INNOVAZIONE E RICERCA
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E DELLE
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FIRENZE
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GENNAIO
2023

L'epatite acuta del paziente pediatrico

9 gennaio 2023

Giuseppe Indolfi

Meyer

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Acute Hepatitis of Unknown Origin: the Outbreak

World Health Organization

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Home / Disease Outbreak News / Item / Acute hepatitis of unknown aetiology – the United Kingdom of Great Britain and Northern Ireland

Acute hepatitis of unknown aetiology – the United Kingdom of Great Britain and Northern Ireland

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15 April 2022

Situation at a glance:

On 5 April 2022, WHO was notified of 10 cases of severe acute hepatitis of unknown aetiology in children under the age of 10 years, across central Scotland. By 8 April, 74 cases had been identified in the United Kingdom. Hepatitis viruses (A, B, C, E, and D where applicable) have been excluded after laboratory testing while further investigations are ongoing to understand the aetiology of these cases. Given the increase in cases reported over the past one month and enhanced case search activities, more cases are likely to be reported in the coming days.

See all DONs related to this event

Read more about Hepatitis

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Acute Hepatitis of Unknown Origin: the Outbreak

WHO/ECDC Surveillance Summary (25 November 2022)

- 572 cases of acute hepatitis of unknown aetiology reported by 22 countries
    - 100 (27% of 371 cases with available information) admitted to ICU
    - 24 (7.5% of 320 cases with available information) received liver transplant
    - 7 (1.7% of 405 cases with available information) died

US CDC (17 August)

- 358 patients under investigation
    - 22 (6%) received liver transplant
    - 13 (4%) died

WHO (12 July)

- 1010 cases from 35 countries in five WHO Regions
    - 46 (5%) received liver transplant
    - 22 (2%) died

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Definitions

Acute hepatitis

inflammation of the liver biochemically characterized by the steep rise of aspartate aminotransferase(AST) and alanine aminotransferase (ALT)

Acute hepatitis of unknown aetiology

is a diagnosis of exclusion where known viruses (including but not limited to hepatitis A to E) and other aetiologies such as autoimmune, toxic and metabolic diseases have been excluded

Acute liver failure

INR ≥ 1.5 in encephalopathic patients or INR ≥ 2.0 in non-encephalopathic patients with no known evidence of chronic liver disease not improving on parenteral administration with vitamin K

Acute Hepatitis of Unknown Origin and ALF

- In children presenting with acute liver failure acute hepatitis of unknown origin is responsible for **45-50%** of the cases

- Acute hepatitis of unknown aetiology can be associated with a high mortality and needs urgent referral to a specialist service with access to liver transplantation

WHO/ECDC Case definition hepatitis of unknown origin

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

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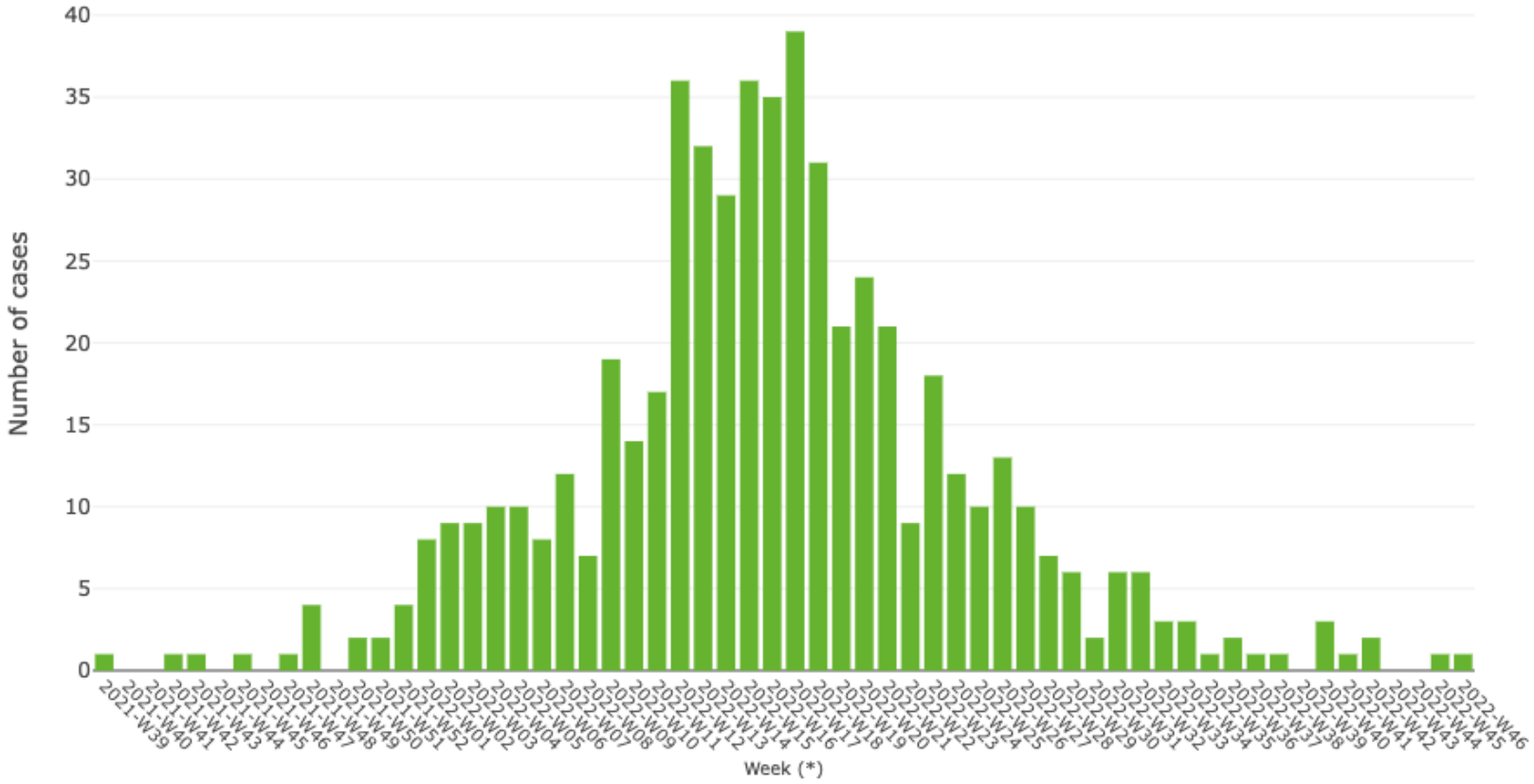
Epidemic curve by date of onset of symptoms or date of hospitalisation, reported from countries in the WHO European region as of 24 November, 2022



Source: Cases reported from countries in the WHO European region according to the WHO/ECDC case definition to the ECDC European Monitoring System (TESSy)*. Note that the UK local case definition includes only cases younger than 16 which means cases aged 16 are unlikely to be reported to TESSy from the UK

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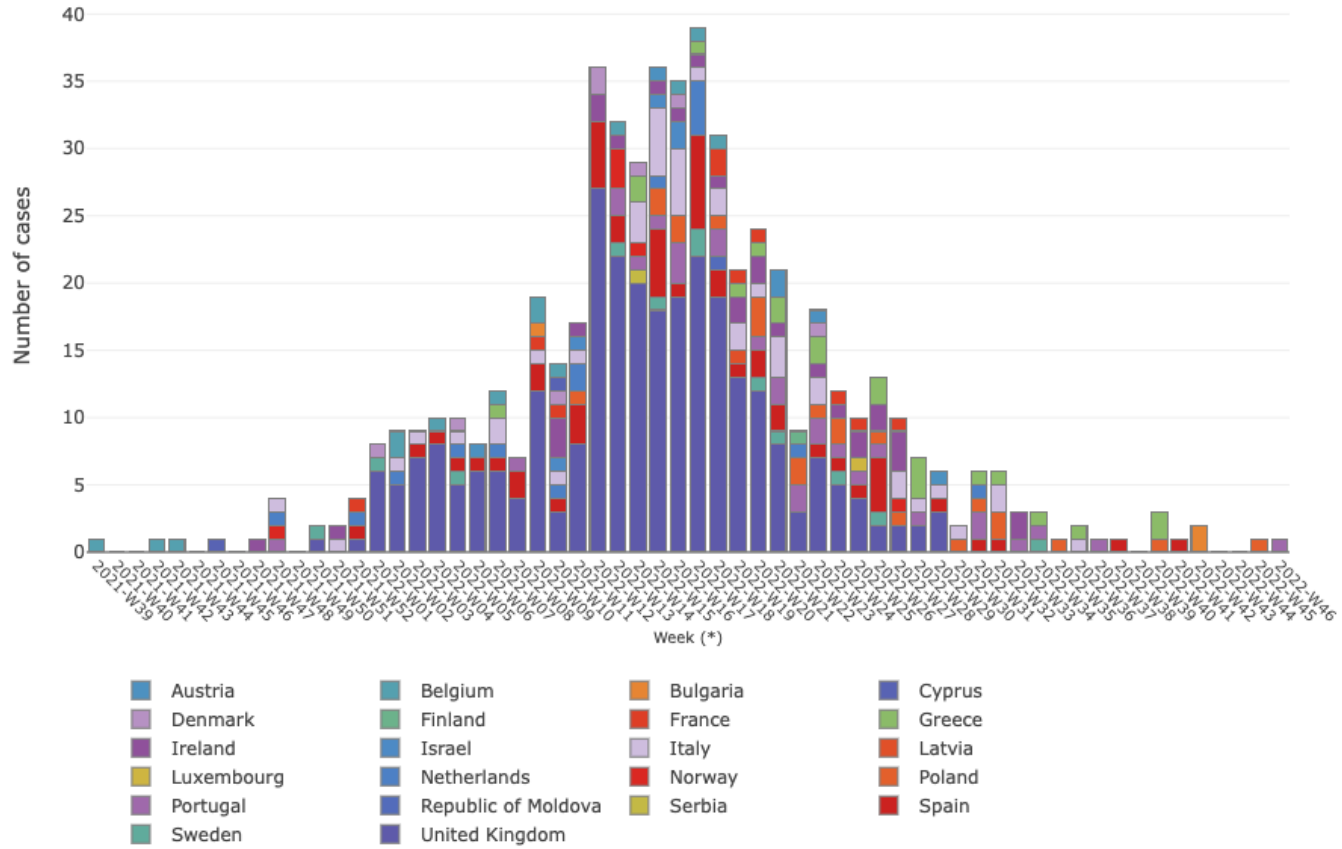
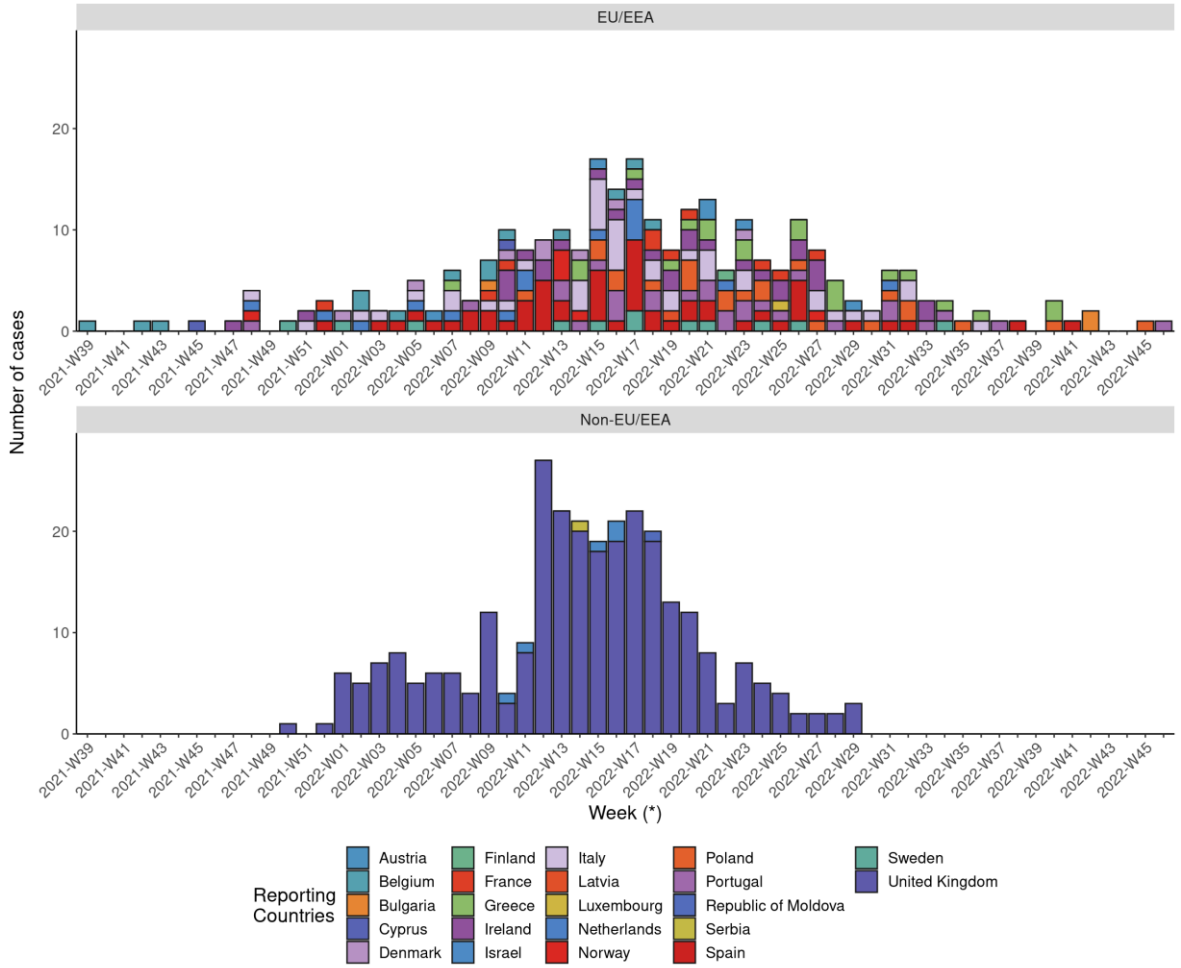
Epidemic curve by country in WHO European region, as of 24 November 2022



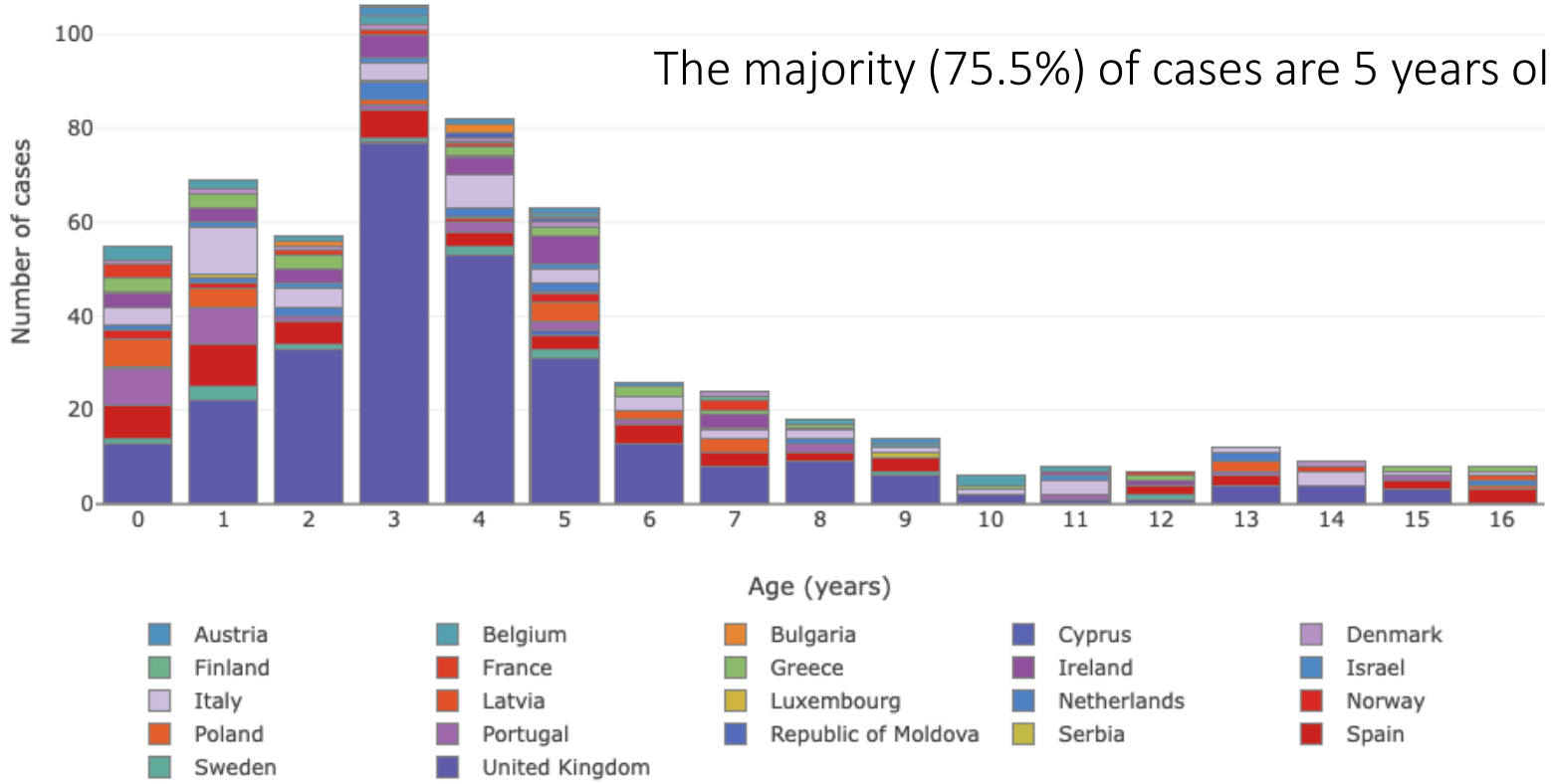
Source: Cases reported from countries in the WHO European region according to the WHO/ECDC case definition to the ECDC European Monitoring System (TESSy)*. Note that the UK local case definition includes only cases younger than 16 which means cases aged 16 are unlikely to be reported to TESSy from the UK

Epidemic curve by area, as of 24 November 2022



Source: Cases reported from countries in the WHO European region according to the WHO/ECDC case definition to the ECDC European Monitoring System (TESSy)*. Note that the UK local case definition includes only cases younger than 16 which means cases aged 16 are unlikely to be reported to TESSy from the UK

Number of cases by age in years, reported from countries in the WHO European region as of 24 November, 2022



Source: Cases reported from countries in the WHO European region according to the WHO/ECDC case definition to the ECDC European Monitoring System (TESSy)*. Note that the UK local case definition includes only cases younger than 16 which means cases aged 16 are unlikely to be reported to TESSy from the UK

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RAPID COMMUNICATION

Investigation into cases of hepatitis of unknown aetiology among young children, Scotland, 1 January 2022 to 12 April 2022

Kimberly Marsh[1,*], Rachel Tayler[2,*], Louisa Pollock[3], Kirsty Roy[1], Fatim Lakha[1], Antonia Ho[4], David Henderson[1], Titus Divala[1], Sandra Currie[1], David Yirrell[1], Michael Lockhart[1], Maria K. Rossi[1], Nick Phin[1]

1. Public Health Scotland, Glasgow, United Kingdom
2. Department of Paediatric Gastroenterology, Hepatology and Nutrition, Royal Hospital for Children, Glasgow, Glasgow, United Kingdom
3. Department of Paediatric Infectious Diseases and Immunology, Royal Hospital for Children, Glasgow, United Kingdom
4. Medical Research Council-University of Glasgow Centre for Virus Research, Glasgow, United Kingdom

- 9 children
- age median 3.9 years

Before admission

- diarrhoea and vomiting (4/4)

At admission

- jaundice (8/9)
- abdominal pain (7/9)
- nausea and malaise (6/9)
- fever not reported

- transaminases > 2,000 IU/L

Euro Surveill 2022;27:2200318

UK Health Security Agency

Age «predominantly» < 5 years

144 cases

- jaundice 68.8%
- vomiting 57.6%

At presentation

- diarrhoea 43.1%
- nausea 25.7%
- abdominal pain 36.1%
- lethargy 48.6%
- fever 28.5%
- respiratory symptoms 18.1%

Update July 2022

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ORIGINAL ARTICLE

A Case Series of Children with Acute Hepatitis and Human Adenovirus Infection

L. Helena Gutierrez Sanchez, M.D., Henry Shiau, M.D., Julia M. Baker, Ph.D., Stephanie Saaybi, M.D., Markus Buchfellner, M.D., William Britt, M.D., Veronica Sanchez, Ph.D., Jennifer L. Potter, M.P.H., L. Amanda Ingram, M.P.H., David Kelly, M.D., Xiaoyan Lu, M.S., Stephanie Ayers-Millsap, M.P.H., Wesley G. Willeford, M.D., Negar Rassaei, M.D., Julu Bhatnagar, Ph.D., Hannah Bullock, Ph.D., Sarah Reagan-Steiner, M.D., Ali Martin, B.S., Michael E. Rogers, D.O., M.P.H., Anna M. Banc-Husu, M.D., Sanjiv Harpavat, M.D., Ph.D., Daniel H. Leung, M.D., Elizabeth A. Moulton, M.D., Ph.D., Daryl M. Lamson, B.S., Kirsten St. George, Ph.D., Aron J. Hall, D.V.M., Umesh Parashar, M.D., Adam MacNeil, Ph.D., Jacqueline E. Tate, Ph.D., and Hannah L. Kirking, M.D.

- October 1, 2021, and February 28, 2022
- 15 children with acute hepatitis
  - 6 (40%) hepatitis with an identified cause
  - **9 (60%) hepatitis without a known cause**
    - **8 (89%) tested positive for human adenovirus**
- median age 2 years 11 months (range, 1 - 6 years)
- before admission
  - diarrhoea (6/9) and vomiting (7/9)
  - upper respiratory symptoms (3/9)
- 3 acute liver failure (2 transplanted)

Clinical characteristics	
Reported symptoms at admission — no. (%)	
Emesis	7 (78)
Diarrhea	6 (67)
Fever	5 (56)
Fatigue	4 (44)
Upper respiratory symptoms‡	3 (33)
Poor appetite	3 (33)
Dark urine	2 (22)
Findings on initial physical examination — no. (%)	
Scleral icterus	8 (89)
Hepatomegaly	7 (78)
Jaundice	6 (67)
Hepatic encephalopathy	1 (11)
Splenomegaly	1 (11)
Ascites	0

Median liver-function measures at admission (range)§	
ALT — U/liter	1724 (602–4696)
AST — U/liter¶	1963 (447–4000)
Total bilirubin — mg/dl	7.0 (0.2–13.5)
INR	1.2 (1.0–7.3)
Ammonia — μmol/liter	73 (49–85)
Median peak liver-function measures (range)§	
ALT — U/liter	1724 (602–4696)
AST — U/liter	1963 (447–4000)
Total bilirubin — mg/dl	7.0 (0.2–28.8)
INR	1.3 (1.1–9.1)
Ammonia — μmol/liter	64 (49–210)

- The median human adenovirus viral load at admission was lower among patients without acute liver failure than among those with acute liver failure (9262.5 vs. 55,340 copies per milliliter)

N Engl J Med 2022;387:620-630

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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., Khalid Sharif, F.R.C.S., F.C.P.S., and Jane Hartley, M.Med.Sc., Ph.D.

- January 1 - April 11 2022
- 44 children < 10 years of age (median 4; range, 1 to 7)

- the children came to medical attention because of **jaundice**
- other features were present at a median of 3 days

(range, 0 to 42) before the onset of jaundice

- 27/30 (90%) tested positive (PCR) for **human adenovirus**
- median viral load **2733 copies/mL** in the 22 children who did not undergo transplantation versus **20,772 copies/mL** in the 5 who did undergo transplantation

- 6 fulminant liver failure received a liver transplant

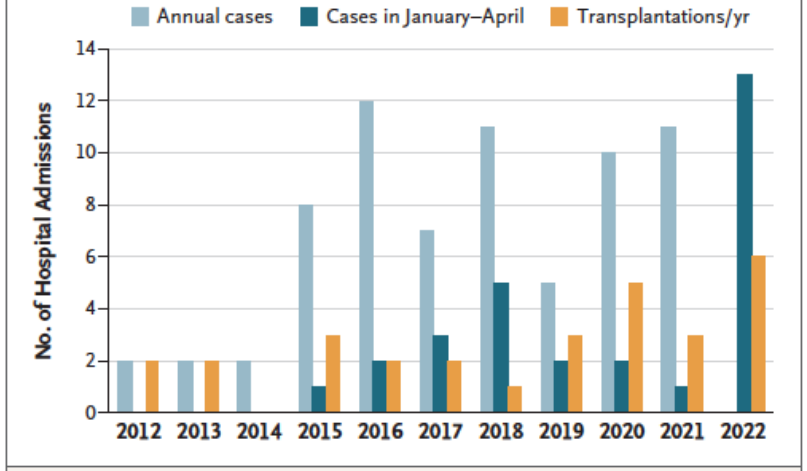

Figure 2. Hospital Admissions for Acute Hepatitis of Unknown Cause and Liver Transplantation for Acute Liver Failure of Unknown Cause.

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.

Table 1. Presenting Symptoms and Ultrasonographic Findings.

Symptom or Finding	All Children (N=44)
	no. (%)
Presenting features	
Jaundice	41 (93)
Vomiting	24 (54)
Diarrhea	14 (32)
Pale stools	13 (30)
Abdominal pain	12 (27)
Lethargy	10 (23)
Dark urine	6 (14)
Coryza	6 (14)
Pyrexia	4 (9)
Pruritus	1 (2)

N Engl J Med 2022;387:611-619

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Table 2. Demographic and Clinical Characteristics of the Patients.*

Variable	Total Cohort (N=44)	Children Who Did Not Undergo Transplantation (N=38)	Children Who Underwent Transplantation (N=6)	Normal Range
Median age (range) — yr	4 (1–7)	4 (1–7)	2 (1–4)	
Sex — no. (%)				
Female	24 (55)	21 (55)	3 (50)	
Male	20 (45)	17 (45)	3 (50)	
Median white-cell count (range) — per mm^3†	9000 (5000–15,000)	8000 (5000–15,000)	10,000 (8000–12,000)	5000–16,000
Median serum bilirubin level (range) — mg/dl				
At presentation	5.8 (0.3–10.6)	5.4 (0.3–10.6)	7.6 (6.9–9.4)	0–1
Peak	8.2 (0.3–17.1)	5.4 (0.3–14.8)	15.8 (11.4–17.1)	0–1
Median alanine aminotransferase level (range) — IU/liter				
At presentation	2558 (53–5897)	2476 (53–5086)	2978 (1798–5897)	0–41
Peak	2858 (603–6279)	2694 (603–5086)	3410 (2819–5897)	0–41
Median γ-glutamyl transferase level (range) — IU/liter‡	122 (25–348)	126 (25–348)	116 (59–165)	0–25
Median serum albumin level (range) — g/liter‡	36 (27–43)	36 (27–43)	35 (31–38)	41–52
Median prothrombin time (range) — sec				
At presentation	14.0 (12.0–28.0)	13.2 (12.0–19.2)	16.6 (15.3–28.0)	9–13
Peak	14.2 (13.0–86.0)	13.7 (15.0–19.2)	50.0 (36.0–86.0)	9–13

N Engl J Med 2022;387:611-619

Histopatology

Alabama

- 6 liver biopsies
- various degrees of hepatitis
- no viral inclusions, immunohistochemical evidence of adenovirus, or viral particles by electron microscopy

Birmingham

- 6 explanted livers and 3 liverbiopsy specimens
- distorted architecture
- mild to diffuse inflammation
- Appropriately sized bile ducts
- hepatocyte ballooning, canalicular cholestasis, and scattered apoptotic bodies

UK Health Security Agency

- 6 explanted livers, 8 biopsies
- non specific pattern (from mild hepatocellular injury to massive necrosis)
- adenovirus immunohistochemistry in the intrasinusoidal lumen (and not in hepatocytes) in 9/14

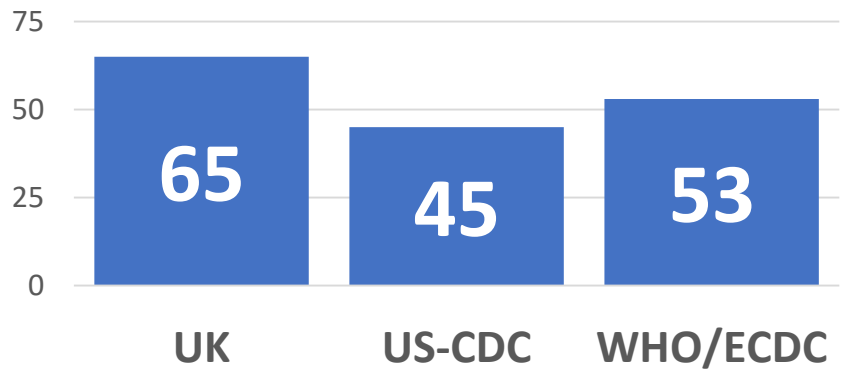
King's (Intensive Care Unit Patients)

- 6 explanted livers
- adenovirus immunostaining negative (6/6)
- portal and perisinusoidal fibrosis (2/6)
- inflammation and necrosis (various degree: moderate, moderate severe)

Aetiology

- temporal and geographical clustering
- non specific prodromal signs and symptoms

adenovirus



UK Health Security Agency update 28 July;
US-CDC Technical report update 17 Aug
www.ecdc.europa.eu/en/hepatitis/joint-weekly-hepatitis-unknown-origin-children-surveillance-bulletin update 30 Sept

SARS-CoV-2 PCR

- 34/196 (17%) UK
- 39/378 (10.3%) WHO/ECDC

SARS-CoV-2 Serology

- 68/108 (63%) WHO/ECDC

Adeno-associated virus 2

Pegivirus

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Comparison of data UK vs other countries in WHO European region, as of 16 June 2022

	UK	Other European countries	P-value
Age 0-5 years	85.9%	80.6%	0.16
ICU/HDU admission	53%	8%	<0.001
Adenovirus infection (all samples)	63.6%	35.3%	p < 0.001

Euro Surveill 2022 Aug;27(31):2200483

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Pathogenesis

Exposure

1. Do some children, due to age or other factors, exhibit an atypical response to their first adenovirus (or other viral) infection, which results in hepatitis?

Return to regular activities may have resulted in a larger than usual number of first infections, and at an older age than usual

"Pathogen –specific/immune related"

2. Is acute hepatitis in children due to a combination of persistent or prior infection with SARS-CoV-2 (or other viruses) and adenovirus, causing an autoimmune phenomenon or superantigen reaction?

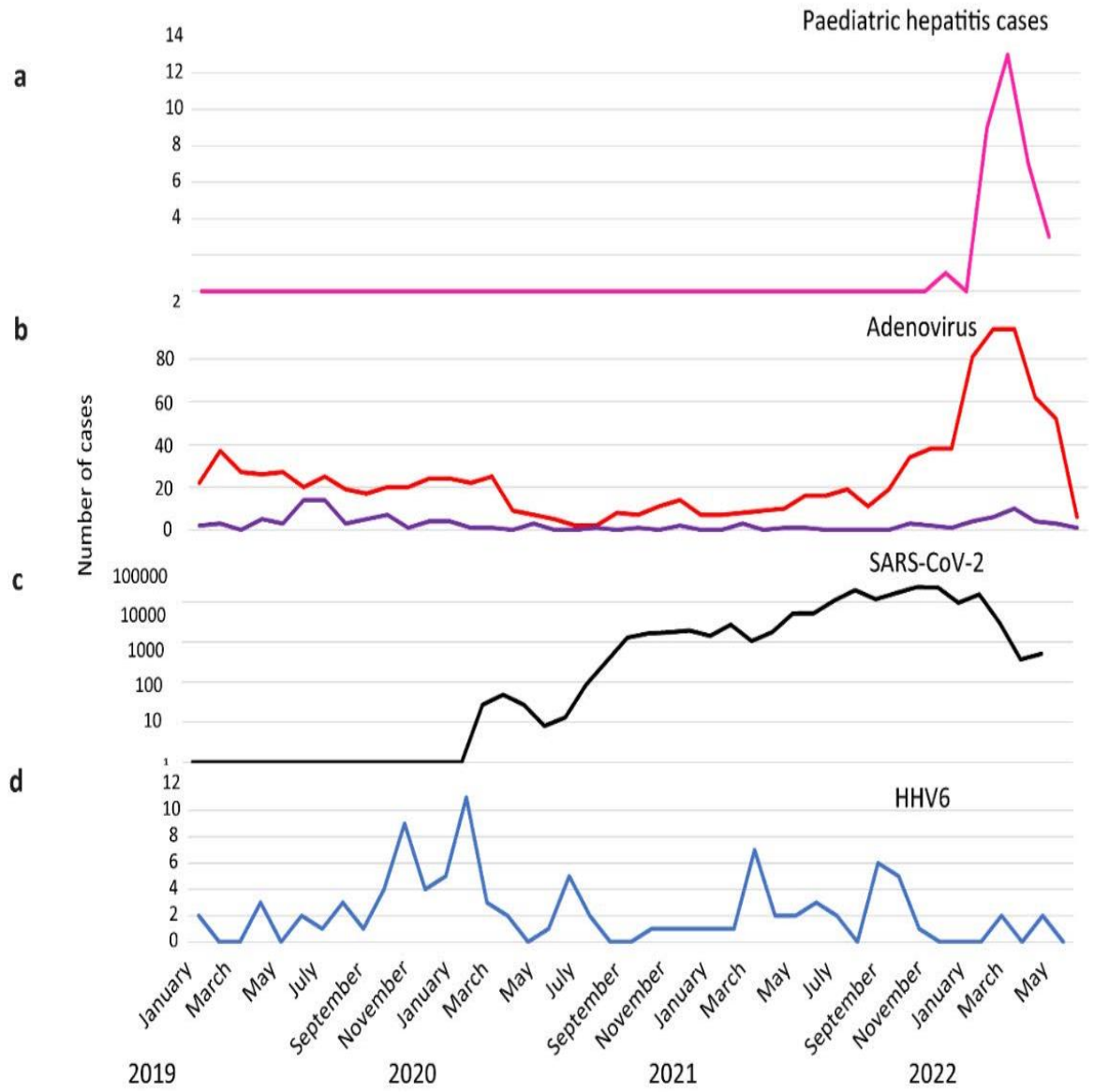
Prevalence of an active SARS-CoV-2 infection is ~10% among persons under investigations for whom data is available, and up to 1/3 report history of prior COVID-19 infection.

"Multifactorial"

2. Are multiple factors contributing to the illnesses seen among reported persons under investigations, as opposed to one primary driver?

30–50% of liver failure in children is idiopathic; there are multiple known and unknown pathways to acute liver failure in children.

Exposures



Ho A, NEJM 2023, in press

The Glasgow study

Metagenomic and target enrichment sequencing and real-time PCR on all samples

- plasma (n=9), liver biopsies (n=4), throat swabs (n=6), faecal samples (n=7) and a rectal swab (n=1), obtained between 7 to 80 days from initial symptom onset

The most frequently detected viral genomes

- Adeno-associated virus-2 (AAV2) in 9/9 patients and in NONE of the 12 controls (adenovirus + but no hepatitis)
- Adenovirus-F41 or -C in 6/9 patients – low reads
- HHV6-B at low level in the liver biopsy samples of 2/4 and 3/4 but in 0/9 in plasma
- 6/9 (67%) of the children displayed evidence of prior exposure to SARS-CoV-2

Ho A, NEJM 2023, in press

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The Glasgow study

HLA typing

- allele positivity in the nine cases plus an additional 11 ISARIC CCP-UK study patients
- compared to 64 Scottish platelet apheresis donor controls

DRB1*04:01 is the primary HLA associated allele

- In patients the frequency was 0.50 vs 0.078 in local controls
- In 599,410 British/Irish North-West European (BINWE) on the Anthony Nolan register, the frequency of DRB1*04:01 is 0.114.10
- Of the nine patients: **8/9 carried the HLA-DRB1*04:01** and 1/9 carried the DRB1*04:07

T helper cell-mediated pathological response triggered by exposure to adenovirus and/or AAV2 infection

Adenovirus related pathology and AAV2 a biomarker of adenovirus infection

SARS-CoV-2 related post infectious pathology

Ho A, NEJM 2023, in press

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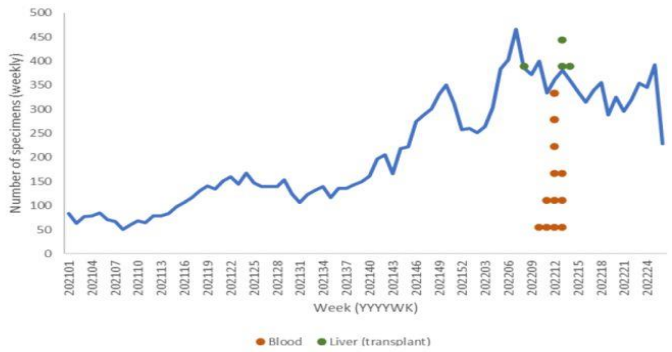
The London study

A



B

Cases	**Liver (n=5)** 5 Birmingham Children's Hospital (received liver transplants)	**Blood (n=17)** 11 UKHSA 5 Glasgow Royal Infirmary 1 NHS Lothian	**Stool (n=5)** 3 Glasgow Royal Infirmary 1 NHS Lothian 1 UKHSA	**Respiratory (n=4)** 2 University Hospital Wales 1 UKHSA 1 Glasgow Royal Infirmary
Controls	**GOSH Blood (n=32)** 1 AdV and CMV, raised ALT 16 AdV, raised ALT 1 CMV and EBV, raised ALT 3 CMV, raised ALT 4 EBV, raised ALT 1 HHV6, raised ALT 1 PIMS-TS 5 SARS-CoV-2 **UKHSA Blood (n=1)** 1 HLH	**PERFORM/ DIAMONDS Blood (n=100)** 24 Non-infectious 20 Critical Illness, raised ALT 18 AdV, normal ALT 14 Non-AdV, raised ALT 8 AdV, normal ALT (blood) 8 Other hepatitis 6 AdV, raised ALT 2 AdV CovidMisC, normal ALT	**GOSH Liver (n=4)** **UKHSA Stool (n=22)** **GOSH Stool/Urine (n=11)** 10 stool 1 urine **NHS Lothian Stool (n=1)**	

C

	Metagenomics		PCR			Whole genome sequencing		
Cases	**DNA (n=10)** 5 liver 5 blood	**RNA (n=7)** 4 liver 3 blood	**AAV2 (n=19)** 11 blood 5 liver 1 stool 2 respiratory	**AdV (n=24)** 15 blood 5 liver 1 stool 3 respiratory	**HHV6 (n=14)** 6 blood 5 liver 1 stool 2 respiratory	**AAV2 (n=17)** 10 blood 4 liver 1 stool 2 respiratory	**AdV (n=16)** 10 blood 4 stool 2 respiratory	**HHV6 (n=4)** 4 liver
Controls			**AAV2 (n=136)** 132 blood 4 liver	**AdV (n=33)** 29 blood 4 liver	**HHV6 (n=34)** 30 blood 4 liver	**AAV2 (n=6)** 4 blood 2 stool	**AdV (n=35)** 1 blood 33 stool 1 urine	

Morfopoulou, NEJM 2023, in press

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The London study

Extensive investigation of 28 cases and 136 control subjects

- Adeno-associated virus-2 (AAV2) present in 94% (16/17) of cases (high viral loads in 91%)
- AAV2 was present less commonly and at much lower titres in controls (6% of 100 immunocompetent and 31% of 32 immunosuppressed controls)
- No evidence by electron microscopy, immunohistochemistry or proteomics of adenovirus or AAV2 viral particles or proteins in explanted livers

Morfopoulou, NEJM 2023, in press

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The London study

- Adeno-associated virus-2 (AAV2) at high titre in blood or liver tissue, a biomarker for cases of unexplained hepatitis?
- Adenovirus-F41 a necessary but not sufficient for development of the unexplained hepatitis
- Hepatic pathology is not due to direct lytic infection by either virus
- High expression of Class II HLA alleles in transplanted cases; increased genetic risk

Adenovirus-F41 outbreaks that followed lifting of restrictions may also have resulted in AAV2 infection, with either or both viruses triggering an immune-mediated hepatitis in genetically susceptible children

Morfopoulou, NEJM 2023, in press

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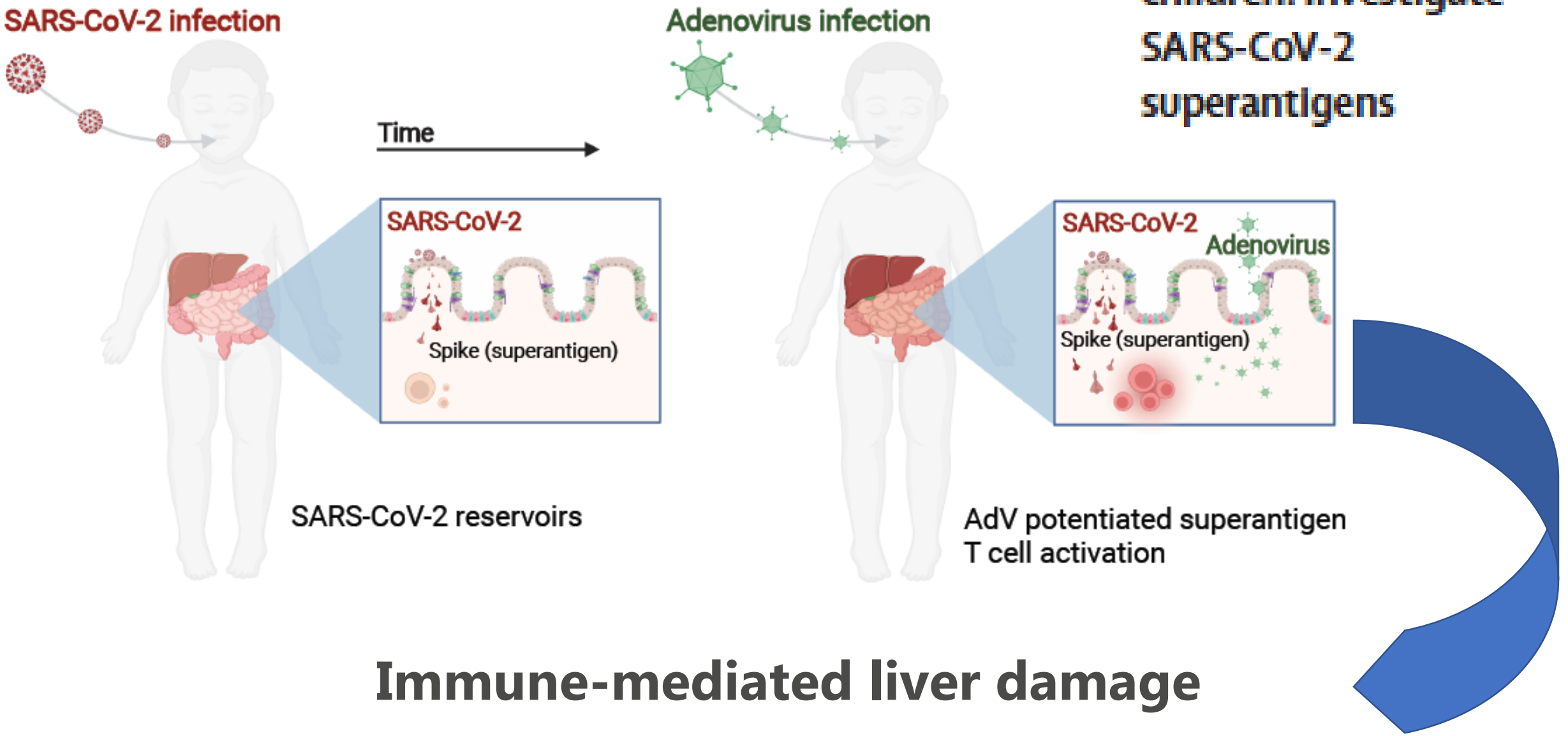
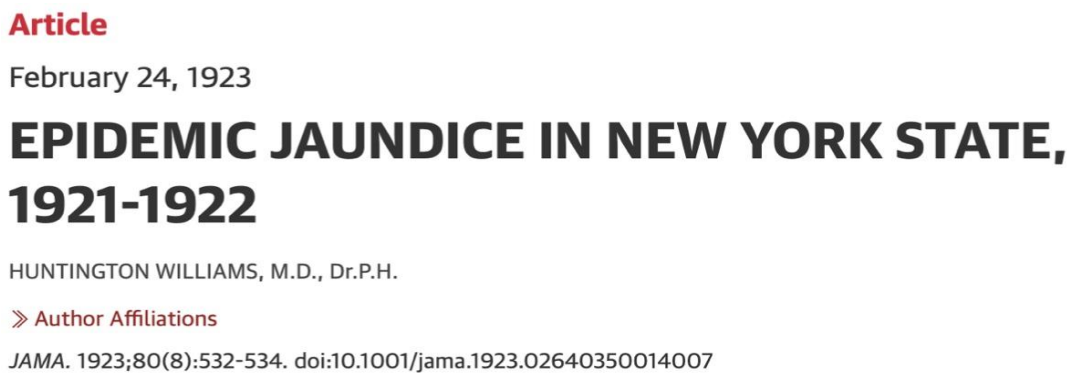
Severe acute hepatitis in children: Investigate SARS-CoV-2 superantigens



Immune-mediated liver damage

Brodin, Lancet Gastroenterol Hepatol 2022

Lessons Learned..



Article

February 24, 1923

EPIDEMIC JAUNDICE IN NEW YORK STATE, 1921-1922

HUNTINGTON WILLIAMS, M.D., Dr.P.H.

» Author Affiliations

JAMA. 1923;80(8):532-534. doi:10.1001/jama.1923.02640350014007

- In the winters of 1921–1922, sporadic cases of hepatitis were recorded in children from various US states, with jaundice raising the alarm for liver disease
- Sanitary supervisor Huntington Williams described an increase in such cases in New York State in young children
- 700 cases with fever, anorexia, nausea, vomiting, abdominal pain, constipation, clay-coloured stools and bile-stained urine lasting 3 days to 1 week, followed by a decrease of abdominal symptoms and onset of jaundice that resolved over several weeks
- 5/700 had ALF and died..

Huntington W JAMA 1923 , Kelly and Stamataki 2022

Conclusions

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

SOCIETAL PAPER

Acute Hepatitis of Unknown Etiology Among Young Children: Research Agenda by the ESPGHAN Hepatology Committee

*Giuseppe Indolfi, †Piotr Czubkowski, ‡Emer Fitzpatrick, §Emmanuel Gonzales, ‖Girish Gupte, ¶Sara Mancell, #Yael Mozer-Glassberg, **Emanuele Nicastro, ††Junge Norman, ‡‡Xavier Stephenne, §§Aglaia Zellos, and ¶Marianne Samyn

J Pediatr Gastroenterol Nutr 2022;75:543-548

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