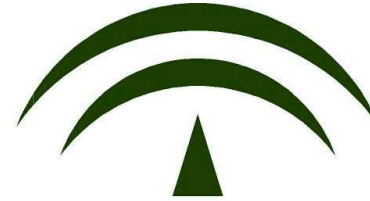


**IMIBIC**

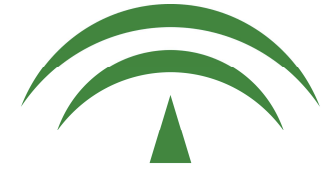
INSTITUTO MAIMÓNIDES DE  
INVESTIGACIÓN BIOMÉDICA  
CÓRDOBA



UNIVERSIDAD DE CÓRDOBA



JUNTA DE ANDALUCÍA  
CONSEJERÍA DE SALUD



JUNTA DE ANDALUCÍA  
CONSEJERÍA DE AGRICULTURA, PESCA Y DESARROLLO R

# Hepatitis E en España

**Antonio Rivero Juárez**

Grupo de Investigación en Enfermedades Infecciosas

Instituto Maimonides de Investigación Biomédica de Córdoba (IMIBIC)

Hospital Universitario Reina Sofía de Córdoba

Universidad de Córdoba

HepEpor



# Conflicto de intereses

- Apoyo línea de investigación:
  - Capital público: Fundación para la investigación en salud (FIS)
  - Capital privado: AbbVie y ViiV Healthcare
- Fuera de esta línea de investigación:
  - Honorarios por conferencias, ponencias y cursos: Bristol Mier Squidd, ViiV Healthcare, Janssen Cilag, MSD, y Roche
- Otros:
  - Ninguna relación comercial o personal con empresas ganaderas o alimentarias
  - No soy vegetariano

# Definición clásica

- Hepatitis aguda
- Transmisión **feco-oral** (Hepatitis *E...nteric*)
- Asociado a **brotes epidémicos** (Hepatitis *E...pidemic*)
- En países del **Suroeste Asiático** (Hepatitis *E...ndemic*)
- Mortalidad en **embarazadas**: 15-20%

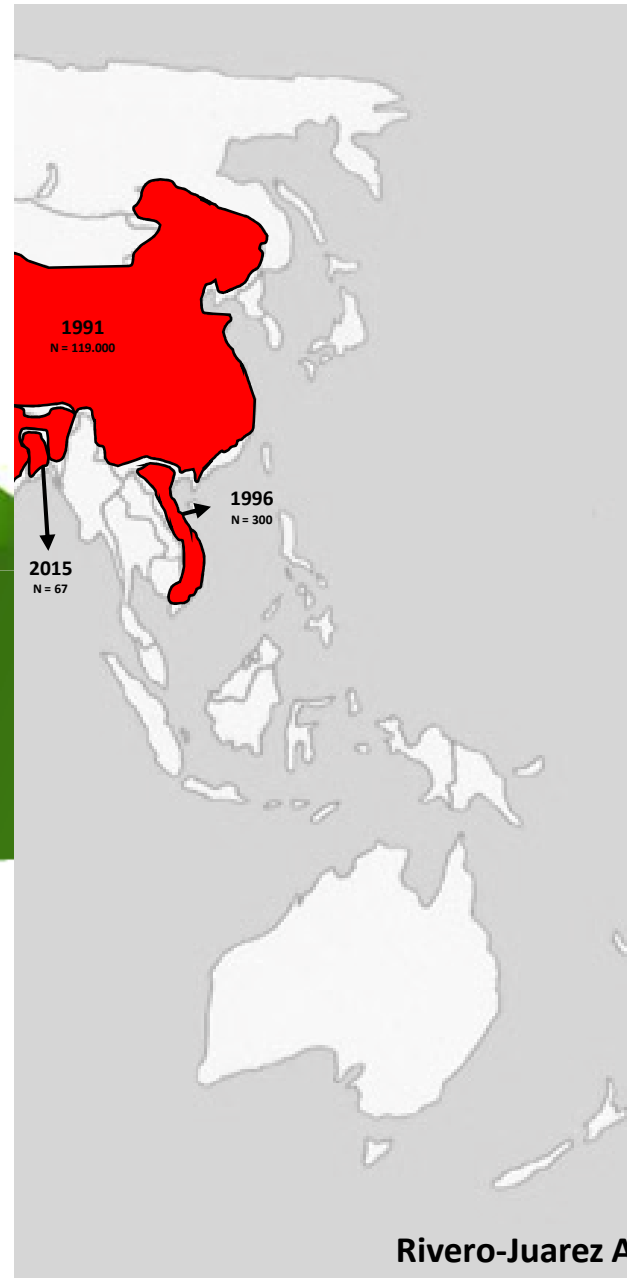
rotos epidémicos po



# WATERBORNE OUTBREAKS OF HEPATITIS E: RECOGNITION, INVESTIGATION AND CONTROL

2014

TECHNICAL REPORT



# Hepatitis E: Enfermedad del viajero

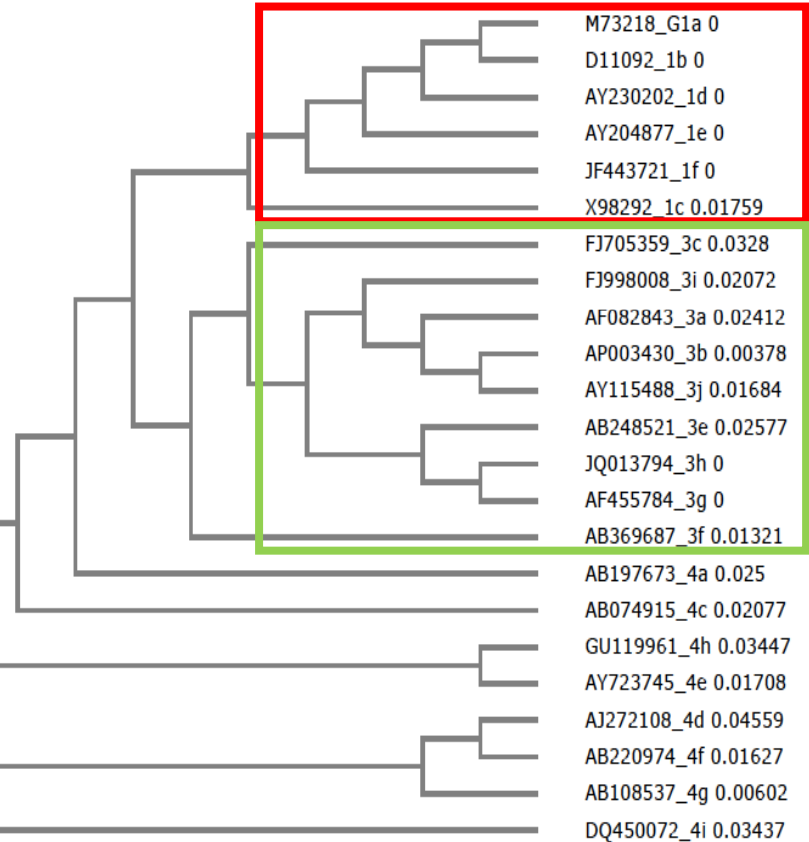
- Entonces, si no se viaja a países endémicos, no hay riesgo de infección

## Non-Travel-Associated Hepatitis E in England and Wales: Demographic, Clinical, and Molecular Epidemiological Characteristics

Samreen Ijaz,<sup>1</sup> Eve Arnold,<sup>2</sup> Malcolm Banks,<sup>8</sup> Richard P. Bendall,<sup>4</sup> Matthew E. Cramp,<sup>6</sup> Richard Cunningham,<sup>7</sup> Harry R. Dalton,<sup>5</sup> Tim J. Harrison,<sup>3</sup> Simon F. Hill,<sup>9</sup> Lorna MacFarlane,<sup>10</sup> Rolf E. Meigh,<sup>11</sup> Shuja Shafi,<sup>12</sup> Martin J. Sheppard,<sup>13</sup> Jacqui Smithson,<sup>14</sup> Melanie P. Wilson,<sup>15</sup> and Chong-Gee Teo<sup>1</sup>

Recent travel history	No. (%) of patients	Mean age (range), years	Men, %	South Asian, %
To area where HEV is hyperendemic	129 (69)	34 (9–85)	81	87
To area where HEV is not endemic	8 (4)	58 (27–76)	100	0
None	17 (9)	68 (51–83)	82	0
Unknown	32 (17)	42 (8–82)	56	94

# Dos “enfermedades” diferentes



**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 hosts)
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*

Quarez. Including all HEV standard strain possessed

Hoofnagle. NE

# En los próximos minutos...

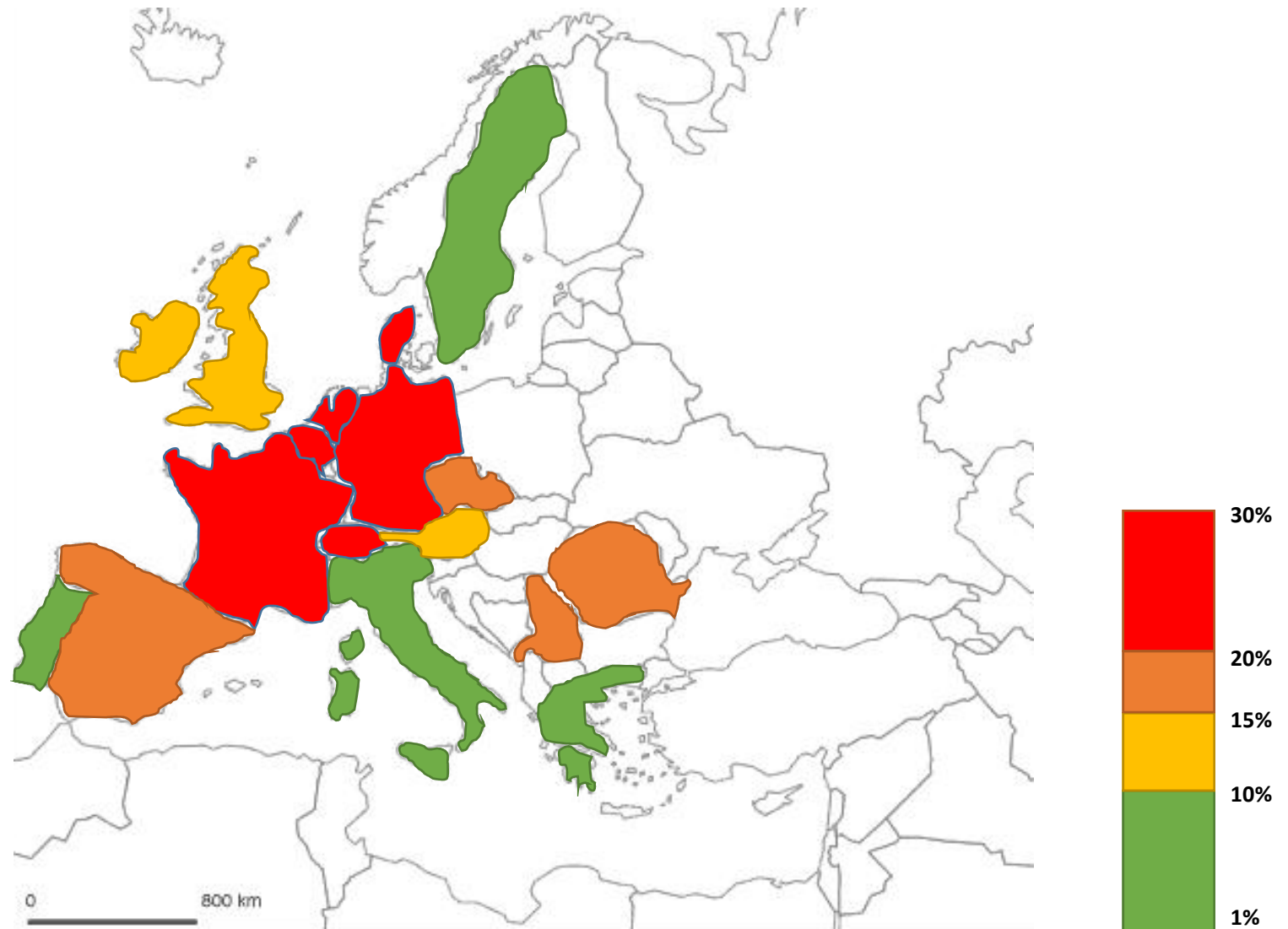
- Situación epidemiológica del VHE en Europa-España
- Transmisión del VHE en España-Europa
- Patogénia: novedades
- Sintomatología: novedades

**convenceros de que el VHE es un grave problema de salud pública en Euro**

Situación epidemiológica



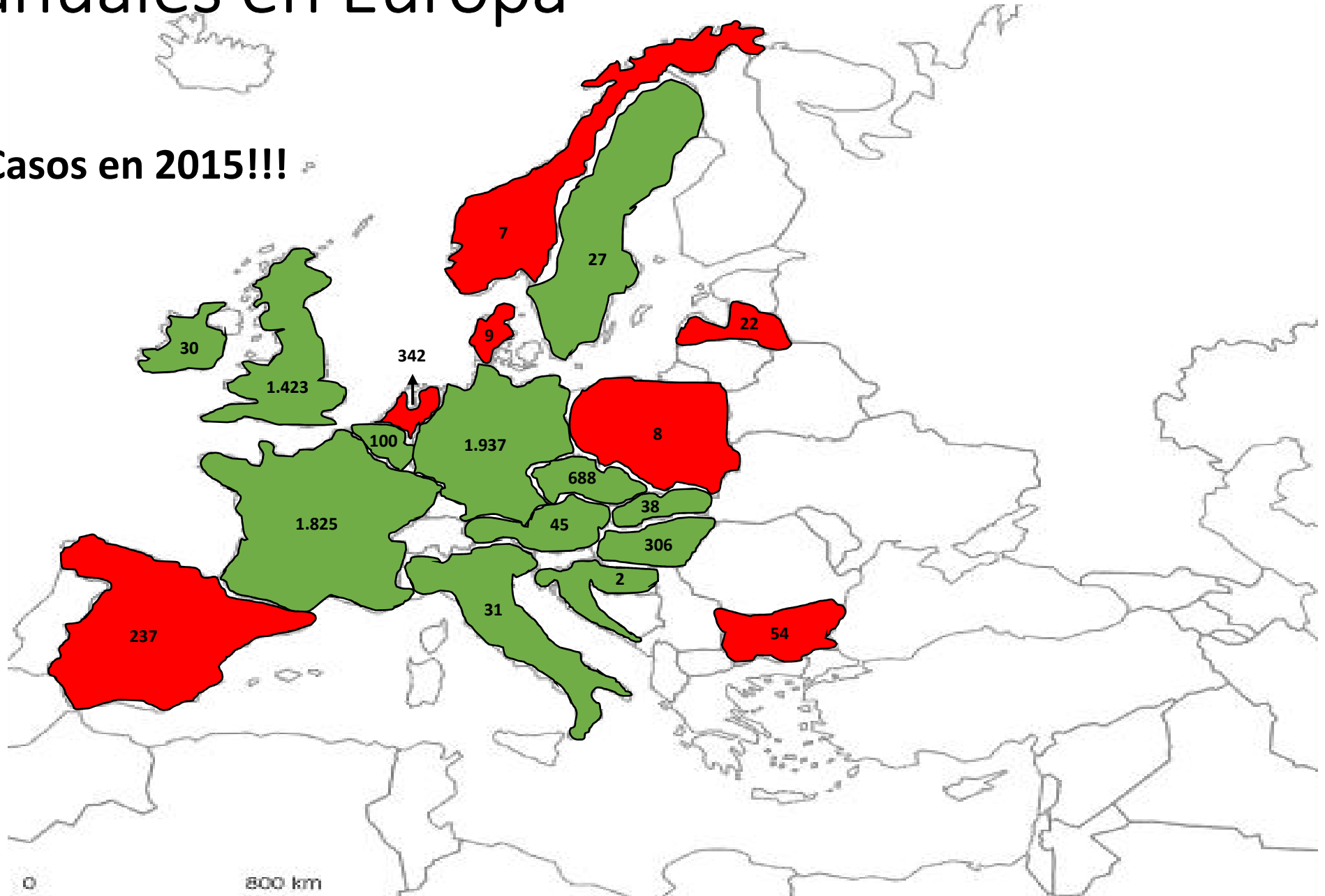
# Seroprevalencia en Europa población general



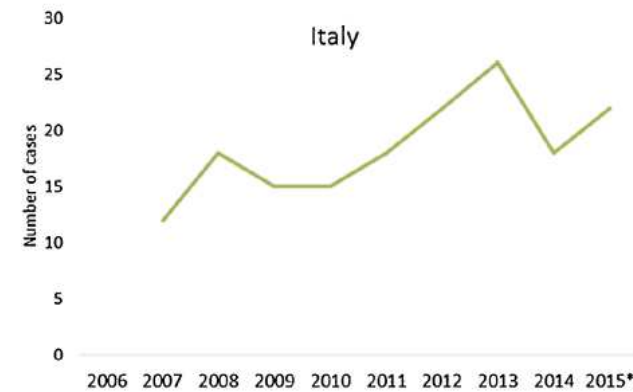
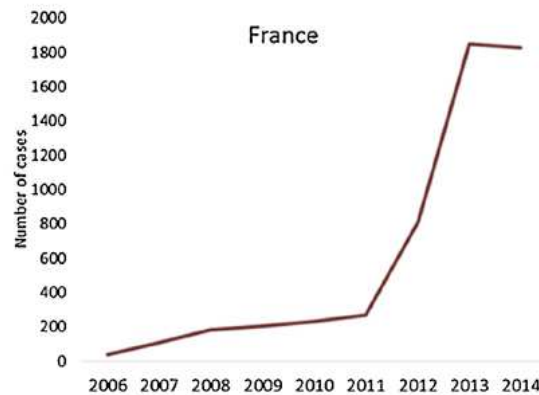
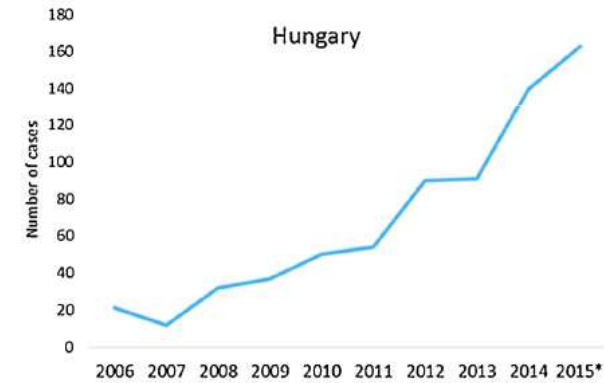
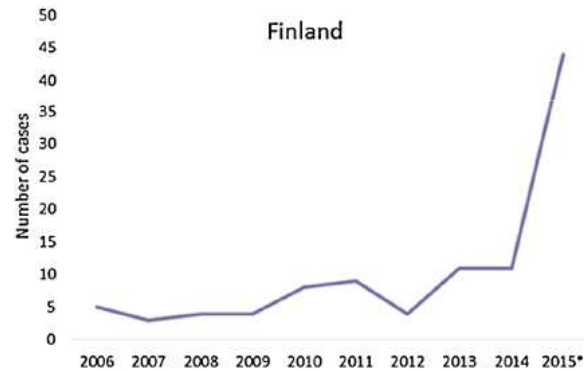
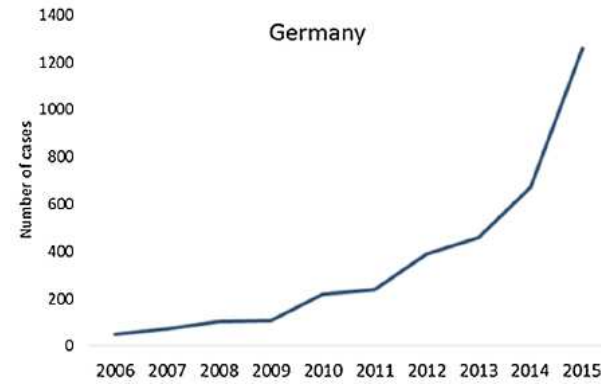
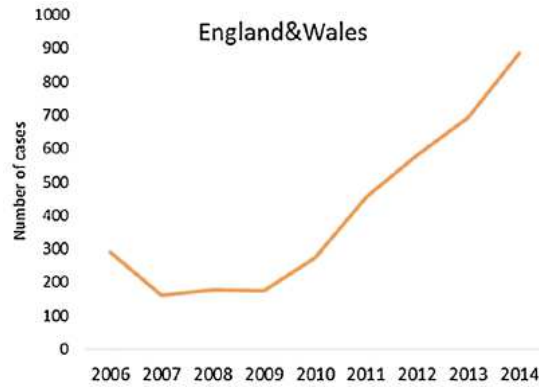
Rivero-Juarez A. All seroprevalence data collected were performed using ELISA

# Casos anuales en Europa

7.131 Casos en 2015!!!



# principal causa de hepatitis aguda en Europa



# Experiencia de Córdoba

- Cribado de VHE en pacientes con hepatitis aguda que acuden a Enfermedades Infecciosas del HURS por consulta a demanda
- Año 2016: 43 pacientes cribados
- Casos de VHE: **9 (20.9%)**

cience

# 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*

# Entornos de mayor riesgo en Europa: Sur de Francia

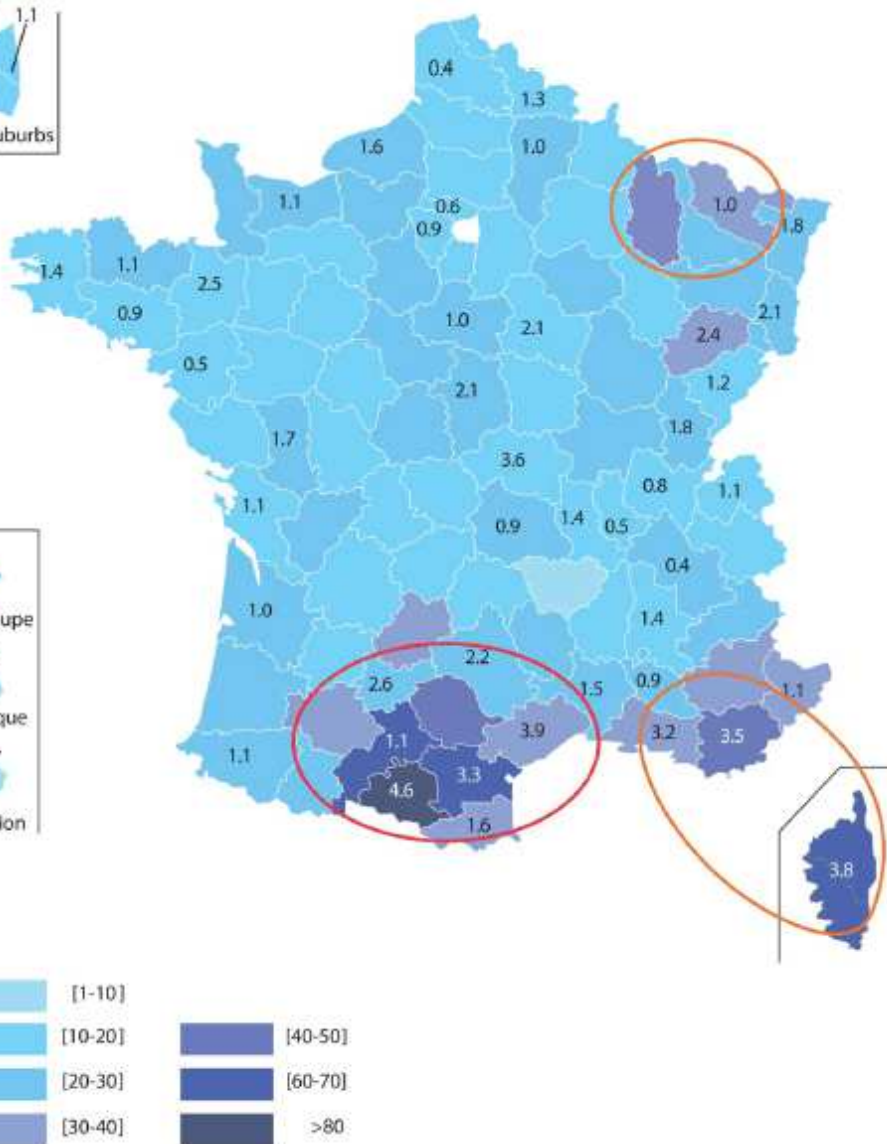


TABLE 2. Factors Associated With IgG Anti-HEV According to Age (<45, >45 Years)

Risk Factor	Grouped Clinically Selected Variables Associated With Anti-HEV IgG Included in the Log Binomial Model Analysis					Log Binomial Model Including Variables Independently Associated With Presence of Anti-HEV IgG				
	RR	SE	z	P > z	95% CI	RR	SE	z	P > z	95% CI
<b>Age &lt;45</b>										
Area	2.26	0.17	13.99	0.00	1.96-2.62	2.26	0.17	10.98	0.00	1.95-2.57
Pig meat	1.81	0.50	2.15	0.03	1.05-3.10	1.81	0.50	2.16	0.03	1.06-3.10
Pork liver sausage	1.47	0.12	4.63	0.00	1.25-1.72	1.47	0.12	4.63	0.00	1.25-1.72
Game	1.26	0.10	2.91	0.00	1.08-1.48	1.26	0.10	2.89	0.00	1.08-1.48
All offal	1.25	0.10	2.84	0.00	1.07-1.46	1.25	0.10	2.82	0.01	1.07-1.46
Oysters	1.25	0.10	2.86	0.00	1.07-1.45	1.25	0.10	2.85	0.00	1.07-1.45
Bottled water	0.90	0.14	-0.67	0.50	0.66-1.23					
<b>Age &gt;45</b>										
Area	1.70	0.09	10.15	0.00	1.53-1.88	1.69	0.09	10.09	0.00	1.53-1.88
Pig meat	1.31	0.32	1.12	0.26	0.82-2.10					
Pork liver sausage	1.26	0.07	4.27	0.00	1.13-1.40	1.27	0.07	4.42	0.00	1.14-1.40
Game	1.13	0.07	2.13	0.03	1.01-1.27	1.14	0.07	2.21	0.03	1.02-1.27
All offal	1.25	0.08	3.36	0.00	1.10-1.43	1.27	0.08	3.66	0.00	1.12-1.43
Oysters	1.05	0.06	0.86	0.39	0.94-1.18					
Bottled water	0.82	0.07	-2.51	0.01	0.70-0.96	0.82	0.06	-2.57	0.01	0.70-0.96

# ntos de mayor riesgo en Europa: Andalucía

## Córdoba<sup>1, 2</sup>

High hepatitis E virus seroprevalence with absence of chronic infection in HIV-infected patients

Antonio Rivero-Juarez <sup>a,\*\*,c</sup>, Loreto Martinez-Dueñas <sup>a,c</sup>, Antonio Martinez-Peinado <sup>a</sup>, Angela Camacho <sup>a</sup>, Celia Cifuentes <sup>b</sup>, Ana Gordon <sup>a</sup>, Mario Frias <sup>a</sup>, Julian Torre-Cisneros <sup>a</sup>, Juan A. Pineda <sup>b</sup>, Antonio Rivero <sup>a,\*</sup>

**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

## Sevilla<sup>3</sup>

Incidence and natural history of hepatitis E vi  
coinfection among HIV-infected patients

Juan A. Pineda<sup>a</sup>, Celia Cifuentes<sup>a</sup>, Manuel Parra, Nicolás Merced  
Elisabet Pérez-Navarro<sup>a</sup>, Antonio Rivero-Juárez<sup>b</sup>, Patricia Mo  
Antonio Rivero<sup>b</sup>, Juan Macías and Luis Miguel Real

**Prevalence:**  
26%

**Incidencia acumulada:**  
19%

1. Rivero-Juarez et al. J Inf
2. Rivero-Juarez et al Zoonoses Pub H
3. Pineda JA

¿Cómo se transmite?





## 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*

**Annals of Internal Medicine**

OBSERVATIONS

Transmission of Hepatitis E Virus by Plasma  
A Case Report

# Viremia en donantes de sangre

Country	Blood Donors HEV RNA Positive	HEV IgG Seroprevalence	Reference
Midi-Pyrénées, Southwest France *	1:1438 (1:2200) **	52.5%	Gallian et al., 2014 [15] Mansuy et al., 2011 [18]
Germany	1:1200 1:4525	29.5%	Vollmer et al., 2012 [16] Baylis et al., 2012 [36] Wenzel et al., 2013 [29]
The Netherlands	1:2671	27.0%	Slot et al., 2013 [37]
England	1:2848 1:7000	* 12.0% 16.0% 16.0%	Hewitt et al., 2014 [13] Ijaz et al., 2012 [38] Beale et al., 2011 [39] Dalton et al., 2008 [4]
Sweden	1:7986	NA	Baylis et al., 2012 [36]
Austria	1:8416	13.5%	Fischer et al., 2015 [40]
Scotland	1:14,520	4.7%	Cleland et al., 2013 [35]

# Resistencia del VHE en hemoderivados

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



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

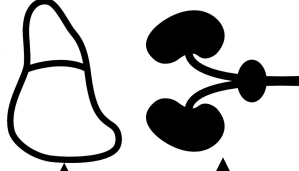
25 June 2015  
EMA/CHMP/BWP/723009/2014  
Committee for Medicinal Products for Human Use (CHMP)

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

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

Patricia E Hewitt, Samreen Jhaz, Su R Brailsford, Rachel Brett, Steven Dicks, Becky Hoywood, Jain T R Kennedy, Alan Kitchen, Poorvi Patel, John Poh, Katherine Russell, Kate Tattmar, Joanne Tossell, Ines Ushiro-Lumb, Richard Steadler

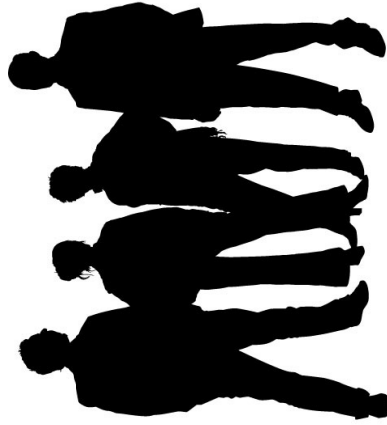
OBSERVATIONS



## Case Report

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

B. Schlosser<sup>1</sup>, A. Stein<sup>2</sup>, R. Neuhaus<sup>3</sup>, S. Pahl<sup>4</sup>, B. Ramez<sup>1</sup>, D.H. Krüger<sup>2</sup>, T. Berg<sup>1,5,\*</sup>, J. Hofmann<sup>2,†</sup>



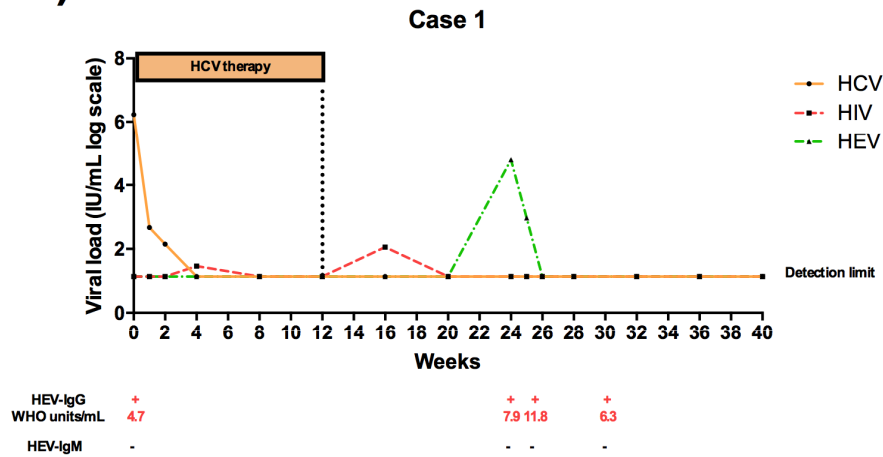
# Impacto de la infección por el VHE en trasplantados

- Rechazo agudo del injerto<sup>1</sup>
- Rápida progresión de la fibrosis hepática<sup>2</sup>
- Aparición de síndrome nefrótico<sup>3</sup>
- Mayor tiempo de excreción del VHE<sup>4</sup>
- Reactivación de una infección ya establecida: Tacrolimus<sup>5</sup>

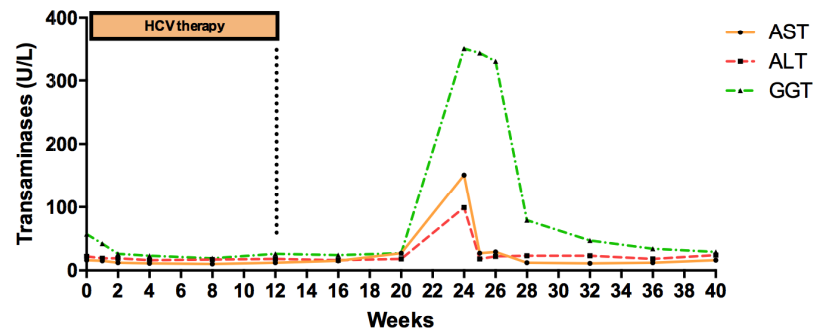
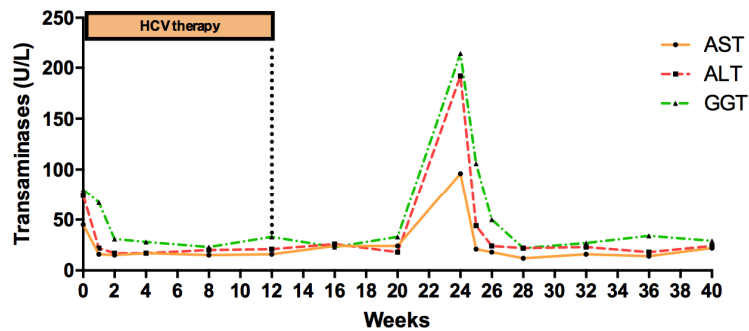
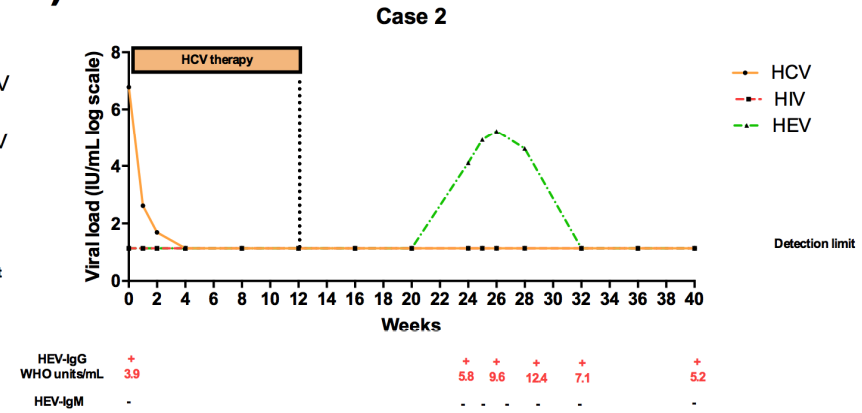
1. Pischke S Liver Transplant
2. Kamar N Transplant
3. Kamar N. Transplant
4. Tavitian S J Clin
5. Le Coutr

# ¿Reactivación/reinfección?

A)



B)





## 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

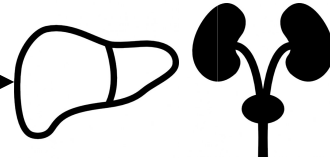
Annals of Internal Medicine

OBSERVATIONS

Transmission of Hepatitis E Virus by Plasma  
A Case Report

Case Report

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

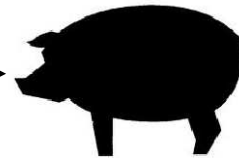


## Liver transplant from a donor with occult HEV infection induced chronic hepatitis and cirrhosis in the recipient

B. Schlosser<sup>1</sup>, A. Stein<sup>2</sup>, R. Neuhaus<sup>3</sup>, S. Pahl<sup>4</sup>, B. Ramez<sup>1</sup>, D.H. Krüger<sup>2</sup>, T. Berg<sup>1,5,\*</sup>, J. Hofman

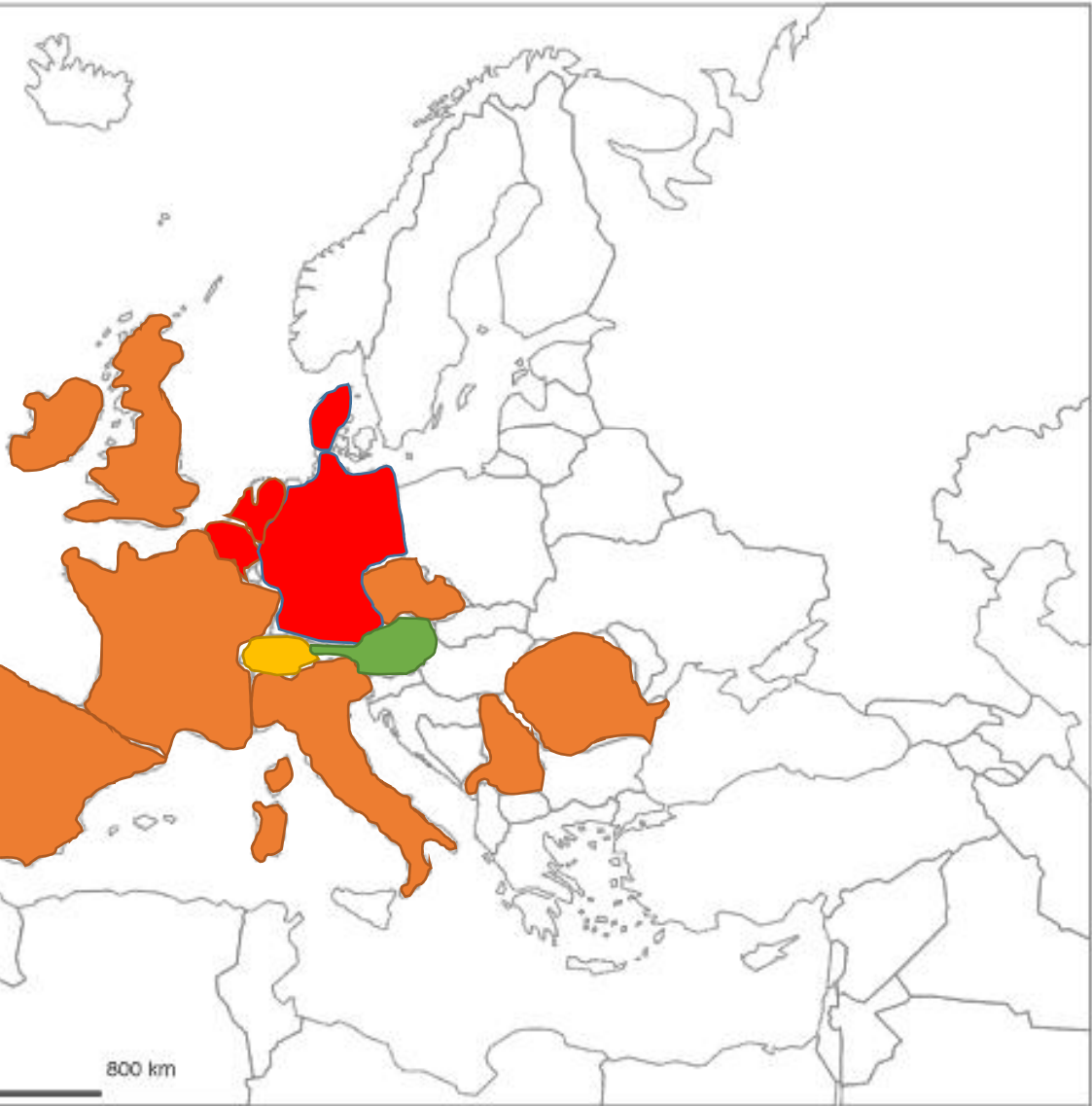
## High Proportion of Asymptomatic Infections in an Outbreak of Hepatitis E Associated With a Spit-Roasted Piglet, France, 2013

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



# Infección VHE en cerdos

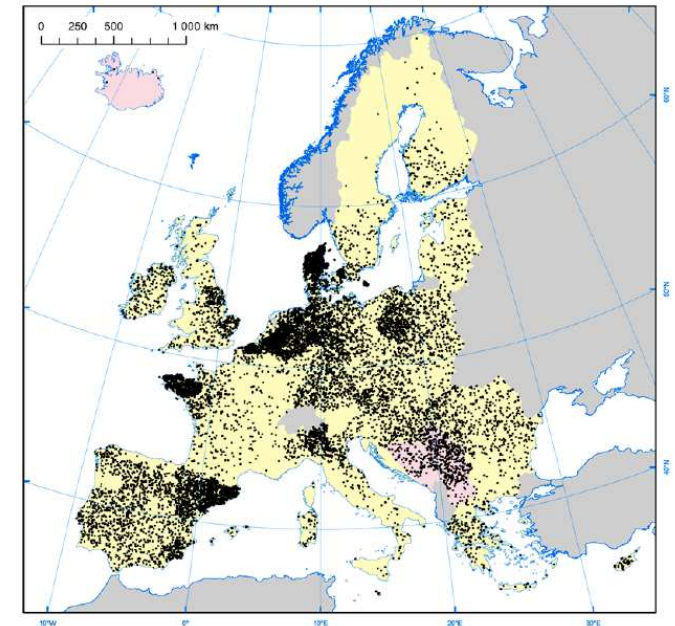
Prevalencia de viremia del VHE en cerdos



Relación prevalencia y consumo de carne de cerdo

Country	Estimated Human HEV Seroprevalence (WT Assay)	Number of Pigs Slaughtered 2013 (Millions)	Human Population 2013 (Millions)	Pigs/Human Ratio **	Pork Consumption (Thousand Tons) ***	Pork Consumption (Kg) per Capita **
France	31.9	23,747	63.9	0.37	1931	30.2
Germany	29.5	58,628	80.6	0.72	4358	54.1
Denmark	19.8	19,108	5.6	3.41	352	62.9
Netherlands	27.0	14,014	16.8	0.83	640	38.1
Belgium	19.7	11,915	11.2	1.06	452	40.4
Spain	14.7	41,418	46.6	0.31	2363	50.7
Switzerland	13.8	No comparative data	8.1	NA	201 *	24.8
Austria	13.9	5417	8.5	0.64	474	55.8
Czech Republic	12.9	2652	10.5	0.25	437	41.6
UK	12.7	10,299	64.1	0.16	1542	24.1
Italy	7.5	13,099	59.8	0.22	2451	41.0

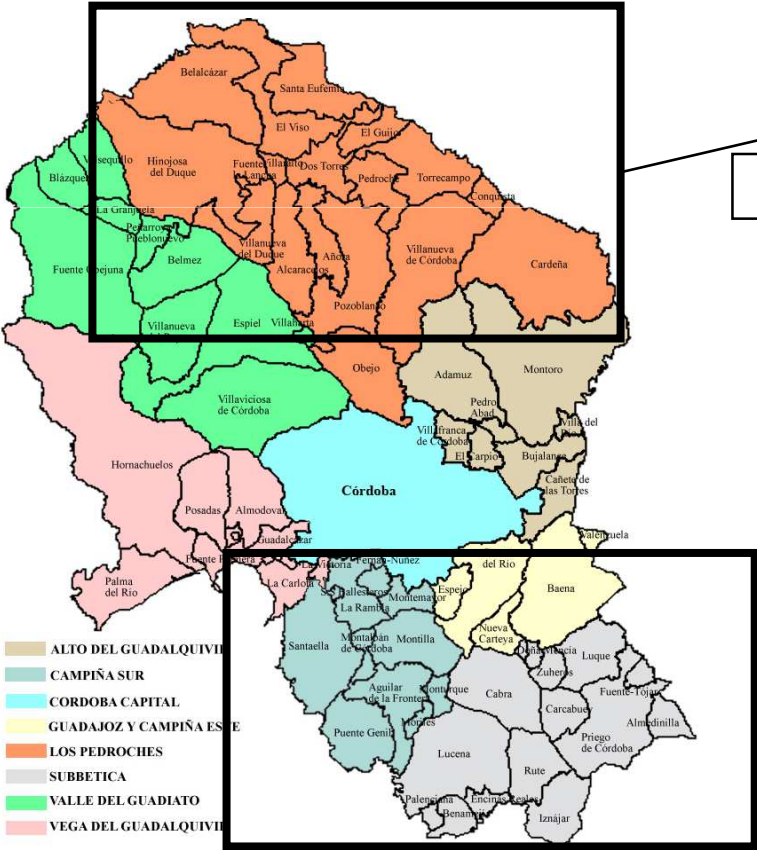
Granjas porcinas





# HepE pork Study:

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



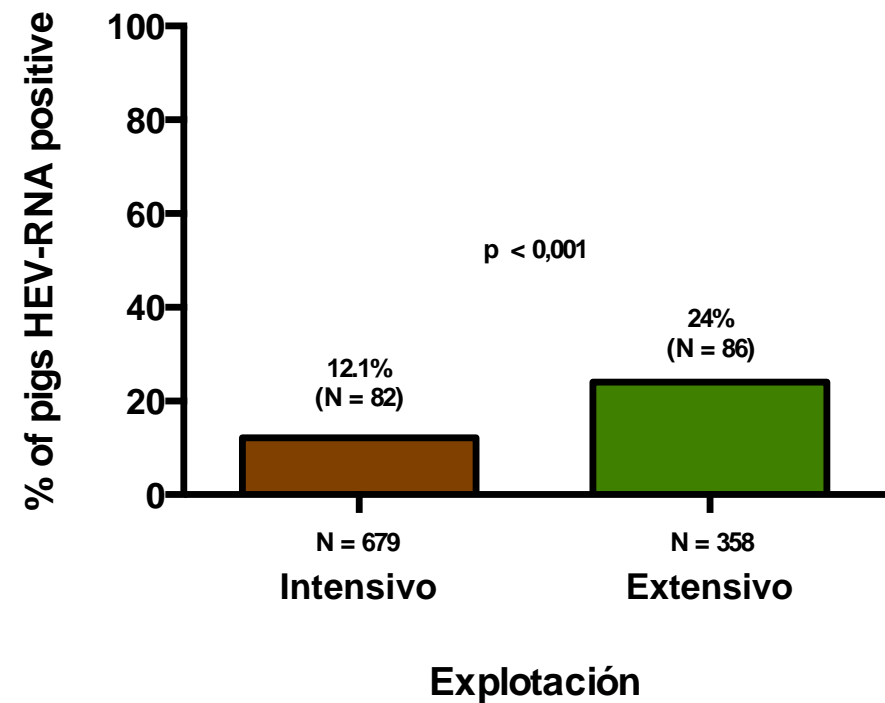
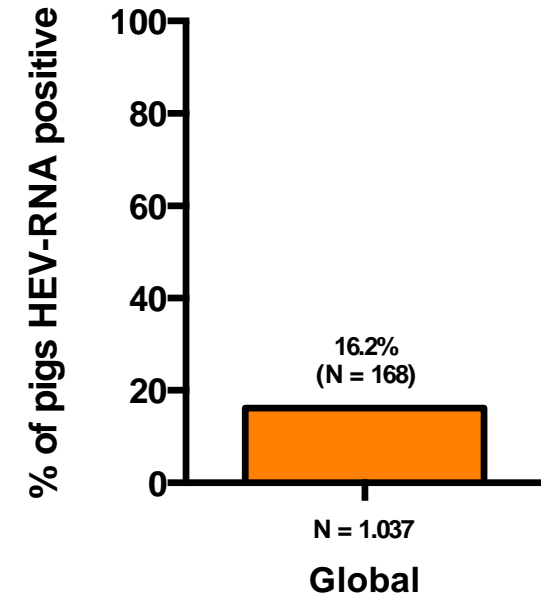
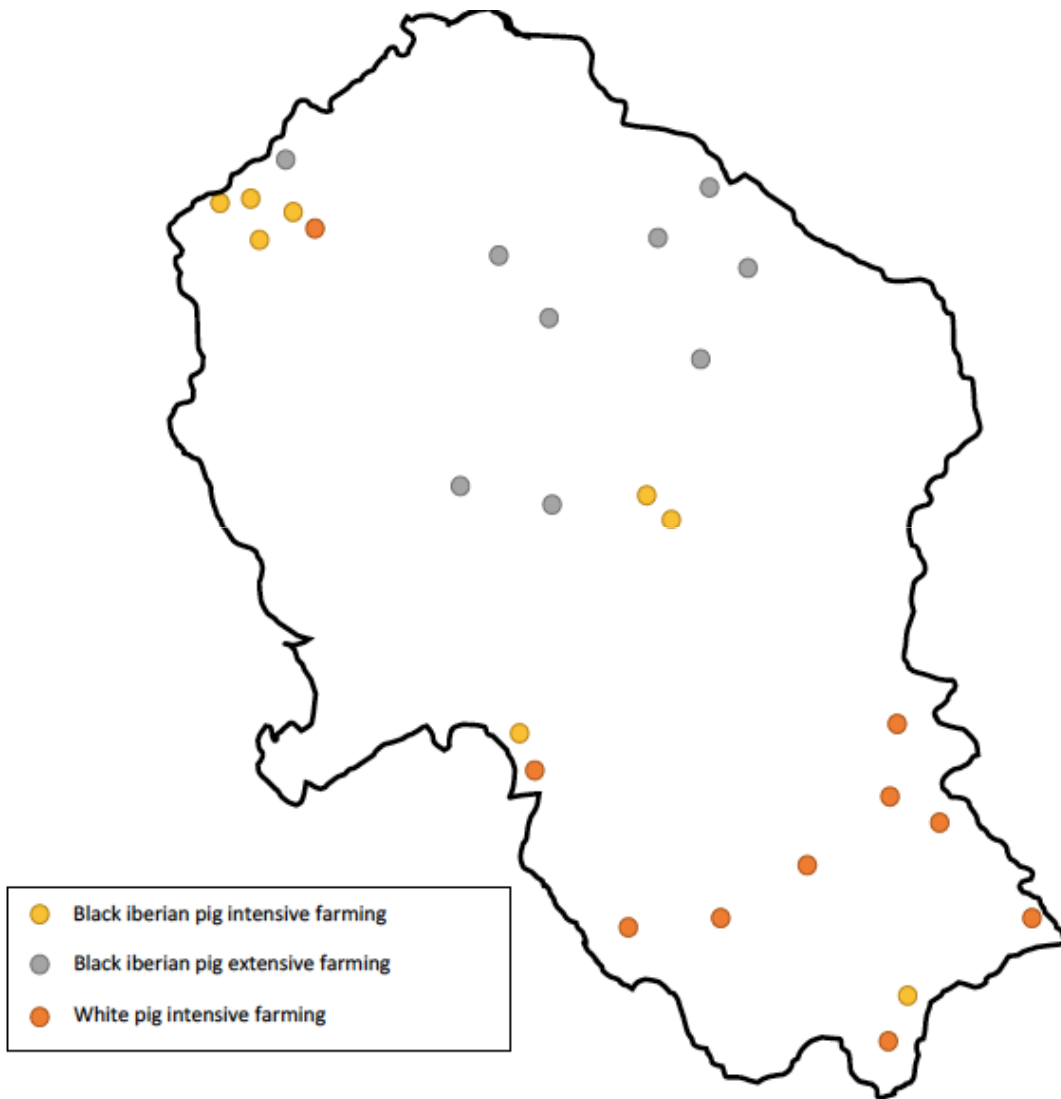
Extensive farming



Intensive farming



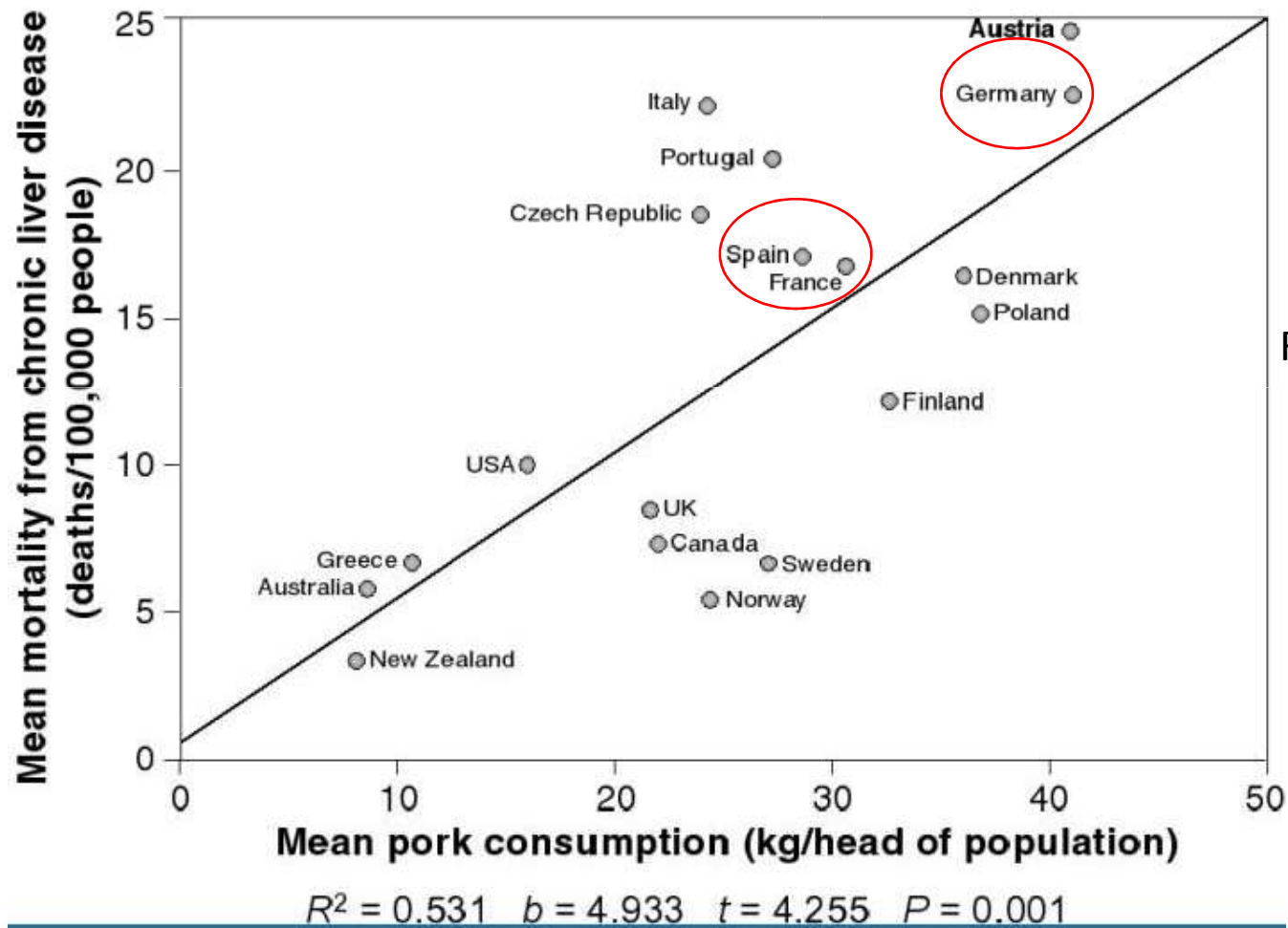
# HepEpork Study:



# Presencia del VHE en alimentos porcinos

Alimento	País	HEV-RNA	Reference
Carne	Italy	6%	Di Bartolo <i>et al.</i> Emerg Infect Dis 2012
	Czech Republic	2.5%	Di Bartolo <i>et al.</i> Emerg Infect 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 Infect 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
	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 Infect Dis 2012
	Spain	3%	Di Bartolo <i>et al.</i> Emerg Infect Dis 2012
	U.K.	3%	Berto <i>et al.</i> Emerg Infect Dis 2012

# Relación consumo de carne de cerdo y muerte



Relación consumo de carne de cerdo y mortalidad en cirróticos

Source: J Viral Hepat © 2012 Blackwell Publishing



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

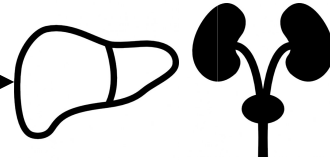
Patricia E Hewitt, Samreen Ijaz, Su R Brailsford, Rachel Brett, Steven Dicks, Becky Haywood, Iain T R Kennedy, Alan Kitchen, Poorvi Patel, John Poh, Katherine Russell, Kate I Tettmar, Joanne Tossell, Ines Ushiro-Lumb, Richard S Tedder

Annals of Internal Medicine

OBSERVATIONS

Transmission of Hepatitis E Virus by Plasma  
A Case Report

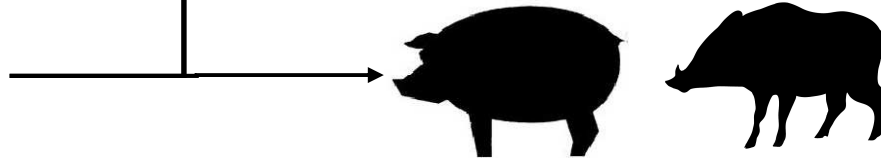
### Case Report



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

B. Schlosser<sup>1</sup>, A. Stein<sup>2</sup>, R. Neuhaus<sup>3</sup>, S. Pahl<sup>4</sup>, B. Ramez<sup>1</sup>, D.H. Krüger<sup>2</sup>, T. Berg<sup>1,5,\*</sup>, J. Hofman

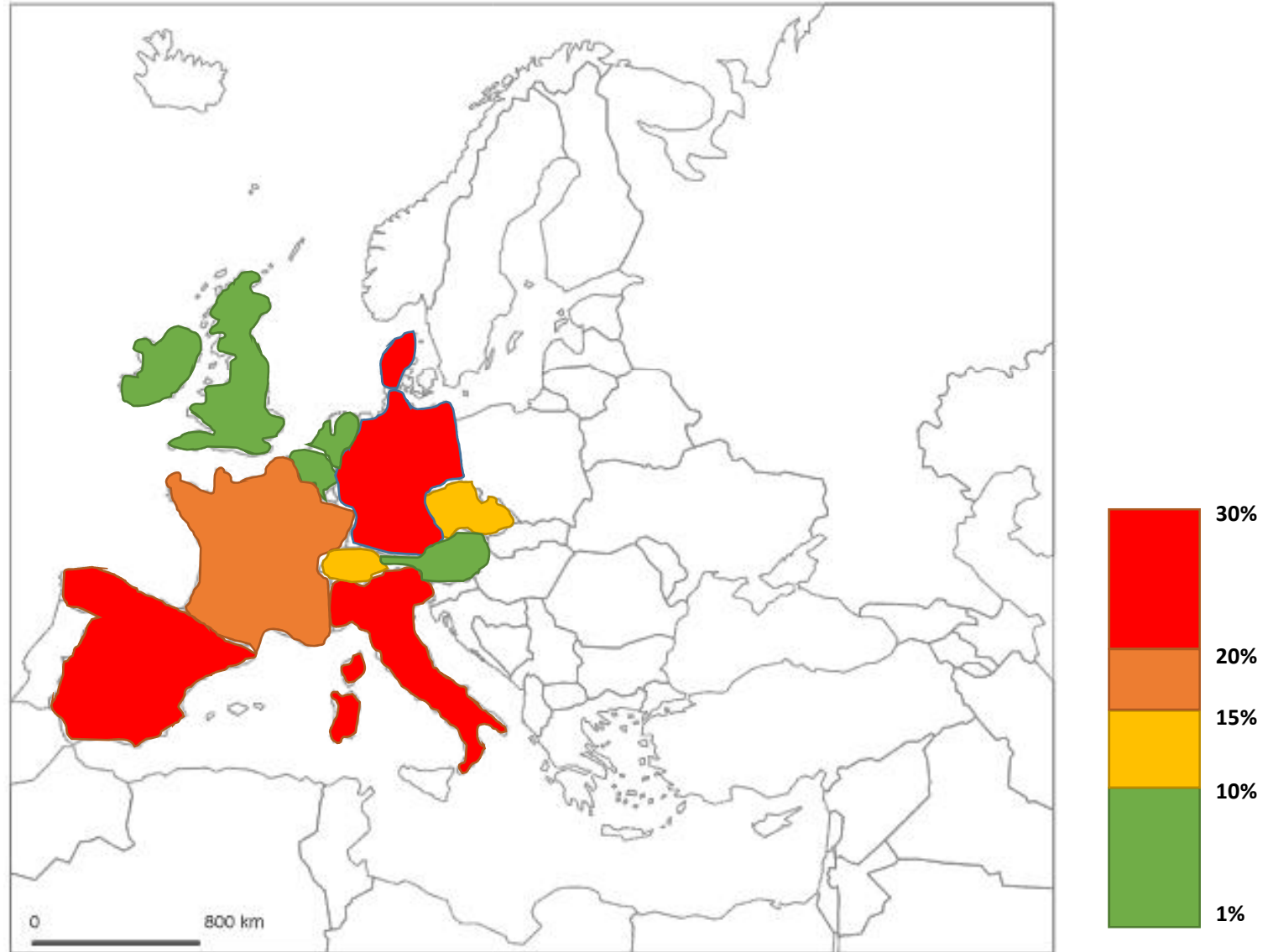
EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER JOURNAL OF HEPATOLOGY



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

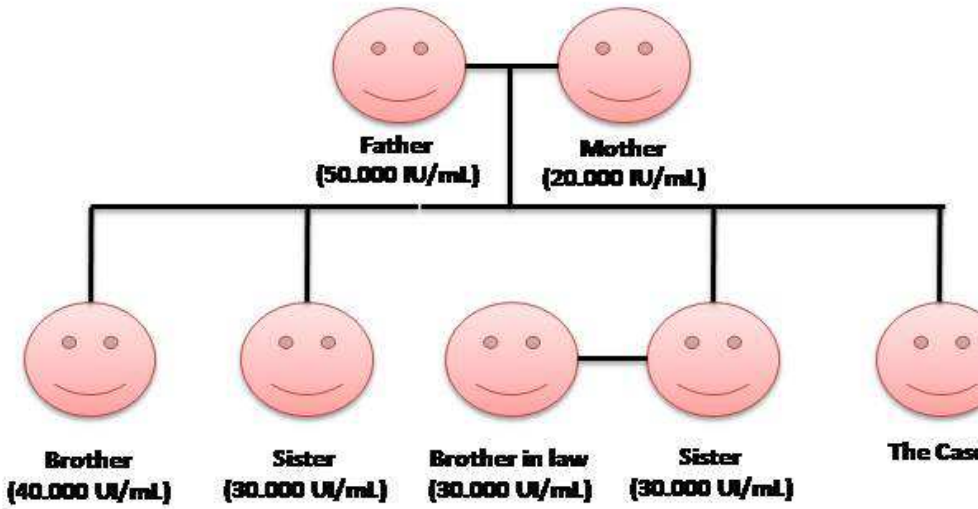
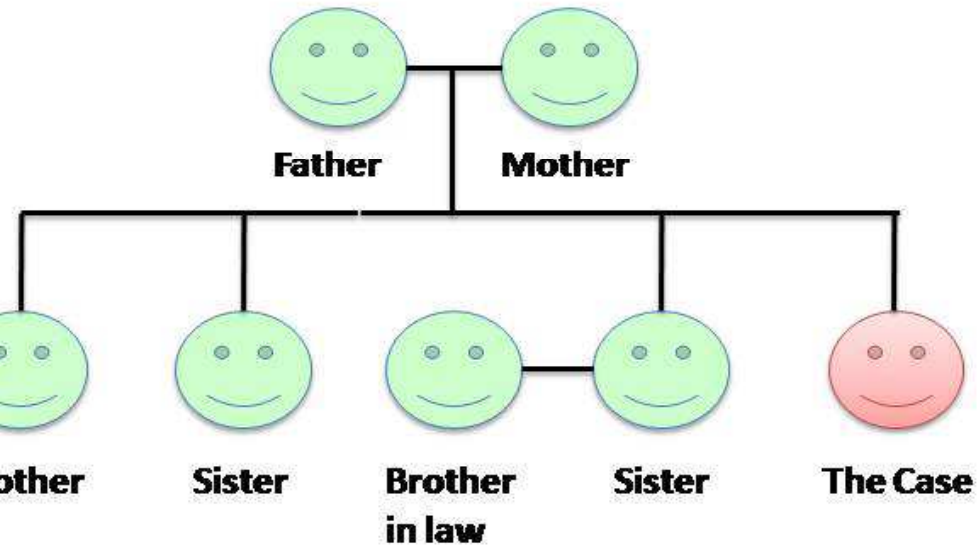
Yvonnick Guillois,<sup>1</sup> Florence Abravanel,<sup>2</sup> Takayuki Miura,<sup>3</sup> Nicole Pavio,<sup>4</sup> Véronique Vaillant,<sup>5</sup> Sébastien Lhomme,<sup>2</sup> Françoise S. Le Guyader,<sup>2</sup> Nicolas Rose,<sup>4</sup> Jean-Claude Le Saux,<sup>2</sup> Lisa A. King,<sup>1</sup>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

# Infección VHE en jabalies





# Brote familiar en Córdoba (n = 7)



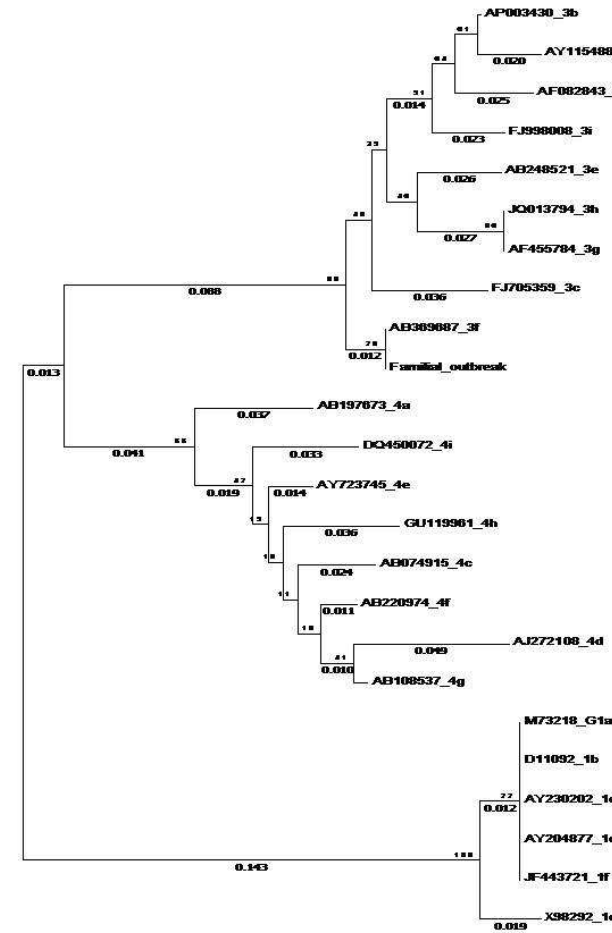
# Outbreak familiar por consumo de jabalí



230.500 copias/gr

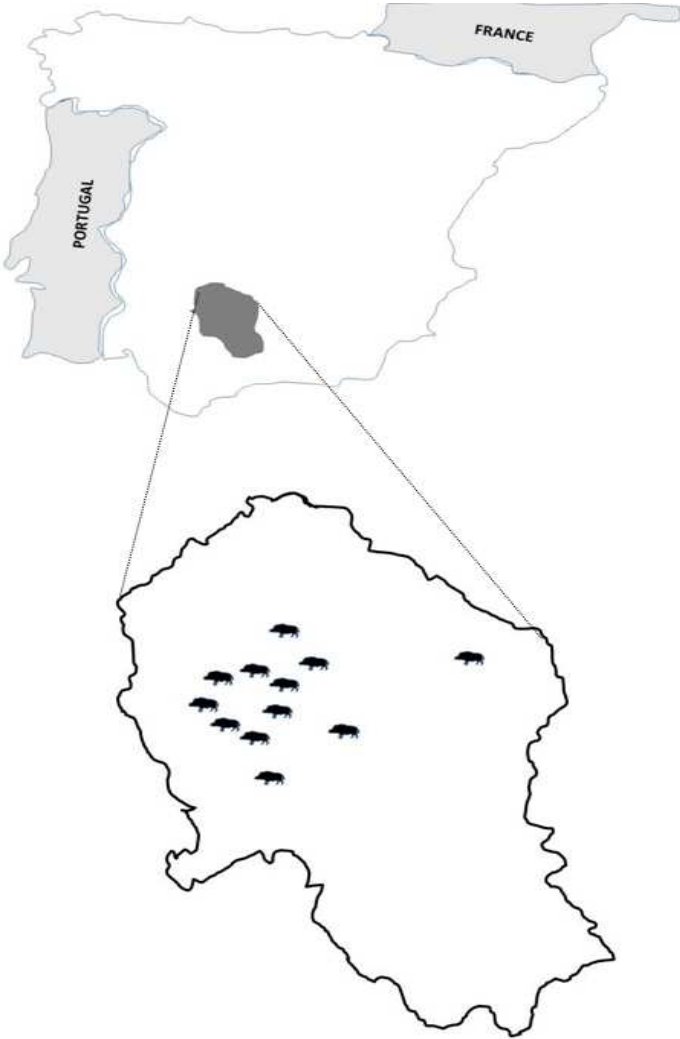


155.300 copias/gr



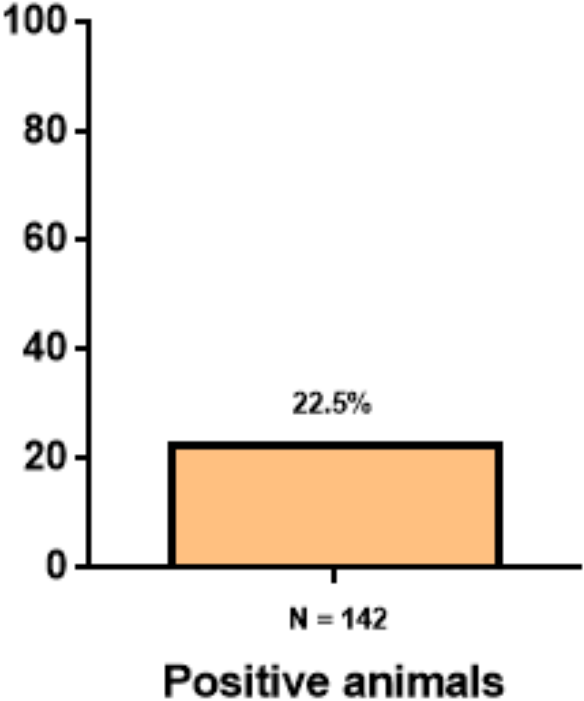


# HepEboar Study

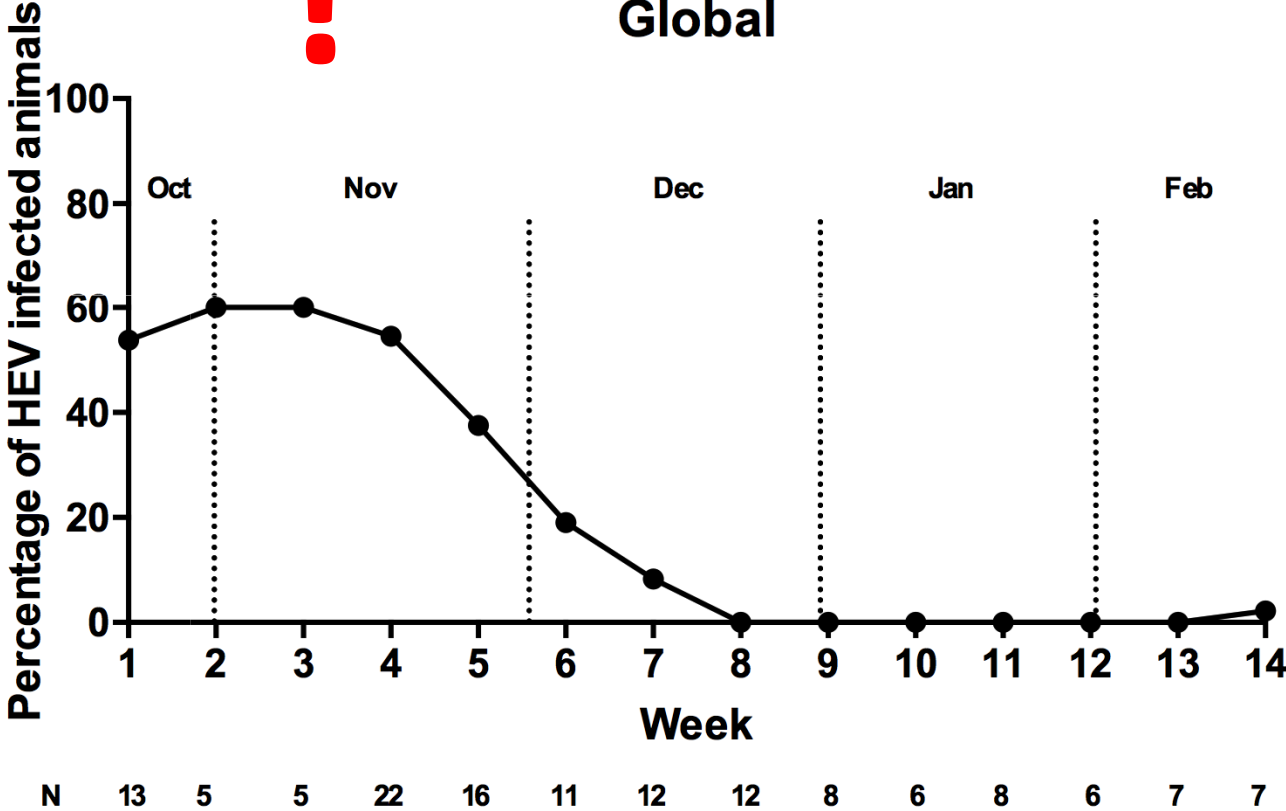


# HepEboar Study

Wild boar



Global





## 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

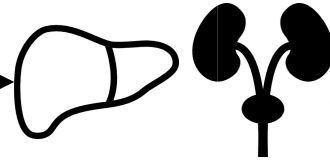
Annals of Internal Medicine

OBSERVATIONS

Transmission of Hepatitis E Virus by Plasma  
A Case Report

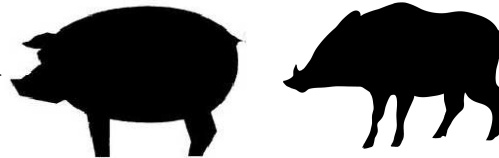
Case Report

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



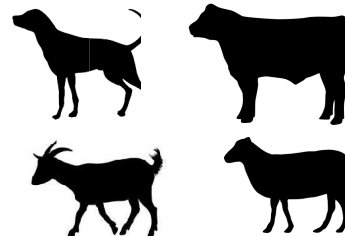
## Liver transplant from a donor with occult HEV infection induced chronic hepatitis and cirrhosis in the recipient

B. Schlosser<sup>1</sup>, A. Stein<sup>2</sup>, R. Neuhaus<sup>3</sup>, S. Pahl<sup>4</sup>, B. Ramez<sup>1</sup>, D.H. Krüger<sup>2</sup>, T. Berg<sup>1,5,\*</sup>, J. Hofman



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

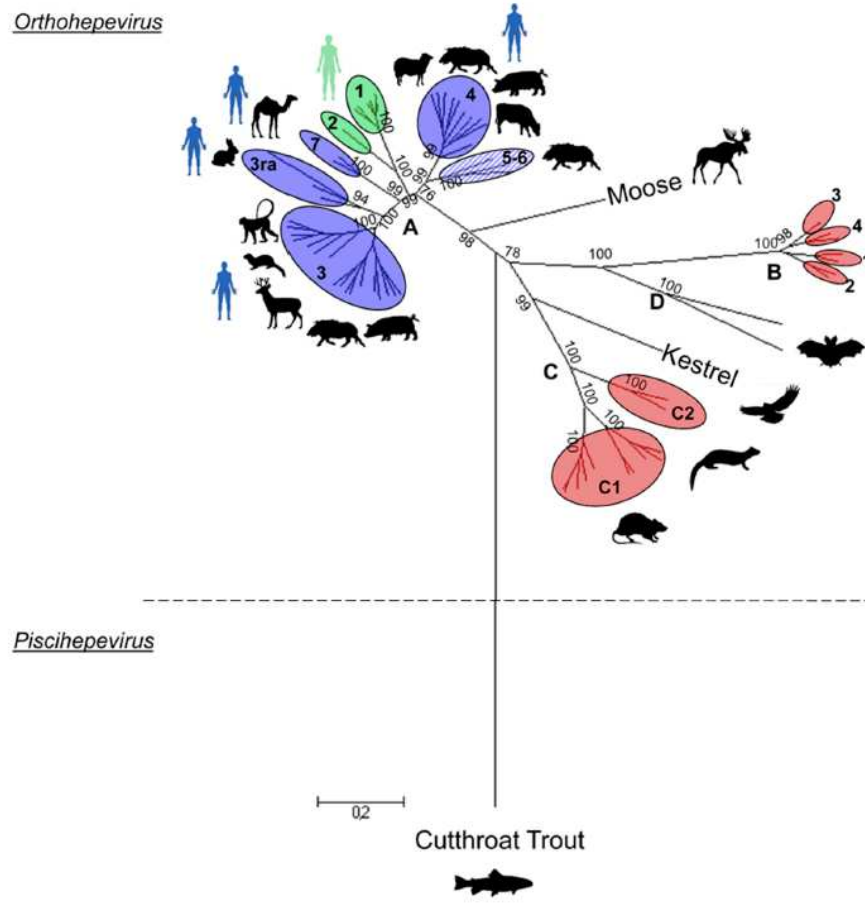
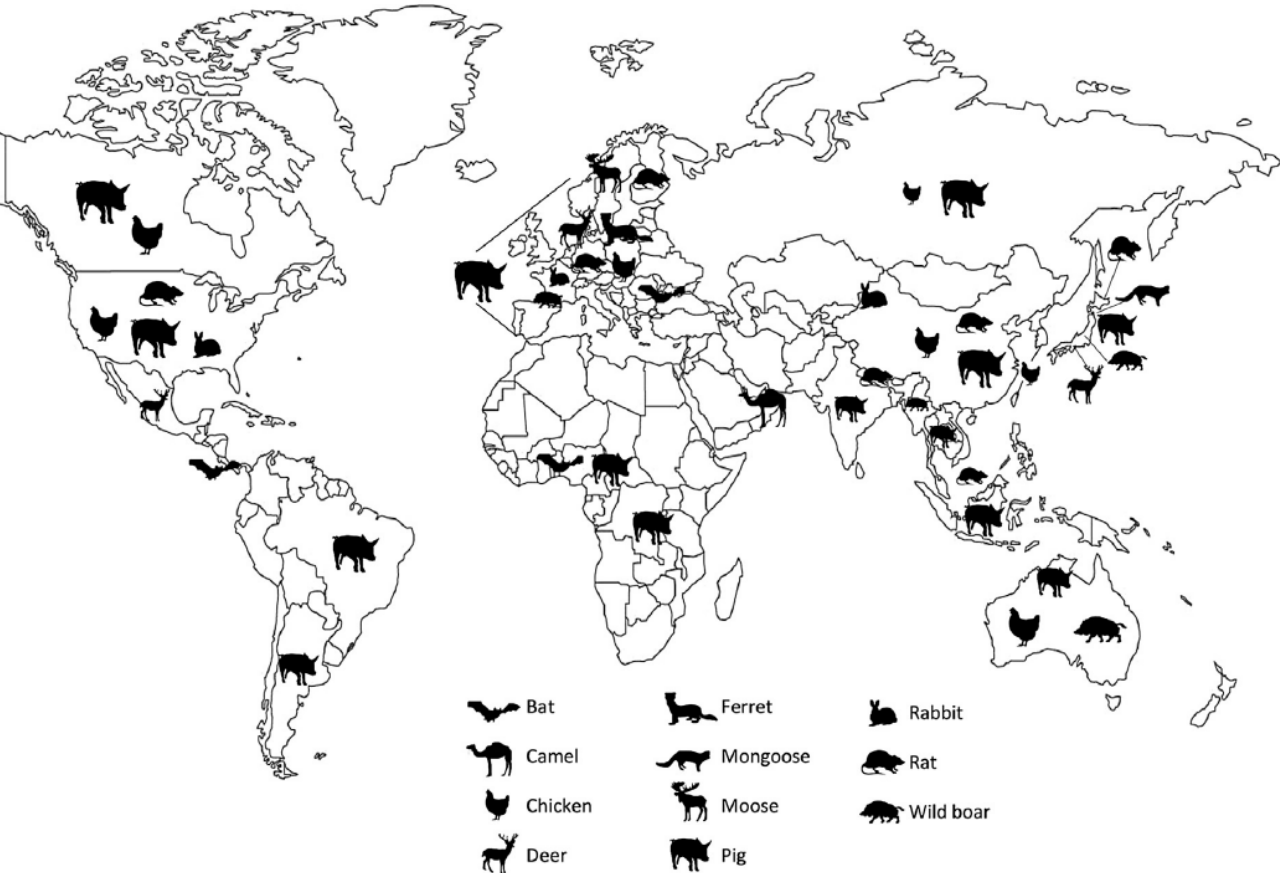
Yvonnick Guillois,<sup>1</sup> Florence Abravanel,<sup>2</sup> Takayuki Miura,<sup>3</sup> Nicole Pavio,<sup>4</sup> Véronique Vaillant,<sup>5</sup> Sébastien Lhomme,<sup>2</sup> Françoise S. Le Guyader,<sup>2</sup> Nicolas Rose,<sup>4</sup> Jean-Claude Le Saux,<sup>2</sup> Lisa A. King,<sup>1</sup>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



CLINICAL AND EXPERIMENTAL VACCINE RESEARCH

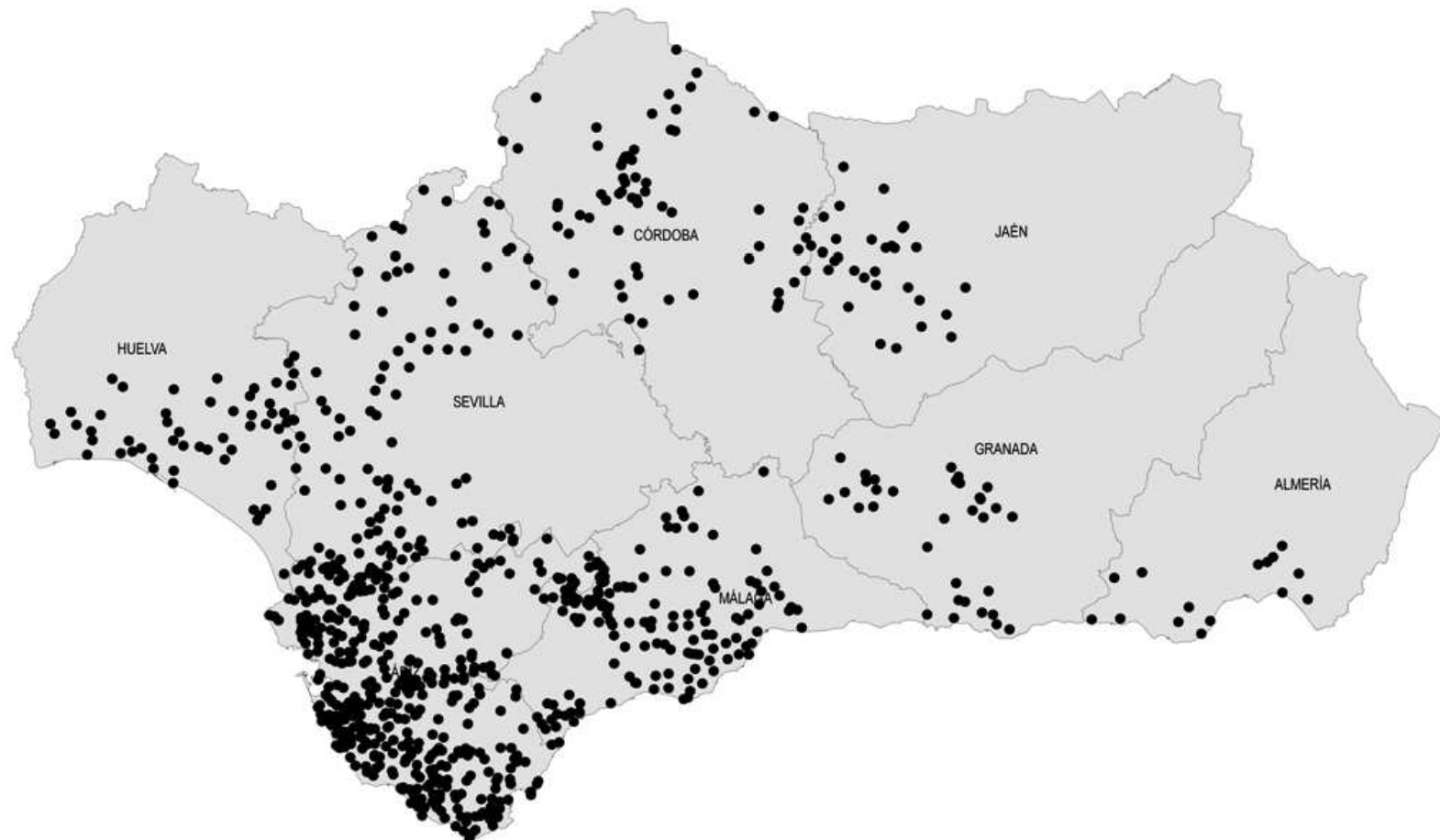
## Hepatitis E virus infections in humans and animals

# Hospedadores del VHE

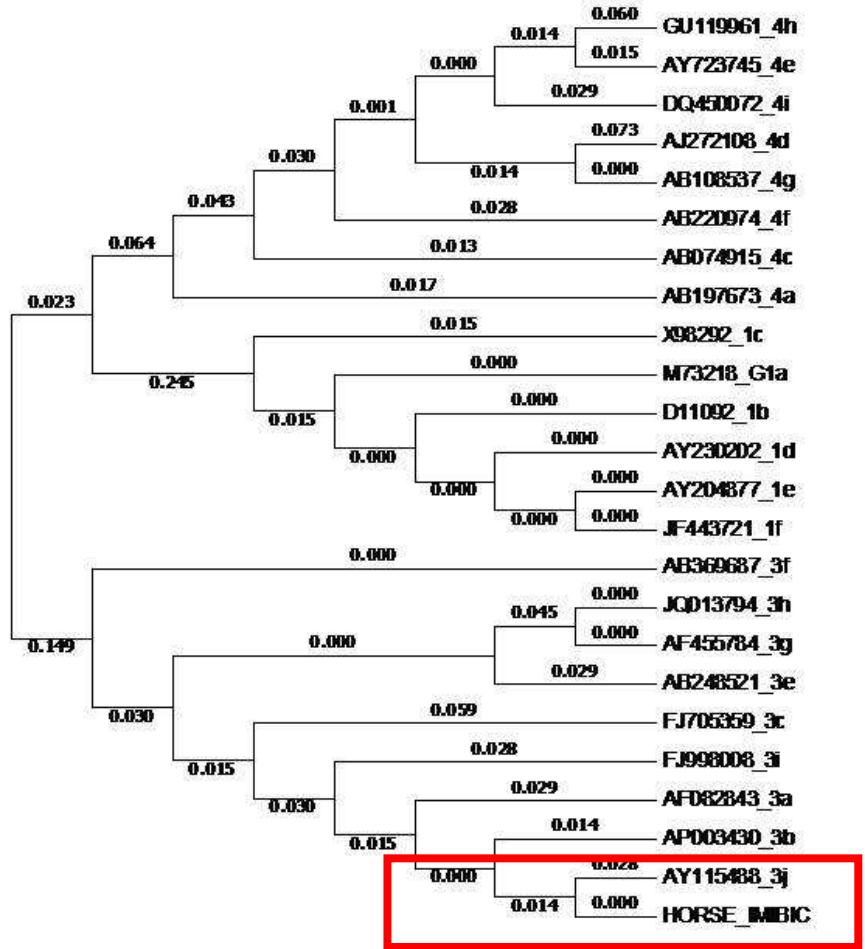
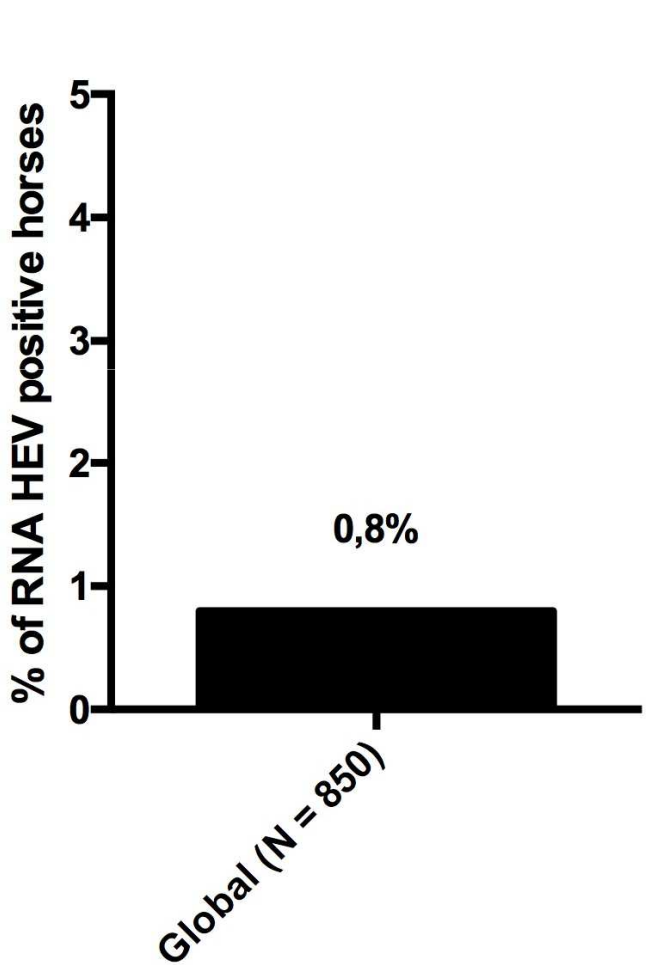


# Estudio HepEhorse

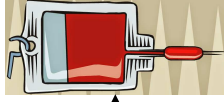
840 caballos testados de Andalucía



# Estudio HepEhorse



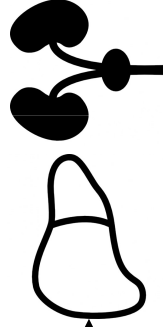




## Hepatitis E virus in blood components: a prevalence and transmission study in southeast England

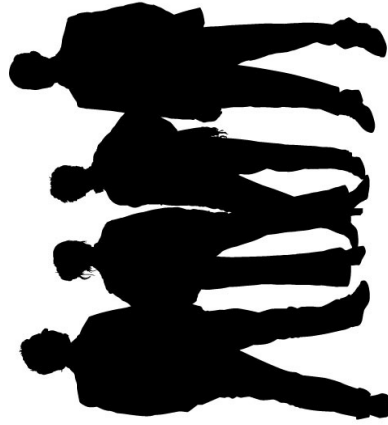
Patricia E Hewitt, Samreen Jjaz, Su R Braisford, Rachel Brett, Steven Dicks, Becky Hoywood, Jain T R Kennedy, Alan Kitchen, Poorvi Patel, John Poh, Katherine Russell, Kate Tettmar, Joanne Tossell, Ines Ushiro-Lumb, Richard T Tedder

### Case Report



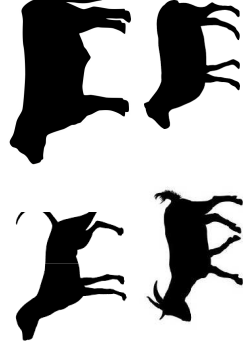
## Liver transplant from a donor with occult HEV infection induced chronic hepatitis and cirrhosis in the recipient

B. Schlosser<sup>1</sup>, A. Stein<sup>2</sup>, R. Neuhaus<sup>3</sup>, S. Pahl<sup>4</sup>, B. Ramez<sup>1</sup>, D.H. Krüger<sup>2</sup>, T. Berg<sup>1,5,\*</sup>, J. Hofman



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

Yvonnick Guillou<sup>1</sup>, Florence Abravanel<sup>2</sup>, Takayuki Miura<sup>3</sup>, Nicole Pavia<sup>4</sup>, Veronique Vaillanc<sup>5</sup>, Sébastien Lhomme<sup>2</sup>, Françoise S. Le Guyader<sup>6</sup>, Nicolas Rose<sup>6</sup>, Jean-Claude Le Saux<sup>7</sup>, Lisa A. King<sup>8</sup>, Jacques Izopet<sup>6</sup>, and Elisabeth Couturier<sup>4</sup>



### 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<sup>1</sup>, 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

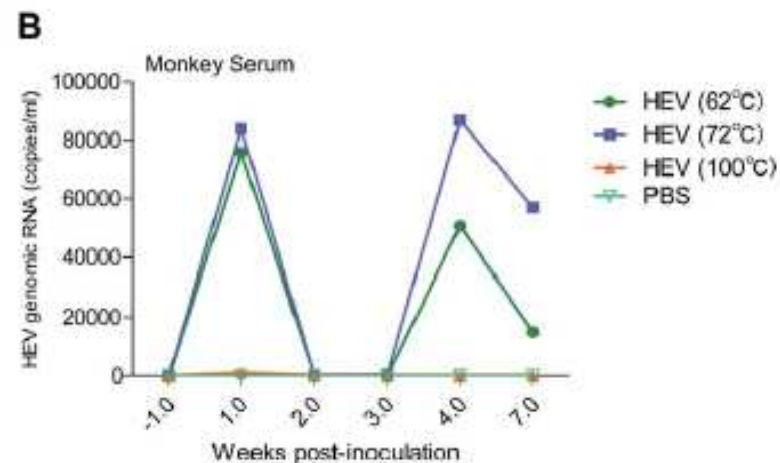
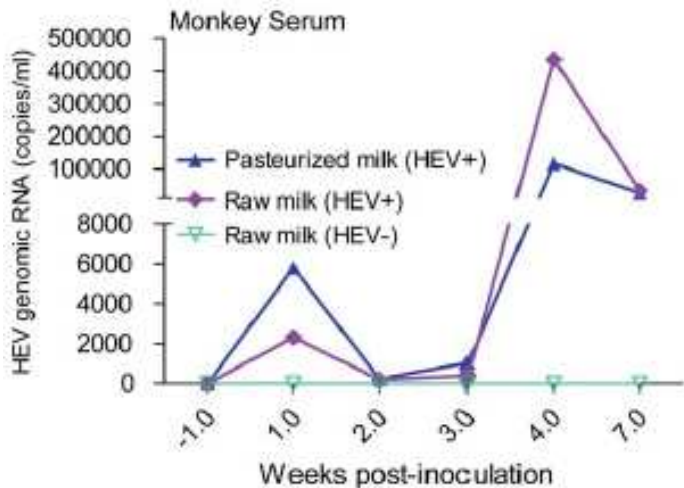
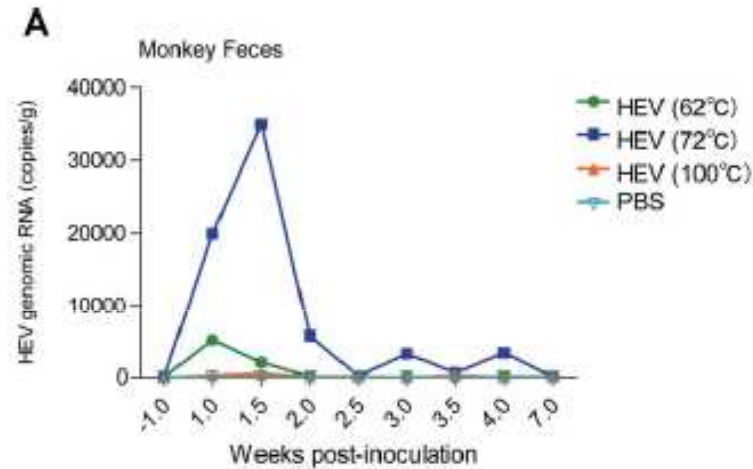
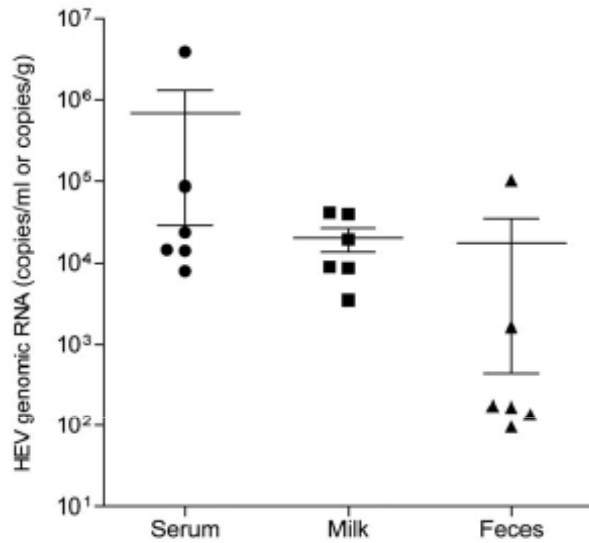
<b>Sample</b>	<b>Oct 22, 2015</b>	<b>Nov 9, 2015</b>	<b>Nov 30, 2015</b>	<b>Dec 18, 2015</b>
<b>Blood</b>	31,324 IU/mL	2,130 IU/mL	670 IU/mL	Negative
<b>Milk</b>	-	1,930 IU/mL	500 IU/mL	Negative



# Leche bovina para consumo

## Excretion of Infectious Hepatitis E Virus Into Milk in Cows Imposes High Risk of Zoonosis

Fen Huang,<sup>1\*</sup> Yunlong Li,<sup>2\*</sup> Wenhai Yu,<sup>2</sup> Shenrong Jing,<sup>1\*</sup> Jue Wang,<sup>1</sup> Feiyan Long,<sup>1</sup> Zhanlong He,<sup>2</sup> Chenchen Yan,<sup>1</sup> Yanhong Bi,<sup>1</sup> Wentao Cao,<sup>1</sup> Chengbo Liu,<sup>1</sup> Xiuguo Hua,<sup>2</sup> and Qiuwei Pan<sup>1</sup>



## Hepatitis E Genotype 3 Shellfish, United Kingdom

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

Domenica Donia<sup>1,\*</sup>, Maria Chiara Dell'Amico<sup>2</sup>, Anna Rita Perrinca<sup>1</sup>, Ilaria Martiniucci<sup>1</sup>, Maurizio Mazzel<sup>1</sup>, Francesco Tolari<sup>1</sup>, Maurizio Divizia<sup>2</sup>

<sup>1</sup>Department of Public Health, University of Bari, Bari, Italy  
<sup>2</sup>Department of Public Health, University of Pisa, Pisa, Italy



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

Patricia E Hewitt<sup>1</sup>, Samreen Jjaz<sup>2</sup>, Su R Braisford<sup>3</sup>, Rachel Brett<sup>3</sup>, Steven Dicks<sup>3</sup>, Becky Hoywood<sup>3</sup>, Jain T R Kennedy<sup>3</sup>, Alan Kitchen<sup>3</sup>, Poorvi Patel<sup>3</sup>, John Poh<sup>3</sup>, Katherine Russell<sup>3</sup>, Kate Tattmar<sup>3</sup>, Joanne Tossell<sup>3</sup>, Ines Ushiro-Lumb<sup>3</sup>, Richard Tedder<sup>3</sup>

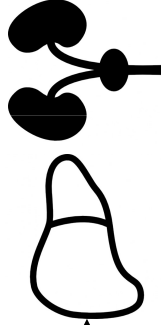
OBSERVATIONS

Annals of Internal Medicine

Transmission of Hepatitis E Virus by Plasma  
A Case Report



### Case Report



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

B. Schlosser<sup>1</sup>, A. Stein<sup>2</sup>, R. Neuhaus<sup>3</sup>, S. Pahl<sup>4</sup>, B. Ramez<sup>1</sup>, D.H. Krüger<sup>2</sup>, T. Berg<sup>1,5,\*</sup>, J. Hofman



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

Yvonnick Guillouis<sup>1</sup>, Florence Abravanel<sup>2</sup>, Takayuki Miura<sup>3</sup>, Nicole Pavia<sup>4</sup>, Veronique Vaillanc<sup>5</sup>, Sébastien Lhomme<sup>2</sup>, Françoise S. Le Guyader<sup>6</sup>, Nicolas Rose<sup>6</sup>, Jean-Claude Le Saux<sup>7</sup>, Lisa A. King<sup>1</sup>, Jacques Izopet<sup>2</sup>, and Elisabeth Couturier<sup>1</sup>



CLINICAL AND EXPERIMENTAL VACCINE RESEARCH

## Hepatitis E virus infections in humans and animals



Isolation of Hepatitis E virus from breast milk during acute infection

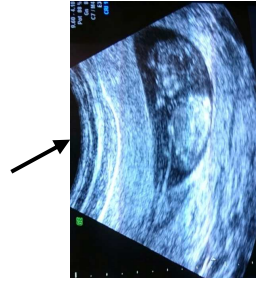
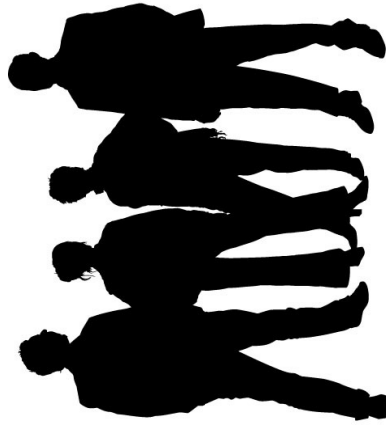
Antonio Rivero-Juarez<sup>1</sup>, Mario Frias, Diego Rodriguez-Cano, Francisca Cuenca-López and Antonio Rivero

# Presencia del VHE en moluscos

<b>Moluscos</b>	<b>Pais</b>	<b>HEV-RNA</b>	<b>Reference</b>
<b>Mejillones</b>	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>
<b>Almejas</b>	France	7.6%	<i>Grodzki et al. AEM 2014</i>
<b>Berberechos</b>	France	12.5%	<i>Grodzki et al. AEM 2014</i>
<b>Ostras</b>	France	4.5%	<i>Grodzki et al. AEM 2014</i>

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

Domenica Donia<sup>1,\*</sup>, Maria Chiara Dell'Amico<sup>1</sup>, Anna Rita Petrinca<sup>1</sup>, Ilaria Martinucci<sup>1</sup>,  
Maurizio Mazzoli<sup>1</sup>, Francesco Tolari<sup>1</sup>, Maurizio Divizia<sup>1,a</sup>  
<sup>1</sup>Department of Public Health, Faculty of Medicine, University of Rome Tor Vergata, Rome, Italy  
<sup>a</sup>Department of Animal Pathology, University of Pisa, Pisa, Italy



Hepatitis, 2015

doi:10.1111/wh.12406

perinatal infection of pregnant rabbits with hepatitis E  
demonstrating high mortality and vertical transmission

Jiu, L., Wang, Y., Zhang, H., Zeng, P., Liu, Q., Zou, L., Wang, and H. Zhuang. Department of  
Infectious Disease Center, School of Basic Medical Sciences, Peking University Health Science Center, Beijing, China

16 February 2014; accepted for publication February 2015

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

Patricia E Hewitt<sup>1</sup>, Samreen Ijaz<sup>2</sup>, Su R Braisford<sup>1</sup>, Rachel Brett<sup>1</sup>, Steven Dicks<sup>1</sup>, Becky Hoywood<sup>1</sup>, Jim T R Kennedy<sup>1</sup>, Alan Kitchen<sup>1</sup>, Poorvi Patel<sup>1</sup>, John Poh<sup>1</sup>,  
Katherine Russell<sup>1</sup>, Kate Tattmar<sup>1</sup>, Joanne Tossell<sup>1</sup>, Ines Ushiro-Lumb<sup>1</sup>, Richard Stedler<sup>1</sup>

OBSERVATIONS

Annals of Internal Medicine

Transmission of Hepatitis E Virus by Plasma  
A Case Report

## Case Report

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

B. Schlosser<sup>1</sup>, A. Stein<sup>2</sup>, R. Neuhaus<sup>3</sup>, S. Pahl<sup>4</sup>, B. Ramez<sup>1</sup>, D.H. Krüger<sup>2</sup>, T. Berg<sup>1,5,\*</sup>, J. Hofman

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

Yvonnick Guillouis<sup>1</sup>, Florence Abravanel<sup>2</sup>, Takayuki Miura<sup>3</sup>, Nicole Pavia<sup>4</sup>, Veronique Vailliant<sup>5</sup>, Sébastien Lhomme<sup>2</sup>,  
Françoise S. Le Guyader<sup>1</sup>, Nicolas Rose<sup>4</sup>, Jean-Claude Le Saux<sup>4</sup>, Lisa A. King<sup>1</sup>, Jacques Izopet<sup>1</sup>, and Elisabeth Couturier<sup>4</sup>

CLINICAL AND  
EXPERIMENTAL  
VACCINE  
RESEARCH

Hepatitis E virus infections in  
humans and animals

HEPATOLOGY

HEPATOLOGY, VOL. 00, NO. 00, 2016

Excretion of Infectious Hepatitis E Virus  
Into Milk in Cows Imposes High Risks  
of Zoonosis

Fen Huang<sup>1</sup>, Yunlong Li<sup>1</sup>, Wentai Yu<sup>2</sup>, Shemong Jing<sup>1</sup>, Jue Wang<sup>1</sup>, Fayuan Long<sup>1</sup>, Zhanhong He<sup>2</sup>, Chenchen Yang<sup>1</sup>,  
Yunhong Bi<sup>1</sup>, Weima Cao<sup>1</sup>, Chengbo Liu<sup>1</sup>, Xuguo Hua<sup>1</sup>, and Qiwei Pan<sup>4</sup>

EASL | JOURNAL OF  
HEPATOLOGY



# Impacto en el embarazo

Author, year, country	Total cases	Attack rate	Mortality (case fatality rate)			
			Overall deaths	Men	Non-pregnant	Pregnant
Khuroo, <sup>7</sup> 1981, Kashmir, India	275	AVH: P: 36/208 (17.3%) 1st trimester: 8.8%, 2nd: 19.4%, 3rd: 18.6% NP: 2.1%, M: 2.8% ALF: P: 22.2%, NP: 0, M: 2.8%	10	2.8%	0%	6/8 (75%) All deaths in third trimester
Vishwanathan <sup>48</sup> 1956, Delhi, India	29300	P: 5.3%, NP: 1.5%, M: 2.8%	65	0.2%		5/48 (10.5%)
Tandon, <sup>49</sup> 1982, Azamgarh, India	152	P: 10.3%, NP: 2.3%, M: 2.6%	18	8.4%	13.4%	39%
Bile, <sup>11</sup> 1993, Somalia	11,413	15%	346	2.9%	3.5%	13.8%
Boccia, <sup>12</sup> 2006, Sudan	253	P: 19.3%	45	13.5%		31.1%
Rab, <sup>50</sup> 1997, Islamabad, Pakistan	3827	P: 21.6%, NP: 10.9% 1st trimester: 28.6%, 2nd: 31.4%, 3rd: 40%, (P=0.57) NS	4	0		4/35 (11.4%) All in 3rd trimester



# Impacto en la gestación: Genotipo 3

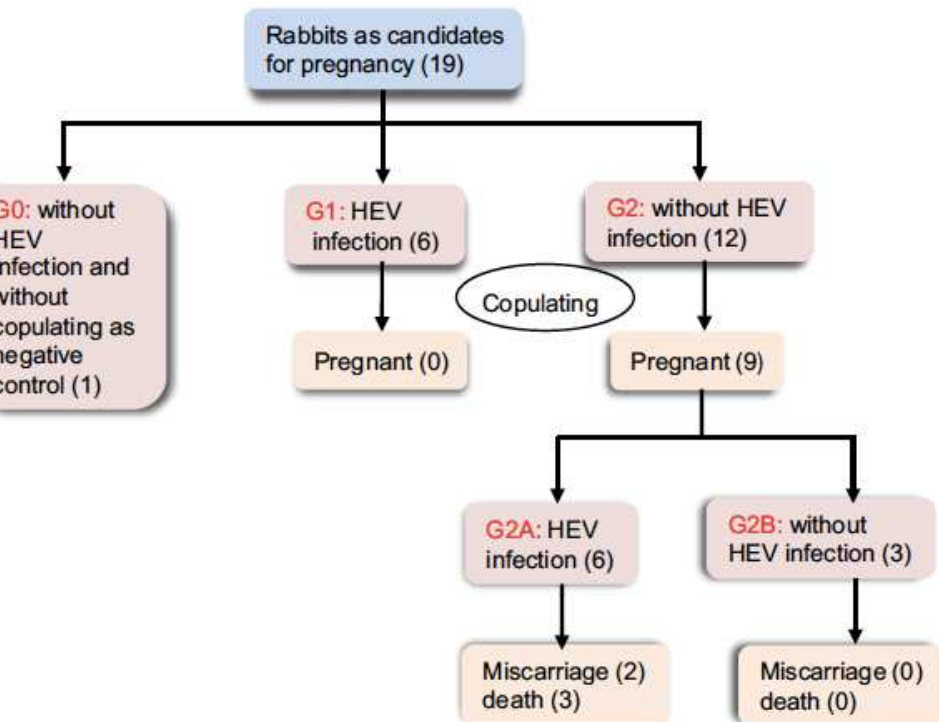


Table 1 Frequency of adverse outcomes in pregnant rabbits with HEV infection

Adverse outcomes	Rabbits with HEV infection (No.)	Rabbits without HEV infection (No.)
Infertility	6/6	3/12
Miscarriage	2/6	0/3
Death	3/4	0/3

# ¿Por qué no se ven casos en Europa?



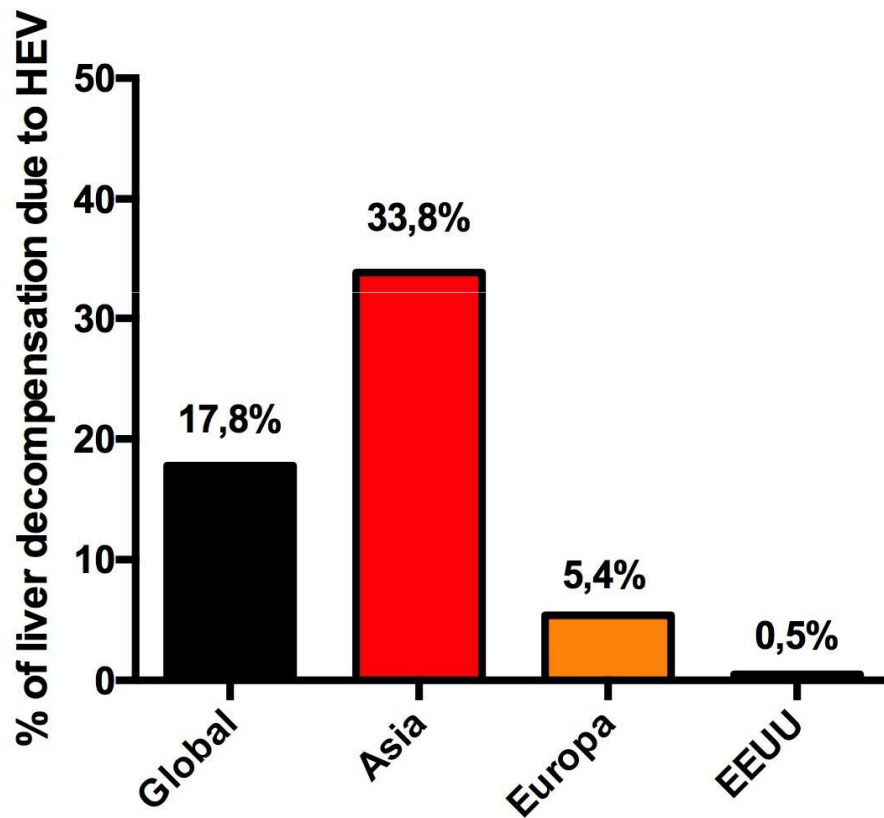
# Novedades en clínica

Más que una hepatitis



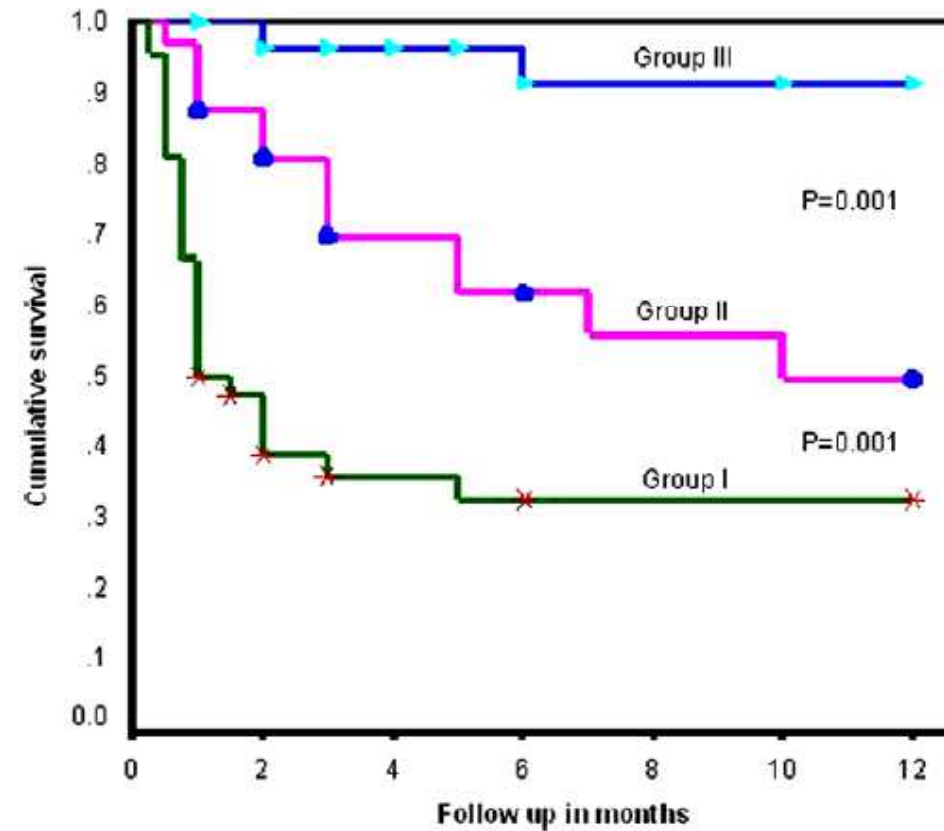
# Impacto en el paciente cirrótico: No solo el GT-1

Descompensaciones hepáticas por VHE



Rivero-Juarez et al Viruses 2017

Mortalidad por VHE en cirróticos



Acharya et al J Hepatol 2007

# Manifestaciones extra-hepáticas

## Non-hepatic manifestations of hepatitis E.

### Acute pancreatitis

### Hematological manifestations

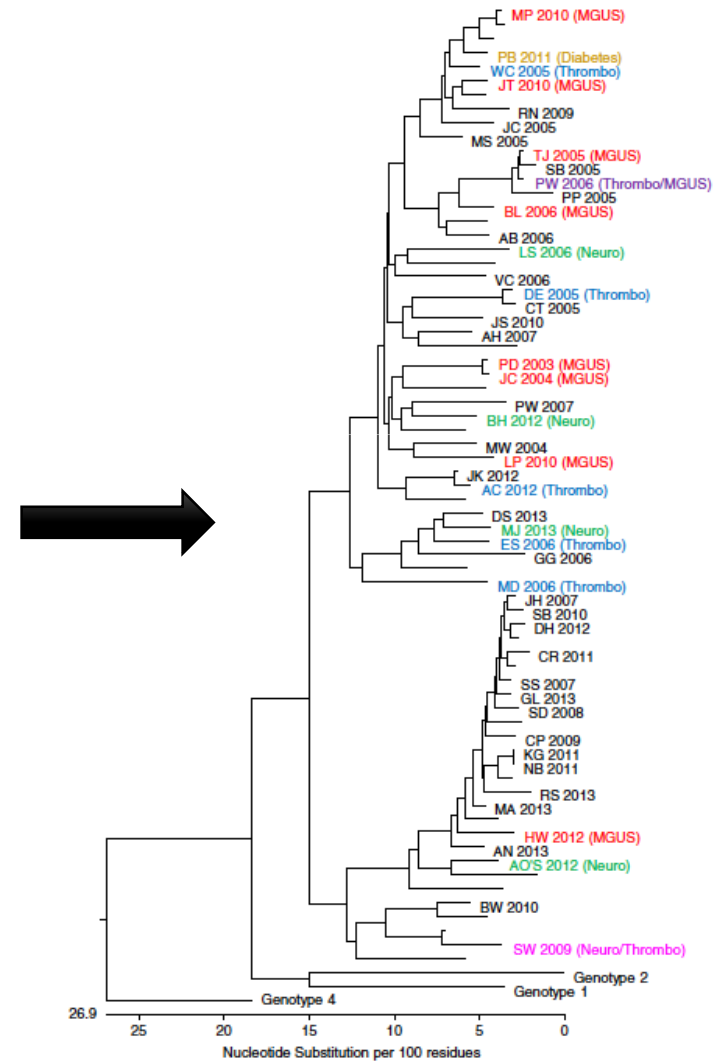
- Thrombocytopenia
- Hemolysis
- Hemolysis secondary to G6PD deficiency
- Immune hemolysis

### Autoimmune phenomena

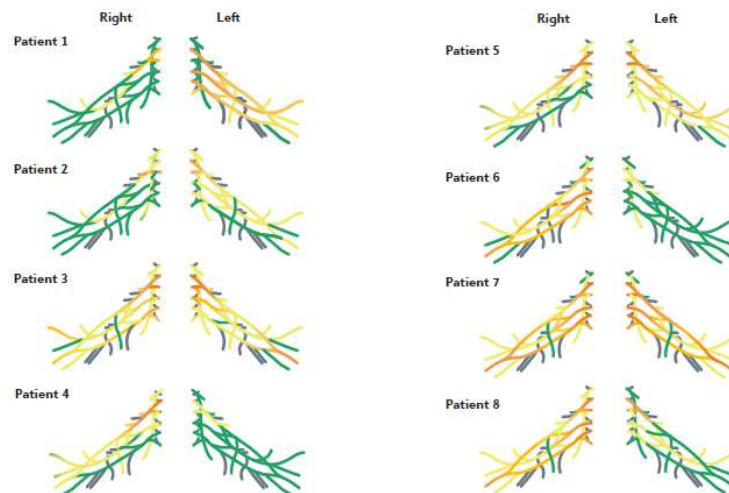
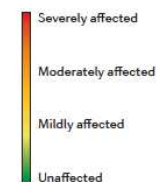
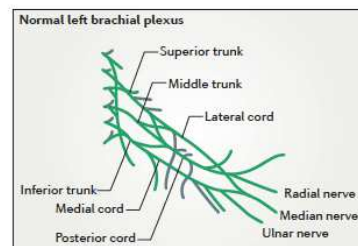
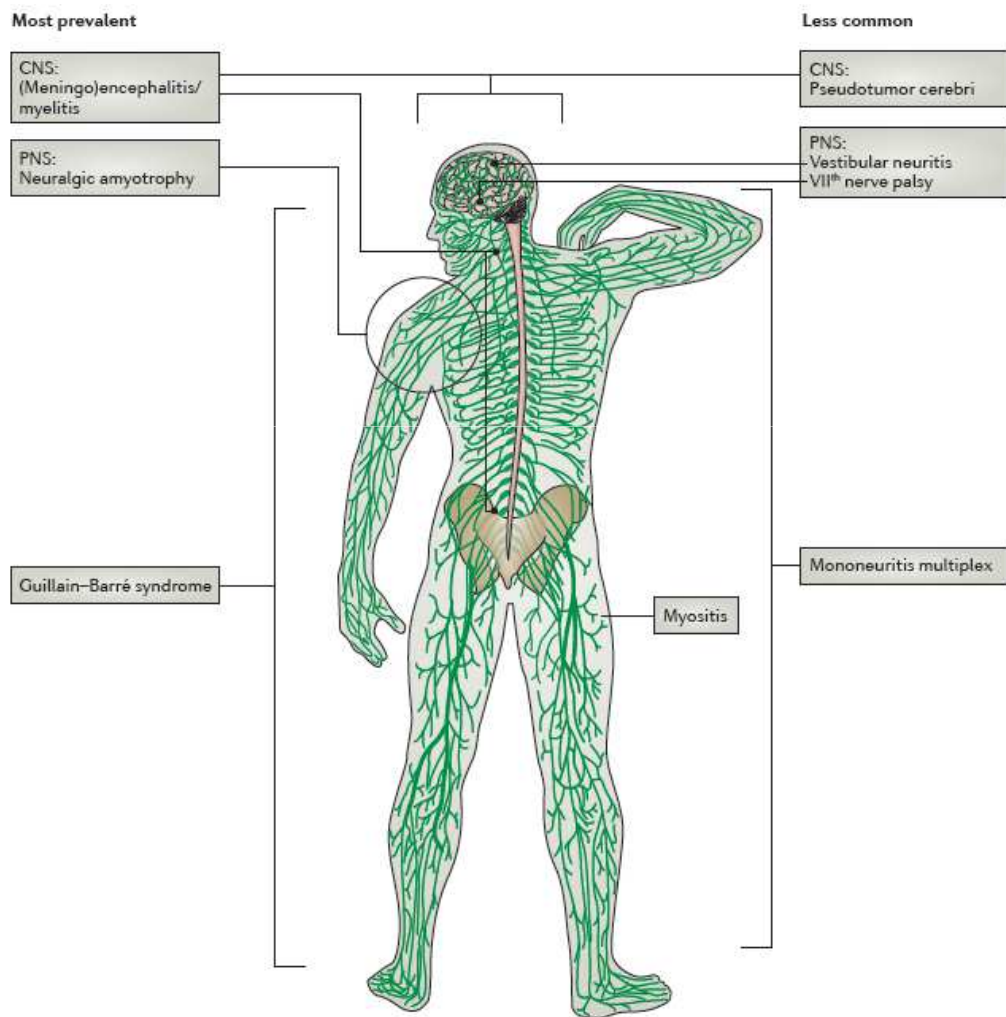
- Membranous glomerulonephritis
- Henoch-Schonlein purpura

### Neurological syndromes

- Guillain-Barre syndrome
- Meningoencephalitis,
- Pseudotumor cerebri
- Nerve palsies: oculomotor nerve, facial nerve
- Bilateral pyramidal syndrome
- Peripheral neuropathy
- Hematological manifestations



# Alteraciones neurológicas



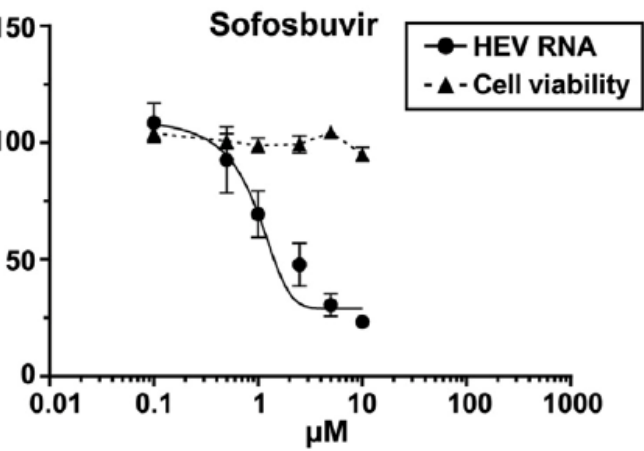
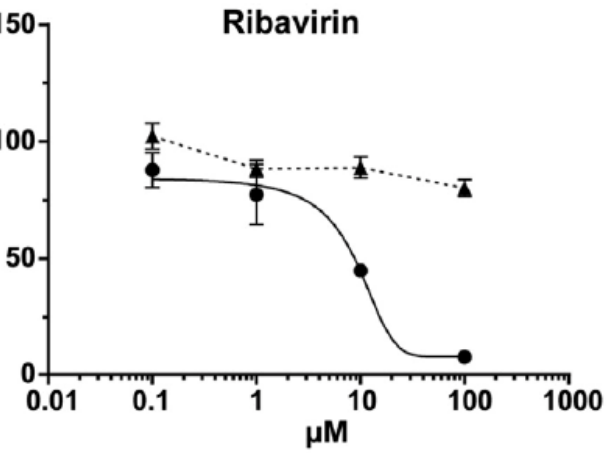
Novedades en tratamiento y  
prevención

# Tratar la hepatitis crónica: ¿con qué?

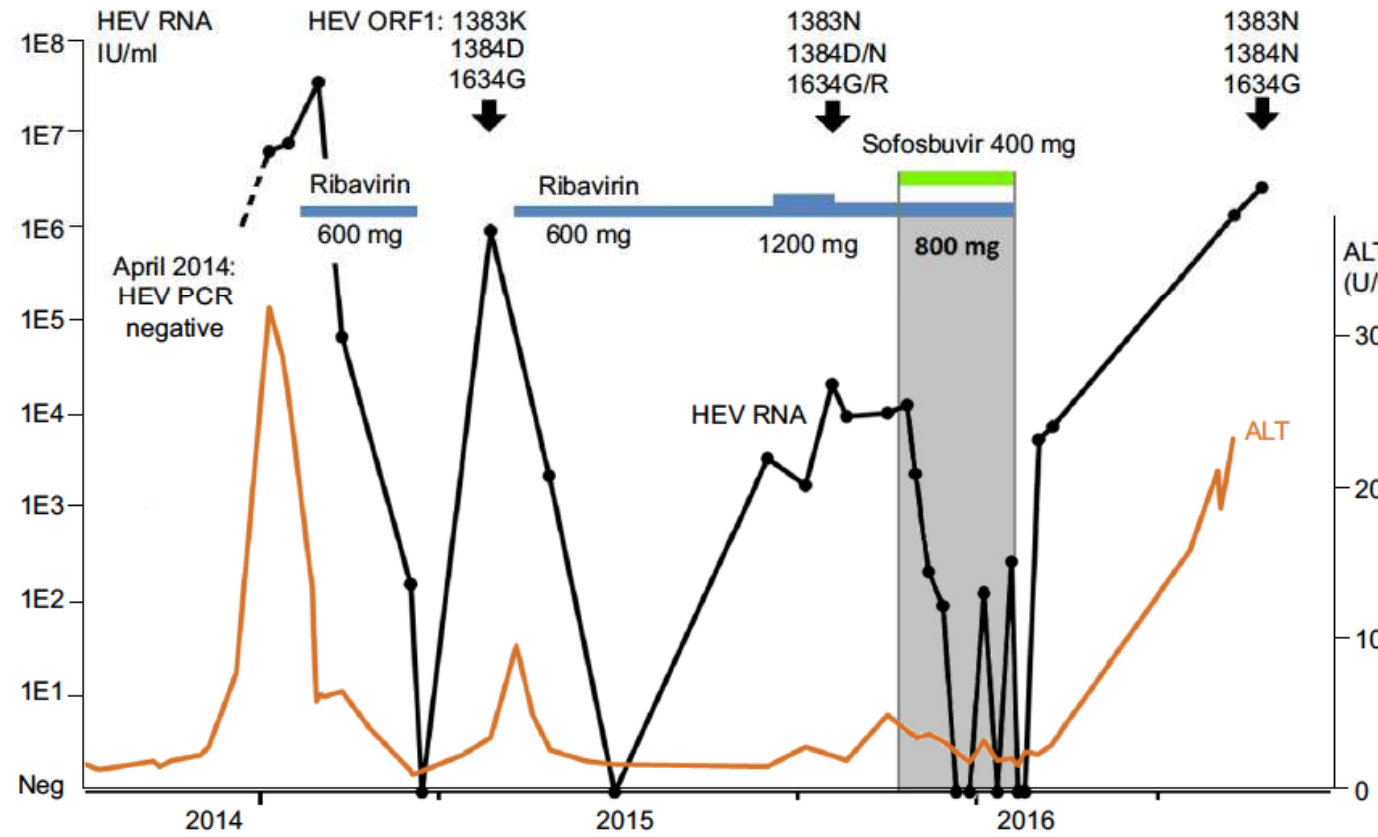
Author (year)	n	Ribavirin dose (mg/day)	Duration, median months (range)	Rapid viral response month (%)	SVR n/n (%)	Definition of SVR, months (%)	Relapses n (%)	No clearance n (%)	No follow-up n (%)
Kamar (2014) [7]	59	600 (29–1200)	3 (1–18)	1 (64) 3 (31)	46/59 (78)	6	10 (17)*	1 (2)	2 (3)
Pischke (2014) [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) <sup>†</sup>	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) <sup>‡</sup>	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) <sup>§</sup>	6	0 (0)	0 (0)	
Ambrosioni (2014) [37]	1	800	>11	6	1/1 (100) <sup>‡</sup>	9	1 (100) <sup>¶</sup>	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*<sup>1</sup>



## *In vivo*<sup>2</sup>



1. Dhao Thi et al Gastroenterology
2. Van der Valk et al J Hepatology

# ¿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



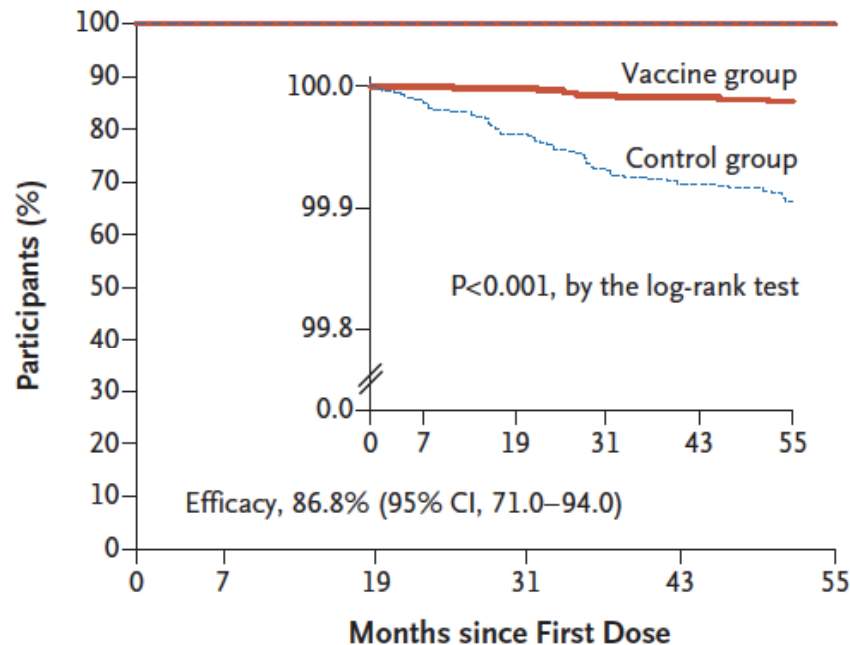
# ¿Y la vacuna?



World Health Organization  
Organisation mondiale de la Santé

Weekly epidemiological record  
Relevé épidémiologique hebdomadaire

1ST MAY 2015, 90th YEAR / 1<sup>er</sup> MAI 2015, 90<sup>e</sup> ANNÉE  
No. 18, 2015, 90, 185–200  
<http://www.who.int/wer>



Group	0	7	19	31	43	55
<b>Number at Risk</b>						
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
<b>Cumulative No. of Participants with Hepatitis E</b>						
Vaccine group	0	0	1	4	5	7
Control group	0	6	22	38	45	53

## WHO position

WHO recognizes the importance of hepatitis E as a public health problem in many developing countries, particularly among special populations such as pregnant women and individuals living in camps for displaced persons and in outbreak situations. The one currently licensed hepatitis E vaccine (HEV 239 vaccine, Hecolin®) is considered a promising vaccine which has shown a high degree of efficacy against hepatitis E disease in 16–65 year-old healthy subjects in China. However, data on the incidence of hepatitis E virus infection and disease worldwide, and the contribution of hepatitis E to mortality in the general population where infection is common, are limited.

*Routine use:* The available data concerning this relatively new vaccine are insufficient, and for some issues there are as yet no data, particularly regarding the immunization of individuals <16 years of age, and the degree of cross-protection the vaccine may confer against HEV genotypes 1, 2, and 3. In the absence of sufficient information at this time, WHO does not make a recommendation on the introduction of the vaccine



# 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.



# Conclusiones

- El VHE es altamente prevalente en Europa
- Muchas vías de transmisión: íntimamente ligadas al mundo animal
- Sintomatología extrahepática emergente
- No existe unas recomendaciones ni consenso para su cribado
- Vacuna no recomendada por la OMS
- Es necesario un plan de contingencia de la enfermedad: “De la granja a la mesa”

# Agradecimientos:



Mario Frías  
Ismael Zafra  
Teresa Brieva  
Diego Rodríguez Cano  
Laura Ruiz  
Ángela Camacho  
Francisca Cuenca  
Isabel Machuca  
Pedro López  
Antonio Martínez  
Antonio Rivero

Ignacio García Bocanegra  
David Cano  
Antonio Arenas  
David Cano  
Fernando Romero  
José Carlos Villamandos

Vicente Fernandez  
Juan Luis Millan

Angeles Risalde  
Pilar Alberdi  
Ursula Höfle  
Christian Gortázar  
Francisco Ruiz Fon

