

Explaining the unexplained hepatitis in children



As *The Lancet Infectious Diseases* went to press, more than 300 probable cases of acute hepatitis in previously healthy children were being investigated around the world. The majority of cases have been reported from the UK (163 as of May 3), but smaller numbers of cases have been reported from across 20 countries. On May 5, the US Centers for Disease Control and Prevention announced that it was investigating 109 cases of paediatric hepatitis of unknown cause reported in the past 7 months across 25 states and territories. So far, more than 20 children have required liver transplants and several have died. Investigations to identify a cause are ongoing, but the most frequent causes of acute hepatitis in children, including hepatitis viruses A–E, have been ruled out.

Adenoviruses have become the major focus of investigations as a substantial number of cases—around 70% of cases according to a WHO media briefing on May 10—have tested positive for them. Adenoviruses are common pathogens that typically cause mild respiratory symptoms, although in the past they have been implicated in hepatitis in immunocompromised children and, more recently, in an immunocompetent adult. Several hypotheses have been proposed for how the pathogenesis of adenoviruses might have changed to cause hepatitis in otherwise healthy children. These include that an immune deficit in children resulting from lack of exposure to pathogens during the COVID-19 pandemic has rendered them more susceptible to adenovirus infection and the rarer outcomes of infection. Alternatively, as has been seen with other respiratory viruses, relaxation of pandemic restrictions could have led to a massive wave of adenovirus infections, allowing a rarer outcome of infection to be detected. Another hypothesis is that past infection or co-infection (with SARS-CoV-2 or an alternative pathogen), or exposure to a toxin, drug, or an environmental factor, have altered the host response to adenovirus infection. Alternatively, what we are seeing is a novel adenovirus capable of causing severe liver disease in children.

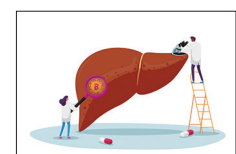
The main suspect is adenovirus subtype 41. A technical briefing from the UK Health Security Agency (UKHSA) on May 6 reported that all 18 cases in the UK that underwent adenovirus typing had subtype 41. Similarly, Baker and colleagues reported that five children with hepatitis of unknown cause identified at a children's hospital in

Alabama between October, 2021, and February, 2022, had adenovirus subtype 41 upon typing.

Not everyone is convinced by the adenovirus hypothesis. Adenovirus subtype 41 has previously only been linked to mild-to-moderate gastrointestinal symptoms. Not all children have tested positive for adenovirus, those who have tested positive have often done so only in whole blood (liver and plasma samples have been largely negative), and concentrations in whole blood have been low—thus precluding performance of whole-genome sequencing to better characterise the virus and any genomic changes that might explain this new phenomenon. Adenoviruses are a common cause of infection and so might be an incidental finding; an ongoing case-control study in the UK seeks to address this.

Other infectious causes are being investigated, including a role for SARS-CoV-2. In the UK, a decline in reports of new cases of paediatric hepatitis of unknown cause in the 2 weeks before May 6 coincided with a decline in cases of SARS-CoV-2. However, the UKHSA warned of lags in reporting of hepatitis cases and said that new cases are still being recorded in Scotland and many cases in England are pending classification. Moreover, few of the reported cases so far have tested positive for SARS-CoV-2 infection. How extensively past infection has been investigated is unclear; the UKHSA reported that serological investigations were ongoing, and Baker and colleagues reported that none of the children in Alabama had a documented history of SARS-CoV-2 infection. It still remains to be seen whether these cases of hepatitis in children are post-infectious sequelae of SARS-CoV-2, potentially falling under the umbrella of multisystem inflammatory disease.

Much attention is being given to the cause of the outbreak. Conspiracy theories on social media abound, with some attributing the cases to COVID-19 vaccines. However, COVID-19 vaccines have been categorically ruled out, most of the children with unexplained hepatitis being too young to receive a COVID-19 vaccine. While identifying the underlying cause is important, considering how unwell the children are and that liver transplantation is possible in only highly specialised centres, it is also important to focus on early case identification and finding effective treatments that can halt progression of the disease. ■ *The Lancet Infectious Diseases*



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For the **US Centers for Disease Control and Prevention** announcement see <https://www.cdc.gov/media/releases/2022/a0505-hepatitis.html>

For the **WHO media briefing** see <https://www.who.int/multi-media/details/who-press-conference-on-covid-19--ukraine-and-other-global-health-issues---10-may-2022#>

For more on **hepatitis in an immunocompetent adult linked to adenovirus** see *J Investig Med High Impact Case Rep* 2022; **10**: 23247096221079192

For the **technical briefing from the UK Health Security Agency** see <https://www.gov.uk/government/publications/acute-hepatitis-technical-briefing#full-publication-update-history>

For the **study from Baker and colleagues** see *MMWR Morb Mortal Wkly Rep* 2022; **71**: 638–40