



A surge in paediatric hepatitis cases could be linked to reduced exposure to a common virus.

# MYSTERIOUS CHILD HEPATITIS CONTINUES TO VEX RESEARCHERS

Cases of liver inflammation among UK children seem to have risen.

By Heidi Ledford

In the three months since UK physicians sounded the alarm about mysterious cases of hepatitis that seemed to be striking young children, researchers have been scrambling to determine the cause – and a possible connection to the coronavirus pandemic has been among the leading hypotheses.

But on 17 June, researchers at the US Centers for Disease Control and Prevention (CDC) published data suggesting that – in the United States at least – rates of hepatitis, or liver inflammation, with an unknown cause had not changed since 2017 among children aged 11 or younger<sup>1</sup>. If true, the finding could confound the pandemic-link theory.

Not everyone is convinced by the data, however, and it is unclear whether the same finding will emerge from other countries. “I can tell you, having worked in this country for 30 years as a liver doctor, we’ve had a huge number of cases in 2022,” says Deirdre Kelly, a paediatric hepatologist at the University of Birmingham, UK. “And I think the United Kingdom’s case ascertainment is extremely good.”

Despite the US results, the CDC continues to explore connections to the pandemic. A 24 June

analysis showed that 26% of 123 children with unexplained hepatitis in the United States had tested positive for COVID-19 before their liver illness<sup>2</sup>. The CDC is now collecting the samples it needs to test for antibodies against SARS-CoV-2, to find out if other children with hepatitis had had infections that went undetected, says David Sugarman, a medical officer in the Division of Viral Diseases at the CDC’s National Center for Immunization and Respiratory Diseases in Atlanta, Georgia. “We’re very much looking at SARS-CoV-2 still,” he says.

## Known and unknown causes

Hepatitis in children has a number of known causes, including infection by viruses such as hepatitis A, and exposure to certain medications, such as paracetamol. But every year, a few unexplained paediatric cases occur.

In early April, the United Kingdom Health Security Agency (UKHSA) notified the public of an apparent uptick in the number of young children with serious liver inflammation. At the time, the agency reported 60 possible cases in children under the age of 10 in 2022. Physicians typically see about 20 such cases a year in the United Kingdom, says Kelly.

Since the start of this year, more than 250 UK

children have had hepatitis – and, by 26 May, a total of about 650 cases in 33 countries had been reported to the World Health Organization. Twelve of the British children required a liver transplant; none has died. In the United States, 11 of 296 children believed to have the condition have died.

## Adenovirus infections

In the United Kingdom and the United States, many of the children with mysterious liver inflammation were also infected with a member of a family of common viruses known as adenoviruses. This has led to speculation that the hepatitis is caused by an adenovirus. But although this is the UKHSA’s leading hypothesis, it is not a broadly popular one. Researchers have pointed out the lack of statistical controls: adenovirus infections often peak in the winter and spring, and it’s unknown what the infection rate was among children who did not develop hepatitis.

There is also a lack of precedents: adenoviruses are not known to cause hepatitis in children with healthy immune systems. And the levels of virus found in most of the children with liver inflammation are low. “I don’t think it’s adenovirus,” says paediatric hepatologist Orit Waisbourd-Zinman at Schneider Children’s Medical Center in Petah Tikva, Israel.

On 10 June, Waisbourd-Zinman published a case series concerning five children with unexplained hepatitis<sup>3</sup>. Only one of them, she says, tested positive for adenovirus. Microbiologist Sumit Rawat at Bundelkhand Medical College in Sagar, India, tested samples from 17 children with unexplained hepatitis and found adenovirus in only 3 of them.

But Waisbourd-Zinman and Rawat both say that all the children they saw either had tested positive previously for SARS-CoV-2, or had family members who had. The UKHSA has also consistently listed COVID-19 as a possible explanation. However, only 15% of the UK children with hepatitis were actively infected with SARS-CoV-2 at the time of their diagnosis, and the agency has not released data on how many had antibodies against the virus, which would have suggested previous infection.

Although none of the hypotheses is a clear winner yet, the timing of the apparent outbreak of hepatitis strongly suggests some connection with the pandemic, says virologist William Irving at the University of Nottingham, UK. The increase in cases could be a consequence of direct damage from past SARS-CoV-2 infection, reduced exposure to viruses during the lockdown or aberrant immune responses triggered by the coronavirus. “This is all hand waving,” he says. “But I feel like the COVID pandemic has to be critical.”

One thing that is clear is that the condition is not linked to COVID-19 vaccination: only a handful of the children in the United Kingdom who developed hepatitis had been vaccinated.

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The CDC study, covering 2017–22, questions any explanations that involve the pandemic. The team picked through data from health-care records, organ-transplant records and laboratory testing of stool samples for adenovirus. In the end, the researchers found no recent increase in the number of paediatric hepatitis cases, transplants or adenovirus-positive stool samples<sup>1</sup>.

### Hidden diagnoses

But Waisbourd-Zinman says that a simple analysis of electronic health records might not reveal the true rates of unexplained hepatitis in children. She attempted a similar study in Israel, she says, but quickly found that she had to dig through health records manually to find buried diagnoses. For example, one case of hepatitis turned out to be the result of medication used during a kidney transplant; another was an infection with a known hepatitis-causing virus. These causes were not coded as such in the records, and a cursory examination would have lumped them with unexplained cases. That noise makes it hard to pick out the truly unexplained cases, she says. “It’s just impossible to see an increase,” she says. “It’s so heterogeneous.”

In April, researchers also determined that rates of unexplained hepatitis in children in mainland Europe were not above the baseline for that region<sup>4</sup>. But Kelly, who consulted on that analysis, notes that it was also limited: as in the United States, Europe’s health-care data are fragmented, she says, and the European survey included only specialist hospitals.

Some countries, including Israel and the United Kingdom, have now asked physicians to report cases of paediatric hepatitis that are not explained by known causes to public-health

**“There might be something special about those children that makes them susceptible.”**

authorities. This, plus the studies that have been launched to pin down the cause of the condition, could shed light on the handful of mysterious paediatric liver inflammation cases that appeared each year – whether or not they are linked to COVID-19 – says Kelly.

“There might be something special about those children that makes them susceptible,” she says. “One of the positive aspects of this is that we might find out what that is.”

1. Kambhampati, A. K. et al. *Morb. Mortal. Wkly Rep.* **71**, 797–802 (2022).
2. Cates, J. et al. *Morb. Mortal. Wkly Rep.* <http://doi.org/10.15585/mmwr.mm7126e1> (2022).
3. Cooper, S. et al. *J. Pediatr. Gastroenterol. Nutr.* <https://doi.org/10.1097/MPG.0000000000003521> (2022).
4. de Kleine, R. H. et al. *Euro. Surveill.* **27**, pii=2200369 (2022).

# RARE ‘TRIPLE’ LA NIÑA CLIMATE EVENT LOOKS LIKELY

Meteorologists warn of a third year of the cooling event, which increases the risk of floods and droughts.

By Nicola Jones

**A**n ongoing La Niña event that has contributed to flooding in eastern Australia and exacerbated droughts in the United States and East Africa could persist into 2023, according to the latest forecasts. The occurrence of two consecutive La Niña winters in the Northern Hemisphere is common, but having three in a row is relatively rare. A ‘triple dip’ La Niña – lasting three years in a row – has happened only twice since 1950.

More La Niña events would increase the chance of flooding in southeast Asia, boost the risk of droughts and wildfires in the southwestern United States, and create a different pattern of hurricanes, cyclones and monsoons across the Pacific and Atlantic oceans, as well as give rise to other regional changes.

La Niña and its counterpart, El Niño, are phases of the El Niño–Southern Oscillation (ENSO) that occur every two to seven years, with neutral years in between. During El Niño events, the usual Pacific winds that blow east to west along the Equator weaken or reverse, causing warm water to gush into the eastern Pacific Ocean, increasing the amount of rain in the region. During La Niña, those winds strengthen, warm water shifts west and the eastern Pacific becomes cooler and drier.

The impacts are far reaching. “The tropical Pacific is huge. If you shift its rainfall, it has a ripple effect on the rest of the world,” says Michelle L’Heureux, a physical scientist at the National Oceanic and Atmospheric Administration (NOAA) Center for Weather and Climate Prediction in College Park, Maryland. During La Niña years, the ocean absorbs heat into its depths, so global air temperatures tend to be cooler.

### Cold snap

The current La Niña started around September 2020 and has been mild-to-moderate most of the time since then. As of April 2022, it intensified, leading to a cold snap over the eastern equatorial Pacific Ocean not seen at that time of year since 1950.

The latest forecast from the World Meteorological Organization, issued on 10 June, gives a 50–60% chance of La Niña persisting until July or September. This will probably increase Atlantic hurricane activity, which



La Niña contributed to flooding in eastern Australia earlier this year.

buffets eastern North America until November, and decrease the Pacific hurricane season, which mainly affects Mexico. NOAA’s climate prediction centre has forecast a 51% chance of La Niña in early 2023.

The weird thing about it, says L’Heureux, is that this prolonged La Niña, unlike previous triple dips, hasn’t come after a strong El Niño, which tends to build up a lot of ocean heat that takes a year or two to dissipate (T. Wakiri and M. Watanabe *Sci. Rep.* **11**, 17465; 2021). “I keep wondering, where’s the dynamics for this?” says L’Heureux.

### Climate correlation

This particularly long La Niña is probably just a random blip in the climate, scientists say.

But the big questions that remain are whether climate change is altering the ENSO, and whether La Niña conditions will become more common in future. Some researchers are warning that climate change could make La Niña-like conditions more likely in future. “We are stacking the odds higher for these triple events coming along,” says Matthew England, a physical oceanographer at the University of New South Wales in Sydney, Australia.

England and others are now working to reconcile discrepancies between climate data and the output of major climate models – efforts that could clarify what is in store for the planet.