

Hepatitis E y viajes

Antonio Rivero Juárez

Grupo de Investigación en Enfermedades Infecciosas

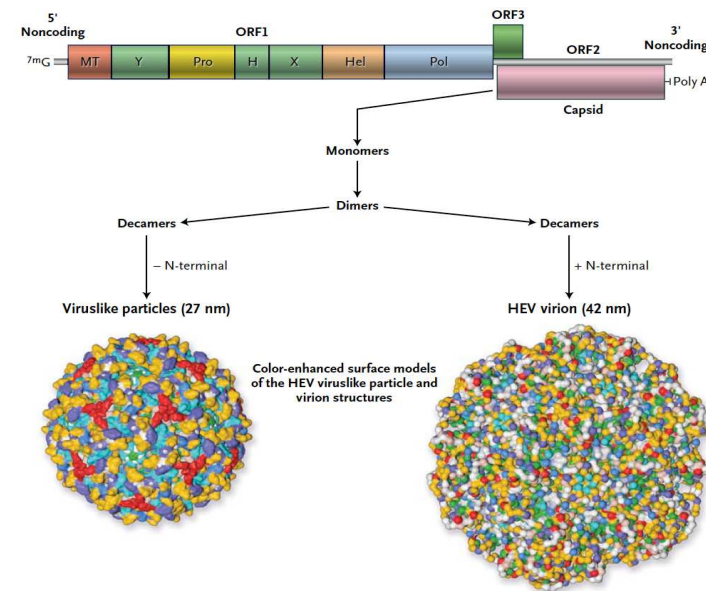
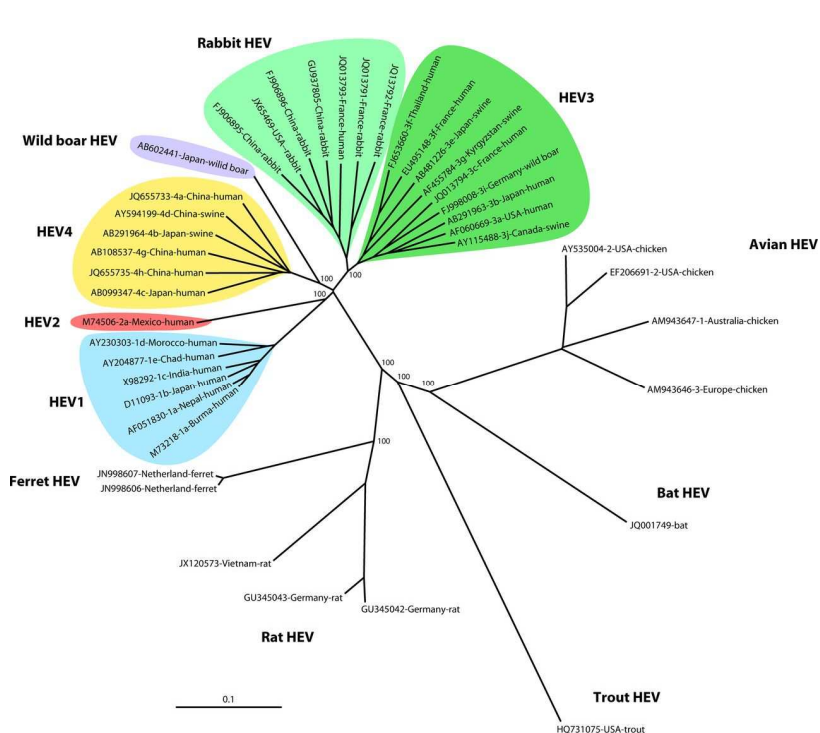
Instituto Maimonides de Investigación Biomédica de Córdoba (IMIBIC)

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Universidad de Córdoba

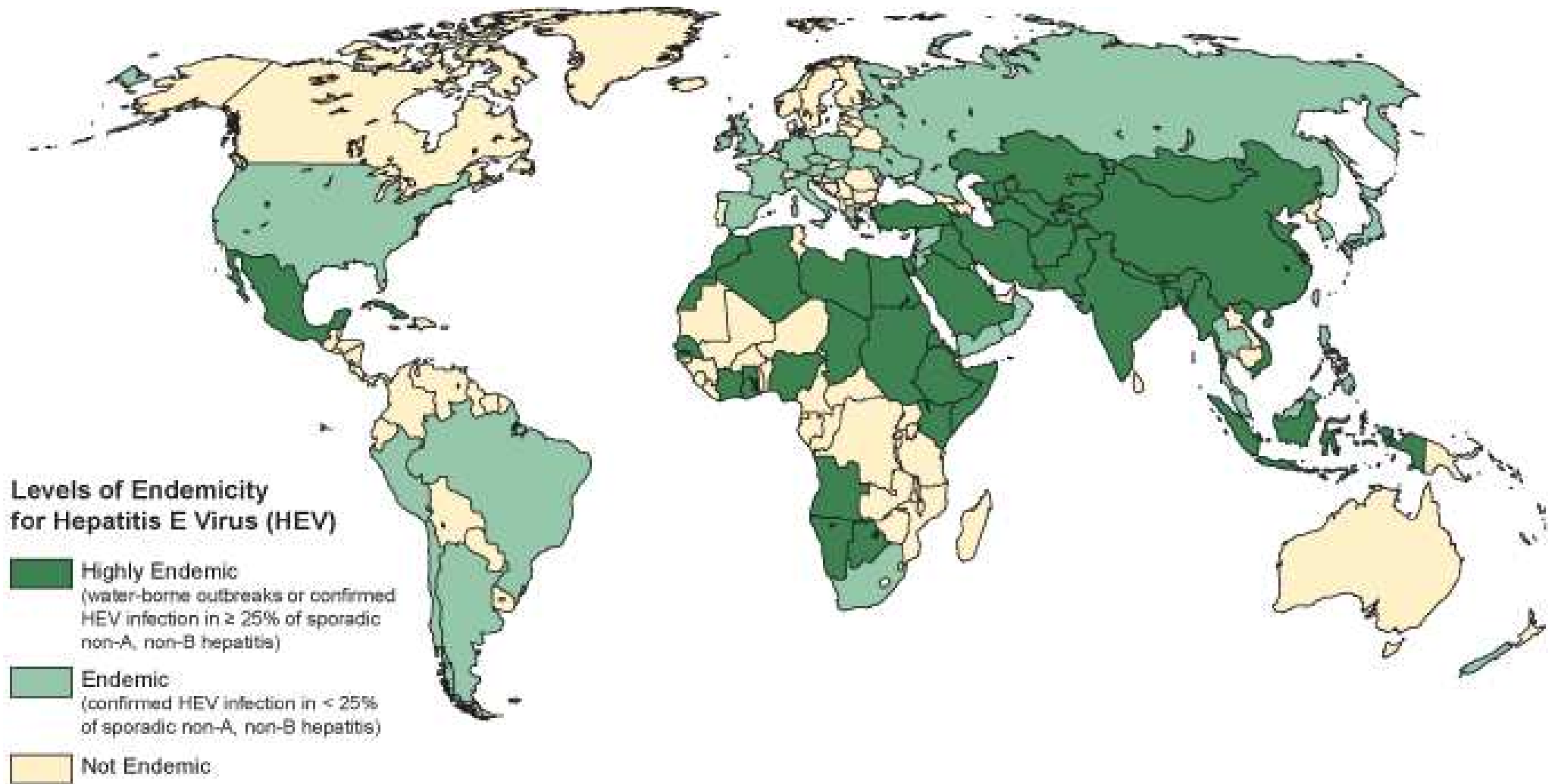
Hepatitis E aspectos virológicos

- *Orthohepeviridae* family¹
- RNA+ non-enveloped: 7,2 kba²
- Four main genotypes that can infect humans³



1. Hepeviridae Study Group. J Gen Virol 2014
2. Hoofnagle. NEJM 2012
3. Kamar. Clin Microb Infect 2014

Distribución Mundial



Dos enfermedades diferentes dependiendo del genotipo

Table 1. Clinical and Epidemiologic Characteristics of HEV Infections According to Genotype.

Characteristic	Genotypes 1 and 2 (Epidemic)	Genotypes 3 and 4 (Autochthonous)
Geographic distribution	Developing countries only	Both developing and developed countries
Pattern of spread	Epidemic and sporadic	Sporadic
Occurrence in United States	Travel-related, imported	Autochthonous
Species specificity	Human	Swine, human (humans are accidental host)
Major mode of spread	Fecal–oral, waterborne	Foodborne
Secondary spread	Uncommon	Extremely rare
Rate of icteric illness	High	Low
Age distribution	Disease rates highest among adolescents and young adults	Disease rates highest among older adults
Sex distribution	Similar disease rates among men and women	Higher disease rates among men
Mortality	High among pregnant women	High among older adults
Extrahepatic features	Few	Neurologic complications
Chronic infection	None	Common in immunosuppressed persons
Therapy	None known	Ribavirin, peginterferon (experimental)
Prevention	Vaccine*	Vaccine*

Dos enfermedades diferentes dependiendo del viaje

Genotipos 1 y 2



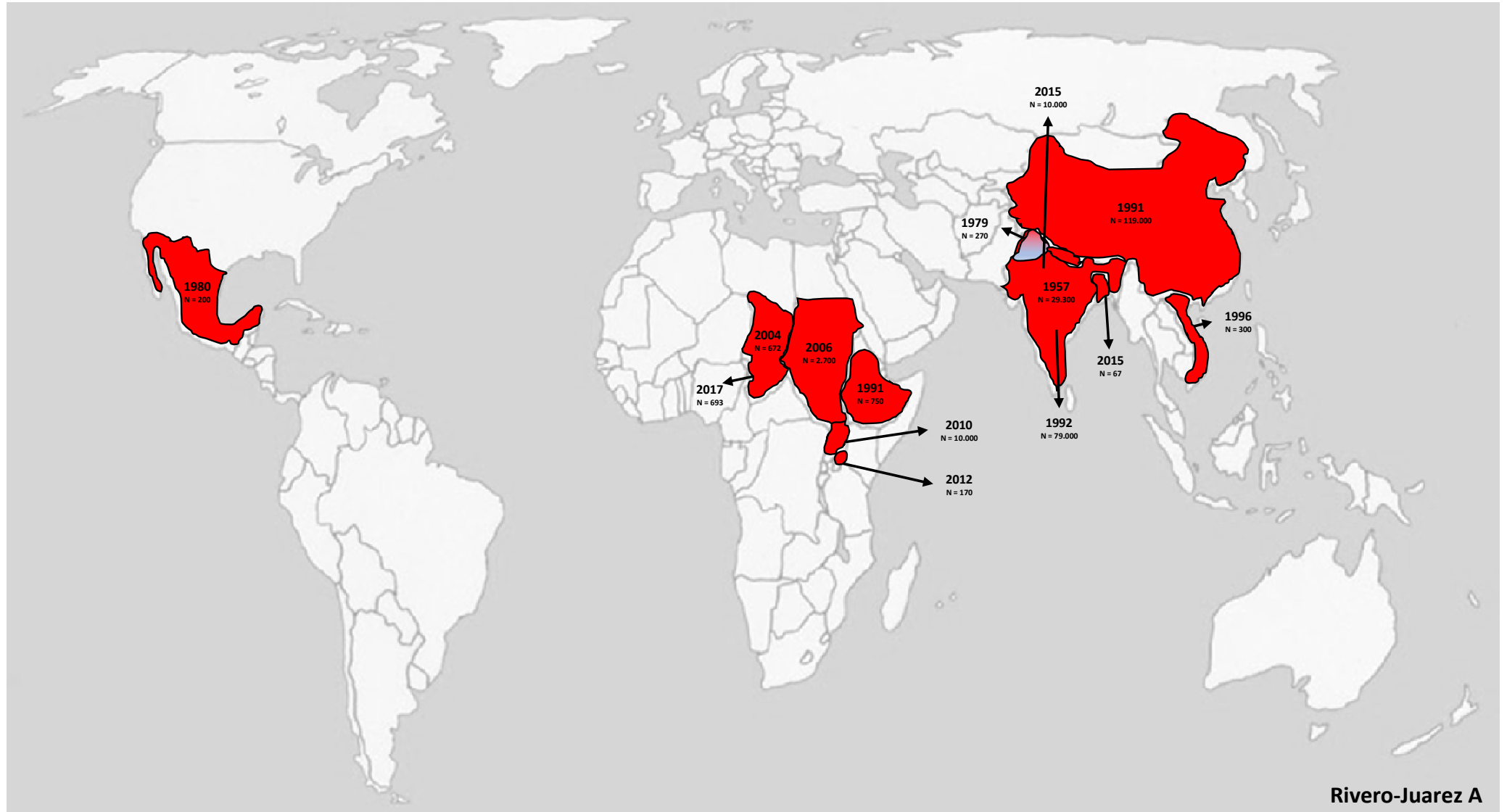
Genotipos 3



Hepatitis E en viajeros

Asia y África (genotipos 1 y 2)

Brotos epidémicos por el VHE



Casos importados por viajes

UK

	No. (%) of patients
Recent travel history	
To area where HEV is hyperendemic	129 (69)
To area where HEV is not endemic	8 (4)
None	17 (9)
Unknown	32 (17)

Australia

Table III - HEV importation rate per 10,000 travellers, July 2004 - December 2014, by country of acquisition.

Country	Number of imported cases	Total travellers	HEV importation rate
Bangladesh	40	23,227	17.22
China*	14	5,742,036	0.02
India	160	527,244	3.03
Indonesia	6	7,295,352	0.01
Nepal	22	12,404	17.74
Pakistan	14	28,226	4.96
Sudan	5	3,652	13.69
Thailand	12	6,320,903	0.02
Vietnam	9	1,264,056	0.07

*Excludes SARs (Special Administrative Regions) and Taiwan. HEV: hepatitis E virus.

Brotes epidémicos recientes en cruceros

9news > health >

HEALTH 3:53am February 23, 2017

Hepatitis E warning for passenger on two Melbourne cruises

By AAP



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Page last updated at 13:00 GMT, Wednesday, 30 April 2008 14:00 UK

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Hepatitis E outbreak on P&O liner

Hundreds of holidaymakers are being tested for Hepatitis E after an outbreak onboard P&O liner Aurora.

Seven passengers contracted the virus during an 11-week world cruise which ended in Southampton on 28 March.

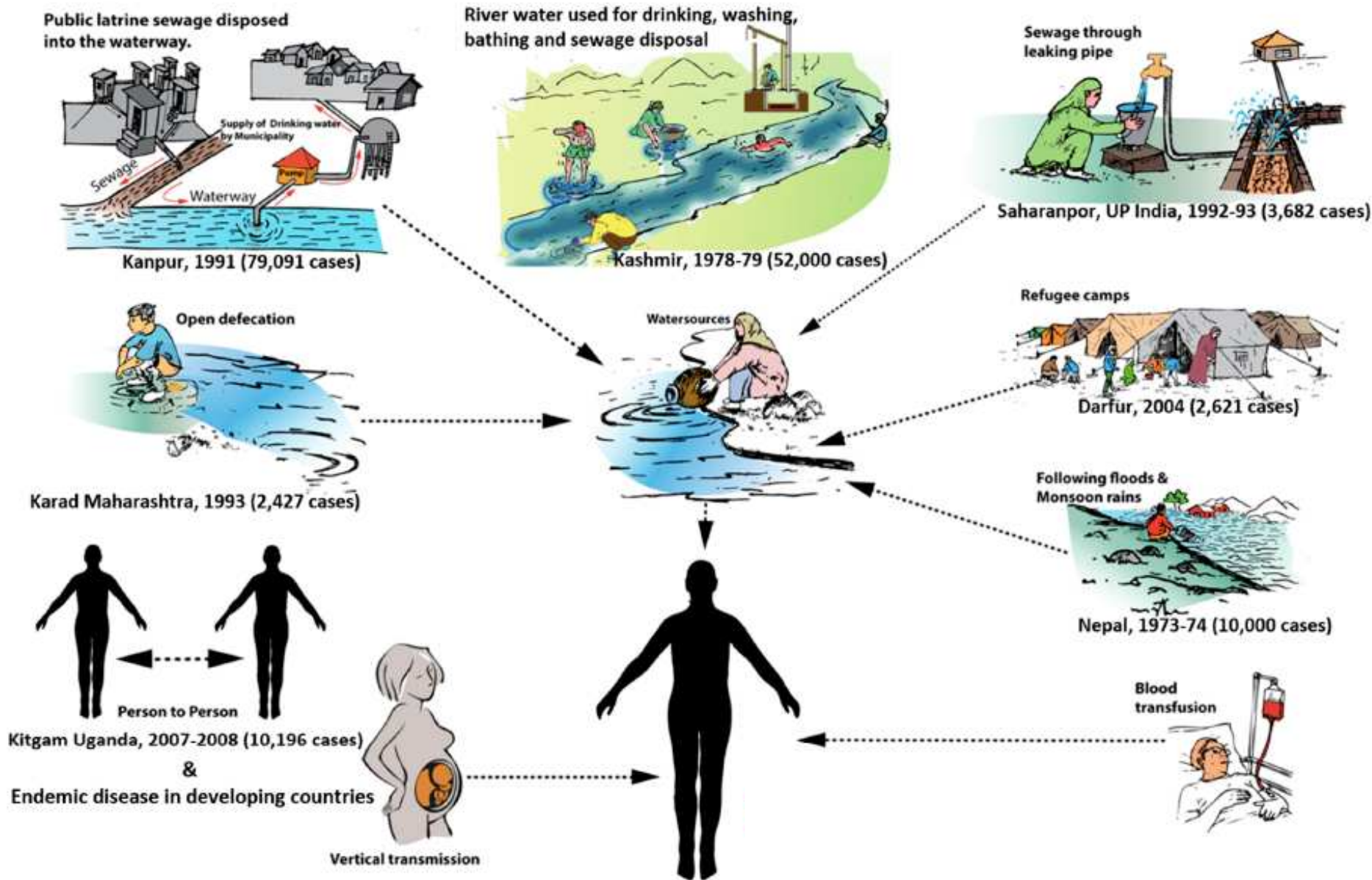
All the passengers onboard were sent a letter from the Health Protection Agency requesting a blood sample.

The HPA advises that the virus, which affects the liver, can be fatal but only in rare cases. P&O said it was cooperating fully with the inquiry.

It is thought the passengers caught the virus through eating or drinking contaminated food.



The Aurora was at the centre of an outbreak of the Norovirus in 2003



Caso típico

- Mujer nacionalidad española de 31 años residente en Madrid
- Acude consulta a demanda a UGC EEII HURS
- Viaje al Norte de India de 17 días de duración.
- Exploración física:
 - Fiebre (38,5°C), Sintomatología digestiva (nausea y diarrea), dolor articular, orina oscura e ictericia.
- Exploración analítica:
 - ALT/AST/GGT: 494/173/167
 - Bilirrubina: 5,7
 - HCV, HBV, HAV, EB, CMV: negativos
- Exploraciones complementarias
 - Elastometría Hepática transitoria: 9 kPa
 - Ecografía: Sin hallazgos de interés
- HEV: PCR 1.370.456 IU/mL genotipo 1

Sintomatología clínica en población general

Clinical symptoms

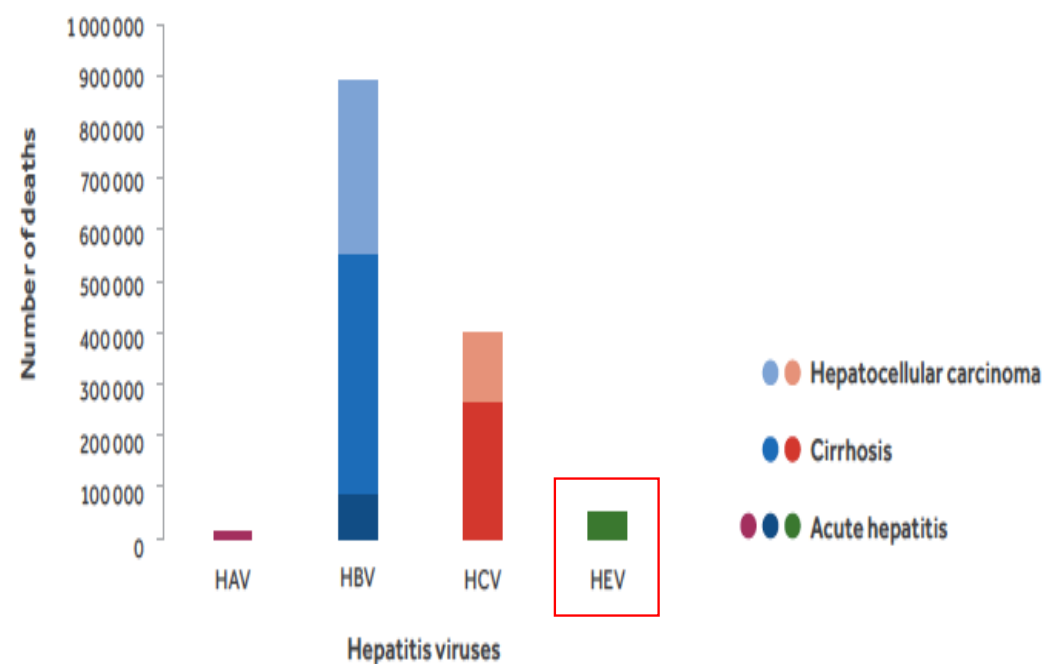
Yellowing of eyes, <i>n</i> (%)	60 (97)
Yellowing of skin, <i>n</i> (%)	48 (77)
Severe weakness, <i>n</i> (%)	61 (98)
Vomiting, <i>n</i> (%)	55 (89)
Loss of appetite, <i>n</i> (%)	58 (94)
Fever, <i>n</i> (%)	48 (77)
Itching, <i>n</i> (%)	30 (48)
Mental irritability, <i>n</i> (%)	19 (31)
Diarrhoea, <i>n</i> (%)	11 (17)
Loss of consciousness, <i>n</i> (%)	2 (3)
Disruption of daily activities, <i>n</i> (%)	42 (67)
Mean duration of disruption in days (range)	14 (2–30)

GLOBAL HEPATITIS REPORT, 2017



THE ROAD TO ELIMINATION BY 2030

Fig. 1. Deaths from viral hepatitis, by virus and type of sequelae, 2015:
most viral hepatitis deaths are due to the late complications of HBV and HCV infection



Poblaciones especiales

- Mujeres embarazadas
- Pacientes con hepatopatía crónica

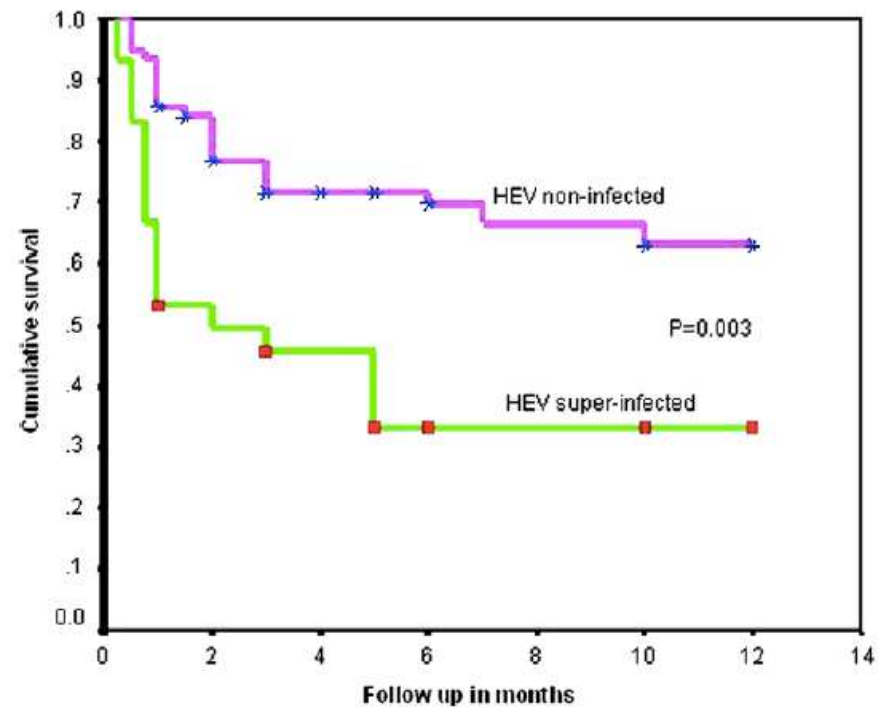
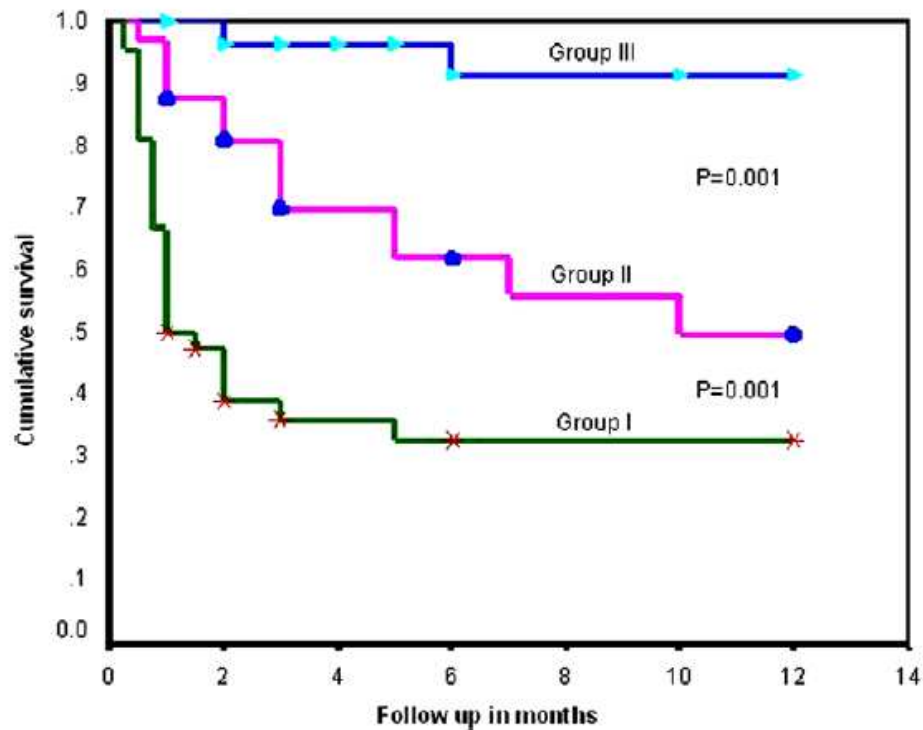
Mujeres embarazadas

TABLE 1 Serologically confirmed hepatitis E outbreaks with reported cases in pregnant women (1987-2015).

Reference	Year	Country	N° of cases	Deaths
Shrestha et al ¹³	1987	Nepal	73	18
Dilawari et al ¹⁴	1987	India	19	3
Khuroo et al ¹⁵	1988	India	30	2
Bile et al ¹⁶	1988-1989	Somalia	346	48
Lubis ¹⁷	1991	Indonesia	19	5
Mast et al ¹⁸	1991	Kenya	28	4
Naik et al ¹⁹	1991	India	48	12
Coursaget et al ²⁰	1991-1993	Djibouti	3	1
Rab et al ²¹	1993-1994	Pakistan	35	4
Goumba et al ²²	2002	Central African Republic	7	1
Boccia et al ²³	2004	Sudan	61	19
Teshale et al ²⁴	2007-2009	Uganda	189	13
ICDDR ²⁵	2008-2009	Bangladesh	21	4
ICDDR ²⁶	2010	Bangladesh	12	3
Rayis et al ²⁷	2010-2011	Sudan	39	11

Pacientes cirróticos

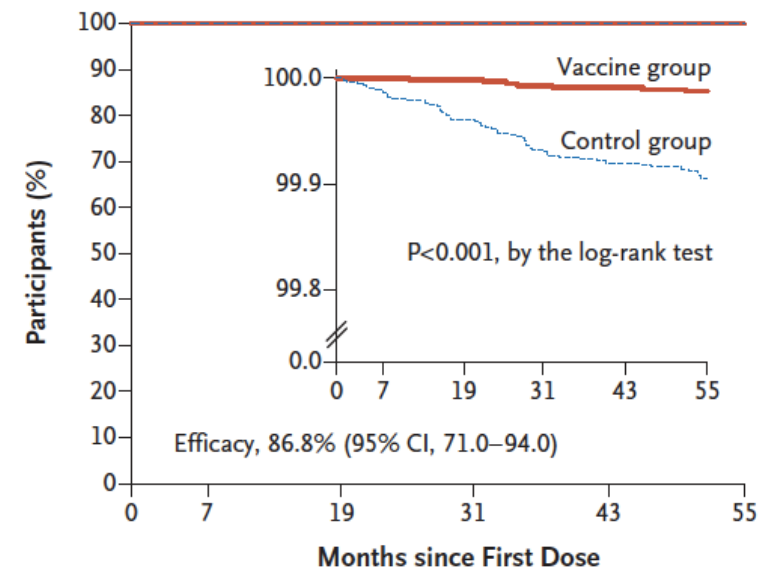
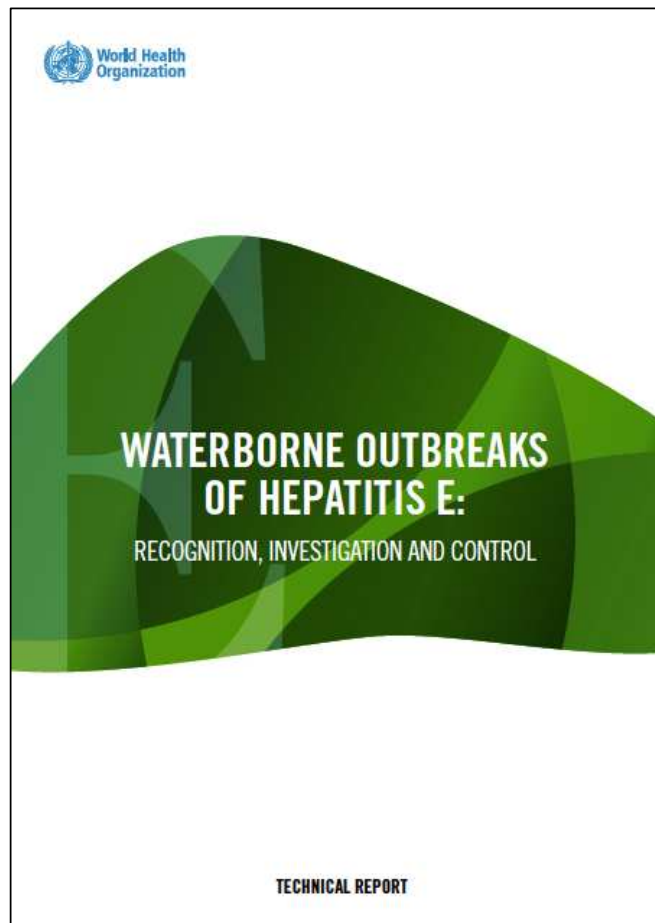
Mortalidad por VHE en cirróticos



Tratamiento

- Tratamiento conservativo
- Uso de RBV solo experiencia en algunos casos con tasas de respuesta variables

Medidas preventivas



No. at Risk						
Vaccine group	56,302	56,215	56,022	55,774	55,484	55,240
Control group	56,302	56,209	55,977	55,718	55,436	55,185
Cumulative No. of Participants with Hepatitis E						
Vaccine group	0	0	1	4	5	7
Control group	0	6	22	38	45	53

Vacunación efectiva

	Pregnant women	Without vaccination		With vaccination		Effect of vaccination	
	Total	Symptomatic cases	Deaths	Symptomatic cases	Deaths	Symptomatic cases	Deaths
Very severely affected zone	16 400	701	173	98	24	-603	-149
Severely affected zone	3263	140	34	20	5	-120	-30
Moderately affected zone	13 056	558	138	78	19	-480	-119
Slightly affected zone	15 549	665	164	93	23	-572	-141
Total	48 268	2064	510	289	71	-1775	-438

Data were modelled using past estimates of the incidence, anti-HEV IgG seroprevalence data from the population of the Kathmandu valley (2010–12) and impacts of hepatitis E during outbreaks in refugee conditions (data were from Basnyat B [unpublished] and reference 5). The modelling was done after the first earthquake (April 25) and before the second one (May 12). Earthquake affected zones are classified by severity as shown in reference 6.

Table: Estimation of the number of deaths among pregnant women with and without hepatitis E vaccination, and potential effect of vaccination, by earthquake affected zone

WHO Position

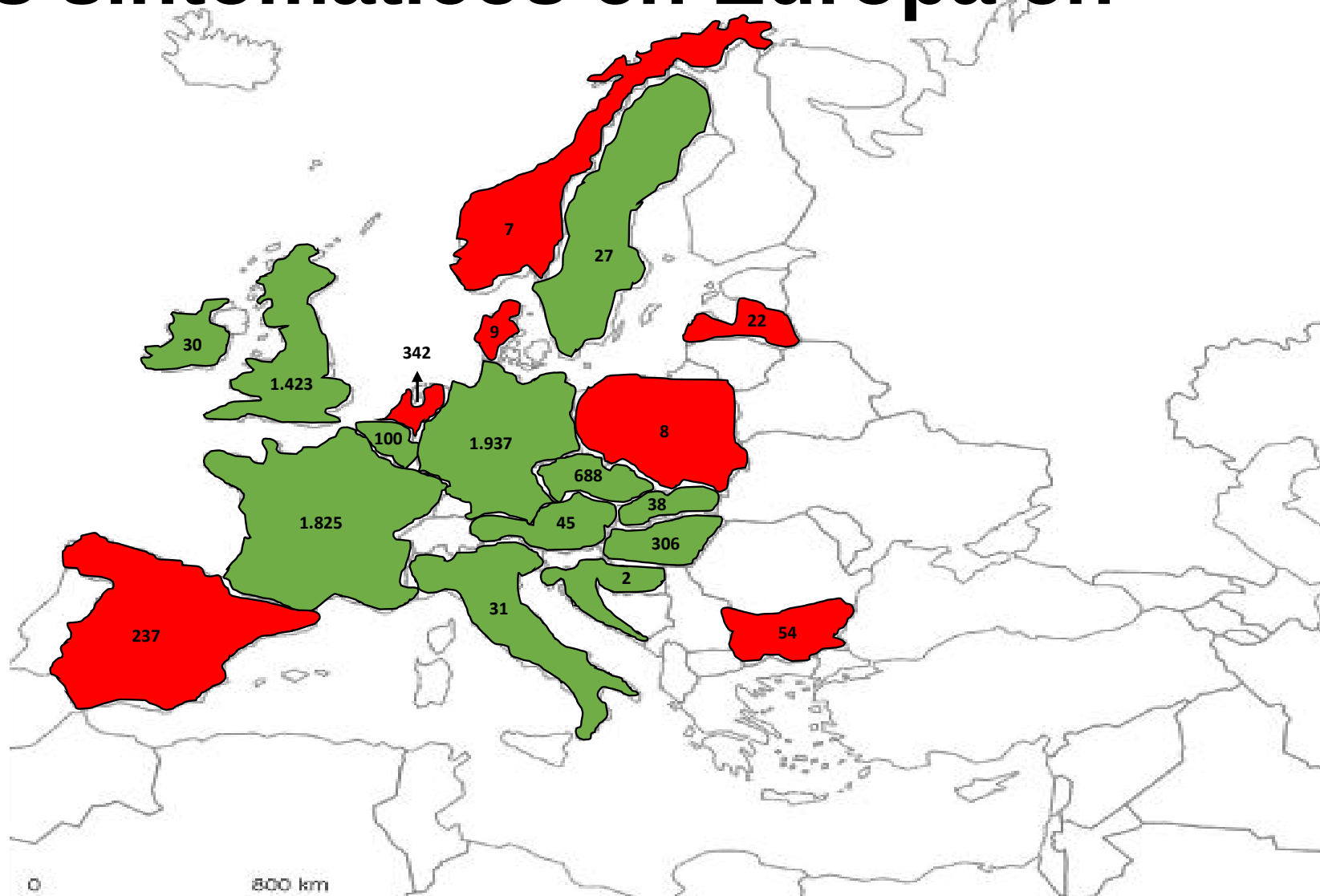
- In outbreak situations (high risk of Hep E) WHO recommends:
 - Considering use of HEV 239 vaccine to mitigate risk of Hep E outbreaks for high risk groups:
 - Pregnant women
 - Travellers
 - Health and humanitarian relief workers
 - Evaluate risk and benefit of vaccination on an individual basis
- To address information gaps WHO recommends:
 - Pre-emptive design of research protocol to study vaccine safety and immunogenicity in outbreak situations among high risk groups.



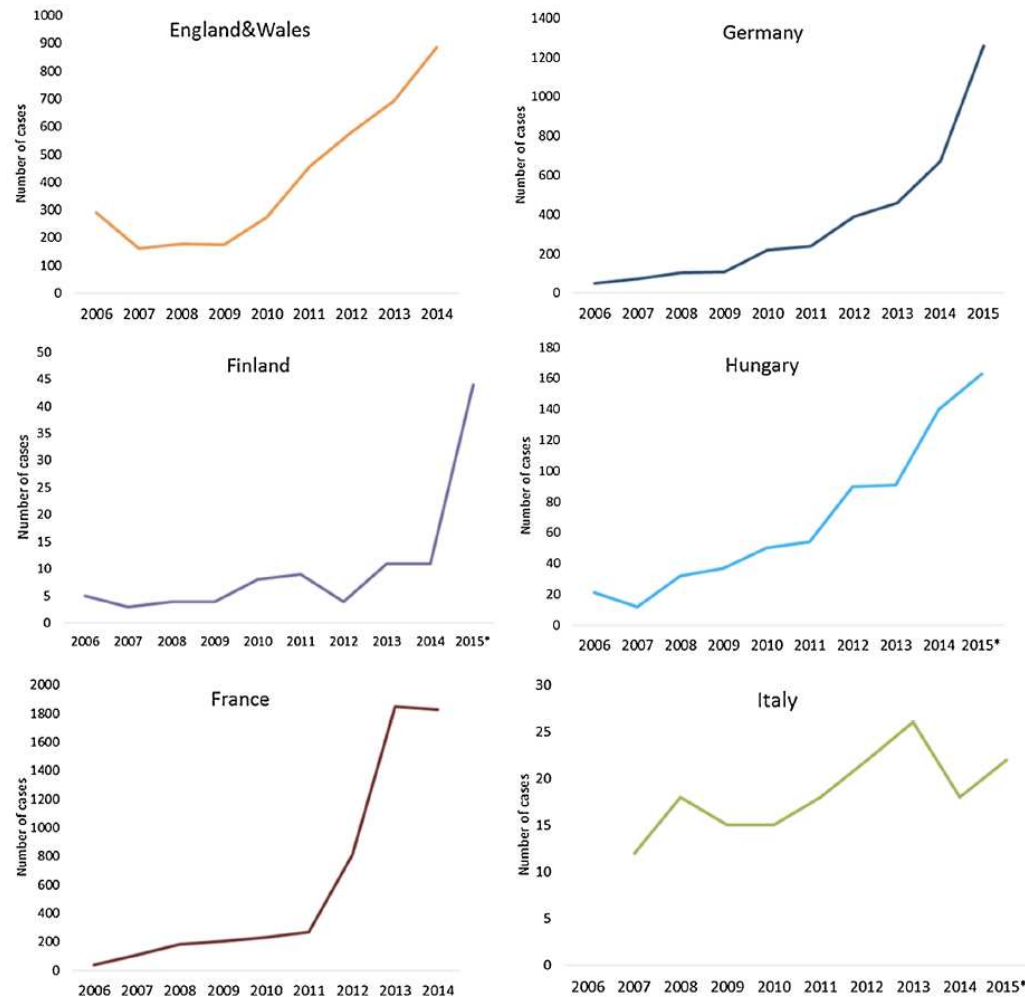
Hepatitis E en viajeros

Europa (genotipo 3) y China (genotipo 4)

Casos sintomáticos en Europa en 2015

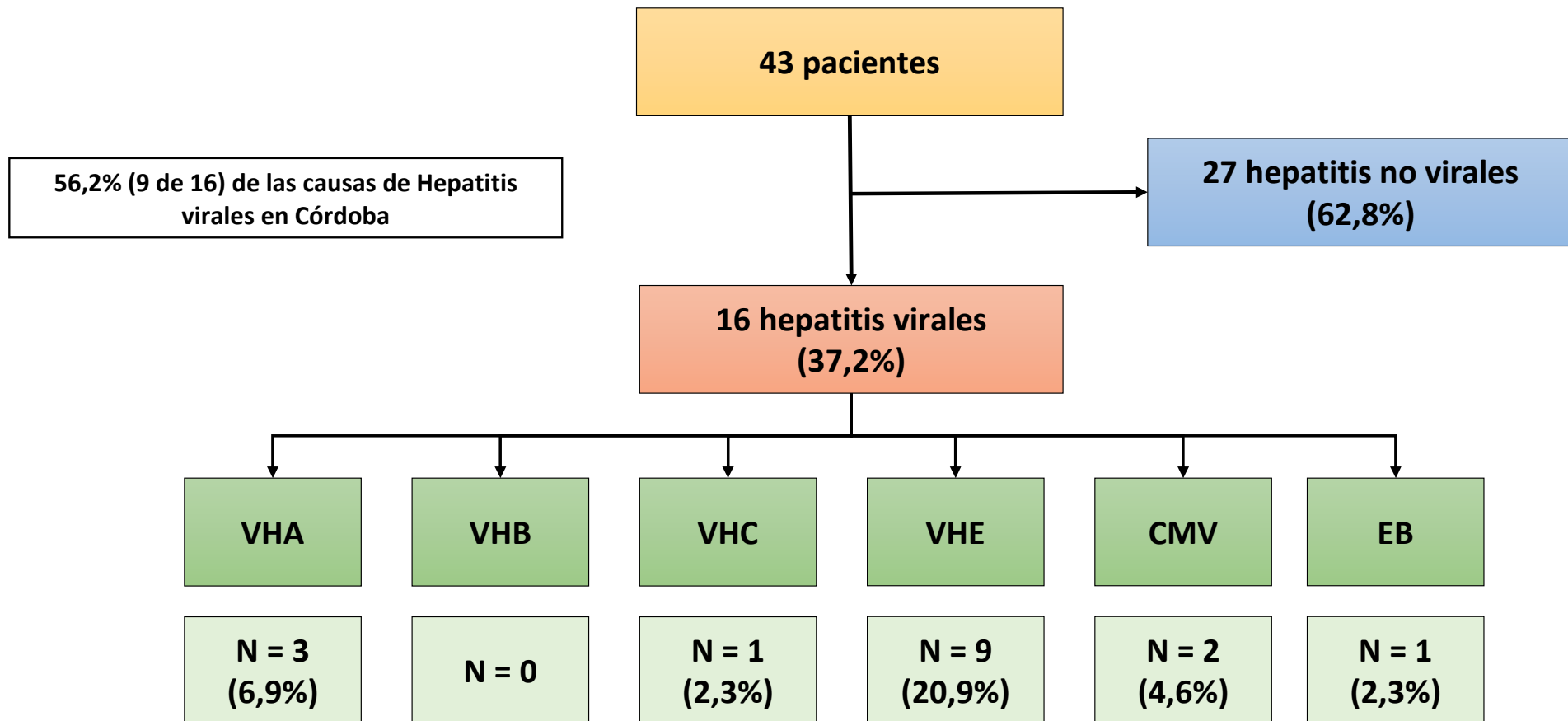


Aumento de casos de Hepatitis E aguda en Europa



Adlhoch et al J Virol 2016

Experiencia de Córdoba 2017



Puntos calientes en Europa: Sur de España



Prevalencia Nacional:
10%

Prevalence:
21.2%

Incidence rate:
7.2 seroconversion /100 patients-year

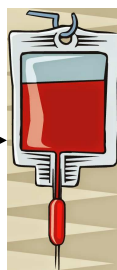
Incidence rate:
Rural: 17.4 seroconversion /100 patients-year
Urban: 5.8 seroconversion / 100 patients-years

Prevalence:
26%

Incidencia acumulada:
19%

Hepatitis E virus in blood components: a prevalence and transmission study in southeast England

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Casos transmisión VHE por transfusiones en Europa

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Inglaterra: 18 casos

Annals of Internal Medicine

OBSERVATIONS

Transmission of Hepatitis E Virus by Plasma Exchange:
A Case Report

Alemania: 1 caso

Hepatitis E Virus Infection in Solid Organ Transplant Recipients, France

Sebastien Lhomme, Laurent Bardiaux, Florence Abravanel, Pierre Gallian, Nassim Kamar, Jacques Izopet

**Francia: 7 casos en
trasplantados**

Red blood cell transfusion-transmitted acute hepatitis E in an immunocompetent subject in Europe: a case report

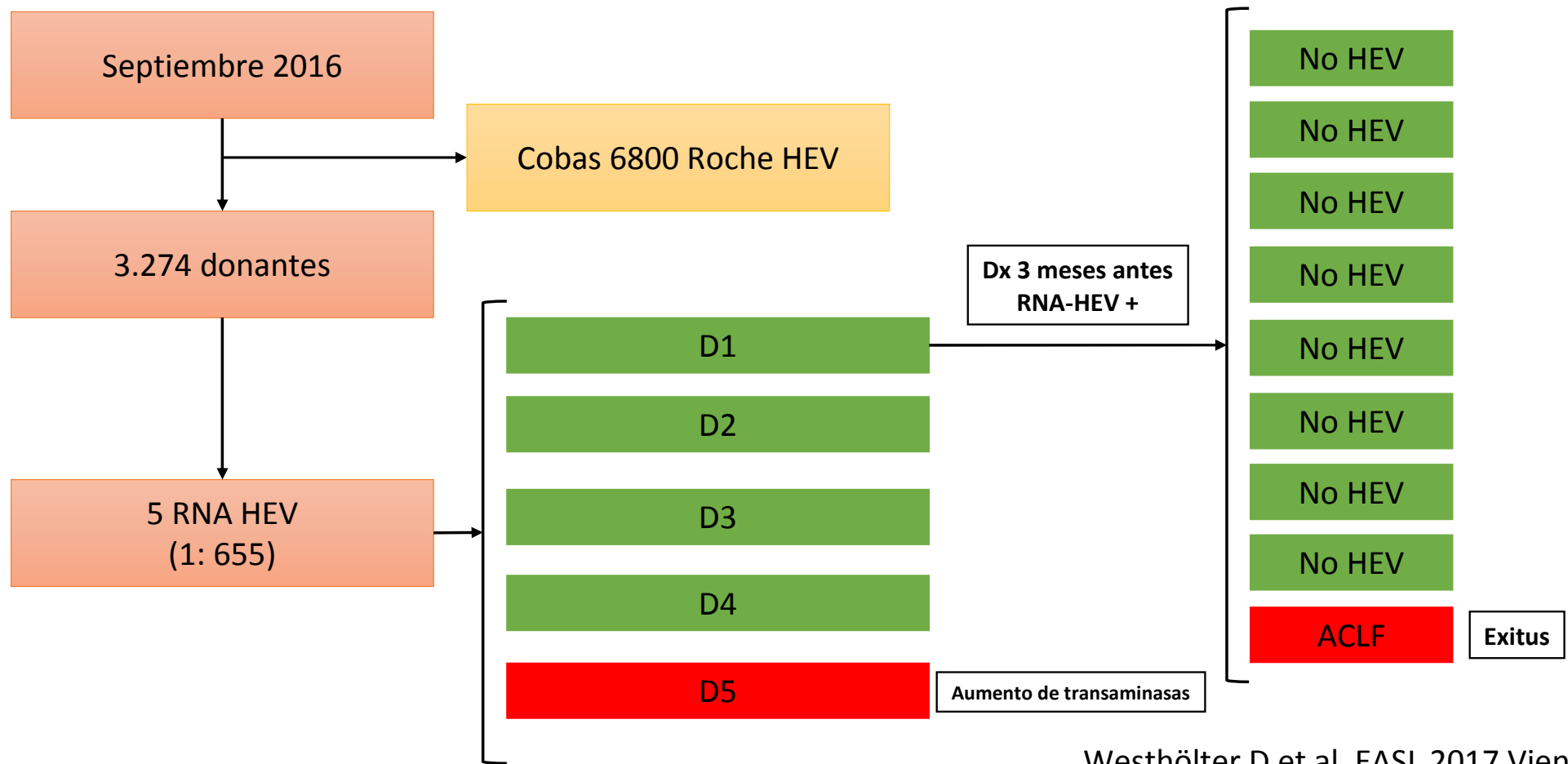
Mar Riveiro-Barciela,^{1,2} Silvia Sauleda,^{2,3} Josep Quer,^{2,4} Fernando Salvador,⁵ Josep Gregori,^{2,4} María Pirón,³ Francisco Rodríguez-Frías,^{2,6} and Maria Buti^{1,2}

España: 1 caso

Viremia en donantes de sangre en Europa

País	Donantes: RNA VHE +	Referencia
Francia	1: 1438	Gallian Emerg Infec Dis 2014
Alemania	1: 1.200	Vollmer et al J Clin Microbiol
	1: 4.525	Baylis et al Vox Sang 2012
Inglaterra	1: 2.848	Hewitt et al Lancet 2014
Suecia	1: 7986	Baylis et al Vox Sang 2012
Austria	1: 8.416	Fischer et al PLoS One 2015
Irlanda	1: 4.997	O'Riordan et al Transfusion 2016
Escocia	1: 14.520	Clealand et al Vox Sang 2013
Holanda	1: 2.671	Harritshøj et al Transfusion 2016
España	1: 3.333	Sauleda et al Transfusion 2015

Proyecto piloto de cribado en Alemania



Resistencia del VHE en hemoderivados

- Lavado con detergentes
- Calor seco
- Pasteurización (1h 60°/72°)
- Acidificación
- Nanofiltración



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 June 2015
EMA/CHMP/BWP/723009/2014
Committee for Medicinal Products for Human Use (CHMP)

Reflection paper on viral safety of plasma-derived
medicinal products with respect to hepatitis E virus

Draft



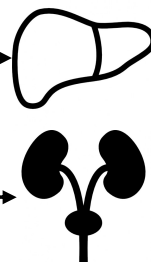
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Case Report

Liver transplant from a donor with occult HEV infection induced chronic hepatitis and cirrhosis in the recipient

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EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER JOURNAL OF HEPATOLOGY

Casos documentados de transmisión por trasplante

Hepatitis E Virus Infection in Solid Organ Transplant Recipients, France

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Molecular detection of hepatitis E virus (HEV) in liver biopsies after liver transplantation

Ulrike Protzer^{1,2}, Friederike Böhm³, Thomas Longerich⁴, Judith Seebach¹, Mojdeh Heidary Navid⁵, Juliane Friemel³, Ewerton Marques-Maggio³, Marion Bawohl³, Mathias Heikenwalder^{1,2}, Peter Schirmacher^{2,4}, Philipp Dutkowski⁶, Pierre-Alain Clavien⁶, Peter Schemmer⁷, Paul Schnitzler⁵, Daniel Gotthardt⁸, Beat Müllhaupt⁹ and Achim Weber³

Case Report



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Hepatitis E virus: an underdiagnosed cause of chronic hepatitis in renal transplant recipients

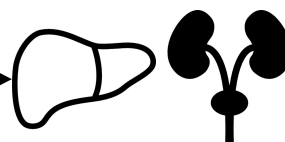
Lhome S Emerg Infect Dis 2017
Protzer U et al Mod Pathol 2014
Schlosser B et al J Hepatol 2012
Moal V et al J Med Virol 2013



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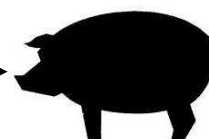


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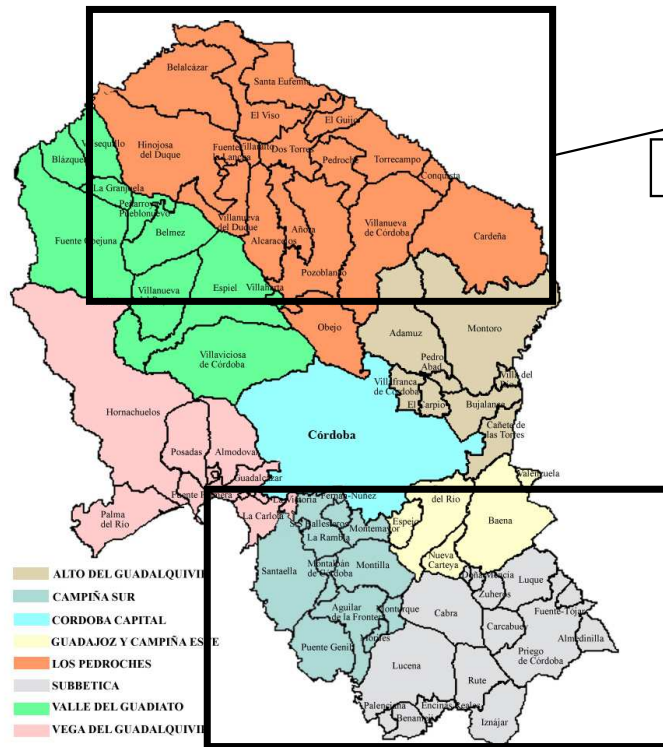
High Proportion of Asymptomatic Infections in an Outbreak of Hepatitis E Associated With a Spit-Roasted Piglet, France, 2013

Yvonnick Guillois,¹ Florence Abravanel,² Takayuki Miura,³ Nicole Pavia,⁴ Veronique Vaillant,⁵ Sébastien Lhomme,² Françoise S. Le Guyader,³ Nicolas Rose,⁴ Jean-Claude Le Saux,³ Lisa A. King,¹ Jacques Izopet,² and Elisabeth Couturier⁵



HepEpork Study:

- Córdoba: 2nd province of Spain in Pork production
- Home-town of Black Iberian pig



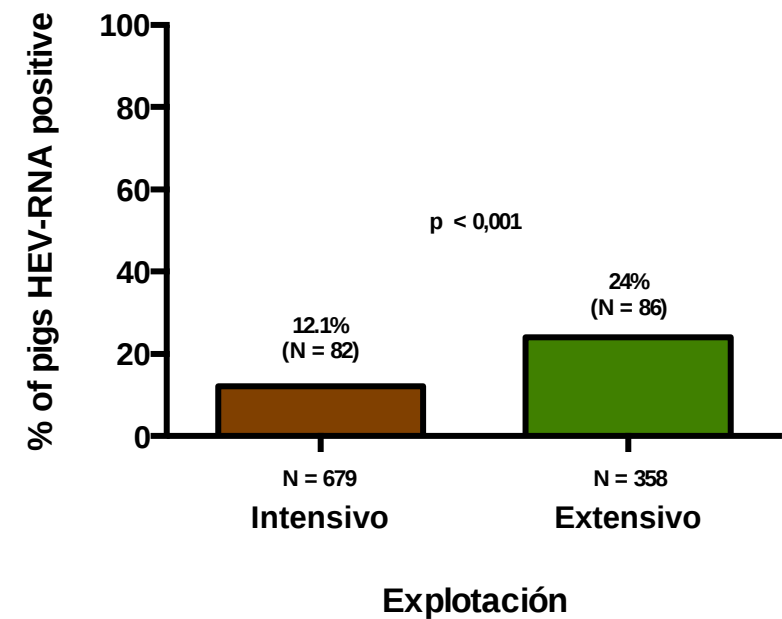
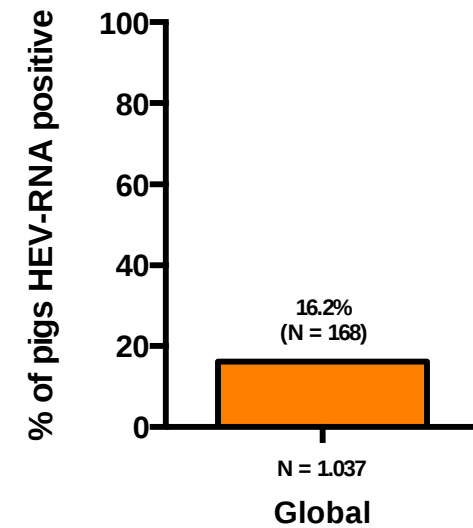
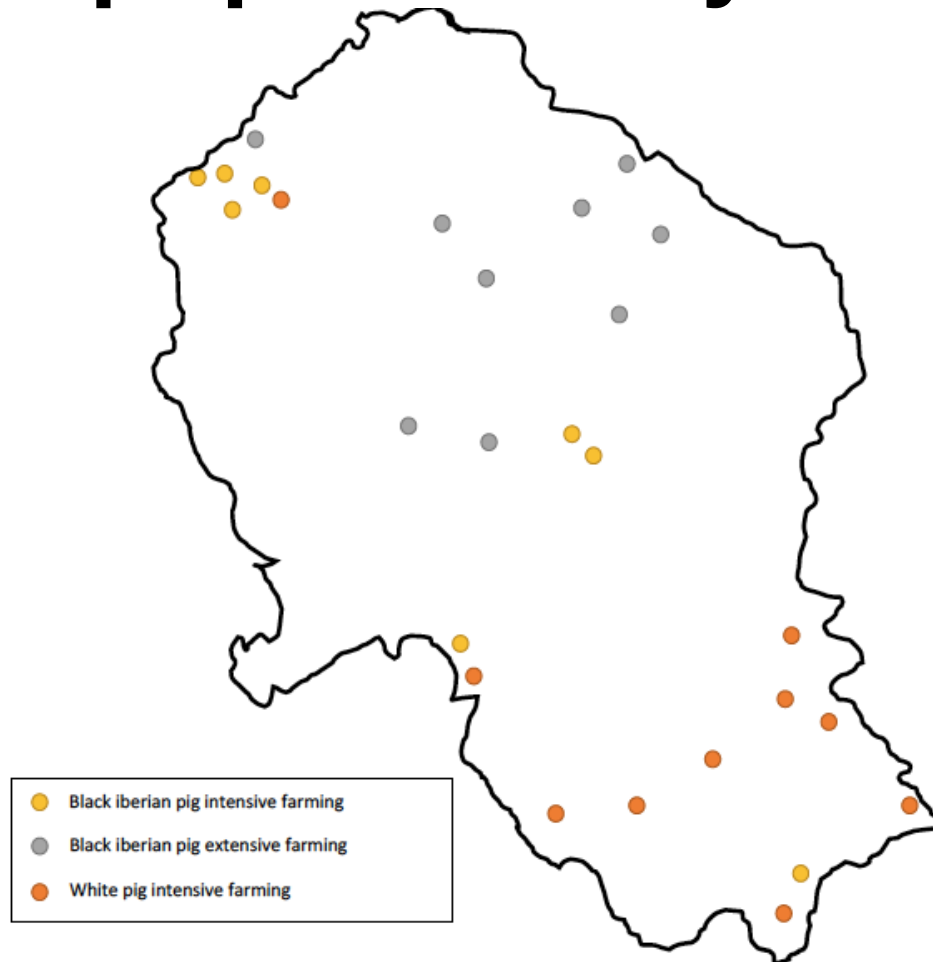
Extensive farming



Intensive farming



HepEpork Study:



Presencia del VHE en alimentos de origen porcinos

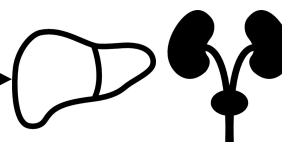
Alimento	País	HEV-RNA	Reference
Carne	Italy	6%	Di Bartolo <i>et al.</i> Emerg Infec Dis 2012
	Czech Republic	2.5%	Di Bartolo <i>et al.</i> Emerg Infec Dis 2012
Salchicha	Italy	22%	Di Bartolo <i>et al.</i> Inter J Food Microb 2015
	Spain	6.4%	Di Bartolo <i>et al.</i> Emerg Infec Dis 2012
	U.K.	9.5%	Berto <i>et al.</i> Emerg Infect Dis 2012
	Germany	20%	Szabo <i>et al.</i> J Food Microbiol 2015
	France	30%	Pavio <i>et al.</i> Emerg Infect Dis 2014
Paté	France	17.2%	Pavio <i>et al.</i> N Emerg Infect Dis 2015
Hígado	Francia	4%	Griergson <i>et al.</i> Emerg Infect Dis 2015
	Netherlands	6.5%	Di Bartolo <i>et al.</i> Inter J Food Microb 2015
	Czech Rep	5%	Di Bartolo <i>et al.</i> Inter J Food Microb 2015
	Italy	6%	Di Bartolo <i>et al.</i> Emerg Infec Dis 2012
	Spain	3%	Di Bartolo <i>et al.</i> Emerg Infec Dis 2012
	U.K.	3%	Berto <i>et al.</i> Emerg Infect Dis 2012



Hepatitis E virus in blood components: a prevalence and transmission study in southeast England

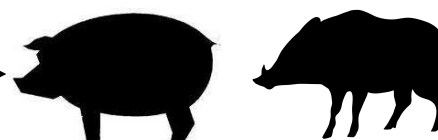
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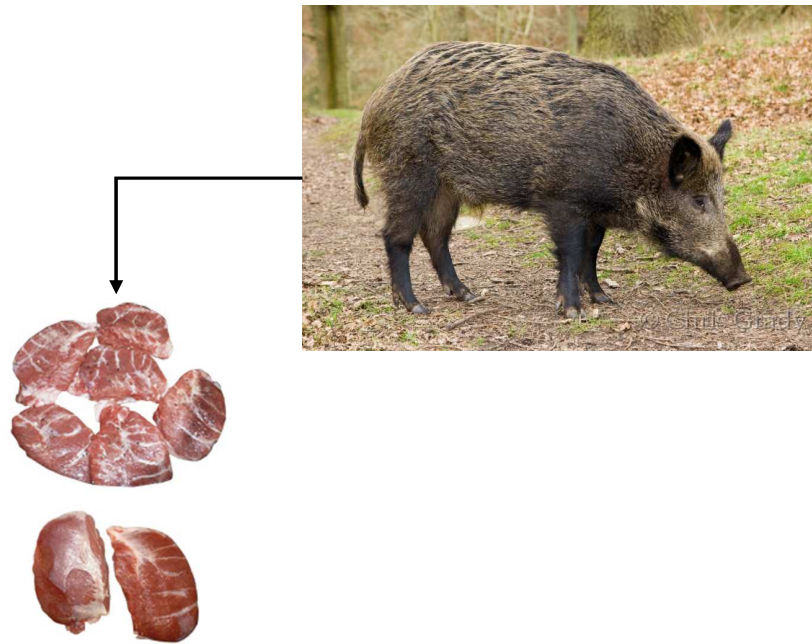
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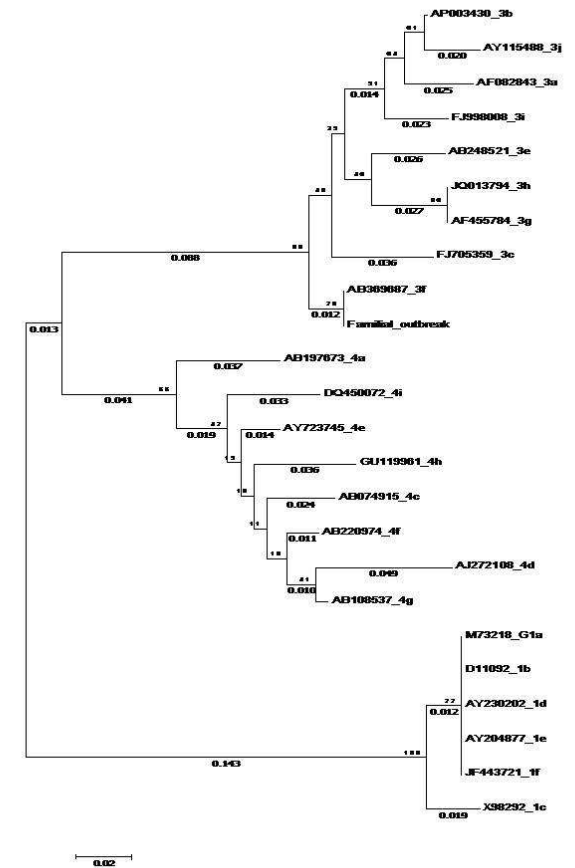
Brote familiar por consumo de jabalí (n = 7)



230.500 copias/gr

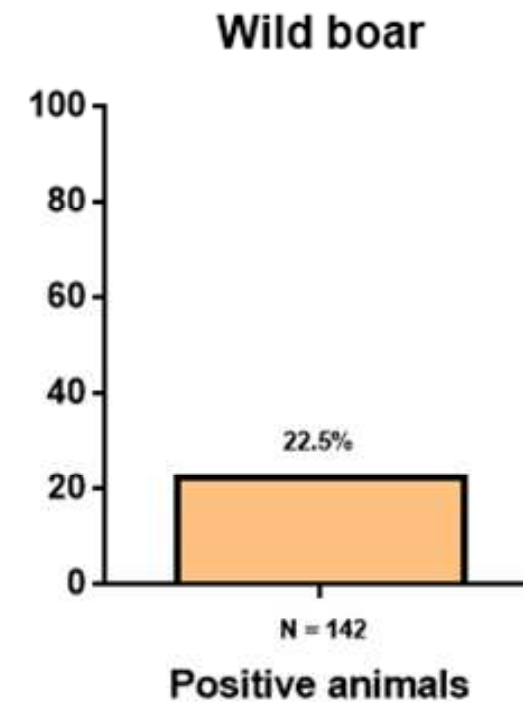
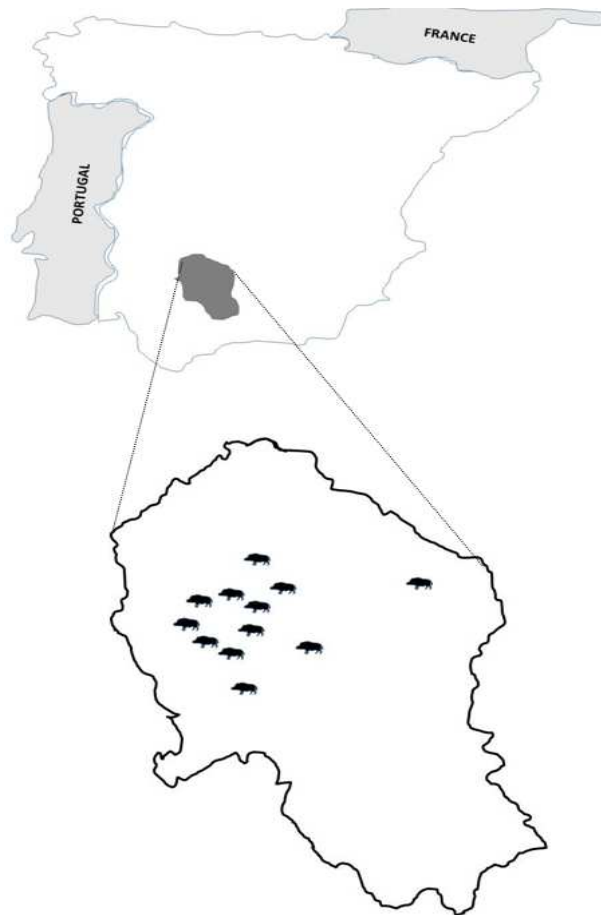


155.300 copias/gr



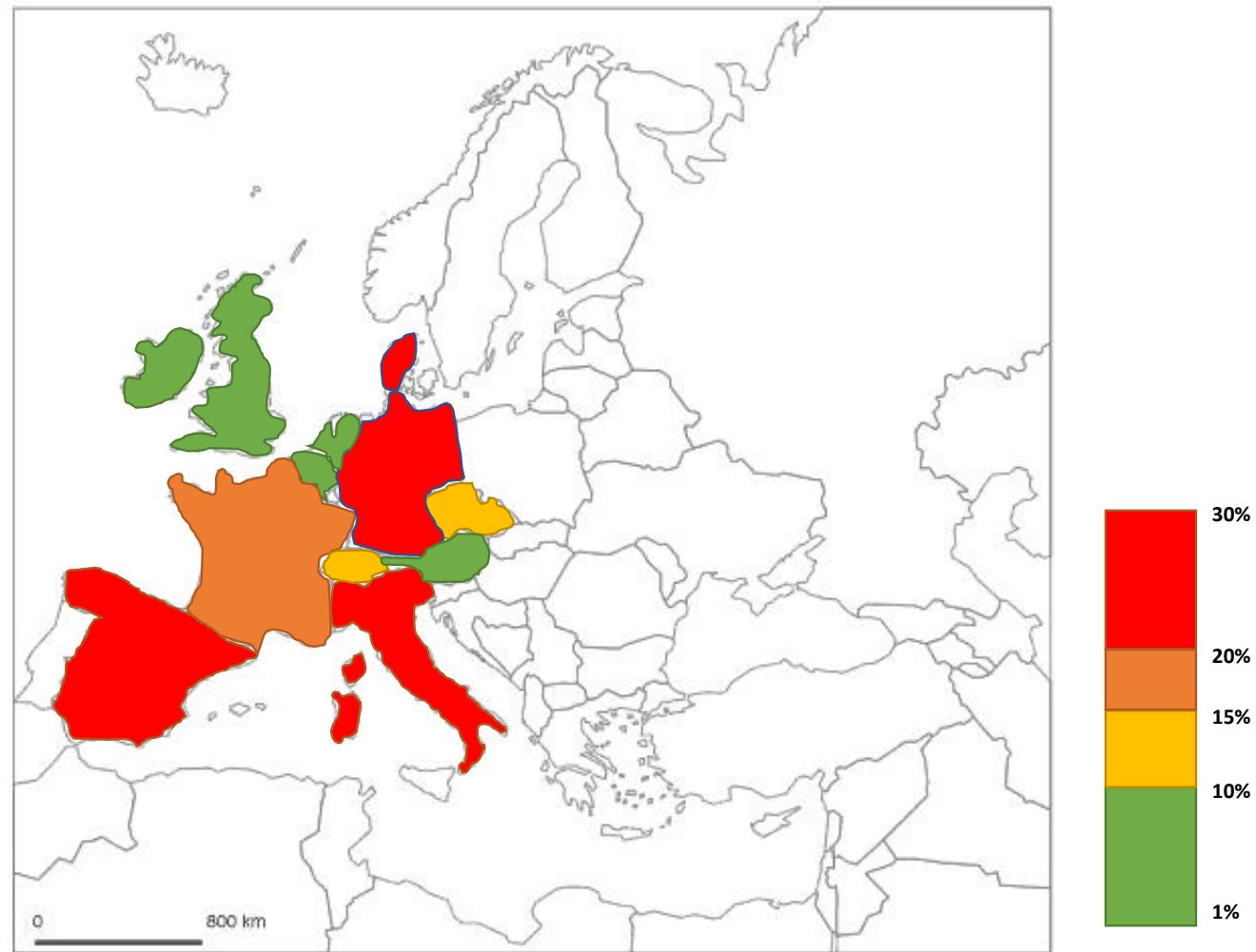
1. Rivero-Juarez Zoonos Publ Health 2017

HepEboar Study



Team Vet-Med. Unpublished data

Infección VHE en jabalies

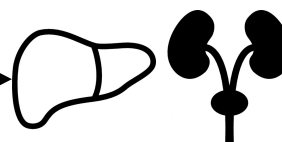




Hepatitis E virus in blood components: a prevalence and transmission study in southeast England

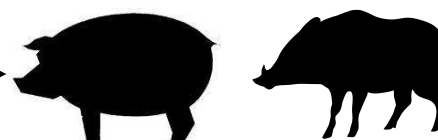
Patricia E Hewitt, Samreen Ijaz, Su R Brailsford, Rachel Brett, Steven Dicks, Becky Haywood, Iain T R Kennedy, Alan Kitchen, Poorvi Patel, John Poh, Katherine Russell, Kate I Tettmar, Joanne Tossell, Ines Ushiro-Lumb, Richard S Tedder

Case Report



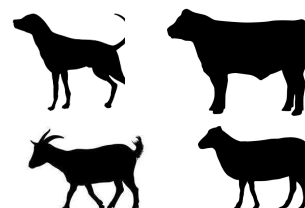
Liver transplant from a donor with occult HEV infection induced chronic hepatitis and cirrhosis in the recipient

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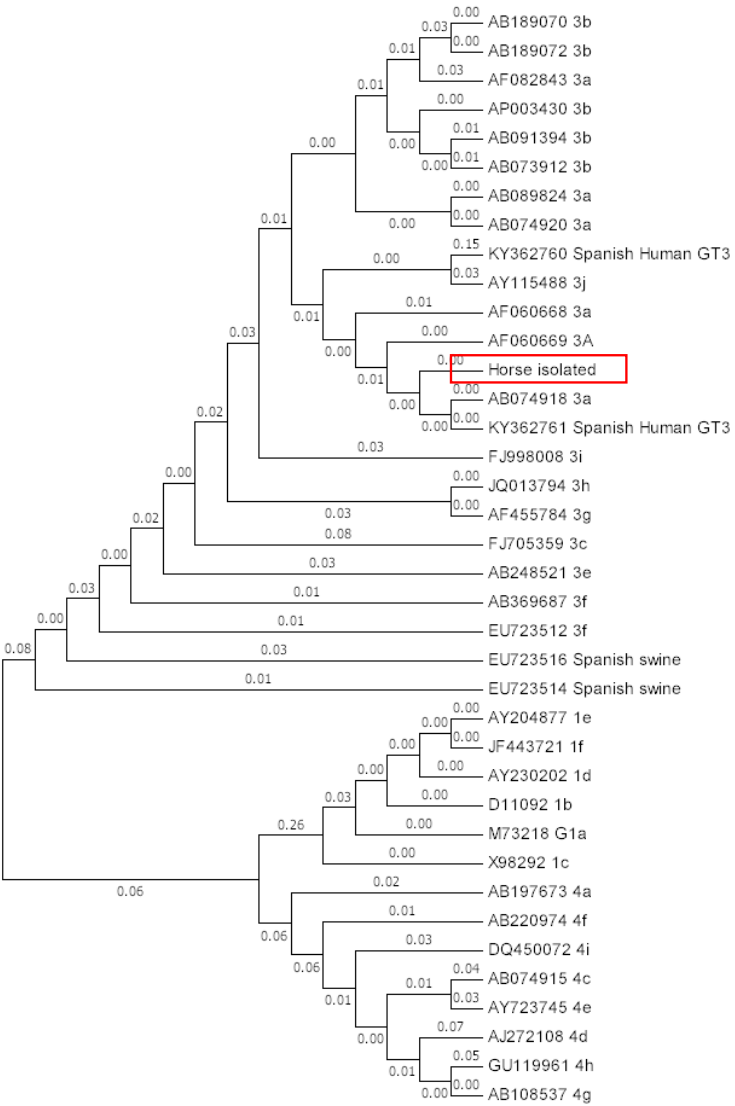
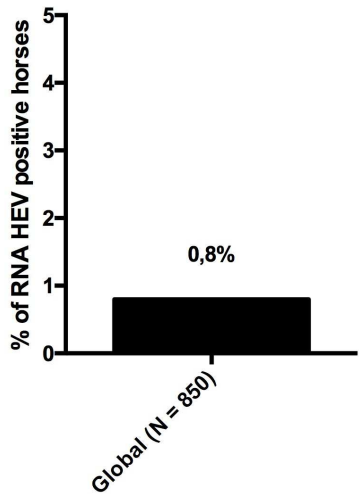
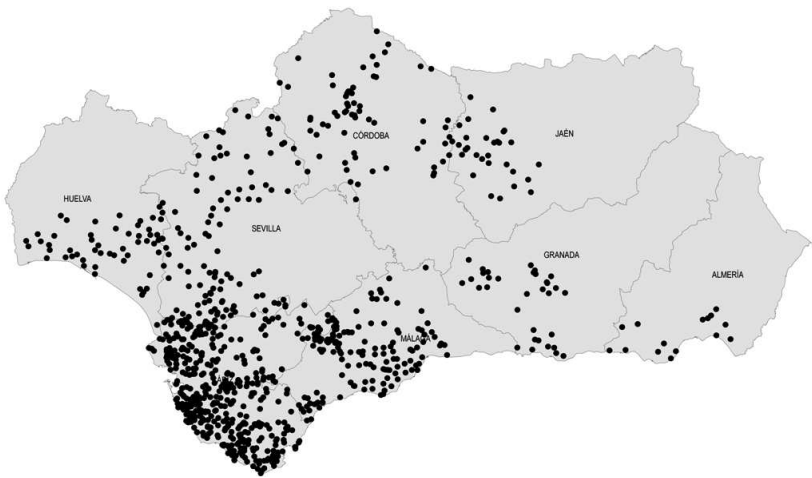
Yvonnick Guillois,¹ Florence Abravanel,² Takayuki Miura,³ Nicole Pavia,⁴ Véronique Vaillant,⁵ Sébastien Lhomme,² Françoise S. Le Guyader,³ Nicolas Rose,⁴ Jean-Claude Le Saux,³ Lisa A. King,¹ Jacques Izopet,² and Elisabeth Couturier³



CLINICAL AND EXPERIMENTAL VACCINE RESEARCH

Hepatitis E virus infections in humans and animals

Estudio HepEHorse

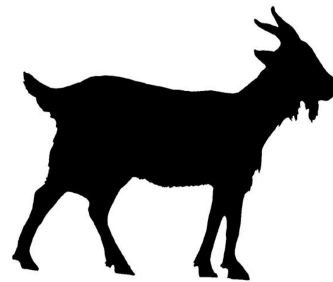


Garcia-Boganegra. Unpublished data

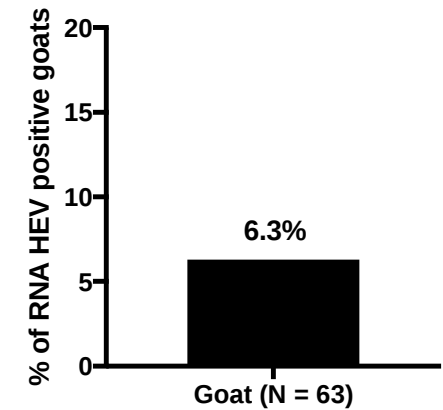
Estudio HepE-Goat



**Explotación ganadera de
Avila**



63 cabras testadas

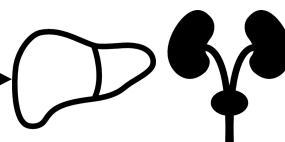




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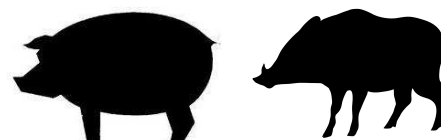
Patricia E Hewitt, Samreen Ijaz, Su R Brailsford, Rachel Brett, Steven Dicks, Becky Haywood, Iain T R Kennedy, Alan Kitchen, Poorvi Patel, John Poh, Katherine Russell, Kate I Tetmar, Joanne Tossell, Ines Ushiro-Lumb, Richard S Tedder

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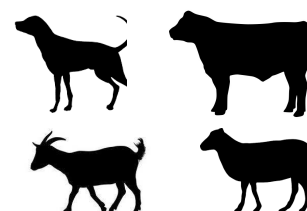
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CLINICAL AND EXPERIMENTAL VACCINE RESEARCH

Hepatitis E virus infections in humans and animals

Isolation of Hepatitis E virus from breast milk during acute infection

Antonio Rivero-Juarez*, Mario Frias, Diego Rodriguez-Cano, Francisca Cuenca-López and Antonio Rivero



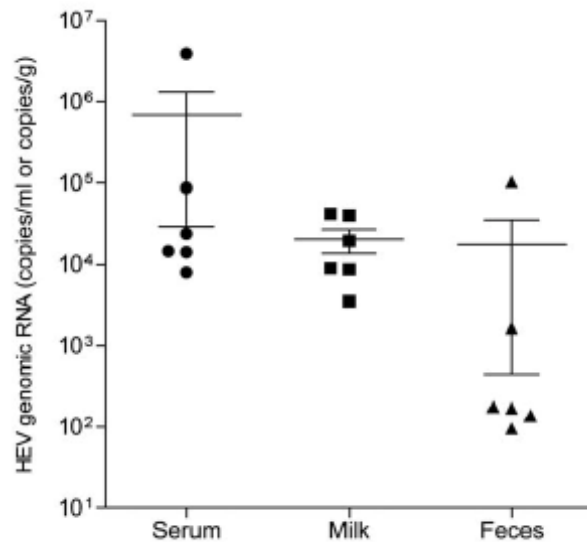
Aislamiento en leche materna

Table 1. Hepatitis E virus concentrations (IU/mL)* in blood and breast milk at different time-points

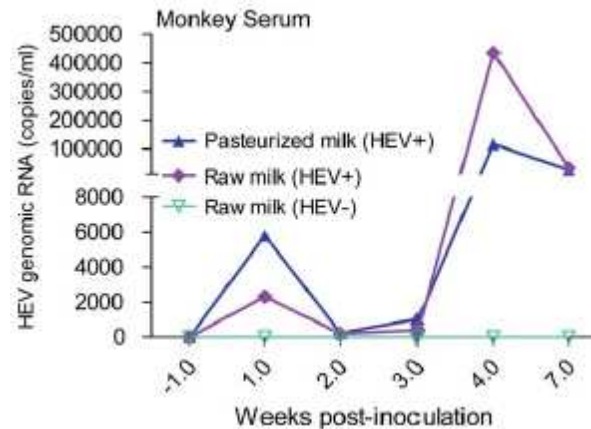
Sample	Oct 22, 2015	Nov 9, 2015	Nov 30, 2015	Dec 18, 2015
Blood	31,324 IU/mL	2,130 IU/mL	670 IU/mL	Negative
Milk	-	1,930 IU/mL	500 IU/mL	Negative

Aislamiento viral en leche bovina

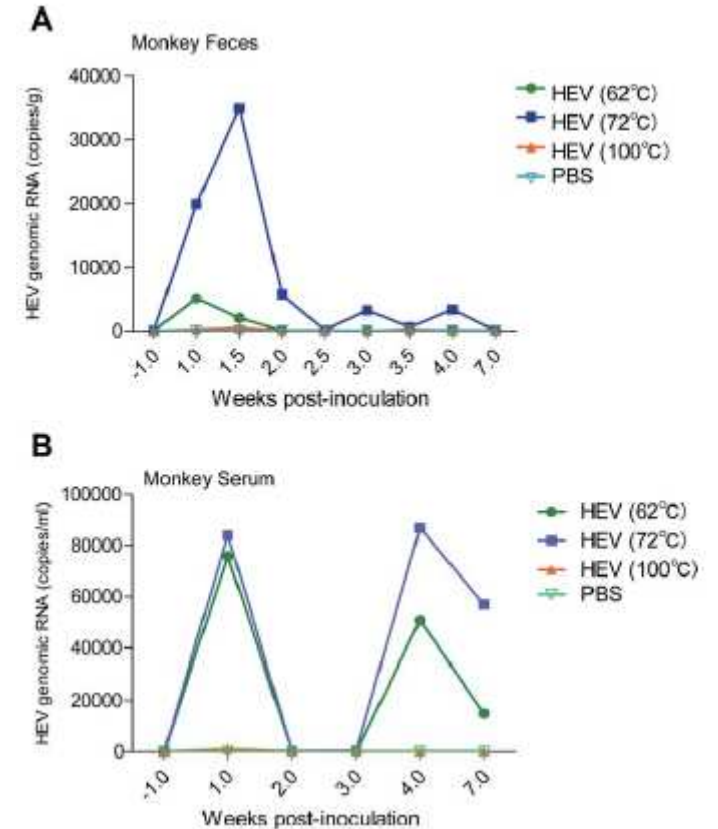
VHE en vacas



Transmisión VHE por leche en modelo animal



Inactivación VHE



Ausencia del VHE en leche Alemania

No Evidence for Zoonotic Hepatitis E Virus Infection
Through Dairy Milk in Germany



400 granjas testadas

400 muestras de tanque

0%

Hepatitis E Virus Genotype 3 in Shellfish, United Kingdom

Presence of hepatitis E RNA in mussels used as bio-monitors of viral marine pollution

Domenica Donia^{a,*}, Maria Chiara Dell'Amico^b, Anna Rita Petrinca^a, Ilaria Martinucci^b, Maurizio Mazzei^b, Francesco Tolari^b, Maurizio Divizia^a

^a Department of Public Health, Faculty of Medicine, University of Rome "La Sapienza", Rome, Italy
^b Department of Animal Pathology, University of Pisa, Pisa, Italy



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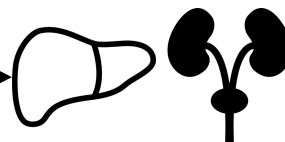
Annals of Internal Medicine

OBSERVATIONS

Transmission of Hepatitis E Virus by Plasma Exchange: A Case Report

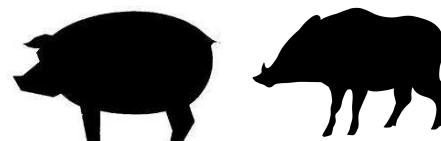
EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER JOURNAL OF HEPATOLOGY

Case Report



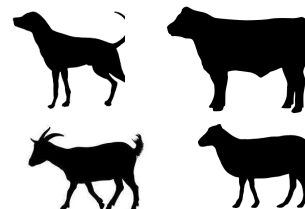
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CLINICAL AND
EXPERIMENTAL
VACCINE
RESEARCH

Hepatitis E virus infections in humans and animals

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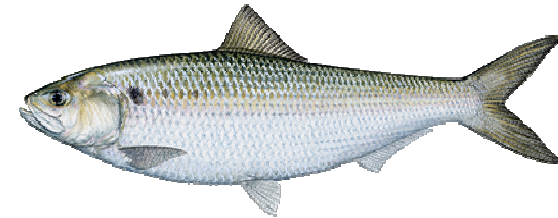
Antonio Rivero-Juarez^{*}, Mario Frias, Diego Rodriguez-Cano, Francisca Cuenca-López and Antonio Rivero



Repercusión de VHE en aguas residuales marinas



?



Presencia del VHE en moluscos

Moluscos	Pais	HEV-RNA	Reference
Mejillones	Italy	8.1%	<i>Donia et al. J Virol Meth 2012</i>
	Finland	0	<i>Diez-Valcarce et al. Food Environ Virol 2012</i>
	Spain	6%	<i>Diez-Valcarce et al. Food Environ Virol 2012</i>
	France	7.4%	<i>Grodzki et al. AEM 2014</i>
	Spain	14.8	<i>Mesquita et al Food Microbiol 2016</i>
	Scotland	85%	<i>Song et al J Med Virol 2010</i>
	England	92%	<i>Crossan et al Emerg Infect Dis 2012</i>
Almejas	France	7.6%	<i>Grodzki et al. AEM 2014</i>
Berberechos	France	12.5%	<i>Grodzki et al. AEM 2014</i>
Ostras	France	4.5%	<i>Grodzki et al. AEM 2014</i>

Repercusión de VHE en aguas residuales riego



Detection of Human Food-Borne and Zoonotic Viruses on Irrigated, Field-Grown Strawberries

Julie Brassard,^a Marie-Josée Gagné,^a Mylène Généreux,^b and Caroline Côté^b

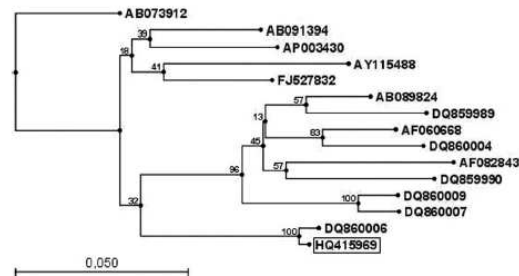


FIG 1 Phylogenetic tree obtained using the neighbor-joining method and based on a 348-bp nucleotide sequence of the 5'-end ORF2 gene of human and swine HEV genotype 3 and swine HEV isolated in this study (indicated in black box). Numbers at nodes represent bootstrap values.

Occurrence of hepatitis A and E and norovirus GI and GII in ready-to-eat vegetables in Italy



V. Terio ^{a,*}, M. Bottaro ^a, E. Pavoni ^b, M.N. Losio ^b, A. Serraino ^c, F. Giacometti ^c, V. Martella ^a, A. Mottola ^a, A. Di Pinto ^a, G. Tantillo ^a

Type of samples		Total no. 911	Positive for HAV	Positive for HEV	Positive for NoV
Mixed salads		619	14	2	0
Carrot	<i>Daucus carota</i> subsp. <i>sativus</i>	53	0	0	0
Valerian	<i>Valeriana officinalis</i>	40	1	0	0
Rocket	<i>Eruca vesicaria</i>	104	3	2	0
Spinach	<i>Spinacia oleracea</i>	10	0	2	0
Iceberg lettuce	<i>Lactuca sativa</i>	18	0	0	0
Romaine lettuce	<i>Lactuca sativa</i> L. var. <i>longifolia</i>	67	0	0	0

Sintomatología clínica en población general

ID	Gender	Age	Risk for HEV infection	ALT/AST (U/L)	Symptoms	Serum HEV viral load (copies/mL)	HEV genotype
1	Male	37	Shellfish consumption	74/52	Jaundice and flu-like symptoms	13.525	3
2	Male	41	Consumption of raw pork	494/173	Fever and asthenia	5.780	3
3	Male	27	Pig farmer	305/122	Digestive symptoms	84.900	3
4	Female	50	Shellfish and raw pork consumption	27/18	Fever and digestive symptoms	41.500	3
5	Male	53	Shellfish and raw pork consumption	132/99	Digestive symptoms and joint pain	3.210	3
6	Male	19	Raw pork consumption	99/151	Jaundice and digestive symptoms	100.500	3
7	Female	51	Raw pork consumption	872/456	Jaundice, fever, and digestive symptoms	71.200	3

Manifestaciones extra-hepáticas

A Reported extrahepatic organ manifestations in the context of hepatitis E virus infection

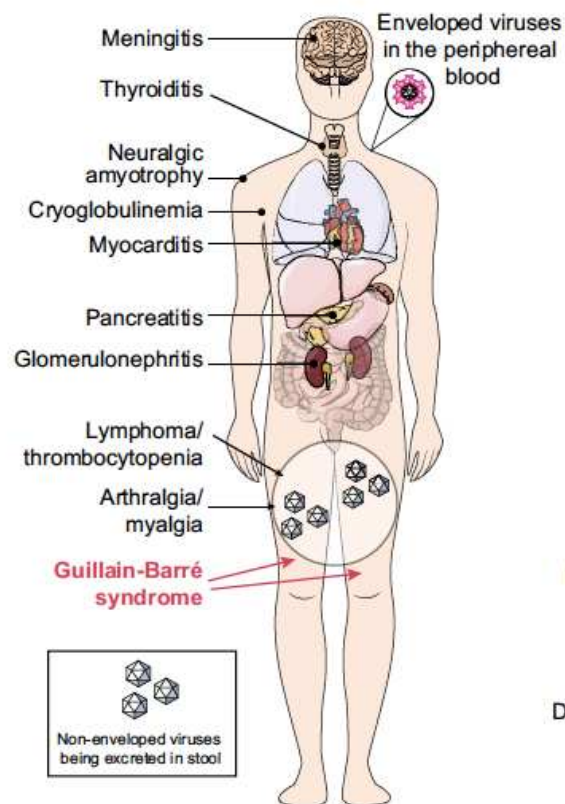
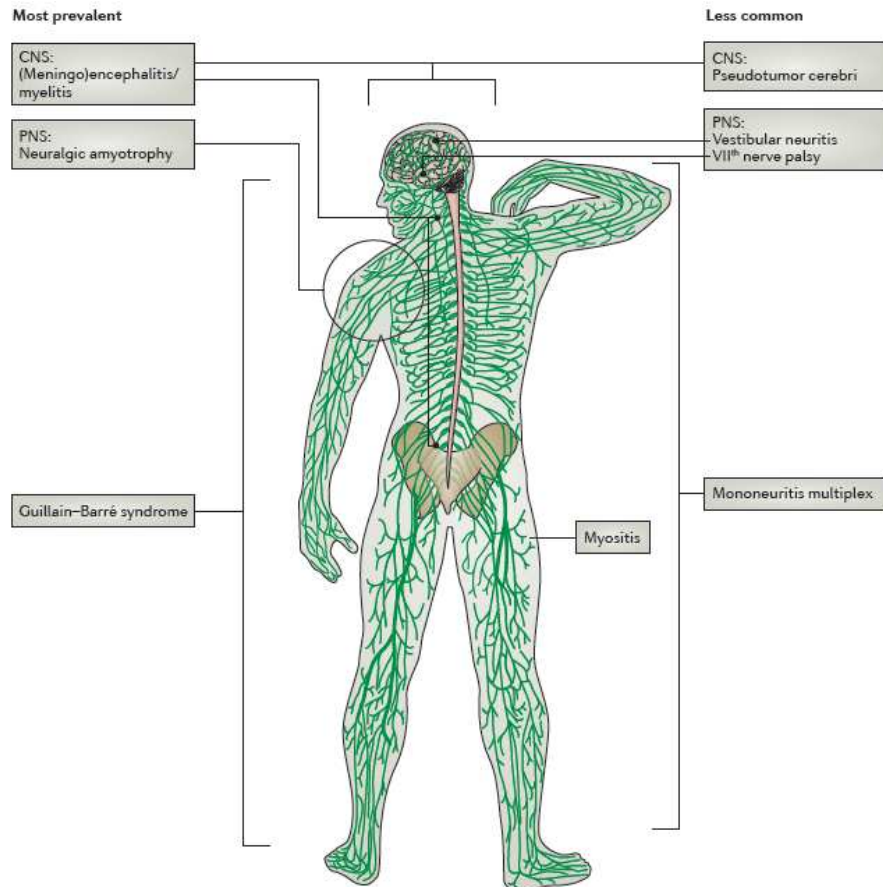


Table 1. Likelihood of causal relationship between HEV infection and assumed extrahepatic manifestation.

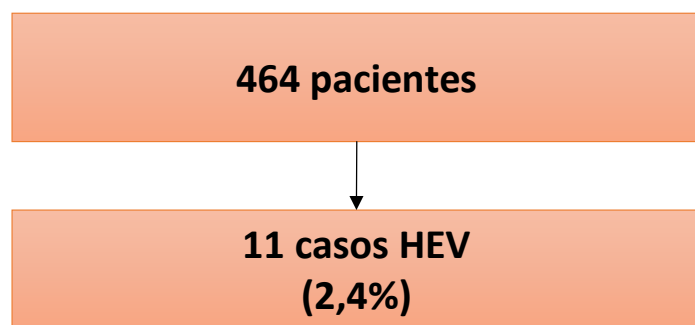
Assumed extrahepatic manifestation	Current data	Hill's criteria	Estimated likelihood of causal relationship
Neuralgic amyotrophy	- Acute HEV infection in 11% of NA patients - HEV replication in neuronal cells proven (<i>in vitro</i>)	- Strong association, temporality - Experimental	Very probable
Guillain-Barré syndrome	- Acute HEV infection in 10% of GBS patients from India and 5% from the Netherlands - HEV replication in neuronal cells proven (<i>in vitro</i>) - Typical post-infectious condition	- Strong association, temporality, consistency (consistent findings in two independent cohorts) - Experimental - Plausibility	Very probable
Cryoglobulinemia	9/10 during HEV infection - Elevated anti-HEV seroprevalence rate in patients with idiopathic cryoglobulinemia - Similar mechanisms described for HCV	- Temporality - Plausibility	Possible
Glomerulonephritis	9/51 patients with renal impairment during chronic HEV infection - Similar mechanisms described for HCV - Evidence from various experimental data	- Strong association, - Plausibility - Experimental	Very probable
Acute pancreatitis	- Large number of reports from HEV-GT1 region describing AP shortly after the diagnosis of acute HEV infection - Known for other viral infections, e.g., HAV/HBV/HCV-infection	- Temporality, consistency - Plausibility	Very probable
Hematological diseases	- Several cases observed. - High incidence of MGUS during HEV infection in a single study (However, it is possible that underlying haematological disease made patients susceptible for HEV infection)	Strong association	Possible
Meningitis	- HEV detection in CSF - HEV replication in neuronal cells proven	- Temporality, plausibility - Experimental	Possible
Autoimmune hepatitis	Elevated anti-HEV seroprevalence rate in AIH patients		Under debate
Thyroiditis	Only single case reports		Doubtful
Myocarditis	- Single cases - Only one single small study, which did not observe an association		Doubtful

Alteraciones neurológicas por VHE



Neurological disorder	No. of cases
Peripheral nervous system diseases:	
Guillain-Barré syndrome	n = 41
Miller Fisher syndrome	n = 2
Neuralgic amyotrophy	n = 37
Polyradiculoneuropathy	n = 2
Bell's Palsy	n = 3
Mononeuritis multiplex	n = 6
Vestibular neuritis	n = 1
Oculomotor palsy	n = 1
Small fiber neuropathy	n = 1
Neuromyopathy	n = 1
Paresthesia	n = 1
Central nervous system diseases:	
Meningoencephalitis	n = 9
Transverse myelitis	n = 1
Meningoradiculitis	n = 2
Pseudotumor cerebri	n = 1
Pyramidal syndrome	n = 1

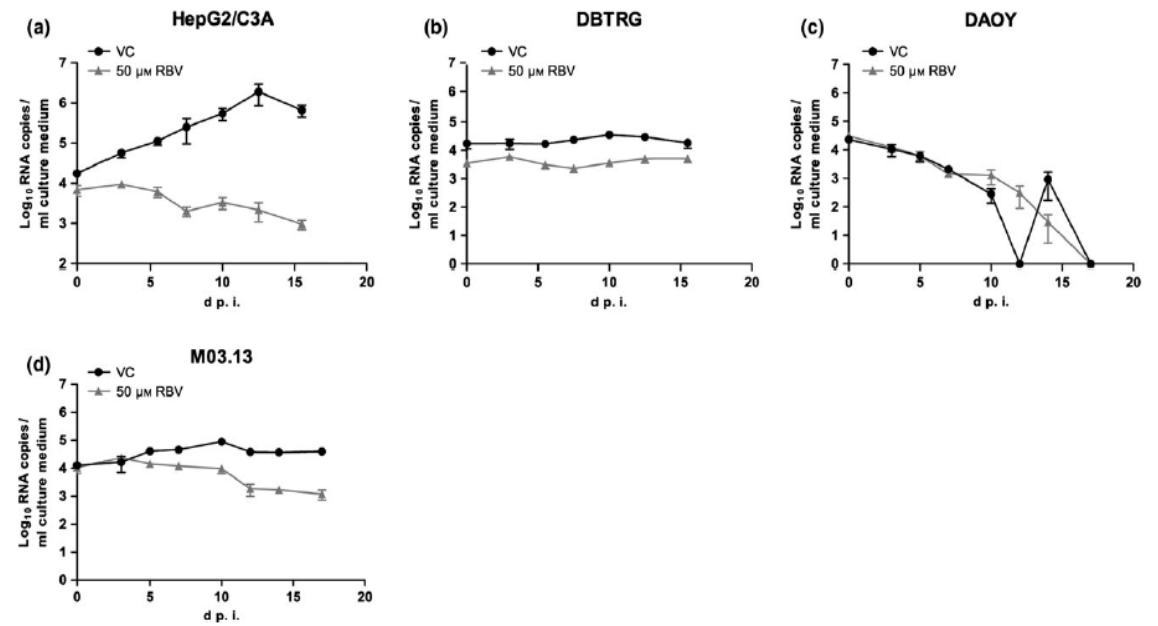
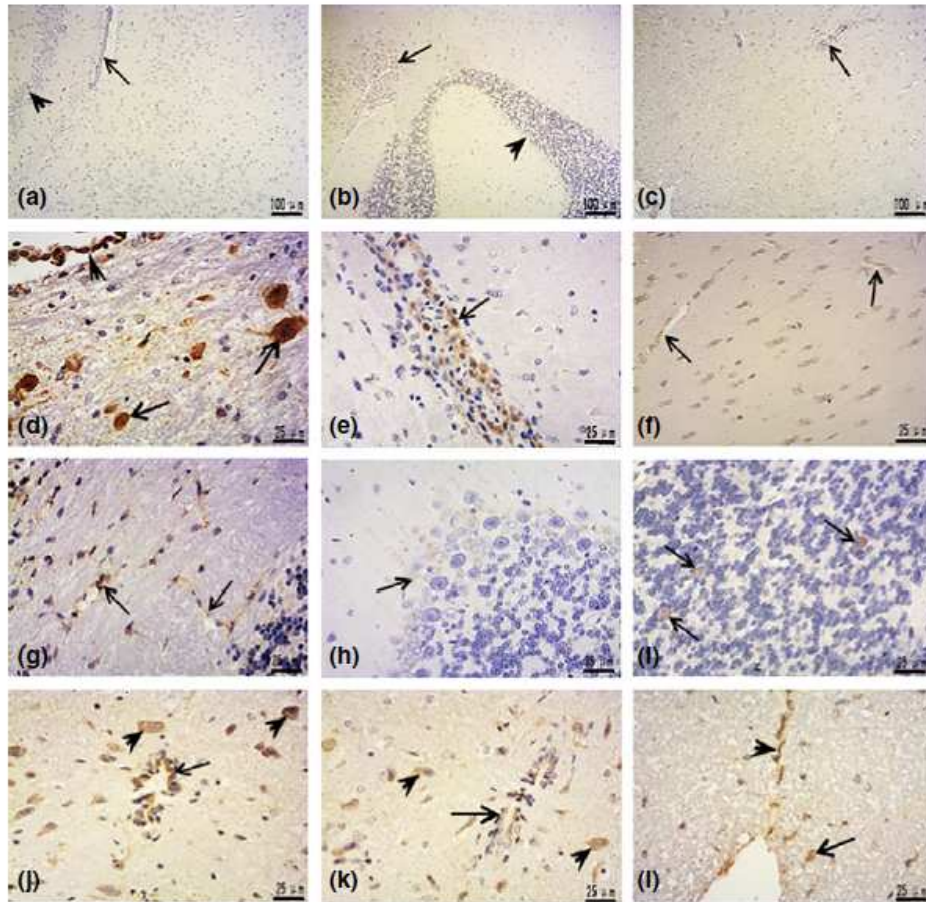
Alteraciones neurológicas por VHE: Acute Non-traumatic neurological injury



Síndrome	N
Neuralgic amyotrophy	3
Cerebral ischemia	4
Epilepsy	2
Encephalitis	1
Ramsay Hunt like syndrome	1

- Ninguno de los casos presentó ictericia ni aumento de transaminasas (ALT media = 28 UI/L)
- Todos los casos fueron varones de mediana edad (>35 años)
- Todos los casos: afectación bilateral del plexo braquial

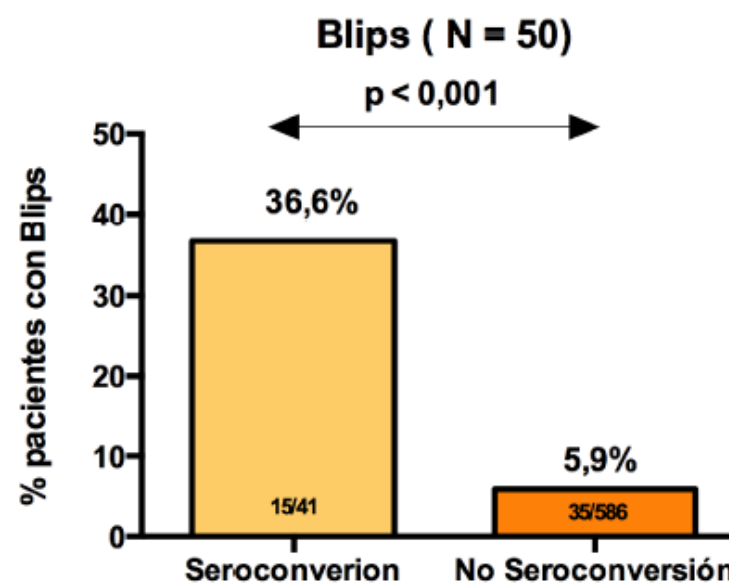
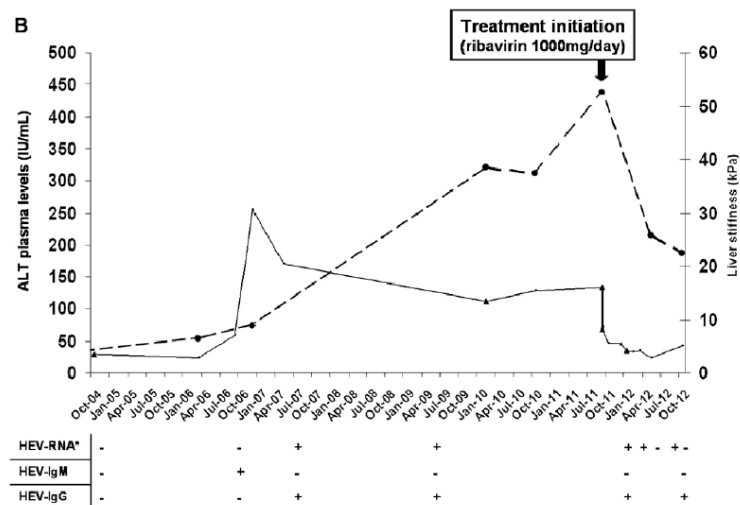
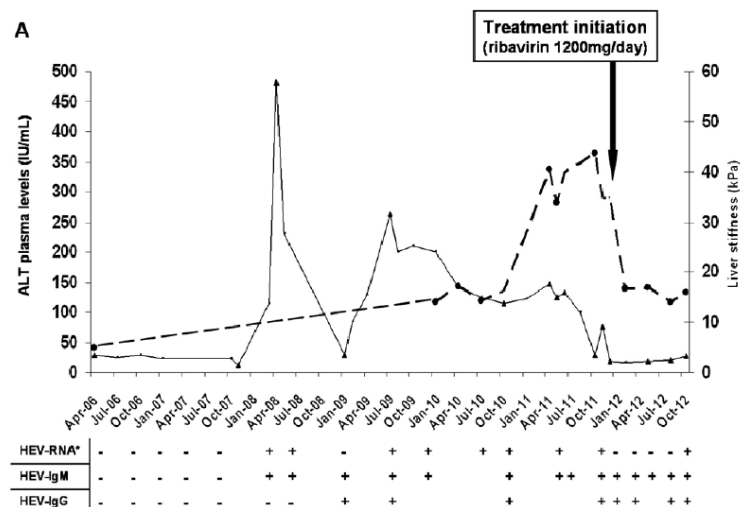
Alteraciones neurológicas por VHE: Replicación en SNC



Consideraciones especiales

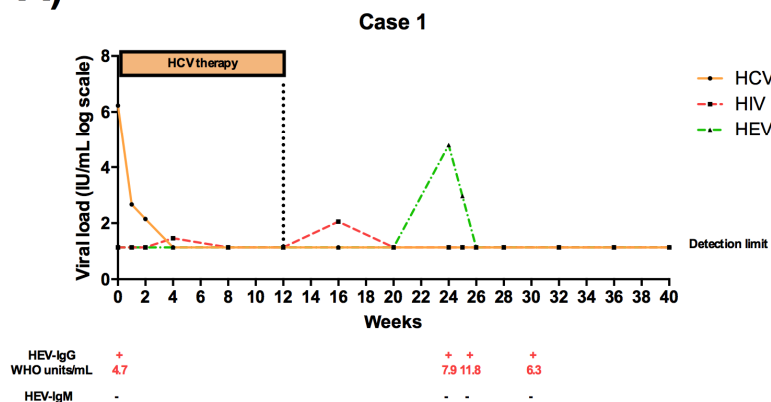
- Pacientes inmunodeprimidos
- Reinfecciones/reactivaciones

VHE en el paciente VIH: cronificación y blip

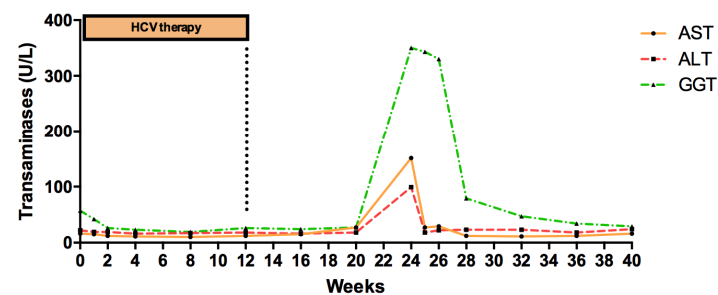
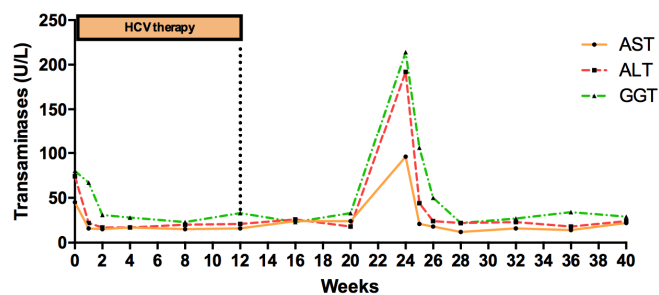
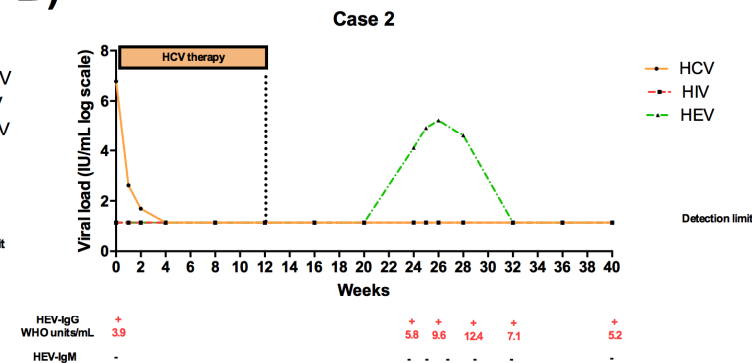


Pacientes con infección pasada: ¿Reactivación o reinfección?

A)



B)



¿Tratar la hepatitis aguda?

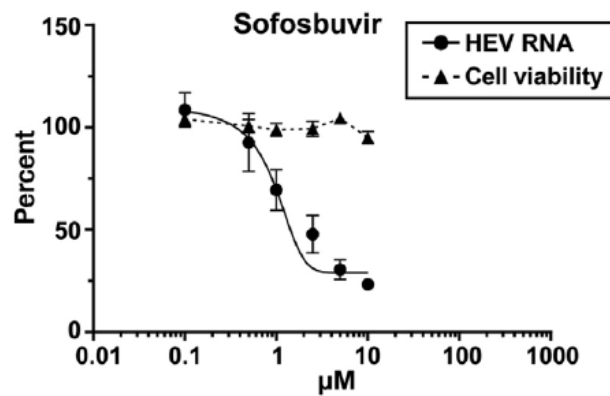
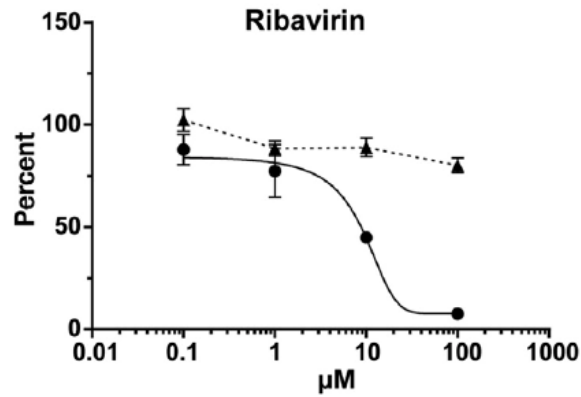
- Experiencia limitada:
 - Monoterapia RBV en inmunodeprimidos sintomáticos: serie de casos
 - Tasas de RVS: 85%
 - ¿Fallos?: mutaciones a RBV
- Consenso:
 - Tratar casos graves
 - Tratar solo en casos de manifestaciones extrahepáticas
- Ensayo clínico en marcha: NCT02558114 (Hospital Vall d'Hebron)

Tratar la hepatitis crónica: ¿con qué?

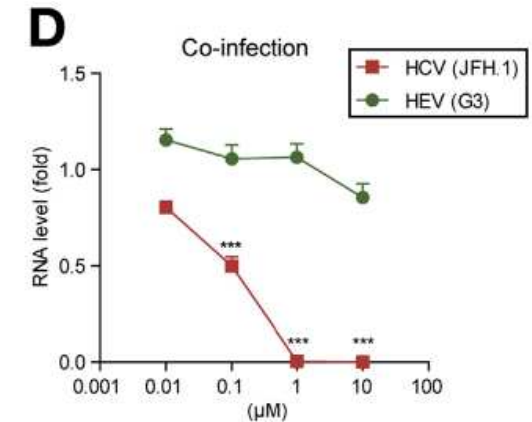
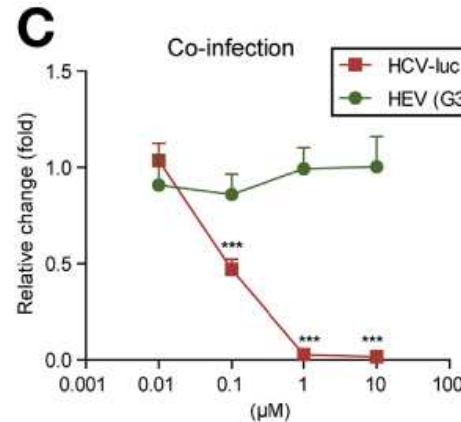
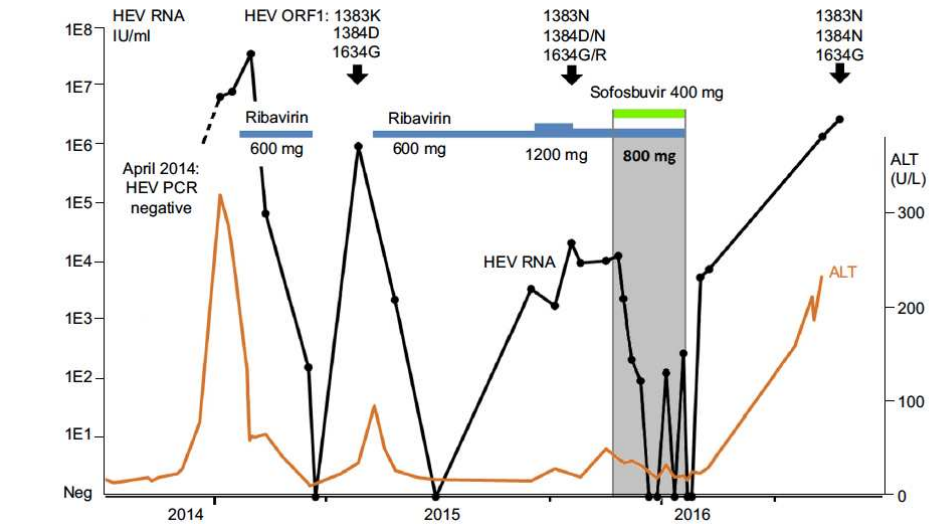
Author (year)	n	Ribavirin dose (mg/day)	Duration, median months (range)	Rapid viral response month (%)	SVR n/n (%)	Definition of SVR, months (%)	Relapses n (%)	No clearance n (%)	No follow-up n (%)
Kamar (2014) [7]	59	600 (29–1200)	3 (1–18)	1 (64) 3 (31)	46/59 (78)	6	10 (17)*	1 (2)	2 (3)
Pischke (2014) [24]	4	600–800	4.5 (1–5)	1 (25) 2 (25) 3 (25)	2/4 (50)	7 (25) 11 (25)	1 (25)		1 (25)
Pischke (2013) [8]	11	600–1000	5 (n = 10) 6 weeks (n = 1) [†]	1 (36) 2 (46)	9/11 (82)	24 (46) 7 (9) 5 (9) 4 (18)	0 (0)		2 (18)
Kamar (2010) [5]	8	400–800	3	2 weeks (50) 3 weeks (12) 2 (38)	5/8 (63)	6 (50) 1 (12)	2 (25)		1 (12)
Pischke (2012) [25]	4	200–800	5	1 (50) <6 weeks (25)	3/4 (75)	NK	0 (0)	1 (25)	
Koning (2013) [9]	3	200–800	8 (3–9)	NK	1/3 (33)	3 (33)	0 (0)	1 (33)	1 (33)
Riezebos (2013) [26]	2	800	4	2 (100)	2/2 (100) [‡]	6 (100)	0 (0)	0 (0)	
Mallet (2010) [27]	2	600–800	3	1 (100)	2/2 (100)	2.5 (100)	0 (0)	0 (0)	
Im (2013) [28]	1	NK	10	6	NA	NA	NA	NA	1 (100)
de Niet (2012) [29]	1	800	3	2	1/1 (100)	6	0 (0)	0 (0)	
Chaillon (2011) [30]	1	17 mg/kg/day	3	1	1/1 (100)	4	0 (0)	0 (0)	
Klein (2014) [31]	1	600	4	2	1/1 (100)	8	0 (0)	0 (0)	
Taton (2013) [32]	1	1000	3	1	1/1 (100)	6	0 (0)	0 (0)	
Neukam (2013) [10]	2	1000–1200	6	1 (50) 4 (50)	0/2 (0)	NK	2 (100) (<5 months)	0 (0)	
Hajji (2013) [33]	1	800	3	2	1/1 (100)	6	0 (0)	0 (0)	
Roux (2013) [34]	1	800	3	3	NA	NA	NA	NA	1 (100)
Giordani (2013) [35]	1	1000	3	2	1/1 (100)	6	0 (0)	0 (0)	
Alric (2011) [36]	1	600	3	2 weeks	1/1 (100) [§]	6	0 (0)	0 (0)	
Ambrosioni (2014) [37]	1	800	>11	6	1/1 (100) [‡]	9	1 (100) [¶]	0 (0)	
Total		200–1200	3 (1–18)		78/105 (74%)	≥6 m: 67/105 (64%)	16/105 (15%)	3/105 (3%)	9/105 (9%)

¿Sofosbuvir?

*In vitro*¹

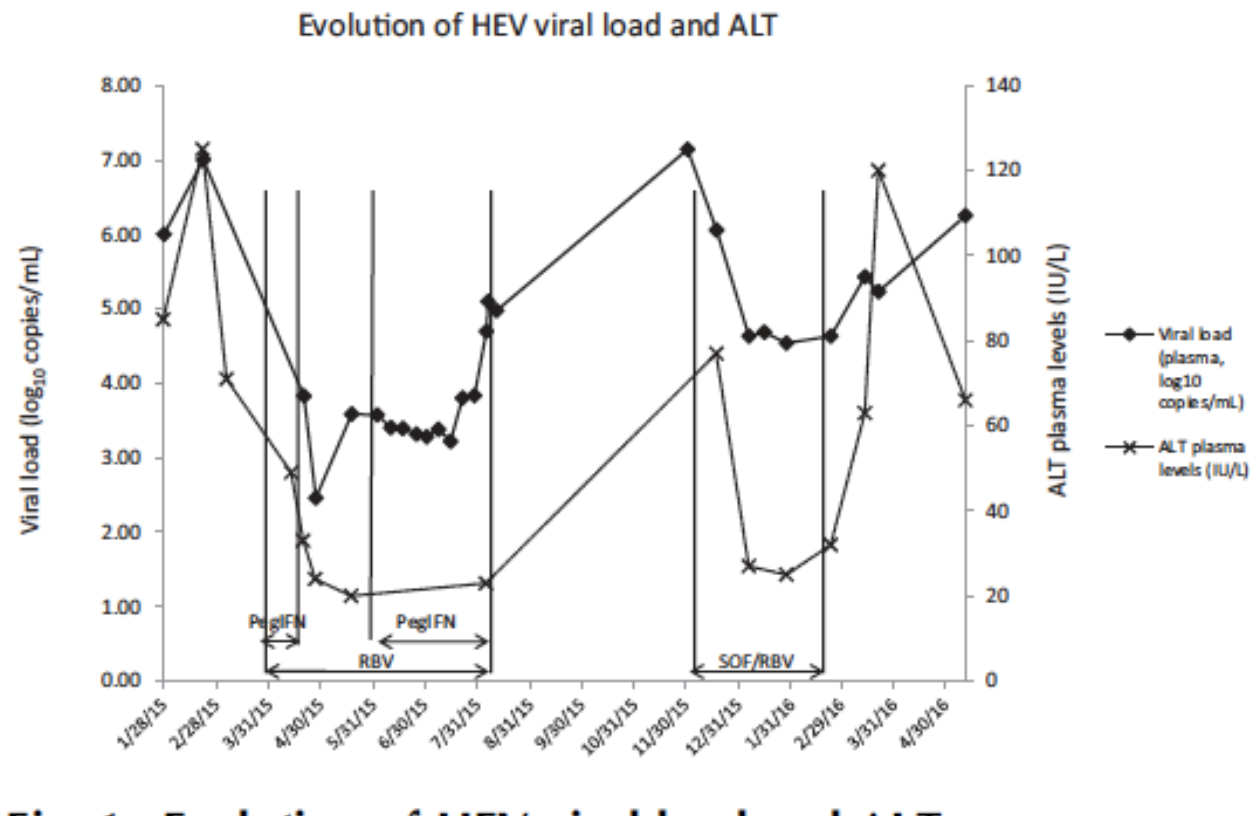


In vivo^{2,3}

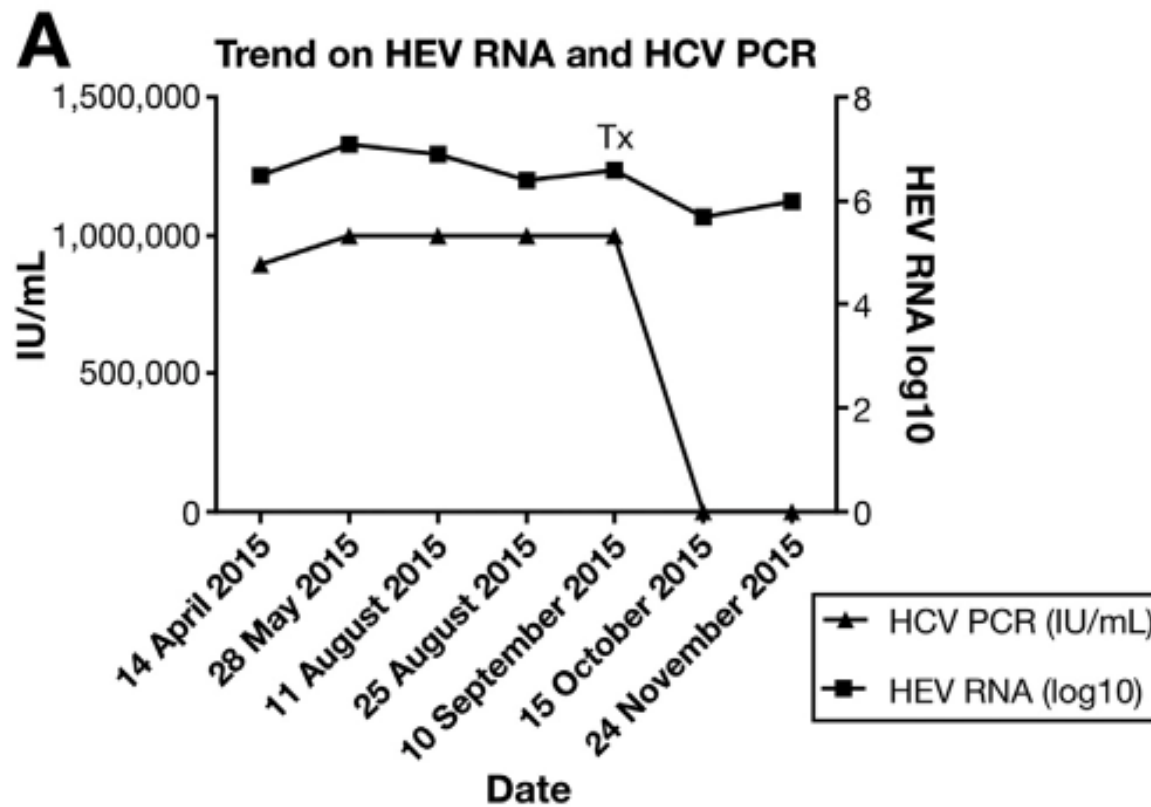


1. Dhao Thi et al Gastroenterol 2016
2. Van der Valk et al J Hepatol 2017
3. Wang W et al Gastroenterol 2016

¿Sofosbuvir y RBV?



¿Sofosbuvir + Daclatasvir?



Prevención: Poblaciones especiales

- Evitar alimentos crudos
- Evitar productos lácteos no pasteurizados
- Evitar alimentos procedentes de fauna salvaje
- Vacuna solo aprobada en China

EUROPE'S NEW HEPATITIS PROBLEM

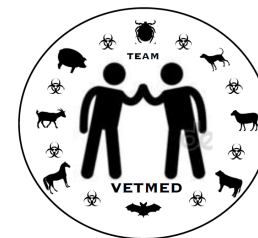
Many get infected with hepatitis E, and a few get very sick. How can the virus be stopped?

By **Kai Kupferschmidt**

Conclusiones

- Hepatitis E principal causa de hepatitis aguda en viajeros
- Dos enfermedades diferentes dependiendo de la zona de viaje:
 - Asia-pacífico:
 - Hepatitis aguda acompañada de ictericia
 - Alta mortalidad en embarazadas y cirróticos
 - Europa:
 - Infección subclínica con sintomatología variable
 - Manifestaciones extrahepáticas
 - Cronificación en inmunodeprimidos
- Ausencia de tratamiento específico
- Prevención por vacunación (Asia) y medidas alimentarias

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