COVID-19 Vaccine Safety Updates

Advisory Committee on Immunization Practices (ACIP)
Oct 21, 2021

Tom Shimabukuro, MD, MPH, MBA
Vaccine Safety Team
CDC COVID-19 Vaccine Task Force

cdc.gov/coronavirus
Topics

- Overview of myocarditis following COVID-19 vaccination
- Update on the safety of Janssen COVID-19 Vaccine
- Safety of a Janssen COVID-19 primary vaccination followed by an additional mRNA COVID-19 vaccination
Myocarditis and Myocarditis with Pericarditis (Myopericarditis) Following COVID-19 Vaccination
Myocarditis and myopericarditis following mRNA COVID-19 vaccination

- Evidence from multiple safety monitoring systems in multiple countries supports the finding of an increased risk of myocarditis and myopericarditis following mRNA COVID-19 vaccination*
  - Risk:
    - Highest in adolescents and young adults
    - Males > females
    - Following dose 2 > dose 1
  - Onset clusters within a few days of vaccination, mostly within a week
  - Cases have tended to be clinically mild


Comirnaty and Spikevax: possible link to very rare cases of myocarditis and pericarditis. Available at Comirnaty and Spikevax: possible link to very rare cases of myocarditis and pericarditis | European Medicines Agency (europa.eu).

Myocarditis and myopericarditis following mRNA COVID-19 vaccination – presentation topics

- Highlights from:
  - U.S. Food and Drug Administration (FDA) monitoring
  - U.S. Department of Defense (DoD) monitoring
  - Department of Veterans Affairs (VA)
  - International surveillance
  - CDC investigation of long-term effects of myocarditis

- Vaccine Adverse Event Reporting System (VAERS) and Vaccine Safety Datalink (VSD) updates on myocarditis and myopericarditis following mRNA COVID-19 vaccination will be provided separately during this safety session
Surveillance Updates of Myocarditis/Pericarditis and mRNA COVID-19 Vaccination in the FDA BEST System

Vaccines and Related Biological Products Advisory Committee
October 14, 2021

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Associate Director for Innovation and Development
Office of Biostatistics and Epidemiology
Center for Biologics Evaluation and Research
US Food and Drug Administration

https://www.fda.gov/media/153090/download
**FDA CBER Active Surveillance Program**

**Center for Biologics Evaluation and Research (CBER)**

**Biologics Effectiveness and Safety (BEST) Initiative**

**Myocarditis/pericarditis in first 1-7 days of receipt of mRNA COVID-19 vaccines in FDA BEST System**

- Incidence rates for mRNA COVID-19 vaccines
- Incidence rate ratios for Moderna versus Pfizer-BioNTech

**Limitations**

- Events were not chart-confirmed
- Partial adjustment for potential confounders
  - Cannot rule out biased estimates
- Large uncertainty of incidence rates and incidence rate ratios
  - Small number of events, wide confidence intervals
- Relies on the assumption that the claims delay for Pfizer is similar to Moderna.
  - Claims delay: the time between the day of service and the day of observation in the database
  - Heterogeneity results across databases are under review

https://www.fda.gov/media/153090/download
Summary

- Incidence rates estimates of myocarditis/pericarditis after mRNA COVID-19 vaccination
  - Highest in males ages 18 to 25 years
  - More events were observed post-Dose 2 than in post-Dose 1
  - Wide range of incidence rates among four BEST databases with wide confidence intervals

- Incidence rate ratio estimates comparing Moderna and Pfizer-BioNTech vaccines
  - Preliminary results do not support a significant difference for males 18-25 years
  - Estimates had large uncertainty
    - Small numbers of observed events
    - Partial adjustment for some potential confounders
• Military Health System continues to identify and follow patients with myocarditis following COVID-19 vaccination

• Overall rate of myocarditis within 7 days of vaccination is 10 cases per million doses, but **risk is strongly dependent on patient age and sex, and vaccine dose and type**; rate of myocarditis in younger (under age 20) males after 2\(^{nd}\) dose mRNA vaccine is >100 cases per million doses

• Approximately two-thirds of patients report feeling fully recovered within 6 weeks of diagnosis; standard American College of Cardiology recommendations limit strenuous activity for 3-6 months; follow-up within Military Health System is ongoing

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June 29, 2021

**Myocarditis Following Immunization With mRNA COVID-19 Vaccines in Members of the US Military**

Jay Montgomery, MD\(^{1,2}\); Margaret Ryan, MD, MPH\(^{1,3}\); Renata Engler, MD\(^4\); Donna Hoffman, MSN\(^{1,2}\); Bruce McLennathan, MD\(^{1,5}\); Limone Collins, MD\(^1\); David Loran, DNP\(^{1,3}\); David Hrcir, MD\(^{1,6}\); Kelsie Herring, MD\(^7\); Michael Plattzer, MD\(^8\); Nehkonti Adams, MD\(^4,8\); Aliye Sanou, MD\(^8\); Leslie T. Cooper Jr, MD\(^9\)

Department of Veterans Affairs active surveillance
Rapid Cycle Analysis (RCA) for COVID-19 vaccines

• Weekly analysis comparing observed to expected number of prespecified outcomes from historical rates adjusting for sequential tests

• Near-real time chart reviews for assessment of specific incident events
  ▪ Initial chart review to assess presumptive events
  ▪ Detailed chart review:
    – Subject matter experts confirm outcomes through defined criteria
    – Evaluates the timeframe of onset (i.e., within risk period)

Collaborators/Federal Partners – CDC, FDA, DOD

Slides courtesy Fran Cunningham, Pharm D, Department of Veterans Affairs
Summary of VA RCA for myocarditis/pericarditis

- Vaccinated population
  - 3.5 million Moderna doses administered (1.84 million dose 1, 1.70 million dose 2)
  - 3.1 million Pfizer-BioNTech doses administered (1.64 million dose 1, 1.46 million dose 2)
  - Limited use of the Janssen vaccine in VA population (~270 thousand doses)
  - 89% male; 60% aged 65+ years old, with Janssen vaccinated cohort younger

- No statistical signals for myocarditis/pericarditis with any COVID-19 vaccine, although limited data available for Janssen vaccine

- 7 chart confirmed myocarditis/myopericarditis cases
  - 6 in males and 1 in a female
  - Median age 37 years (range 24-66 years)
  - Median onset 3 days (range 1-18 days)
  - Most after dose 2: Pfizer-BioNTech dose 2 (n=4) and dose 1 (n=1), Moderna dose 2 (n=2)
  - Highest rate in 18-39-year-olds
  - All cases clinically resolved

- Absence of myocarditis signal in VA data likely due to age differences in VA population

Slides courtesy Fran Cunningham, Pharm D, Department of Veterans Affairs


ENHANCED EPIDEMIOLOGICAL SUMMARY
Myocarditis and Pericarditis Following Vaccination with COVID-19 mRNA Vaccines in Ontario: December 13, 2020 to August 7, 2021


Comirnaty and Spikevax: possible link to very rare cases of myocarditis and pericarditis

CDC enhanced surveillance for myocarditis outcomes after mRNA COVID-19 vaccination in VAERS case reports*

- **Purpose:** Assess functional status and clinical outcomes among individuals reported to have developed myocarditis after mRNA COVID-19 vaccination

- **Methods:** A two-component survey conducted at least 90 days after the onset of myocarditis symptoms
  - Patient survey: Ascertains functional status, clinical symptoms, quality of life, and need for medication or other medical treatment
  - Healthcare provider (e.g., cardiologist): Gather data on cardiac health and functional status

- **Timeline:** data collection August 2021–November 2021 (anticipated)

As of August 2021, VAERS had received 826 reports of myocarditis or myopericarditis after COVID-19 vaccination that met case definition.

To date, around 680 patients have reached 90 days post-myocarditis diagnosis:

- Of these, 282 (41%) have received at least one phone call:
  - Of the 282 patients who have received a call, 168 (60%) completed the survey and 67 (24%) were unreachable or declined to participate.
  - Of the 168 patients surveyed, 132 (79%) provided cardiologist or healthcare provider contact information:
    - Of the 132 cardiologist or healthcare providers, 26 have completed the survey.
    - Remaining 106 in the process of being contacted.

Update on the Safety of Janssen COVID-19 Vaccine

Narayan Nair, MD
Division Director– Division of Epidemiology,
Office of Biostatistics and Epidemiology, Center for Biologics Evaluation and Research, FDA
October 15, 2021

https://www.fda.gov/media/153132/download
Adverse Event Reporting under EUA

**Vaccine Recipients**
- Voluntary Reporting
  - Spontaneous reports
  - Solicited reports from v-safe program

**Vaccination Providers**
- Mandatory Reporting
  - Vaccination administration errors (providers only)
  - Serious adverse events (SAEs)
  - Multisystem Inflammatory Syndrome
  - Cases of COVID-19 that result in hospitalization or death

**Vaccine EUA Sponsor**
- Monthly Periodic Safety Reports
  - Analysis of aggregate AE data
  - Newly identified safety concerns

**VAERS**
- Screening of all incoming SAEs
- Literature review
- Data Mining
- Potential safety signals will be further evaluated

**CDC**
- Review of all Adverse Events of Special Interest (AESI)
- Data Abstraction

**FDA**
- Coordination Data Sharing

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https://www.fda.gov/media/153132/download
### Most Commonly Reported Adverse Events to VAERS after Janssen COVID-19 Vaccine - 14,688,615 doses of vaccine administered (data as of 10/7/21)

<table>
<thead>
<tr>
<th>Adverse Event (MedDRA Preferred Term)*</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>16,408 (26.1)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>13,939 (22.2)</td>
</tr>
<tr>
<td>Chills</td>
<td>11,717 (18.6)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>11,202 (17.8)</td>
</tr>
<tr>
<td>Pain</td>
<td>10,553 (16.8)</td>
</tr>
<tr>
<td>Nausea</td>
<td>8,495 (13.5)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>8,469 (13.5)</td>
</tr>
<tr>
<td>Pain In Extremity</td>
<td>6,265 (10.0)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>4,931 (7.8)</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>4,230 (6.7)</td>
</tr>
</tbody>
</table>

*Terms are not mutually exclusive
Existing safety concerns

Emerging potential safety concerns

- FDA and CDC continue to follow cases of GBS, and TTS reported to VAERS following Janssen COVID-19 vaccination
  - Information regarding these adverse events are currently communicated in EUA Fact Sheets

- FDA and CDC continue to assess cases of myocarditis, pericarditis, ITP, TEE reported to VAERS following Janssen COVID-19 vaccination
  - Preliminary analysis of unadjudicated cases in VAERS reveal an increased observed to expected ratio of myocarditis/pericarditis, and ITP

- FDA Near Real-Time Surveillance of 16 potential outcomes does not reveal safety signals for these adverse events at this time

https://www.fda.gov/media/CDC/153132/download
Vaccine Safety Datalink (VSD) Rapid Cycle Analysis (RCA) findings for Janssen COVID-19 vaccine

- VSD conducts RCA, which is near real-time sequential monitoring for prespecified surveillance outcomes of interest
- A relatively small number of Janssen COVID-19 vaccinations (~440 thousand) administered compared to mRNA COVID-19 vaccinations (~14 million)
- No statistical signals detected for any VSD RCA prespecified surveillance outcomes following Janssen COVID-19 vaccination in the 1–21-day risk interval
- Descriptive analysis indicates an imbalance of Guillain-Barré syndrome (GBS) cases following Janssen COVID-19 vaccination compared to mRNA COVID-19 vaccination with proportionally more GBS cases being observed after Janssen COVID-19 vaccination
Thrombosis with thrombocytopenia syndrome (TTS)

This is an official
CDC HEALTH ALERT

Cases of Cerebral Venous Sinus Thrombosis with Thrombocytopenia after Receipt of the Johnson & Johnson COVID-19 Vaccine

Summary
As of April 12, 2021, approximately 6.85 million doses of the Johnson & Johnson (J&J) COVID-19 vaccine (Janssen) have been administered in the United States. The Centers for Disease Control and Prevention (CDC) and the U.S. Food and Drug Administration (FDA) are reviewing data involving six U.S. cases of a rare type of blood clot in individuals after receiving the J&J COVID-19 vaccine that were reported to the Vaccine Adverse Events Reporting System (VAERS). In these cases, a type of blood clot called cerebral venous sinus thrombosis (CVST) was seen in combination with low levels of blood platelets (thrombocytopenia). All six cases occurred among women aged 18–48 years. The interval from vaccine receipt to symptom onset ranged from 6–13 days. One patient died. Providers should maintain a high index of suspicion for symptoms that might represent serious thrombotic events or thrombocytopenia in patients who have recently received the J&J COVID-19 vaccine. When these specific type of blood clots are observed following J&J COVID-19 vaccination, treatment is different from the treatment that might typically be administered for blood clots. Based on studies conducted among the patients diagnosed with immune thrombocytopenic thrombosis, treatment after the AstraZeneca COVID-19 vaccine in Europe, the pathogenesis of these rare and unusual adverse events after vaccination may be associated with platelet-activating antibodies against platelet factor-4 (PF4), a type of protein. Usually, the anticoagulant drug called heparin is used to treat blood clots. In this setting, the use of heparin may be harmful, and alternative treatments need to be given.

CDC will convene an emergency meeting of the Advisory Committee on Immunization Practices (ACIP) on Wednesday, April 14, 2021, to further review these cases and assess potential implications on vaccine policy. FDA will review that analysis as it also investigates these cases. Until that process is complete, CDC and FDA are recommending a pause in the use of the J&J COVID-19 vaccine out of an abundance of caution. The purpose of this Health Alert is, in part, to ensure that the healthcare provider community is aware of the potential for these adverse events and can provide proper management due to the unique treatment required with this type of blood clot.

Background
VAERS is a national passive surveillance system jointly managed by CDC and FDA that monitors adverse events after vaccinations. The six patients (after 6.85 million vaccine doses administered) described in these VAERS reports came to attention in the latter half of March and early April of 2021 and developed symptoms a median of 9 days (range = 6–13 days) after receiving the J&J COVID-19 vaccine. Initial presenting symptoms were notable for headache in five of six patients, and back pain in the sixth who subsequently developed a headache. One patient also had abdominal pain, nausea, and vomiting. Four developed focal neurological symptoms (focal weakness, aphasia, visual disturbance) prompting presentation for emergency care. The median days from vaccination to hospital admission was 15 days (range = 10–17 days). All were eventually diagnosed with

https://emergency.cdc.gov/han/2021/han00442.asp
Reporting rates of confirmed TTS cases (N=47) in VAERS after Janssen COVID-19 vaccination (15.3 million doses administered as of Oct 13, 2021†)

<table>
<thead>
<tr>
<th>Age group</th>
<th>Females (n=34)</th>
<th>Males (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TTS cases</td>
<td>Doses admin.</td>
</tr>
<tr>
<td>18–29 yrs</td>
<td>4</td>
<td>1,130,467</td>
</tr>
<tr>
<td>30–39 yrs</td>
<td>11</td>
<td>1,079,231</td>
</tr>
<tr>
<td>40–49 yrs</td>
<td>9</td>
<td>1,145,500</td>
</tr>
<tr>
<td>50–64 yrs</td>
<td>8</td>
<td>2,053,566</td>
</tr>
<tr>
<td>65+ yrs</td>
<td>2</td>
<td>1,115,936</td>
</tr>
</tbody>
</table>

- Cases include 5 deaths related to complications from TTS following Janssen COVID-19 vaccination
  - Median age 37 years (range 29–52 years); 4 of 5 female; all 5 had cerebral venous sinus thrombosis
  - None received heparin; median platelet count nadir 15,000/µL (range 9,000-31,000/µL)
  - Anti-PF4 antibody ELISA testing performed for 4 decedents, all positive with optical density values >2.0

* Source of doses administered: https://covid.cdc.gov/covid-data-tracker/#vaccinations
† Reporting rate = TTS cases per 1 million Janssen COVID-19 vaccine doses administered
Summary of Janssen COVID-19 safety monitoring

- Existing safety concerns for Janssen COVID-19 vaccine
  - Current evidence suggests a causal association for TTS, though the condition is rare (47 confirmed cases after 15.3 million Janssen COVID-19 vaccinations administered)
    - Most cases are in women, with most aged 18-49 years old
  - Monitoring in VAERS and VSD suggest a possible association between Guillain-Barré syndrome and Janssen COVID-19 vaccination

- CDC, FDA, and federal partners will continue to assess emerging potential safety concerns (myocarditis/pericarditis, immune thrombocytopenia, thromboembolic events)
Safety of Janssen COVID-19 Primary Vaccination Followed by an Additional mRNA COVID-19 Vaccine Dose: Vaccine Safety Datalink (VSD)
VSD Rapid Cycle Analysis (RCA)

- VSD is monitoring the safety of COVID-19 vaccines weekly for prespecified outcomes of interest
- As of October 16, 2021, approximately 14.3 million doses have been administered and around 7.2 million members are fully vaccinated

<table>
<thead>
<tr>
<th>COVID-19 vaccine combination</th>
<th># of people fully vaccinated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderna + Moderna</td>
<td>2,711,487</td>
</tr>
<tr>
<td>Pfizer-BioNTech + Pfizer-BioNTech</td>
<td>4,026,967</td>
</tr>
<tr>
<td>Janssen one dose only</td>
<td>442,299</td>
</tr>
<tr>
<td>Janssen + mRNA dose</td>
<td>5,463</td>
</tr>
<tr>
<td><strong>Janssen + mRNA dose</strong> (with a minimum of 60 days between doses)</td>
<td><strong>3,662</strong></td>
</tr>
</tbody>
</table>
VSD demographics in persons with Janssen primary + additional mRNA vaccine dose with a minimum of 60 days between doses

n = 3,662
<table>
<thead>
<tr>
<th>VSD COVID-19 vaccine prespecified surveillance outcomes</th>
<th>Settings</th>
<th>Risk window (days)</th>
<th>Exclude if COVID-19 in the prior X days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute disseminated encephalomyelitis</td>
<td>E, I</td>
<td>1-21, 1-42</td>
<td></td>
</tr>
<tr>
<td>Acute myocardial infarction – <strong>First Ever</strong></td>
<td>E, I</td>
<td>1-21, 1-42</td>
<td>30 days</td>
</tr>
<tr>
<td>Acute respiratory distress syndrome</td>
<td>E, I</td>
<td>0-84</td>
<td>42 days</td>
</tr>
<tr>
<td>Anaphylaxis – <strong>First in 7 days</strong></td>
<td>E, I</td>
<td>0-1</td>
<td></td>
</tr>
<tr>
<td>Appendicitis</td>
<td>E, I</td>
<td>1-21, 1-42</td>
<td></td>
</tr>
<tr>
<td>Bell’s palsy – <strong>First Ever</strong></td>
<td>E, I, O</td>
<td>1-21, 1-42</td>
<td>30 days</td>
</tr>
<tr>
<td>Cerebral venous sinus thrombosis</td>
<td>E, I</td>
<td>1-21, 1-42</td>
<td>30 days</td>
</tr>
<tr>
<td>Disseminated intravascular coagulation</td>
<td>E, I</td>
<td>1-21, 1-42</td>
<td>42 days</td>
</tr>
<tr>
<td>Encephalitis / myelitis / encephalomyelitis</td>
<td>E, I</td>
<td>1-21, 1-42</td>
<td>30 days</td>
</tr>
<tr>
<td>Guillain-Barré syndrome</td>
<td>E, I</td>
<td>1-21, 1-42</td>
<td></td>
</tr>
<tr>
<td>Immune thrombocytopenia</td>
<td>E, I, O</td>
<td>1-21, 1-42</td>
<td>30 days</td>
</tr>
<tr>
<td>Kawasaki disease</td>
<td>E, I</td>
<td>1-21, 1-42</td>
<td></td>
</tr>
<tr>
<td>Multisystem inflammatory syndrome in children/adults</td>
<td>E, I</td>
<td>0-84</td>
<td></td>
</tr>
<tr>
<td>Myocarditis / pericarditis – <strong>First in 60 Days</strong></td>
<td>E, I</td>
<td>1-21, 1-42</td>
<td>30 days</td>
</tr>
<tr>
<td>Narcolepsy / cataplexy</td>
<td>E, I, O</td>
<td>0-84</td>
<td></td>
</tr>
<tr>
<td>Pulmonary embolism – <strong>First Ever</strong></td>
<td>E, I</td>
<td>1-21, 1-42</td>
<td>30 days</td>
</tr>
<tr>
<td>Seizures</td>
<td>E, I</td>
<td>1-21, 1-42</td>
<td>30 days</td>
</tr>
<tr>
<td>Stroke, hemorrhagic</td>
<td>E, I</td>
<td>1-21, 1-42</td>
<td>30 days</td>
</tr>
<tr>
<td>Stroke, ischemic</td>
<td>E, I</td>
<td>1-21, 1-42</td>
<td>30 days</td>
</tr>
<tr>
<td>Thrombosis with thrombocytopenia syndrome – <strong>First Ever</strong></td>
<td>E, I</td>
<td>1-21, 1-42</td>
<td>30 days</td>
</tr>
<tr>
<td>Thrombotic thrombocytopenic purpura</td>
<td>E, I</td>
<td>1-21, 1-42</td>
<td>30 days</td>
</tr>
<tr>
<td>Transverse myelitis</td>
<td>E, I</td>
<td>1-21, 1-42</td>
<td></td>
</tr>
<tr>
<td>Venous thromboembolism – <strong>First Ever</strong></td>
<td>E, I, O</td>
<td>1-21, 1-42</td>
<td>30 days</td>
</tr>
</tbody>
</table>

*Abbreviations: E=ED, I=Inpatient, O=Outpatient*
VSD Rapid Cycle Analysis (RCA)

- Among the 3,662 persons who received a Janssen primary vaccination and a subsequent mRNA vaccination at a minimum interval of 60 days after the Janssen primary dose, 2 prespecified surveillance outcomes* were detected in the 1–42-day risk interval

<table>
<thead>
<tr>
<th>Prespecified outcome (n=2)</th>
<th>Patient sex</th>
<th>Patient age in years</th>
<th>Interval b/w Janssen primary dose &amp; subsequent mRNA vaccination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute myocardial infarction</td>
<td>Male</td>
<td>50–64</td>
<td>125 days</td>
</tr>
<tr>
<td>Seizure</td>
<td>Female</td>
<td>25–29</td>
<td>142 days</td>
</tr>
</tbody>
</table>

* Both were following a Pfizer-BioNTech vaccine dose
VSD summary of heterologous dose safety

- Limited data are available on a Janssen primary vaccination followed by an additional mRNA COVID-19 vaccination at a minimum interval of 60 days after the Janssen primary vaccination.
  - There is a lack of evidence to date of a safety problem with respect to any of the prespecified VSD surveillance outcomes for this vaccination practice.
What can you do for vaccine safety?

- Report adverse events following vaccination to VAERS even if you aren’t sure if the vaccination caused the adverse event
- Enroll yourself in v-safe
- Healthcare providers, encourage your patients to enroll in v-safe
- Parents and guardians, you can enroll your children in v-safe

Please get involved, your participation matters
Acknowledgments

Thanks to the many people who made analysis of these data possible:

- **VAERS Team**
  - VAERS TTS abstraction team
  - VAERS Myopericarditis abstraction team
  - VAERS data team
- **Clinical Immunization Safety Assessment Project**
- **CDC team investigating long-term effects of myocarditis**
- **VSD Team, VSD participating sites, and investigators from Kaiser Permanente Northern California and the Marshfield Clinic Research Institute**
- **CDC COVID-19 Data Monitoring and Reporting Group**
- **FDA/Center for Biologics Evaluation and Research**
- **U.S. Department of Defense**
- **U.S. Department of Veterans Affairs**
Disclaimer

- The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention (CDC)

- Mention of a product or company name is for identification purposes only and does not constitute endorsement by CDC
Thank you!

For more information, contact CDC
1-800-CDC-INFO (232-4636)

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