Severe acute hepatitis cases of unknown aetiology in Ireland

Prepared by HPSC on 15/12/2022, data as of 15/12/2022 09:00

Background

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.[1]

As of 24 November 2022, 572 cases of acute hepatitis among children aged 16 and under have been reported from 22 EU/EEA countries (Austria, Belgium, Bulgaria, Cyprus, Denmark, Finland, France, Greece, Ireland, Israel, Italy, Latvia, Luxembourg, the Netherlands, Norway, Poland, Portugal, Republic of Moldova, Serbia, Spain, Sweden and the United Kingdom). Seven deaths and twenty four liver transplants have been reported associated with this disease in the European region. The majority of cases (76%) are aged five years or younger. According to the latest ECDC/WHO Situation Update the aetiology and pathogenic mechanisms of disease are still under investigation. A possible association with current adenovirus infection has been identified; of cases tested for adenovirus, 52% tested positive. Other hypotheses and possible co-factors are also under investigation. Most cases continue to be reported as sporadic, unrelated cases.[2]

Studies conducted by researchers in the UK are summarised in a recent Epi-Insight article. Two studies identified co-infection with Adeno associated virus type 2 (AAV2) and adenovirus associated with this syndrome. One of these studies also found a possible link to a specific human leucocyte antigen gene allele, DRB1*04:01, and hypothesised that children with this mutation may be more likely to have a pathological immune response to infection with adenovirus and/or AAV2.

Irish response

Following the initial international alert of paediatric cases of hepatitis of unknown aetiology and subsequent identification of suspect Irish cases meeting the same clinical profile, a multidisciplinary Incident Management Team was established by the HSE in early April 2022. Cases are notified under Infectious Diseases (Amendment) (No. 3) Regulations 2003 (regulation 14) whereby doctors and directors of diagnositic laboratories are required to notifiy unusual clusters or changing patterns of any illness, and individual cases, that may be of public health concern.

Data on cases, collected by clinical teams in paediatric hospitals, laboratories and public health, have been collated and analysed in order to understand the aetiology and risk factors for the disease. Anonymous data are shared with ECDC and WHO as part of the international efforts to understand this event. The IMT continues to monitor the

national and international situation relating to this event, collecting and analysing data on Irish cases meeting the case definition (described below).

This report summarises the epidemiological situation in relation to cases meeting the case definition in Ireland. These data are provisional and subject to change as results from investigations become available over time.

The following working case definition matches that used by WHO/ECDC with the exception of the 'Possible' case category, which is unique to Ireland. This additional classification was agreed by the national IMT to ensure that all suspect cases could be identified and investigated appropriately. Cases meeting this case definition are reported to the Departments of Public Health and the HPSC.

Working case definition in Ireland

For the purposes of case identification, the national IMT agreed to adopt the following case definition:

- **Confirmed**: N/A at present
- **Probable**: A person presenting with an acute hepatitis (non hepA-E*) with serum transaminase >500 IU/L (AST or ALT), who is 16 years and younger, since 1 October 2021
- **Possible**: A person presenting with an acute hepatitis (non hepA-E*) with serum transaminase between 200 and 500 IU/L(AST or ALT), and cholestatic who is 16 years and younger, since 1 October 2021
- **Epi-linked:** A person presenting with an acute hepatitis (non hepA-E*) of any age who is a close contact of a probable case, since 1 October 2021.

*If hepatitis A-E serology results are awaited, but other criteria met, these can be reported and will be classified as "pending classification". Cases with other explanations for their clinical presentation are discarded.

Persons under investigation (PUI): When potential cases, who have some features of this disease, are notified by clinicians, they are first called 'persons under investigation', until clinical history and laboratory tests (specifically hepatitis A-E serology) are available, at which time they are either categorised as cases, or discarded, if another cause for their hepatitis has been found.

Descriptive epidemiology Ireland

As of 15th December 9:00, **thirty six probable cases of severe acute hepatitis** of unknown aetiology have been identified in Ireland: **two probable cases underwent liver transplantation; one probable case (non-transplant) died. Seven possible cases** of severe acute hepatitis of unknown aetiology have also been identified and some other potential cases are currently under investigation and classified as PUIs.

Thirty five of the thirty six probable cases had at least one test for adenovirus (blood, stool, respiratory, serum or other specimen type). Of these seventeen (49%) tested positive. Twenty two cases were tested for adeno-associated virus type 2 (AAV2). AAV2 was detected in 64% (n=14) of these cases. Thirty probable cases had a SARS-CoV-2 PCR or antibody test. No cases tested positive on PCR test (tests for current infection) and 18 (60%) tested positive for SARS-CoV-2 antibodies (current or past infection). The other most commonly detected organism was human herpesvirus 7 (HHV-7); of 21 cases tested, 12 were positive (57%). Thirteen cases also tested positive for rhino/enterovirus and small numbers tested positive for other pathogens.

Table 1 summarise the probable cases. Figure 1a and 2b show the number of probable and possible cases by week of onset and week of hospitalisation. Figure 2 shows the % of probable cases with each clinical symptom, where information on symptoms was reported. Figure 3 shows available laboratory results to date. The percentage positive for some organisms should be treated with caution due to low numbers tested.

Table 1. Summary table of probable cases as of Thursday 15th December 09:00

Characteristics	Number	%
Age		
<1	4	11.1
1-4 yrs	19	52.8
5-11 yrs	11	30.6
12-16 yrs	2	5.6
Median age	3	
Age range	0 - 15	
Sex		
Male	18	50.0
Female	18	50.0
Ethicity		
White Irish	32	88.9
Other	4	11.1
International travel		
Yes	8	22.2
No	21	58.3
Unknown	7	19.4
Household pets		
Yes	19	52.8
No	8	22.2
Unknown	9	25.0
SARS-CoV-2 vaccination status		
Vaccinated	3	8.3
Not vaccinated	23	63.9
Unknown	10	27.8
COVID in close contacts		
Yes	20	55.6
No	8	22.2
Unknown	8	22.2
Clinical		
Hospitalised - Non ICU	27	75.0
Hospitalised - ICU	7	19.4
Not hospitalised	1	2.8
Hospitalisation status not known	1	2.8
Transplant		
Had liver transplant	2	5.6
Total	**36**	

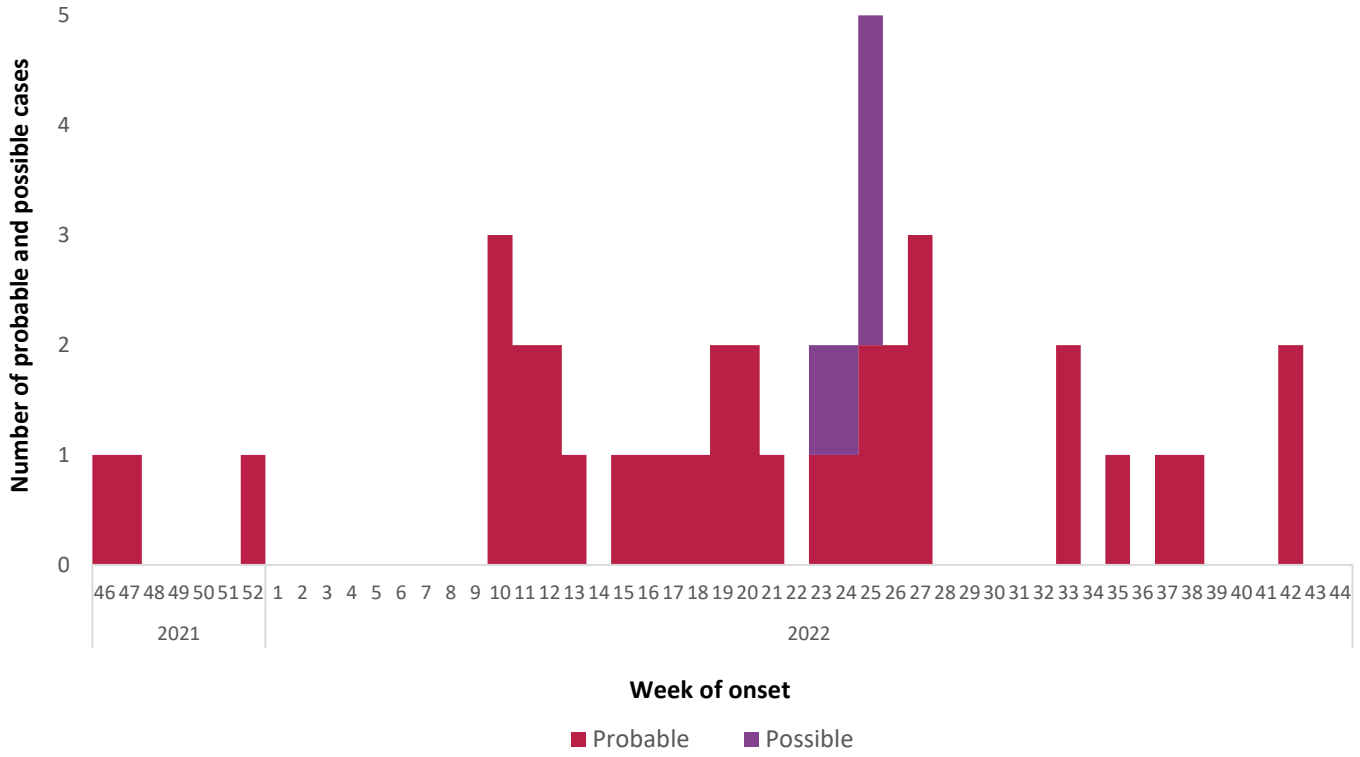

Figure 2a. Number of probable and possible cases by week of onset of symptoms*
*Onset date not yet reported for two possible cases.

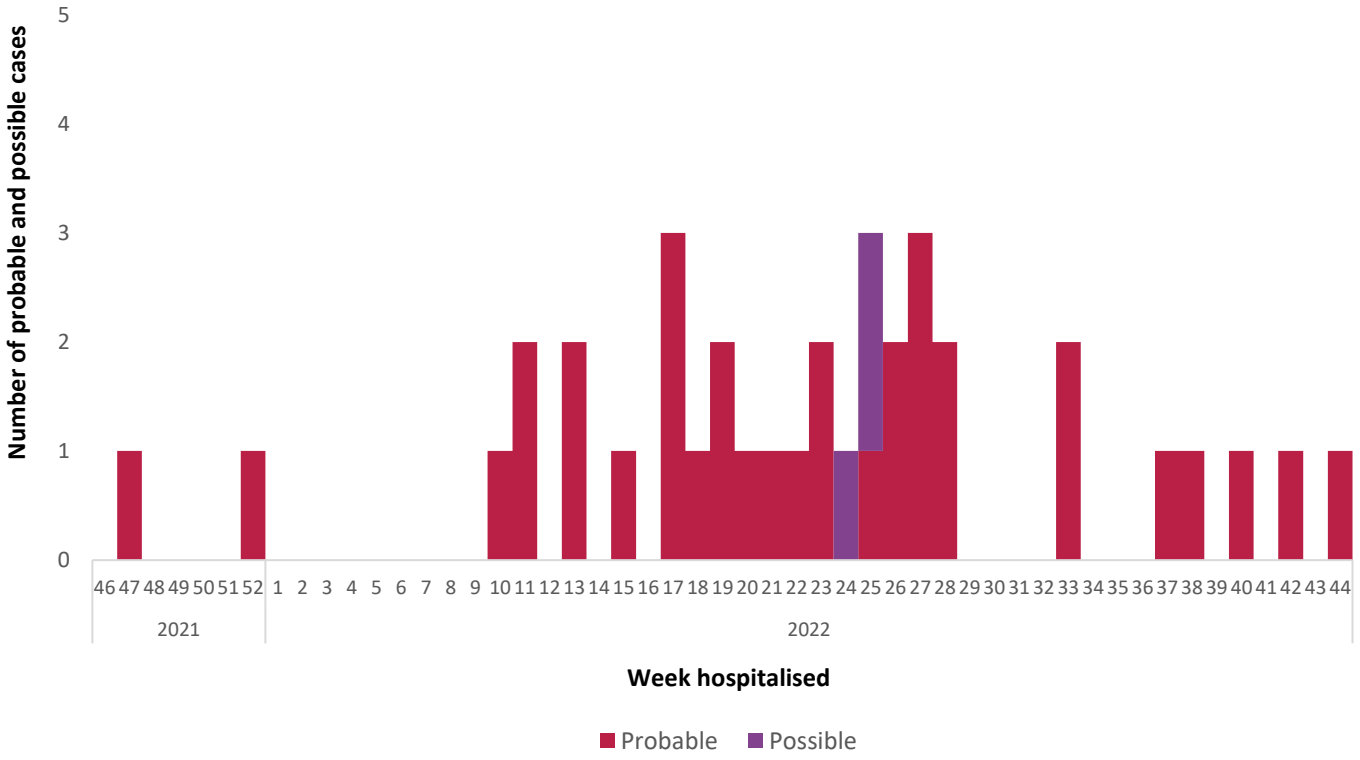

Figure 2b. Number of probable and possible cases by week of hospitalisation*
*One probable case was not admitted to hospital. One probable case and three posible cases were recently identified in an outpatient setting. Limited data are available for these patients and It is not yet known if they were hospitalised. Date of hospitalisation is not yet known for one additional possible case.

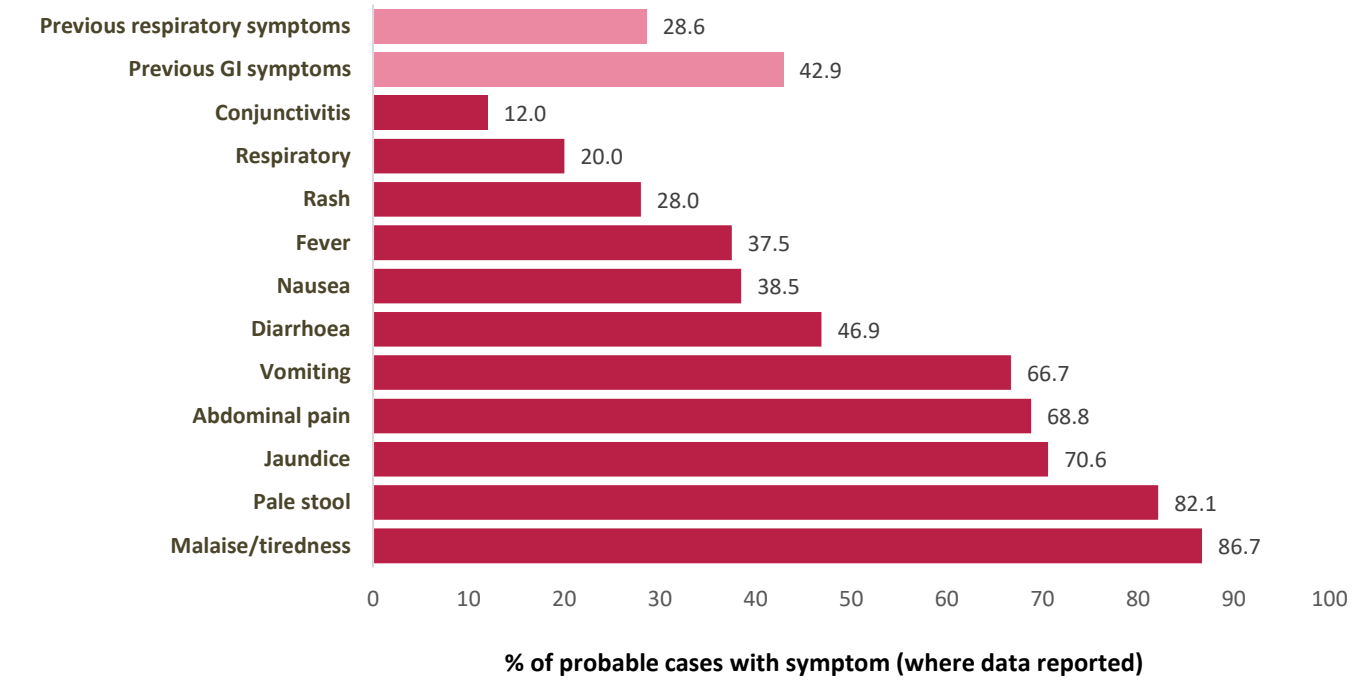

Figure 3. Frequency of each clinical symptom for probable cases where information on symptom was reported (varied by symptom, n=25 to 35)

*Respiratory or gastrointestinal symptoms experienced in weeks prior to hospital admission – difficult to determine if due to separate illness or illness leading to hepatitis-related hospitalisation in some cases. Therefore a case may be reported as having had respiratory symptoms, diarrhoea and vomiting and also previous respiratory or gastrointestinal symptoms.

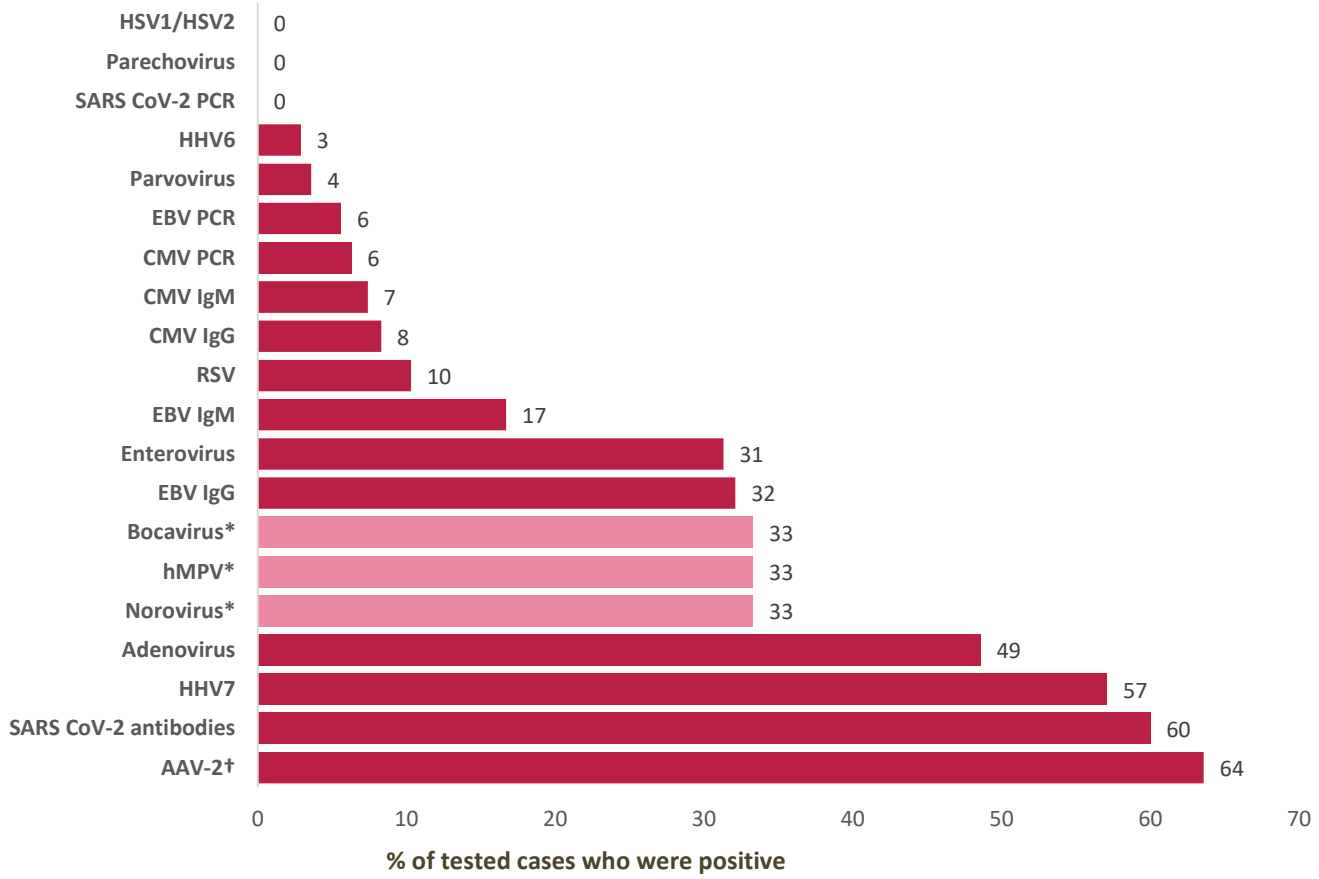

Figure 4. % of probable cases positive for each organism where results reported (varied by pathogen, n=3 to 36)

†Adeno-Associated Virus-2

*The number of cases tested was low for hMPV (n=3), Norovirus (n=6) and Bocavirus (n=3)

HLA results

Based on data provided to HPSC to date, eighteen probable cases have undergone HLA testing. Of these thirteen tested positive for DRB1*04:01, two were positive for DRB1*04:07 and three had normal DRB1 alleles.

Acknowledgements

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