

Trends in Acute Hepatitis of Unspecified Etiology and Adenovirus Stool Testing Results in Children — United States, 2017–2022

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In November 2021, CDC was notified of a cluster of previously healthy children with hepatitis of unknown etiology evaluated at a single U.S. hospital (1). On April 21, 2022, following an investigation of this cluster and reports of similar cases in Europe (2,3), a health advisory* was issued requesting U.S. providers to report pediatric cases† of hepatitis of unknown etiology to public health authorities. In the United States and Europe, many of these patients have also received positive adenovirus test results (1,3). Typed specimens have indicated adenovirus type 41, which typically causes gastroenteritis (1,3). Although adenovirus hepatitis has been reported in immunocompromised persons, adenovirus is not a recognized cause of hepatitis in healthy children (4). Because neither acute hepatitis of unknown etiology nor adenovirus type 41 is reportable in the United States, it is unclear whether either has recently increased above historical levels. Data from four sources were analyzed to assess trends in hepatitis-associated emergency department (ED) visits and hospitalizations, liver transplants, and adenovirus stool testing results among children in the United States. Because of potential changes in health care-seeking behavior during 2020–2021, data from October 2021–March 2022 were compared with a pre-COVID-19 pandemic baseline. These data do not suggest an increase in pediatric hepatitis or adenovirus types 40/41 above baseline levels. Pediatric hepatitis is rare, and the relatively low weekly and monthly counts of associated outcomes limit the ability to interpret small changes in incidence. Ongoing assessment of trends, in addition to enhanced epidemiologic investigations, will help contextualize reported cases of acute hepatitis of unknown etiology in U.S. children.

Data in this report were obtained from the National Syndromic Surveillance Program (NSSP), the Premier Healthcare Database Special Release (PHD-SR), the Organ

Procurement and Transplant Network (OPTN), and Labcorp, a large commercial laboratory network. NSSP collects electronic health data from EDs in all 50 states and the District of Columbia, representing 71% of nonfederal EDs in the United States. ED visits associated with hepatitis of unspecified etiology among children aged 0–4 and 5–11 years during January 2018–March 2022 were identified via *International Classification of Diseases, Tenth Revision, Clinical Modification* (ICD-10-CM) discharge diagnosis codes[§] (3); data were queried on May 26, 2022, and restricted to facilities with high data quality[¶] and consistent reporting during 2018–2022. Data on hospitalizations associated with hepatitis of unspecified etiology were obtained on May 25, 2022, from PHD-SR, which includes inpatient records from approximately 1,000 hospitals. Hospital admissions among children aged 0–4 and 5–11 years during January 2019–March 2022 were identified using the same ICD-10-CM codes as were used for ED data. Data on pediatric liver transplants were obtained on May 20, 2022 from the national registry managed by OPTN; these included monthly counts of liver transplants performed among patients aged <18 years in the United States during January 2017–March 2022, for whom the primary diagnosis at time of transplant was acute hepatic necrosis of unknown etiology.** Labcorp data, accessed on June 6, 2022, included deidentified results for all stool specimens tested for adenovirus types 40/41^{††} (Logical Observation Identifiers Names and Codes

[§] ICD-10-CM codes queried by NSSP and PHD-SR were as follows: B17.8 (other specified acute viral hepatitis); B17.9 (acute viral hepatitis, unspecified); B19.0 (unspecified viral hepatitis with hepatic coma); B19.9 (unspecified viral hepatitis without hepatic coma); K71.6 (toxic liver disease with hepatitis, not elsewhere classified); K72.0 (acute and subacute hepatic failure); K75.2 (nonspecific reactive hepatitis); and K75.9 (inflammatory liver disease, unspecified). These codes were previously used in a technical briefing published by the United Kingdom Health Security Agency.

[¶] To reduce artifactual impact from changes in reporting patterns, analyses were restricted to facilities with a coefficient of variation $\leq 35\%$ and $>70\%$ discharge diagnosis informativeness during 2018–2022. Visit data from a monthly average of 1,817 facilities were included in this analysis from state and regional jurisdictions representing 44 states.

** Recipient diagnosis at the time of liver transplant was acute hepatic necrosis (AHN) drug other specify; AHN etiology unknown; or AHN other, specify. <https://optn.transplant.hrsa.gov/patients/by-organ/liver/>

^{††} Adenovirus types 40 and 41 are both associated with acute gastroenteritis. Most commercial diagnostic tests do not distinguish between these two types.

* https://emergency.cdc.gov/han/2022/pdf/CDC_HAN_462.pdf

[†] Since April 2022, providers have been encouraged to report to public health authorities persons under investigation for acute hepatitis meeting the following definition: children aged <10 years with elevated aspartate aminotransferase or alanine aminotransferase levels (>500 U/L) with an unknown etiology for their hepatitis since October 1, 2021.

[LOINC] code 82209–8) among children aged 0–4 and 5–9 years during October 2017–March 2022.

Weekly numbers of ED visits during October 2021–March 2022 were compared with a prepandemic baseline (January 2018–February 2020) using a modified Farrington Method^{§§} (5). Monthly hospitalizations and liver transplants during October 2021–March 2022 were compared with those for the same months (January–March and October–December) during the calendar years 2017, 2018, and 2019, as available, using the Wilcoxon rank sum test. Data on hospitalizations and liver transplants during January 2020–September 2021 were excluded from each respective baseline because of possible impacts of the COVID-19 pandemic. Monthly stool specimen results are presented as total tests (all specimens with a negative or positive result) and percentage positive for adenovirus types 40/41. The percentage of stool specimens testing positive for adenovirus types 40/41 during October 2021–March 2022 was compared with that during the same months (October–March) of 2017–2018, 2018–2019, and 2019–2020, to minimize potential effects of seasonality. Analyses were conducted in R (version 4.1.1; R Foundation). This activity was reviewed by CDC and was conducted consistent with applicable federal law and CDC policy.^{¶¶}

Compared with a pre-COVID-19 pandemic baseline, no increase in weekly ED visits with hepatitis-associated discharge codes was observed during October 2021–March 2022 among children aged 0–4 or 5–11 years (Figure 1). During January 2019–March 2022, a median of 22 (range = 9–29) and 10 (range = 4–19) hepatitis-associated hospitalizations among children aged 0–4 and 5–11 years, respectively, were recorded each month (Figure 2) (Supplementary Figure, <https://stacks.cdc.gov/view/cdc/118245>). No significant changes were detected in the number of hepatitis-associated hospitalizations during October 2021–March 2022 compared with the same months before the COVID-19 pandemic among children aged 0–4 years (22 and 19.5, respectively, $p = 0.26$) or 5–11 years (12 and 10.5, respectively, $p = 0.42$). A median of four (range = 0–10) liver transplants occurred among persons aged <18 years each month during January 2017–March 2022 (Figure 2) (Supplementary

Figure, <https://stacks.cdc.gov/view/cdc/118245>). No significant increase in the number of monthly liver transplants was observed during October 2021–March 2022 (five) compared with the same months during 2017–2019 (four) ($p = 0.19$). During October 2017–March 2022, the monthly number of adenovirus tests ranged from 184 to 1,759 among children aged 0–4 years and from 140 to 725 among children aged 5–9 years (Figure 3). Among both age groups, the number of adenovirus tests was highest in March 2022. During October–March in 2017–2018, 2018–2019, and 2019–2020, the monthly percentage of specimens positive for adenovirus types 40/41 ranged from 5% to 19% among children aged 0–4 years and from 3% to 14% among children aged 5–9 years. After a decrease in testing volume and percentage positive during April 2020–September 2021, the percentage of specimens positive for adenovirus types 40/41 during October 2021–March 2022 returned to, but did not exceed, prepandemic levels in both age groups.

Discussion

Data from four large administrative databases were analyzed to assess trends in pediatric hepatitis and percentage of stool specimens positive for adenovirus type 40/41. These data indicate that neither outcome has recently increased above pre-COVID-19 pandemic levels. Although this ecologic analysis cannot conclusively confirm or refute a potential association between pediatric hepatitis and adenovirus, it provides useful context for the ongoing investigation.

Data from two large electronic health record systems and the liver transplant registry did not indicate an increase in pediatric ED visits or hospitalizations associated with hepatitis of unspecified etiology or pediatric liver transplants in the United States. Historical data on pediatric hepatitis from other countries are also limited. Although the United Kingdom has observed increases in hepatitis among children aged 1–4 years when comparing 2022 with previous years (6), data from multiple other European and non-European countries have been inconclusive (7,8).

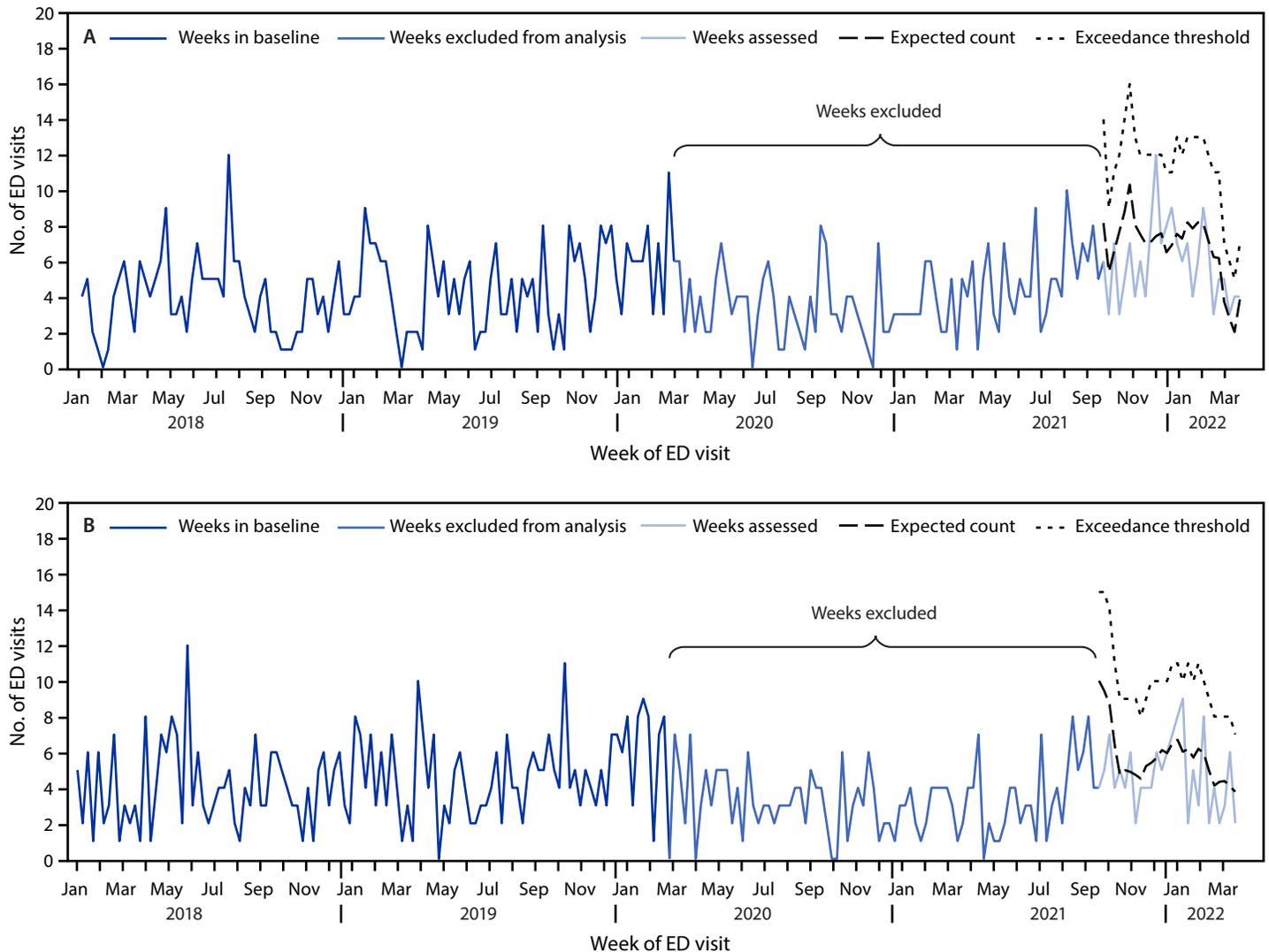
The percentage of specimens positive for adenovirus types 40/41 among children aged 0–4 and 5–9 years did not appear to increase above prepandemic historical levels, although the total number of specimens submitted for testing has increased over time. The United Kingdom has reported an increase in the number of adenovirus-positive stool specimen test results among children aged 1–4 years compared with prepandemic levels. However, United Kingdom data on testing volume and thus, percentage positive for adenovirus, are currently unavailable (6).

The findings in this report are subject to at least seven limitations. First, although liver transplants are well-documented, cases of hepatitis of unknown etiology are not reportable in the United States. This analysis assessed trends using electronic health data

^{§§} To monitor for recent anomalous increases in weekly trends, the modified Farrington algorithm was applied to ED visits during the weeks ending January 6, 2018, through the week ending April 2, 2022, excluding a predefined early pandemic period (weeks ending March 7, 2020, through October 2, 2021). The modified Farrington algorithm has traditionally been used on weekly count time series spanning multiple years. Weighted quasi-Poisson regression models are fit to multiple year baselines with a time term and 10-level factor to account for seasonality. The weighting strategy used by this algorithm is intended to down-weight baseline observations associated with historical outbreaks. When unweighted, baseline observations with abnormally high counts result in alerting thresholds that are too high and a reduction in sensitivity.

^{¶¶} 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.

FIGURE 1. Emergency department visits with hepatitis-associated *International Classification of Diseases, Tenth Revision, Clinical Modification* codes*[†] by week[§] of visit among children aged 0–4 years (A) and 5–11 years (B) — National Syndromic Surveillance Program, United States, January 2018–March 2022



Abbreviations: ED = emergency department; ICD-10-CM = *International Classification of Diseases, Tenth Revision, Clinical Modification*.

* ICD-10-CM Codes queried for hepatitis were as follows: B17.8 (other specified acute viral hepatitis); B17.9 (acute viral hepatitis, unspecified); B19.0 (unspecified viral hepatitis with hepatic coma); B19.9 (unspecified viral hepatitis without hepatic coma); K71.6 (toxic liver disease with hepatitis, not elsewhere classified); K72.0 (acute and subacute hepatic failure); K75.2 (nonspecific reactive hepatitis); and K75.9 (inflammatory liver disease, unspecified).

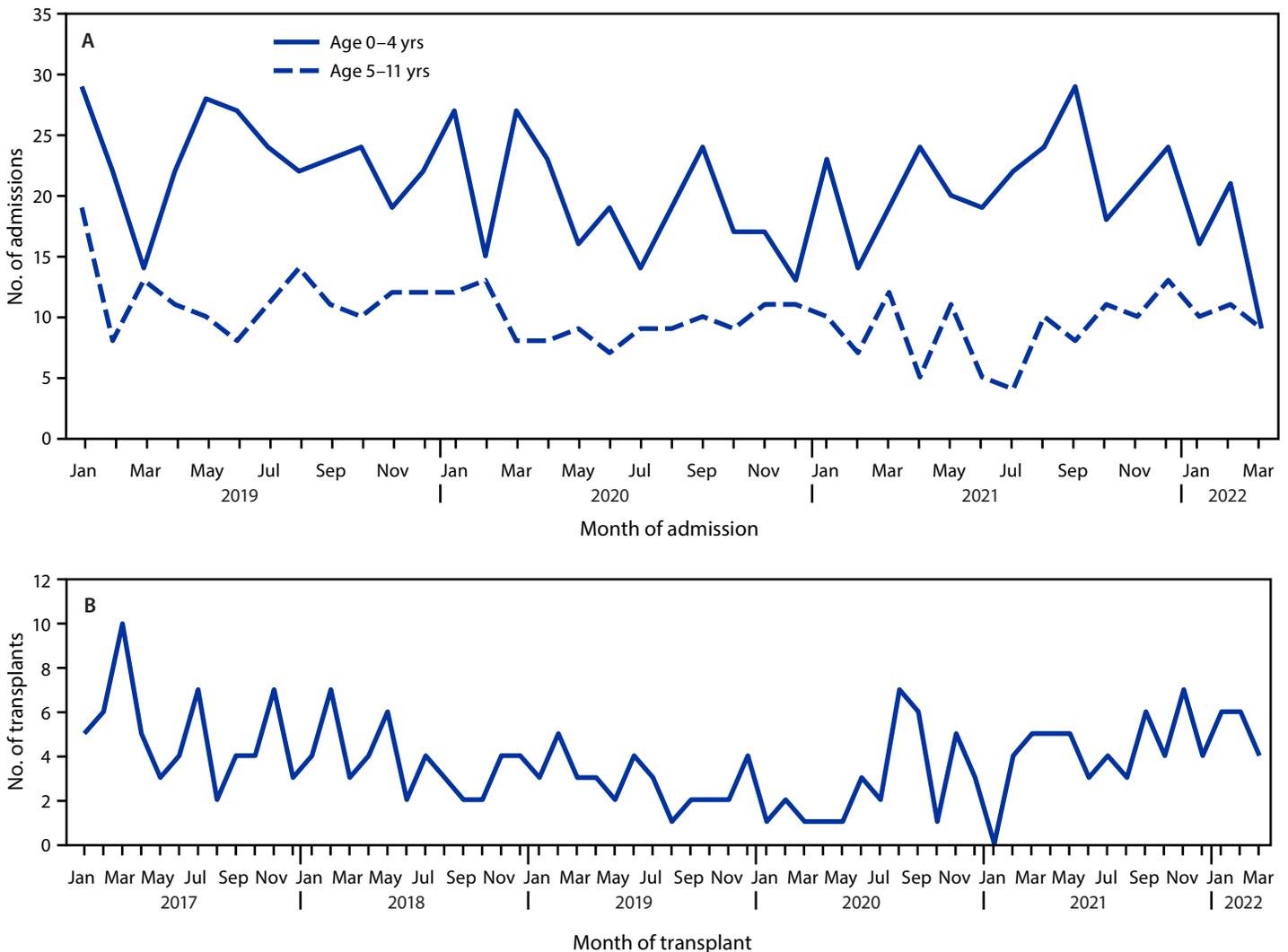
[†] To reduce artifactual impact from changes in reporting patterns, analyses were restricted to facilities with a coefficient of variation $\leq 35\%$ and $>70\%$ discharge diagnosis informativeness during 2018–2022. Visit data from a monthly average of 1,817 facilities were included in this analysis from state and regional jurisdictions representing 44 states.

[§] Weeks in baseline = January 2018–February 2020. Weeks excluded from analysis = March 2020–September 2021; this period was excluded from analysis because of possible effects of the COVID-19 pandemic. Weeks assessed = October 2021–March 2022. Expected counts = expected visit counts calculated from weighted regression model fit to baseline data. Exceedance threshold = upper bound defined as the 95th percentile of the negative binomial distribution with plug-in estimates for the mean and dispersion parameter. Weeks with observed weekly counts falling above this threshold were considered to be anomalies.

on pediatric hepatitis of unspecified etiology as a proxy, but the exact baseline remains unknown, as does the accuracy and completeness of the diagnostic codes used for identification. Second, data on hospitalizations and liver transplants have up to a 2–3-month lag between outcome and report; March 2022 data might be underreported. Third, the COVID-19 pandemic likely

affected observed patterns during the analysis period because of its effects on health care-seeking behavior (9) and infectious disease epidemiology during 2020–2021, and these patterns might still be normalizing. Prepandemic data are limited to 2017–2019, and it is not known whether these data represent a reliable baseline. Fourth, although NSSP and PHD-SR capture a

FIGURE 2. Hospitalizations with hepatitis-associated *International Classification of Diseases, Tenth Revision, Clinical Modification* codes* among children aged 0–4 and 5–11 years, by month of admission (A)[†] and liver transplants[§] among persons aged <18 years, by month of transplant (B)[¶] — United States, January 2019–March 2022 and January 2017–March 2022



Abbreviations: AHN = acute hepatic necrosis; ICD-10-CM = *International Classification of Diseases, Tenth Revision, Clinical Modification*.

* ICD-10-CM Codes queried for hepatitis were as follows: B17.8 (other specified acute viral hepatitis); B17.9 (acute viral hepatitis, unspecified); B19.0 (unspecified viral hepatitis with hepatic coma); B19.9 (unspecified viral hepatitis without hepatic coma); K71.6 (toxic liver disease with hepatitis, not elsewhere classified); K72.0 (acute and subacute hepatic failure); K75.2 (nonspecific reactive hepatitis); and K75.9 (inflammatory liver disease, unspecified).

[†] Premier Healthcare Database Special Release.

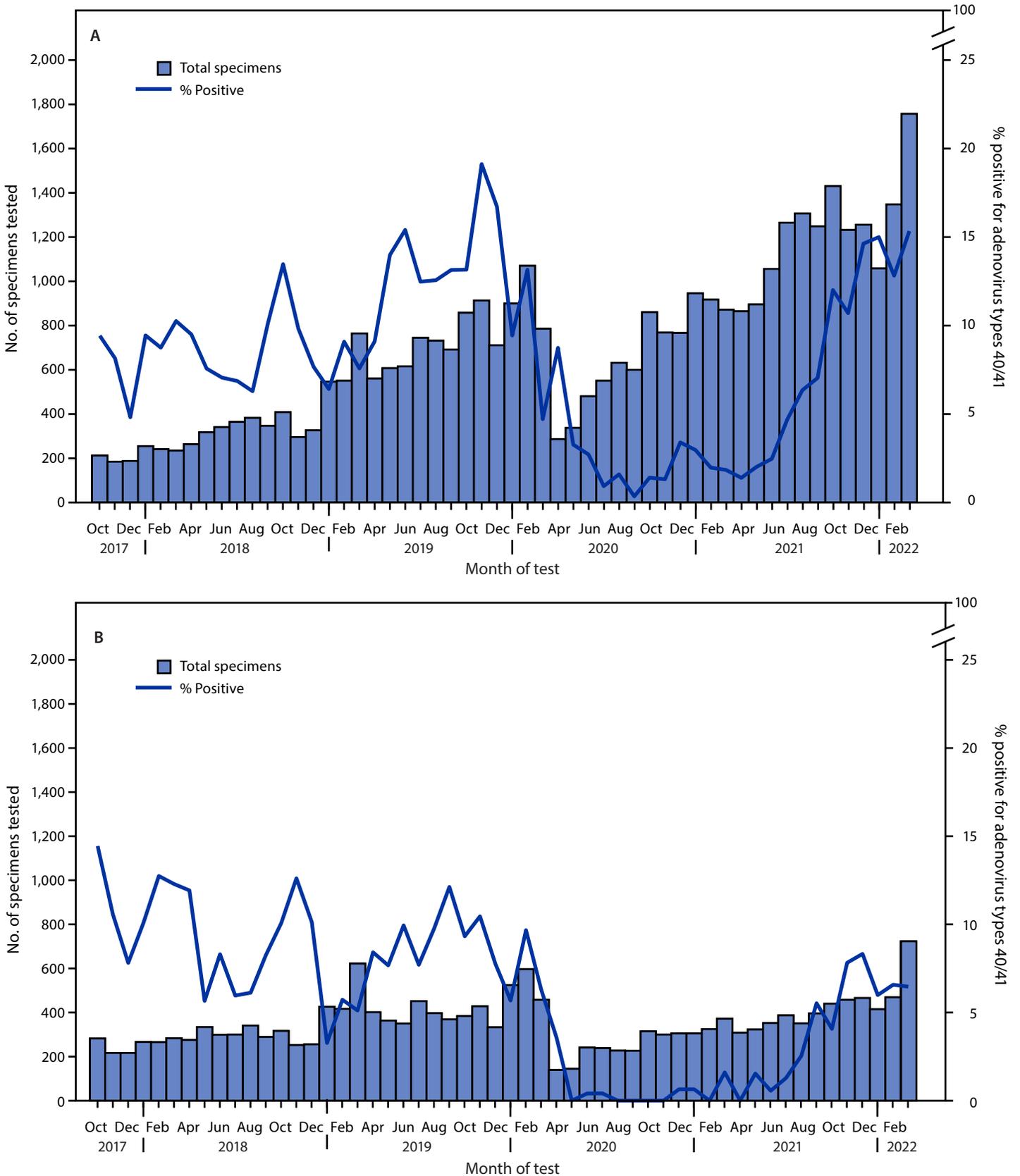
[§] Recipient diagnosis at the time of liver transplant was AHN drug other specify; AHN etiology unknown; or AHN other, specify.

[¶] Organ Procurement and Transplant Network.

large number of ED visits and hospitalizations, respectively, they do not cover the entire U.S. population, nor do they represent the same catchment areas. Similarly, Labcorp data represent only one large laboratory network and are not deduplicated to the patient level. The extent to which changes in testing volume might be due to changes in laboratory market share or test-ordering practices could not be determined, although the percentage of positive test results should not be substantially affected. Fifth, although the Labcorp assay cannot distinguish

between adenovirus types 40 and 41, nearly 90% of adenovirus detections in U.S. children with gastroenteritis are type 41 (10). Sixth, cases of acute hepatitis of unknown etiology are generally rare; thus, small changes in incidence might be difficult to detect and interpret. Finally, these results are intended to provide an overview of trends in pediatric acute hepatitis of unspecified etiology and adenovirus types 40/41 in the United States and cannot be used to infer or disprove a causal link between these two illnesses.

FIGURE 3. Number of stool specimens tested for adenovirus types 40/41 and percent positivity among children aged 0–4 years (A) and 5–9 years (B) — Labcorp, United States, October 2017–March 2022



Summary**What is already known about this topic?**

Following identification of pediatric hepatitis cases of unknown etiology in the United States and the United Kingdom, CDC issued a request in April 2022 for U.S. providers to report additional cases. Many reported cases had test results positive for adenovirus, which is not known to cause hepatitis in immunocompetent children.

What is added by this report?

Analyses of four data sources did not indicate recent increases in hepatitis-associated emergency department visits or hospitalizations, liver transplants, or adenovirus types 40/41 percent positivity among U.S. children compared with pre-COVID-19 pandemic levels.

What are the implications for public health practice?

Current data do not suggest an increase in pediatric hepatitis or adenovirus types 40/41 above pre-COVID-19 pandemic baseline levels; continued surveillance is important to monitor changes over time.

These analyses, based on four data sources, did not indicate a recent increase in hepatitis-associated ED visits or hospitalizations among children aged 0–11 years, liver transplants among children aged 0–17 years, or percentage of specimens positive for adenovirus types 40/41 among children aged 0–9 years in the United States compared with pre-COVID-19 pandemic levels. The potential role of adenovirus in the etiology of the newly reported hepatitis cases is unknown; ongoing investigations are assessing this hypothesis along with the possible role of other factors, including current or past infections with SARS-CoV-2, the virus that causes COVID-19. It remains unknown whether the recently reported cases represent a novel etiology of pediatric acute hepatitis or a previously existing phenomenon that is now being detected. The rarity of this outcome makes it difficult to detect small changes, and pandemic-associated disruptions in health care-seeking behavior and infectious disease epidemiology might still be normalizing. Ongoing assessment of trends in addition to enhanced epidemiologic investigations will help contextualize reported cases of acute hepatitis of unknown etiology in U.S. children.

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