, with rates increasing with age. Mortality caused by influenza and pneumonia was estimated to be 17.1/100,000, with overall rates slightly higher among females (17.6/100,000) than males (16.6/100,000). According to the American Heart Association's Heart Disease and Stroke Statistics database 2020 update, overall mortality rate from sudden cardiac death is 97.1/100,000 [73]. All-cause mortality rates for infants (<1y) and neonates (<28 days) were reported to be 579.2/100,000 live births and 384.3/100,000 live births, respectively, and higher among males than females [77].

A VAERS study of reported deaths among individuals vaccinated with any vaccine found an estimated rate of 1/million vaccine doses distributed [78]. Events occurred most frequently among those < 1y (54.2%). A cohort study using VSD data on medically insured adults and children who had received ≥ 1 vaccine found a mortality rate (deaths within 60 days of vaccination) of 442.5/100,000 PY [79].

3.3.2. Pregnancy loss, including spontaneous abortion (SAB)

Early pregnancy loss (before 13w of gestation) is common, with an estimated rate of 10% among all clinically recognized pregnancies; this rate increases with age (9%–17% at 20–30y; 80% at 45y [80] (Supplemental Table 16). An NVSS study estimated an overall rate of SAB (fetal loss before 20w) of 17.9/1,000 among women 15–44y [81]. National estimates of SAB range from approximately 10–25% among women 15–44y when including losses of clinically unrecognized pregnancies [82–86].

3.3.3. Fetal death (FD)

Estimates of FD (intrauterine death of a fetus prior to delivery) are available through NVSS (Supplemental Table 17). The national rate of FD at gestational age ≥ 20 w is estimated to be 595/100,000 live births and FD [87–88]. Rates vary based on race, plurality, marital status, and gestational age at time of FD. Cause of death is available for approximately 60% of FDs (2015–2017), and 89.5% of cases fall into one of five categories: FD of unspecified cause (28.7%); fetus affected by complications of placenta, cord, and membranes (26.5%); fetus affected by maternal complications of pregnancy (13.9%); congenital malformations, deformations, and chromosomal abnormalities (10.8%); and fetus affected by maternal conditions that may be unrelated to present pregnancy (9.6%) [87]. The stillbirth (fetal loss at or after 20w gestation) rate in VSD (2007–2015) was 5.2/1,000 live births and stillbirths [89].

3.3.4. Kawasaki disease (KD)

Incidence rates from population-based and hospitalization studies of KD vary greatly by age, sex, ethnicity, and/or geographical location (Supplemental Table 18). The risk for males is approximately 1.5 times higher than for females, and rates are highest for children < 5y. In the continental U.S., incidence ranges from 9 to 20 cases/100,000 children < 5y, and a hospitalization rate of 19.8/100,000 children < 5y was reported for 2016 [90]. Incidence among children < 5y varied geographically from 15.9/100,000 in western New York [91] to 50.4/100,000 in Hawaii. The highest rate in American children was found in children < 5y of Japanese descent (210.5/100,000) [92].

Studies in children < 18y reported the overall rates for KD ranged from 6.4/100,000 [93] for all U.S. children to 16.3/100,000 in Hawaii [92]. Using the National Kids' Inpatient Database and the NIS, a study of children < 18y reported a hospitalization rate of 7.5/100,000; hospitalization data reflect the incidence of KD, since most young children with KD are hospitalized [94].

KD incidence increases in winter and spring, suggesting possible associations with preceding viral infections or environmental

risk factors [95]. A study of VAERS data did not show an elevated KD risk for licensed vaccines [96], and a VSD study (1996–2006) found that vaccination was associated with a transient decrease in KD incidence during predefined risk periods following each vaccine administration (1–14 days, 1–28 days, 1–42 days). [97]. COVID-19 is known to cause microvascular damage and several cases of Kawasaki-like disease associated with COVID-19 have been reported in the literature, but a causal relationship between COVID-19 and KD has not been established [98].

3.3.5. Multisystem inflammatory syndrome (MIS)

MIS is a new and rare condition associated with COVID-19. In published literature, incidence rates were limited for MIS in children (MIS-C) and not available for MIS in adults (MIS-A). CDC reported 1,288 total cases of MIS-C as of December 4, 2020 [99]. A study on MIS-C in New York state reported a rate of 2/100,000 among COVID-19 patients < 21y [100] (Supplemental Table 19). MIS-C may be difficult to distinguish from KD given similarities in clinical manifestations. Future studies should assess the incidence of MIS as more data become available.

3.3.6. Anaphylaxis

Incidence rates of anaphylaxis, a rare and potentially life-threatening systemic hypersensitivity reaction, varied by age and gender across available studies. A population-based epidemiological study using three national databases that sourced data from hospital and emergency department (ED) records and death certificates found anaphylaxis-related hospitalization rates increased from 21.0 to 25.1/million (1999–2009; annual percentage change, 2.23%) [101] (Supplemental Table 20). An REP study (2001–2010) reported a rate of 42/100,000 PY, with males having a slightly higher rate than females (43.8 vs. 40.1/100,000 PY) [102]. In contrast, a study of Florida ED records found females to have a higher rate than males (8.7 vs. 6.6/100,000) [103].

A retrospective review of inpatient and ED records of pediatric anaphylaxis patients seen at a Chicago institution reported a rate of 30.5/100,000 ED visits (1986–1990) and 38/100,000 ED visits (2002–2006) [104]. Food allergens (43%) were the most common anaphylaxis etiology.

A VSD study to determine rates of anaphylaxis after vaccination in children and adults found 33 confirmed cases determined to be vaccine-related following 25,173,965 vaccine doses administered, yielding a rate of 1.31/million vaccine doses administered during a predefined risk period of 0–2 days [105]. Rates were slightly higher in females (1.45/million doses administered vs. 1.14/million doses administered for males), with onset occurring within 20 h of administration. The study included predominantly inactivated influenza vaccine and, thus, higher estimates seen for other vaccines (e.g., herpes zoster vaccine = 6.58/million doses administered) were likely unstable due to small numbers. In a report from Germany, a rate as high as 11.8/million vaccine doses administered was found in children following AS03-adjuvanted A(H1N1) pandemic influenza vaccine [106]. In Medicare beneficiaries ≥ 65 y (2015–2019), incidence of vaccine-attributable anaphylaxis was estimated at 11.69/100,000 PY, 0.88/million doses, and 0.96/million vaccination visits[Goud, Dec. 2020, personal communication].

3.3.7. Idiopathic or immune thrombocytopenic purpura (ITP)

Available background estimates for ITP incidence in the general population were limited (Supplemental Table 21). A study of two large integrated private healthcare claims databases found a rate of 6.1/100,000, with rates higher among females than males (6.7 vs. 5.5/100,000) and peaks in the lowest (8.1/100,000 for 0–4y) and oldest age groups (13.7/100,000 for ≥ 65 y) [107].

A study of commercial claims data for children < 18y found a rate of 8.8/100,000 PY, with peak rates among those < 2y

(14.8/100,000 PY) [108]. A VSD population study of children < 18y estimated a rate of 2.7/100,000 PY [109]. Another study of hospital records at a large children's hospital in Alabama reported a rate of 4/100,000 [110]. Although rates differ across studies, possibly due to inclusion criteria, there was little variation in rates between males and females.

Multiple studies were available assessing the known association of ITP as an adverse event after MMR vaccination. A retrospective study of children (aged 6w–17y) insured in managed care organizations found a rate of 1.9/100,000 doses of MMR vaccine administered [111]. A VSD study of children < 18y found a rate of 1/40,000 doses of MMR vaccine administered to children 12–23 m, which indicated low attributable risk [112]. Another VSD study of children 12–23 m comparing separate MMR + varicella (V) and combined MMRV vaccination detected no difference in risk of ITP between vaccination formulations [113].

3.3.8. Vaccine-mediated enhanced disease (VMED)

Vaccine-mediated enhanced disease (VMED), or vaccine-associated enhanced disease, is a modified and/or severe presentation of an infectious disease affecting individuals exposed to the wild-type pathogen after having received vaccine designed to prevent infection. VMED is not known to occur with any currently licensed vaccines but classically followed administration of prototype inactivated measles and respiratory syncytial virus (RSV) vaccines which resulted in atypical measles and enhanced RSV infection, respectively [114]. VMED is a theoretical concern for COVID-19 vaccines based on observations with some Middle East respiratory syndrome (MERS) and SARS-CoV-1 experimental vaccines in certain animal models [115]. VMED would be the result of infection with wild-type virus, therefore the incidence of VMED would be related to the incidence of infection in a population and could probably not be assessed reliably using background rates. Surveillance is planned to detect the potential occurrence of VMED following COVID-19 vaccines using concurrent comparisons.

3.4. Further discussion

To our knowledge, this is the first large-scale compilation of U.S. incidence rates for medical conditions that are historically or generally monitored as AESI for vaccine safety. These rates may be useful for epidemiological analyses that assess adverse events temporally associated with COVID-19 vaccination and for surveillance of new vaccines in the future.

There are limitations to this review. Many of the studies only provided rates based on general population estimates and may not be generalizable to different age, sex, and racial/ethnic subgroups. For some conditions, available estimates that met inclusion criteria were from older data sources and should be updated when new data become available. Medical conditions assessed, such as neurological disorders, may be triggered by confounding factors such as prior infections, environmental factors (e.g., seasonality), foreign substances (e.g., medications), and individual genetic susceptibility that were not considered in some studies. Estimated rates may vary due to the quality of data sources used by the original researchers; differences in case ascertainment methods, case definitions and diagnostic criteria; geographical differences; and potential selection biases, such as the healthy vaccinee effect. At present, published estimates of background rates of clinical conditions that occur in COVID-19-infected patients are limited; however, as more data become available, information on specific background rates of medical outcomes in the infected population will be elicited, and new vaccine-related AESI may also be identified. Other factors, such as changes in healthcare utilization during

the COVID-19 pandemic, may impact incidence rates. These factors should be considered in future studies.

4. Conclusion

In evaluating adverse events following immunization, it is important to understand background rates of medical conditions in the population since many conditions would be expected to occur at some given rate incidentally regardless of vaccine exposure. It is especially important to consider this when interpreting safety data for new vaccines, such as the COVID-19 vaccines, with which we have limited experience beyond clinical trial data. This review describes background incidence rates of medical conditions that will be tracked as AESI during safety monitoring following COVID-19 vaccination. By noting extant studies and available data sources, this review also provides a foundation for monitoring spontaneous adverse event reports, evaluating rare outcomes following vaccination in health databases, contextualizing adverse events, and setting expectations in communications with the public.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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