Hepatitis infantiles de origen desconocido

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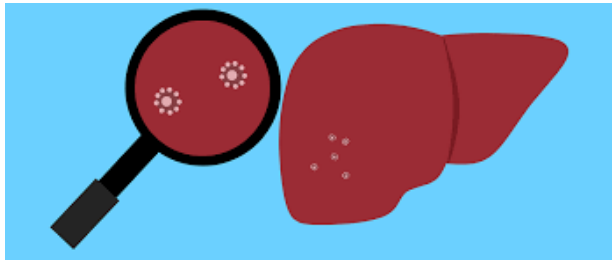
¡NEW OUTBREAK AT A GLANCE!

- El 5 de abril de 2022, UK notifica a la OMS 10 casos de hepatitis aguda grave de etiología desconocida (HOD) en niños menores de 10 años (entre 11 meses y 5 años) en Escocia.
- El 8 de abril 2022, UK reporta 74 casos de hepatitis no A, B, C, D, E
- El 10 de abril 2022, Irlanda notifica 5 casos



12 ABRIL 2022 EL ECDC INSTA A LA RED DE VIGILANCIA DE HEPATITIS A BUSCAR Y NOTIFICAR CASOS DE HEPATITIS GRAVES DE ORIGEN DESCONOCIDO EN POBLACIÓN INFANTIL

ecdc
EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

DEFINICIÓN DE CASO

Working case definitions include.

- **Confirmed:** A person presenting with an acute hepatitis (non-hepatitis viruses A, B, C, D, E) with aspartate transaminase (AST) or Alanine transaminase (ALT) over 500 U/L, who is 10 years old and under, since 1 January 2022.
- **Possible:** A person presenting with an acute hepatitis (non-hepatitis viruses A-E) with AST or ALT over 500 U/L, who is 11-16 years old, since 1 January 2022.
- **Epi-linked:** A person presenting with an acute hepatitis (non-hepatitis viruses A-E) of any age who is a close contact of a confirmed case since 1 January 2022

13 de abril 2022

EL PAÍS

Sociedad

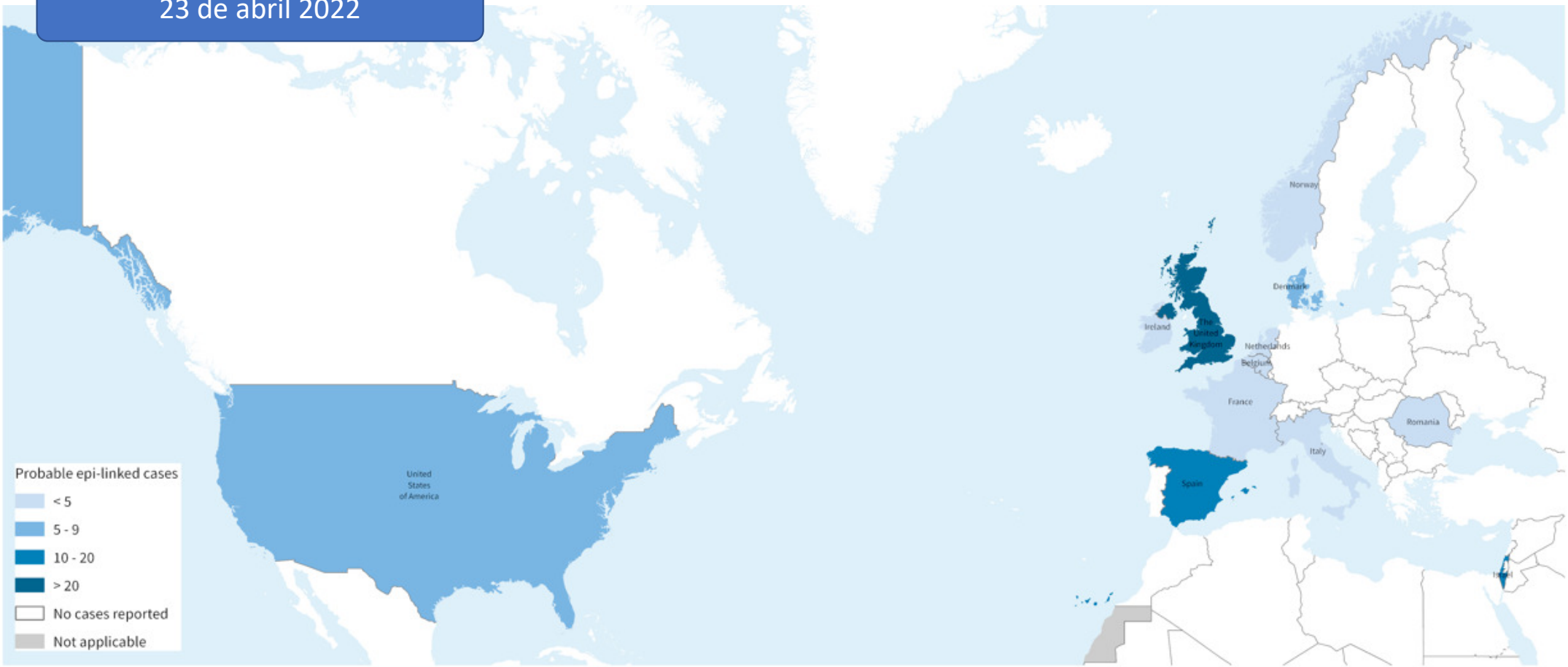
SUSCRÍBETE

SALUD >

Detectados en España tres casos de una hepatitis infantil de origen desconocido

Los diagnósticos se producen tras una alerta internacional de la OMS y el ECDC iniciada en el Reino Unido, que ha atendido en sus hospitales a 74 niños. Uno de los menores españoles y seis británicos han necesitado un trasplante de hígado

23 de abril 2022



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Data Source: World Health Organization, United Kingdom Health Security Agency
Map Production: WHO Health Emergencies Programme
Map Projection: WGS 1984 World Mercator
Request ID: RITM00064

World Health Organization

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CRONOLOGÍA DE DETECCIÓN DE CASOS A NIVEL MUNDIAL DURANTE ABRIL-MAYO 2022

April 5th
Scotland: 10 cases

April 8th
United Kingdom: 74 cases

April 10th
Ireland: 5 cases

April 12nd
The ECDC alerts Hepatitis Network members to find and report cases that match the UK report

April 13th -15th
USA: 9 cases
Denmark: 6 cases
Netherlands: 4 cases
Spain: 3 cases
France: 2 cases

April 19th
Israel: 12 cases
Rumania: 1 case
Belgium: 1 case

April 20th
Italy: 2 cases

April 21st
Norway: 2 cases
UK: 114 cases
Spain: 13 cases

April 24th
Israel: 20 cases

April 30th
Singapore: 1 case

May 3rd
Sweden: 7 cases
Palestine: 1 case

May 6th
Austria: 2 cases
Belgium: 3 cases
Cyprus: 2 cases
Poland: 1 case
Germany: 1 case
Italy: 35 cases
Netherlands: 6 cases
Romania: 4 cases
Serbia: 1 case
Japan: 7 cases
Singapore: 1 case
USA: 109 cases
Costa Rica: 1 case
Mexico: 1 case
Spain: 22 cases
UK: 163 cases
Slovenia 1 case
Portugal: 4 cases

May 9th
Portugal: 8 cases
Argentina: 8 cases
Brazil: 16 cases
Canada: 7 cases
Indonesia: 15 cases

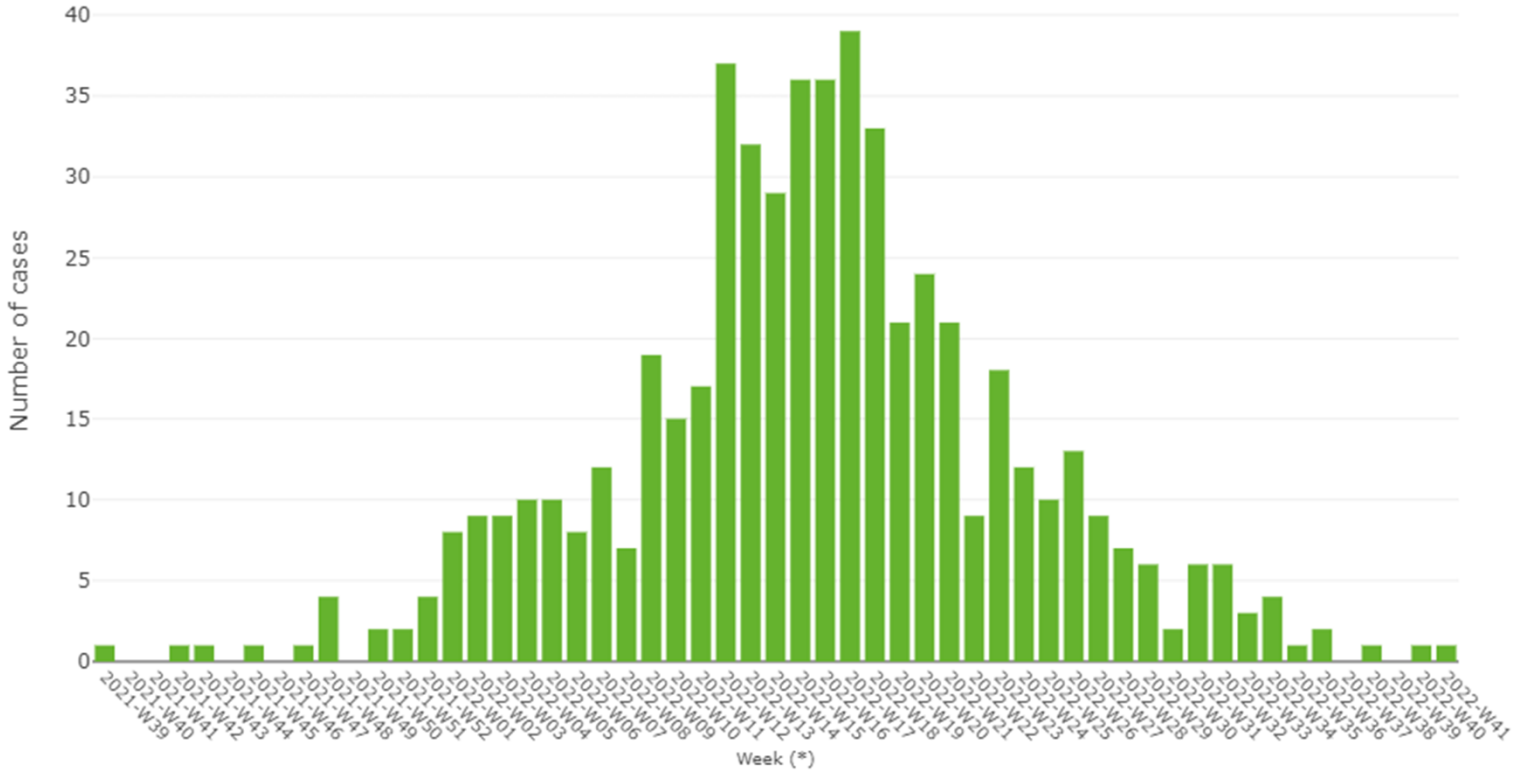
May 10th
Norway: 4 cases
Sweden: 9 cases
Canada: 8 cases

May 11st
Canada: 12 cases
Indonesia: 21 cases

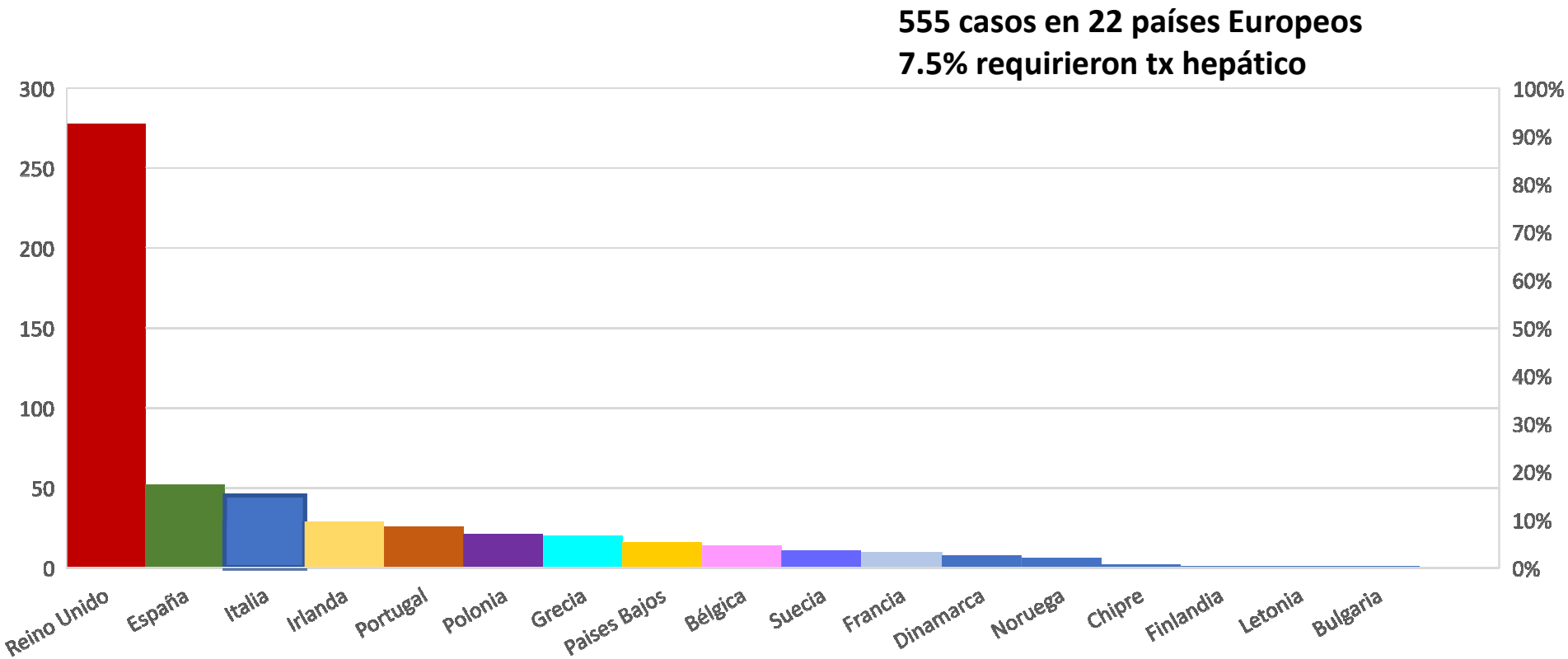
May 12nd
Ireland: 6 cases
UK: 176 cases
Greece: 3 cases
Brazil: 28 cases
Mexico: 4 cases
Malaysia: 1 case

May 13rd
Belgium: 12 cases
Norway: 5 cases
Spain: 26 cases
USA: 115 cases
Japan: 12 cases

Curva epidémica por inicio de síntomas y semana epidemiológica de los casos detectados en Reino Unido y la Unión europea, hasta el 29 de septiembre de 2022.



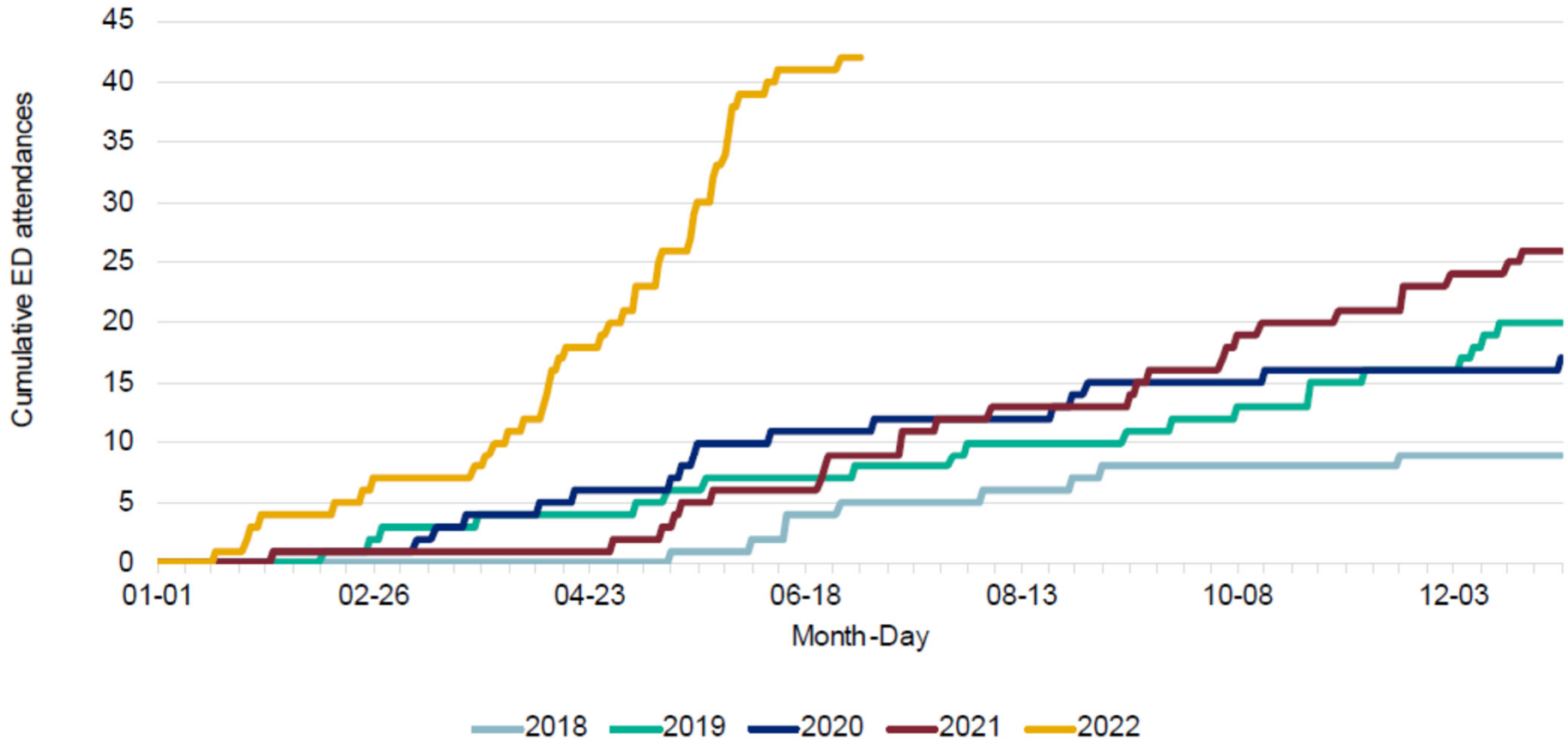
Distribución actual por países europeos



Hepatitis de Origen Desconocido. Centro de Coordinación de Alertas y Emergencias Sanitarias.. Publicado 05 de octubre 2022

Figure 16A. Cumulative daily number of ED attendances for children aged 1 to 4 years, with a 'liver condition'* primary diagnosis, 1 April 2018 to 3 July 2022 (see notes on page 43)**

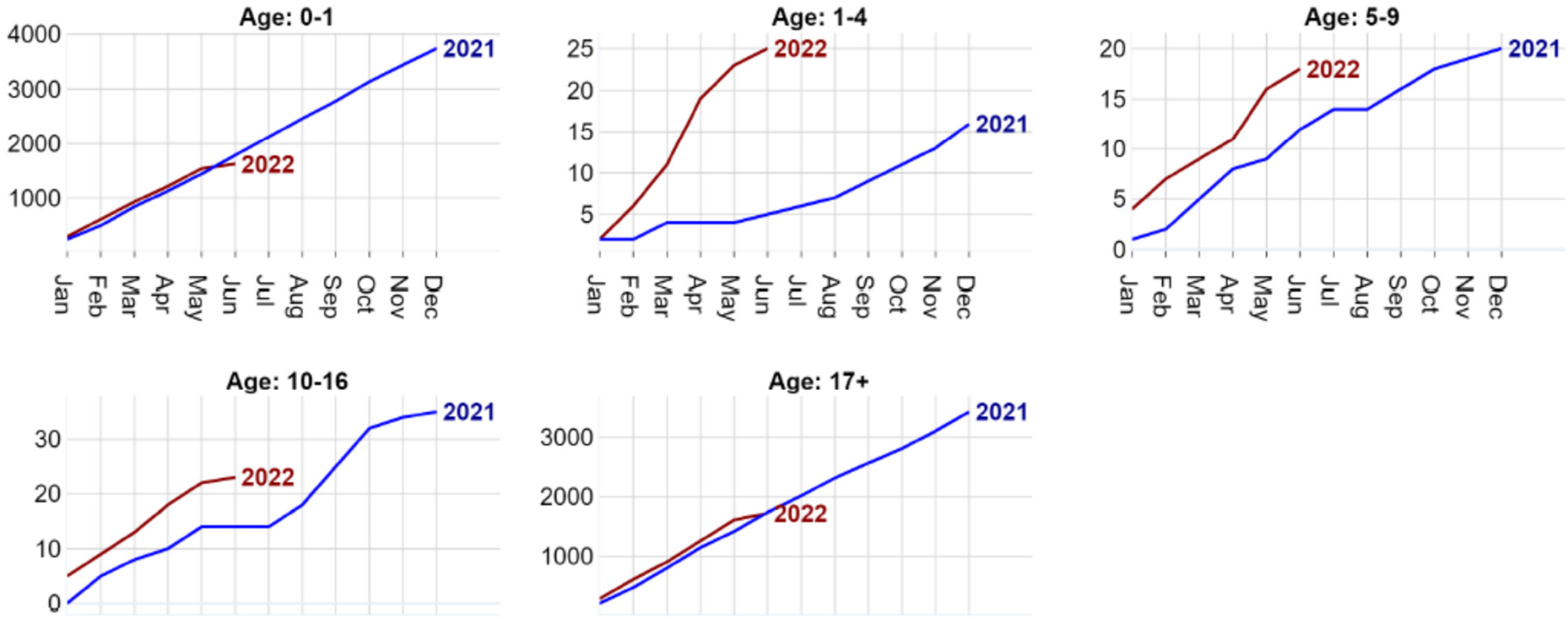
Supplementary data is not available for this figure.



UK Health Security Agency. Investigation into acute hepatitis of unknown aetiology in children in England: Technical briefing 4. July 26, 2022.

Figure 18. Monthly cumulative admissions presented to Emergency Care with jaundice, by age group

Supplementary data is not available for this figure.



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Casos notificados en España por Comunidades Autónomas durante 2022: 1 enero a 30 octubre 2022

CCAA	Nº casos investigación
Andalucía	4
Aragón	1
Baleares	5
C. Valenciana	1
Canarias	1
Castilla y León	2
Castilla-La Mancha	3
Cataluña	9
Galicia	6
Madrid	17
Murcia	3
Total	52

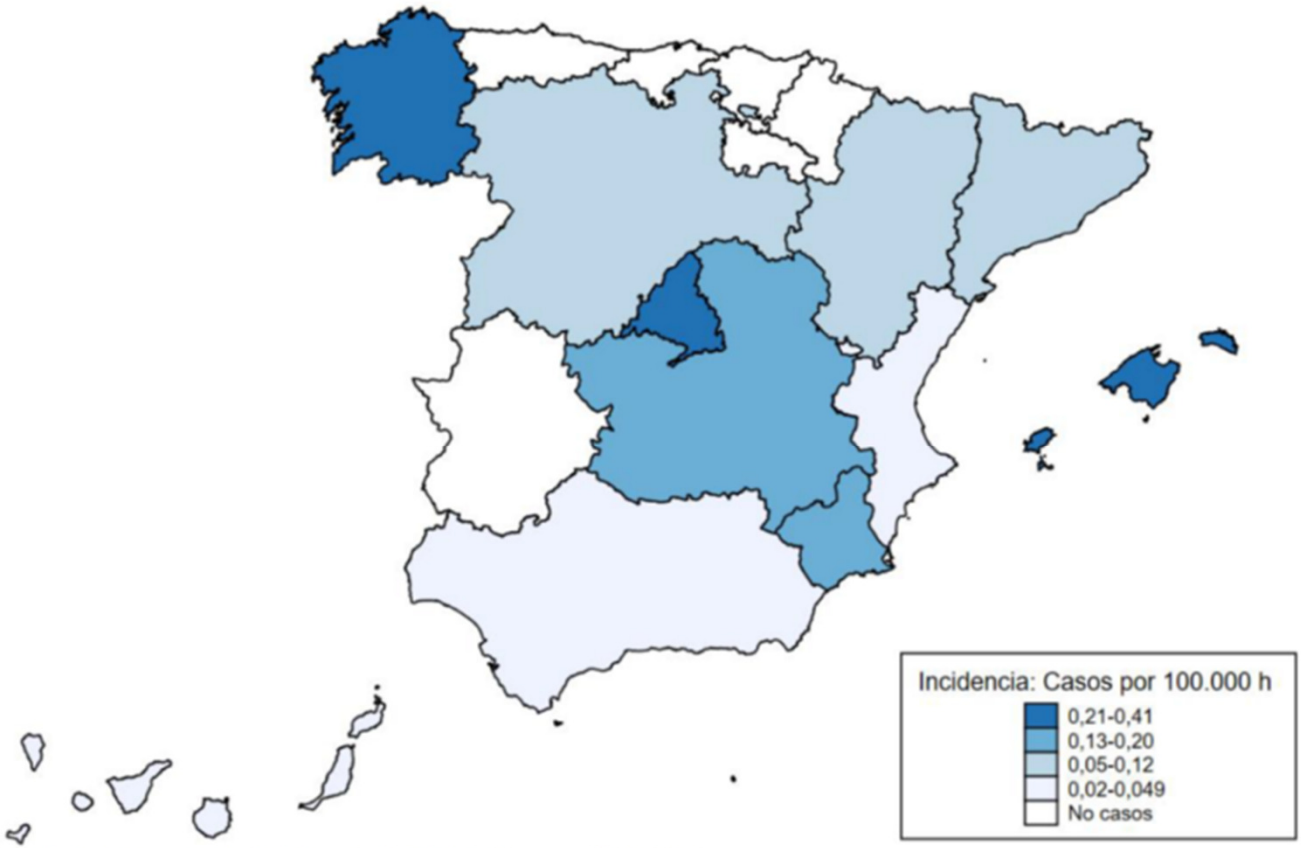
Incidencia similar a años anteriores

No se ha detectado ningún caso con vínculo epidemiológico.

Trasplante hepático: 3 pacientes (5.7%).
Exitus: 2 pacientes (3.8% del total de casos)

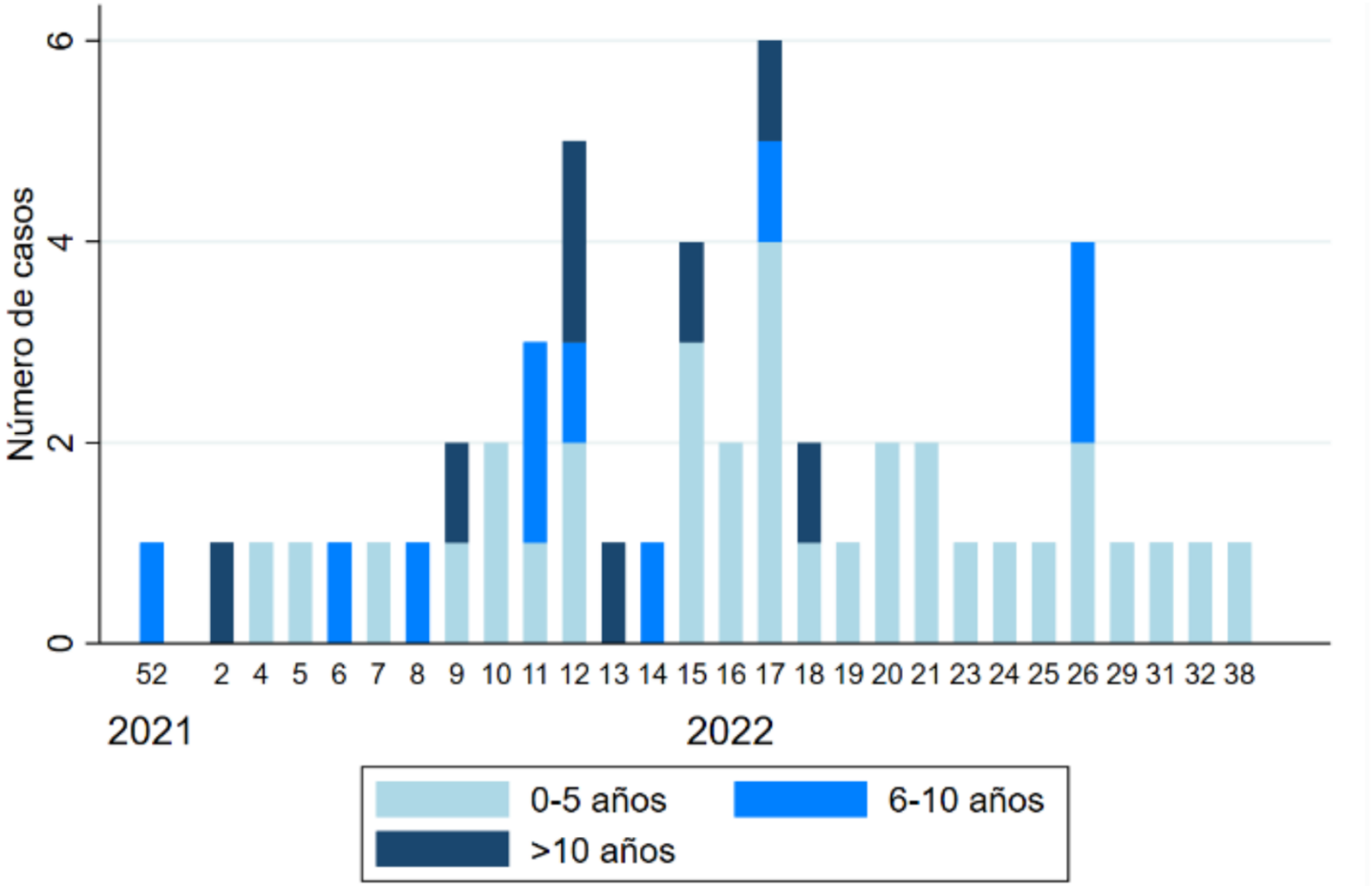
Hepatitis de Origen Desconocido. Centro de Coordinación de Alertas y Emergencias Sanitarias.. Publicado 05 de octubre 2022

Incidencia acumulada



Fuente:Red Nacional de Vigilancia Epidemiológica (RENAVE)

Casos diagnosticados en España: entre el 1 de enero de 2022 y el 3 de octubre de 2022



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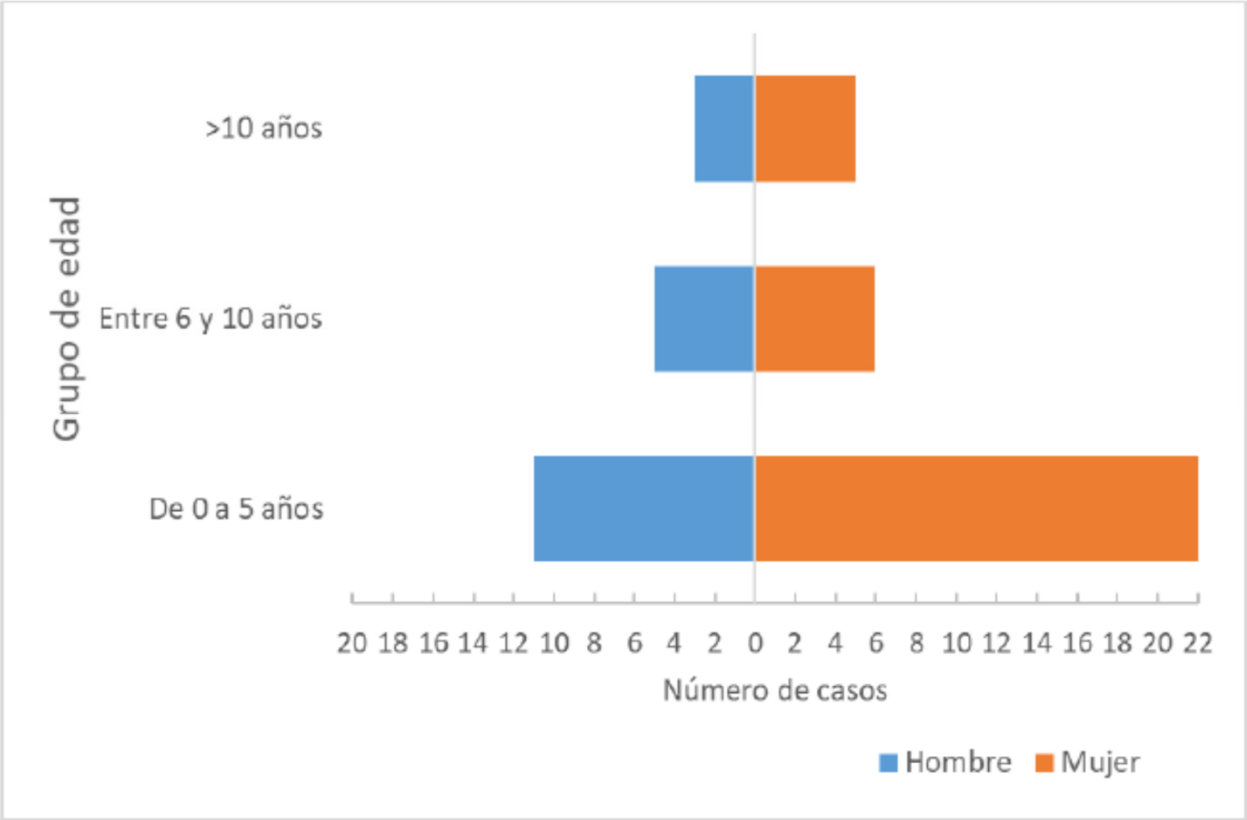
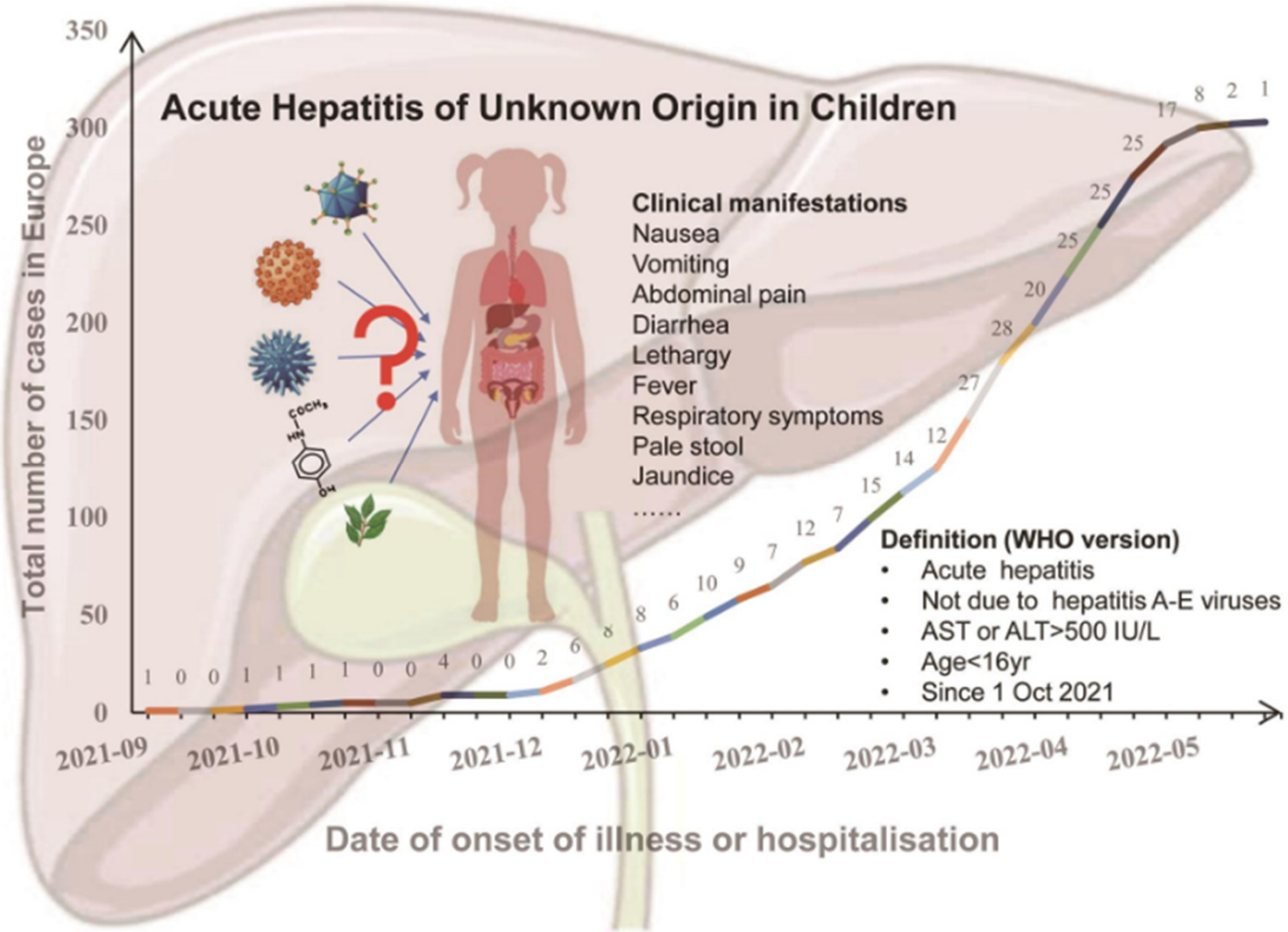
Distribución por sexo y grupos de edad



- Mediana de edad: 3 años (RIQ 0 - 16).
- Sexo: 33 niñas (63,5%) y 19 niños (36,5%).

Hepatitis de Origen Desconocido. Centro de Coordinación de Alertas y Emergencias Sanitarias.. Publicado 05 de octubre 2022

CLÍNICA



Zhang LY, *et al. J Clin Transl Hepatol.* 2022;10(3):522-530. doi: 10.14218/JCTH.2022.00281.

HIPOTESIS SOBRE LA ETIOLOGÍA HEPATITIS ORIGEN DESCONOCIDO

JAMA Network | Open

Original Investigation | Pediatrics

Characterization of a Hepatitis Outbreak in Children, 2021 to 2022

Emma C. Alexander, MBBS; Akash Deep, MD

- Revisión sistemática hepatitis origen desconocido población pediátrica 2021-2022
- 1643 casos – 22 estudios
- 7% Trasplante hepático
- 1% exitus
- Posibles agentes etiológicos:
  - Adenovirus (F41)
  - Virus Adenoasociado 2 (AAV2)
  - SARS-CoV-2

Key Points

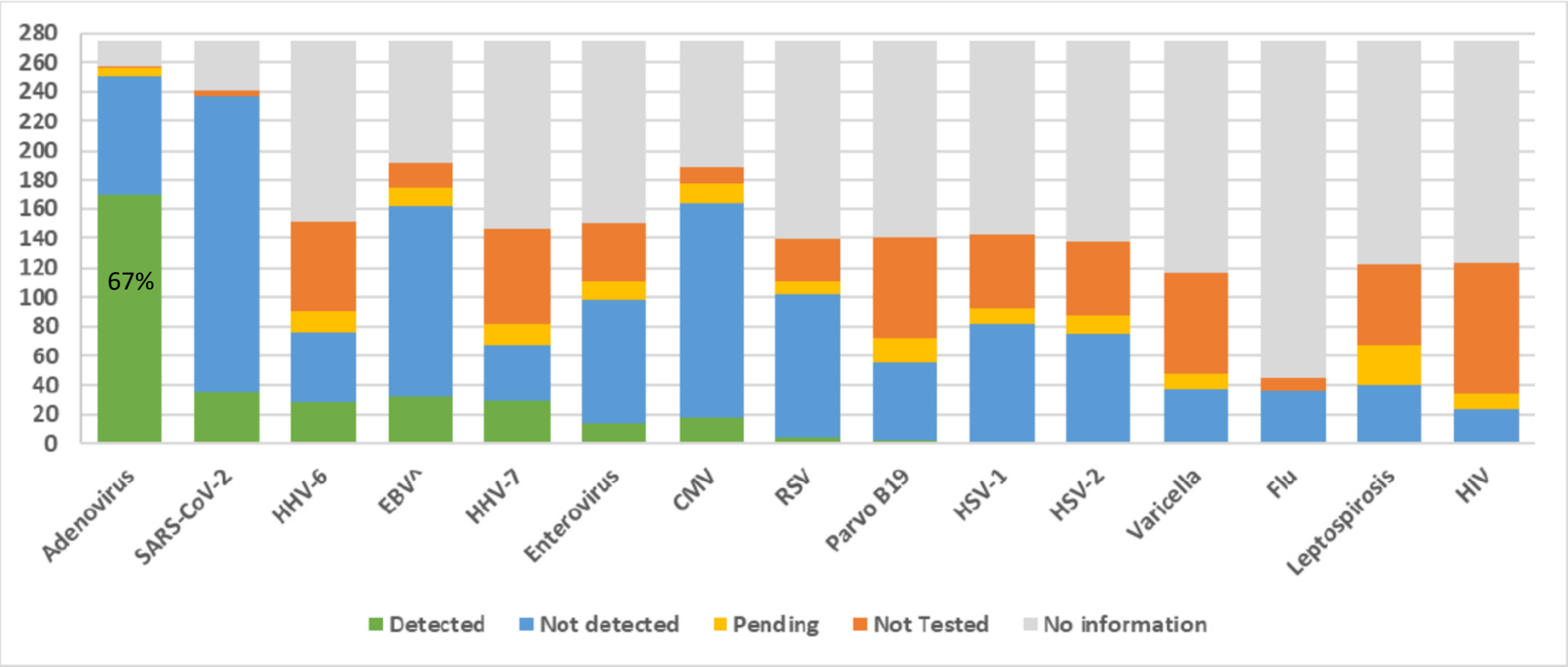
Question What is the available evidence regarding cases of hepatitis of unknown etiology in children in 2021 to 2022?

Findings This systematic review without meta-analysis identified 1643 cases across 22 studies, with 120 children (7%) receiving liver transplants and 24 deaths (1%). Testing focused on adenovirus, SARS-CoV-2, and adeno-associated virus 2.

Meaning These findings suggest that the cause of novel hepatitis in children remains undetermined, but the potential role of adenovirus, adeno-associated virus 2, and SARS-CoV-2 requires further exploration in multicenter collaborative studies.

Figure 3. Pathogens tested for and results in cases in UK

Supplementary data is not available for this figure.



SARS-CoV-2 testing presented here is based on testing around hospital admission or attendance.
^ including one past positive.

Of 274 UK cases, 251 were tested for adenovirus. Adenovirus was detected in 170 (67.7%), and not detected in 81 (32.3%) cases.

UK Health Security Agency. Investigation into acute hepatitis of unknown aetiology in children in England: Technical briefing 4. July 26, 2022

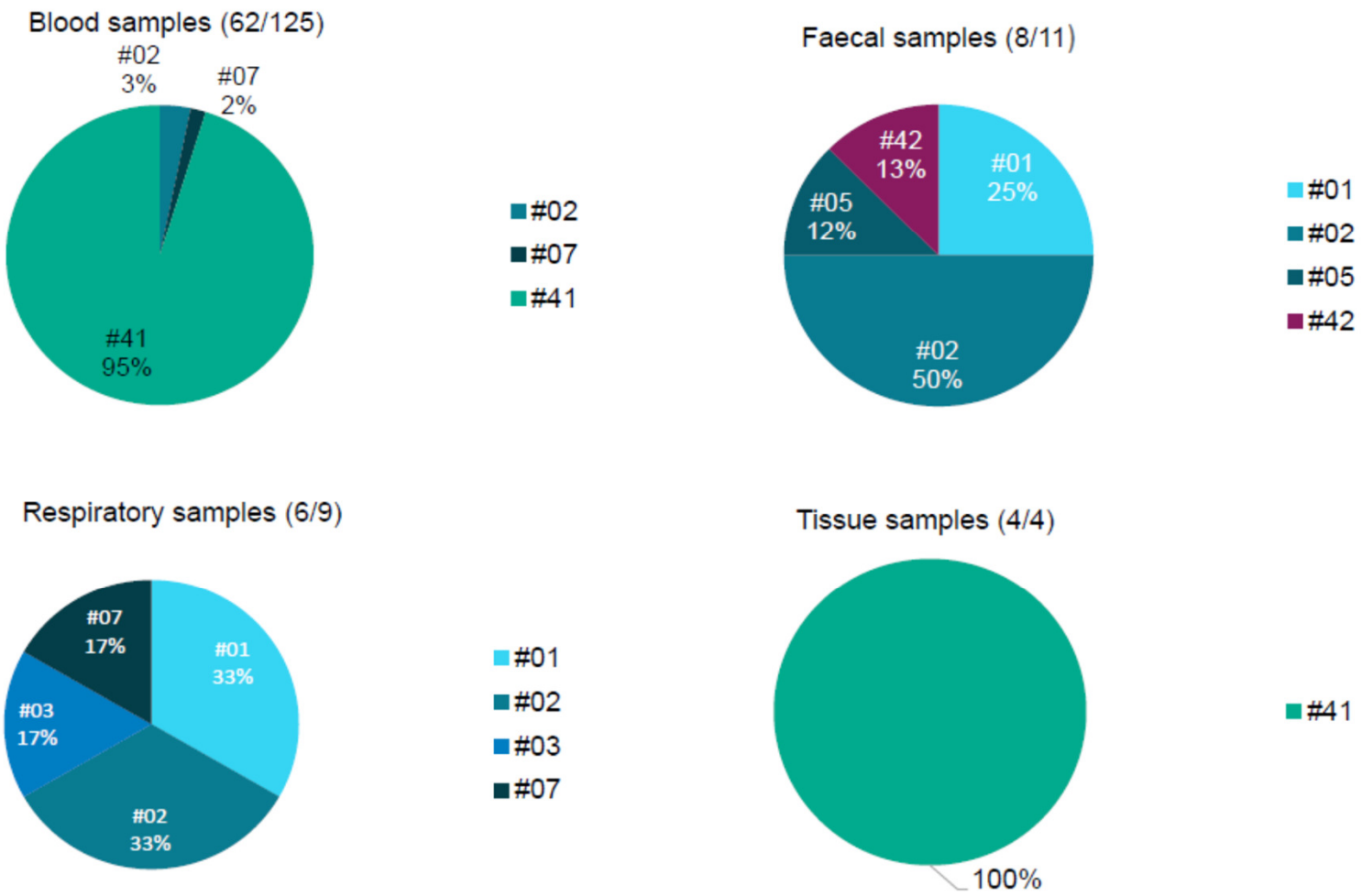
Table 3. Adenovirus testing* results of cases resident in England

Adenovirus testing	Number of cases	Number of cases with each sample type (there may be multiple samples per case)			
		Blood	Stool	Respiratory	Other or unknown
Positive (% positivity, excluding pending)	122 (68.9%)	106 (71.1%)	24 (30.0%)	15 (22.4%)	21 (46.7%)
Negative	55	43	56	52	24
Pending	6	5	11	8	14
Total tested	**183**	**154**	**91**	**75**	**59**

* Testing locations: any diagnostic laboratory.

UK Health Security Agency. Investigation into acute hepatitis of unknown aetiology in children in England: Technical briefing 4. July 26, 2022

Figure 5. Diversity of adenovirus subtype in case samples. Hexon sequencing result following detection by PCR



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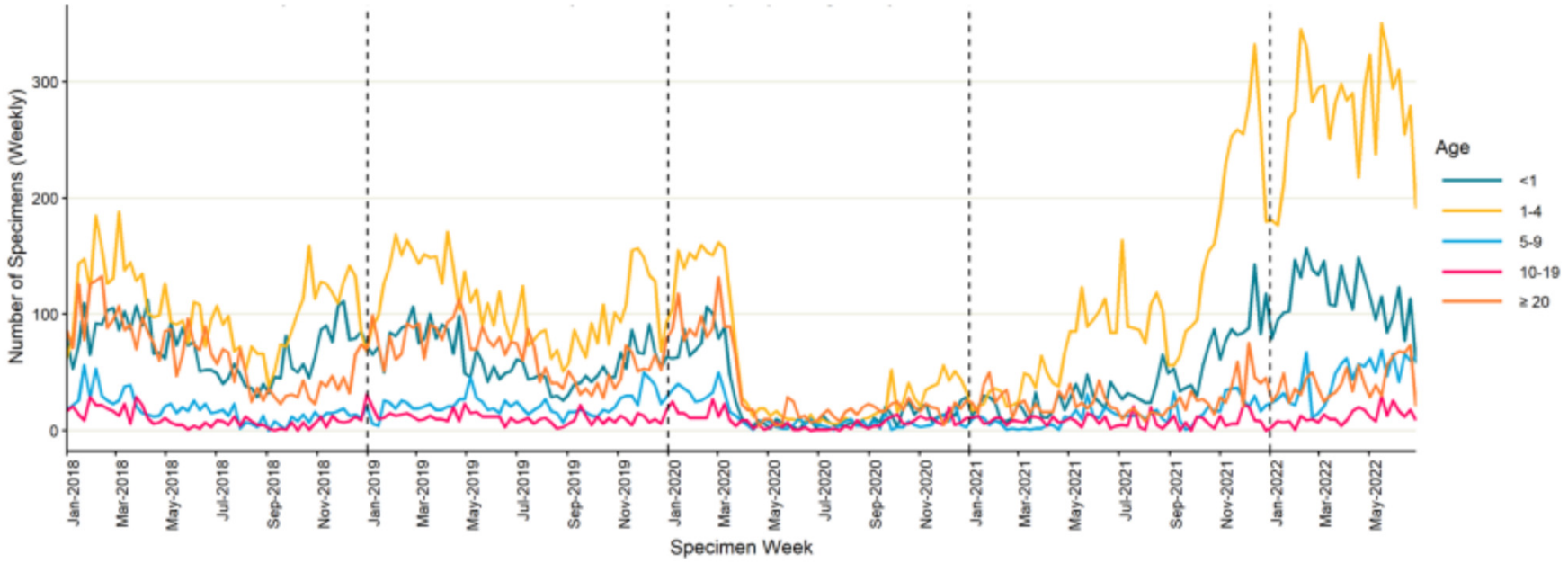
Episodios de adenovirus (muestras positivas) en Inglaterra por edades, desde el 1 de enero de 2017 al 3 de julio de 2022.



UK Health Security Agency

Preliminary findings from a UK case-control study to investigate association of adenovirus with acute hepatitis (non-A to E)

En un estudio de casos y controles emparejado por frecuencia en todo el R.U, los análisis de regresión multivariable indicaron que los casos tenían **MAYORES PROBABILIDADES DE INFECCIÓN CONCOMITANTE POR ADENOVIRUS EN COMPARACIÓN CON LOS CONTROLES**

74 casos - 225 controles
Pareados por edad, región, mismo mes procedimiento de muestras

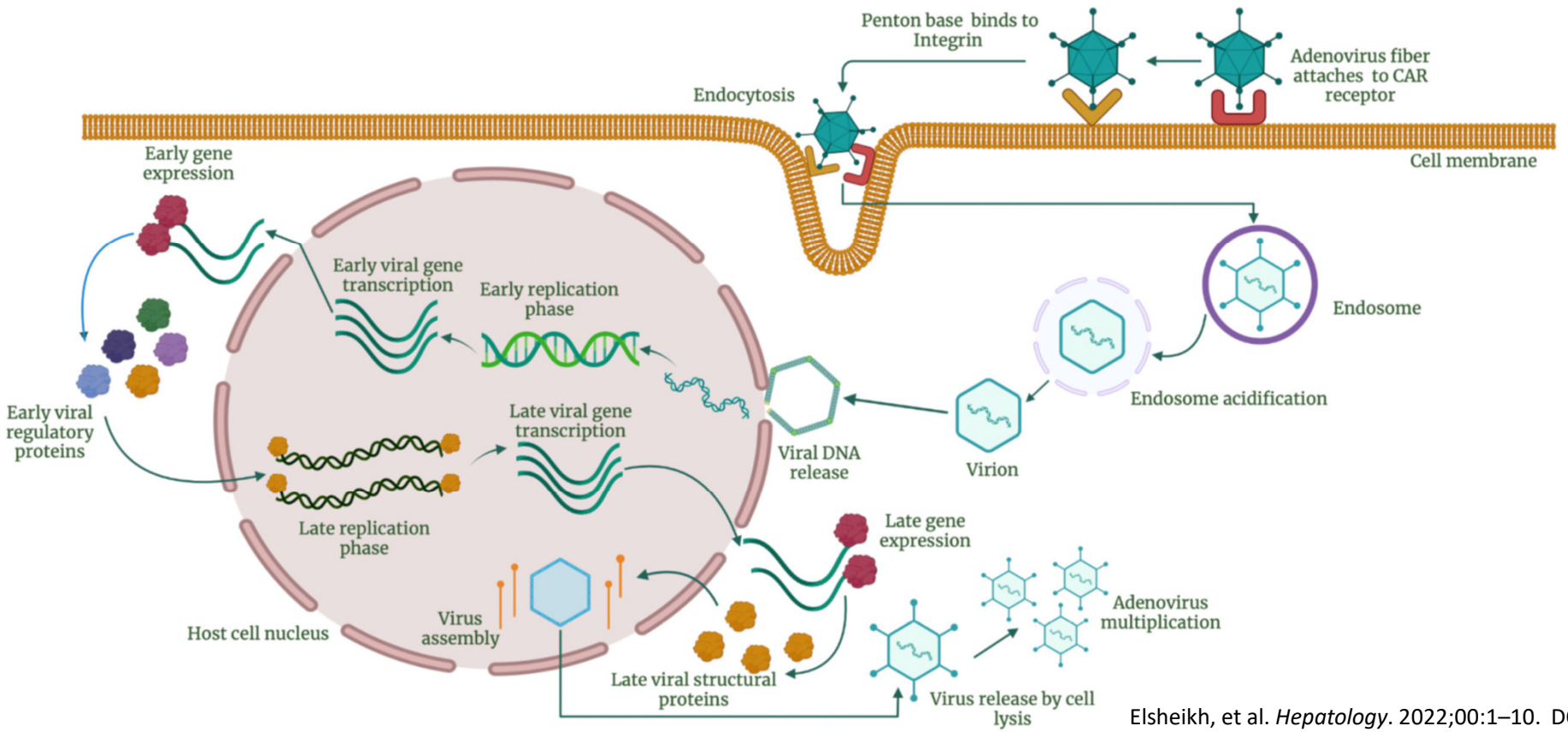
(odds ratio ajustado [ORa] 35,27, IC del 95 % 15,23 a 81,68).

Datos completos pendientes de publicación.

UK Health Security Agency. Investigation into acute hepatitis of unknown aetiology in children in England: Technical briefing 4. July 26, 2022

Mecanismo acción de Adenovirus F41

- HAdV-F40 y HAdV-F41 únicos adenovirus asociados con síntomas gastrointestinales.
- Estructura proteínas fibrosas que permiten acceso y replicación intracelular.

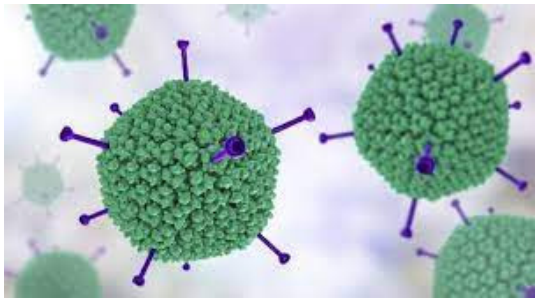


Elsheikh, et al. *Hepatology*. 2022;00:1–10. DOI: 10.1002/hep.32682

Adenovirus F-41: ¿Qué papel juega?:

Hunting down the cause of acute hepatitis in children

- ¿Hepatotóxico? – no demostrado efecto tóxico directo en lisis hepatocelular (no elevada detección AdV en hepatocitos)
- Interacción con otros posibles cofactores: toxinas ambientales (micotoxinas-alimentos, fármacos: paracetamol)
- Otros virus asociados: AAV2, VHH6, SARS-CoV2
- Factores genéticos/inmunológicos



Dhawan. The Lancet **Vol 399 June 18, 2022**

Severe Hepatitis in Pediatric Coronavirus Disease 2019

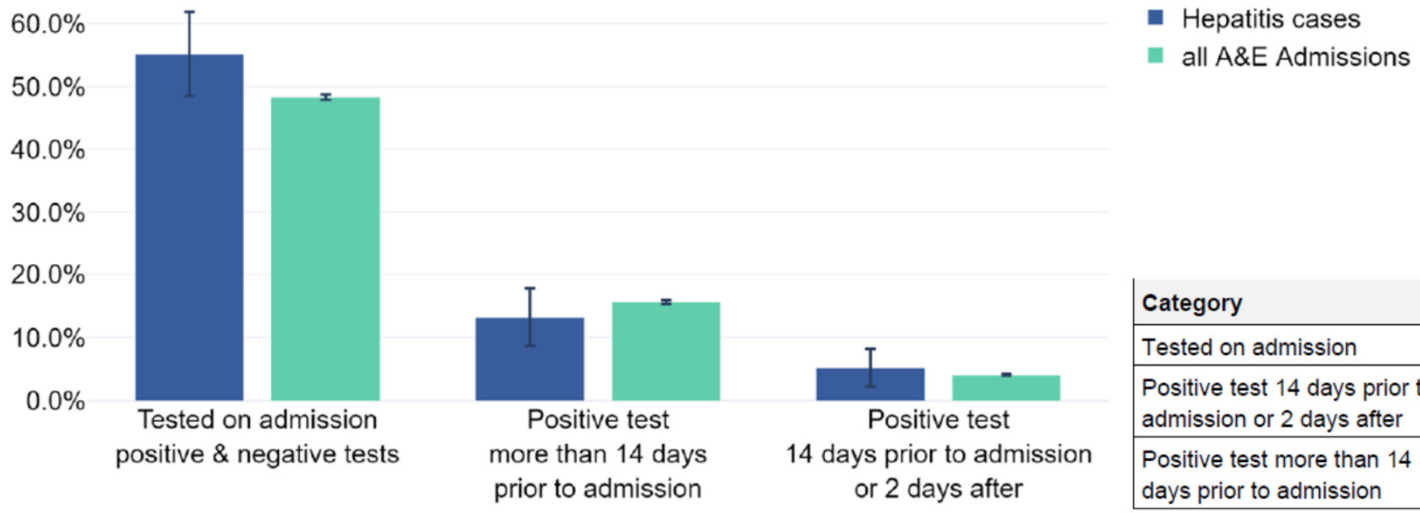
*Swati Antala, †Tamir Diamond, ‡Larry K. Kociolek, †Amit A. Shah, and *Catherine A. Chapin

ABSTRACT

Hepatic involvement in coronavirus disease 2019 (COVID-19) is typically characterized as mild hepatitis with preserved synthetic function in children. Severe hepatitis is a rare complication of COVID-19 infection that has not been extensively described in the pediatric population. We report a case series of four previously healthy children who presented with significant hepatitis as the primary manifestation of COVID-19 infection. Two of these patients met criteria for acute liver failure. None of the patients had respiratory symptoms. One patient was found to have complement dysfunction resulting in microangiopathic features and was treated successfully with eculizumab. This case is in line with adult post-mortem data showing that more severe cases of hepatic dysfunction secondary to COVID-19 infection may be associated with complement activation and microangiopathic features. Liver function should be evaluated in cases of severe COVID-19, and severe acute respiratory syndrome coronavirus 2 infection should be considered as a cause of acute severe hepatitis even in patients without significant respiratory or other systemic symptoms.

- Serie de casos pediátricos
- Fallo hepático agudo con COVID19 sin síntomas respiratorios

SARS-CoV-2 testing rates and proportion of patients testing positive por acute hepatitis 01/01/22 01/06/22



Category	Hepatitis cases (%)	All A&E admissions (%)
Tested on admission	53.7% (CI: 47.3 to 60.2)	48.5% (CI: 48.1 to 48.9)
Positive test 14 days prior to admission or 2 days after	4.4% (CI: 1.7 to 7.1)	4.0% (CI: 3.8 to 4.2)
Positive test more than 14 days prior to admission	11.9% (CI: 7.7 to 16.1)	15.6% (CI: 15.3 to 15.9)

Error bars represent 95% confidence intervals of the standard error of proportion.
Positivity: proportion of cases with a positive test result.

UK Health Security Agency. Investigation into acute hepatitis of unknown aetiology in children in England: Technical briefing 4. July 26, 2022.

THE LANCET
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CORRESPONDENCE | VOLUME 7, ISSUE 7, P594-595, JULY 01, 2022

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

Petter Brodin • Moshe Arditi

Published: May 13, 2022 • DOI: https://doi.org/10.1016/S2468-1253(22)00166-2

Teoría de los superantígenos

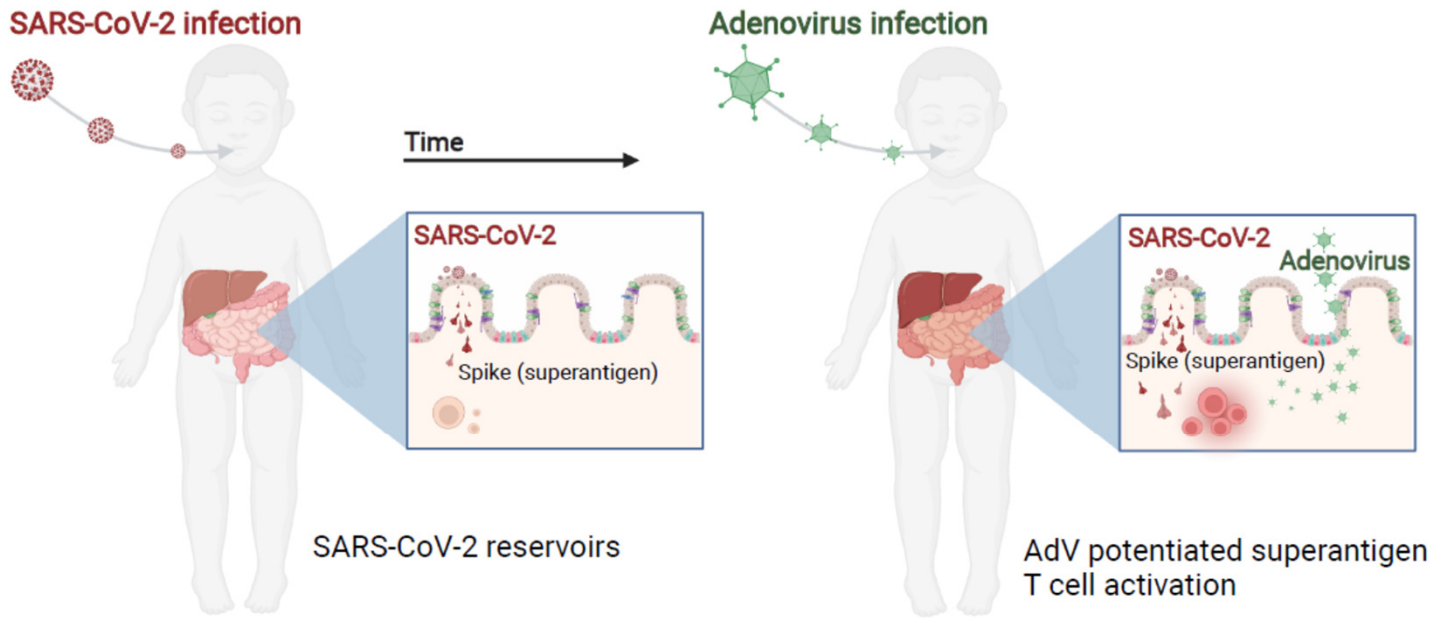
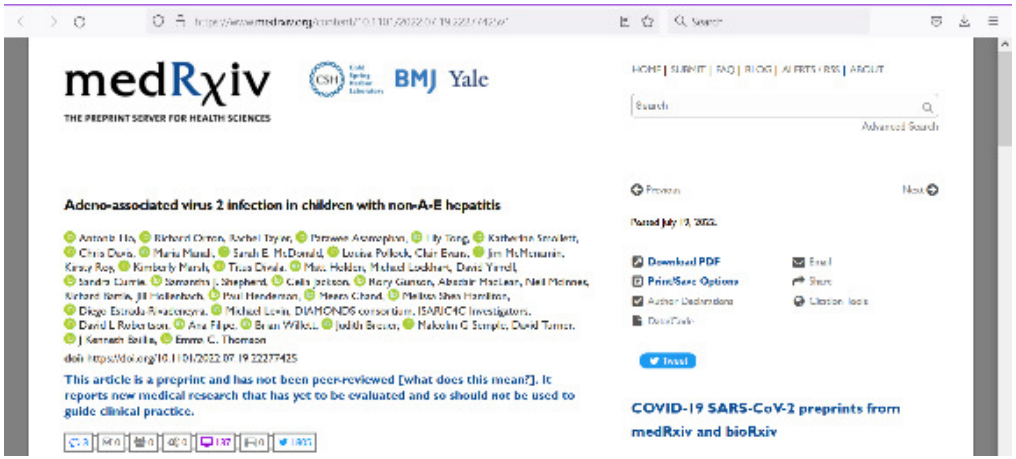


Figure 1. Hypothesis of AdV potentiated SARS-CoV-2 superantigen-mediated pathology in severe, acute hepatitis. Following infection with SARS-CoV-2 virus, viral reservoirs have been reported and could over time lead to repeated super-antigen mediated immune cell activation as shown in Multisystem inflammatory syndrome, MIS-C. If such viral reservoirs are present and a child is subsequently infected with AdV, this superantigen-mediated effect could be much more pronounced and potentially give rise to immunopatthology such as the recently reported acute, severe hepatitis which is why evidence of such immunopathology should be investigated in these cases.

Estudios metagenómicos

- Estudio en UCL y GOSH (Londres, UK)
- Estudio Medical Research Council UK–University of Glasgow Centre for Virus Research



GENOMIC INVESTIGATIONS OF ACUTE HEPATITIS OF UNKNOWN AETIOLOGY IN CHILDREN

- Métodos genómicos, proteómicos e inmunohistoquímicos
- University College London y Great Ormond Street Hospital (GOSH)
- Participantes 28 casos HOD y 136 controles.
- Resultados: **fuerte asociación de virus Adeno-asociados 2 (AAV2): sangre o tejido hepático de niños infectados por Adenovirus-F41.**

CASOS HEPATITIS	CONTROLES
10/11 niveles elevados en plasma de AAV2 5/5 tejido hepático explantado: elevados niveles AAV2 y bajos niveles de AdV y VHH6	Plasma Bajos niveles AAV2: 6/100 – inmunocompetentes. 11/32 – inmunodeprimidos 1/4 tejido hepático: bajos niveles AAV2 y no AdV

En 4 de los 5 niños trasplantados, estaba presente el alelo **HLA DRB1*04:01**.

Morfopoulou S, Buddle S, Torres Montaguth OE, et al. Genomic investigations of acute hepatitis of unknown aetiology in children. *medRxiv*. Preprint posted online July 28, 2022.

Adeno-associated virus 2 infection in children with non-A-E hepatitis

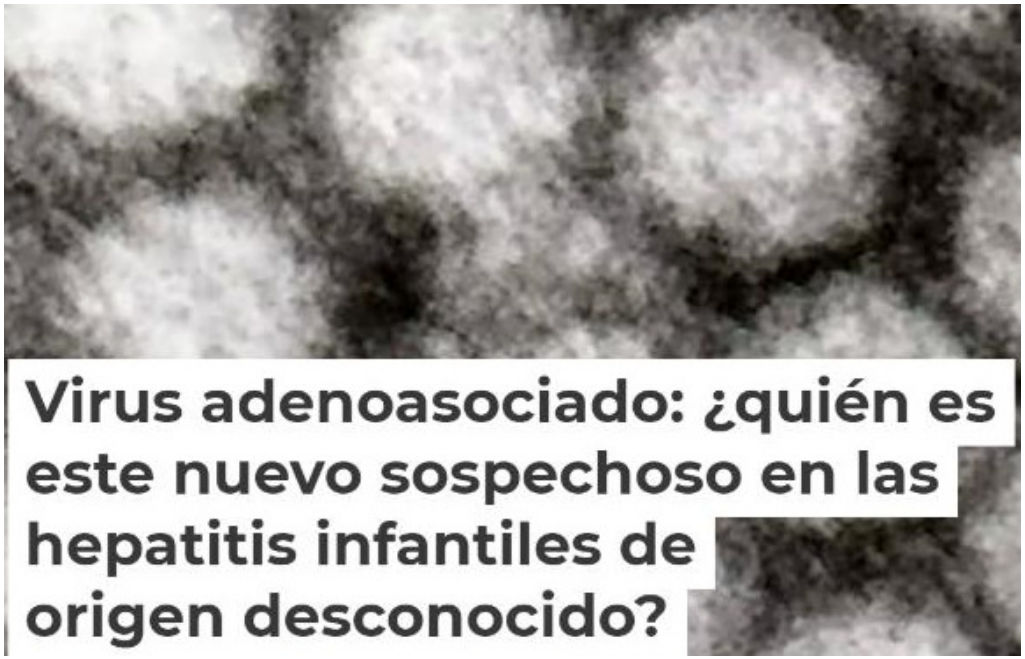
- Métodos genómicos, proteómicos e inmunohistoquímicos
- El Consejo de Investigación Médica - Centro University of Glasgow Centre for Virus Research
- 9 casos hepatitis origen desconocido con detección de AdV-F41 y 45 controles del estudio DIAMONDS.

CASOS HEPATITIS	CONTROLES 45 (12 infección por AdV sin hepatitis, 33 hepatitis otras etiologías)
9/9 AAV2 plasma 4/4 AAV2 tejido hepático	Plasma: 0/12 AAV2- infección por AdV sin hepatitis 0/33 AAV2 - hepatitis otra etiología

- SARS-CoV-2 no fue detectado por PCR y secuenciación en ninguna muestra clínica, incluidas muestras de hígado en casos o controles.

En 8 de 9 casos escoceses (88,9%) el HLA portaba el alelo **HLA-DRB1*04:01**. La frecuencia de este alelo en el grupo control de la población escocesa (n=974) fue del 8,9%.

Ho A, Orton R, Tayler R, et al. Adeno-associated virus 2 infection in children with non–A-E hepatitis. *medRxiv*. Preprint posted online July 19, 2022.



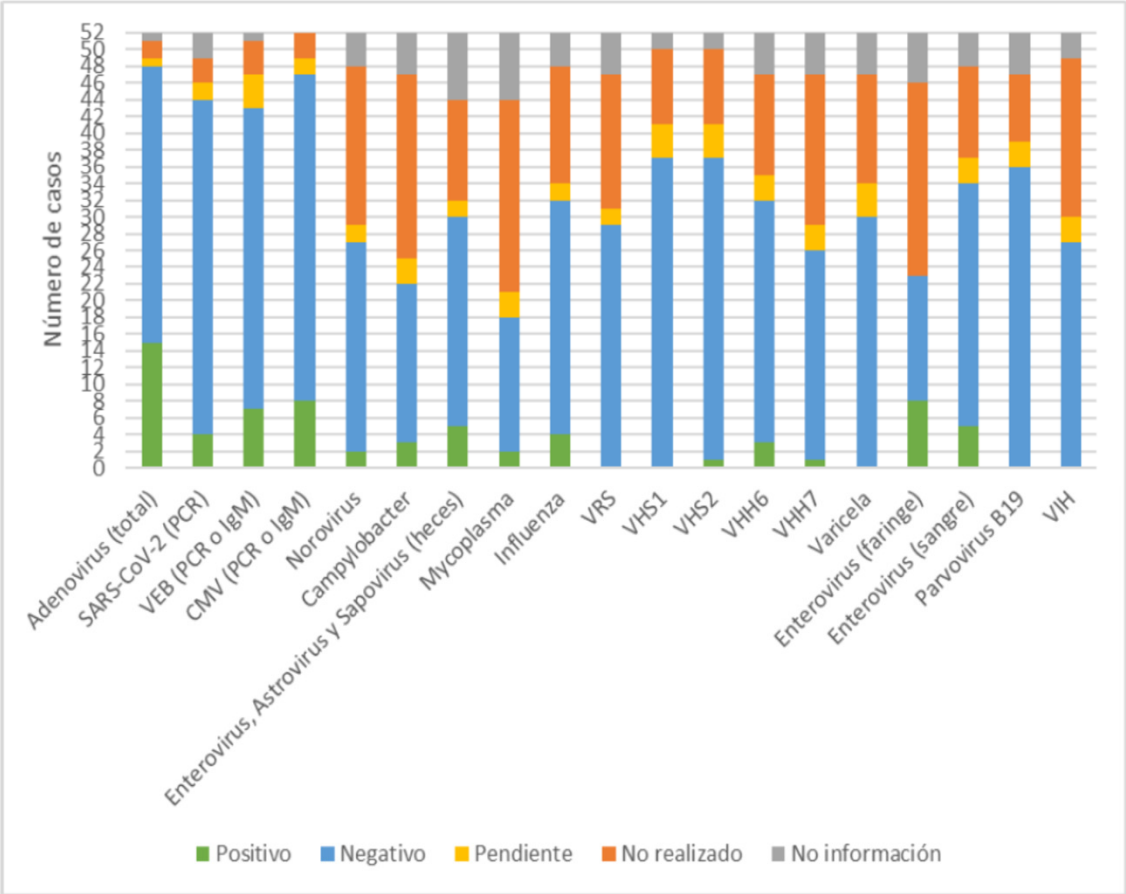
CARACTERÍSTICAS VIRUS ADENOASOCIADOS

- virus de ADN más pequeños
- Endémicos en humanos y en múltiples especies de vertebrados.
- Pertenecen al género *Dependoparvovirus*, familia *Parvoviridae*.
- Se conocen al menos 13 serotipos naturales
- Necesitan virus “auxiliar” como un adenovirus o un herpesvirus para su replicación
- Patogenicidad no conocida.
- son uno de los vectores más utilizados para gran variedad de aplicaciones de terapia génica

Resultados de los análisis en España para los diferentes microorganismos en investigación

32 casos estudiados:

- 15/32 (47%) detección de adenovirus
- Mediante metagenómica, se han detectado 8 casos de virus adeno-asociados (AAV), Seis de ellos corresponden a AAV tipo 2.
- En 15 casos se ha encontrado más de un patógeno
- En 10 casos: ningún patógeno (3 tienen el estudio metagenómico pendiente).
- No hay una etiología viral clara, aunque resulta frecuente la detección de adenovirus



Fuente: Red Nacional de Vigilancia Epidemiológica. Centro Nacional de Epidemiología. Centro Nacional de Microbiología. Instituto de Salud Carlos III, con datos hasta el 3 de octubre de 2022.

Original Investigation | Pediatrics

Characterization of a Hepatitis Outbreak in Children, 2021 to 2022

Emma C. Alexander, MBBS; Akash Deep, MD

Management and Treatment Offered

Regarding therapies, a number of studies reported use of corticosteroids, including studies from Israel,[12] India,[20] Scotland,[31] and the US.[15,17,19] Children with a disease process propagated by a dysfunctional immune response may be thought likely to respond to immunosuppression. However, in the presence of adenoviremia for some patients, many clinicians might hesitate before prescribing corticosteroids. Until pathogenesis is clarified, it would also be difficult for any clinician to await response to immunosuppression rather than proceeding to transplant, in a child with MSOF at imminent risk of death and satisfying the liver transplant listing criteria.

Among other therapies, cidofovir, a selective inhibitor of viral DNA polymerases, has previously been used to treat patients with severe adenovirus infection, even in the absence of immune dysfunction.[48] Cidofovir was used in 2 centers in the UK[10,29] and the US.[15,17] Cidofovir is used in these cases because patients with ALF, MSOF, and adenoviremia are inherently in a state of innate immune dysfunction.[49]

Corticoterapia:
disregulación inmunológica.

Cidofovir:
inhibidor DNA polimerasa adenovirus.
2 estudios realizados en UK y USA – situación adenoviremia

CONCLUSIONES

- Mayoría de los casos de HOD son < 6 años, mayor proporción de niñas.
- A diferencia de los observado en Reino Unido, en España y otros países europeos, hasta el momento no se ha encontrado una causa común, ni se ha observado un aumento por encima de lo esperado.
- Dada la detección casos graves y el gran interés a nivel internacional de conocer mejor e investigar acerca de las etiologías, se considera importante continuar con la vigilancia e investigación
- Es fundamental determinar el papel del adenovirus, AAV-2 y SARS-CoV2 en el contexto actual.
- Comprender la fisiopatología de este brote puede mejorar las opciones terapéuticas. Si el mecanismo es postinfeccioso-inflamatorio-inmunológico los fármacos inmunomoduladores podrían evitar la progresión de la enfermedad y la necesidad de trasplante hepático.
- Ante aparición de nuevos casos de HOD se recomienda el envío de muestras biológicas al Centro Nacional de Microbiología para continuar realizando estudios complementarios.

GRACIAS