



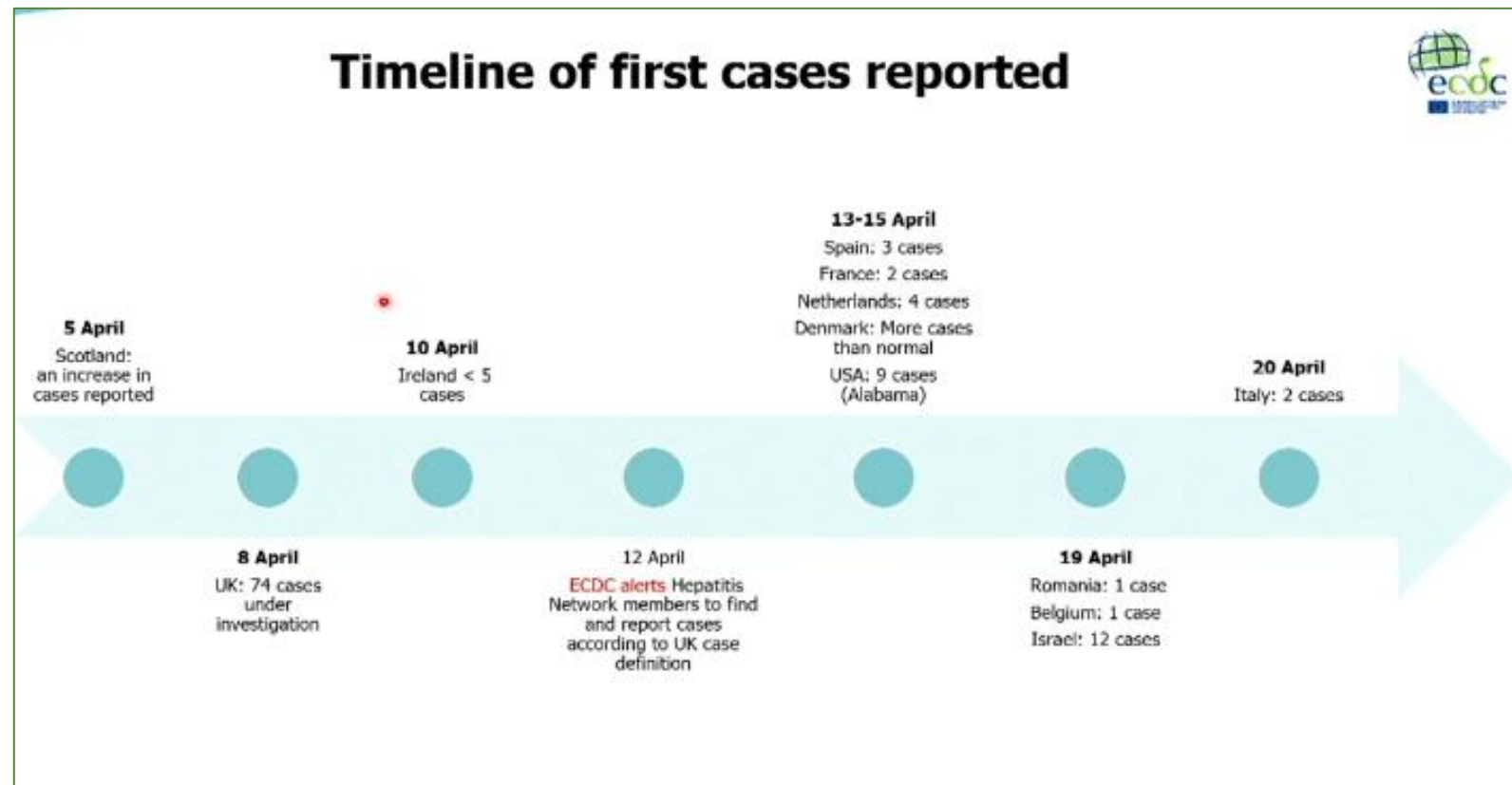
Una nuova epatite in età pediatrica

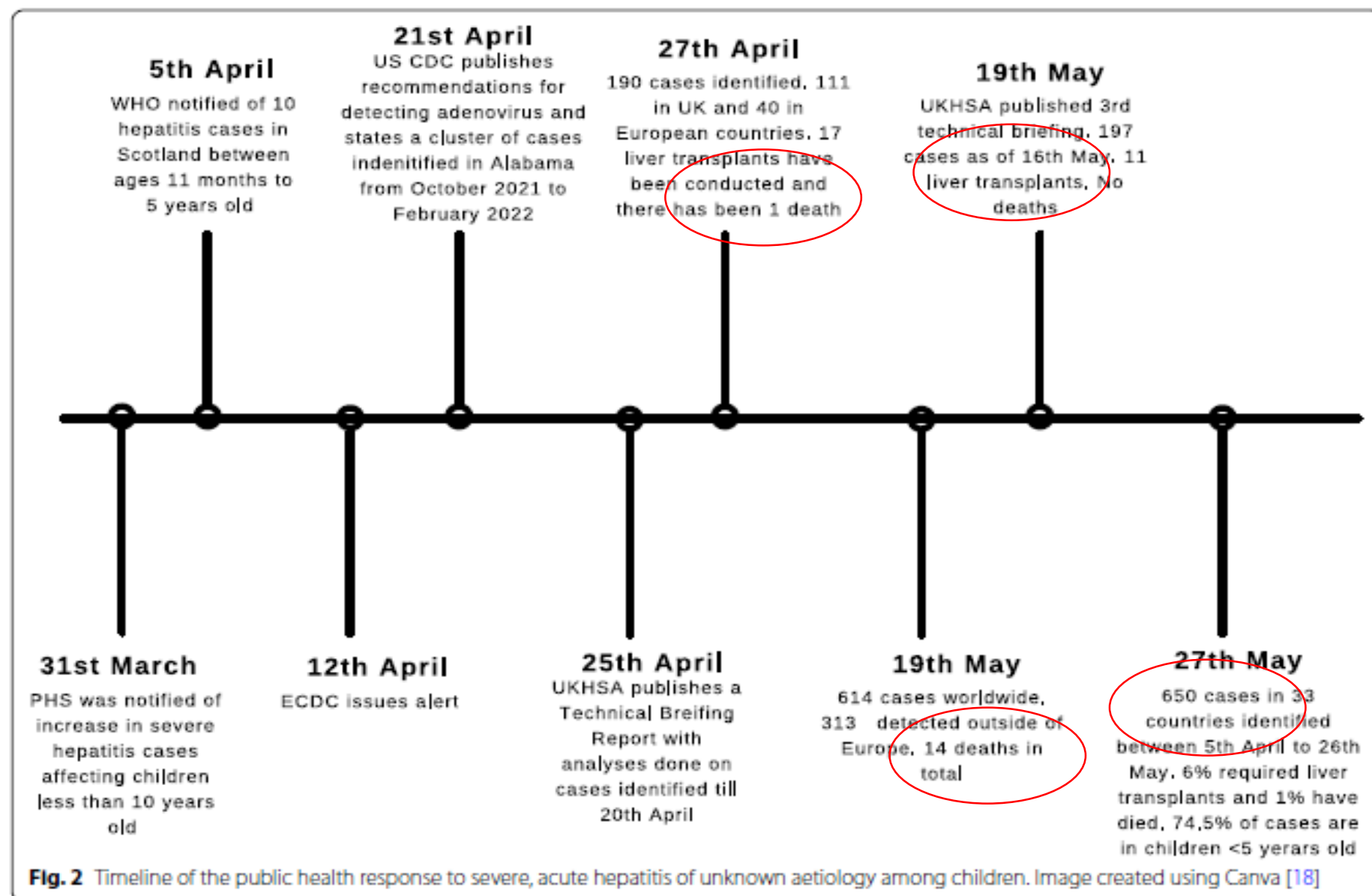
Vania Giacomet

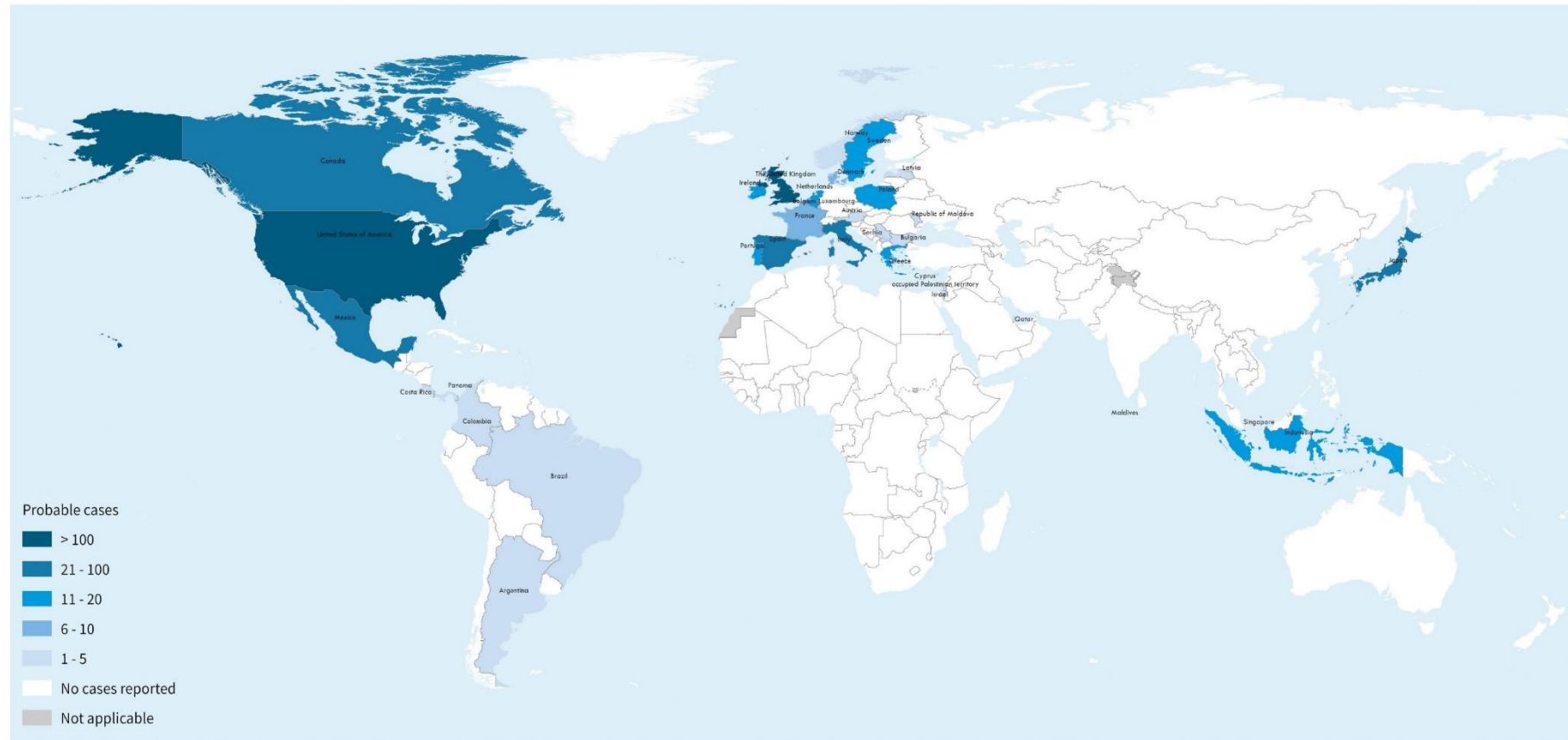
Pediatria Infettivologica Ospedale SACCO, ASST FBF SACCO

Università di Milano

- ❑ In October 2021, five pediatric patients with hepatitis of unknown cause were identified in children at a hospital in **Alabama**. The children had significant liver illness, including some with liver failure, with no known cause
- ❑ As of 21 April 2022, at least 169 cases of acute hepatitis of unknown origin have been reported from 11 countries in the WHO European Region and one country in the WHO Region of the Americas
- ❑ By 11 May, around 450 probable cases of acute hepatitis of unknown cause had been reported worldwide, with 163 in the UK by 3 May







The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of WHO concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: World Health Organization
Map Production: WHO Health Emergencies Programme
Map Date: 12 July 2022



As of **8 July of 2022**, WHO have reported **1010** probable cases of severe acute hepatitis of unknown origin among pediatrics in **35 countries in five WHO regions**. Of the probable cases, **45 children (5%) needed a transplant** and **22 (2%) deaths**. Half of the probable cases reported from the WHO European Area (21 countries reported **484 cases**), including 272 cases (27% of global cases) from the UK. The second highest number of cases was reported from the **Americas (n=435)**, including 334 from the United States), followed by the Pacific West (n=70) and South-east Asia (n=19) and the Eastern Mediterranean region (n=2). Seventeen countries have reported more than five possible cases. The actual number of cases may be underestimated, in part because of the limited advanced surveillance schemes available. The number of cases is expected to change as more information and verified data become available (WHO World Health Organization (WHO) Multi-Country-Acute, Severe Hepatitis of Unknown Origin in Children. 2022. July 22)

Distribution of probable cases of severe acute hepatitis of unknown aetiology in children by WHO Region since 1 October 2021, as of 8 July 2022

WHO Region	Probable cases	Cases requiring liver transplants	SARS-CoV-2 positive by PCR (Number of positive cases)	Adenovirus positive by PCR+ (Number of positive cases)	Adenovirus type 41 (Number of positive cases)	Deaths
Americas	435	24	18	9	1	13
Eastern Mediterranean	2	0	Not available	1	Not available	1
Europe	484	22	54	193	30	2
Southeast-Asia	19	0	Not available	Not available	Not available	6
Western Pacific	70	0	6	6	0	0
Cumulative*	1010	46	78	209	31	22

WHO working case definition

- Confirmed case: Not available at present
- Probable case: A person presenting with an acute hepatitis (non hepatitis A-E¹) with serum transaminase >500 IU/L (AST or ALT), who is 16 years and younger, since 1 October 2021
- Epidemiologically linked: A person presenting with an acute hepatitis (non hepatitis A-E¹) of any age who is a close contact of a probable case, since 1 October 2021

¹ If hepatitis A-E serology results are pending, but other criteria are met, these can be reported and will be classified as “pending classification”. Cases with other explanations for their clinical presentation are discarded. Delta testing is not required, as it is only undertaken in persons who are HBsAg positive to establish presence of co-infection.

Epidemiological curve of probable cases of severe acute hepatitis of unknown aetiology with available data, by week, by WHO region, as of 8 July 2022 (n=571)

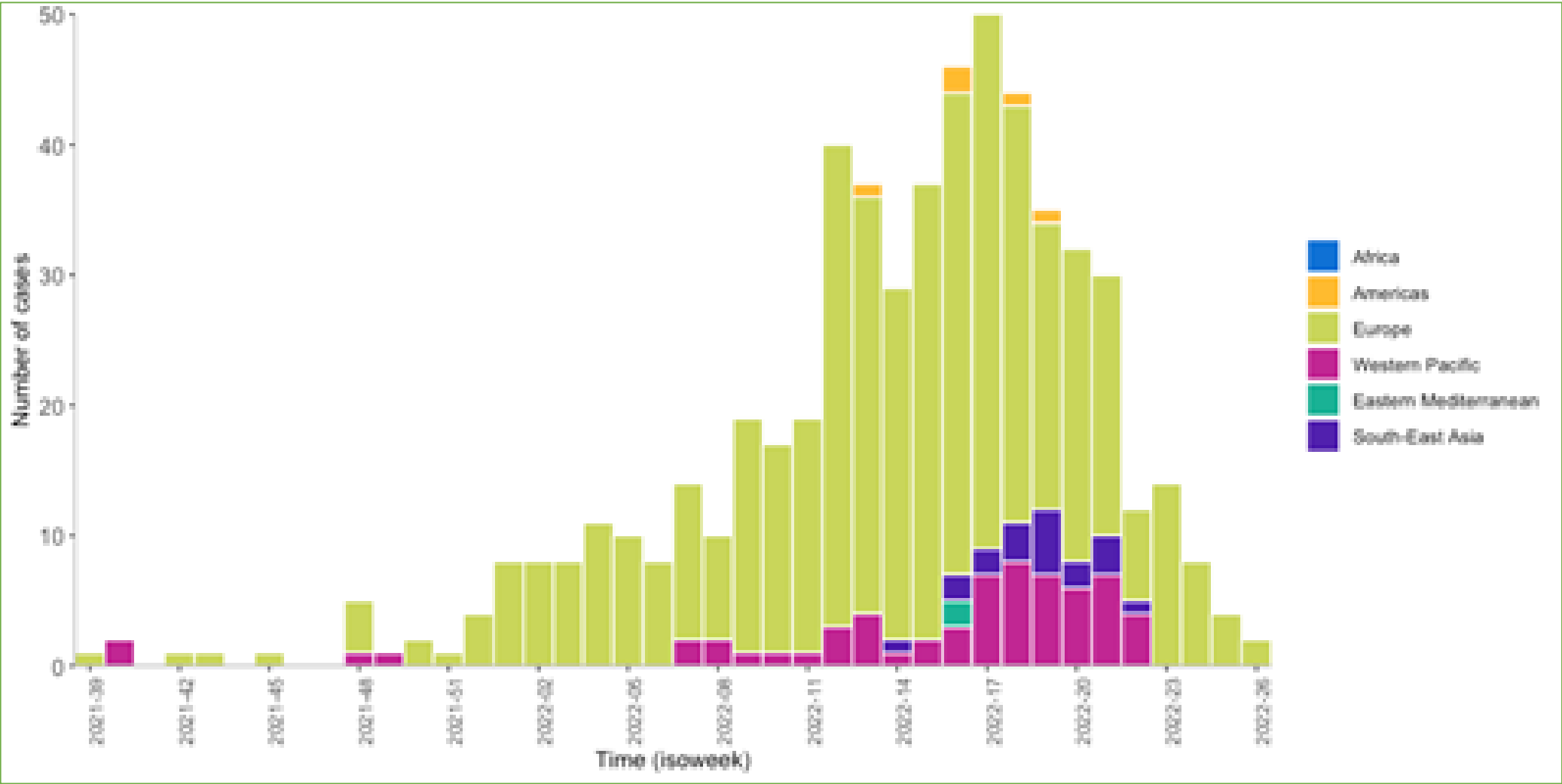
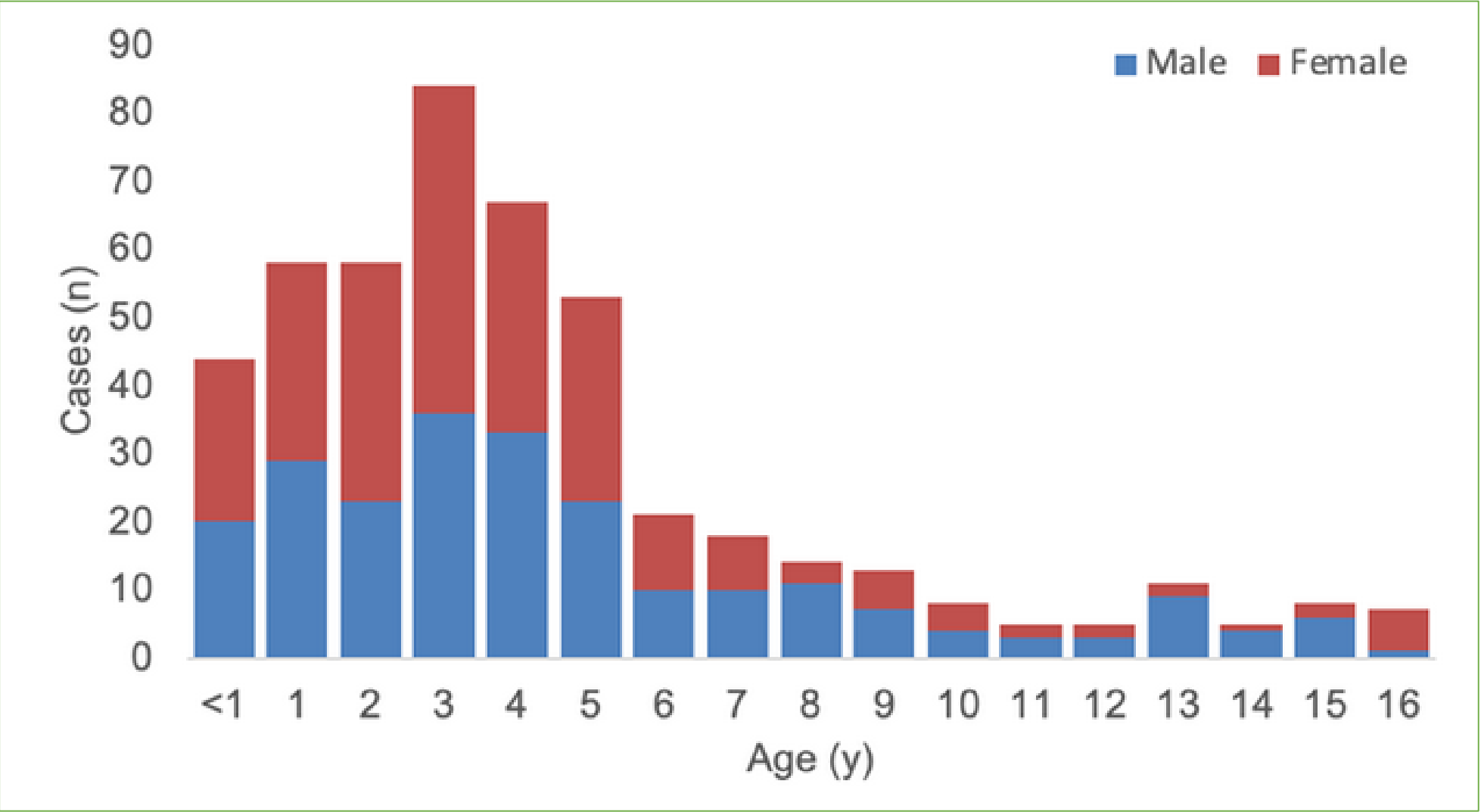


Figure includes cases for which dates of symptom onset, hospitalization, or notification were reported to WHO (n= 571). The date of symptom onset was used when available (n=384). If unavailable, the week of hospitalization (n=163), or the week of notification (n=24), was used. WHO World Health Organization (WHO) Multi-Country-Acute, Severe Hepatitis of Unknown Origin in Children. 2022. Jul 22

Age and gender distribution of reported probable cases of severe acute hepatitis of unknown aetiology with available data, as of 8 July 2022 (n=479)





Joint ECDC-WHO Regional Office for Europe Hepatitis of Unknown Origin in Children Surveillance Bulletin

30 September 2022

Case Definition

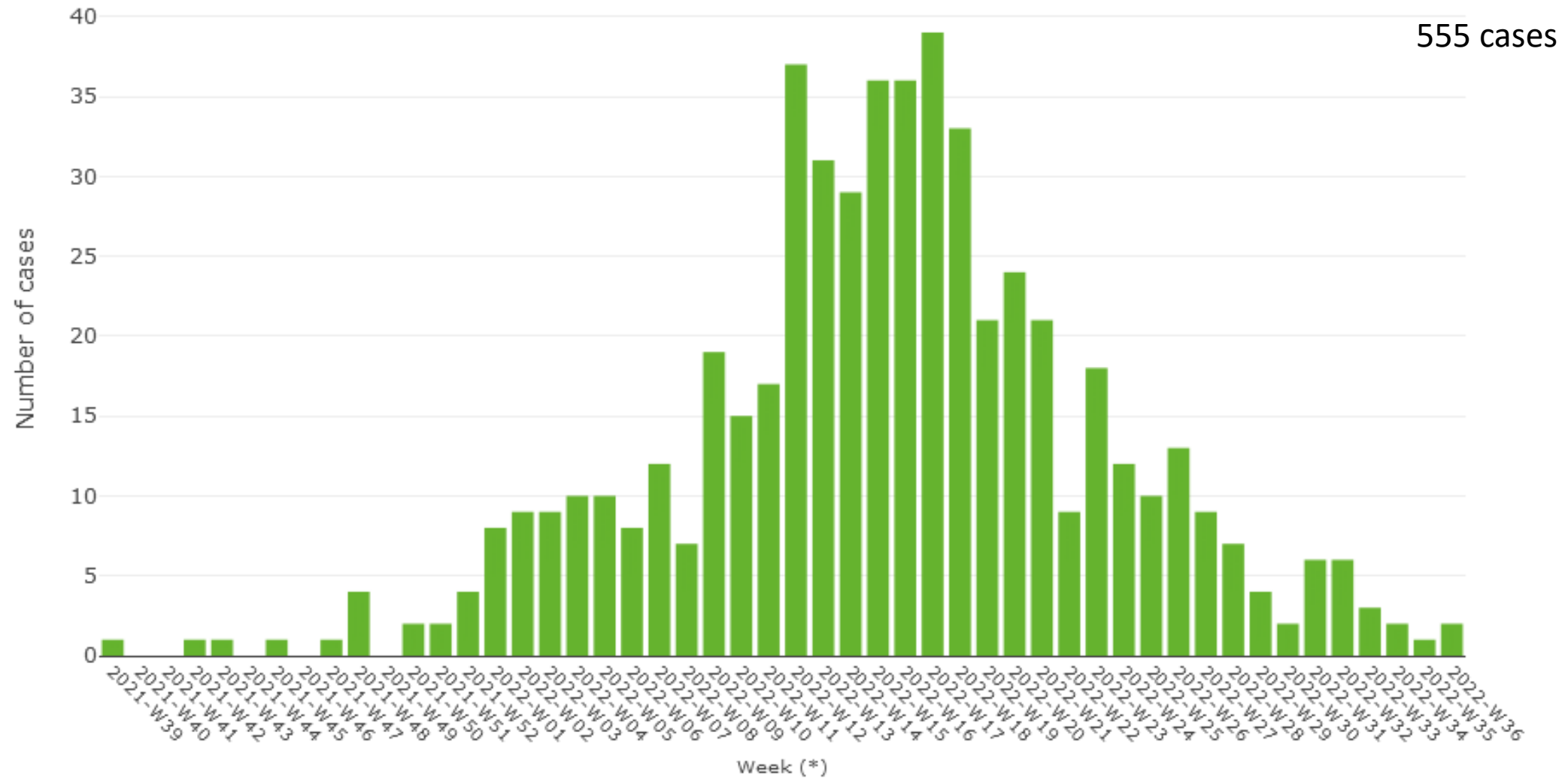
Cases of hepatitis of unknown origin should be reported to TESSy if they meet any of the following criteria:

- **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.
- **Epi-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.
- **Discarded:** A subject previously classified as case, that following further investigations did not meet the case definition criteria.

*Cases of hepatitis with known aetiology such those due to specific infectious diseases, drug toxicity, metabolic hereditary, or autoimmune disorders should not be reported under this protocol.

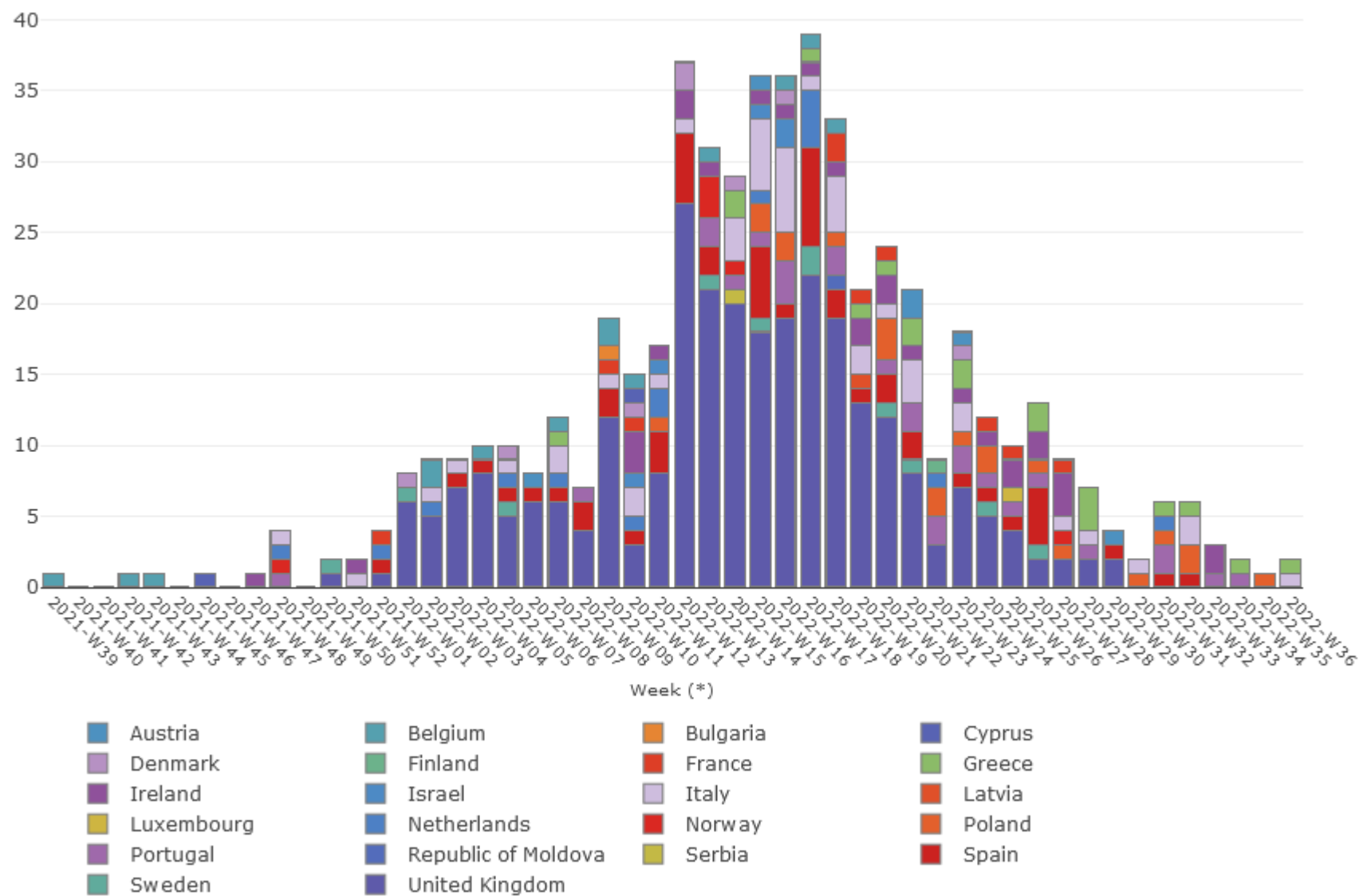
Note that the UK local case definition includes only cases younger than 16 years which means cases aged 16 years are not reported to TESSy from the UK.

Number of cases per week by date of onset of illness or date of hospitalisation



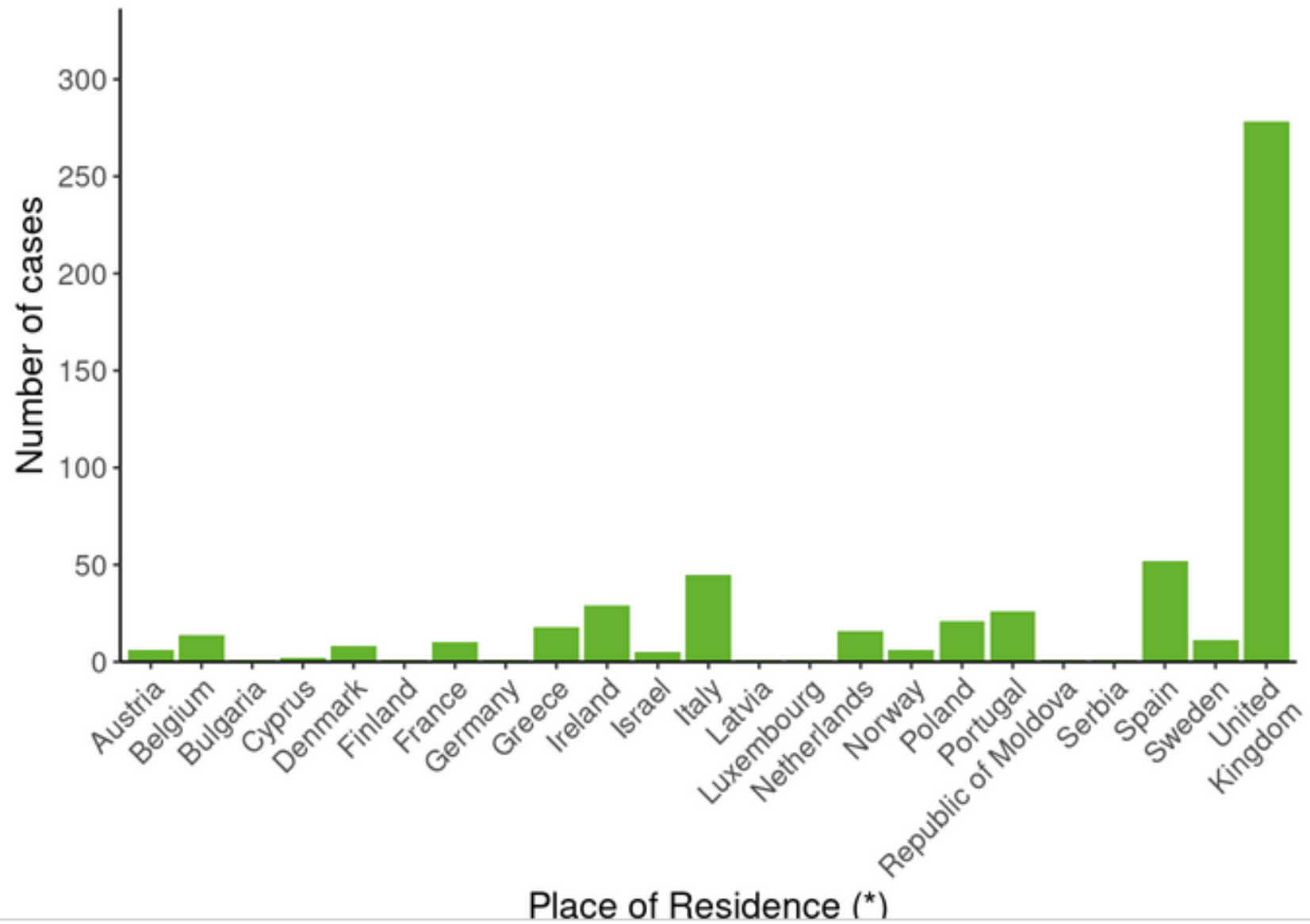
Information on date of onset of illness was available for 376 cases; the majority of cases (75,9%) are 5 years old or younger.

Number of cases per week by date of onset of illness or date of hospitalisation, and reporting country

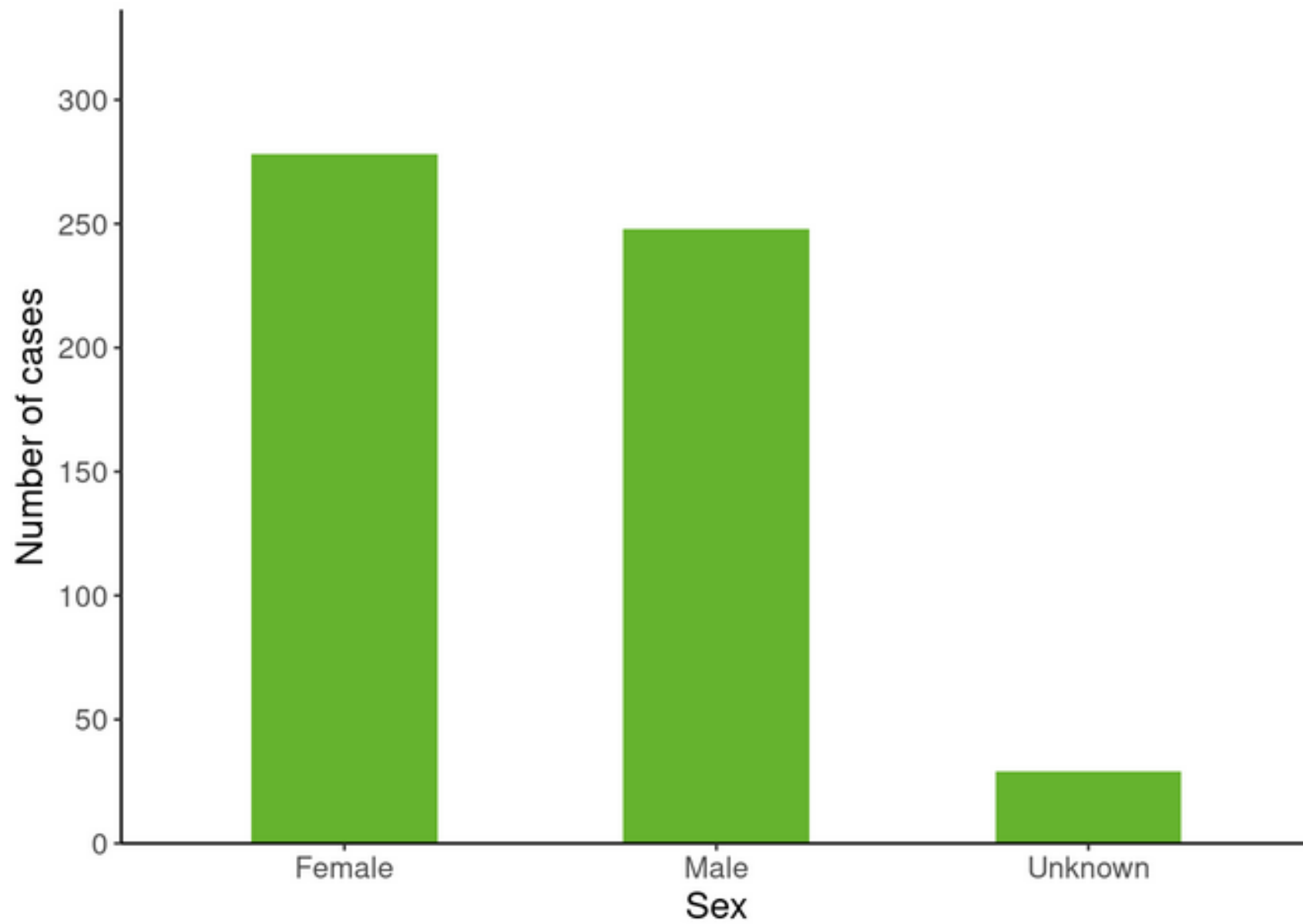


As of 30 September 2022, **555** cases of acute hepatitis of unknown aetiology have been reported by **22** countries: (Austria (6), Belgium (14), Bulgaria (1), Finland (1) Cyprus (2), Denmark (8), France (10), Greece (20), Ireland (26), Israel (5), Italy (45), Latvia (1), Luxembourg (1), the Netherlands (16), Norway (6), Poland (21), Portugal (26), Republic of Moldova (1), Serbia (1), Spain (52), Sweden (12), and the United Kingdom (278)).

Number of cases by place of residence (*)



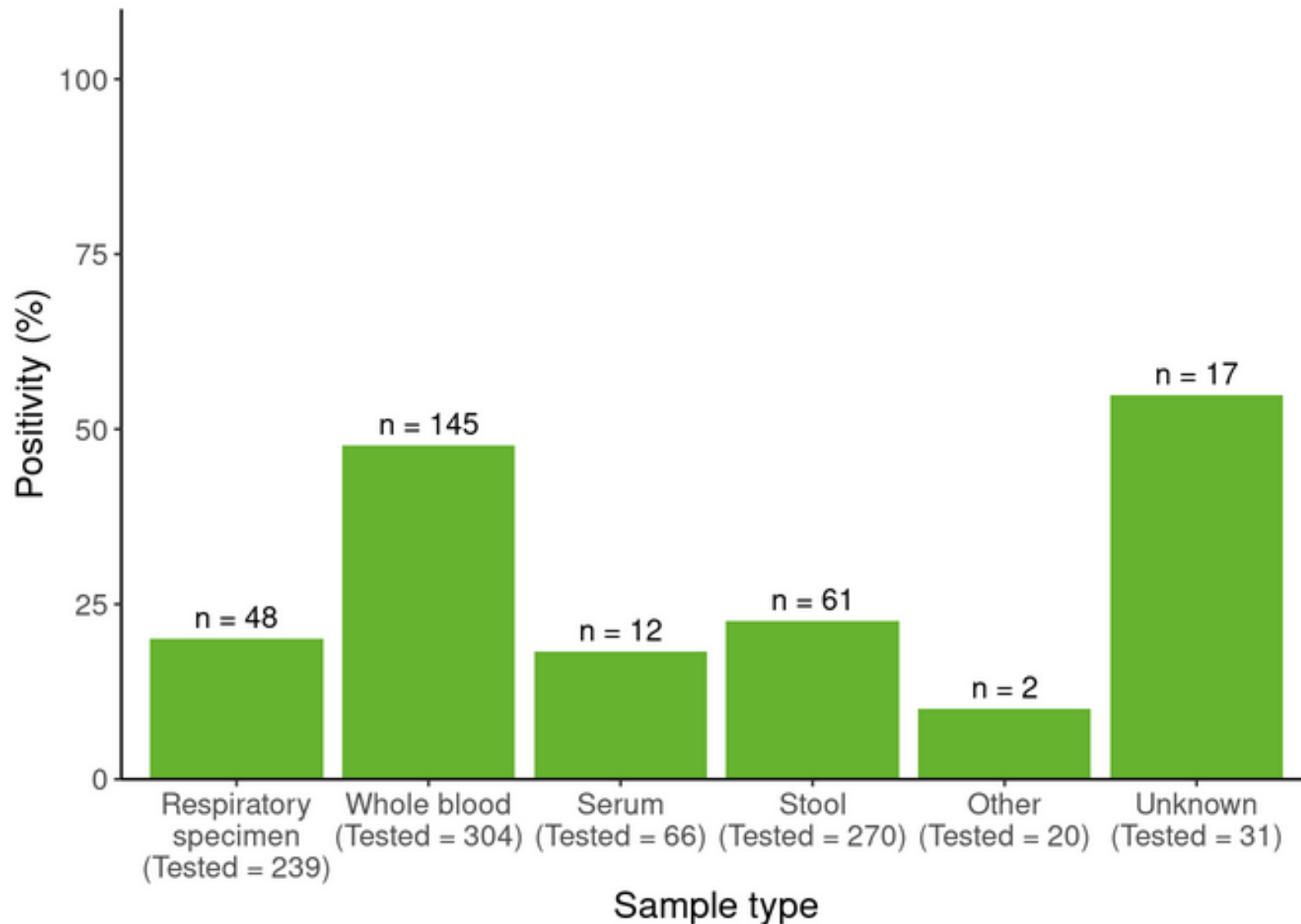
Number of cases by sex



Pathogens

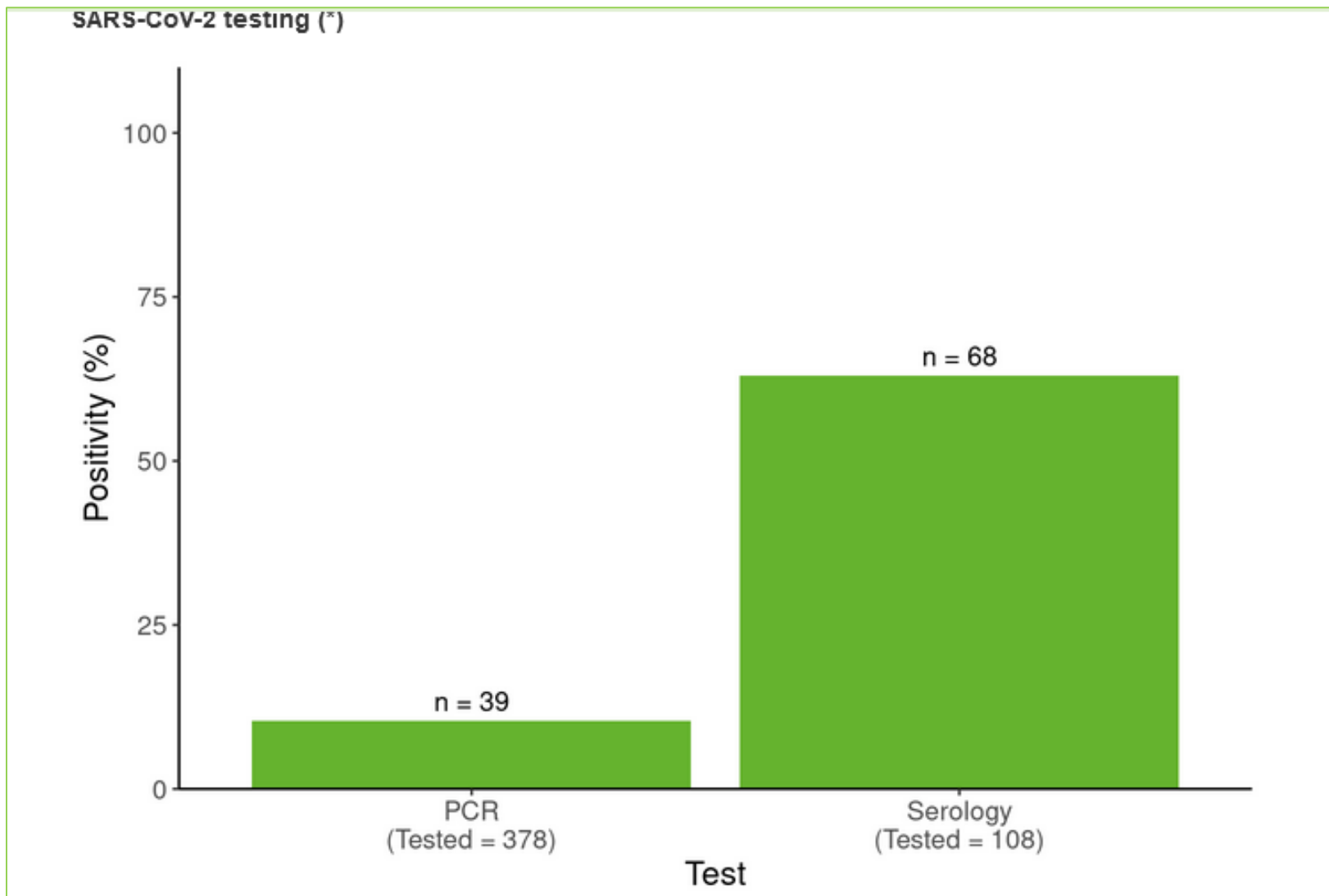
Tested	Positive	Negative	Indeterminate
SARS-CoV-2 (n = 353)	11.0% (n = 39)	88.7% (n = 313)	0.3% (n = 1)
CMV (n = 303)	8.3% (n = 25)	91.4% (n = 277)	0.3% (n = 1)
EBV (n = 268)	16% (n = 43)	83% (n = 222)	1% (n = 3)
Adenovirus (n = 404)	54% (n = 218)	46% (n = 186)	
HSV1 (n = 181)	1.7% (n = 3)	97.8% (n = 177)	0.6% (n = 1)
RSV (n = 164)	4% (n = 6)	96% (n = 158)	
Parvovirus (n = 136)	2% (n = 3)	98% (n = 133)	
HHV6 (n = 152)	18.4% (n = 28)	80.9% (n = 123)	0.7% (n = 1)
Influenzavirus (n = 124)	4% (n = 5)	96% (n = 119)	
HIV (n = 80)		100% (n = 80)	
Mycoplasma (n = 79)	3% (n = 2)	96% (n = 76)	1% (n = 1)
HHV7 (n = 109)	31% (n = 34)	69% (n = 75)	
Enterovirus (n = 91)	22% (n = 20)	78% (n = 71)	
Varicella (n = 68)	4% (n = 3)	96% (n = 65)	
Parainfluenza (n = 44)	11% (n = 5)	89% (n = 39)	
Leptospira (n = 35)		100% (n = 35)	
HPeV (n = 31)		100% (n = 31)	
Legionella (n = 19)		100% (n = 19)	
ASOT (n = 16)	6% (n = 1)	94% (n = 15)	
Bocavirus (n = 12)	8% (n = 1)	92% (n = 11)	

Adenovirus test positivity (*) by specimen type



435 cases were tested for adenovirus by any specimen type and had a valid positive or negative result. Of these, 231 (53,1%) tested positive. The positivity rate was the highest in whole blood specimens (49,8%).

Typing data are only available for eight cases: type 31 (n = 1), type 40 (n = 3), type 41 (n = 5), and type other (n = 2).



Of the 378 cases PCR tested for SARS-CoV-2, 39 (10,3%) were positive. Serology results for SARS-CoV-2 are only available for 106 cases, of which 67 (63.2%) resulted positive. Of the 159 cases with data on COVID-19 vaccination, 141 (88,7%) were unvaccinated.

(*) Positivity calculated using specimens for which the result is known.

SARS-CoV-2 PCR: Result of SARS-CoV-2 PCR taken after onset of hepatitis

SARS-CoV-2 serology: Result of SARS-CoV-2 serology during this episode of hepatitis (Positive = Positive unspecified/IgG/IgM detected).

Of the 67 children with a positive serology result, 19 (28.4%) had a positive result for adenovirus by any sample, and 46 (68.7%) also had a positive result for any other pathogen.

Clinical presentation- signs and symptoms

Be aware of the symptoms of liver inflammation, which include:

- fever
- fatigue
- loss of appetite
- nausea
- vomiting
- abdominal pain
- dark urine
- light-colored stools
- joint pain
- jaundice

Non-specific

Abdominal pain
Anorexia
Myalgia
Diarrhoea
Nausea
Fever
Respiratory symptoms

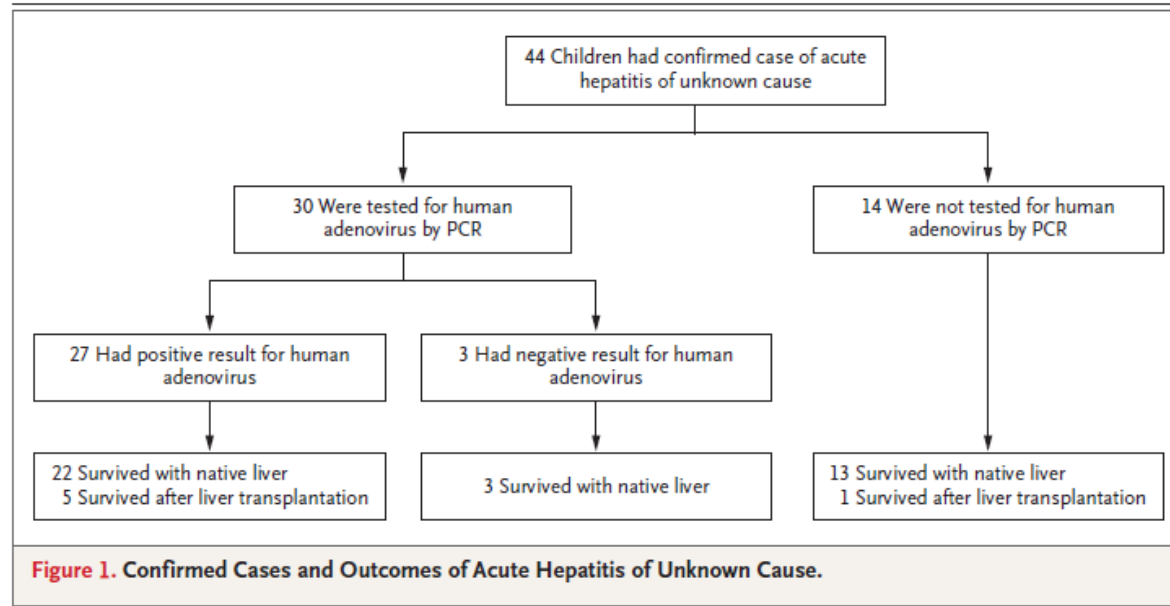
Cholestatic hepatitis

Jaundice
Dark urine
Pale stools
Pruritus

ORIGINAL ARTICLE

Clinical Spectrum of Children with Acute Hepatitis of Unknown Cause

Chayarani Kelgeri, M.D., Michael Couper, M.B., Ch.B., Girish L. Gupte, M.D., Alexandra Brant, M.Sc., Mitul Patel, M.D., Lauren Johansen, M.B., B.S., Joseph Valamparampil, M.D., Evelyn Ong, F.R.C.S., Hermien Hartog, Ph.D., M.T.P.R. Perera, M.D., Darius Mirza, M.S., F.R.C.S., Indra van Mourik, M.D.,



From January and April 2022 the number of children underwent liver transplatation were higher than the numbers in the previous years between 2012 and 2021

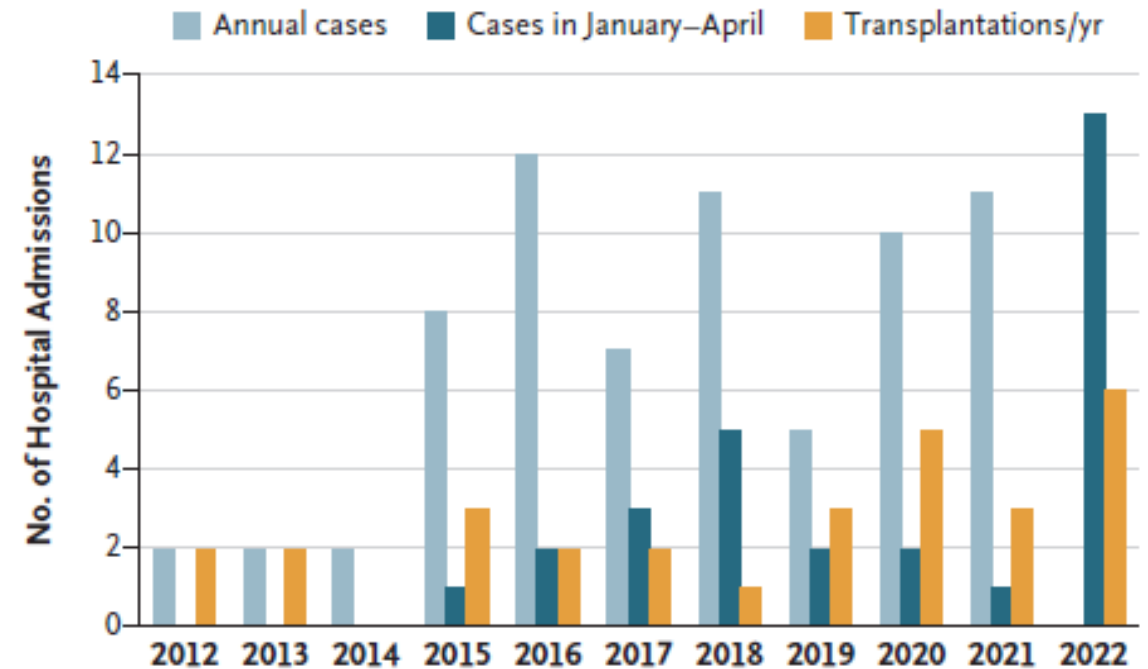


Figure 2. Hospital Admissions for Acute Hepatitis of Unknown Cause and Liver Transplantation for Acute Liver Failure of Unknown Cause.

Annual data from 2012 through 2021 and data for the months from January through April between 2012 and 2022 are shown. Data for transplantations in 2022 are for January 11 through April 11.

Case numbers of acute hepatitis of unknown aetiology among children in 24 countries up to 18 April 2022 compared to the previous 5 years

Van Beek, Eurosurveillance 2022

TABLE

Numbers of reported possible, probable, and severe cases of acute hepatitis of unknown aetiology among children aged 16 years and under, European (n = 17) and non-European (n = 7) countries, 1 January–18 April 2022

Country	Reporting hospitals (n = 52)	Possible cases (n = 49)	Probable cases (n = 111)	Possible or probable severe cases (n = 36)
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Survey ESPID in 52 Hospitals/ 24 Regions

Comparison unknown hepatitis during 2022 to the previous 5 years:

It has been reported increase in the number of probable cases in 6 regions (Italy, Spain, Sweden, UK, Ukraine and Israel) and significant increase of severe cases in 5 regions

Probable case numbers were elevated in 6 hospitals in Italy, Spain, Sweden, the UK, Ukraine, and Israel in 2022 compared with the previous years (of 20 hospitals with probable cases and data reported for previous years).

Severe cases (n = 36) were by 16 hospitals. Severe case numbers were elevated in five hospitals in Italy, Poland, Spain, Sweden, and the UK in 2022 compared with previous years (of 13 hospitals with severe cases and data reported for previous 5 years).



Kent

Cite this as: *BMJ* 2022;378:o1876

<http://dx.doi.org/10.1136/bmj.o1876>

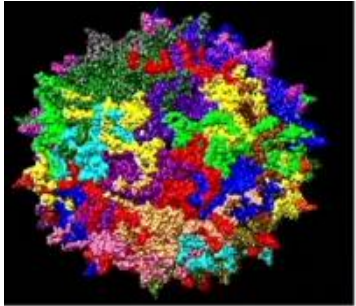
Published: 26 July 2022

Paediatric hepatitis is linked to infection with two viruses, studies find

Jacqui Wise

Glasgow Study

9 cases/58 controls



AAV2: adeno associated virus 2: member of parvovirus family

- upregulation of AAV2 due to adenovirus or to another viral infection
- upregulation of AAV2 due to liver injury

underdetermined role in the pathogenesis of the syndrome

- 89% of children with unknown hepatitis had differences in the human leucocyte antigen gene (DRB1 04:01) and this allele is found in only 16% of the general Scottish population

The gene encodes a receptor which presents viruses or other pathogens to the immune system and this suggests there may be a link to an immune cause of the hepatitis

This gene mutation was more commonly present in the Northern Europe and children with this mutation may be more susceptible to infection with AAV2 or adenovirus



Kent

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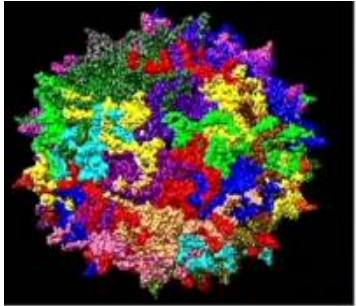
<http://dx.doi.org/10.1136/bmj.o1876>

Published: 26 July 2022

Paediatric hepatitis is linked to infection with two viruses, studies find

Jacqui Wise

Great Hormond Street Hospital and UCL Institute of Child Health

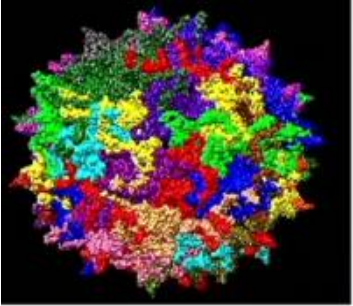


28 cases and 136 controls

High levels of AAV2 were detected In 5 of cases who underwent live transplatation and in 16/17 non transplanted cases

- AAV2 + human adenovirus may trigger unexplained pediatric hepatitis in children who are susceptible because of their HLA class II allele

Other Hypotesis



A normal adenovirus infection

-abnormal susceptibility or host response due to lack of exposure during Covid 19 infection

Or

- Abnormal suceptibility or host response due to Covid19 coinfection
- A novel variant adenovirus
- A post – infection SARS-CoV 2
- A drug, toxin exposure (no infectious causes)
- A new variant of Covid 19
- Co-infection with SARS-CoV2 or other pathogens



Red Book[®] Online

Red Book Online Outbreaks: Hepatitis Cases Possibly Associated with Adenoviral Infection

October 5, 2022

NASPGHAN/AASLD Guidance for Acute Hepatitis Outbreak in Children

Who to test: Determination of hepatitis requires review of routine laboratory tests to assess for the presence of liver injury. Symptoms are generally non-specific thus consideration for testing should be made for any child presenting with:

- Fever
- Fatigue
- Loss of appetite
- Nausea
- Vomiting
- Abdominal pain
- Dark urine
- Light-colored stools
- Easy bleeding/bruising

Special consideration should be made for patients with the following history or physical exam findings:

- Jaundice/scleral icterus
- Known sick contacts
- Recent overseas travel
- Enlarged liver or spleen
- Ascites
- Peripheral edema

What to test: Simple blood tests are all that are needed to diagnosis hepatitis. In addition, studies that reflect overall liver function, such as coagulation (blood clotting) studies, are often informative. The following tests should be considered in children in whom hepatitis is suspected:

- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- Bilirubin (both total and fractionated)
- Prothrombin time (PT) and International normalized ratio (INR)

When to re-test: Minor elevations in screening tests may be common and repeat bloodwork within a 3–5-day window should be carefully considered in any patient whose clinical symptoms persist. Worsening symptoms or any suggestion of clinical deterioration should prompt earlier testing and likely clinical evaluation by a healthcare provider. Importantly, in children <10 years of age in whom the ALT or AST is found to be elevated >500 IU/L, the CDC is currently recommending **specific testing for Adenovirus** (<https://www.cdc.gov/ncird/investigation/hepatitis-unknown-cause/hcp.html>), and this can be performed at the time of testing follow-up.



Red Flags and When to Refer: While acute hepatitis often resolves with supportive care, the clinical course can be dynamic, and clinicians should be cognizant of a potential for rapid deterioration. Consultation with a pediatric gastroenterologist or transfer to a Children's Hospital with a liver transplant program should be considered if:

- Any INR measurement ≥ 1.5
- Rising INR and bilirubin levels
- ALT > 500 IU/L
- Concerns for hepatic encephalopathy (sleepiness, fatigue, altered mental status)
- New onset jaundice or scleral icterus
- New onset easy bleeding or bruising



Istituto Superiore di Sanità

EpiCentro - L'epidemiologia per la sanità pubblica

Epatite virale

Definizione di caso

Secondo quanto riportato nella Circolare del 23 maggio 2022 del ministero della Salute, la definizione inizialmente adottata dall'ECDC e rispondente a quella utilizzata in UK, è stata rivista. Quella attualmente proposta dall'OMS-ECDC non include "casi confermati" e utilizza il limite di 16 anni e il periodo dal 1 ottobre 2021 come criteri per essere più sensibili nell'identificazione dei casi.

La definizione di caso in corso prevede i seguenti criteri:

- *Caso confermato*: non applicabile al momento.
- *Caso probabile*: soggetto di età ≤ 16 anni, che presenta un'epatite acuta (con test negativo ai virus dell'epatite A, B, C, D, E) e con aspartato aminotransferasi (AST) o alanina aminotransferasi (ALT) superiore a 500 U/L, dal 1° ottobre 2021.
- *Caso correlato epidemiologicamente*: soggetto di qualsiasi età che presenta un'epatite acuta (con test negativo ai virus epatici A, B, C, D, E) contatto stretto di un caso probabile, dal 1° ottobre 2021.

Ovviamente, la definizione di caso sarà aggiornata sulla base delle indicazioni dell'OMS-ECDC.

Sorveglianza nazionale

Fin dalle prime segnalazioni internazionali, il Ministero della Salute si è attivato per organizzare azioni di risposta, in coordinamento con l'Istituto Superiore di Sanità (ISS) e con le Regioni a livello nazionale e con ECDC e OMS a livello internazionale.

Le Regioni/P.A. sono state costantemente informate e aggiornate sulla situazione epidemiologica, sollecitate per la ricerca attiva dei casi sulla base delle definizioni di caso fornite dall'OMS.

È stata attivata la sorveglianza basata sugli eventi gestita dal Network Italiano di Epidemic Intelligence, istituito formalmente con la circolare del Ministero della Salute n. 0047345 del 19 ottobre 2021.

Inoltre, la rete SEIEVA (Sistema epidemiologico integrato delle epatiti virali acute), già attiva presso l'ISS in coordinamento con i referenti territoriali, è stata allertata e attivata per la raccolta dei dati epidemiologici e clinici delle epatiti acute, trasmessi poi al Ministero della Salute.

All'ISS è anche attiva la sorveglianza genomica SARS-CoV-2 per condividere i dati relativi al sequenziamento dei ceppi di SARS-CoV-2 dei casi pediatrici di epatite acuta grave a eziologia sconosciuta in cui dovesse essere confermata l'infezione. Questo per permetter di valutare meglio se l'infezione da SARS-CoV-2 sia un evento incidentale, dovuto alla alta circolazione del virus in Europa, o se debba essere considerata il fattore eziologico di queste forme di epatite.



L'epidemiologia per la sanità pubblica
Istituto Superiore di Sanità

Segnalazioni

Il Ministero della Salute, nella Circolare del 23 aprile 2022 e poi nella Circolare del 23 maggio 2022 sollecita la segnalazione di ogni eventuale caso di epatite acuta che risponda alla definizione di caso scrivendo una e-mail con oggetto "Segnalazione caso Epatite di origine sconosciuta" ai due indirizzi di posta elettronica:

- malinf@sanita.it (Direzione Generale della Prevenzione sanitaria, Ufficio 5 – Prevenzione delle Malattie Trasmissibili e Profilassi Internazionale, Ministero della Salute)
- epa2022@iss.it (Dipartimento di Malattie Infettive, ISS)

Al fine di uniformare la raccolta delle informazioni è stata predisposta un'apposita scheda di segnalazione ([Allegato 1 della Circolare del 23 maggio 2022](#), pdf 677 kb).

Conclusions

- ❑ The new cases of acute hepatitis of unknown origin are not a new clinical phenotype
- ❑ The temporal and geographical clustering suggests a possible epidemiological phenotype
- ❑ Adenovirus could have a role in the pathogenesis but still a cause-effect correlation should be demonstrated