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Technical Proposal: Myocarditis Outcomes after mRNA COVID-19 Vaccination Investigation, United States

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Background

- CDC and its partners are actively investigating reports of myocarditis and pericarditis occurring after mRNA COVID-19 vaccination (Pfizer-BioNTech and Moderna), particularly in adolescents and young adults. Most cases have been observed in males after dose 2 of mRNA COVID-19 vaccine.

- Myocarditis is inflammation of the heart muscle, and pericarditis is inflammation of the lining around the heart.

- Available data from short-term follow-up suggest that symptoms have resolved in most individuals with myocarditis and/or pericarditis after COVID-19 vaccination (MMWR July 2021 and Advisory Committee on Immunization Practices (ACIP) meeting August 2021). But information is not yet available about longer-term outcomes.

- CDC continues to recommend that persons aged 12 years and older get a COVID-19 vaccination.

- The Food and Drug Administration (FDA) has updated the Emergency Use Authorization (EUA) patient/caregiver and provider fact sheets to include a warning about myocarditis and pericarditis after mRNA COVID-19 vaccination. The package insert for the Pfizer-BioNTech (COMIRNATY) COVID-19 Vaccine also includes a warning about myocarditis and pericarditis.

- Describing longer-term outcomes in persons with myocarditis after mRNA COVID-19 vaccination is important to further assess the benefit-risk balance of mRNA COVID-19 vaccination. This information will also be useful to inform clinical guidance for COVID-19 vaccination.

Objectives

Primary

1. To describe health and functional outcomes in persons with myocarditis after mRNA COVID-19 vaccination
2. To assess recovery of the heart in persons with myocarditis after mRNA COVID-19 vaccination

Secondary

1. To describe health and functional outcomes in persons with pericarditis after mRNA COVID-19 vaccination

2. To assess recovery of the heart in persons with pericarditis after mRNA COVID-19 vaccination

Population

- Cases of myocarditis (per CDC case definitions) after mRNA COVID-19 vaccination[1] reported to the Vaccine Adverse Event Reporting System (VAERS)
    - Adolescents aged 12–17 years (priority)
    - Young adults aged 18–29 years (priority)
    - Adults aged ≥30 years

Methods

- Cases identified in VAERS that meet the CDC case definition of myocarditis with or without pericarditis after mRNA COVID-19 vaccination[1] (MMWR Table 1) will be assessed at least 3 months after adverse event onset date or receipt of the VAERS report. The VAERS form includes fields for patient name, phone number, and mailing address.

- CDC staff will conduct surveys with vaccine recipients, parents or guardians and healthcare providers. Prior to initiating follow-up efforts, CDC staff will contact state health departments to inform them about the project.

- Patient follow-up information will be obtained through two main methods described below.
    - Survey for vaccine recipient (patient) and/or parent or guardian.
        - The patient or parent or guardian will be contacted by mail to inform them about the survey and provide them with a phone number to call to schedule a phone survey. If the patient's name is not provided on the VAERS form, then the healthcare provider reporting to VAERS may be contacted to help notify the patient or parent about the opportunity to complete a phone survey with CDC staff.
    - Survey with cardiologist or other healthcare provider following patient for myocarditis and/or pericarditis.
        - If contact information is available to contact both the patient/parent and cardiologist, then they may be completed concurrently. If the contact information for the cardiologist is unclear, then the patient/parent survey should be completed first to obtain this information.

- **Survey 1**: Survey of patient and/or parent or guardian
    - Trained CDC staff will conduct a brief phone survey at least 3 months after onset of the patient's myocarditis symptoms or receipt of their VAERS report to assess for health outcomes and functional outcomes in cases of myocarditis. These include presence of ongoing symptoms (e.g., chest pain), need for emergency medical care, school/work attendance, and sports/exercise activity. Information will also be collected about medical history and whether they are back to their baseline health (prior to onset of the myocarditis). In addition, the survey will ask whether the person had 1 or 2 doses of COVID-19 vaccine before the onset of myocarditis. For those

[1] Cases of myocarditis after Janssen COVID-19 vaccine may also be followed; cases of pericarditis after COVID-19 vaccines may also be followed.

persons who had 1 dose before the myocarditis, the survey will also assess if they received dose 2 of COVID-19 vaccine since the onset of myocarditis. In addition, the survey will assess if the patient had a nasal or throat swab test that was positive for COVID-19 before the myocarditis.

- During this interview, information will also be collected about the name and phone number of the cardiologist or other healthcare provider following the patient that can be used for Survey 2 of cardiologist/healthcare provider below. The patient or parent will also be asked whether they have been cleared for sports participation by the cardiologist/provider.

- An additional optional opportunity will be offered to complete a validated health-related quality of life assessment tool (HRQOL) over the phone to assess health and functional status. The tool is EQ-5D-5L, which is validated for use in persons aged ≥12 years. Permission from the company owning the tool has been obtained.

- This survey will be conducted with the vaccine recipient for cases that have reached the age of legal adulthood (age of majority) as defined by their state of residence, on the date of interview (≥18 years in most states). For adolescent cases that are younger than the age of legal adulthood, the survey will be conducted with the parent/guardian, with or without the adolescent. The EQ-5D-5L quality of life tool requires direct interview of the patient, and it may not be feasible to complete this for all adolescents.

- The interviewer will also ask if the individual or parent would be interested in being contacted for potential participation in future research studies of myocarditis.

- **Survey 2**: Survey of cardiologists or other healthcare provider
  - Heart recovery outcomes will be assessed through a survey of the cardiologist (or other healthcare provider who is providing follow-up care for the patient or has access to medical records). If contact information is available without contacting the patient or parent, then Survey 2 may be conducted whenever it is feasible.

  - To maximize flexibility, the healthcare provider survey will be available in two versions – phone and electronically. The phone version will be available first; both will use a REDCap case report form.

  - The phone survey can be completed in one call; trained staff will conduct the calls and may be the same staff conducting the patient/parent survey.
    - The REDCap survey may require a two-step process because the online survey cannot include patient identifiers. In this model a code linking the survey to the VAERS number for the patient could be provided in a phone call or secure email/fax to the cardiologist or their office. The REDCap survey would follow with the coded identifier.

- The survey for the cardiologist/healthcare provider includes questions that can be administered by non-medical staff over the phone. Most answers are categorical (e.g., normal, abnormal, not done); date of the procedure will be noted. If multiple tests or procedures were done for the same test, the survey will collect the first date at which the testing became normal or the date of the most recent result of the abnormal test. The survey will also assess changes from the time of acute illness as well as future follow up plans, including scheduled tests.

  - Information about the following procedures or tests will be collected:
    - Electrocardiogram (ECG)
    - Echocardiogram
    - Cardiac MRI
    - Exercise test (stress test)
    - Ambulatory rhythm monitoring (Holter monitor, Zio Patch)
    - Troponin level
    - Coronary angiography (for persons aged ≥30 years)

  - Information will also be collected about current symptoms and medications used for the myocarditis. The survey will also assess whether the cardiologist considered the patient cleared for sports and if they considered the heart fully recovered or not. In addition, the survey will ask about medical history before the myocarditis episode, including whether the patient had a history of myocarditis or pericarditis before COVID-19 vaccination. It will also assess whether the patient had laboratory confirmed SARS-CoV-2 infection prior to, or at the time of the myocarditis episode.

- Clinical subject matter expert additional follow-up:
  - Additional medical records will be obtained for patients who are identified from Survey 1 (parent-caregiver/patient) or Survey 2 (cardiologist/healthcare provider) to have clinically severe outcomes (e.g., additional hospitalization), lack of full cardiac recovery, or selected abnormal test results. These cases will be referred to CDC medical officers or investigators for further assessment that may include review with Clinical Immunization Safety Assessment (CISA) Project investigators or cardiologists.
  - Assessment may include additional medical records review and discussion with the patient's cardiologist or other healthcare providers. Pertinent medical records will be transferred securely to VAERS, CISA eFax, or to CDC via another secure method.

- Persons who are known to have died, based on the information reported to VAERS, will not be contacted by the project's call center staff members. Evaluation of any deaths reported to VAERS will be conducted according to standard processes used to evaluate deaths after COVID-19 vaccination. On a case-by-case basis, parent/guardian or provider may be contacted to obtain information using selected survey questions or unstructured interviews. Information obtained through phone interviews will be collected on case report forms, ideally through direct data entry into a secure CDC REDCap database.

- Information collected via the REDCap survey has an advantage of not requiring additional data entry. Descriptive analysis of functional outcomes and recovery status of the heart by age group and vaccine product will be conducted.

- Additional follow-up: As part of the activity, Survey 1 and/or Survey 2 may be repeated, particularly in patients who have not fully recovered at the initial follow-up assessment.

- The initial phase of follow-up would start in August 2021 and assess cases of myocarditis for whom at least 90 days have passed since the onset of myocarditis. An interim analysis would be completed during 2021, with a goal of providing preliminary summary information to the ACIP, if requested.

- A follow-up assessment may be completed at a later time for cases of pericarditis (without myocarditis) identified in VAERS that meet the CDC case definition for pericarditis after COVID-19 vaccination (MMWR Table 1) using the methods described in this proposal.

Human subjects considerations: The myocarditis outcomes investigation project was considered by the human subjects program at CDC as a public health surveillance activity (non-research). Verbal consent will be obtained at the start of calls to the patients or parents. Data collected in this surveillance project will be covered under applicable policies for CDC, VAERS, and the CISA Project. The survey data are anticipated to be covered under the CISA 308d CDC Assurance of Confidentiality. Medical records, if requested as part of this surveillance, will be uploaded and stored with other medical records in the VAERS virtual private network (VPN), through standard processes.

Collaboration: The project will be a collaboration with the COVID-19 Vaccine Task Force; Vaccine Safety Team; myocarditis outcomes investigation activity; and CDC's Immunization Safety Office, Division of Healthcare Quality Promotion (DHQP), including the VAERS and CISA Project Teams. In addition, cardiologists and other experts from CDC and CISA sites will provide technical input (Vanderbilt University (lead) and Duke University (co-lead) CISA sites). State health departments and other CDC partners may also collaborate.

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