

## Supplemental Information

### V-safe Health Surveys

Health surveys are sent via text messages that link to web-based surveys on days 0 to 7 after vaccination; then weekly through 6 weeks after vaccination; and then 3, 6, and 12 months after vaccination. Health surveys sent in the first week include questions about injection site and systemic reactions and health impacts.

### V-safe Definitions for Injection Site Reaction, Systemic Reaction, Health Impact, and Reaction Severity

Injection site reactions include itching, injection site pain, redness, and swelling.

Systemic reactions include abdominal pain, myalgia, chills, diarrhea, fatigue, fever, headache, joint pain, nausea, rash, and vomiting.

Health impacts include whether the adolescent was unable to complete normal daily activities, missed work or school, or received care from a medical professional because of new symptoms or conditions.

Injection site and systemic reactions can be further described by severity as mild (noticeable, but not problematic), moderate (limit normal daily activities), or severe (make daily activities difficult or impossible).

### Adverse Events of Special Interest (AESI)

AESI are adverse events selected for further review because they were observed during pre-authorization trials, were of known historical interest (eg, anaphylaxis, death), were observed postauthorization (eg, myocarditis, thrombosis with thrombocytopenia syndrome), or there is a biological plausibility for them to occur postvaccination (eg, MIS-C or multisystem inflammatory syndrome in adults following COVID-19 vaccines; SSPE following measles-containing vaccines). Reports of AESI are further assessed to determine if the reported patient meets a standardized case

definition, such as the Brighton Collaboration case definition for Guillain-Barre Syndrome (GBS), or were clinically diagnosed by a physician specializing in the pertinent field (eg, a neurologist diagnosing Guillain-Barre Syndrome). Additional sources of information include patient medical records and interviews with a provider participating in the patient's care. AESI for COVID-19 vaccines include the following:

- Acute respiratory distress syndrome
- Anaphylaxis
- Bell's palsy
- Cerebral venous sinus thrombosis
- Encephalitis, myelitis, encephalomyelitis
- Guillain-Barre syndrome
- Immune thrombocytopenia
- Ischemic stroke
- Kawasaki's disease
- Myopericarditis
- MIS-C
- Narcolepsy
- Pulmonary embolism
- Seizure
- Thrombosis with thrombocytopenia syndrome
- Thrombotic thrombocytopenic purpura
- Venous thromboembolism

### Methods for Surveillance for MIS-C

As previously described,<sup>13</sup> we conducted enhanced surveillance for MIS-C in persons ages 12 to 20 years for the period December 14, 2020 through August 31, 2021. We identified potential cases using VAERS, CDC's MIS-C national surveillance system, and clinician or health department outreach to CDC, including through Clinical Immunization Safety Assessment Project consultations. Medical records were reviewed and a multidisciplinary team adjudicated cases using the 2020 CDC MIS-C definition.<sup>11</sup> For the period September 1, 2021 through May 10, 2022,

potential cases among adolescents ages 12 to 17 years who had onset within 90 days of their last COVID-19 vaccine dose were identified using VAERS. Medical records were reviewed and adjudicated by CDC physicians using the same 2020 CDC MIS-C definition; for some cases, Clinical Immunization Safety Assessment project clinicians assisted with adjudication.

### US Centers for Disease Control and Prevention 2020 Case Definition for MIS-C

Must meet all the following clinical and laboratory criteria:

- Age <21 years with subjective or objective (>38.0°C) fever for 24 hours or longer
- Clinically severe illness requiring hospitalization
- Multisystem (2 or more) organ system involvement
  - Cardiac: eg, elevated troponin, elevated B-type natriuretic peptide or N-terminal pro hormone BNP, arrhythmia, coronary artery aneurysm, cardiac dysfunction, or shock
  - Renal: eg, acute kidney injury or renal failure
  - Respiratory: eg, pneumonia, acute respiratory distress syndrome, pulmonary embolism
  - Hematologic: eg, elevated D-dimer, thrombophilia, or thrombocytopenia
  - Gastrointestinal: eg, elevated bilirubin, elevated liver enzymes, or diarrhea
  - Dermatological: eg, rash or mucocutaneous lesions
  - Neurologic: eg, cerebrovascular accident, aseptic meningitis, encephalopathy, or headache
- No alternative plausible diagnosis
- Laboratory evidence of inflammation: 1 or more of: elevated C-reactive protein, erythrocyte sedimentation rate, fibrinogen, procalcitonin, D-dimer, ferritin, lactic acid

- dehydrogenase, interleukin 6, or neutrophils; or reduced lymphocytes or albumin
  - Current or recent positive Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) reverse transcriptase polymerase chain reaction, antigen, or serology test; or exposure to a suspected or confirmed COVID-19 case within the 4 weeks before onset of symptoms\*
- \* For this investigation, only SARS-CoV-2 serology results from serum obtained before IVIG administration were used to meet the serology component; we allowed any prior history of a positive SARS-CoV-2 nucleic acid amplification test (NAAT) or antigen test to meet the NAAT/antigen component (ie, without a time cut-off); the exposure criterion was not used.

**MedDRA Search Terms for Myocarditis**

- Atypical mycobacterium pericarditis
- Autoimmune myocarditis
- Autoimmune pericarditis
- Bacterial pericarditis

- Coxsackie myocarditis
- Coxsackie pericarditis
- Cytomegalovirus myocarditis
- Cytomegalovirus pericarditis
- Enterovirus myocarditis
- Eosinophilic myocarditis
- Hypersensitivity myocarditis
- Immune-mediated myocarditis
- Myocarditis
- Myocarditis bacterial
- Myocarditis helminthic
- Myocarditis infectious
- Myocarditis meningococcal
- Myocarditis mycotic
- Myocarditis post infection
- Myocarditis septic
- Pericarditis
- Pericarditis adhesive
- Pericarditis constrictive
- Pericarditis helminthic
- Pericarditis infective
- Pericarditis mycoplasmal
- Pleuropericarditis
- Purulent pericarditis
- Troponin I increased
- Troponin increased
- Troponin T increased
- Viral myocarditis
- Viral pericarditis

**Case Definition for Myocarditis**

We applied the CDC working case definition of acute myocarditis.<sup>16 A</sup>

probable case of acute myocarditis was defined as the presence of signs and symptoms (1 or more new or worsening of the following: chest pain, pressure, or discomfort; dyspnea or shortness of breath or pain with breathing; palpitations; or syncope; or 2 or more of the following in children ages ≤11 years: irritability, vomiting, poor feeding, tachypnea, or lethargy); and 1 or more new findings of elevated troponin, electrocardiogram findings consistent with myocarditis, abnormal cardiac function or wall motion on echocardiogram, or cardiac MRI findings consistent with myocarditis. A confirmed case of acute myocarditis was defined as the presence of signs and symptoms (1 or more new or worsening of the following: chest pain, pressure, or discomfort; dyspnea or shortness of breath or pain with breathing; palpitations; or syncope; or 2 or more of the following in children ages ≤11 years: irritability, vomiting, poor feeding, tachypnea, or lethargy); and 1 or more new findings of histopathologic findings consistent with myocarditis; cardiac MRI findings consistent with myocarditis in the presence of a troponin level above the upper limit of normal; and no other identifiable cause for these findings. Both probable and confirmed cases of myocarditis were included for analysis.

**SUPPLEMENTAL TABLE 10** VAERS Search Terms Used to Identify Potential Cases of MIS-C After Receipt of COVID-19 Vaccine

Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms	Multisystem Inflammatory Syndrome in Children, Multisystem Inflammatory Syndrome, SIRS (Systemic Inflammatory Response Syndrome)
Text string search terms	"MIS-C," "MISC," "MIS;" "Multisystem inflammatory syndrome;" "Multisystem inflammatory;" "Multisystem inflammation;" "Multisystem" + "inflammation;" "Multisystem" + "inflammatory"