Severe acute hepatitis cases of unknown aetiology in children in Ireland

Prepared by HPSC, data as of 11/07/2023

Background

An increase in severe acute hepatitis of unknown aetiology in children (HUAC) was first reported by the United Kingdom (UK) to the World Health Organization's International Health Regulations (IHR) notification system on April 5th 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 reported suspected cases.

By November 24th 2022, 572 cases of severe acute hepatitis among children aged 16 and under had been reported by 21 EU/EEA countries and the United Kingdom (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 were reported in association with this syndrome in the European region. The majority of cases (76%) were aged five years or younger. Most cases were reported as sporadic, with no epidemiological links detected. According to the most recent ECDC/WHO Situation Update the aetiology and pathogenic mechanisms of disease were still under investigation. A possible association with human adenovirus (HAdV) infection was identified; of cases tested for HAdV, 52% tested positive. Other hypotheses and possible co-factors remained under investigation at the time this report was published.

A UK case control study (Genomic investigations of unexplained acute hepatitis in children | Nature), involving 38 HUAC cases and 66 controls, identified high levels of adeno-associated virus type 2 (AAV2) DNA in liver tissue and blood/plasma/stool samples in 27 out of the 28 cases tested (96%), but low levels of HAdV DNA. Replication of AAV2 requires coinfection with a helper virus, such as adenovirus or herpesvirus, and low levels of adenovirus and human herpesvirus 6 (HHV-6) were detected in 87% (33/38) and 73% (19/26) of cases tested, respectively. Little or no AAV2 DNA was found in blood from age-matched, immunocompetent children. Increased human leukocyte antigen (HLA) class II expression was also detected in liver tissue from cases compared to healthy controls. HLA class II genes are involved in the immune response to infections and variations in these genes in individuals can influence susceptibility to autoimmune diseases). HLA typing was carried out for 13 cases and 12 (92%) were found to have the HLA-DRB1*04:01 allele. The team hypothesised that high levels of AAV2 replication products aided by HAdV and/or HHV-6 may have triggered immune-mediated hepatic disease in genetically and immunologically predisposed children.

Similar results were found in a case control study in Scotland (Adeno-associated virus 2 infection in children with non-A–E hepatitis | Nature). Recent infection with AAV2 was detected in plasma and liver samples in 26 out of 32

(81%) cases of HUAC compared to 5 out of 74 (7%) samples from unaffected individuals. Metagenomics and target enrichment next-generation sequencing (NGS) was done on all available clinical samples from the first nine recruited patients. The viral genome detected most frequently in plasma samples from affected patients was AAV2 (9 out of 9 cases). Adenovirus was detected at lower read counts in six out of the nine patients and HHV-6 was detected in 3 out of 4 plasma samples. HLA typing was done for 27 cases and 25 (93%) were found to have the HLA-DRB1*04:01 allele compared to 16% of controls. Based on the findings of the study, the authors hypothesised that the outbreak of HUAC cases in Scotland was associated with AAV2 infection (most likely acquired as a co-infection with HAdV/HHV-6) in combination with disease susceptibility related to HLA class II status.

Irish response

Following the initial international alert of paediatric cases of hepatitis of unknown aetiology and subsequent identification of suspected Irish cases meeting the same clinical profile, a multidisciplinary Incident Management Team was established by the HSE in April 2022. Cases were notified under Infectious Diseases (Amendment) (No. 3) Regulations 2003 (regulation 14) whereby doctors and directors of diagnostic 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, were collated and analysed in HPSC in order to understand the aetiology and risk factors for the disease. Anonymous data were shared with ECDC and WHO as part of the international efforts to understand this syndrome. The IMT declared the active investigation closed on May 12th 2023, following a sustained decline in cases. CHI Crumlin are continuing to monitor the situation and have agreed to alert HPSC if they detect an increase in case numbers.

This report summarises the epidemiological situation in relation to HUAC cases meeting the case definition in Ireland. These cases were reported to the Departments of Public Health and HPSC.

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.

This case classification matches that used by WHO/ECDC with the exception of the 'Possible' case category, which is unique to Ireland. This additional classification was agreed at the national IMT 06/05/2022.

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

Descriptive epidemiology Ireland

As of 11th July 2023, **forty four probable cases of severe acute hepatitis** of unknown aetiology were identified in Ireland: **two probable cases underwent liver transplantation; one probable case (non-transplant) died. Three possible cases** of severe acute hepatitis of unknown aetiology were also identified and one further potential case was classified as a PUI due to a missing hepatitis E result.

All of the forty four probable cases had at least one test for adenovirus (blood, stool, respiratory, serum or other specimen type). Of these twenty (46%) tested positive. AAV2 was detected in 18 out of 31 cases tested (58%). This was the most commonly detected pathogen in Irish HUAC cases. Other commonly detected organisms were human herpesvirus 7 (HHV-7) (n=18/33, 55% of cases tested), rhino/enterovirus (n=16/28, 57% of cases tested) and enterovirus (n=15/41, 37% of cases tested). HHV-6 was only detected in one of the 44 cases tested. Forty one probable cases had a SARS-CoV-2 PCR/antigen test (tests for current infection) and none were positive. SARS-CoV-2 antibodies (current or past infection) were detected in 22 out of 37 cases tested (60%).

Table 1 summarises the probable cases. Figures 1a and 1b 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. The percentage positive for some organisms should be treated with caution due to lower numbers tested.

Table 1. Summary table of probable cases as of July 11th 2023

Characteristics	Number	%
Age		
<1	6	13.6
1-4 yrs	25	56.8
5-11 yrs	11	25.0
12-16 yrs	2	4.5
Median age	3	
Age range	0 - 15	
Sex		
Male	22	50.0
Female	22	50.0
Ethnicity		
White Irish	37	84.1
Other	3	6.8
Unknown	4	9.1
International travel		
Yes	10	22.7
No	25	56.8
Unknown	9	20.5
SARS-CoV-2 vaccination status		
Vaccinated	3	6.8
Not vaccinated	33	75.0
Unknown	8	18.2
Clinical		
Hospitalised - Non ICU	35	79.5
Hospitalised - ICU	8	18.2
Not hospitalised	1	2.3
Transplant		
Had liver transplant	2	4.5
Total	**44**	

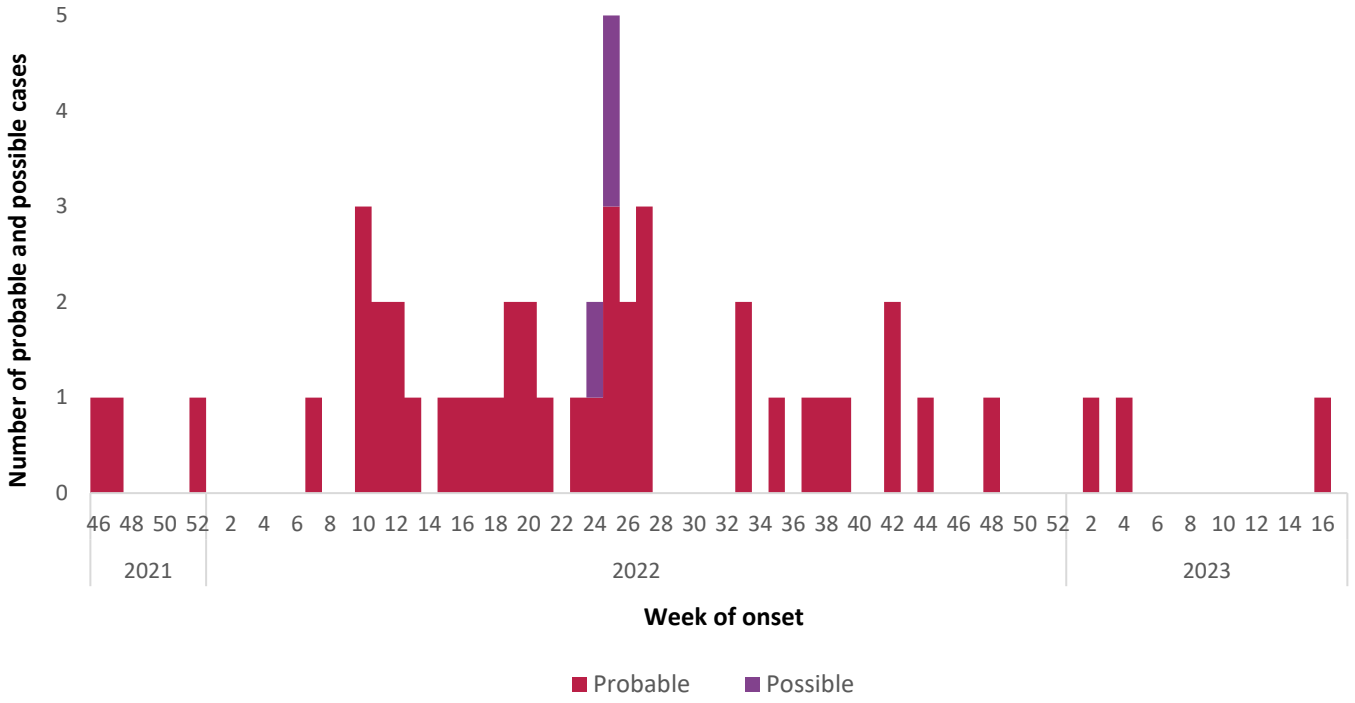

Figure 1a. Number of probable and possible cases by week of onset of symptoms (Nov 15th 2021- April 22nd 2023)

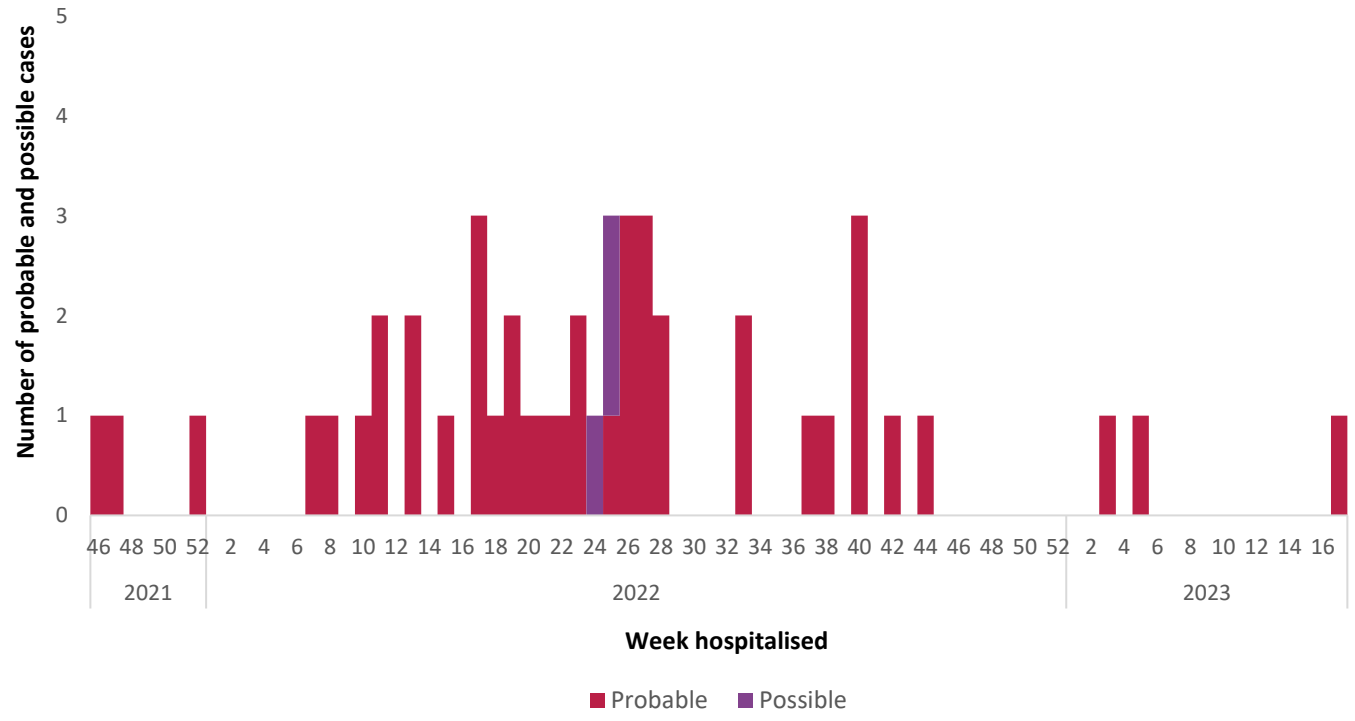

Figure 1b. Number of probable and possible cases by week of hospitalisation* (Nov 15th 2021- April 25th 2023)
*One probable case was not admitted to hospital.

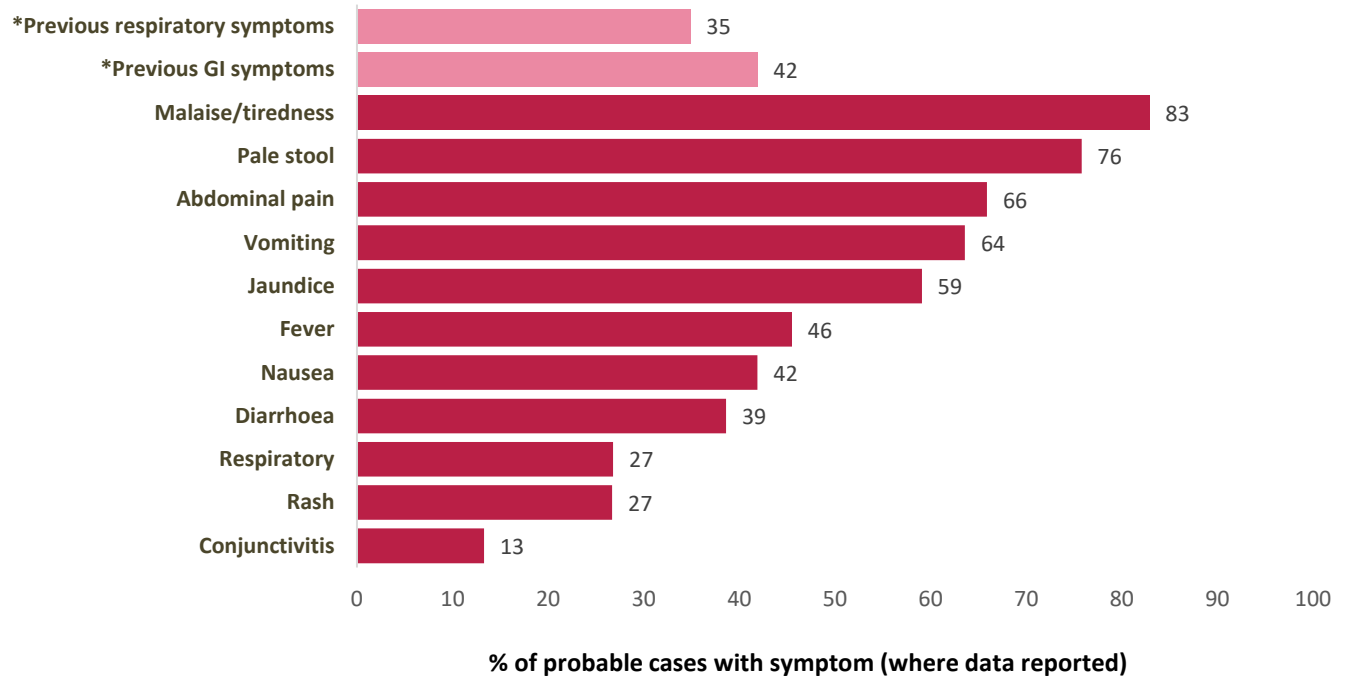

Figure 2. Frequency of each clinical symptom for probable cases where information on symptoms was reported (varied by symptom, n = 30 to 44)

*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.

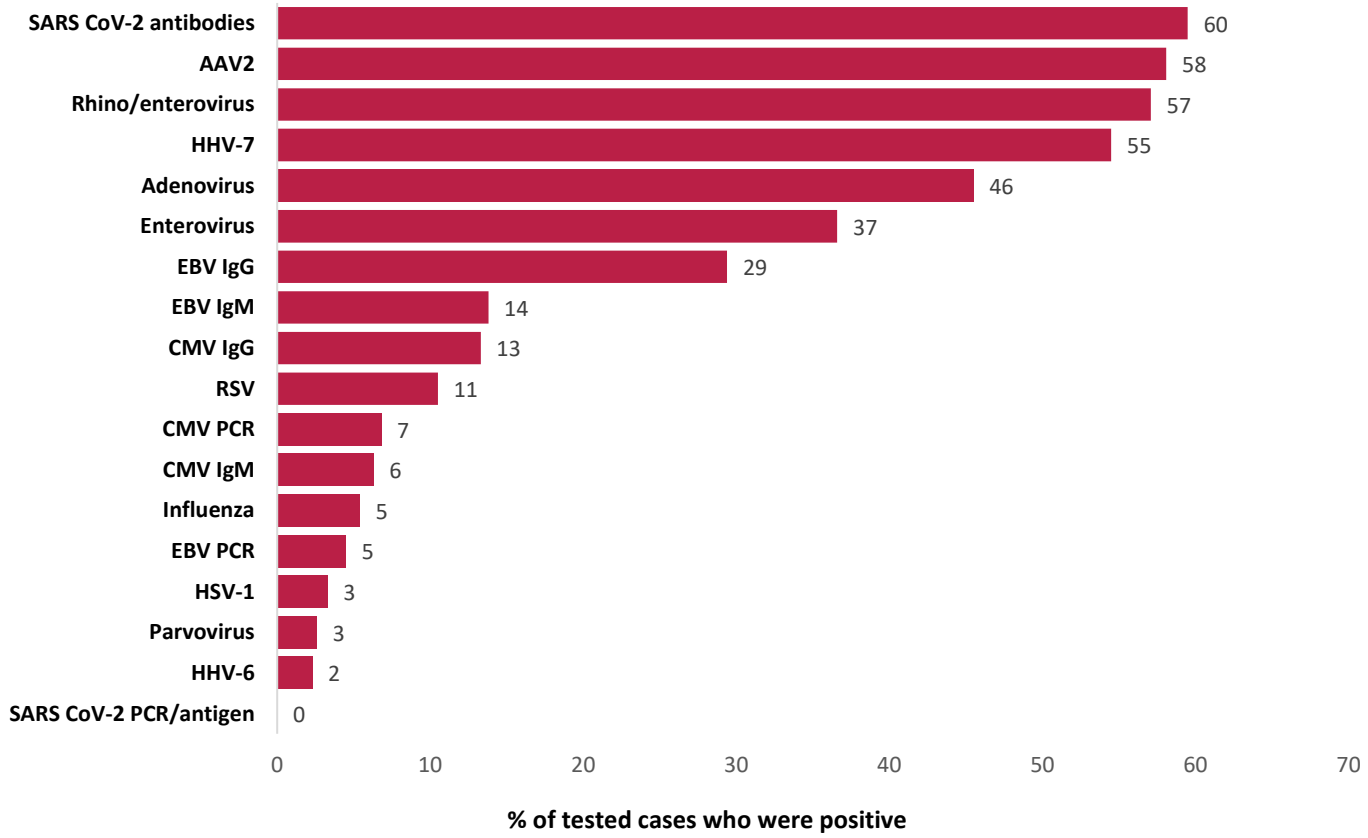

Figure 3. % of probable cases positive for each organism where results reported (varied by pathogen, n = 28 to 44)

*AAV2 - adeno associated Virus 2, HHV-6/-7 - human herpesvirus 6/7, EBV - Epstein-Barr virus (HHV-4), CMV – Cytomegalovirus, HSV-1 - herpes simplex virus type 1, RSV - respiratory syncytial virus.

HLA results

Based on data provided to HPSC, thirty two probable cases underwent HLA testing. Of these, 53% (n=17) were positive for the HLA class II DRB1*04:01 allele. This was significantly higher than the 20% of 250 individuals in Ireland tested as part of a study of donors recruited to the Irish Unrelated Bone Marrow Registry (IUBMR). The second most commonly reported HLA class II DRB1 allele was DRB1*03:01, but the distribution of this allele did not differ significantly between the Irish hepatitis uknown aetiology cases (9/32, 28%) and the IUBMR study cohort (33%). The prevalence of two other alleles was higher in children with hepatitis unknown aetiology compared to the IUBMR cohort: HLA-DRB1*11:01 (13% compared to 4%) and HLA-DRB1*04:07 (9% compared to 2%), but the number of HUAC cases with these alleles was low (n=4 and n=3, respectively).

Autoantibody results

Forty probable cases (91%) had LKM, ANA and SMA autoantibody results. Three tested positive for both LKM and for ANA/SMA autoantibodies, four tested positive for LKM alone and eight tested positive for ANA/SMA, but not LKM. The cases that tested positive for LKM were categorised as having autoimmune hepatitis type II (AIH II) and the remaining cases testing positive for ANA/SMA autoantibodies were categorised as autoimmune hepatitis type I (AIH I), resulting in 7 cases with AIH II (17.5%), an additional 8 cases with AIH I (20%) and autoantibodies not detected for the remaining 25 cases (62.5%) who were tested.

Thirty one cases had HLA typing and autoantibody results. No association was detected between having the HLA-DRB1*04:01 allele and being diagnosed with autoimmune hepatitis in these cases. A statistically significant association was detected between having the HLA-DRB1*03:01 allele and being diagnosed with autoimmune hepatitis type II; four out of 5 cases with AIH II, who also had a HLA result, had the HLA-DRB1*03:01 allele (80%) compared to 17% (1/6) with AIH I and 20% (4/20) who did not have autoimmune hepatitis. No significant association was identified between having autoimmune hepatitis and liver transaminase levels, or autoimmune hepatitis and disease severity in the Irish HUAC cases.

Acknowledgements

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