

Interim Analysis of Acute Hepatitis of Unknown Etiology in Children Aged <10 Years — United States, October 2021–June 2022

Jordan Cates, PhD^{1,*}; Julia M. Baker, PhD^{1,2,*}; Olivia Almendares, MSPH¹; Anita K. Kambhampati, MPH¹; Rachel M. Burke, PhD¹; Neha Balachandran, MBBS^{1,3}; Eleanor Burnett, MPH¹; Caelin C. Potts, PhD¹; Sarah Reagan-Steiner, MD⁴; Hannah L. Kirking, MD¹; David Sugerman, MD¹; Umesh D. Parashar, MD, MBBS¹; Jacqueline E. Tate, PhD¹; Hepatitis of Unknown Etiology Group

On April 21, 2022, CDC issued a health advisory[†] encouraging U.S. clinicians to report all patients aged <10 years with hepatitis of unknown etiology to public health authorities, after identification of similar cases in both the United States (1) and Europe.[§] A high proportion of initially reported patients had adenovirus detected in whole blood specimens, thus the health advisory encouraged clinicians to consider requesting adenovirus testing, preferentially on whole blood specimens. For patients meeting the criteria in the health advisory (patients under investigation [PUIs]), jurisdictional public health authorities abstracted medical charts and interviewed patient caregivers. As of June 15, 2022, a total of 296 PUIs with hepatitis onset on or after October 1, 2021, were reported from 42 U.S. jurisdictions. The median age of PUIs was 2 years, 2 months. Most PUIs were hospitalized (89.9%); 18 (6.1%) required a liver transplant, and 11 (3.7%) died. Adenovirus was detected in a respiratory, blood, or stool specimen of 100 (44.6%) of 224 patients.[¶] Current or past infection with SARS-CoV-2 (the virus that causes COVID-19) was reported in 10 of 98 (10.2%) and 32 of 123 (26.0%) patients, respectively. No common exposures (e.g., travel, food, or toxicants) were identified. This nationwide investigation is ongoing. Further clinical data are needed to understand the cause of hepatitis in these patients and to assess the potential association with adenovirus.

Clinicians and health departments began retrospectively and prospectively identifying PUIs on April 21, 2022. A PUI was

defined as a person aged <10 years with elevated (>500 U/L) aspartate aminotransferase (AST) or alanine aminotransferase (ALT), an unknown etiology for the hepatitis, and onset on or after October 1, 2021. Comprehensive investigations of PUIs included rapid reporting of preliminary information, medical chart abstractions, caregiver interviews, laboratory testing, and tissue specimen examination. Upon identification of a PUI, jurisdictional health departments sent preliminary information (basic demographic information, date of hepatitis diagnosis, adenovirus testing results, and patient outcome) to CDC. Medical chart abstraction used standardized forms to collect information on demographic characteristics, signs and symptoms of illness, underlying health conditions, laboratory results (pathogen testing, biomarkers, and toxicology), radiologic findings, tissue pathology findings, vaccination history, and diagnoses and treatment received. Patient caregiver interviews collected information on demographic characteristics, household structure, symptoms, health care use, medical and medication history, and potential exposures (e.g., close contacts, diet, and toxicants). Adenovirus nucleic acid amplification testing (e.g., polymerase chain reaction [PCR]) of blood, respiratory, or stool specimens or rectal swabs was requested at the discretion of the treating clinician and conducted at a diagnostic or reference laboratory.^{**} Available specimens that yielded positive results for adenovirus were further characterized using Sanger sequencing of the six hypervariable regions of the hexon gene to determine adenovirus type (2). Formalin-fixed, paraffin-embedded (FFPE) liver biopsy, explant, or autopsy tissue specimens underwent routine evaluation at the clinical institutions, and residual FFPE tissue specimens

*These authors contributed equally to this report.

† <https://emergency.cdc.gov/han/2022/han00462.asp>

§ <https://www.who.int/emergencies/disease-outbreak-news/item/2022-DON368>

¶ Adenovirus-positive results on respiratory, blood, or stool specimen types but excluded PUIs with pending or unknown test results (test results might not have been available at the time of data collection).

** <https://www.cdc.gov/ncird/investigation/hepatitis-unknown-cause/laboratories-testing-typing.html>



were submitted to CDC for additional pathologic evaluation and diagnostic testing (3,4). This investigation was reviewed by CDC and conducted consistent with applicable federal law and CDC policy.^{††} Data were managed using REDCap electronic data tools hosted at CDC,^{§§} and SAS (version 9.4; SAS Institute) was used to conduct all analyses.

As of June 15, 2022, a total of 296 PUIs were reported from 42 U.S. jurisdictions. There was no apparent temporal clustering of hepatitis diagnoses among these children, although a peak in diagnoses coincided with the release of the health advisory (Figure 1). The median age at time of illness was 2 years, 2 months (range = 1 month–9 years, 8 months), and the largest percentage of PUIs (37.8%, 112) were Hispanic or Latino children, followed by White, non-Hispanic children (32.4%, 96) (Table). Among all reported PUIs, 266 (89.9%) required hospitalization, 18 (6.1%) required a liver transplant, and 11 (3.7%) died. Preliminary reports indicated that among 224 PUIs receiving adenovirus testing, 100 (44.6%) had a positive result in any specimen type, including 31 of 71 (43.7%) who underwent testing of whole blood (Figure 1).

Data from 123 PUIs with medical chart abstraction and interviews were available for detailed analyses; completion

of data collection is pending for the remaining 173 PUIs. Compared with all reported PUIs, those with completed medical chart abstraction and interview data were similar demographically, by date of hepatitis diagnosis and by percentage of positive adenovirus test results. Systemic and gastrointestinal signs and symptoms (86.2% and 87.8%, respectively) were common and included vomiting (61.8%), fatigue (55.3%), and jaundice (57.7%) (Table). The median interval between symptom onset and clinical evaluation was 4 days (IQR = 2–9 days). The median peak AST and ALT levels were 2,254.5 U/L (IQR = 802.5–4,266.5) and 1,744.5 U/L (IQR = 710.5–3,358.5), respectively. Thirty-seven (30.1%) patients received a diagnosis of acute liver failure^{**} and 15 (12.2%) had hepatic encephalopathy. The clinical assessments of four PUIs were consistent with potential autoimmune hepatitis based on liver biopsy results or other laboratory testing.

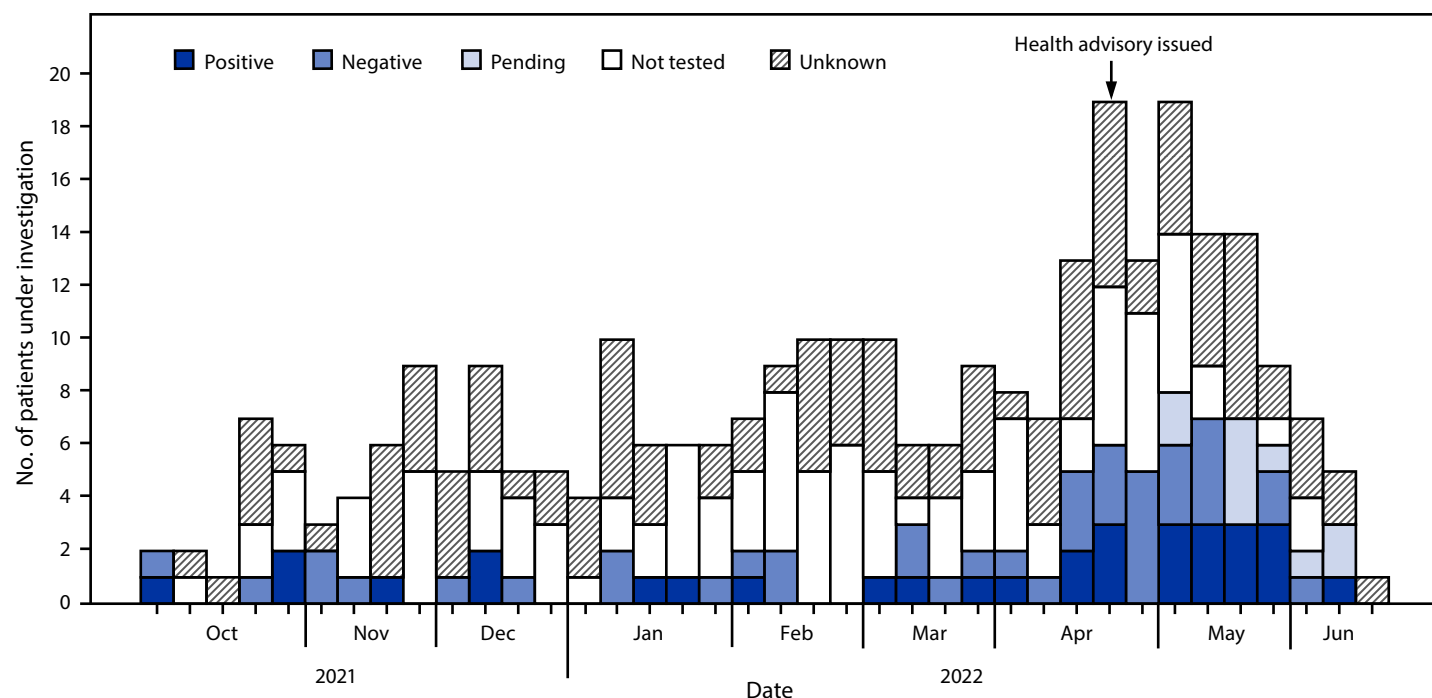
Medical records of the 123 PUIs with available chart abstractions and interviews indicated testing for and identification of a range of pathogens; adenovirus was detected most frequently

^{**} Acute liver failure (ALF) was based on the number of patients reported to have ALF in their medical chart. Twenty-four (64.9%) of the 37 patients were confirmed to meet the clinical definition for ALF based on laboratory markers and hepatic encephalopathy diagnosis (AST >500 U/L or ALT >500 U/L and either international normalized ratio (INR) >1.5 with hepatic encephalopathy or INR >2 without hepatic encephalopathy).

^{††} 45 C.F.R. part 46.102(l)(2), 21 C.F.R. part 56; 42 U.S.C. Sect. 241(d); 5 U.S.C. Sect. 552a; 44 U.S.C. Sect. 3501 et seq.

^{§§} <https://projectredcap.org/>

FIGURE 1. Patients under investigation for pediatric hepatitis of unknown etiology* reported to CDC (N = 296), by week of hepatitis presentation and stratified by results of preliminary adenovirus testing using whole blood — United States, October 2021–June 2022



* <https://emergency.cdc.gov/han/2022/han00462.asp>

TABLE. Demographic and clinical characteristics and potential exposures of patients under investigation for hepatitis of unknown etiology (N = 296) — United States, October 2021–June 2022

| Characteristic | No. (%) |
|---|-------------|
| All PUIs (N = 296, 100%) | |
| Age, yrs, median (range) | 2.2 (0–9.7) |
| Sex | |
| Male | 172 (58.1) |
| Female | 121 (40.9) |
| Unknown | 3 (1.0) |
| Race and ethnicity | |
| Hispanic or Latino | 112 (37.8) |
| White, non-Hispanic | 96 (32.4) |
| Black, non-Hispanic | 29 (9.8) |
| Asian, non-Hispanic | 11 (3.7) |
| Multiple race, non-Hispanic | 9 (3.0) |
| American Indian or Alaska Native, non-Hispanic | 5 (1.7) |
| Native Hawaiian or other Pacific Islander, non-Hispanic | 3 (1.0) |
| Unknown or missing | 31 (10.5) |
| Outcome | |
| Hospitalized* | 266 (89.9) |
| Received liver transplant† | 18 (6.1) |
| Died‡ | 11 (3.7) |
| PUIs with completed medical chart abstractions and interviews (n = 123, 42%) | |
| Measure of severity of acute hepatitis¶ | |
| Acute hepatitis with acute liver failure | 37 (30.1) |
| Acute hepatitis without acute liver failure | 86 (69.9) |
| Signs and symptoms during illness | |
| Any respiratory | 49 (39.8) |
| Cough | 34 (27.6) |
| Rhinorrhea | 22 (17.9) |
| Congestion | 20 (16.3) |
| Any gastrointestinal | 108 (87.8) |
| Vomiting | 76 (61.8) |
| Diarrhea | 61 (49.6) |
| Abdominal pain | 48 (39.0) |
| Any systemic | 106 (86.2) |
| Fatigue | 68 (55.3) |
| Decreased appetite | 65 (52.9) |
| Fever | 51 (41.5) |
| Hepatitis signs and symptoms | 84 (68.3) |
| Jaundice | 71 (57.7) |
| Dark-colored urine | 44 (35.8) |
| Hepatic encephalopathy | 15 (12.2) |
| Underlying medical conditions | |
| Any** | 44 (35.8) |
| None | 74 (60.2) |
| Unknown | 5 (4.1) |
| History of previous liver transplant | 1 (0.8) |
| Other testing or etiologies | |
| Potential autoimmune hepatitis | 4 (3.3) |
| Potential acetaminophen toxicity | 1 (0.8) |

(Figure 2). Among PUIs with adenovirus test results from any specimen type, 49.5% (48 of 97) received a positive test result (Table). Adenovirus was detected in 37.8% (14 of 37) of whole blood specimens, 34.4% (11 of 32) of plasma specimens, 30.0% (12 of 40) of stool specimens, and 30.1% (22 of 73) of respiratory specimens. Typing was attempted for 13 specimens, six of which were species F (type 41), one

TABLE. (Continued) Demographic and clinical characteristics and potential exposures of patients under investigation for hepatitis of unknown etiology (N = 296) — United States, October 2021–June 2022

| Characteristic | No. (%) |
|--|--------------|
| Adenovirus positivity, no. positive/total no. tested (%) | |
| Any specimen type | 48/97 (49.5) |
| Whole blood | 14/37 (37.8) |
| Plasma | 11/32 (34.4) |
| Respiratory | 22/73 (30.1) |
| Stool | 12/40 (30.0) |
| Serum | 0/3 (—) |
| SARS-CoV-2 | |
| Current SARS-CoV-2 infection,†† no. positive/total no. tested (%) | 10/98 (10.2) |
| History of SARS-CoV-2 infection | 32 (26.0) |
| Received ≥1 dose of a COVID-19 vaccine | 5 (4.1) |
| Household structure and exposures inside and outside the home | |
| No. of children aged <10 yrs in household,§§ median (range) | 1 (0–4) |
| Parental report of daily acetaminophen use during 2 mos preceding illness (any duration) | 11 (8.9) |
| Attended a child care facility or school during month preceding illness | 51 (42.5) |
| Patient never attended a child care facility or school | 69 (56.1) |
| Any domestic or international travel during 2 mos preceding illness | 24 (20.2) |
| Any international travel during 2 mos preceding illness¶¶ | 2 (1.6) |
| Any pets in the household*** | 53 (43.1) |

Abbreviations: ALF = acute liver failure; PUI = patient under investigation.

* Denominator includes four PUIs with unknown hospitalization data.

† Denominator includes 16 PUIs with unknown liver transplant data. Medical chart abstraction is pending for six (33.3%) of the 18 PUIs who received a liver transplant.

§ Denominator includes 25 PUIs with unknown death data. Medical chart abstraction is pending for four (36.4%) of the 11 deaths.

¶ ALF was based on the number of patients reported to have ALF in their medical chart. Twenty-four (64.9%) of the 37 cases were confirmed as meeting the clinical definition of ALF based on laboratory markers and hepatic encephalopathy diagnosis (aspartate aminotransferase >500 or alanine aminotransferase >500 and either [international normalized ratio >1.5 and hepatic encephalopathy] or [international normalized ratio >2 without hepatic encephalopathy]). Denominator includes 12 PUIs with unknown status for ALF.

** The specific underlying conditions reported included asthma (five, 4.1%), congenital heart disease (five, 4.1%), diabetes mellitus (one, 0.8%), seizure (one, 0.8%), history of liver transplant (one, 0.8%) premature birth (12, 9.8%), developmental disorder (eight, 6.5%), atopic or allergic conditions excluding asthma (eight, 6.5%), other chromosomal or congenital disorder (five, 4.1%), abnormal gastrointestinal tract or nutritional disorders (six, 4.9%), other disorders (11, 8.9%) (tracheomalacia, spinal arteriovenous malformation, obesity, history of elevated hepatic enzymes of unclear etiology, neonatal abstinence syndrome, anemia, pseudohypoparathyroidism, or heart murmur).

†† For SARS-CoV-2 infection, nine patients received positive reverse transcription–polymerase chain reaction test results and one received a positive antigen test result.

§§ Excluding the patient under investigation.

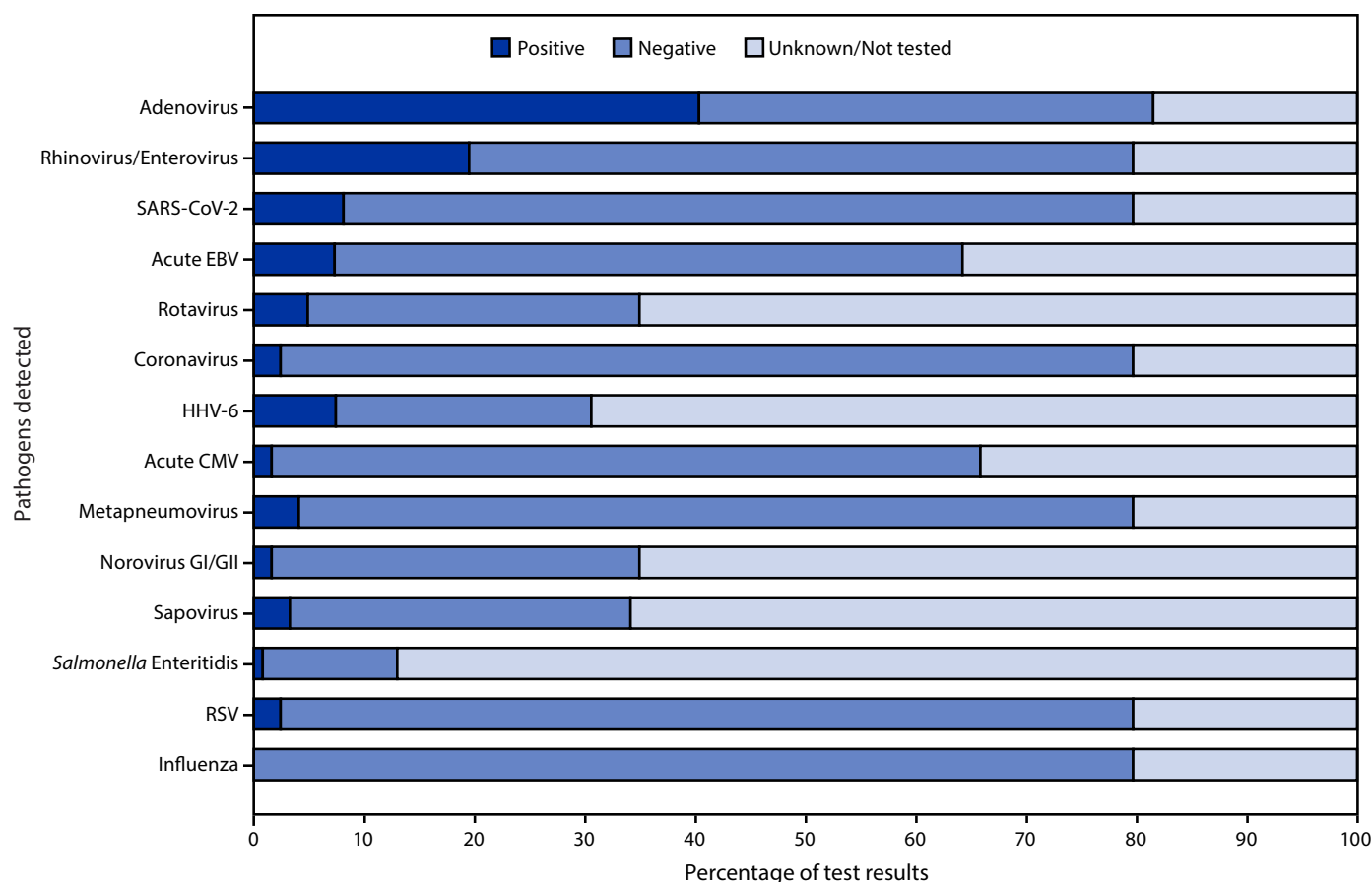
¶¶ Country visited was Mexico.

*** Thirty-nine (73.6%) reported a dog.

was species C (type C1); six could not be typed.*** Overall, 98 (79.7%) PUIs with available chart data received testing for current SARS-CoV-2 infection, 10 (10.2%) which received a

*** Adenovirus type C1 was identified in a nasopharyngeal swab. Specimens reported as “could not be typed” were those in which sequencing was attempted, and insufficient sequencing information was obtained to identify the adenovirus type.

FIGURE 2. Pathogens^{*,†,§,¶} detected during illness among a subset of patients under investigation for pediatric hepatitis of unknown etiology with completed medical chart abstraction and parental interviews (N = 123) — United States, October 2021–June 2022



Abbreviations: CMV = cytomegalovirus; EA = early antigen; EBV = Epstein-Barr virus; HHV = human herpesvirus; IgG = immunoglobulin G; IgM = immunoglobulin M; PCR = polymerase chain reaction; RSV = respiratory syncytial virus; RT-PCR = reverse transcription–polymerase chain reaction; VCA = viral capsid antigen.

* Adenovirus test results: positive = adenovirus detected in any specimen type; negative = all tested specimens negative.

† Current SARS-CoV-2 detection: positive SARS-CoV-2 RT-PCR or antigen test result during current illness.

§ Acute EBV: positive EBV VCA IgM or EA IgG test result, or diagnosis of primary EBV in the medical chart.

¶ Acute CMV: based on clinical diagnosis, verified by PCR/IgM test result.

positive test result. History of SARS-CoV-2 infection, based on documentation in the medical chart, antibody testing, or parental report, was reported for 32 (26.0%) patients. The median interval from prior SARS-CoV-2 infection to hepatitis diagnosis was 133 days (IQR = 77–283; nine with unknown date of prior infection). Five (4.1%) patients had received at least 1 dose of a COVID-19 vaccine. Other commonly detected pathogens included rhinovirus/enterovirus (24.5%, 24 of 98 tested), acute Epstein-Barr virus^{†††} (11.4%, nine of 79), and rotavirus (14.0%, six of 43). Adenovirus and SARS-CoV-2 were co-detected in 3.5% (three of 86) of patients receiving testing.

^{†††} Acute Epstein-Barr virus (EBV) infection was defined as a positive EBV viral capsid antigen immunoglobulin (Ig) M or early antigen IgG test result, or diagnosis of primary EBV infection in the medical chart.

Among 36 PUIs for whom information on pathologic evaluation of liver biopsy, explant, or autopsy tissues was available, 25 (65.8%) had evidence of active or acute hepatitis, and none had viral inclusions. As previously reported, liver biopsies from six patients with adenovirus infection had no immunohistochemical evidence of adenovirus and no viral particles identified by electron microscopy (1).

Approximately one third of patients were the only child in the household aged <10 years. Fewer than one half (42.5%) of children attended a child care facility or school in the month before becoming ill, and 56.1% had never attended a child care facility or school. At present, no exposures (e.g., travel, food, or toxicants) were common among the PUIs, and no epidemiologic links were identified among PUIs in preliminary analyses.

Discussion

As of June 15, 2022, a total of 296 PUIs with pediatric hepatitis of unknown etiology have been reported to CDC. Illness severity at the time of initial clinical evaluation ranged from elevated liver enzymes without acute liver failure to acute liver failure requiring liver transplantation, and there were 11 deaths. Most cases occurred in children aged <5 years. Adenovirus was the most commonly detected pathogen (45% of PUIs), and among a limited subset of 13 patients with typing data available, adenovirus type 41 was the predominant type.

This ongoing U.S. investigation coincides with and complements investigations of similar cases globally. As of May 26, 2022, the World Health Organization had reported 434 probable cases^{§§§} of acute pediatric hepatitis of unknown etiology in 32 other countries, primarily in Europe.^{¶¶¶} Notable similarities among cases identified across these investigations are emerging, including young age (77.9% of European cases were in children aged ≤5 years), frequent adenovirus detection (53.9% of European cases), and identification of adenovirus type 41.^{****}

It is not unusual for the cause of hepatitis in children to remain unknown; some estimates suggest that no etiology is identified in nearly one third of children with acute liver failure (5). The patients included in this investigation likely represent a heterogeneous group of hepatitis etiologies. The findings from liver tissue examinations were nonspecific and can be observed in hepatitis due to infectious or noninfectious causes; however, the findings were not consistent with typical adenoviral hepatitis observed among immunocompromised children (6). Adenovirus is not a known cause of hepatitis in otherwise healthy children (7); however, the recent identification of adenovirus in specimens from several PUIs raises the question of whether a new pattern of disease is emerging in this population or if adenovirus might be an underrecognized cause or cofactor in previously indeterminate cases of pediatric hepatitis.

Current U.S. data do not suggest an increase in pediatric hepatitis of unknown etiology or percent positivity for adenovirus types 40/41 over baseline levels (8). Additional hypotheses are under investigation, including the potential role of previous SARS-CoV-2 infection and adeno-associated virus-2, a nonpathogenic parvovirus that has been detected in a high proportion of cases in the United Kingdom (9). Potential changes in patterns of exposure to adenovirus and immune

naivety are also being considered. COVID-19 vaccination is unlikely to be related to these cases, given the low percentage of PUIs who were vaccinated and that nearly three quarters of PUIs were ineligible for COVID-19 vaccination based on age <5 years.

The findings in this report are subject to at least four limitations. First, this was a descriptive analysis, precluding definitive conclusions regarding potential associations between adenovirus or other risk factors and hepatitis. Second, this report describes preliminary data; CDC continues to receive data for current and new (including retrospectively identified) PUIs. Third, the retrospective identification of PUIs might limit the accuracy of both ascertainment and information obtained during interviews. Children with the most severe outcomes might have been more likely to be recalled by clinicians and reported retrospectively. Among the children who died, limitations in information that was immediately available made it difficult to further characterize the deaths. Finally, the hypothesized association between adenovirus and hepatitis might have led to increased adenovirus testing and reporting of children having positive test results.

CDC continues to partner with U.S. jurisdictions to investigate cases of pediatric acute hepatitis of unknown etiology. Clinicians are encouraged to continue to report patients meeting the criteria in the health advisory to jurisdictional public health authorities and to consider adenovirus testing of blood, respiratory, stool, and residual fixed liver tissue specimens, as well as SARS-CoV-2 antibody testing. Hepatitis of unknown etiology remains rare among young children. Nonetheless, parents and caregivers should contact their child's health care provider if their child shows any signs or symptoms of hepatitis.^{††††} Additional data from this ongoing investigation are needed to better understand the cause and pathophysiologic mechanism of hepatitis in these patients.

^{††††} Signs and symptoms of liver inflammation include fever, fatigue, loss of appetite, nausea, vomiting, abdominal pain, dark urine, light-colored stools, joint pain, and jaundice.

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^{§§§} World Health Organization probable case definition: acute hepatitis (non hep A–E) with serum transaminase >500 IU/L (AST or ALT) in a person aged ≤16 years, since October 1, 2021.

^{¶¶¶} <https://www.who.int/emergencies/disease-outbreak-news/item/DON-389>

^{****} <https://cdn.cdc.europa.eu/novhep-surveillance/>

Stacy Holzbauer, Sarah Lim, Ruth Lynfield, Anna Strain, Minnesota Department of Health; Mike Reh, Nebraska Department of Health and Human Services; Laura Taylor, New Jersey Department of Health; Abby L. Berns, Rhode Island Department of Health; Bryan Boyle, Zoe Durand, Amanda Gagnon, Tennessee Department of Health; Grace Lee, Alyssa McKenzie, Elizabeth Mytty, Louisiana Department of Health; Dalton Dessi, Tiffanie Fulton-Kennedy, Thomas C. Troelstrup, Florida Department of Health; Kelly Haywood, Lori Lloyd, Veronica Quintero, Wes Stubblefield, Burnestine Taylor, Alabama Department of Health; Stephanie Ayers-Millsap, Jefferson County Department of Health, Alabama; Sandra Henley, Mobile County Health Department, Alabama; Matthew Leslie, Maeve Marsh, Megan Toth Patel, Illinois Department of Health; Jeff Weigel, Panhandle Health District, Idaho; Victoria O'Dell, Central District Health, Idaho; Kimberly Dillon, Idaho Division of Public Health; Allison Longenberger, Hannah Lund, Lisa McHugh, Nottasorn Plipat, Sharon Watkins, Pennsylvania Department of Health; Raiza Amiling, Vannalyn de Leon, Prabhu Gounder, Mirna Jewell, Emily Kajita, Michael Lim, Wesley Moss, Han Wu, Los Angeles County Department of Public Health, California; Kentaro F. Abe, Alice Chen, Jennie Chen, Junlin Chen, Carol Glaser, Hugo Guevara, Jill Hacker, April Hatada, Monica P. Haw, Cora Hoover, Chantha Kath, Will Probert, Kyle Rizzo, Lauren J. Stockman, California Department of Public Health; Amanda Mandi, Robert Ramaekers, Iowa Department of Public Health; Tabatha Heaton, Chandni Patel, Virginia Department of Health; Bryon Backenson, Nitin Ghadge, and Michele McClenaghan, New York State Department of Health; Catherine M. Brown, Mary DeMartino, Stephen Fleming, Glen R. Gallagher, Rosa Hernandez, Lawrence C. Madoff, Marisa Nazareno, Sandra Smole, Dylan B. Tierney, Massachusetts Department of Public Health; Alexis W. Burakoff, Meghan Hudziec, Shannon R. Matzinger, Kaitlin Wolff, Colorado Department of Public Health and Environment; Samuel R. Dominguez, Children's Hospital Colorado; Kelly Garcia, Neha Shanker, North Carolina Department of Health and Human Services; Matthew Collins, Jesse Knibbs, Connor Martin, Lauren Milroy, Layne Mounsey, Jena Rasor, Mary-Elizabeth Steppig, Indiana Department of Health; Alisa Bochnowski, Maureen Sullivan, Kelly Wroblewski, Association of Public Health Laboratories; Elizabeth Marlowe, Quest Diagnostics; Marc Roger Couturier, ARUP Laboratories; Sylvianette Luna Anavitate, Carmen Rodriguez, Puerto Rico Department of Health; Amanda Jara, Georgia Department of Public Health; Molly V. Parsch, Michael Schurfranz, Louisville Public Health and Wellness, Kentucky; Faith Boldt, Pennyryle District Health Department, Kentucky; Dalen Traore, Kentucky Department for Public Health; Rudrani Ghosh, Jessamine County Health Department, Kentucky; Sara Chronister, Charla A. DeBolt, Sofia Husain, Esther Lam, Kali Turner, Washington State Department of Health; Jennifer Nybo, Tacoma-Pierce County Health Department, Washington; Hilary Armstrong, Eileen Benoliel, Shauna Clark, Jennifer Lenahan, Christopher White, Public Health – Seattle & King County, Washington; Susan Babcock, Snohomish Health District, Washington.

Summary

What is already known about this topic?

During October 2021–February 2022, a cluster of children with hepatitis of unknown etiology and adenovirus infection was identified in the United States. On April 21, after reports of similar cases in other countries, CDC advised clinicians to report patients aged <10 years with hepatitis of unknown etiology to public health authorities.

What is added by this report?

During October 1, 2021–June 15, 2022, a total of 296 U.S. pediatric patients received a diagnosis of hepatitis of unknown etiology, with adenovirus detected among 45%. Preliminary analyses have not identified common exposures (e.g., travel or toxicants).

What are the implications for public health practice?

The investigation is ongoing; further clinical data are needed to understand the cause of these cases and to assess the potential association with adenovirus.

Hepatitis of Unknown Etiology Group

Melissa M. Coughlin, CDC; Bettina Bankamp, CDC; Julu Bhatnagar, CDC; Lindsey Blythe Coulter Estetter, CDC; Luciana Silva-Flannery, CDC; Hannah Bullock, CDC; Negar Rassaei, CDC; Everardo M. Vega, CDC; Xiaoyan Lu, CDC; Erin R. McKeever, CDC; Debra Wadford, California Department of Public Health; Christina Morales, California Department of Public Health; Chao-Yang Pan, California Department of Public Health; Kirsten St. George, Wadsworth Center, New York State Department of Health, University at Albany; Daryl M. Lamson, Wadsworth Center, New York State Department of Health; L. Amanda Ingram, Alabama Department of Public Health; Theresa Dulski, CDC Epidemic Intelligence Service, Arkansas Department of Health; Tameika Reed, Arkansas Children's Hospital; Liam Hicks, Arizona Department of Health Services; J Bradford Bertumen, CDC Epidemic Intelligence Service, California Department of Public Health; Bonnie L. Dao, Los Angeles County Department of Public Health; Diana M. Tapay, Colorado Department of Public Health and Environment; Michael J. Kacka, CDC Epidemic Intelligence Service; Paul Gacek, Connecticut Department of Public Health, Epidemiology and Emerging Infections Program; Nikki M. Kupferman, Delaware Department of Health and Social Services; Angeni Cordova, Delaware Department of Health and Social Services; Ashley Gent, Florida Department of Health; Kati Touchstone, Florida Department of Health; Melissa Tobin-D'Angelo, Georgia Department of Public Health; Ami Gandhi, Georgia Department of Public Health; Kris Carter, CDC Center for Preparedness and Response; Kathryn Turner, Idaho Department of Health and Welfare; Lori Saathoff-Huber, Illinois Department of Public Health; Judy Kauerauf, Illinois Department of Public Health; Nicole Stone, Indiana Department of Health; Bethany Hodge, Kentucky Department for Public Health; Julie Hand, Louisiana Department of Health; Christine Nguyen,

Massachusetts Department of Public Health; Juliana Jacoboski, Massachusetts Department of Public Health; Emer S. Smith, Maine CDC, State of Maine Department of Health and Human Services; Chloe Manchester, Maine CDC, State of Maine Department of Health and Human Services; Macey Ladisky, Michigan Department of Health and Human Services; Genny Grilli, Minnesota Department of Health; Alexandra Berkley, Missouri Department of Health and Senior Services; Jennifer Hanson, Mississippi State Department of Health; Carla Boutwell, Mississippi State Department of Health; Erin Ricketts, CDC Epidemic Intelligence Service; Lana Deyneka, North Carolina Department of Health and Human Services; Lindsey VanderBusch, North Dakota Department of Health; Derek Julian, Nebraska Department of Health and Human Services; Matthew Donahue, Nebraska Department of Health and Human Services; Reed Magleby, CDC Epidemic Intelligence Service, New Jersey Department of Health; Deepam Thomas, New Jersey Department of Health; Anna M Stadelman, CDC Epidemic Intelligence Service, New Mexico Department of Health; Ali Garcia, Office of Public Investigations and Epidemiology, State of Nevada; Bridget J. Anderson, New York State Department of Health; Youjung Byun, New York State Department of Health; Aprielle Wills, New York City Department of Health and Mental Hygiene; Page Keating, New York City Department of Health and Mental Hygiene; Brandi Taylor, Ohio Department of Health; Courtney Dewart, CDC Center for Preparedness and Response, Ohio Department of Health; Mike Mannell, Oklahoma State Department of Health; Lauren Orkis, Pennsylvania Department of Health; Meghan Murray, CDC Epidemic Intelligence Service, Pennsylvania Department of Health; Iris Cardona Gerena, Departamento de Salud de Puerto Rico; Melissa Marzán Rodríguez, Departamento de Salud de Puerto Rico; Patricia McAuley, Rhode Island Department of Health; Hayden Hedman, CDC Epidemic Intelligence Service, South Dakota Department of Health; Jessica Schultz, Tennessee Department of Health; Christa Cook, Texas Department of State Health Services; Ryan Wallace, Texas Department of State Health Services; Amelia Salmanson, Utah Department of Health and Human Services; Dawn Saady, Virginia Department of Health; Amanda Dodd, Washington State Department of Health; Kimberly Carlson, Washington State Department of Health; Thomas Haupt, Wisconsin Department of Health Services.

Corresponding author: Jordan Cates, ncirddvdgast@cdc.gov.

¹Division of Viral Diseases, National Center for Immunization and Respiratory Diseases, CDC; ²Epidemic Intelligence Service, CDC; ³Cherokee Nation Assurance, Tulsa, Oklahoma; ⁴Division of High-Consequence Pathogens and Pathology, National Center for Emerging and Zoonotic Infectious Diseases, CDC.

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