



# MÁSTER EN HEPATOLOGÍA



Universidad  
de Alcalá

Asignatura: Hepatitis Virales

## Hepatitis E virus: What is new?

**Maria Buti MD**

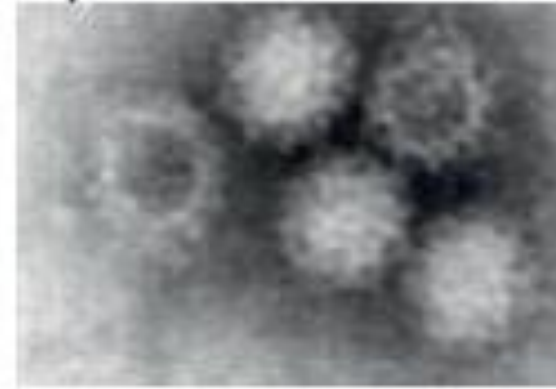
Liver Unit, Internal Medicine Department

# Epidemiology

- First cause of Acute Hepatitis
  - Worldwide, in Europe, in France and the UK
- 20 million Cases/year
  - -70.000 deaths/year
  - > 3 million symptomatic patients
- In Europe: 2 million cases
  - Mainly autochthonous cases

# HEV

- HEV is a small, non-enveloped, positive sense, single-stranded RNA virus
- *Orthohepevirus* genus under the *Hepeviridae* family
- At least, 8 HEV genotypes



# HEV in developed countries

## Acute hepatitis E

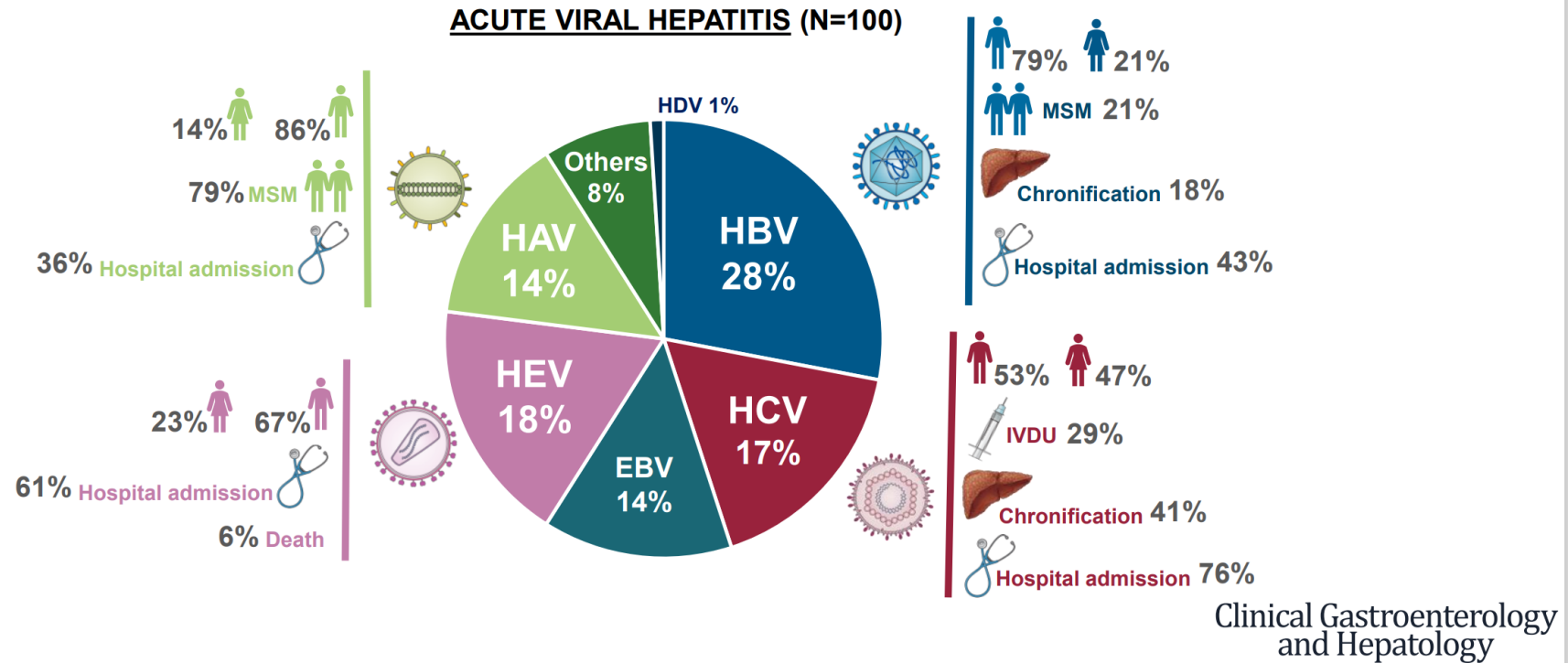


Symptomatic

**Asymptomatic**

**98%?**

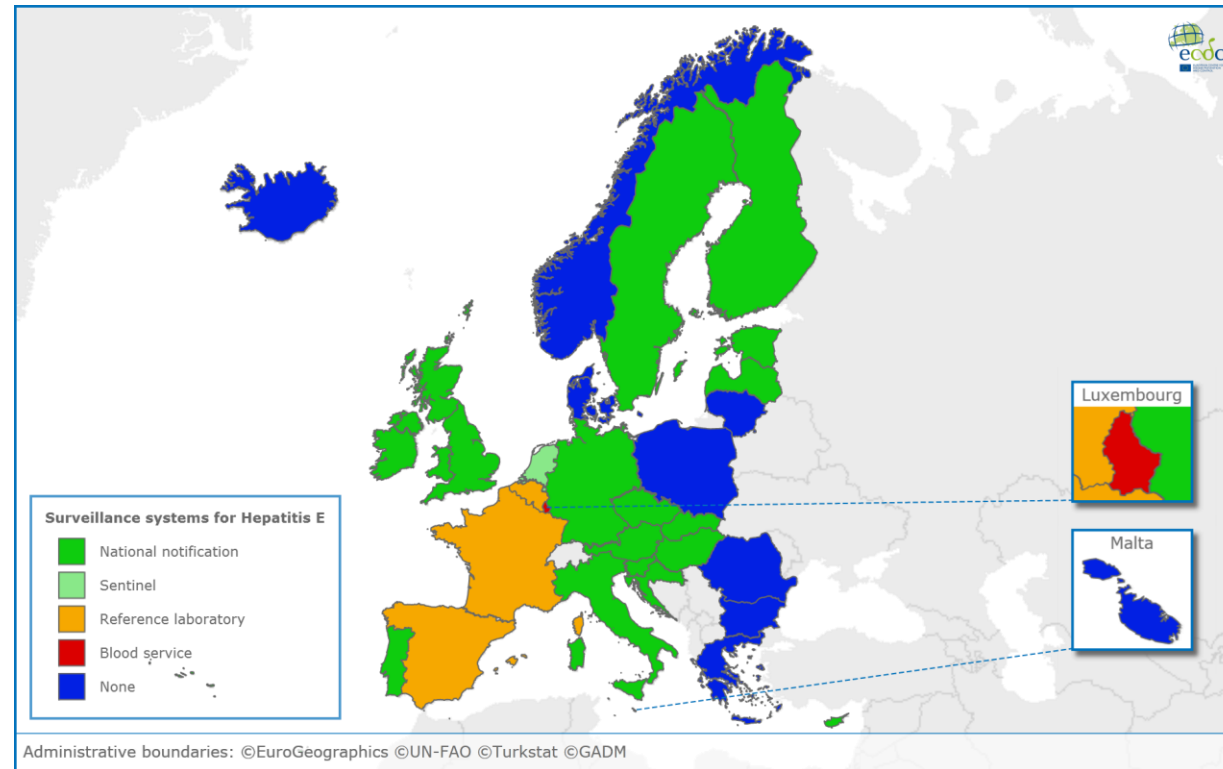
# Acute Hepatitis E in Spain



# Surveillance of hepatitis E in Europe

- One of the most common causes of acute hepatitis in the EU/EEA
- Evidence of increasing number of autochthonous cases in Europe
- Hepatitis E is not notifiable at EU level
- Populations under surveillance, case definitions and reporting systems, are set by Member States

# HEV surveillance systems in EU/EEA, 2015

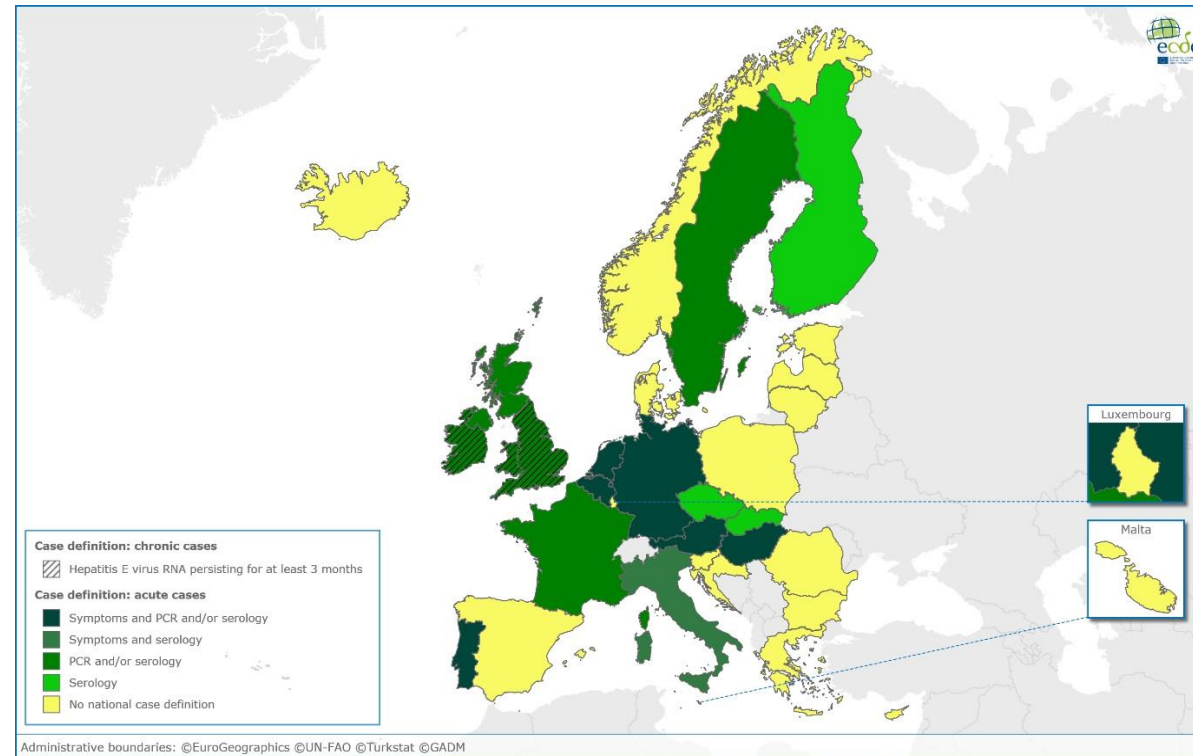


**20 EU/EEA countries with HEV-specific surveillance**

<https://ecdc.europa.eu/en/publications-data/hepatitis-e-eueea-2005-2015>  
<https://eurosurveillance.org/content/10.2807/1560-7917.ES.2017.22.26.30561>

## HEV case definitions in EU/EEA surveillance systems

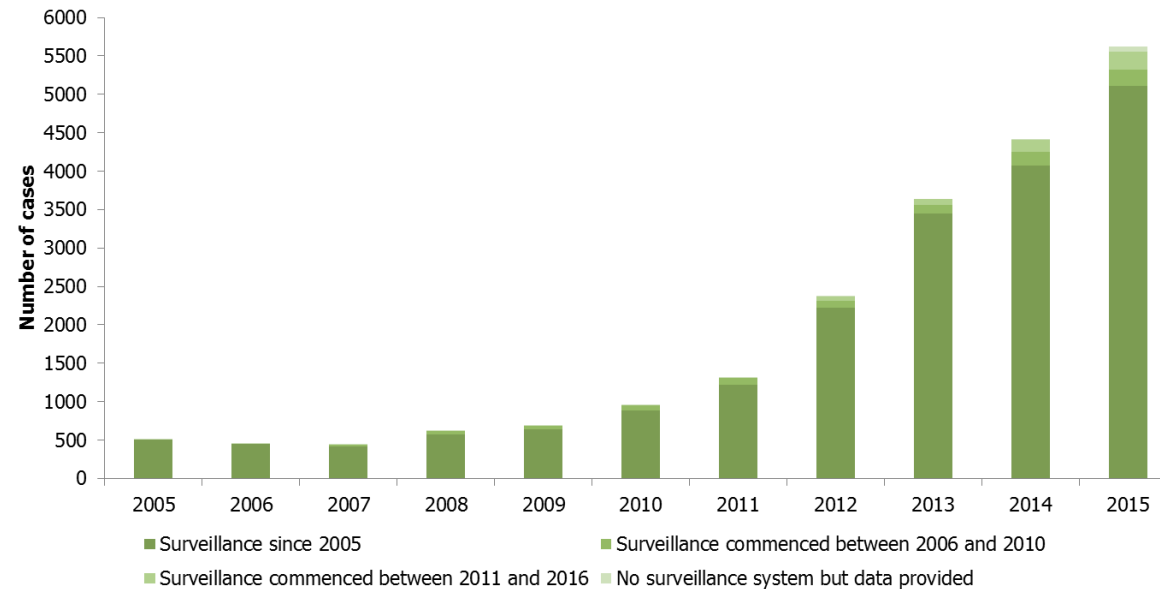
Case definitions varied across countries, two countries with case definitions for chronic cases



<https://ecdc.europa.eu/en/publications-data/hepatitis-e-eueea-2005-2015>  
<https://eurosurveillance.org/content/10.2807/1560-7917.ES.2017.22.26.30561>



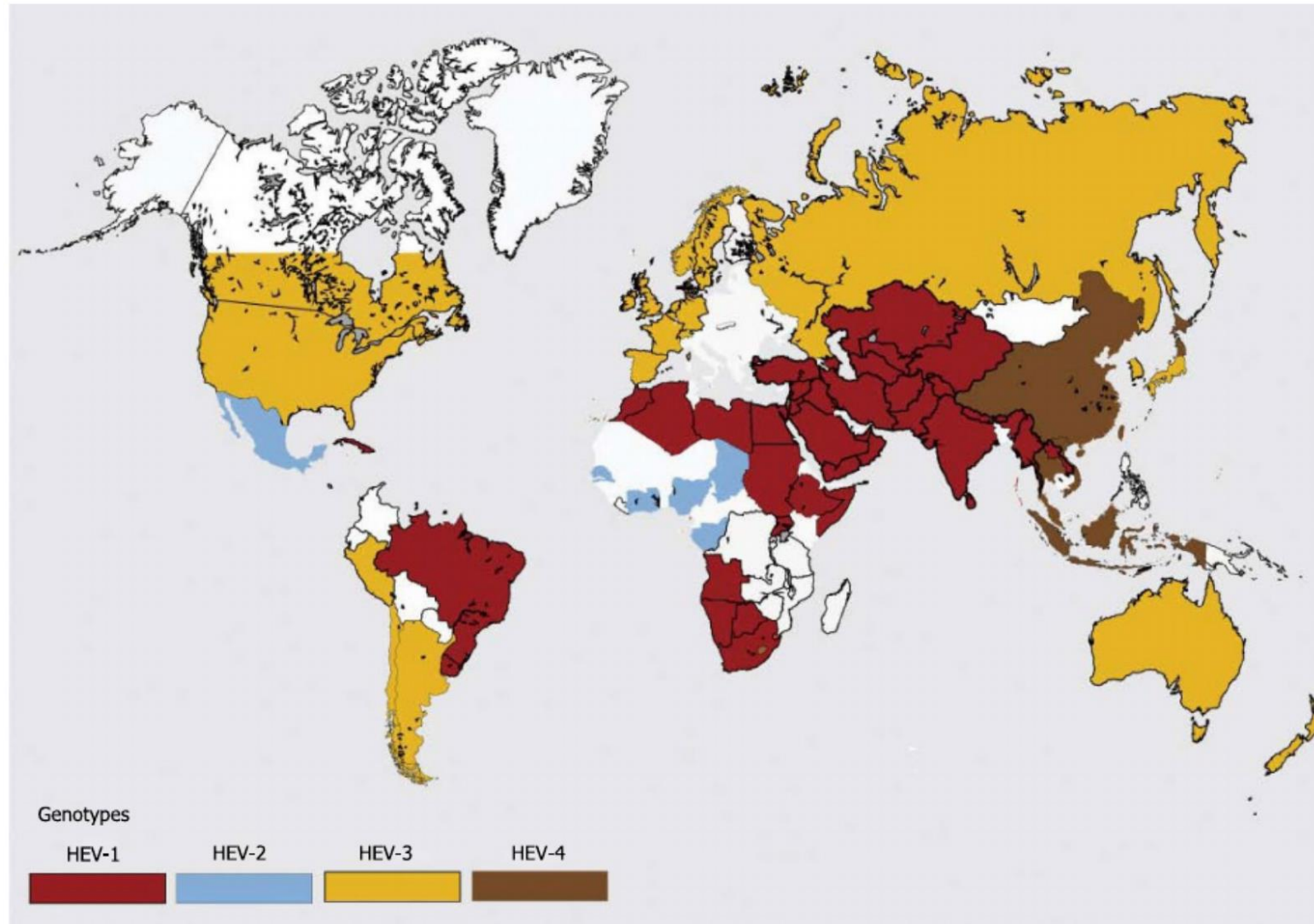
## Number of laboratory-confirmed cases of HEV by year and start of surveillance, 22 EU/EEA Member States, 2005–2015\*



- 10-fold increase 2005–2015 due locally acquired infections
- 78% of cases reported from France, Germany and UK

\* Data available for: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Estonia, Finland, France, Germany, Hungary, Italy, Latvia, Netherlands, Norway, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden, United Kingdom

# Worldwide distribution of HEV

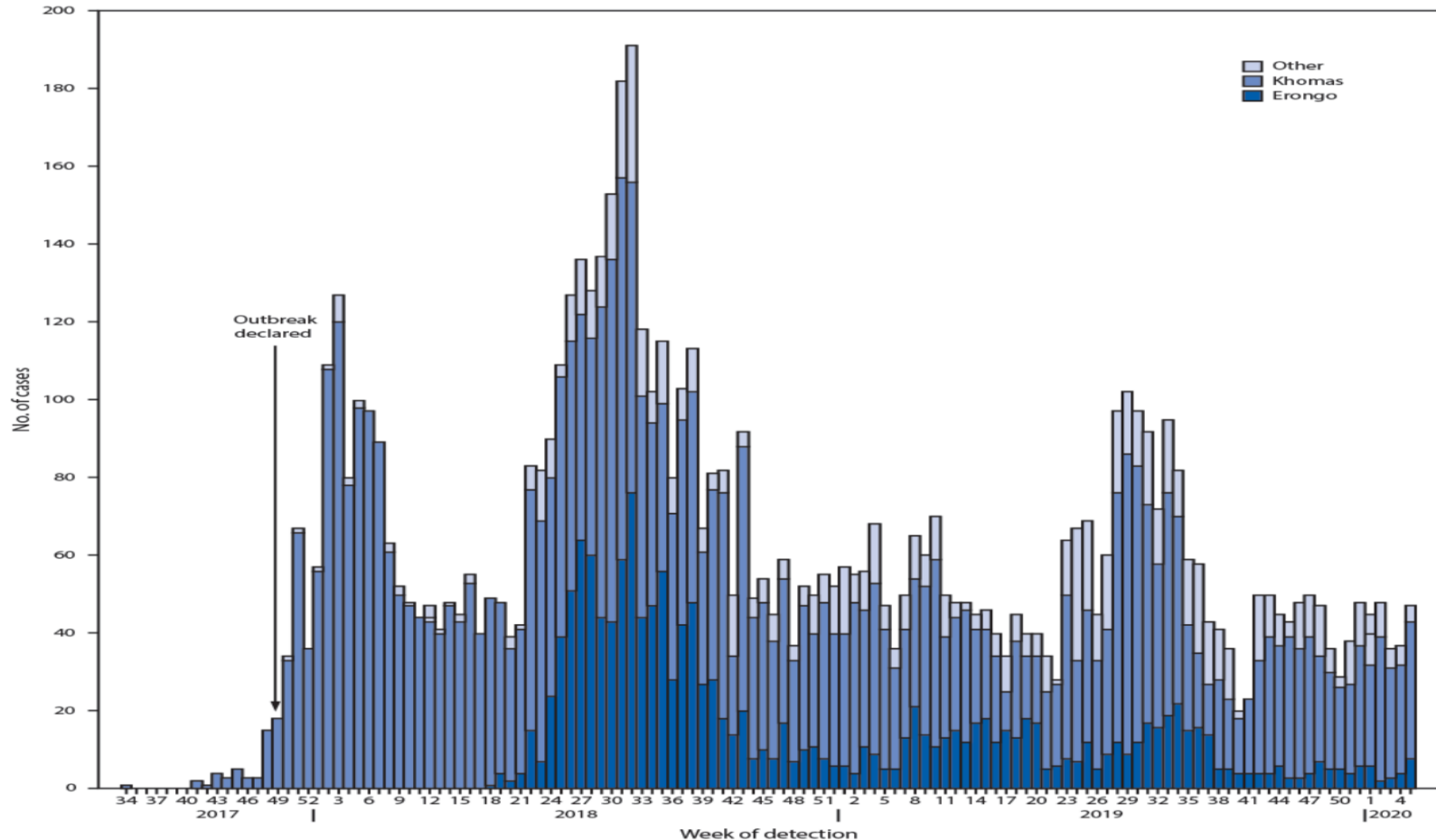


# HEV genotypes

Characteristics	HEV 1 and 2	HEV3 and 4
Source of infection	Obligate human pathogen	Zoonotic Blood supply
Route of infection	Faecal-oral via infected water	Consumption of infected pork Blood supply
Outbreaks	Yes	No
Clinical attack rate	1:5	< 1:10
Demographics	Mainly affects young adults	Mainly affects older men Male:female ratio 3:1
Chronic infection	No	Yes in immunosuppressed individuals
Occurrence of second HEV infection	Yes	Yes
Neurological sequelae	Yes	Yes

# Last HEV outbreak in Namibia

Number of hepatitis E cases (N = 7,247), by week of case detection and region of country\* — Namibia, 2017–2020



<https://www.cdc.gov/mmwr/volumes/69>

# HEV Infection During Pregnancy is Usually Fatal

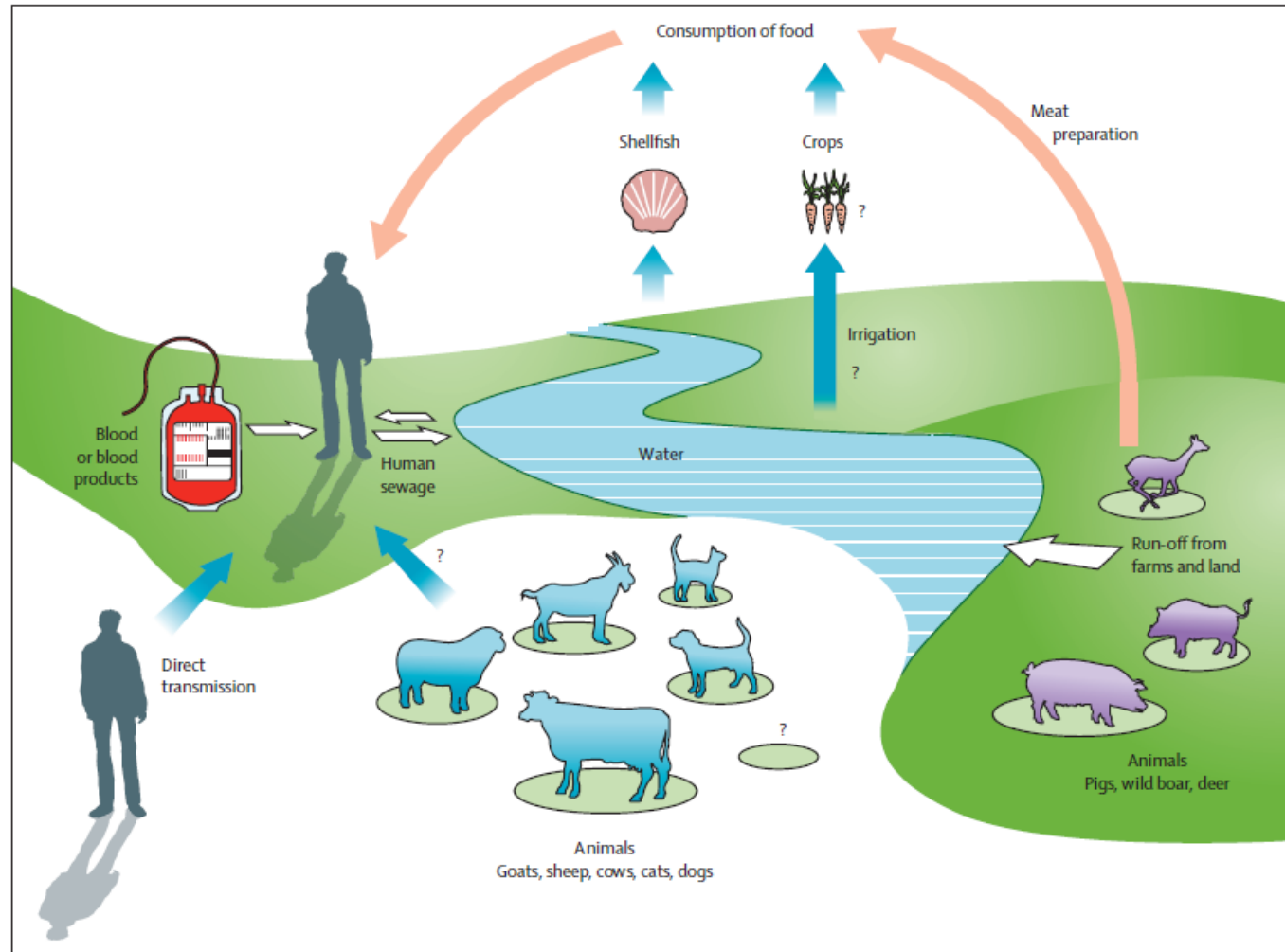


- Mortality rate up to 19%
- High perinatal mortality and prematurity rates

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# Routes of transmission of Hepatitis E





August 25, 2016

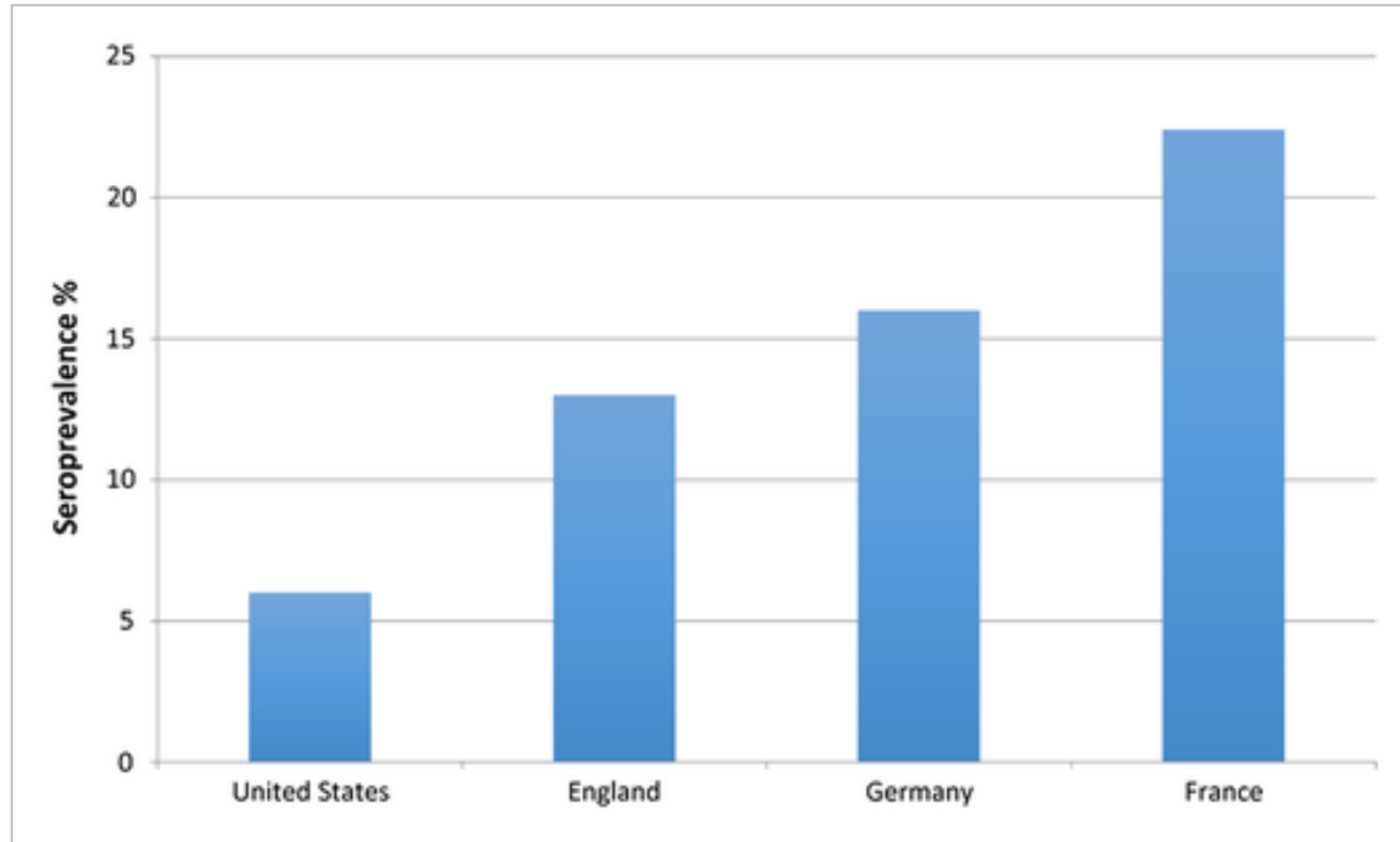
# EUROPE'S NEW HEPATITIS PROBLEM



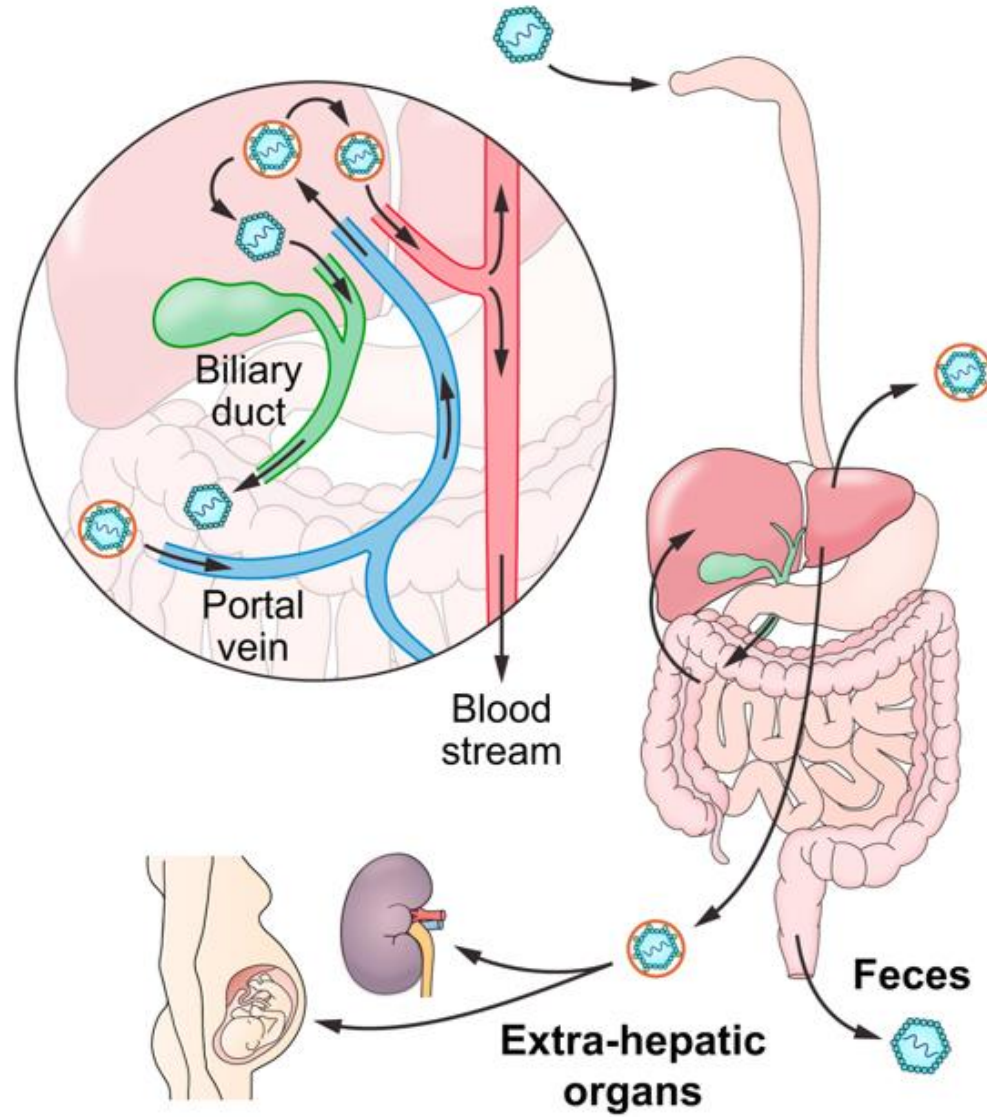
# Europe vs. US



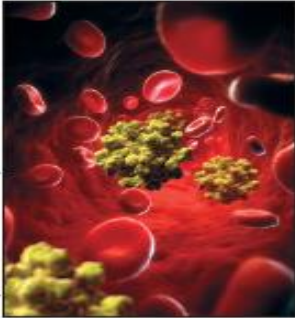
# HEV seroprevalence



# Life Cycle



# HEV RNA prevalence in blood donors

Co				
USA				
Nethe				
Germa				
Spain		Sauleda	9998	1/3332
<p><b>The Lancet. January 2014</b></p> <p><b>Should we screen blood products for hepatitis E virus RNA ?</b></p>				
<p><b>EASL Clinical Practice Guidelines on hepatitis E virus infection</b>★</p> <p>European Association for the Study of the Liver*</p>				
Netherlands				1/1321
		<p><b>Recommendations</b></p> <ul style="list-style-type: none"> <li>• Patients with abnormal LFTs after receiving blood products should be tested for HEV. (A1)</li> <li>• EASL recommends that blood donor services screen blood donors for HEV by NAT, informed by local risk-assessment and cost-effectiveness studies, both of which may vary considerably by geographical location. (A1)</li> </ul>		

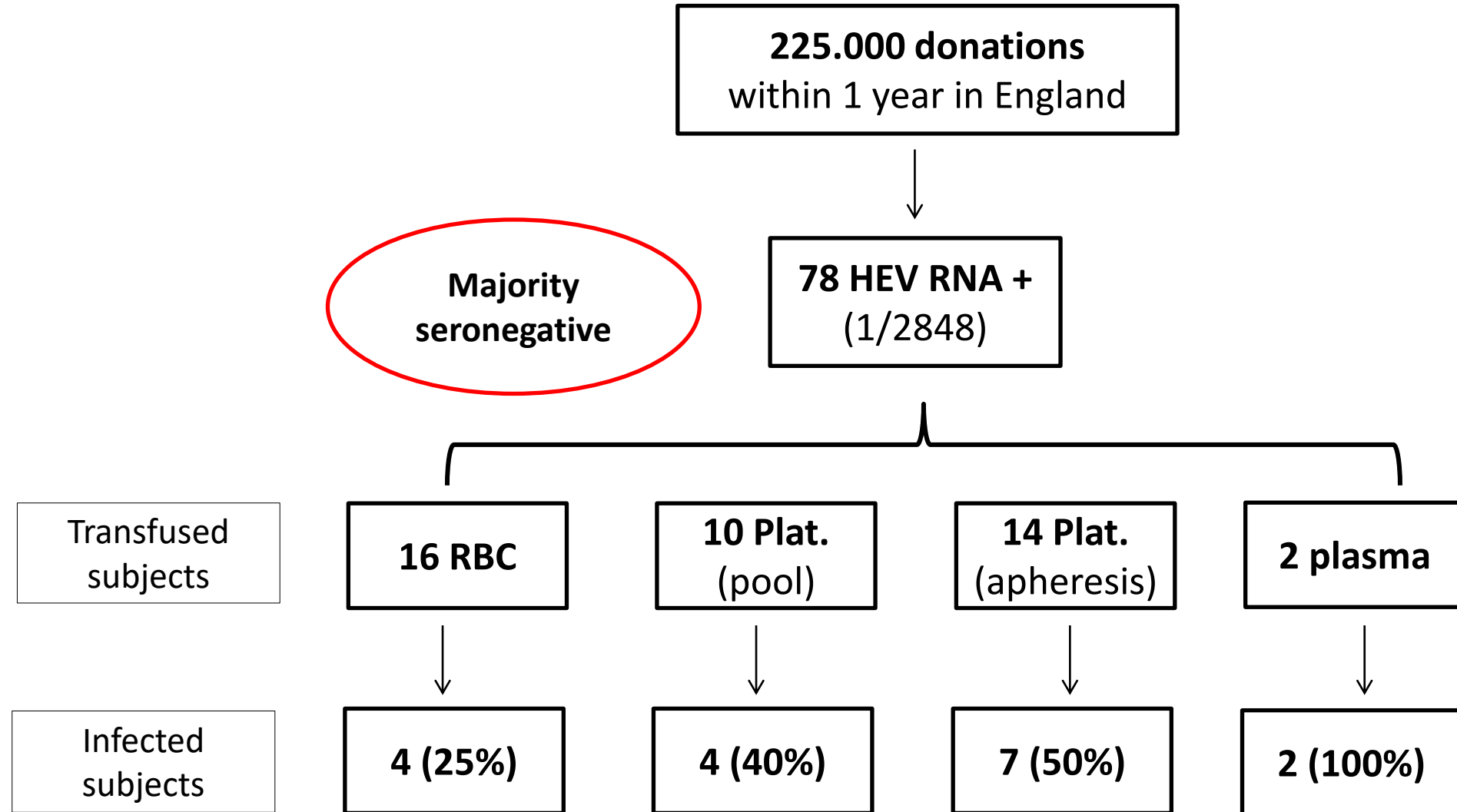
Cleland A, *et al.* Vox Sang 2013;105:283-9; Xu C, *et al.* Transfusion. 2013;53:2505-11; Juhl D, *et al.* Transfusion. 2014;54:49-56; Slot E, *et al.* Euro Surveill. 2013 ;18(31); Sauleda S, *et al.* Transfusion 2015;55:972-9; Ma L, *et al.* The Journal of international medical research 2015;43:257-262; Stramer SL, *et al.* Transfusion; 2016;56(2):481-8; Hogema BM, *et al.* Transfusion 2016;56(3):722-8.

# HEV RNA prevalence in blood donors

Country	Year	Author	N Subjects	HEV RNA
USA	2013	Xu	1939	0/1939
Netherlands	2013	Slot	40176	1/2363
Germany	2014	Juhl	1019	1/4252
Spain	2015	Sauleda	9998	1/3332
China	2015	Ma	816	0/816
USA	2016	Stramer	18829	1/9500
Netherlands	2016	Hogema	59474	1/1321

Cleland A, *et al.* Vox Sang 2013;105:283-9; Xu C, *et al.* Transfusion. 2013;53:2505-11; Juhl D, *et al.* Transfusion. 2014;54:49-56; Slot E, *et al.* Euro Surveill. 2013 ;18(31); Sauleda S, *et al.* Transfusion 2015;55:972-9; Ma L, *et al.* The Journal of international medical research 2015;43:257-262; Stramer SL, *et al.* Transfusion; 2016;56(2):481-8; Hogema BM, *et al.* Transfusion 2016;56(3):722-8.

# Hepatitis E in blood products



13/18 were immunosuppressed

# HEV and the blood supply

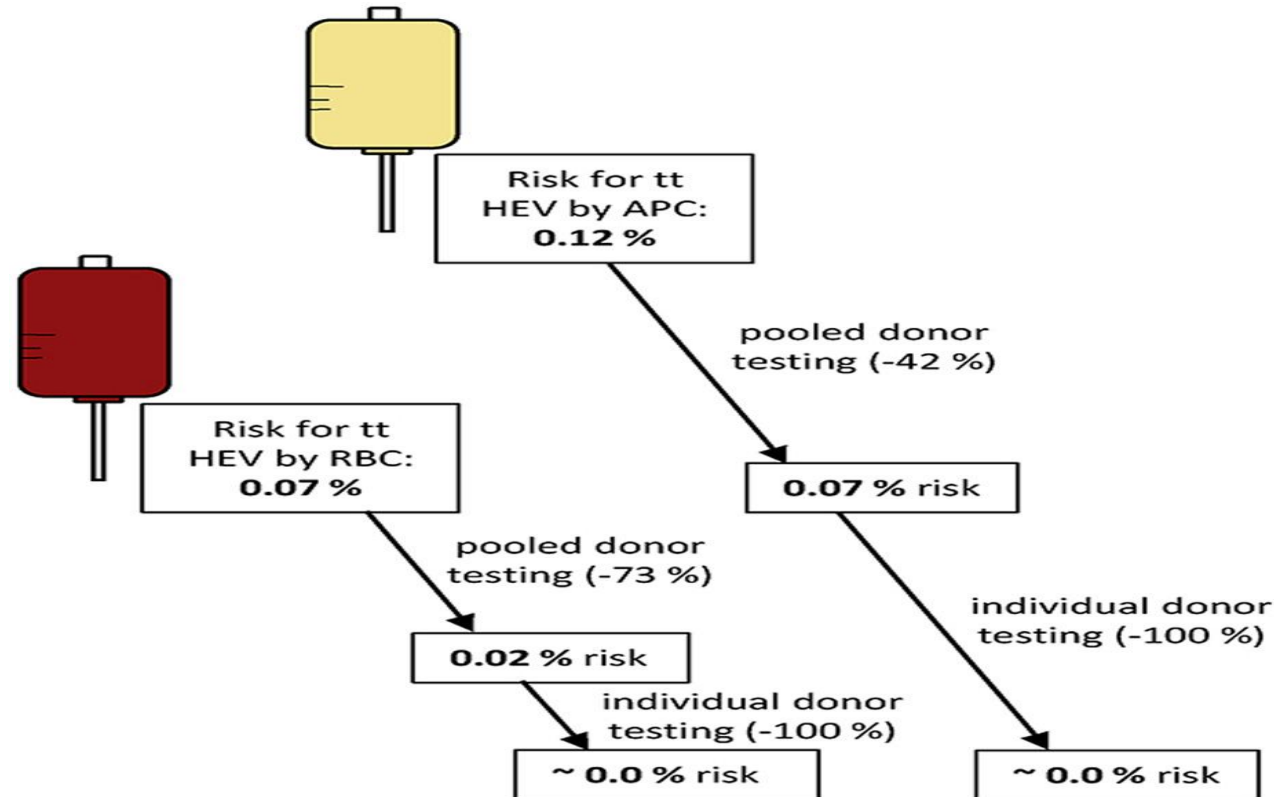


- HEV can also be transmitted iatrogenically
  - Through infected blood and blood products
- Universal, targeted or partial screening for HEV in donors:
  - Ireland, the UK, the Netherlands, and Japan
  - Germany: voluntary HEV screening by some blood transfusion companies

Recommendations			Grade of evidence	Grade of recommendation
• Patients with abnormal LFTs after receiving blood products should be tested for HEV	A	1		
<b>Blood donor screening</b>				
• Blood donor services should screen blood donors for HEV by NAT, informed by local risk assessment and cost-effectiveness studies	A	1		

# Risk of transfusion-transmitted hepatitis E virus infection from pool-tested platelets and plasma

31 of 16,236 donors (0.19 %) HEV RNA positive. 3 TBDs had virus loads 710 and 2000 IU/ml, a significant risk for tt hepatitis E



Screening of BDs with an LOD of 2000 IU/ml reduced the risk for tt HEV infection by about 73% for red blood cell concentrates whereas merely a 42% risk reduction was achieved for platelet and fresh frozen plasma transfusions

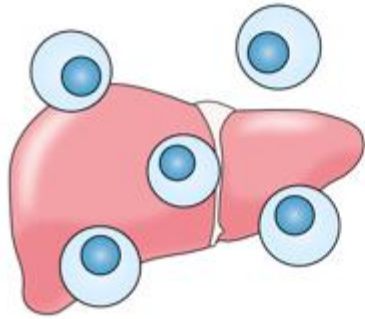


# Neurologic manifestations in 200 acute hepatitis E cases (French National Reference Center)

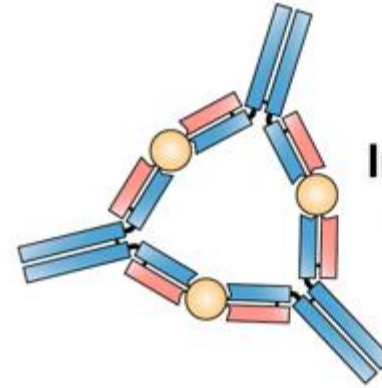
	Immuno Competent N=137	Immuno compromised N=63
<b>Neurological symptoms</b>	<b>31 (22.6%)</b>	<b>2 (3.2%)</b>
Neuropathic pain	13 (42%)	1 (50%)
Painless sensory disorders	8 (26%)	1 (50%)
Neuralgic amyotrophy	6 (19%)	0 (0%)
Guillain Barre syndrome	1 (3%)	0 (0%)
Meningitis	1 (3%)	0 (0%)
Diplopia	1 (3%)	0 (0%)



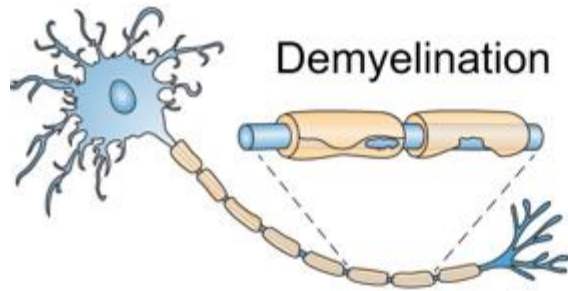
# Pathogenesis



**Immune cell-mediated injury**

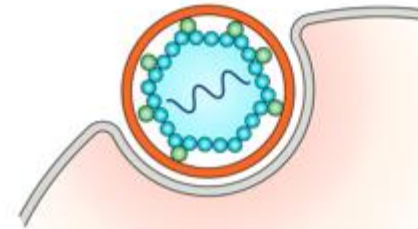


**Immune complex-mediated injury**



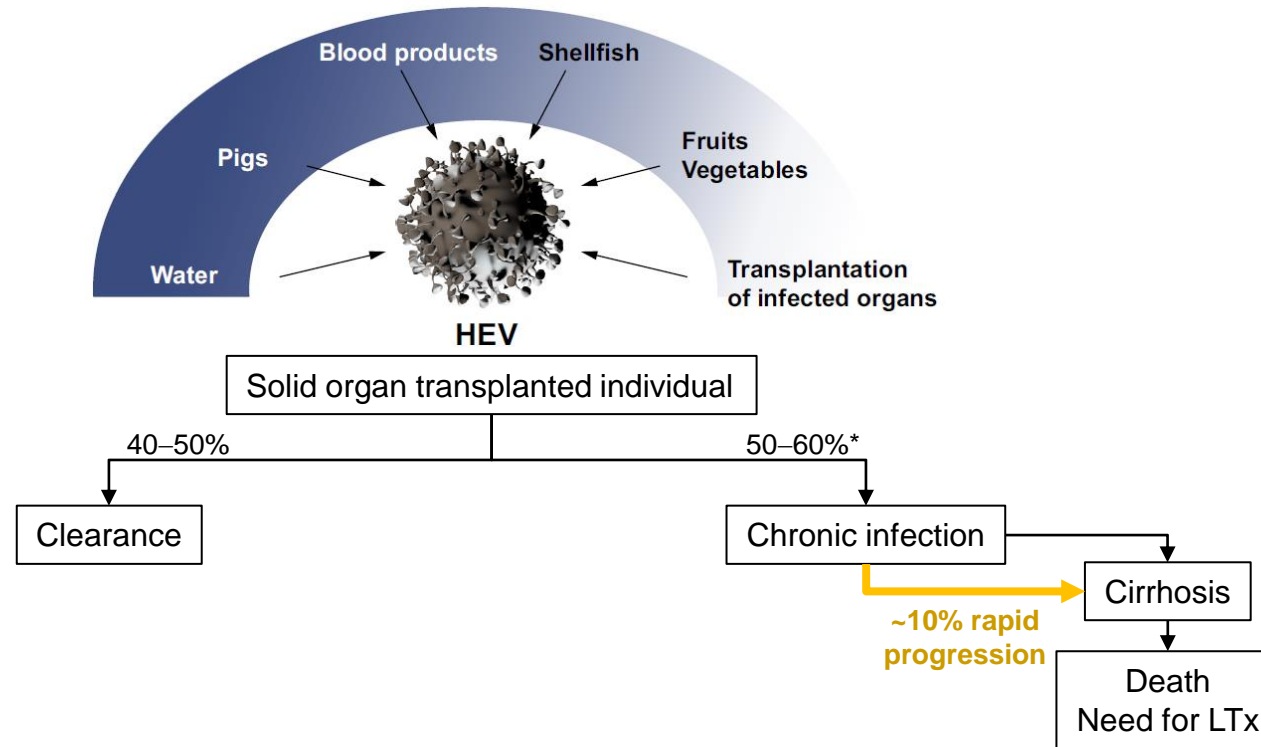
**Demyelination**

**Molecular mimicry**



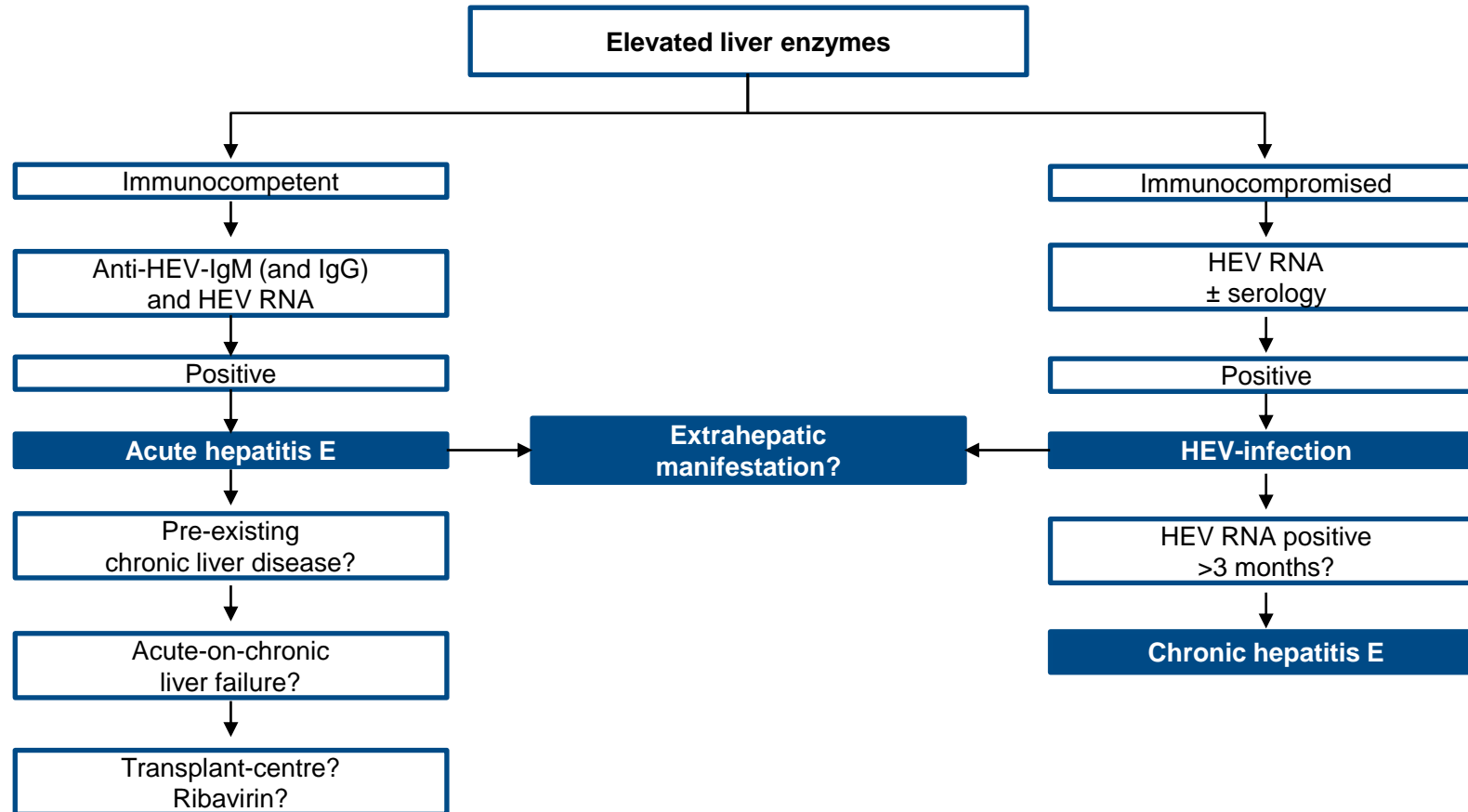
**Direct toxicity**

# Transmission and disease progression in transplanted individuals



\*Possible increased likelihood for LTx recipients, only GT 3  
Behrendt P, et al. J Hepatol 2014;61:1418-29

# Diagnostic algorithm for HEV infection



# Direct Tests

✓ **HEV RNA:** PCR or TMA, LoD 10-60 UI/ml

*Abravanel, J Clin Microbiol 2013 ; Gallian, Transfusion 2017*



Cobas 6800  
Roche ®



Procleix Grifols ®,  
Panther Hologic ®



Real Star HEV V2 Altona®  
**Quantitative**

**Qualitative**

✓ **HEV Ag**      specificity : 100 %

sensitivity: 91 %

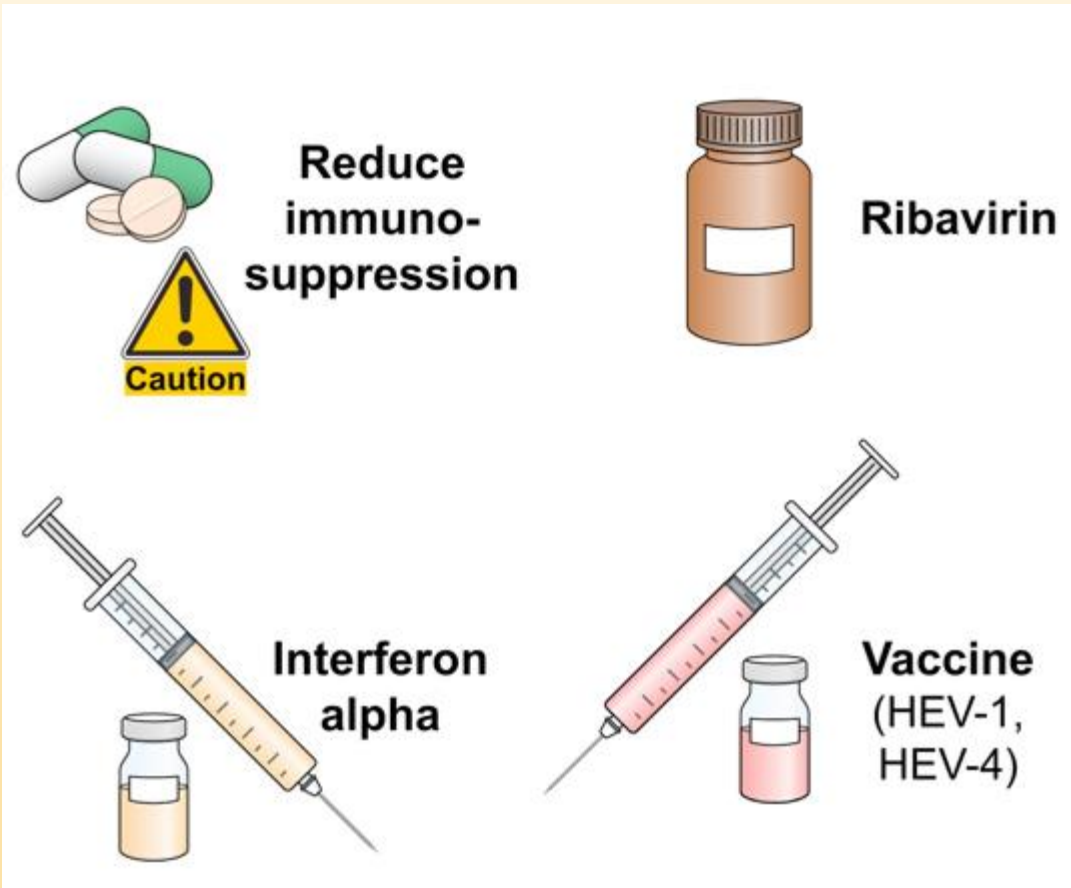
80 % immunocompétent

94 % immunosuppressed

analytical sensitivity < PCR or TMA

*Wen, J Clin Microbiol 2015 ; Trémeaux, J Clin Virol 2016 ; Behrendt, J Infect Dis 2016*

# Therapy and Prevention

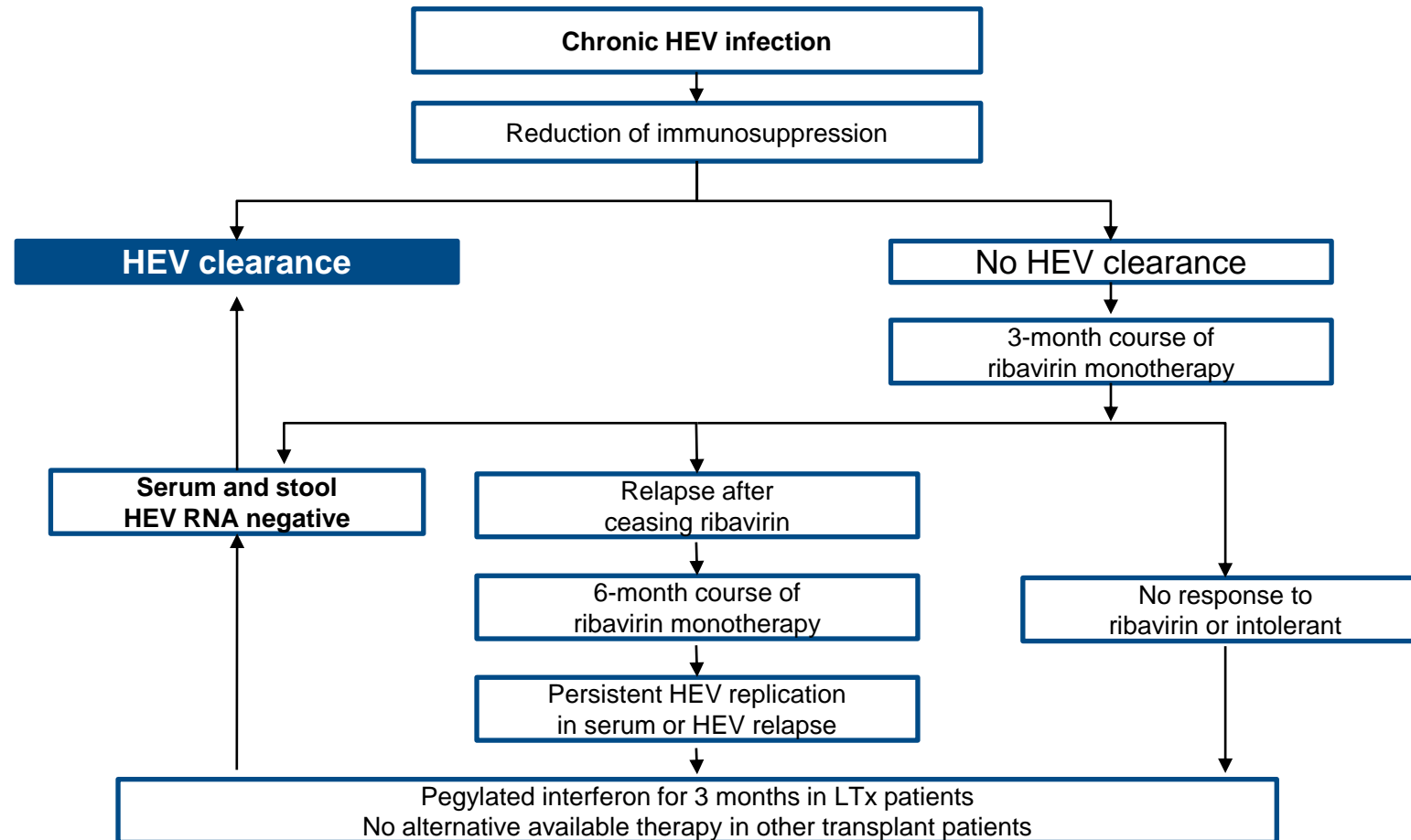




- Acute HEV infection does not usually require antiviral therapy\*
- Most cases of HEV infection are spontaneously cleared
  - Some patients may progress to liver failure
  - Ribavirin
    - Early therapy of acute HEV may shorten course of disease and reduce overall morbidity

Recommendation	Grade of evidence	Grade of recommendation
• Ribavirin treatment may be considered in cases of severe acute hepatitis or acute-on-chronic liver failure	C	2

# Management of patients not clearing HEV infection





# Treatment of chronic hepatitis E

## Role of Sofosbuvir

*J Hepatol.* 2017 Jan;66(1):242-243. doi: 10.1016/j.jhep.2016.09.014. Epub 2016 Oct 1.

**Sofosbuvir shows antiviral activity in a patient with chronic hepatitis E virus infection.**

van der Valk M<sup>1</sup>, Zaaijer HL<sup>2</sup>, Kater AP<sup>3</sup>, Schinkel J<sup>2</sup>.

*Hepatology.* 2018 Dec 14. doi: 10.1002/hep.30428. [Epub ahead of print]

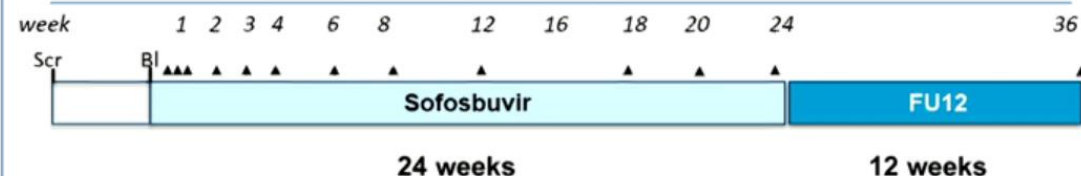
**Sofosbuvir and Ribavirin Eradication of Refractory Hepatitis E in an Immunosuppressed Kidney Transplant Recipient.**

Drinane M<sup>1</sup>, Jing Wang X<sup>2</sup>, Watt K<sup>2</sup>.

### HepNet SofE study

Patients with chronic hepatitis E  
N=9

Prospective, open label, single-arm, multicenter, phase II pilot trial



3 centers in Germany (Charite, Berlin; UKE, Hamburg; MHH, Hannover) recruited 10 patients from January to May 2018

	HEV RNA decline median	HEV RNA decline >1log
Week 2	1.1 log	N=3
Week 12	0.76 log	N=3
Week 24 (EOT)	0.40 log	N=2
Follow-up 12 weeks	+ 0.11 log	N=0

**0/9 patients achieved the primary endpoint**



- Consumption of undercooked meat from pigs, wild boar, and deer is a clear risk factor for HEV infection in Europe
  - *In vitro* food preparation data inconclusive
- Risk of patient-to-patient transmission is poorly defined
  - Sexual transmission has been described in MSM
  - Stool contains high amounts of infectious HEV particles
    - Strict hygiene is required
- A vaccine has been developed but is only licensed in China

Recommendations	Grade of evidence	Grade of recommendation
• Immunocompromised individuals and those with chronic liver diseases should avoid consumption of undercooked meat (pork, wild boar and venison) and shellfish	B	1
• Suggested that immunocompromised patients consume meat only if it has been thoroughly cooked to $\geq 70^{\circ}\text{C}$	B	2

# Take home messages- Hepatitis E infection

 Most common source of acute hepatitis worldwide

 Increasing number of autochthonous cases

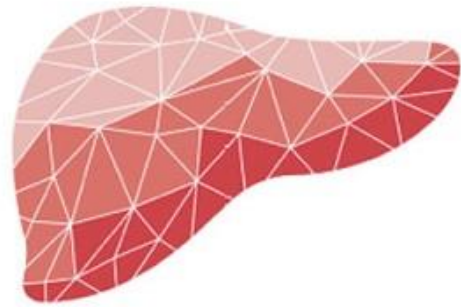
**Rule out in all  
acute hepatitis!**

 Zoonosis (meat) and transfusion-transmitted

 Extrahepatic manifestations, mainly neurological

 Usually self-limited

 Risk of chronic infection if immunosuppression



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