

Increase in severe acute hepatitis cases of unknown aetiology in children

28 April 2022

Summary

An increase in severe acute hepatitis cases of unknown aetiology among previously healthy children was first reported by the United Kingdom (UK) to the World Health Organization's International Health Regulations (IHR) notification system on 5 April 2022 (testing had excluded viral hepatitis types A, B, C, D and E and other known causes of acute hepatitis). Following this alert, the United States and several European Union, European Economic Area (EU/EEA) and other countries have reported suspected cases.

As of 20 April 2022, 111 cases had been reported from the UK, and as of 27 April 2022 approximately 55 probable and confirmed cases have been reported from 12 EU/EEA countries. An additional 12 cases have been reported from the United States (US), 12 from Israel, and one from Japan. The clinical picture is of severe acute hepatitis requiring hospitalisation with jaundice and markedly elevated liver transaminases. In most cases to date, the onset of jaundice was preceded by a gastrointestinal illness with vomiting, diarrhoea, and nausea. Information on the outcome of the cases is still being collected. So far, most patients for whom information is available have recovered, but a number have progressed to acute liver failure and required liver transplantation.

Detailed epidemiological and laboratory investigations of the cases are still ongoing to help determine the underlying aetiology. Cases have been tested for a range of different infectious causes, and the most common pathogens found were adenovirus and SARS-CoV-2. In England and Scotland, 75.5% and 50% of cases respectively tested positive for adenovirus. Subtyping of 11 cases from the UK investigation found that these were all type 41F, which is the same subtype identified among several of the cases reported from the US. Other adenoviruses were also found in some non-blood samples among the UK cases investigated. Information on testing in the EU/EEA is incomplete, but among cases reported 10 tested positive for adenovirus. Statistical exceedance compared to positive tests in previous years in the detection of many viruses in the community has been reported by the UK, including a marked recent exceedance in adenovirus detections in faecal samples among children aged 1-4 years.

Early epidemiological investigations of cases from the UK based on trawling questionnaires have failed to identify a common exposure of note (including food, medicines, or toxins). Toxicological analysis of specimens collected from cases as part of the UK investigation is ongoing. Although epidemiological links were reported from the Scottish investigation for two pairs of cases, no other clusters have been reported. Across all reporting countries, the majority of cases to date have not had significant past medical history.

Based on these investigations, the current leading hypothesis is that a cofactor affecting young children having an adenovirus infection, which would be mild in normal circumstances, triggers a more severe infection or immune-mediated liver damage. Other aetiologies (e.g. other infectious or toxic agents) are still under

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investigation and have not been excluded but are considered less plausible. The disease pathogenesis and routes of transmission are also still unknown. The disease is quite rare and evidence around human-to-human transmission remains unclear; cases in the EU/EEA are sporadic with an unclear trend. As a result, the risk for the European paediatric population cannot be accurately assessed. However, considering the reported cases with acute liver failure, with some cases requiring liver transplantation, the potential impact for the affected paediatric population is considered high. Access to highly specialised paediatric intensive care and transplantation services may further impact outcomes. Considering the unknown aetiology, the affected paediatric population, and the potential severe outcome, this currently constitutes a public health event of concern.

It is essential to establish surveillance at the national level for EU/EEA countries as soon as possible to collect detailed epidemiological, clinical, virological, and other information, including toxicological analyses, on cases. Additional information for hypothesis testing should be collected in the context of analytical studies looking at other factors and potential co-factors such as recent infections, personal and environmental determinants. Specific studies should be designed to identify risk factors for infection and for severe illness, to investigate routes of potential transmission, to describe the full clinical spectrum, and to ascertain whether the same aetiological agent causes different clinical presentations depending on age and other conditions. ECDC will provide guidance and coordination to EU/EEA countries planning to set up such studies.

Further investigations include an assessment of the underlying level of acute viral infections circulating in the community, in particular adenoviruses, by age, and whether this is above what would normally be expected.

Public health authorities should communicate with paediatricians, general practitioners and other medical specialists to inform about the need for active case finding and reporting of new cases.

Testing appropriate samples from symptomatic children for adenoviruses as well as for other viruses that can cause hepatitis should be performed early after symptom onset. ECDC recommends an extensive set of tests to help identify the causative agent or co-factors.

Cases fulfilling the case definition should be reported to The European Surveillance System (TESSy) as soon as possible. Case records can be updated as more test results become available.

As the aetiology remains unknown, effective control measures cannot be defined at this stage. Faecal-oral exposure to viruses such as adenoviruses is more likely for young children. We therefore recommend reinforcing general good hygienic practices (including careful hand hygiene, cleaning and disinfection of surfaces) in settings attended by young children.

Event background

On 5 April 2022, the United Kingdom (UK) reported to the World Health Organization's IHR notification system an increase in acute hepatitis cases of unknown aetiology among previously healthy children aged under 10 years from Scotland in whom viral hepatitis types A, B, C, D and E had been excluded [1]. By April 8, 72 similar cases had been identified across the UK [2], most of which were between two and five years of age [1]. As of 20 April 2022, a total of 111 cases had been reported from the UK [1].

The cases recorded in the UK occurred in previously healthy children and presented with clinical symptoms and signs of severe acute hepatitis, including jaundice and increased aspartate transaminase (AST) or alanine transaminase (ALT) greater than 500 IU/L [3]. Some of the cases reported gastrointestinal symptoms such as abdominal pain, diarrhoea and vomiting in the preceding weeks. Few cases presented with fever. Most children were hospitalised and several progressed to acute liver failure (ALF) requiring admission to specialist paediatric liver units and in a few cases liver transplantation.

Early epidemiological investigations from the UK based on a detailed questionnaire used to collect data about food and drink intake and personal habits of cases failed to identify a common exposure of note among cases. No link to COVID-19 vaccination was identified, and most cases were too young to have been included in the current UK COVID-19 vaccination schedules.

Based on these early clinical and epidemiological findings, the incident team in the UK hypothesised that an infective agent was the most likely cause of acute hepatitis in these children, but toxicological causes still needed to be ruled out.

On April 8, ECDC requested EU/EEA countries intensify case finding and report any confirmed and possible cases as defined by the UK case definition. [4]. Consequently, cases have been identified in 12 European countries. As of 27 April 2022, approximately 55 cases have been reported from across the EU/EEA (in Austria, Belgium, Denmark, France, Germany, Italy, Ireland, Norway, Poland, Romania, Spain, and the Netherlands).

Outside Europe, nine cases of acute hepatitis among children aged one to six years have been reported in the state of Alabama in the US. Two of these cases required liver transplants [5,6]. Several of these cases tested positive for adenovirus serotype 41 [5]. On 25 April 2022, three additional suspected cases of acute hepatitis

among children aged under 10 years and with a potential link to adenovirus infection were reported by the public health authorities in Illinois [7]. The US Centers for Disease Control and Prevention (CDC) are conducting further investigations, but results are still pending. Furthermore, on 19 April 2022, the Israeli Ministry of Health reported 12 cases of acute hepatitis among young children [8]. Limited information is currently available, and these cases are under investigation. On 25 April 2022, one case was reported from Japan. This case is under 16 years of age, is hospitalised, but has not yet required a liver transplant. In addition, the case tested negative for SARS-CoV-2 and adenovirus [9].

Epidemiological investigations to date

Clinical

Many cases had gastrointestinal symptoms in the weeks preceding the onset of jaundice, and of the 81 cases investigated in England¹ the most common symptoms reported included jaundice (74%), vomiting (73%), pale stools (58%), diarrhoea (49%), and nausea (39.5%). Other symptoms reported from the cases in England included lethargy (55.6%) and fever (29.6%). Respiratory symptoms have only been reported for one fifth (19.8%) of all cases. These clinical findings are consistent with those described among cases reported by Scotland, although none of the Scottish cases were reported to have had fever [3].

Although all cases had high transaminase levels in line with the case definition, most of the children reported from Scotland had transaminases over 2000 IU/L [3].

To date, seven of the 81 cases in England and one of the 13 reported cases in Scotland required a liver transplantation. This proportion is consistent with that among cases identified in EU/EEA countries (see Table 1).

Histopathological examinations from cases across the EU/EEA are ongoing, but results are not yet available.

Microbiological

Most testing information available from cases reported to date is from England, although not all cases have been tested for the same set of pathogens [10]. Overall, 40 of 53 that were tested for adenovirus were positive (75%). Quantitative PCR showed that adenovirus DNA levels were approximately 12 times higher among cases who received a liver transplant compared to those who did not. However, the timing of sampling since symptom onset was variable and limited inferences can be made on this finding. Typing data are available for the 11 cases with adenovirus detected in blood, and all were type 41F. Other adenoviruses were detected from non-blood samples from some cases. Whole genome sequencing is under way. Adenovirus was detected more commonly in blood/serum samples than in stool or respiratory samples.

SARS-CoV-2 testing data on hospital admission were available from 61 cases, of which 10 (16%) were positive. Of these, seven had also tested positive in the six weeks prior to admission and three cases were coinfecting with both adenovirus and SARS-CoV-2. The UKSHA reports that this level of positivity over almost 4 months is not unexpected given the community infection rate and prevalence across the period of investigation, thus not allowing to draw any firm conclusion.

In Scotland, five of the 13 cases had a recent positive test for SARS-CoV-2, of which two were reported to have had COVID-19 infection in the preceding three months, two within 11 days of admission, and one point-of-care test was positive upon admission. Additionally, five of the 13 cases tested positive for adenovirus in faecal, respiratory and/or blood samples. Other pathogens were detected in small numbers in England and Scotland [3] [4].

A data linkage analysis conducted in England, showed that since the end of 2021 there was an increase in the number of children younger than 10 years of age that experienced concurrent or temporally close infections with both adenovirus and SARS-CoV-2. However, similar findings have been seen for other childhood infections in the same period [4].

Epidemiological

Cases identified in England were mostly between three and five years of age (65.4%), with a median age of three years, and 54.4% were female. The majority were white (87.5%), where information was available. This age and gender distribution was similar for the cases detected in Scotland, where the median age among 13 cases was 3.9 years and seven were female. All cases detected in Scotland were white.

Trawling questionnaires have been administered to 60 cases so far in England and to 13 cases in Scotland. These questionnaires cover demographics, disease symptoms, medical and medication history, family structure, recent

¹ Denominator includes cases with reported information and cases with unknown information.

household/close contact illness, parental occupations, food and water consumption, health service utilisation, travel, animal exposure, and potential exposures to toxicants. To date, no notable features or common exposures (including medicines or toxins) and no association with prior immune suppression have been identified through the questionnaire administered in England. No family clusters have been identified. In the Scottish investigation, epidemiological links have been reported for two cases who had contact with two other cases. None of the cases had any significant past medical history including immune suppression. One case had an underlying condition but had been in good health at the time of onset.

Several data sources have been used in England and Scotland to understand whether the number of acute hepatitis cases of unknown origin and adenovirus detections in the community are higher than expected. Data from specialist paediatric liver units in England indicate that the number of admissions for acute hepatitis of unknown cause in 2022 and as of 25 April is equal to or higher than the total number of annual admissions in previous years. In addition, the number of very urgent liver transplants for acute liver failure due to unknown cause in England among children below 10 years of age during the first quarter of 2022 is greater than previous annual counts between 2009 and 2019. This signal has not been observed among older children.

An additional possible signal has been observed in hospital admissions of children for non-A-E hepatitis between 1 and 4 years of age in England between February and March 2022 (14 and 15 admissions, respectively compared to 0-8 between November 2020 and January 2021) based on ICD-10 codes. However, the numbers are small. No increases have been observed in syndromic surveillance of liver disease emergency department attendances and notifications of acute hepatitis reported as 'other' (and excluding hepatitis A, B, C, D, and E).

The number of positive adenovirus tests from 1–4-year-olds from diagnostic laboratories is higher compared to the previous five years, with 200-300 cases being reported per week between November 2021 and March 2022 compared to 50-150 cases per week in the pre-pandemic period and less than 50 cases per week between March 2020 and May 2021. This increase in younger age groups began in November 2021. In Scotland, adenovirus case numbers have returned to pre-pandemic levels during 2022 compared to fewer cases observed in 2020–21. High circulation of the virus was observed during the first months of 2022, especially in the age group 1-4 years [3].

In the first months of 2022, statistical exceedances have been detected in England from laboratory data on pathogens reported by the NHS and public health laboratories. Statistical exceedances have been observed in adenovirus, enterovirus, human metapneumovirus, rhinovirus and norovirus in under 10-year-olds since the end of 2021 and in respiratory syncytial virus since late summer of 2021, likely attributed to behaviour changes and population susceptibility after a period of low incidence during the pandemic [11]. The exceedance of adenovirus in routine laboratory data is primarily driven by enteric samples in the age groups 1–4-year-olds, but exceedance is also seen for respiratory adenovirus among younger children. No increase in positivity of respiratory samples was noted in data from sentinel laboratories across England. Prevalence of SARS-CoV-2 infection was also high during this time in the UK. An analysis conducted in Denmark shows that during week 12/2022 there was a marked peak in the detection of viruses in respiratory samples, in particular rhinovirus, SARS-CoV-2, and other coronaviruses.

High adenovirus circulation in the community was also observed in Germany during the first months of 2022 [12].

Toxicology

The UK team is currently undertaking detailed toxicological investigations for organic compounds and metals on a number of their cases and healthy controls [4]. The preliminary investigations have not highlighted any significant findings, and there was no evidence of toxicity resulting from paracetamol (assessment for paracetamol toxicity is common clinical practice in liver centres) or aflatoxin B1. The UK Health Security Agency (UKHSA) is undertaking confirmatory testing.

Working hypotheses on possible aetiology

Based on the findings from the investigations so far, the UKHSA [4] have a number of working hypotheses, which they rank in order of best to worst fit to the available data. These are provisional and likely to be modified as the investigation evolves:

- '1. A cofactor affecting young children which is rendering normal mild adenovirus infections more severe, or causing them to trigger immunopathology. The cofactor may be:
 - a. susceptibility, for example due to lack of prior exposure to adenoviruses during the pandemic
 - b. a prior infection with SARS-CoV-2 or another infection, including an Omicron restricted effect
 - c. a coinfection with SARS-CoV-2 or another infection
 - d. a toxin, drug or environmental exposure
2. A novel variant adenovirus, with or without a contribution from a cofactor as listed above.
3. A drug, toxin or environmental exposure.
4. A novel pathogen either acting alone or as a coinfection.
5. A new variant of SARS-CoV-2.'

Disease background

Acute hepatitis in children

Clinical presentation and aetiological causes

Hepatitis is a condition characterised by the inflammation of the hepatic parenchyma [13]. The inflammation may be acute, lasting typically less than six months with a subsequent normalisation of liver function, or it may be chronic [14].

Non-infectious causes of hepatitis in children include immunologic conditions (e.g. autoimmune diseases), metabolic diseases (e.g. Wilson's disease, tyrosinemia) and exposure to toxins or drugs (e.g. acetaminophen). The most common infectious agents are the primary hepatotropic viruses (Hepatitis A, B, C, D, E). Other viruses that may cause acute hepatitis include Epstein-Barr virus (EBV), cytomegalovirus (CMV), parvovirus, enteroviruses, adenoviruses, rubella virus, herpes viruses (HHV-1, HHV-2, HHV-6, HHV-7) and human immunodeficiency virus (HIV). Other infectious agents that may cause hepatitis include *Brucella* spp, *Coxiella burnetii*, and *Leptospira*.

Common symptoms of acute hepatitis include myalgia, nausea, vomiting, lethargy, fatigue, fever, abdominal pain, and diarrhoea. These symptoms sometimes persist for several weeks. A high proportion of acute infections with the hepatitis viruses are asymptomatic and for hepatitis A and B, the infection is much more likely to produce a minor or asymptomatic illness among children than among adults [15]. Jaundice is commonly associated with acute hepatitis, but many viral hepatitis cases may not show this feature. Death from acute viral hepatitis is rare and usually results from the development of fulminant hepatitis, acute liver failure (ALF) with hepatic encephalopathy. The risk of ALF resulting from fulminant viral hepatitis is associated with increasing age and pre-existing liver disease. Impaired coagulation with a prolonged prothrombin time is one of the classic markers of ALF. Hepatic encephalopathy can be subtle, especially in infants. Bone marrow failure occurs in a few children with ALF, ranging from mild pancytopenia to aplastic anaemia [16]. Without liver transplantation, mortality in children with ALF is very high. In up to 50% of ALF cases in children, the cause cannot be identified, and they are classified as indeterminate [17]. The treatment of indeterminate ALF cases is general supportive measures and liver transplantation.

Adenovirus infections

Virological features

Adenoviruses are non-enveloped viruses with a linear double-stranded DNA (dsDNA) genome. Adenovirus genomes share a central conserved part that can be used for detection purposes. Human adenoviruses (HAdV) are separated into seven genetically distinguishable species (A-G) and are currently classified into more than 50 serologically distinct types [18]. Different serotypes display different tissue tropisms and clinical manifestations of infection [18].

Circulation

Adenoviruses circulate throughout the year. In the USA, the highest numbers of detections of adenoviruses associated with conjunctivitis in a 30-year study period have been from July to September and the lowest from April to June every year [19]. Higher circulation of adenoviruses has been detected in Brazil in April-May and July to October [20] and in China higher prevalence was peaking in April and October [21]. Uncertainties remain about the seasonality of adenovirus in the EU/EEA and whether it is type-specific.

Routes transmission

Transmission can occur by direct contact with infected individuals through inhalation of droplets, faecal-oral route, and conjunctival inoculation, or indirectly through exposure to contaminated objects (fomites) [18].

Infections may spread rapidly among closed populations, for example in hospitals, schools and nurseries, and severe outbreaks of respiratory infection or keratoconjunctivitis due to HAdV have been described linked to a variety of virus types. Some outbreaks of more severe disease have been reported among groups of immunocompromised people [20-26].

Clinical presentation

The incubation period for respiratory adenoviruses is estimated to range between two and 14 days and for enteric ones between three and 10 days [29].

The incidence of adenovirus infection peaks between the ages of six months and five years, but the highest incidences have been described among children under two years of age.

HAdVs cause a wide range of clinical manifestations depending on virus type. The most common clinical features are keratoconjunctivitis (HAdV types 5, 8, 19 and 37), acute respiratory symptoms (HAdV types 1-5, 7, 14 and 21), urethritis in men by types 8 and 37, or gastroenteritis (HAdV-types 31, 40 and 41) [30]. More rare manifestations include kidney disease, haemorrhagic cystitis, or hepatitis [29]. Adenovirus (HAdV-40 and HAdV-41) is considered one of the most important causative agents of acute viral gastroenteritis in young children [18].

Although HAdV infections are generally self-limiting, immunocompromised individuals are at higher risk for developing severe and disseminated disease [31]. Associated cases of hepatitis have mostly been reported in immunocompromised patients [32,33]. However, a few case reports of adenovirus hepatitis among immunocompetent children have been reported [31-33].

Latent infection with HAdVs may occur with the virus residing in renal, lymphoid, or other tissues for many years, with reactivation sometimes occurring in severely immunosuppressed individuals [18].

Testing

Depending on the clinical presentation, appropriate specimens for diagnosis include faeces, respiratory specimens (i.e. nasopharyngeal swab, nasopharyngeal/transtracheal aspirate, bronchial alveolar lavage), conjunctival swabs, urine, genital secretions and biopsy specimens (e.g. of liver or spleen). Isolation of virus from blood provides strong evidence of invasive or disseminated disease.

Adenovirus infection can be diagnosed using different types of tests including antigen detection, polymerase chain reaction (PCR), virus isolation and serology. PCR to detect the virus in respiratory specimens, stool, blood, urine or other specimens is the most common approach to establish diagnosis [18].

Typing can be done using type-specific monoclonal antibodies (reagents commercially available), or using molecular methods (e.g. PCR and sequencing). Different genome types within serotypes are identified by restriction enzyme analysis, multiplex PCR techniques or sequencing targeting AdV fiber and hexon genes. Whole genome sequencing (WGS) has enabled the expansion of information on genetic makeup of AdV. WGS has been used for example for the detection of recombinants between different AdV types [18].

Serology can detect significant rises in levels of antibodies between serum specimens collected during acute illness and convalescence two to four weeks later. Serological methods are not used as first-line diagnostic methods.

Intermittent and/or persistent shedding of adenovirus after an acute infection is common, which makes clinical interpretation of a positive molecular test challenging [29]. In addition, there are reports that adenovirus infection is difficult to confirm by histopathology [35,36].

Commercial tests are available for the diagnosis of respiratory or gastrointestinal adenovirus in multiplex assays.

Treatment

Treatment of adenovirus infection is supportive. Current antiviral therapy options for adenovirus infections are limited, and while evidence from controlled trials is lacking, there are reports of the successful intravenous use of cidofovir in immunocompromised patients with severe adenoviral disease [39]. Intravenous immunoglobulins are also used as adjunctive treatment in immunocompromised patients as they contain high titres of neutralising antibodies for adenovirus [40].

A live, oral adenovirus vaccine for types 4 and 7 has been licensed by the US Food and Drug Administration for prevention of respiratory tract infection in people aged 17–50 years [29].

Prevention and control

Adenovirus is a non-enveloped virus resulting in limited virucidal effectiveness of alcohol-based disinfectants [41]. Adenoviruses may survive for extended periods on skin and environmental surfaces [42]. Decontamination requires specific agents such as chlorine or heat. Bleach-based solutions at higher concentrations (10%) have shown to be able to disinfect contaminated surfaces or medical instruments [43].

Hand hygiene, respiratory hygiene, and cough etiquette are general measures that could be strengthened in the context of high levels of adenovirus circulation in the community. Outbreaks of healthcare-associated adenovirus infections should be managed by implementing careful cohorting of patients, and appropriate use of disposable gloves, gowns, and goggles by healthcare staff.

Surveillance of HAdV is not systematically performed across the EU/EEA countries, although some countries might collect data on confirmed cases through laboratory notification or linked to outbreak investigations. Similarly, no typing data are routinely available across EU/EEA countries to serve as a baseline.

Epidemiological update for EU/EEA countries and the UK

EU/EEA countries

Several European countries have issued alerts through clinical and public health networks in recent days and have subsequently reported cases to ECDC.

Below is a summary of the information available in the public domain for each country as of 27 April 2022. Further case finding and investigations are ongoing. To date, the level of clinical detail available for each case is variable, but efforts are ongoing to standardise the information collected.

Table 1 shows information on cases reported to ECDC as of 27 April 2022. These are classified as confirmed and possible, according to the case definition used by the UK [2], which ECDC asked countries to use early in the outbreak. [4]

Confirmed: A person presenting with an acute hepatitis (non hepA-E*) with serum transaminase >500 IU/l (Aspartate Transaminase-AST or Alanine Transaminase-ALT), who is 10 years and under, since 1 January 2022.

Possible: A person presenting with an acute hepatitis (non hepA-E*) with serum transaminase >500 IU/l (AST or ALT), who is 11 to 16 years, since 1 January 2022.

Epi-linked: A person presenting with an acute hepatitis (non hep A-E*) of any age who is a close contact of a confirmed case, since 1 January 2022.

Most cases reported were aged 10 years or younger and it is possible that countries have prioritised detection in that age group; additional cases are under investigation.

In the EU/EEA, a total of approximately 55 cases have been reported. Ten tested positive for adenovirus and three cases tested positive for SARS-CoV2. Five children required liver transplantation.

Table 1. Summary of cases of severe acute hepatitis of unknown aetiology according to case definition used by the UK, with symptom onset since 1 January 2022, as of 27 April 2022 (EU/EEA countries) and as of 20 April 2022 (UK)

Country	Number of cases	Age range (years)	Adenovirus testing results*	SARS-CoV-2 test results*	Onset	Required liver transplant	N. of cases above the expected
Austria	2	<10	One negative	<i>Both had previous SARS-CoV-2 infection</i>	February 2022 – April 2022		
Belgium	2	Up to 10	One positive (stool)	<i>Both had previous SARS-CoV-2 infection</i>	February – March 2022		
Denmark	6	Up to 16	All Negative	<i>One recent SARS-CoV-2 infection</i>	January – April 2022		Yes
France	2	<10	One positive				No
Germany	1	5	Positive	Negative	January 2022		No
Ireland	Fewer than 5	2 to 11	One positive (stool)	All Negative	Since early March		Yes
Italy	17	<16	Two positive and two negative	One positive and four negative	Since early March	1	
Netherlands	4	11 months – 8 years	Two positive	One positive	Since late February	3	Yes
Norway	2	<6 years	One positive (Blood)	<i>One recent SARS-CoV-2 infection</i>	Since March	0	No
Poland	1	7	Pending	<i>Previous SARS-CoV-2 infection</i>	Late April		No
Romania	1	4	Negative	Negative	Late March		No
Spain	12 (excluding one case with symptom onset in December 2021)	18 months to 16 years	One positive	One positive and <i>one previous SARS-CoV-2 infection</i>	Early January to April 2022	1	No
United Kingdom**	111	< 16 years	40 positive	10 positive	Reported since 1 January 2022 – some had onset prior	10	Yes
EU/EEA total	Approx. 55		10	3		5	
EU/EEA and UK total	Approx. 166		50	13		15	

*Incomplete information on how many of the reported cases in each country were tested for adenovirus and SARS-CoV-2 infections.

**Data for the UK are as of 20 April 2022. Data on adenovirus and SARS-CoV-2 testing relate to the 81 cases reported in England.

Austria

Two cases of severe acute hepatitis of unknown aetiology have been reported in Austria and involve children under 10 years old. Both children experienced symptoms between February and April, as well as gastrointestinal symptoms in the weeks preceding the onset of acute hepatitis. Both children were hospitalised and are in stable condition.

Belgium

In Belgium, two cases have been reported in children aged up to 10 years. In one case, adenovirus was detected in a stool sample, and in the other the results from the various sites are still pending. Both had previous SARS-CoV-2 infection.

Denmark

Denmark reported five cases in children younger than 10 years from January 2022 onwards and one case older than 10 years. All cases were negative for adenovirus and for SARS-CoV-2. One case had a SARS-CoV-2 infection two months prior to presentation. One case tested positive for influenza A. No liver transplants or deaths have occurred among cases. Sentinel surveillance shows no sign of increase in adenovirus infections in the country. This may be above the level of normal, as in Denmark there are around two cases of ALF of unknown origin in children under 18 years detected annually.

France

France reported two cases under 10 years, with onset of symptoms in mid-March. Both cases presented as severe acute hepatitis, but no liver transplantations were required. One case tested positive for adenovirus. A metabolic disorder and an underlying genetic liver disease are suspected in both children. Investigations are ongoing.

At present, no signal of increased cases of hepatitis of unknown origin has been detected from the network of paediatric hepatologists. Syndromic surveillance in emergency units has not observed any signal either, and data from the transplant agency have not shown an increase in transplanted cases or in cases requiring a liver transplantation.

Ireland

Ireland reported fewer than five cases. One case tested positive for adenovirus. None of the cases tested positive for SARS-CoV-2. No epidemiological links were identified between cases. The number of cases of hepatitis of unknown aetiology in this age group is greater than expected and an alert has been sent to clinicians. Investigations are ongoing by public health authorities.

Italy

Italy reported a total of 17 cases across various Italian regions. Eight cases are considered probable, while nine are awaiting classification. The ages of cases have not been confirmed but all children are under 16 years. The cases exhibited symptoms from early March. A total of two cases tested positive for adenovirus, while two others tested negative. Data for four patients were not available. Regarding COVID-19 infection, one patient tested positive for SARS-CoV-2 and showed very low viral load, four cases tested negative, and data for three patients were unavailable.

Germany

Germany reported one case, a five-year-old child who developed symptoms of acute hepatitis and was hospitalised in January 2022. The child previously suffered gastrointestinal symptoms. The case tested positive for adenovirus and negative for SARS-CoV-2.

The Netherlands

The Netherlands reported four cases, aged 11 months to eight years. All four cases presented as ALF and three of them have received a liver transplant. Two cases tested positive for adenovirus, of which one also tested positive for SARS-CoV-2 and rotavirus. The cases live in four different regions of the country and there is no clear epidemiological link between them. The centre that performed the transplantations usually carries out three to four transplants in children a year, so the number observed is considered above normal.

Norway

Norway reported two cases, aged one and five years. Both exhibited symptoms in March and were hospitalised in April. One child had a previous SARS-CoV-2 infection and tested positive for adenovirus upon admission (PCR test). Both children had severe hepatitis without ALF and are recovering well.

Poland

Poland reported one case, a seven-year-old who experienced symptoms of acute hepatitis in April and was hospitalised. Symptoms of fatigue and vomiting in the preceding days have been reported. The child had a previous COVID-19 infection and a negative SARS-CoV-2 test on admission. Further investigations are ongoing.

Romania

Romania reported one case, a four-year-old. The child tested negative in respiratory samples for SARS-CoV-2, adenovirus, and more than 15 other pathogens. They had a positive result for anti-SARS-CoV-2 IgG Ab.

Spain

Spain has reported a total of 12 cases in children with onset of symptoms since 1 January 2022. One additional case had been detected with symptoms in late December 2021.

The confirmed cases (three boys, five girls) were aged 18 months to seven years and had onset of symptoms between 2 January 2022 and 24 March 2022. The probable cases (two boys, two girls, and one unknown) were aged 12 to 16 years and had onset of symptoms between 30 December 2021 and 1 April 2022. Of all cases, one required a liver transplant.

One case had a history of SARS-CoV-2 infection and one tested positive for SARS-CoV-2. One had a positive sample for adenovirus. One case had previous chemotherapy treatment. One case had a travel history to the UK.

The expected number of cases of acute hepatitis of an unknown cause in this age group in Spain would be around four to 10 cases at this time of year (based on data from the period 2016-2020).

Increased adenovirus activity in the community has not been seen in Spain so far, but the public health authorities are reviewing surveillance registries for changes in incidence of adenovirus infections.

The United Kingdom

The UK identified a total of 111 cases in children below 16 since January 2022 and as of April 20, 2022. Of these cases, 81 are in England, 14 are in Scotland, 11 in Wales, and five in Northern Ireland. All the children affected presented to health services between January 2022 and 18 April 2022. In total, 10 children have received a liver transplant, while 53% (N=43) of cases have recovered. In England, 34 potential cases are awaiting classification pending further data.

With regards to the 81 cases reported in England, cases are mainly between three to five years of age (median age three years), 54.4% are female, and 87.5% are white.

ECDC risk assessment

This assessment is based on the evidence available to ECDC at the time of publication.

Risk assessment question

What is the risk in the EU/EEA of severe acute hepatitis of unknown aetiology in children?

The reported incidence of severe paediatric acute hepatitis of unknown origin in the EU/EEA is usually very low, although no systematic surveillance of this entity is undertaken. As the aetiological agent of the reported acute hepatitis cases remains unknown and under investigation, the risk to the European paediatric population cannot currently be accurately assessed.

The likelihood of seeing an increase in severe acute hepatitis of unknown origin in children cannot be quantified due to the lack of evidence as regards the aetiological agent, the routes of transmission (including from potential asymptomatic infections) and risk factors. The current leading hypothesis is that a cofactor affecting young children having an adenovirus infection, which would be mild in normal circumstances, triggers a more severe infection or immune-mediated liver damage. An increase in the circulation of adenovirus in young children has been observed in the UK coinciding with increased detection of severe hepatitis in young children. If adenovirus is proven to be the causative or contributing agent of this event, similar increases in the circulation of adenovirus may lead to an increase of severe hepatitis in children in other European countries. With the implementation of enhanced surveillance activities, we expect that more cases will be identified and reported.

Considering that some of the reported cases needed liver transplantation, the potential impact for the affected paediatric population is considered high. Capacities for transplantation and for the support of paediatric liver failure patients vary widely among EU/EEA countries. Therefore, access to highly specialised paediatric intensive care and transplantation services may affect outcomes, especially if the number of cases rises.

Further epidemiological and laboratory investigations and structured collection of data in the framework of ad hoc surveillance are urgently required to enable an accurate assessment of the phenomenon.

Options for response

The current priority is to determine the underlying aetiological factors, the disease pathogenesis, and risk factors for severity of cases of acute severe hepatitis among children.

Case finding, testing, and reporting

ECDC advises Member States to develop ad hoc surveillance for this outbreak at the national level, and to analyse data on clinical and epidemiologic characteristics of cases as well as the microbiological characteristics of identified pathogens. For each case, public health authorities should employ a trawling questionnaire for hypothesis generation. All suspected cases should also undergo an exhaustive screening for identification of a possible cause, including both infectious and non-infectious agents. Furthermore, a detailed history of preceding infections, such as gastrointestinal infections and SARS-COV-2 infections, should be collected for cases and their close contacts. Member States are also encouraged to collect and analyse any available data on the baseline incidence of paediatric severe acute hepatitis of unknown origin, such as from syndromic surveillance, hospital admission and discharge records, admissions to liver transplant units etc., to ascertain any potential increase in incidence in the country.

Case definition

Active case finding of acute hepatitis cases in children in the EU/EEA should continue in a coordinated manner and according to the proposed ECDC-WHO case definition, as outlined in the [Reporting Protocol for hepatitis of unknown origin](#) and as described below. The proposed case definition differs from the one used by the UKHSA as it does not include confirmed cases, pending data on aetiology. It also uses the cut-off of 16 years as a common criterion to enable wider catchment of cases.

Cases that have already been reported to ECDC through other means (EpiPulse, EWRS or email) should also be reported to TESSy.

Joint ECDC/WHO case definition

Confirmed: Not applicable at present.

Probable: 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 or younger, since 1 October 2021.

Epidemiologically linked: 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.

*Cases of hepatitis with known aetiology should not be reported under the [Reporting Protocol for hepatitis of unknown origin](#)

Case finding

Public health authorities in EU/EEA countries should enhance awareness among local clinicians on this outbreak using dedicated communication channels for paediatricians, hospital specialists taking care of hospitalised children with acute hepatitis, general practitioners, and emergency room physicians, and ensure that they are informed about the situation, the current case definition and the requirement for reporting cases and information in a timely manner. Standardised case reporting forms should be provided to facilitate the collection of analysable information. It is particularly important that clinicians at specialised liver units are made aware of the case definition and requirements for reporting.

Case investigation

Public health authorities can use the trawling questionnaire form provided by the UK to investigate cases. This is available in [EpiPulse](#) [accessible to authorised users only]. ECDC is adapting this form and will publish an updated version on the ECDC website. Public health authorities can also adapt the form to their national context and ensure that local public health authorities and/or clinicians are informed accordingly and trained on using it. The results from the questionnaire should be collated at national level to enable the identification of potential common exposures among cases. If countries identify any common exposures between their cases based on the questionnaire, this information should be shared in [EpiPulse](#) [accessible to authorised users only].

Since it is essential to rapidly identify risk factors for developing severe hepatitis in children and to determine the aetiology and underlying pathologic mechanism, case control studies should be set up without delay. For each case

detected, it is recommended to identify three sets of controls:

1. Hospitalised children matched by age, condition's severity, and time, recruited from the same hospital where cases are admitted. Laboratory investigations can be carried out on residual sera, white blood cells, and plasma to identify possible infectious, immunological, and genetic markers of disease and personal disease determinants.
2. Close contacts such as siblings and classmates to investigate personal, environmental, and behavioural differences between cases and controls. This type of analysis could provide insights into disease determinants and pathogenesis.
3. If resources allow close contacts that are positive for the same infectious agents of the case, to identify determinants of severity and pathogenetic mechanisms.

Since such studies would require collection of specimens from cases and controls, study protocols should be developed (and ethical approvals sought) in advance and shared and international collaboration is underway to help coordinate such studies across countries.

When a severe case of hepatitis in a child is identified, public health professionals are also encouraged, where possible, to perform wider case finding around the case and ask about any recent history of gastrointestinal symptoms or jaundice and SARS-CoV-2 infection among household members and any classmates at school or day care contacts.

Furthermore, public health authorities are encouraged to search for outbreaks of adenovirus (or other viruses) in the specific community from which the case(s) came. This could include reviewing data from local laboratories for recent infections or reviews of local syndromic surveillance data. In closed settings such as schools or day care, sampling for viruses (see Table 2) can also be considered.

Reporting of cases

Collating and reviewing data at the supranational level should enable a better characterisation of the event, including the definition of its magnitude and temporal and geographical evolution, thus contributing to the identification of the causative agent or factors.

Case based reporting has been set up in [TESSy](#) (accessible to authorised users only) and countries are encouraged to report cases promptly to this platform using the [Reporting Protocol for hepatitis of unknown origin](#). Countries are also encouraged to update the records when more information becomes available.

Testing

In addition to case finding, when testing probable and epidemiologically linked cases, appropriate samples should be collected to perform the tests outlined in Table 2. ECDC recommends the early collection of multiple specimen types from the cases under investigation and testing with different diagnostic methods for prompt detection of possible causative agents (Table 2). Countries should include adenovirus testing for children with severe acute hepatitis, at the same time of testing for hepatitis A-E. Preliminary data indicate that whole blood is an important sample matrix to test for viruses. Specialist care should be sought rapidly while waiting for test results if clinical conditions start to worsen. Microbiological findings for each case should be reported in TESSy.

If diagnostics are not available locally, then specimens should be referred to national laboratories, including for typing and pathogen characterisation.

Quantification of positive PCR findings in blood samples should be conducted with cycle threshold (Ct) value as proxy, and if possible, using sequential sampling over a longer time period.

Institutes with metagenomic capacities can consider metagenomic analyses of samples for probable and epidemiologically linked cases. Samples for potential analysis can include blood and available liver biopsies but can be extended to any relevant samples.

As the aetiology remains unknown, relevant toxicology and environmental studies should also be considered where possible. Laboratory screening for metabolic and autoimmune diseases are recommended in order to exclude other non-infectious causes.

Table 2. Recommended testing approach for probable (and epi-linked) cases of severe acute hepatitis

Sample type	Test type	Pathogen
Blood	Serology	Hepatitis A, B, C, D*, E/ Cytomegalovirus (CMV)/Epstein-Barr virus (EBV), Varicella, HIV, SARS-CoV-2 anti-S, SARS-CoV-2 anti-N (only if locally available), Adenovirus**
	Serology	<i>Brucella</i> spp, <i>Barthoneilla henselae</i> , <i>Borrelia burgdorferi</i> (if epidemiologically appropriate)
	Culture	If clinically indicated i.e. fever, as per routine procedures for bacterial pathogens
	Culture	Adenovirus, CMV, EBV, HSV, influenza
	PCR***	Adenovirus**, enteroviruses, CMV, EBV, HSV, HHV6 and 7, parechovirus, hepatitis A, C, E.
	Toxicological screening	Liquid Chromatography / High Resolution Mass Spectrometry (LC/HRMS), Gas Chromatography / Mass Spectrometry (GC/MS), Inductively Coupled Plasma Mass Spectrometry (ICPMS), in a case control study
Throat swab	PCR	Respiratory virus screening by multiplex assay (including influenza, adenovirus, parainfluenza, rhinovirus, respiratory syncytial virus, human bocavirus 1-3 etc), SARS-CoV-2, enteroviruses, human metapneumovirus (hMPV)
	Culture	Streptococcus group A
Stool or rectal swab	PCR	Enteric viruses screening by multiplex assay (including, norovirus, enteroviruses, rotavirus, astrovirus, sapovirus)
	PCR	Enteric bacterial pathogens (incl. <i>Salmonella</i> , if a screening panel is used)
	Culture	<i>Campylobacter</i> , <i>Salmonella</i> , <i>Shigella</i> , <i>E.coli</i> 0157
	Culture	Adenovirus, Enteroviruses, Rotavirus
Urine	PCR	<i>Leptospira</i>
	Culture	If clinically indicated, as per routine procedures for bacterial pathogens
	Toxicological screening	Inductively Coupled Plasma Mass Spectrometry (ICPMS)

*Testing for hepatitis D only in cases positive for hepatitis B.

**Note that for adenovirus testing, detection has been found to be superior in whole blood compared to serum.

***Please provide Ct values as a proxy of nucleic acid quantification when available.

Typing

It will be important to store specimens (e.g. serum and EDTA blood, nasopharyngeal/throat swabs (for bacterial and viral testing), faecal and urine specimens) for possible further diagnostic testing and typing as required. Adenovirus and/or SARS-CoV-2 positive samples should be typed, and results reported as soon as possible to TESSy. Adenovirus typing protocols targeting the regions of the hexon gene exist, but optimisation aspects should be considered especially when applying existing protocols to new types of sample matrices. Typing PCR based on existing protocols have been applied in combination with sequencing in the UK. However, efforts to optimise protocols for typing of adenovirus from blood are ongoing and laboratories pursuing typing should be aware of sensitivity and interpretation aspects. Type confirmation in the UK has been based on a combination of positive diagnostic PCR, typing PCR and targeted sequencing [42-44].

Albeit a protocol for whole genome sequencing of adenovirus directly from blood has not yet been agreed, ECDC encourages countries to pursue whole genome sequencing of positive adenovirus blood samples and share consensus genomes with ECDC or upload to international databases (e.g. ENA, GenBank).

Provided that protocols for further subtyping are available, support can be provided via ECDC outsourced services. Support can be available through ECDC outsourced WGS services. If countries need ECDC support for sequence-based typing, please contact Typing@ecdc.europa.eu.

Reporting of laboratory results

Results from laboratory testing should be reported promptly to TESSy, including positive and negative findings as per reporting protocol. It is recommended to share genome sequence data in public domain (ENA/SRA) to allow easy access for all international stakeholders, or alternatively share with ECDC for inclusion in multi-country analysis.

Epidemiological awareness

- Member States are encouraged to carry out further assessment and investigations to establish if there are relevant signals above what would normally be expected. These could include the following: review of emergency department and hospital admissions for liver disease, including transplant records. These studies can be used to determine the expected number of acute hepatitis cases with unknown aetiology and to assess if cases since 1 October 2021 exceed the expected number of admissions and/or transplants. A number of ICD 10 codes are associated with non-A-E acute hepatitis and have been used in similar studies in the UK [4].
- Review of data from any operating syndromic surveillance systems to understand if there are any signals above what would normally be expected. Options for syndromic surveillance could include the syndromes of jaundice and/or gastrointestinal symptoms.
- Review available information on adenovirus circulation (e.g. laboratory testing data) in the community, if possible by type of specimen (respiratory and faecal) and by age group, to understand if circulating levels exceed what would be expected.
- Consider carrying out retrospective and prospective wastewater surveillance for adenovirus, although standards are not well established [47].
- There are currently very limited whole genome adenovirus sequence data available in the public domain, particularly for enteric adenoviruses. Academic and clinical centres that have or can generate adenovirus whole genome sequencing data are asked to share consensus genomes to an International Nucleotide Sequence Database Collaboration such as GenBank to assist characterisation of circulating adenovirus strains internationally [4].

Member States are encouraged to share the findings of such investigations in [EpiPulse](#) (accessible to authorised users only).

Potential control measures

Provided that human enteric adenovirus infection remains the more likely aetiological cause of these acute hepatitis cases, close contact with an infected person should be considered the most likely route of exposure. The faecal oral route of transmission should be considered the most likely transmission route, particularly in young children and particularly as regards HAdV 41 [48]. However, as the current evidence for the aetiology and transmission is weak, recommended measures should reflect general good hygienic practice.

Careful hand hygiene and respiratory etiquette should be implemented in day care settings which experience outbreaks of gastroenteritis. Single use gloves should be considered for staff members changing diapers, followed by careful hand hygiene. Thorough disinfection of surfaces should be undertaken.

In healthcare settings standard and contact precautions should be followed for all probable and confirmed cases and respiratory precautions should be added if cases have any respiratory symptoms. In hospitals with probable acute hepatitis cases, according to the case definition above, patient transfers or staff mobility between the different hospital units should be limited to avoid transmission. Cohorting of probable cases of acute hepatitis with other patients should also be avoided. Adenoviruses can survive on surfaces and fomites such as towels and are not easily inactivated by alcohol-based hand gels and even hand washing. Disinfection of medical equipment may require higher concentration bleach solutions (e.g. 10%) or other high level disinfection products.

Risk communication

Public health authorities should engage with the public in order to:

- Enhance awareness among parents of small children about the need to look out for hepatitis-compatible symptoms (e.g. jaundice, vomiting, abdominal pain and pale stool, etc.), and inform them about the recommended course of action should they see such symptoms in their children. Information should be provided about who to contact for medical advice, as per national/local regulations. Parents should be reminded of the importance of hygiene measures such as hand washing, and respiratory etiquette which help reduce the spread of many of the viruses that are under investigation as potential causes.
- Communicate that much remains unknown about this event, including the causative agent. It is important that the public is made aware that this event concerns a very rare condition, that case finding continues, and a range of other investigations are ongoing in an effort to identify the causative agent. Even if adenovirus plays a role, this disease does not seem to have the features of a transmissible disease. As more knowledge becomes available, it may be necessary for the authorities to adapt advice about prevention and control.
- Systematically monitor social media and other outlets for unfounded rumours or misinformation circulating around possible causes of the outbreak and respond accordingly with updated information based on what is currently known.

Limitations

The main limitation in the current risk assessment is the lack of certainty on the aetiological agent, which means that it is not possible to properly assess the risk and define appropriate control measures. Although a viral aetiology has been proposed, this has so far not been proven. In addition, there is substantial uncertainty regarding the true number of cases of acute hepatitis of unknown aetiology in children in EU/EEA countries, as well as globally, as many national surveillance systems focus on viral hepatitis of known aetiology (e.g. A, B, C) and are not designed to detect changes in incidence of acute hepatitis of unknown aetiology. The use of different case definitions has also so far made collection of systematic and comparable data challenging.

Several unknowns remain including, but not limited to, the following:

- The aetiological agent;
- The pathogenetic mechanism of disease;
- The characteristics of the most affected populations, including key demographic characteristics;
- The clinical spectrum of disease;
- Whether there are any risks or predisposing factors for infection or severe disease; and
- Transmission route(s) and the extent of transmission, if any.

This assessment is undertaken based on information known to ECDC at the time of publication.

Source and date of request

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All experts have submitted declarations of interest, and a review of these declarations did not reveal any conflict of interest.

Disclaimer

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This report was written with the coordination and assistance of an Internal Response Team at the European Centre for Disease Prevention and Control. All data published in this risk assessment are correct to the best of our knowledge at the time of publication. Maps and figures published do not represent a statement on the part of ECDC or its partners on the legal or border status of the countries and territories shown.

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