



CONSULTATIVE SIGNAL ASSESSMENT
PRIMARY RISK ASSESSMENT
EVIDENCE BASED RISK ASSESSMENT
PUBLIC HEALTH EVENT ASSESSMENT

**INCREASE IN SEVERE ACUTE HEPATITIS OF UNKNOWN AETIOLOGY IN
CHILDREN, EUROPE, APRIL 2022**

Date of the signal	Date of the PRA	Signal provider	Experts consultation	Method
06/04/2022	22/04/2022	UK	Permanent experts: Nicolas Ledent (COCOM), Sanne Lenaerts (FOD), Tinne Lernout (Sciensano), Alessandro Pellegrino (AViQ), Dirk Wildemeersch (AZG) Specific experts : Ruth De Bruyne (UZ Gent), Géraldine De Muylder (Sciensano), Naima Hammami (AZG), Benoît Kabamba-Mukadi (UCL), Sofieke Klamer (Sciensano), Michael Peeters (Sciensano), Marijke Reynders (AZ ST Jan), Xavier Stephenne (UCL), Steven Van Gucht (Sciensano), Marc Van Ranst (UZ Leuven), Thomas Vanwollegghem (UZ Antwerpen), Erika Vlieghe (UZ Antwerpen)	Meeting 22/04/2022, update by mail 26/04
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Signal

On April 6 2022, the United Kingdom reported an increase in severe acute hepatitis cases in children, with markedly elevated transaminases. Confirmed cases were reported in England, Scotland, Wales and Northern Ireland (1-3). Most of the cases were between 2 and 5 years old. Retrospectively, cases of severe liver injury in children, without known cause, were already reported in October 2021 in Alabama, US (4).

The cause of hepatitis in these cases is unknown. The common viruses that can cause hepatitis (hepatitis viruses A, B, C, D and E) have not been detected in any of the cases. Some of the children hospitalised in the UK tested positive for SARS-CoV-2 and others for adenovirus. Potential causes currently being investigated in the UK include infection with adenovirus, coronavirus, other infections or environmental causes.

There is currently no clear connection between the reported cases (except of a link between 2 pairs of cases in Scotland), and there is no known association with travel. There is also no suspicion of a link to the COVID-19 vaccine.

As of 21 April 2022, at least 169 cases of acute hepatitis of unknown origin from 11 countries in the WHO European region have been reported (5).

Description

Cause known?

Most cases of acute hepatitis in children are caused by hepatitis viruses A and E. However, for the current cases in the UK, the cause remains unknown. Initial hypotheses about the aetiology focused on an infectious agent or a possible toxic exposure. Detailed information collected through a questionnaire to cases about food, drink and personal habits failed to identify any common exposure. An infectious cause, and more specifically adenovirus, is considered most likely based on the clinical and epidemiological features of the cases under investigation in the UK (1,2). It is hypothesised that there could either be a new variant circulating which is causing severe hepatitis in children, or that the routinely circulating variant is particularly affecting younger children who are immunologically naïve following a lower level of circulation of adenovirus during the COVID-19 pandemic. Other infectious causes being explored include increased severity of disease following infection with Omicron BA.2 or infection by an as yet uncharacterised SARS-CoV-2 variant (2).

The UKHSA has ruled out a link to the COVID-vaccine since none of the currently confirmed cases in the UK have been vaccinated.

Of the 13 cases reported by Scotland for which detailed information is available regarding testing, three tested positive for SARS-CoV-2 infection, five tested negative and two were documented to have had an infection in the three months before presentation. Eleven of these 13 cases had results for adenovirus testing and five tested positive. Out of the 108 cases in total in the UK as of 21 April, 77% tested positive for adenovirus.

Adenovirus infections in children are common and usually result in a mild illness, with cold-like symptoms, vomiting and diarrhoea. The majority of people infected with an adenovirus do not have any complications. While adenoviruses do not commonly cause hepatitis, it is a known rare complication usually among immunocompromised individuals, but it had already been described in immunocompetent children and adults (6-8).

Unexpected/unusual

Acute infectious hepatitis in children is a rare cause of hospital admission, as described in a British paediatric study (9).

In Scotland, the number of cases of severe hepatitis of unknown origin identified since January 2022 is higher than expected. The number of children presenting acutely with abnormal liver function tests in March 2022 compared with those in March 2019 as well as March 2020 and 2021 also confirmed higher-than-expected numbers in 2022 among children under 5 years of age, but not in older children (2,9).

As in Scotland, surveillance data for adenovirus in Belgium, from the sentinel laboratories (results based on NFS only, not from stool samples), show a lower circulation in 2020-2021 in the context of the COVID-19 measures, but no return to pre-pandemic levels yet in 2022 (see Annex 1). The NRC hepatitis also didn't identify an unusual increase in hepatitis cases in children for which samples are sent to the NRC. This number ranges between 40 and 200 cases a year. Up to now, a total of 169 requests for samples from children \leq 10 years have been registered, but most of them in a context of an hepatitis A outbreak.

Severity

The cases in the United Kingdom presented clinically with severe acute hepatitis, with increased levels of liver enzymes (aspartate transaminase/aspartate aminotransferase (AST) or alanine transaminase/alanine aminotransferase (ALT) greater than 500 IU/L) and many cases with jaundice. Some of the cases reported gastrointestinal symptoms, including abdominal pain, diarrhoea and vomiting in the preceding weeks. Most cases did not have fever. Cases had been admitted to the hospital for a minimum of 6 days. Some of the cases required care at specialist children's liver units and a few had to undergo liver transplantation. Prior to their admission, cases were reported as generally healthy.

Dissemination in Belgium

As of 25 April 2022, one probable case (fulfilling the ECDC case definition) has been identified in Belgium and reported to ECDC (through Epi-pulse), a 10-years old child (diagnosis on 18/02/2022). A stool sample was positive for adenovirus. A second case (a 14-months old child with increased AST on 21/03/2022 and positive for adenovirus), has been reported through the ongoing European surveys, but hepatitis E results are still pending. To have same numbers reported, this case has also been reported to ECDC (as possible case). Other possible cases are still investigated.

Risk of (inter)national spread

Following the alert, around 30 cases of acute hepatitis among children aged 10 and under have also been reported from nine EU/EEA countries to ECDC: Denmark [5], France [2], Ireland [$<$ 5], Italy [3], the Netherlands [4], Norway [2], Romania [1], Spain [7] and the case in Belgium. Seven cases have tested positive for adenovirus. Four cases have required a liver transplant. In other countries (Italy and Sweden) cases of acute hepatitis of unknown origin in children were reported in the media.

In addition, nine cases of acute hepatitis among children aged between 1 and 6 years who also tested positive for adenovirus have been reported in the state of Alabama in the United States, several cases testing positive for serotype 41 (4). Investigations are also ongoing by the US CDC.

The Israeli Ministry of Health also reported 12 cases of acute hepatitis among young children, two of which received transplants.

Preparedness and response

Preparedness

Testing capacity for various pathogens exists in Belgium through different National Reference Centers.

The system of Mandatory notification at regional levels allows to quickly collect information on “unusual events”.

Specific control measures (surveillance, control, communication)

Following the alerts from Scotland and the UK, informal requests for information have been sent to hospital paediatricians (n=24).

ECDC is also collecting data in collaboration with the Member States, WHO, the European Association for the Study of the Liver (EASL), the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) and the European Society for Paediatric Infectious Diseases (ESPID). Multidisciplinary surveys were initiated among a broad number of hospitals to quickly assess the extent, geographical distribution, and potential aetiology of this outbreak in Europe.

International surveys:

- ESPID: https://www.espid.org/news.aspx?Group=dates&Page=latest_news
- ERN-RARE-LIVER: <https://ec.europa.eu/eusurvey/runner/pediatricACLF>

Public health impact

Public health impact in Belgium

In a context of unknown origin, the impact on public health in Belgium is difficult to assess. So far, the number of cases seems to remain low.

Recommendations

- Although adenovirus has been identified in a large proportion of cases, it is important to continue exploring other possible causes, for instance via metagenomics analyses.
- **Case definition.** For reporting to EpiPulse/ECDC, the case definition proposed by the ECDC will be used: “A probable case is defined as a person presenting with an acute hepatitis (non-hepatitis viruses A, B, C, D and E) with aspartate transaminase (AST) or alanine transaminase (ALT) over 500 IU/L, who is 16 years old and under, since 1 October 2021. An Epi-linked case is a person presenting with an acute hepatitis (non-hepatitis viruses A, B, C, D and E) of any age who is a close contact of a probable case since 1 October 2021”. Possible cases can also be reported to ECDC (= probable case pending HEV result). However, for investigation in Belgium, the case definition should be broader and also include cases with lower AST/ALT but abnormal direct bilirubin and/or jaundice, especially in immunocompromised patients (in which transaminases are expected to increase less markedly). In the request for reporting, the possibility should also be given to report unexplained acute hepatitis above 16 years of age (after thorough investigation to exclude potential causes).
- Define the epidemiological data that should be collected for suspected cases.
- Inform physicians and request to report cases fulfilling the case definition to the regional health authorities.
- Collect information from the clinical laboratories in Belgium on numbers of ALT/AST values > 500 IU/L in children < 16 during since January 2022.

Actions

- Letter to be sent (by the RMG) with criteria for reporting cases to the regional health authorities, to: paediatricians and infectiologists, directly and through the

professional associations (BVIKM/SBIMC, BVK/SBP, VVK, GBPF, BESPCHAN and BASL).

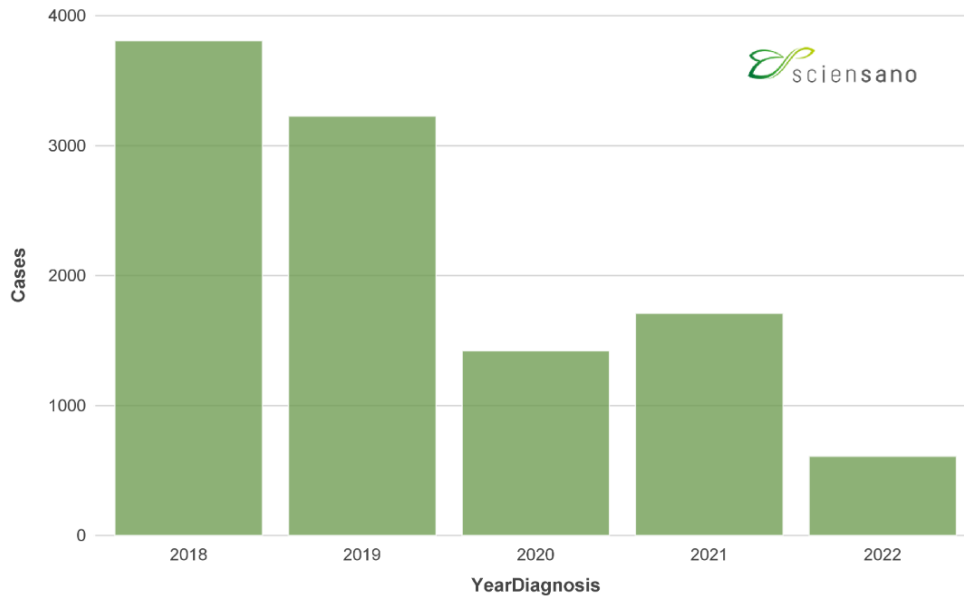
- The letter will also contain recommendations for tests to be performed for future suspicions → RMG with input from Sciansano and the regions.
 - Inform also GPs on the event and case definition through associations and the Flash of May → RMG and Sciansano.
 - Prepare a common questionnaire for data collection → Sciansano and regions
 - Mailing to clinical laboratories to request data on high ALT-AST values in children → through Sciansano
 - Perform Adenovirus subtyping in confirmed cases, if positive for the virus.
 - Check if testing of waste water samples for adenovirus is possible/relevant.
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REFERENCES

1. Increase in hepatitis (liver inflammation) cases in children under investigation [Internet]. GOV.UK. [cited 2022 Apr 20]. Available from: <https://www.gov.uk/government/news/increase-in-hepatitis-liver-inflammation-cases-in-children-under-investigation>
2. Marsh K, Tayler R, Pollock L, Roy K, Lakha F, Ho A, et al. Investigation into cases of hepatitis of unknown aetiology among young children, Scotland, 1 January 2022 to 12 April 2022. *Eurosurveillance*. 2022 Apr 14;27(15):2200318.
3. Increase in acute hepatitis of unknown origin among children – United Kingdom [Internet]. European Centre for Disease Prevention and Control. 2022 [cited 2022 Apr 21]. Available from: <https://www.ecdc.europa.eu/en/news-events/increase-acute-hepatitis-unknown-origin-among-children-united-kingdom>
4. CDC. <https://www.cdc.gov/media/releases/2022/s0421-hepatitis-alert.html>
5. WHO. <https://www.who.int/emergencies/disease-outbreak-news/item/multi-country-acute-severe-hepatitis-of-unknown-origin-in-children>
6. Munoz FM, Piedra PA, Demmler GJ. Disseminated adenovirus disease in immunocompromised and immunocompetent children. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 1998 Nov;27(5):1194–200.
7. Kiwan P, Hamod DA (2017) Adenoviral Hepatitis in an Immunocompetent Child: Case report. *J Pediatr Neonatal Care* 7(3): 00290. DOI: [10.15406/jpnc.2017.07.00290](https://doi.org/10.15406/jpnc.2017.07.00290)
8. Khalifa A, Andreias L, Velpari S. Adenovirus Hepatitis in Immunocompetent Adults. *J Investig Med High Impact Case Rep*. 2022 Feb 28;10:23247096221079190.
9. Braccio S, Irwin A, Riordan A, Shingadia D, Kelly DA, Bansal S, et al. Acute infectious hepatitis in hospitalised children: a British Paediatric Surveillance Unit study. *Arch Dis Child*. 2017 Jul 1;102(7):624–8.

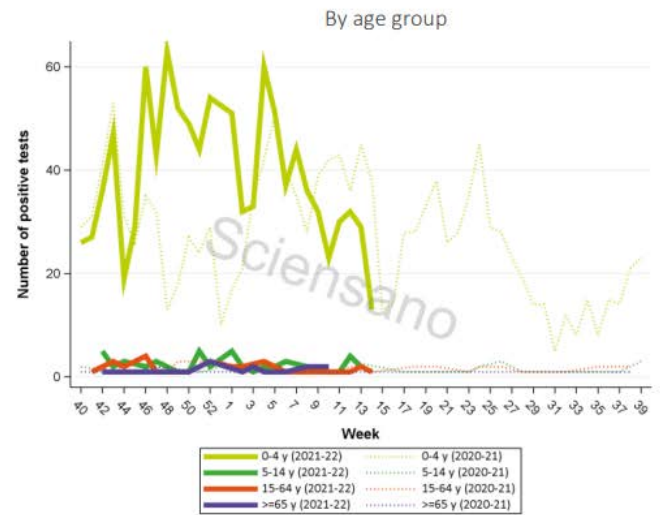
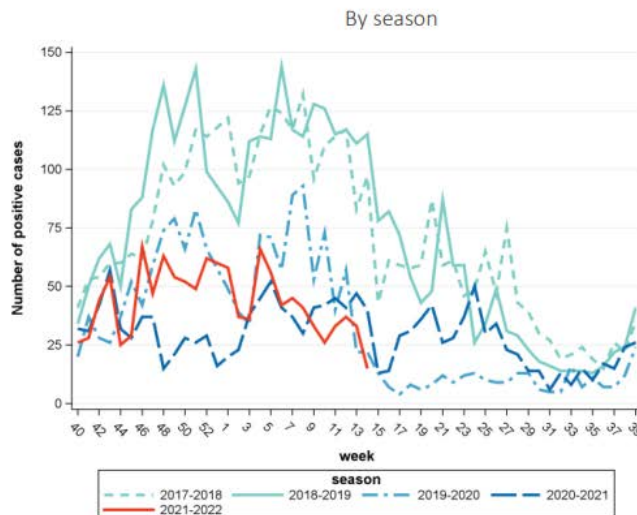
ANNEX 1 : SURVEILLANCE RESULTS FOR ADENOVIRUS IN BELGIUM

Reported cases of Adenovirus per YearDiagnosis
(2022 2021 2020 2019 2018)



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Adenovirus



Source:

[https://epidemiology.wiv-](https://epidemiology.wiv-isp.be/ID/diseases/SiteAssets/Pages/Influenza/WeeklyBulletinRespiratoryInfections.pdf)

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