7ª Edición de Sesiones Clínicas Interhospitalarias de Hepatitis 2023

Hepatitis emergentes

Antonio Rivero-Juárez

IMIBIC/HURS/UCO/CIBERINFEC

¿Virus causantes de hepatitis?

Hepatitis A

Hepatitis B – Hepatitis D

Hepatitis C

Hepatitis E

Virus herpes 1, 2, 6 y 8

Virus Epstein-Barr

Citomegalovirus

Virus varicela-zoster

Adenovirus

Virus Zika

Virus Dengue

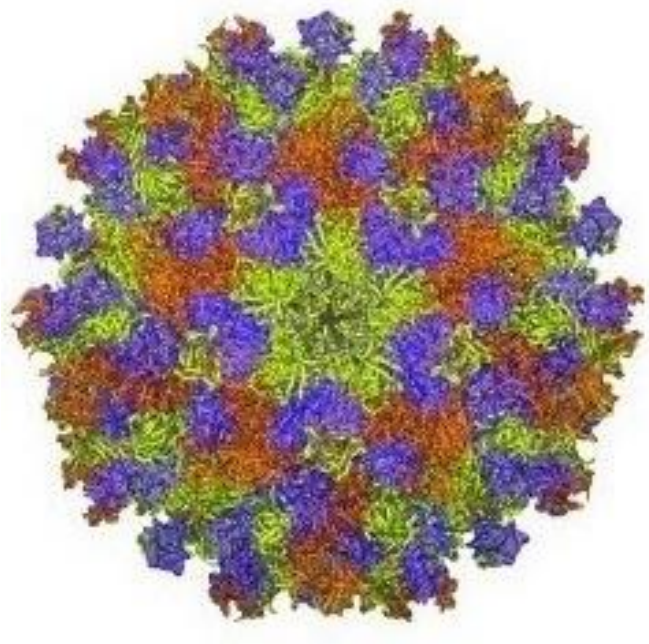
Virus Fiebre Amarilla

Virus fiebre hemorrágica Crimea-Congo

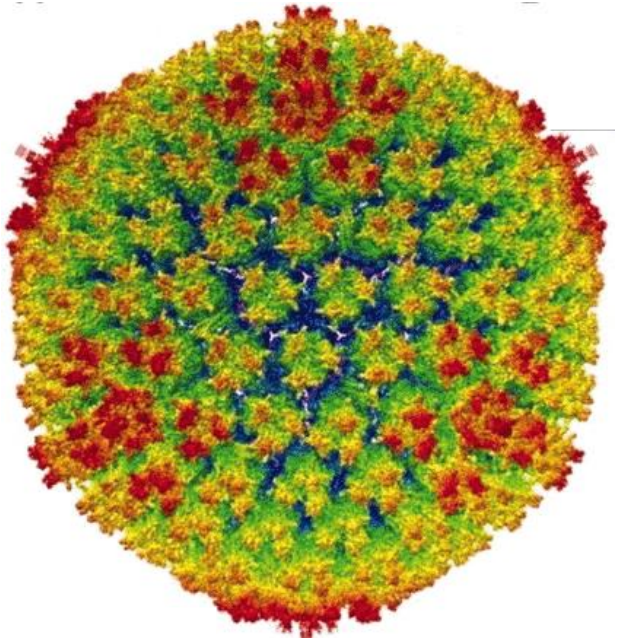
Virus Ebola

Virus Chikungunya

Rocahepevirus ratti



Adenovirus 41F



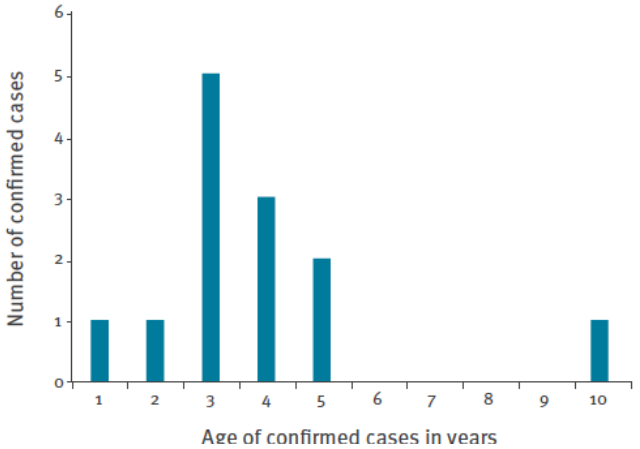
Adenovirus 41F y Adenovirus asociado

Hepatitis fulminantes infantiles

Epidemiología: Origen de la alerta casos en Escocia (12 de abril)

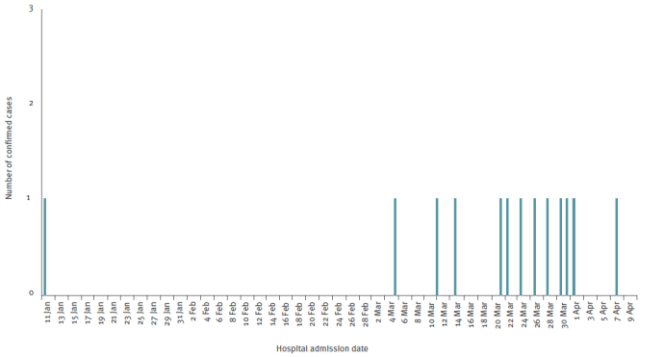
IDENTIFICACIÓN PRIMEROS CASOS

- 5 casos de hepatitis aguda grave (enero a marzo)
- Casos esperados en Escocia para el año 2022 solo 4
- Tres niños fueron derivados a Unidad de trasplante hepático
- Manifestaciones clínicas y analíticas antes del ingreso:
  - Vómitos en las semanas anteriores
  - Ictericia
  - ALT > 2.000 U/L
  - Negativo a agentes frecuentes



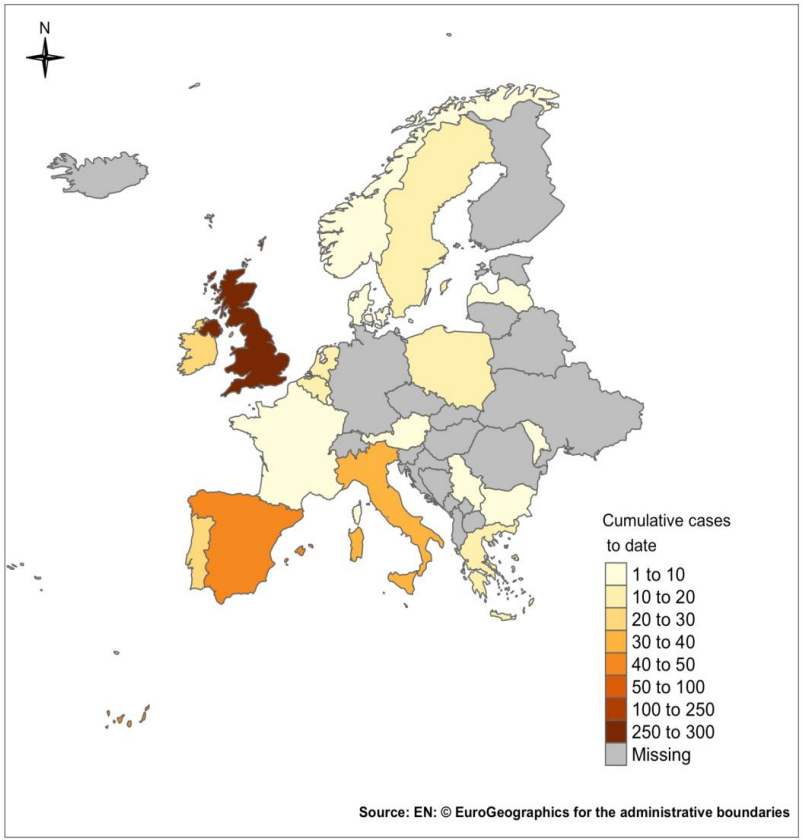
IDENTIFICACIÓN RETROSPECTIVA DE CASOS

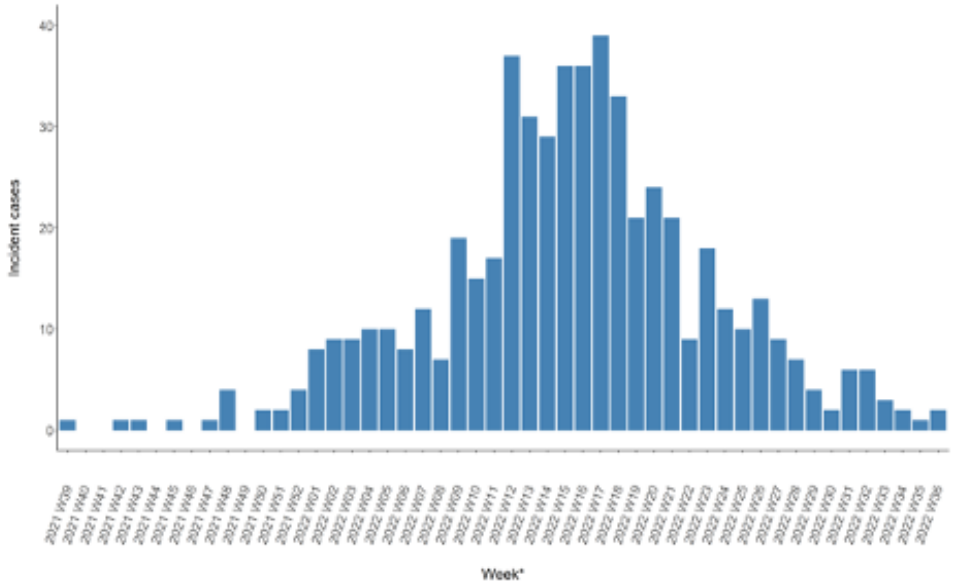
- 13 casos concentrados en 3 semanas
- Mediana de edad 3,9 años (IQR: 3,6-4,6 años)
- Siete eran niñas
- Todos caucásicos.
- Todos los casos vivían en el centro de Escocia (2 relacionados)
- Ninguno fiebre
- Sin con comorbilidades previas



Marsh et al Eurosurveillance April 2022

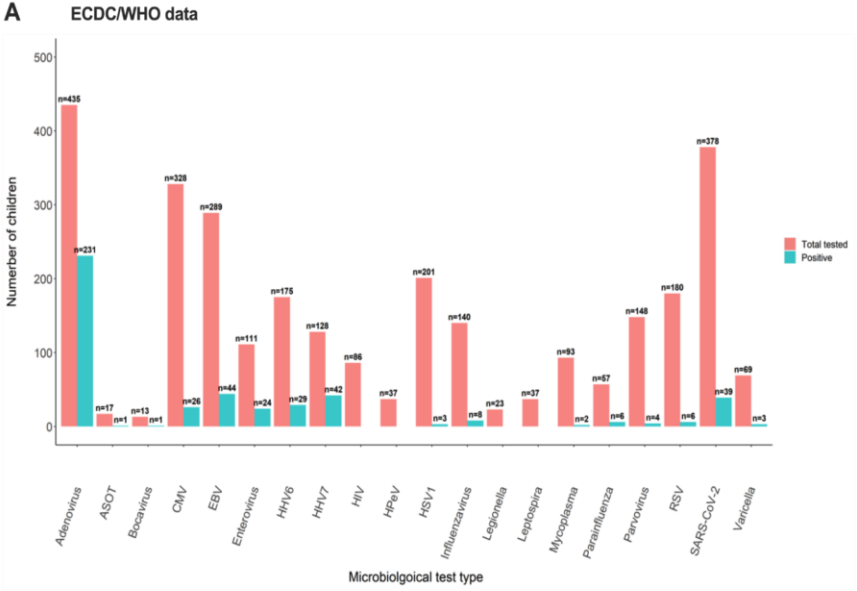
Epidemiología: Situación actual en Europa

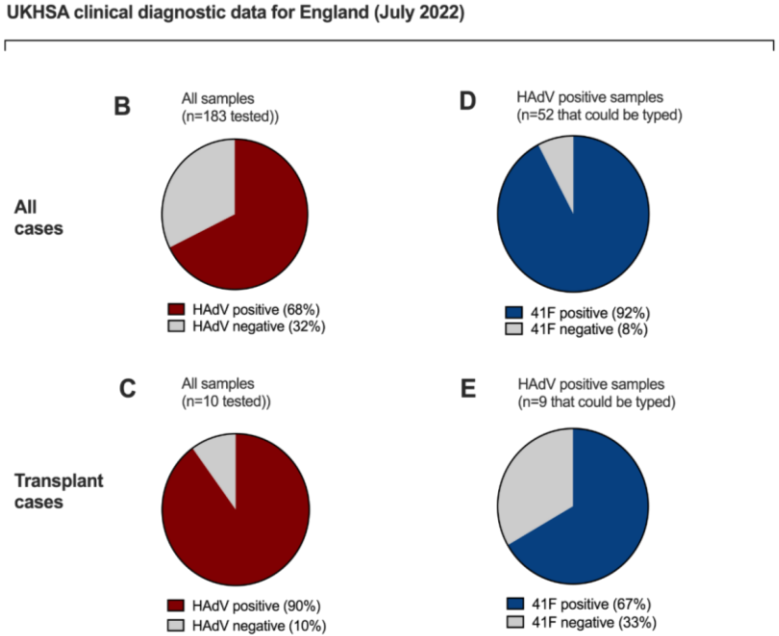




ESGVH Frontiers Pharmacology 2022

Etiología: Adenovirus 41F

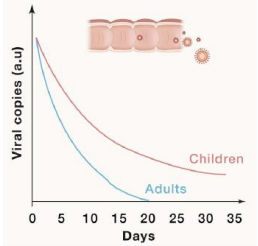




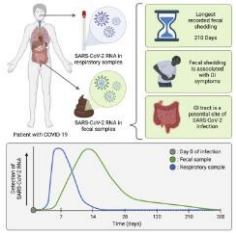
ESGVH Frontiers Pharmacology 2022

Etiología: Adenovirus 41F como agente causal +SARSCoV2

Reservorio digestivo



Brodin Immunity 2022

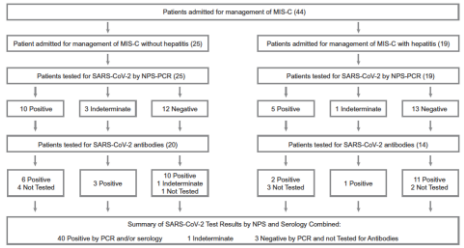


Natarajan et al Med 2022

¿?

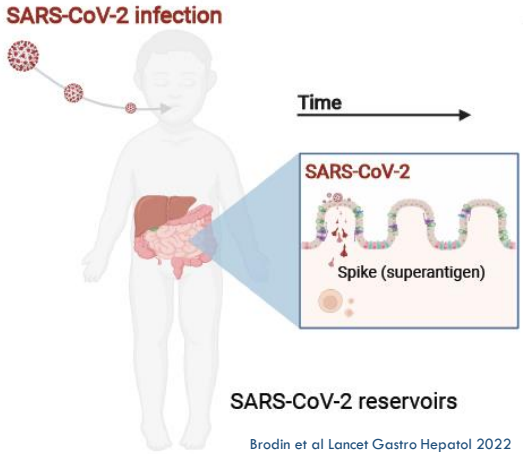
MIS-C

Fallo hepático y MIS-C



Cantor et al Hepatol 2020

SARS-CoV-2 infection

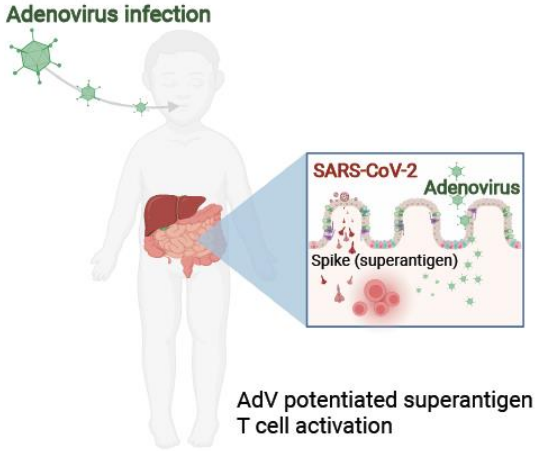


SARS-CoV-2 reservoirs

Brodin et al Lancet Gastro Hepatol 2022

MIS-C-like

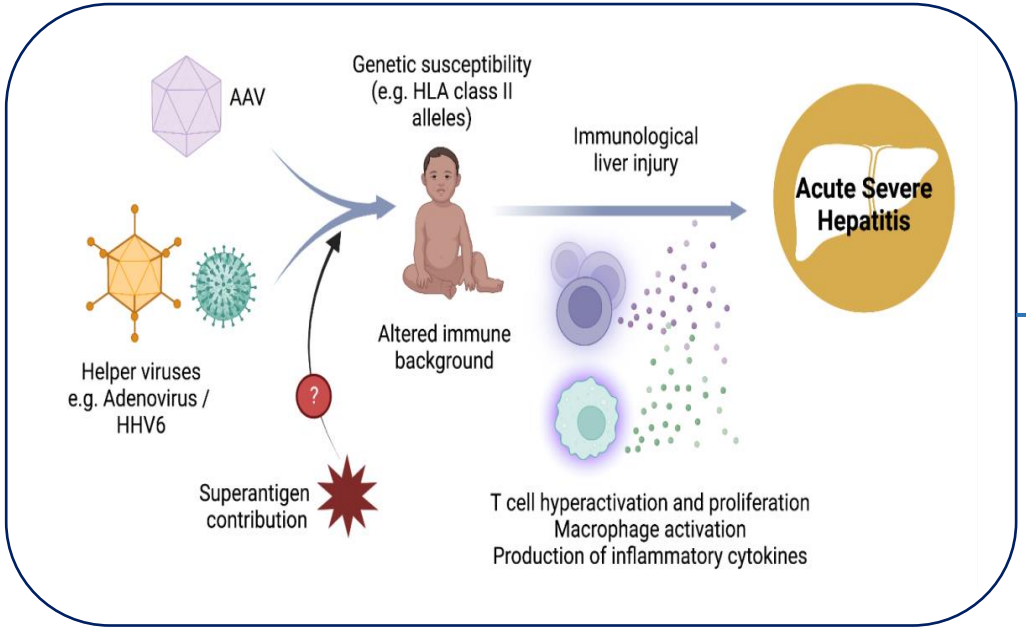
Adenovirus infection

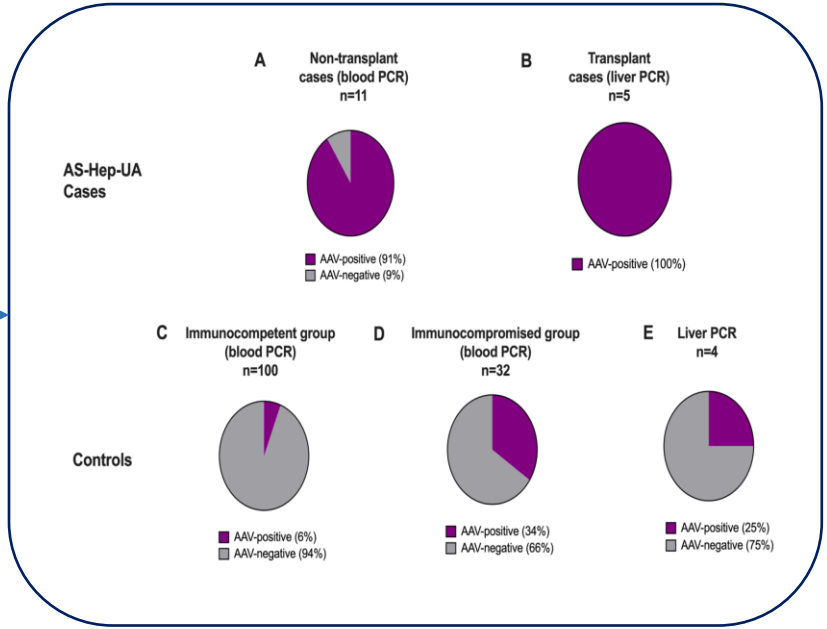


AdV potentiated superantigen T cell activation

Brodin et al Lancet Gastro Hepatol 2022

Etiología: Adenovirus 41F + otros virus + susceptibilidad genética (HLA-DRB1*04:01)





ESGVH Frontiers Pharmacology 2022

Novedades:

nature

https://doi.org/10.1038/s41586-023-05948-2

Accelerated Article Preview

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

Received: 21 July 2022

Accepted: 10 March 2023

Accelerated Article Preview

Cite this article as: Ho, A. et al. Adeno-associated virus 2 infection in children with non-A-E hepatitis. *Nature* https://doi.org/10.1038/s41586-023-05948-2 (2023)

Antonia Ho, Richard Orton, Rachel Tayler, Patawee Asamaphan, Vanessa Herder, Chris Davis, Lily Tong, Katherine Smollett, Maria Manali, Jay Allan, Konrad Rawlik, Sarah E. McDonald, Elen Vink, Louisa Pollock, Louise Gannon, Clair Evans, Jim McMenamin, Kirsty Roy, Kimberly Marsh, Titus Divala, Matthew T. G. Holden, Michael Lockhart, David Yirrell, Sandra Currie, Maureen O'Leary, David Henderson, Samantha J. Shepherd, Celia Jackson, Rory Gunson, Alasdair MacLean, Neil McInnes, Amanda Bradley-Stewart, Richard Battle, Jill Hollenbach, Paul Henderson, Miranda Odam, Primrose Chikowore, Wilna Oosthuyzen, Meera Chand, Meli… Michael Levin, Nikos Avramidis, Erola … DIAMONDS consortium, ISARIC4C inv… David L. Robertson, Ana da Silva Filipe… David Turner, J. Kenneth Baillie & Emm…

nature

https://doi.org/10.1038/s41586-023-05949-1

Accelerated Article Preview

Adeno-associated virus type 2 in US children with acute severe hepatitis

Received: 11 September 2022

Accepted: 10 March 2023

Accelerated Article Preview

Cite this article as: Servellita, V. et al. Adeno-associated virus type 2 in US …

Venice Servellita, Alicia Sotomayor Gonzalez, Daryl M. Lamson, Abiodun Foresythe, Hee Jae Huh, Adam L. Bazinet, Nicholas H. Bergman, Robert L. Bull, Karla Y. Garcia, Jennifer S. Goodrich, Sean P. Lovett, Kisha Parker, Diana Radune, April Hatada, Chao-Yang Pan, Kyle Rizzo, J. Bradford Bertumen, Christina Morales, Paul E. Oluniyi, Jenny Nguyen, Jessica Tan, Doug Stryke, Rayah Jaber, Matthew T. Leslie, Zin Lyons, Hayden D. Hedman, Umesh Parashar, Maureen Sullivan, Kelly Wroblewski, M. Steven Oberste, Jacqueline E. Tate, Julia M. Baker, David Sugerman, Caelin Potts, … Preeti Chhabra, L. Amanda Ingram, Henry Shiau, William Britt, …utierrez Sanchez, Caroline Ciric, Christina A. Rostad, Jan Vinjé, …rking, Debra A. Wadford, R. Taylor Raborn, Kirsten St. George & …iu

nature

https://doi.org/10.1038/s41586-023-06003-w

Accelerated Article Preview

Genomic investigations of unexplained acute hepatitis in children

Received: 25 July 2022

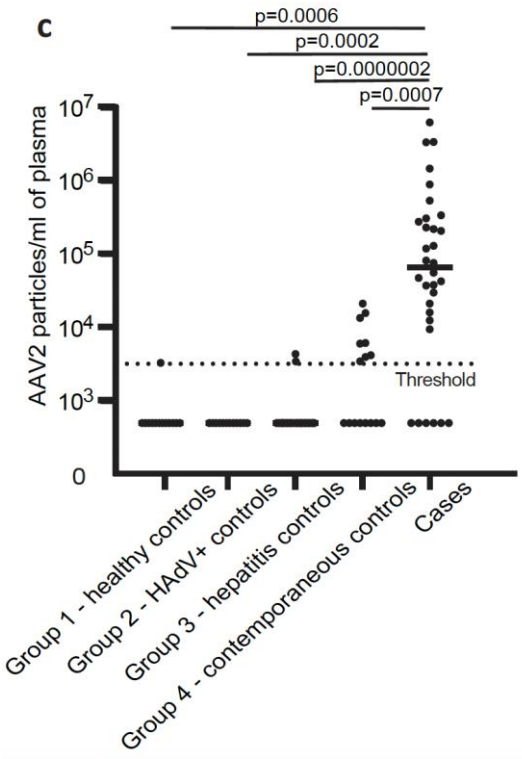
Accepted: 23 March 2023

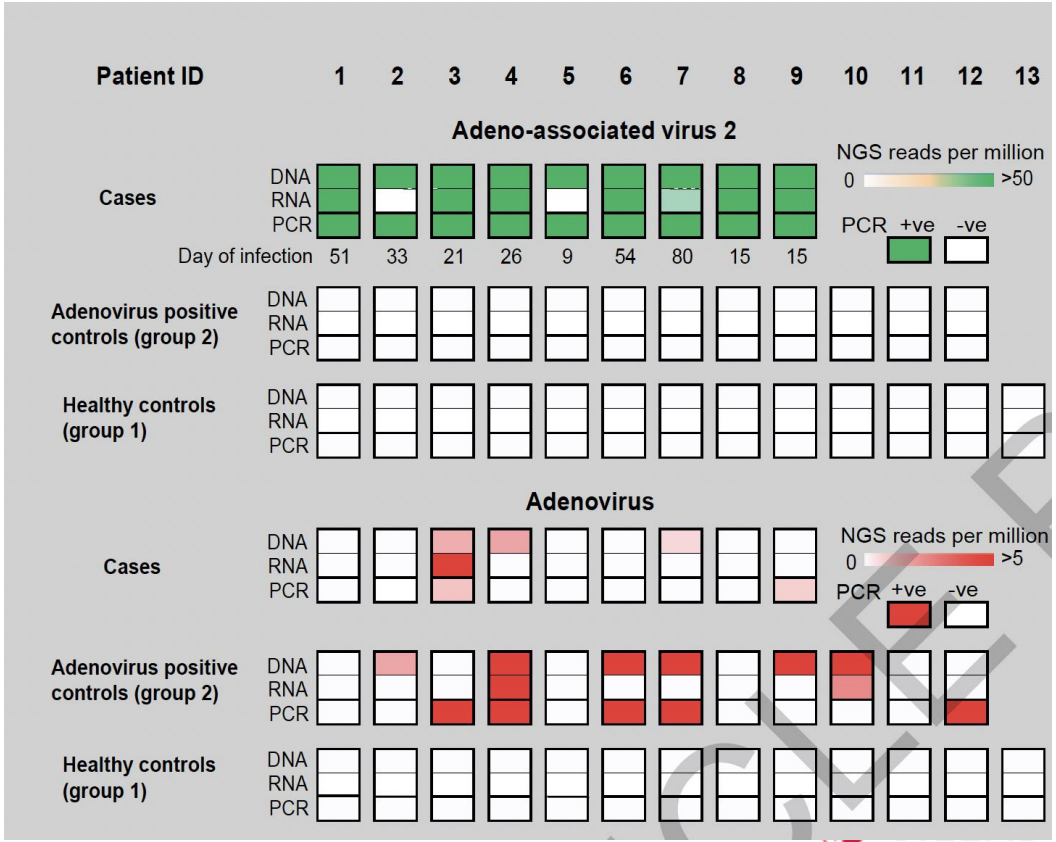
Accelerated Article Preview

Cite this article as: Morfopoulou, S. Genomic investigations of unexplained acute hepatitis in children. *Nature* https://doi.org/10.1038/s41586-023-06003-w (2023)

Sofia Morfopoulou, Sarah Buddle, Oscar Enrique Torres Montaguth, Laura Atkinson, José Afonso Guerra-Assunção, Mahdi Moradi Marjaneh, Riccardo Zenezini Chiozzi, Nathaniel Storey, Luis Campos, J. Ciaran Hutchinson, John R. Counsell, Gabriele Pollara, Sunando Roy, Cristina Venturini, Juan F. Antinao Diaz, Ala'a Siam, Luke J. Tappouni, Zeinab Asgarian, Joanne Ng, Killian S. Hanlon, Alexander Lennon, Andrew McArdle, Agata Czap, Joshua Rosenheim, Catarina Andrade, Glenn Anderson, Jack C. D. Lee, Rachel Williams, Charlotte A. Williams, Helena Tutill, Nadua Bayzid, Luz Marina Martin Bernal, Hannah Macpherson, Kylie-Ann Montgomery, Catherine Moore, Kate Templeton, Claire Neill, Matt Holden, Rory Gunson, Samantha J. Shepherd, Priyen Shah, Samantha Cooray, Marie Voice, Michael Steele, Colin Fink, Thomas E. Whittaker, Giorgia Santilli, Paul Gissen, Benedikt B. Kaufer, Jana Reich, Julien Andreani, Peter Simmonds, Dimah K. Alrabiah, Sergi Castellano Hereza, Primrose Chikowore, Miranda Odam, Tommy Rampling, Catherine Houlihan, Katja Hoschler, Tiina Talts, Cristina Celma, Suam Gonzalez, Eileen Gallagher, Ruth Simmons, Conall Watson, Sema Mandal, Maria Zambon, Meera Chand, James Hatcher, Surjo De, Kenneth Baillie, Malcolm Gracie Semple, DIAMONDS Consortium, PERFORM Consortium, ISARIC Consortium, Joanne Martin, Ines Ushiro-Lumb, Mahdad Noursadeghi, Maesha Deheragoda, Nedim Hadzic, Tassos Grammatikopoulos, Rachel Brown, Chayarani Kelgeri, Konstantinos Thalassinos, Simon N. Waddington, Thomas S. Jacques, Emma Thomson, Michael Levin, Julianne R. Brown & Judith Breuer

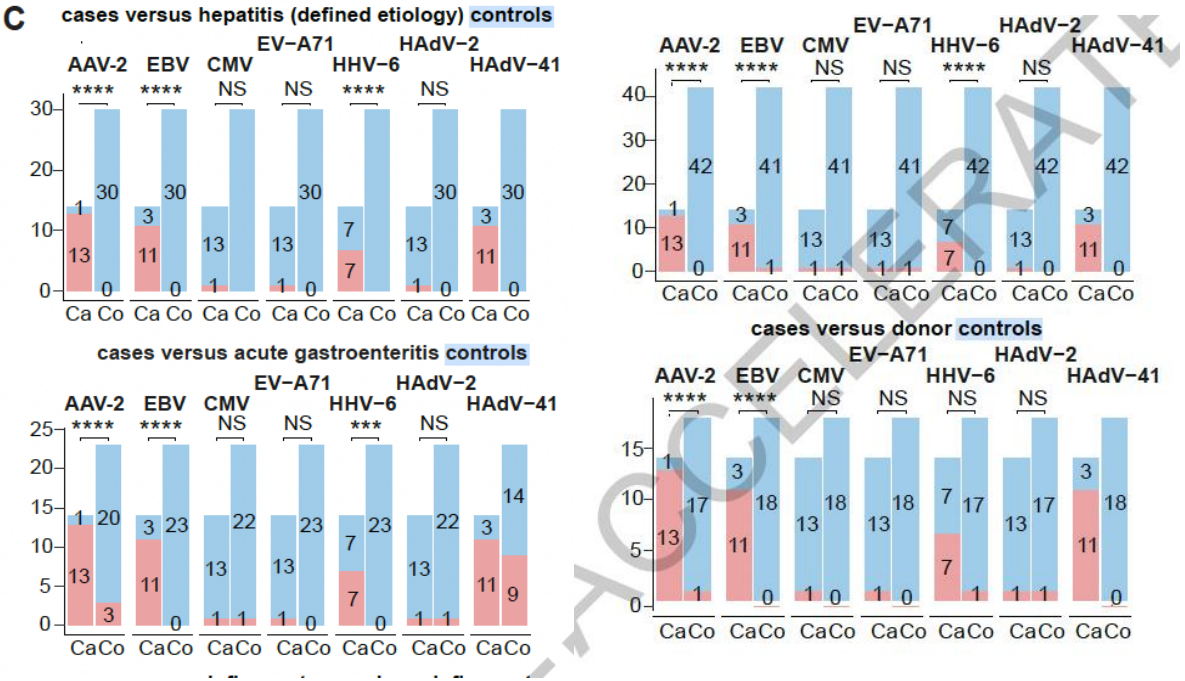
Estudio UK: AAV2 y HV6

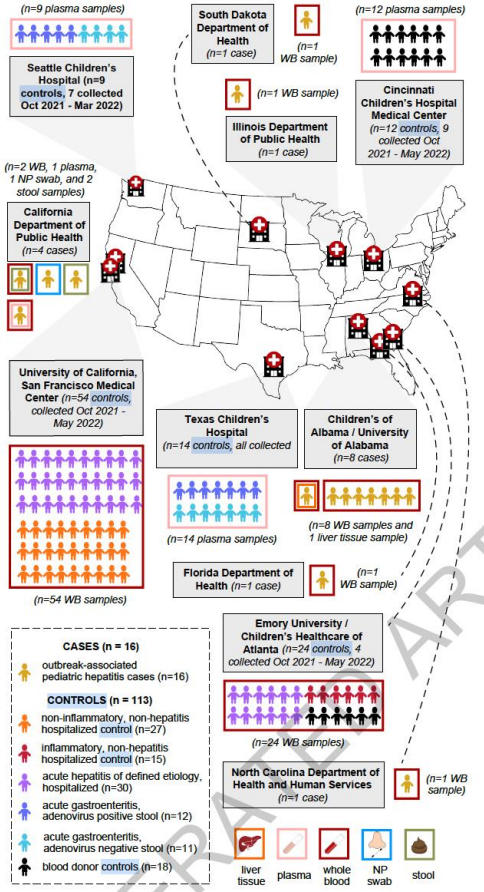




Ho et al Nature 2023

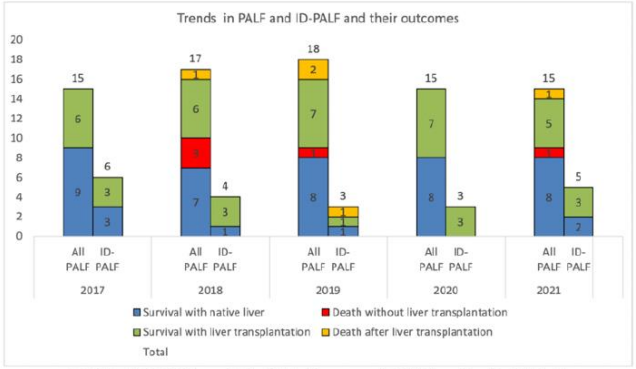
Estudio UK: AAV2 y HV6





Servellite et al Nature 2023

Trend of Indeterminate PALF
The 2022 outbreak



2017-2021 – ID-PALF was 26% of all PALF

10 cases of ID-PALF
in Jan to June 2022

Jan to June 2022
ID-PALF was 58.8% of all PALF

Adenoviraemia in ID-PALF –
Not a new or rare disease

Trends in the community of adenovirus infection from any site (1-4 years of age)

2017-2019	2020-2021	Jan to June 2022
Adenoviraemia in 6/13 (46%) of ID-PALF	No Adenoviraemia in ID-PALF	Adenoviraemia in 10/10 (100%) of ID-PALF
200 to 300 cases per week	*<50 cases per week*	*200 to 300 cases per week*

Comparison of cases of ID-PALF with adenoviraemia

Cases in 2017-2019 (n=6) **Vs** Cases in 2022 (n=10)

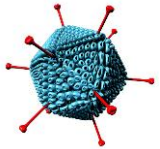
More frequent hepatic encephalopathy, hypotension requiring vasoactive medications and higher plasma ammonia levels (admission and peak). with similar native liver survival in 2022

Jagadisan et al J Hepatol 2023

Consideraciones personales

Distribución Mundial con mayor incidencia en UK

→ Único país con vigilancia real + factores genéticos



Agente causal herpes 6 y Adenovirus 41 potenciado por replicación AAV2

→ No determinado en ningún hospital del SNS. Sin necesidad de HAdv – igual que otros virus (HDV)

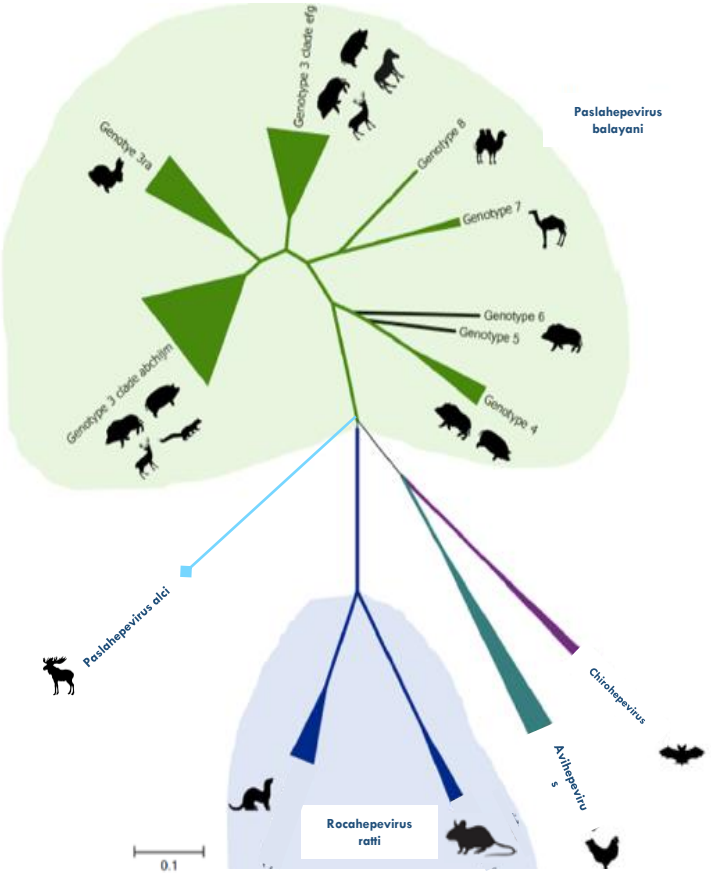
¿Consecuencia pandemia CoVID-19?

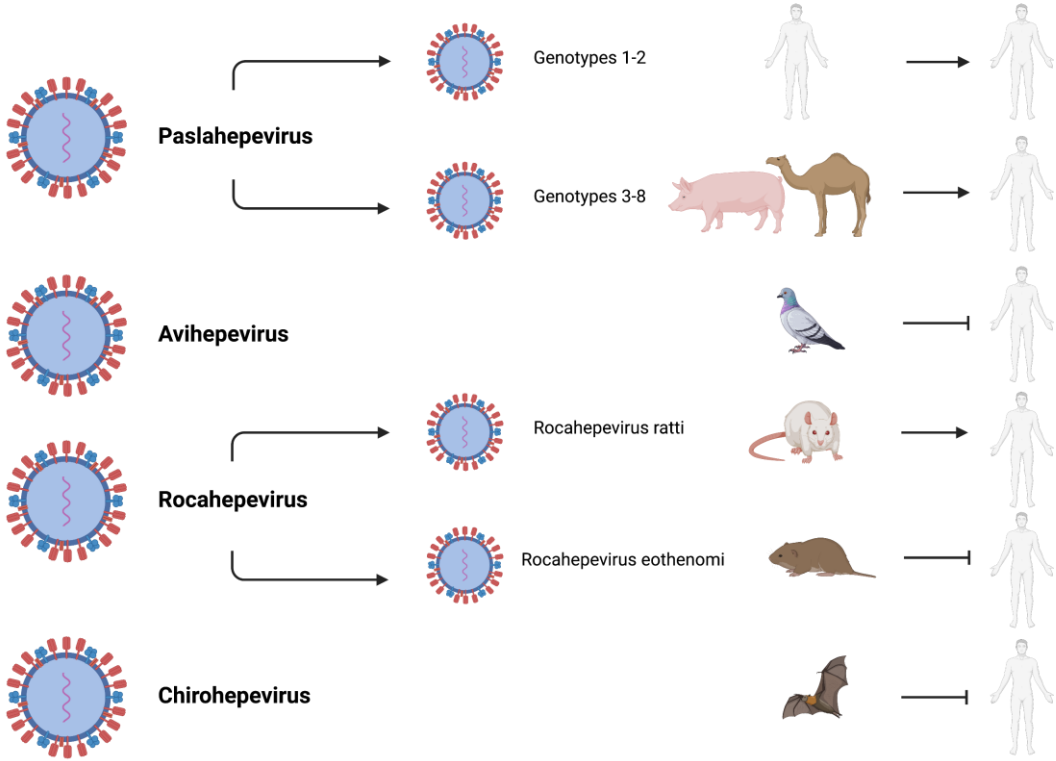
→ ¿Cuál es el papel en el adulto?

GILEAD
Creating Possible

Rocahepevirus ratti

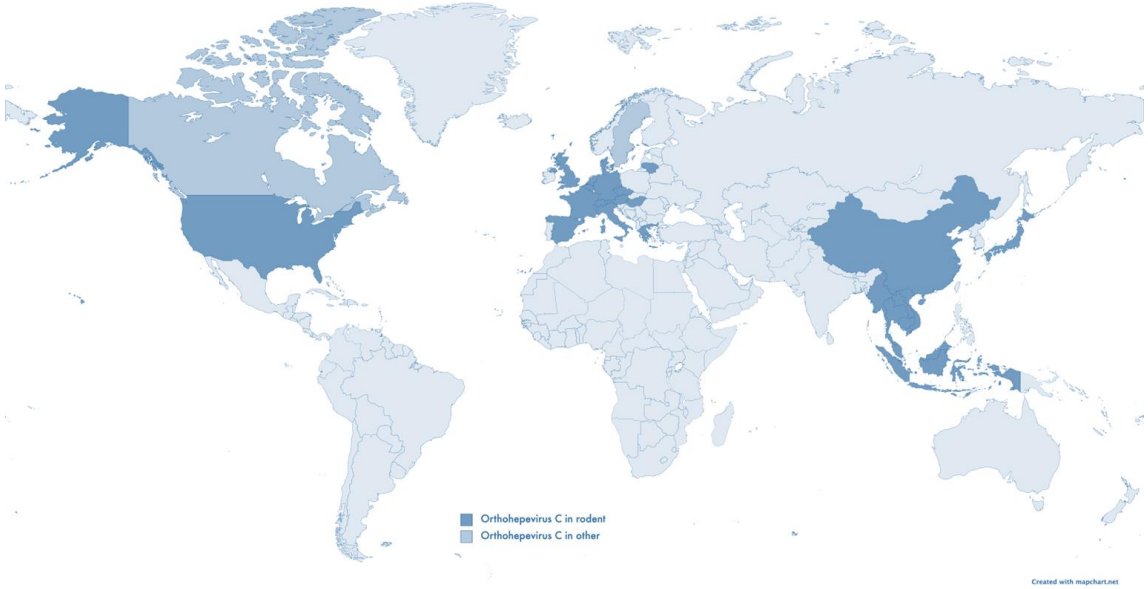
El primo del virus de la Hepatitis E





Rivero-Juarez A (original figure created with Mega)

Rivero-Juarez A (original figure created with Biorender)



Genotype C1

Mus musculus
Apodemus chevrieri

Rattus rattus
Rattus norvegicus
Rattus ratoides
Rattus tanezumi

Bandicota indica

Eothenomys chinensis

Microtus arvalis

Suncus murinus

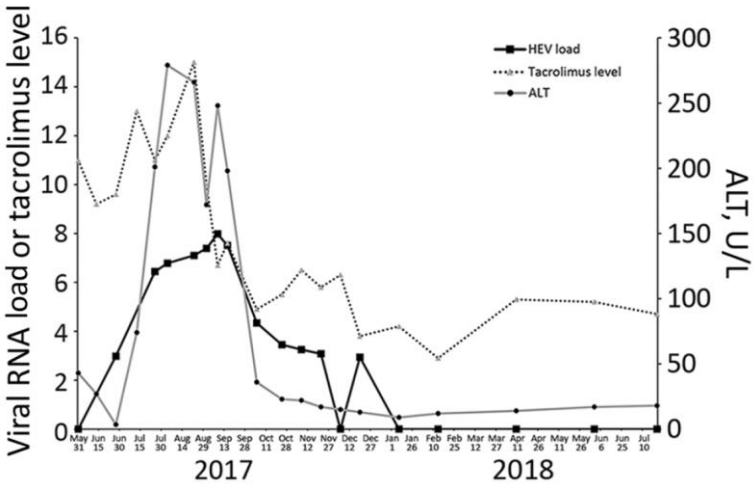
Genotype C2

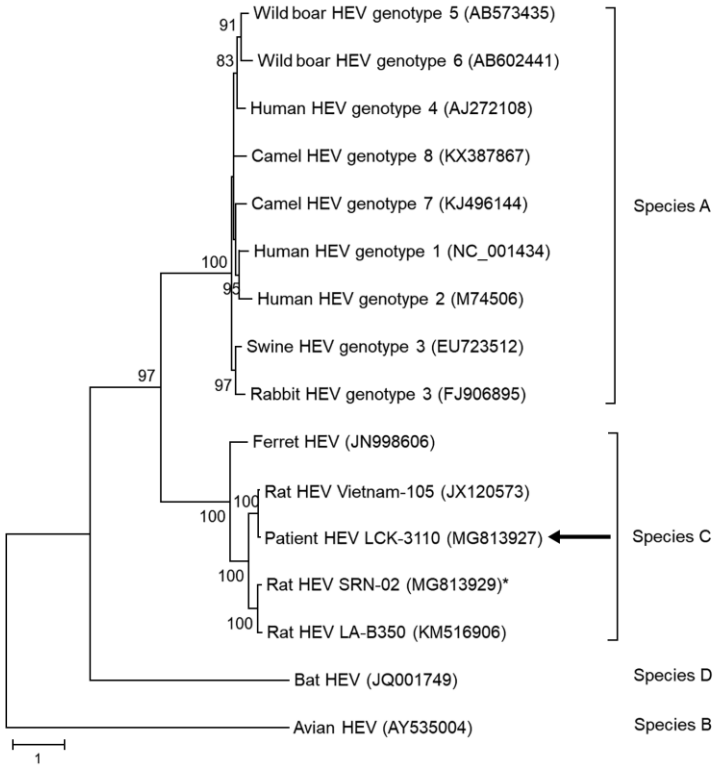
Mustela putorius

Genotype C3

Maxomys surifer

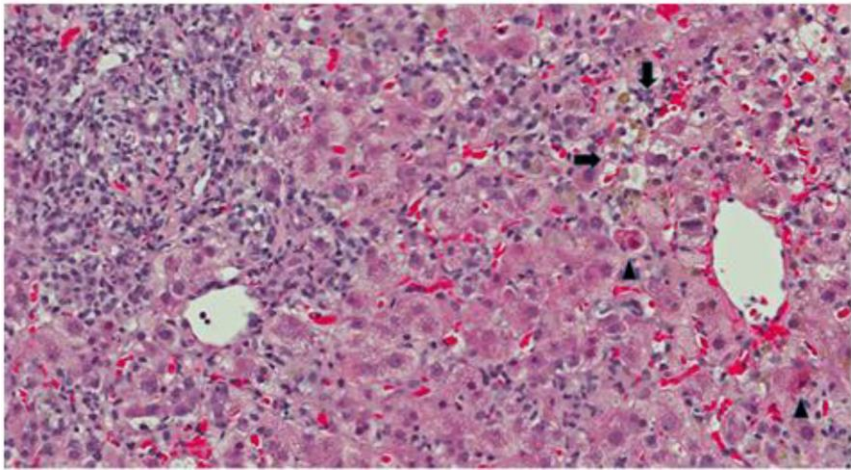
Rat Hepatitis E Virus as Cause of Persistent Hepatitis after Liver Transplant

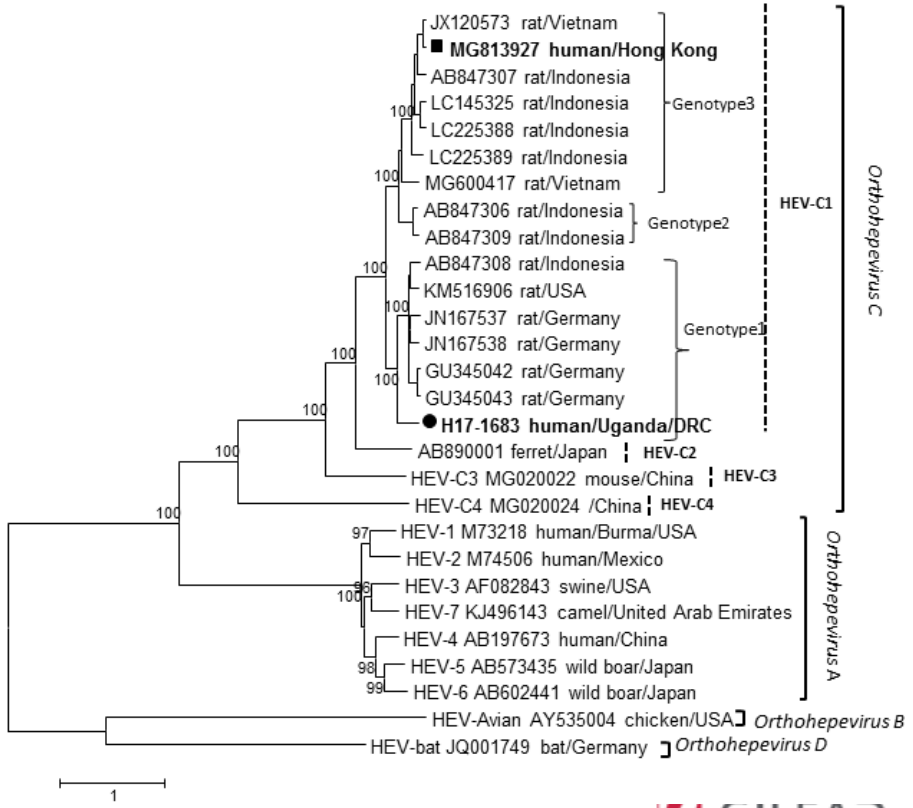




Sridhar *et al* Emerg Infect Dis 2018

Rat Hepatitis E Virus Linked to Severe Acute Hepatitis in an Immunocompetent Patient



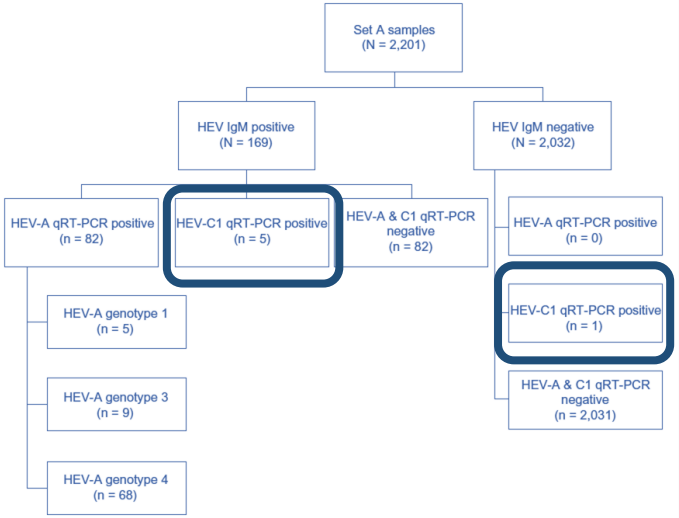


Andonov *et al* J Infect Dis 2019

Retrospective screening

Transmission of Rat Hepatitis E Virus Infection to Humans in Hong Kong: A Clinical and Epidemiological Analysis

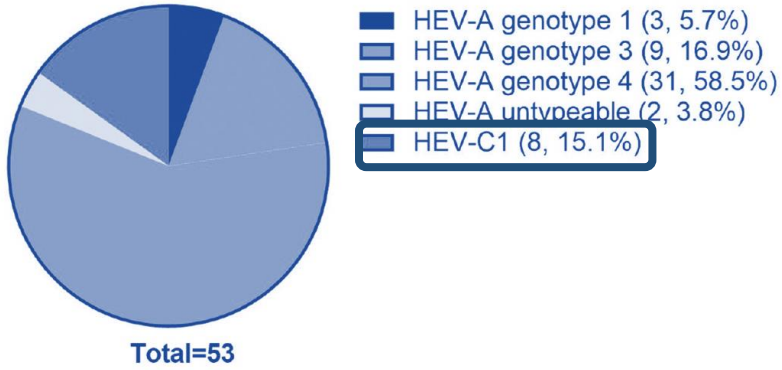
Sridhar *et al* Hepatology 2021



Prospective screening

Hepatitis E virus species C infection in humans, Hong Kong

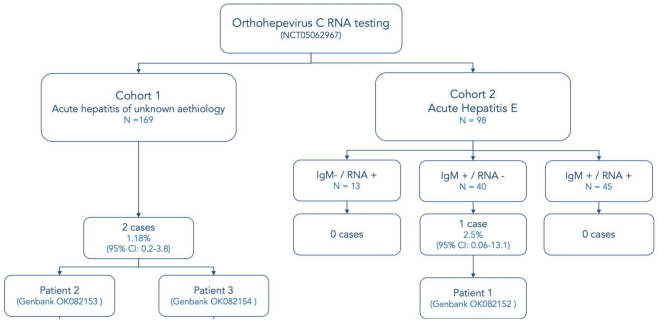
Sridhar *et al* Clin Infect Dis 2022



Retrospective screening

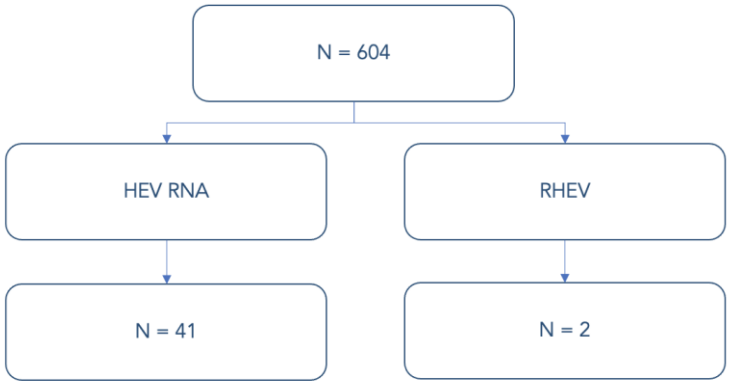
Orthohepevirus C infection as an emerging cause of acute hepatitis in Spain: First report in Europe

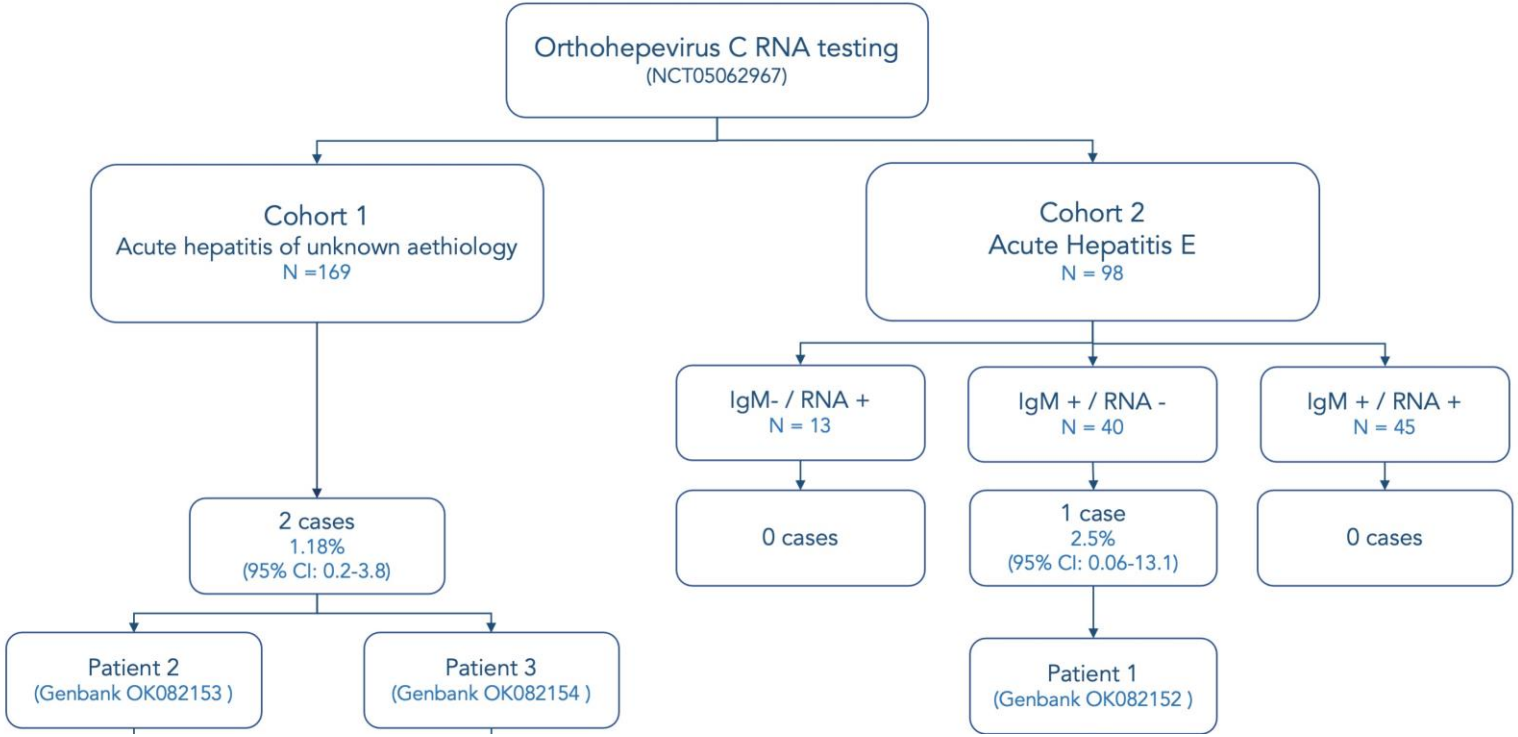
Rivero-Juarez *et al* J Hepatology 2022



Prospective screening

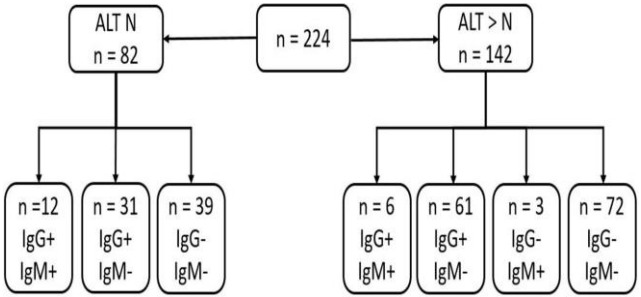
Corona-Mata et al ECCMID 2023





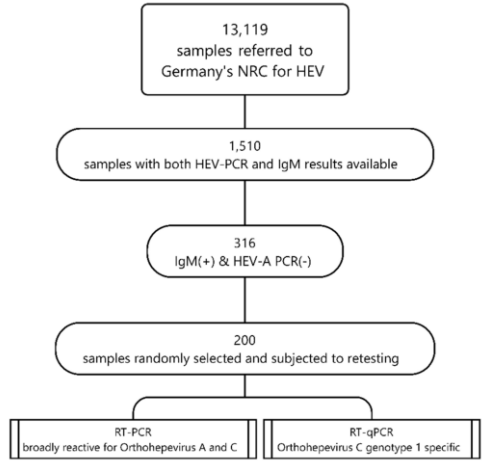
Rivero-Juarez *et al* J Hepatology 2022

Rat Hepatitis E Virus: Presence in Humans in South-Western France?

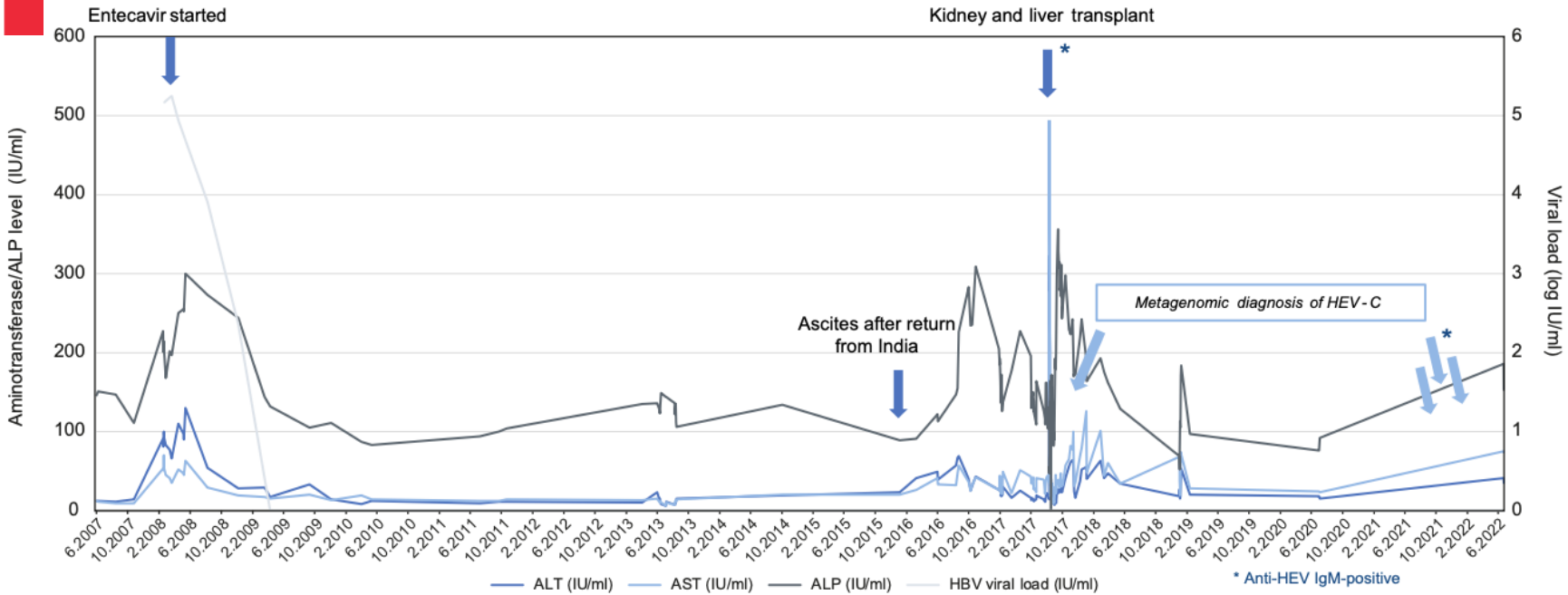


Parraud et al Frontiers Microb 2021

No Evidence for Orthohepevirus C in Archived Human Samples in Germany, 2000–2020



Faber et al Viruses 2022



Rodriguez et al J Hepatology 2023

	2021	2022	2023	Global
HEV	• Wastewater = 1 of 43 • Patients = 4 of 107	• Wastewater = 0 of 52 • Patients = 13 of 162	• Wastewater = 0 of 11 • Patients = 5 of 35	• Wastewater = 1 of 106 (0.9%) • Patients = 22 of 304 (7.2%) • Rodents = 0 of 20
RHEV	• Wastewater = 42 of 43 • Patients = 0 of 107	• Wastewater = 48 of 50 • Patients = 2 of 162	• Wastewater = 10 of 11 • Patients = 0 of 35	• Wastewater = 100 of 106 (94.3%) • Patients = 2 of 304 (0.7%) • Rodents = 11 of 20 (55%)

Casares-Jimenez *et al* Undereview

	Patient 1* (Index Case)	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Age	56	71	67	81	74	73	67	43
Sex	M	F	M	M	M	M	M	M
Chronic medical conditions/organ transplants	Liver transplant (2017)	Rheumatoid arthritis	Kidney transplant (1999)	Prostate cancer	Kidney transplant (2003)	Hypertension, diabetes mellitus	Metastatic cancer	HIV infection
Hepatitis B carrier/treatment	Yes/Entecavir	No	No	No	Yes/Tenofovir	No	No	No
Immunosuppressive medication	Prednisolone Mycophenolate Tacrolimus	Methotrexate Sulfasalazine	Prednisolone Cyclosporin A Sirolimus	None	Prednisolone Mycophenolate Everolimus	None	None	None
Exposure to rodents or rodent feces	Yes	No	No	No	No	No	No	No
Travel outside Hong Kong	No	No	Yes (Japan)	No	No	No	No	No
Infection type	Persistent	Acute	Persistent	Acute	Persistent	Acute	Subclinical	Persistent
Reason for presentation	Abnormal LFTs	Malaise	Abnormal LFTs	Malaise	Abnormal LFTs	Abnormal LFTs	N/A	Abnormal LFTs
Hepatitis onset time	July 2017	April 2017	May 2018	April 2019	May 2018	June 2019	N/A	May 2019
HEV-IgM/IgG†	+/+	+/+	–/+	+/+	+/+	+/+	–/+	+/–
Peak ALT (U/L)	279	498	141	410	133	498	20	685
Peak bilirubin (βmol/L)	21	10	12	14	11	<3	6	14
Peak prothrombin time (s)	13.8	12.7	10.9	12.6	20.4	N/A	9.9	11.6
Liver imaging findings	Normal	Parenchymal disease	Fatty liver	Normal	Fatty liver	N/A	Normal	NA
Received ribavirin	Yes	No	Yes	No	No	No	No	No
Mortality	No	No	No	No	Yes	No	No	No

Immunosupressed Partially immunosupressed Immunocompetent

Sridhar *et al* Hepatology 2021

Variable	Patient 1	Patient 2	Patient 3
Cohort of origin	Cohort 2	Cohort 1	Cohort 1
Age (years)	62	30	54
Sex	Male	Male	Male
Year of the sample	2020	2018	2019
Region	Southern Spain	Southern Spain	Northern Spain
Location	Córdoba	Seville	Vitoria
Significant underlying disorder	Metastatic oral cancer	No	No
Concomitant medication	Amoxicillin and clavulanic acid* dexamethasone†	No	Atorvastatine‡
Exposure to domestic animals	No	No	No
Exposure to wild animals	No	No	No
Exposure to rodents	No	No	No
Consumption of raw or undercooked meat	Yes	Yes	No
Travel outside Spain	No	No	No
Blood transfusion	No	No	No
Other risk practice for HEV	No	Cleaning staff	Unknown
IgG anti-HEV antibodies	Positive	Negative	Positive
IgM anti-HEV antibodies	Positive	Negative	Negative
Peak ALT (U/L)	400	554	173
Peak AST (U/L)	340	549	137
Peak GGT (U/L)	630	72	536
Peak bilirubin (mg/dl)	8.4	0.7	1.09
Hospital admission	Yes	No	No
Intensive care unit admission	Yes	No	No
Infection outcome	Death by liver and renal failure	Self-limited	Self-limited

Immunosupressed Partially immunosupressed Immunocompetent

Rivero-Juarez *et al* J Hepatology 2022

Multimodal investigation of rat hepatitis E virus antigenicity: Implications for infection, diagnostics, and vaccine efficacy

HEV-C1 sera
- ✓ Low sensitivity (0%) of antigen assays
- ✓ Low sensitivity (20 – 40%) of IgM assays
- ✓ Variable sensitivity (10 – 70%) of IgG assays

Table 2. Positive detection rate (sensitivity) of commercial HEV-IgG and IgM assays.

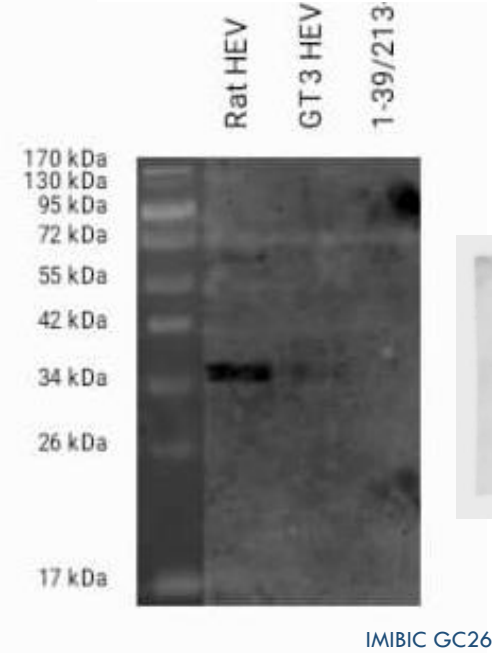
Assay	Positive detection rate (%) Panels A + B (HEV-A; n = 39)	Panel C (HEV-C1; n = 10)	*p* value*
Wantai IgM	36/39 (92.3)	4/10 (40)	<0.005
Bei'er IgM	35/39 (89.7)	3/10 (30)	<0.005
Novus IgM	35/39 (89.7)	2/10 (20)	<0.005
Wantai IgG	34/39 (87.2)	7/10 (70)	0.333
Bei'er IgG	25/39 (64.1)	1/10 (10)	0.003
Novus IgG	28/39 (72)	1/10 (10)	<0.005

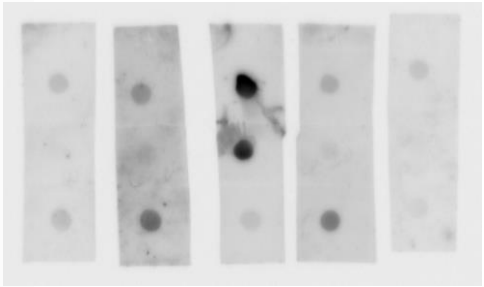
HEV, hepatitis E virus; HEV-A, HEV species *A*; HEV-C1, HEV species *C*.
*Inter-column *p* values calculated by Fisher's exact test; intra-column *p* values (presented in text) calculated by McNemar's test.

Points to be assesed:
False positive for HEV – cross-reaction
Lack of commercial IgG or IgM assays

Sridhar *et al* J Hepatology 2021

FRIEDRICH-LOEFFLER-INSTITUT
FLI
Bundesforschungsinstitut für Tiergesundheit
Federal Research Institute for Animal Health





IMIBIC GC26 Interim data

Serological and molecular survey of hepatitis E virus in cats and dogs in Spain

Caballero-Gomez *et al* Trans Emerg Dis 2022a

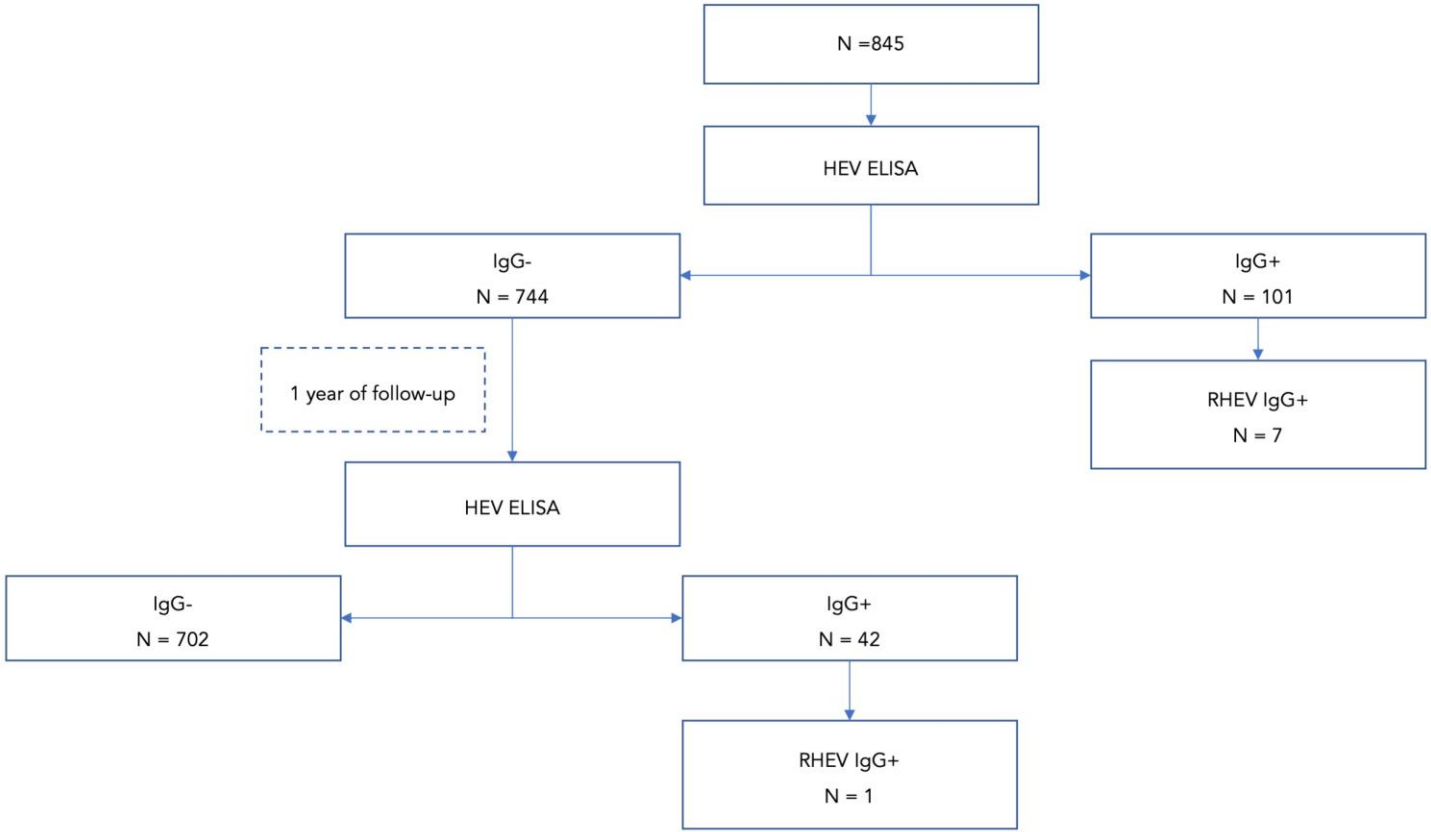
Hepatitis E virus in the endangered Iberian lynx (*Lynx pardinus*)

Caballero-Gomez *et al* Trans Emerg Dis 2022b

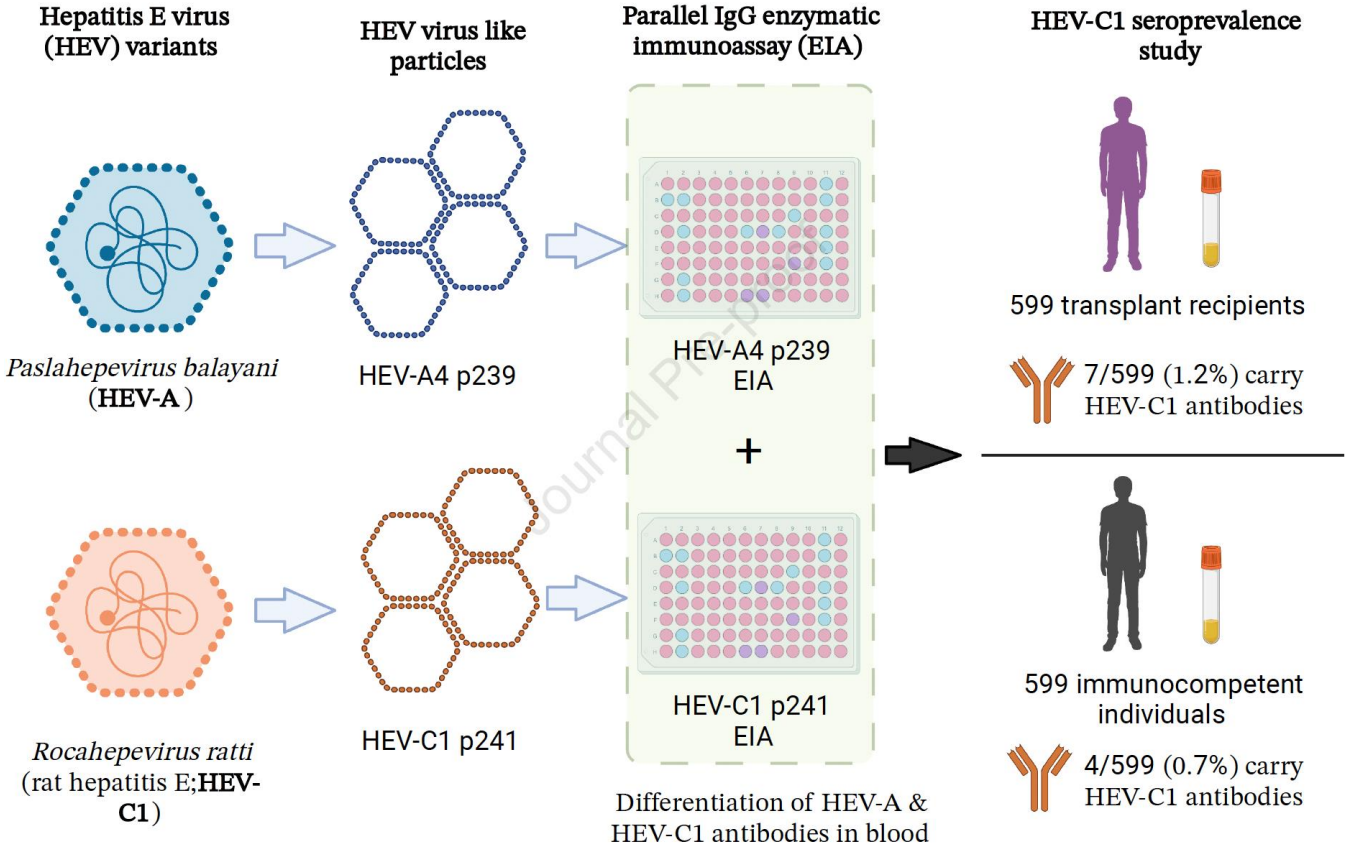
Monitoring of hepatitis E virus in zoo animals from Spain, 2007–2021

Caballero-Gomez *et al* Trans Emerg Dis 2022c

GILEAD
Creating Possible



Rivero-Juarez *et al* Undereview

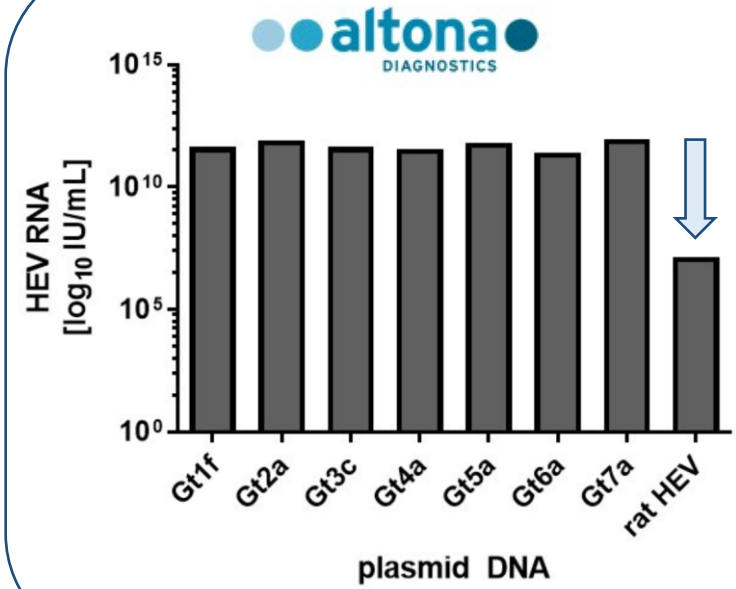


Situ *et al* JHEP Rep

In-house

Reference	PCR
Johne et al J Gen Virol 2010	Nested
Lack et al Emerging 2013	Nested
Li et al J Gen Virol 2011	Nested
Li et al J Gen Virol 2015	qPCR
Shielke et al Virol J 2009	Nested
Drexler et al J Virol 2012	Nested
Shirsta et al Hepatology 2020	qPCR
	Whole genome sequence

Commercial



Behrendt et al Liv Inter 2021

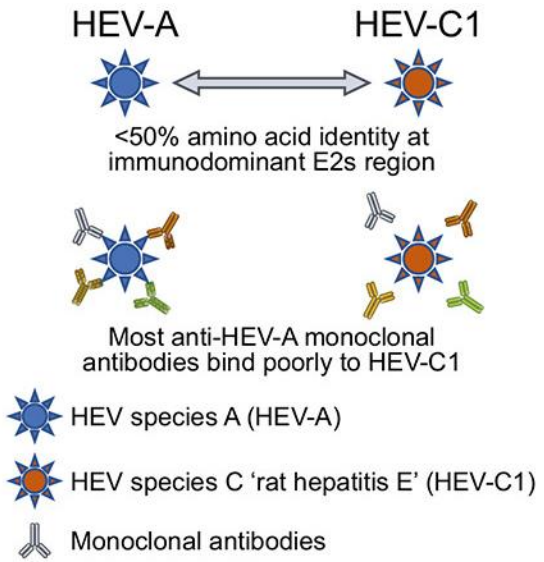
Points to be assesed:
Need and spceific approach
Lack of comercial assays

Characteristic	HEV-C1 Group (n = 9)	HEV-A Group (n = 12)
Sex, male	7 (77.8)	9 (75)
Mean age, y	59.8	52.8
Immunosuppressive condition		
Liver transplant	2 (22.2)	1 (8.3)
Kidney transplant	3 (33.3)	6 (50.0)
Heart transplant	0 (0.0)	1 (8.3)
Lung transplant	0 (0.0)	1 (8.3)
HSCT	1 (11.1)	1 (8.3)
Hematological malignancy	1 (11.1)	2 (16.7)
Advanced HIV	1 (11.1)	0 (0.0)
Rheumatic disorder	1 (11.1)	0 (0.0)
Hepatitis E outcomes		
Spontaneous resolution	1/9 (11.1)	0/12 (0.0)
Early ribavirin with SVR[a]	1/9 (11.1)	2/12 (16.7)
Persistent infection	7/9 (77.8)	10/12 (75.0)
Outcomes of persistent hepatitis E		
Death before treatment	2/7 (28.6)	2/10 (20.0)
Resolved with reduced immunosuppression	0/7 (0.0)	1/10 (10.0)
SVR on ribavirin	4/7 (57.1)	4/10 (40.0)
Ribavirin nonresponder	0/7 (0.0)	2/10 (20.0)
Responsive, but not attained SVR at time of study	1/7 (14.3)	1/10 (10.0)

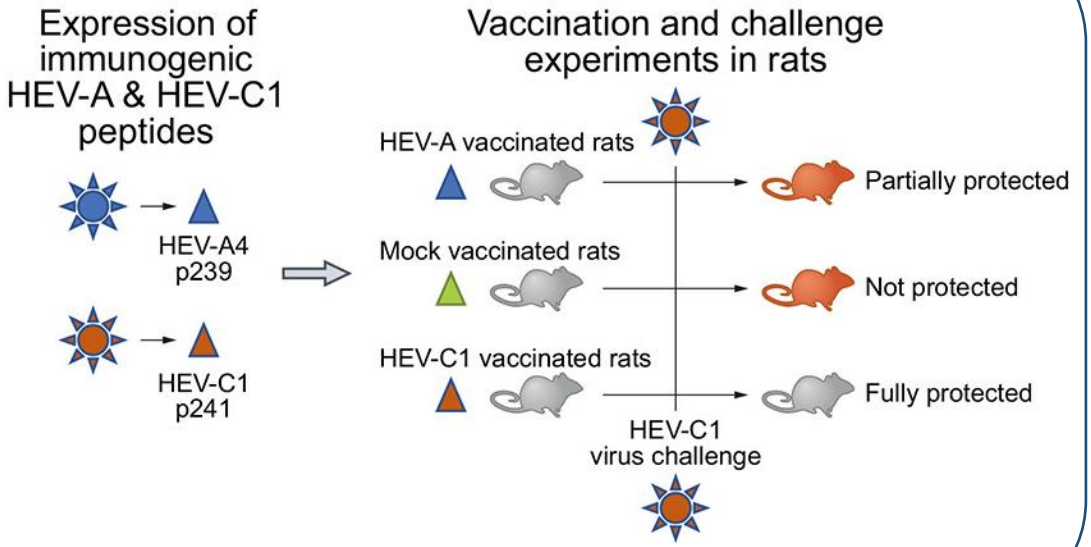
Patient	P1[a]	P3[b,c]	P8[b]	P12[c,d]	P15[d]	P16[d]
Reason for starting RBV	Persistent hepatitis E	Persistent hepatitis E	Persistent hepatitis E	Persistent hepatitis E	Persistent hepatitis E	Acute hepatitis E; Imminent transplantation
RBV dosage[e]	800 mg daily	1st course 200 mg daily → 400/200 mg alt day → 400 mg daily 2nd course: 600 mg/day	800 mg daily	600 mg daily → 400 mg daily	800 mg daily	800 mg daily
RBV duration	32 weeks	1st course: 24 weeks 2nd course: 14 weeks	15 weeks	20 weeks	32 weeks	10 weeks
Response	SVR	SVR after second course	SVR	SVR	Pending SVR	SVR
Side effects	None	Anemia	None	Anemia	None	Anemia

Sridhar *et al* Clin Infect Dis 2021

Antibodies



Protection and neutralization



Sridhar *et al* J Hepatology 2021

Consideraciones personales

- Especie presente en todo el mundo
- Presencia en España

→ ¿Cómo se transmite?

- Causa emergente de hepatitis aguda
- Necesidad de cribado específico

→ Necesidad de implementación del diagnóstico molecular en el SNS- ¿Con qué?

- Evaluar la dimensión
- Síndromes asociados

→ Gehep tiene mucho que decir en los próximos años

INICIO | PROGRAMA | COMITÉS | COMUNICACIONES | INSCRIPCIONES Y ALOJAMIENTO | BECAS | PATROCINADORES | SEDE | CONTACTO

Plazo límite para el envío de comunicaciones: **25 de junio de 2023**

GILEAD
Creating Possible