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

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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 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

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† 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
†† 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/

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).

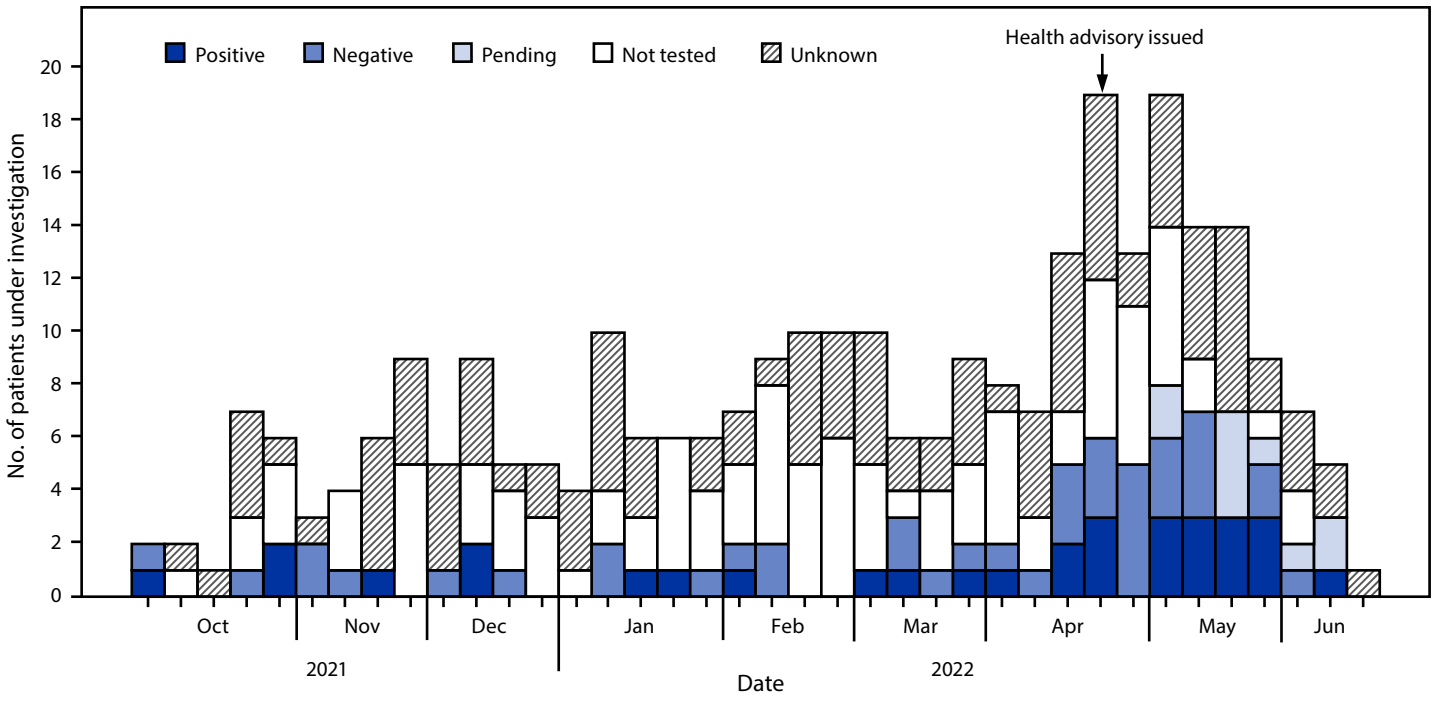
Data from 123 PUIs with medical chart abstraction and interviews were available for detailed analyses; completion of data collection is pending for the remaining 173 PUIs. Compared with all reported PUIs, those with completed medical chart abstraction and interview data were similar demographically, 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 (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 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 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

[¶¶] 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.

[***] 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 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)
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, pseudohypoaldosteronism, 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.

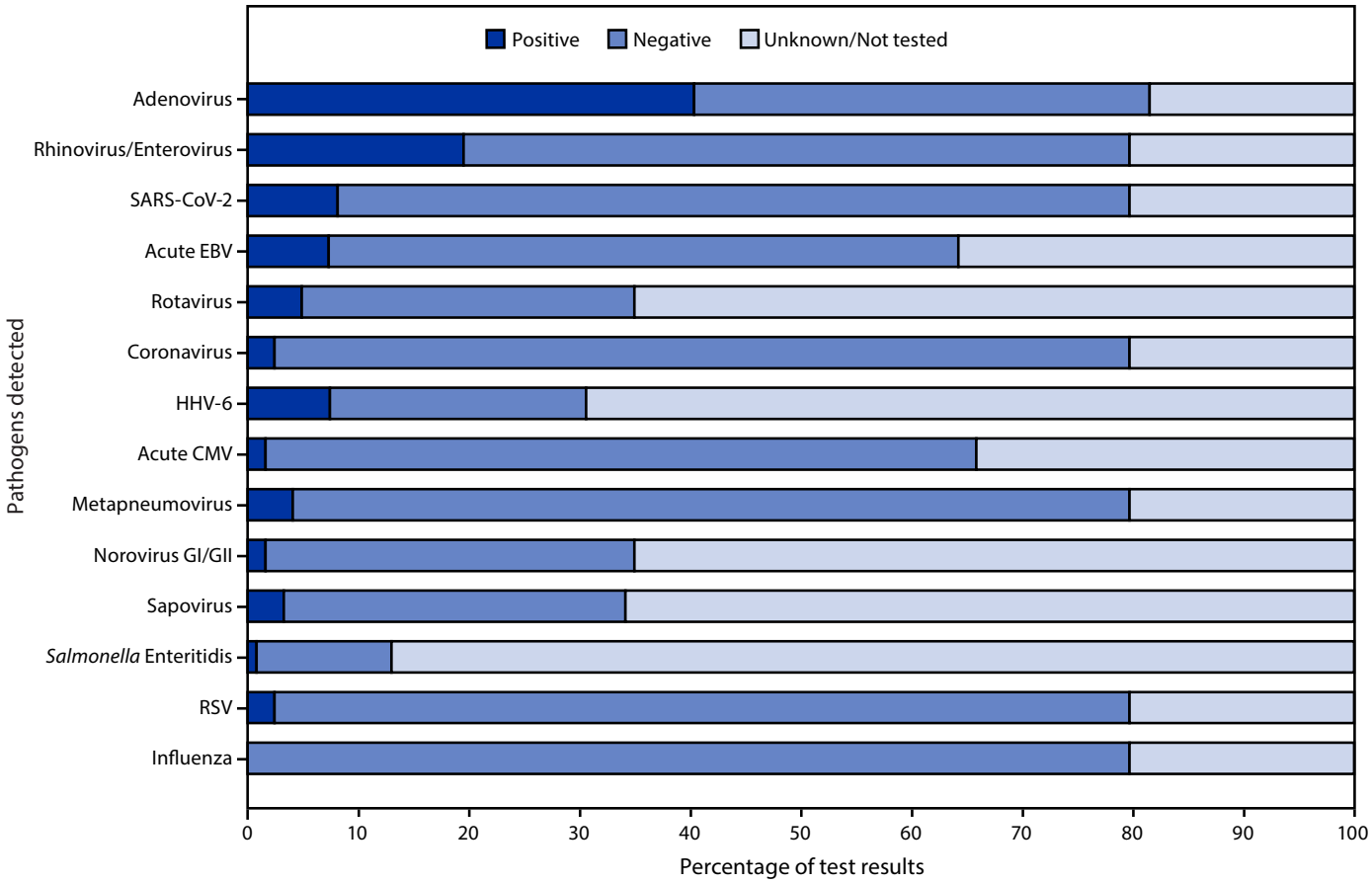
*** Thirty-nine (73.6%) reported a dog.

was 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.

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

††† 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.

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.

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

[§§§] 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

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 heterogenous 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.

[****] https://cdn.ecdc.europa.eu/novhep-surveillance/

[††††] 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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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.

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