MÁSTER EN HEPATOLOGÍA

UAM Universidad Autónoma de Madrid

Universidad de Alcalá

Asignatura: Hepatitis Virales

“HEPATITS E”

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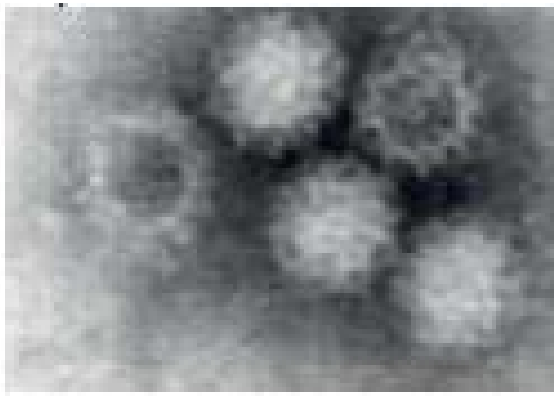
Epidemiology

- 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

WHO. Viral Hepatitis 2015
EASL Guidelines 2018

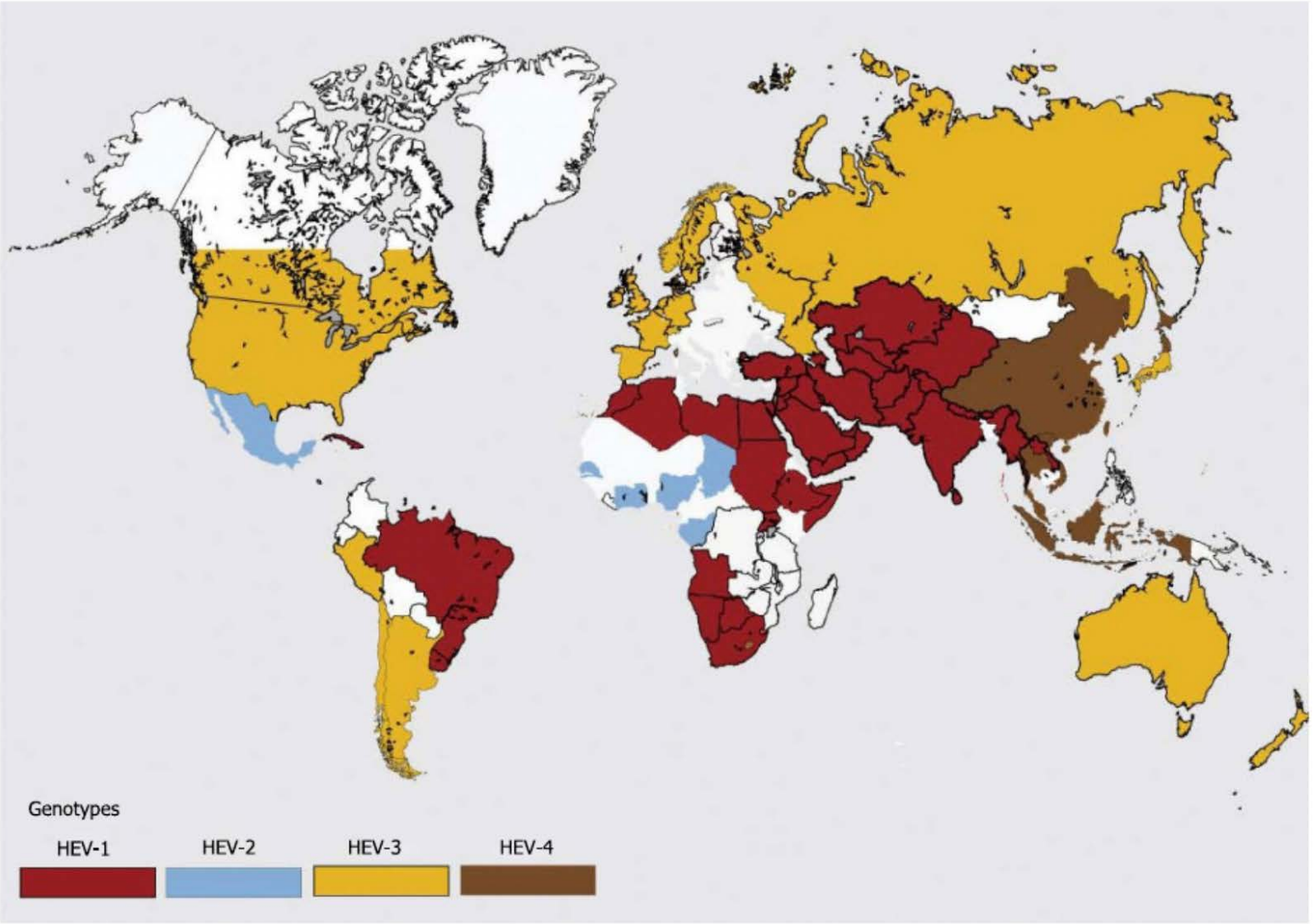
HEV

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



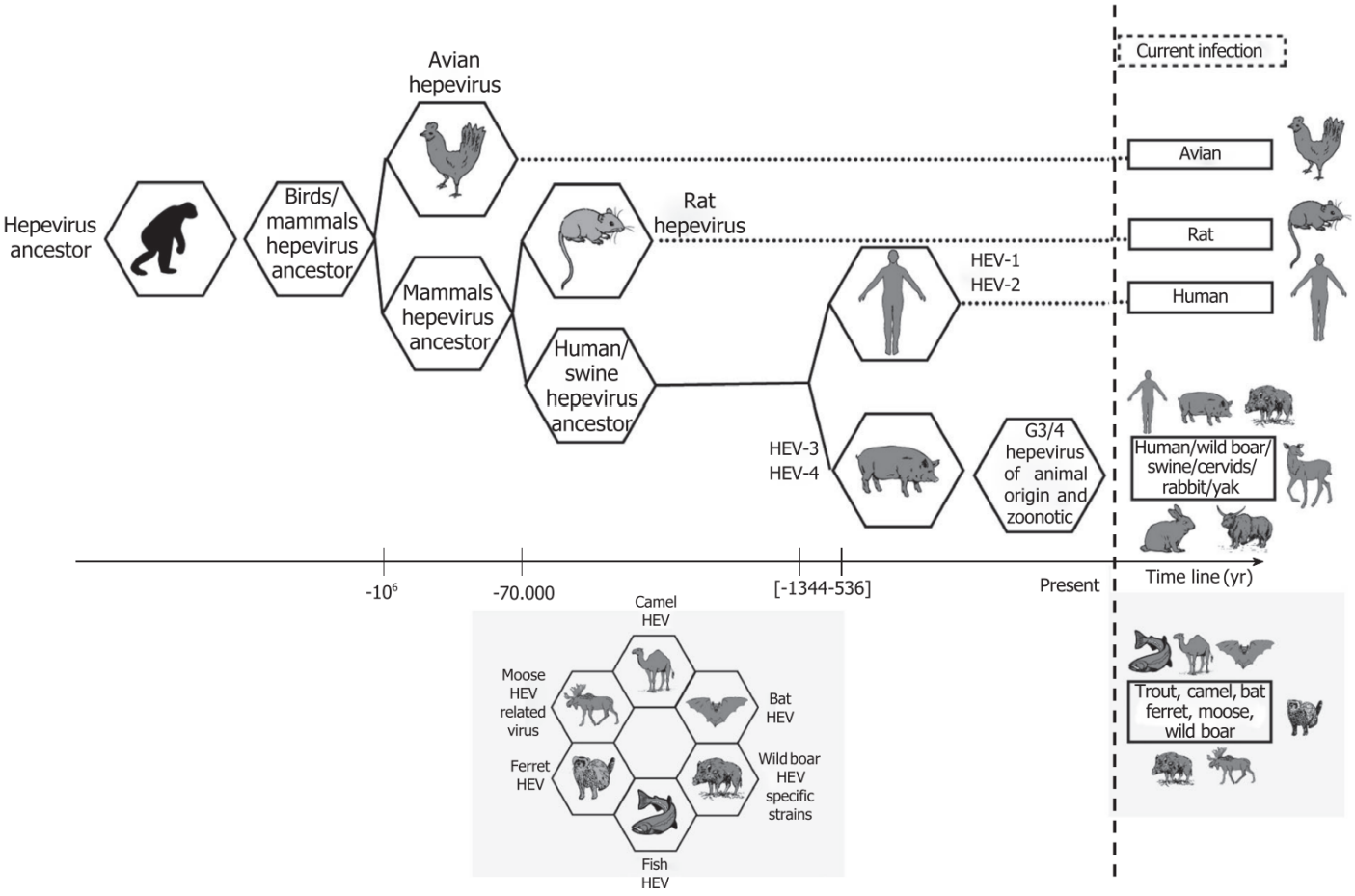
- At least,8 HEV genotypes

Worldwide distribution of HEV



Purcell RH. J Hepatol, 2008

Hepatitis E and mammals



Seth A et al. Clinical Liver Disease

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

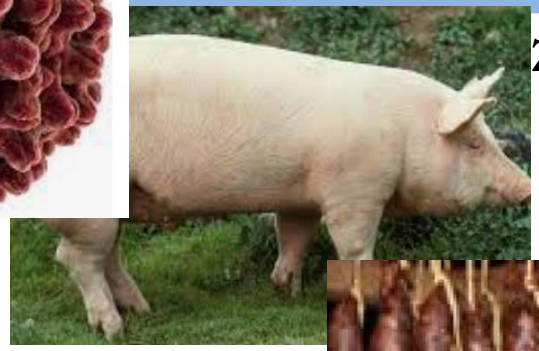
Hepatitis E : a virus with different faces

Genotype 1 and 2

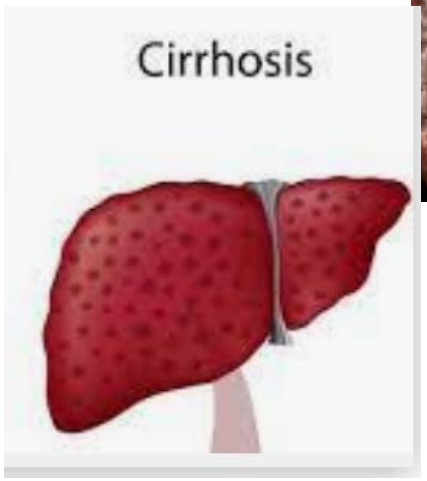
Large outbreaks

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

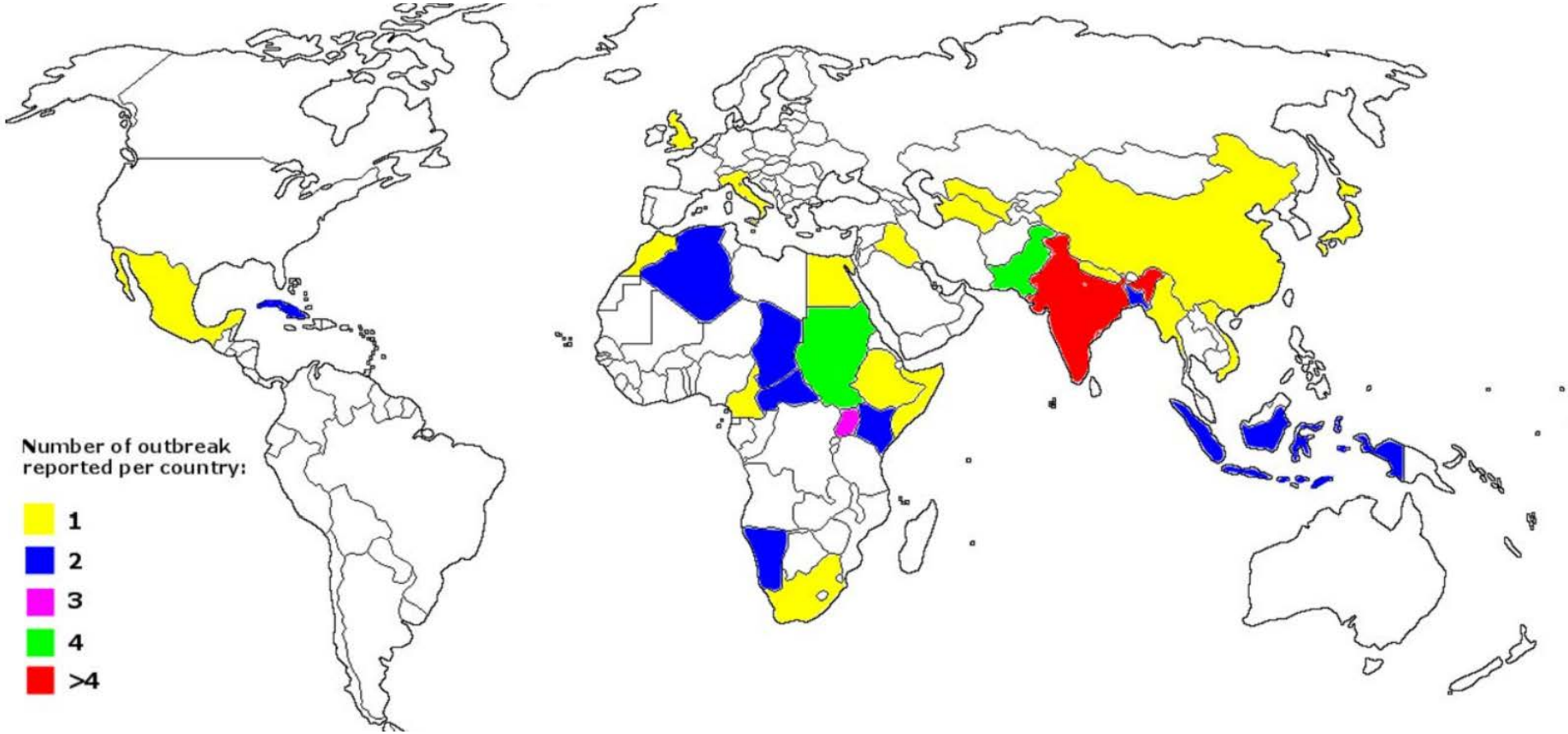
Genotype 3 and 4



Zoonosis



The Global HEV outbreak distribution

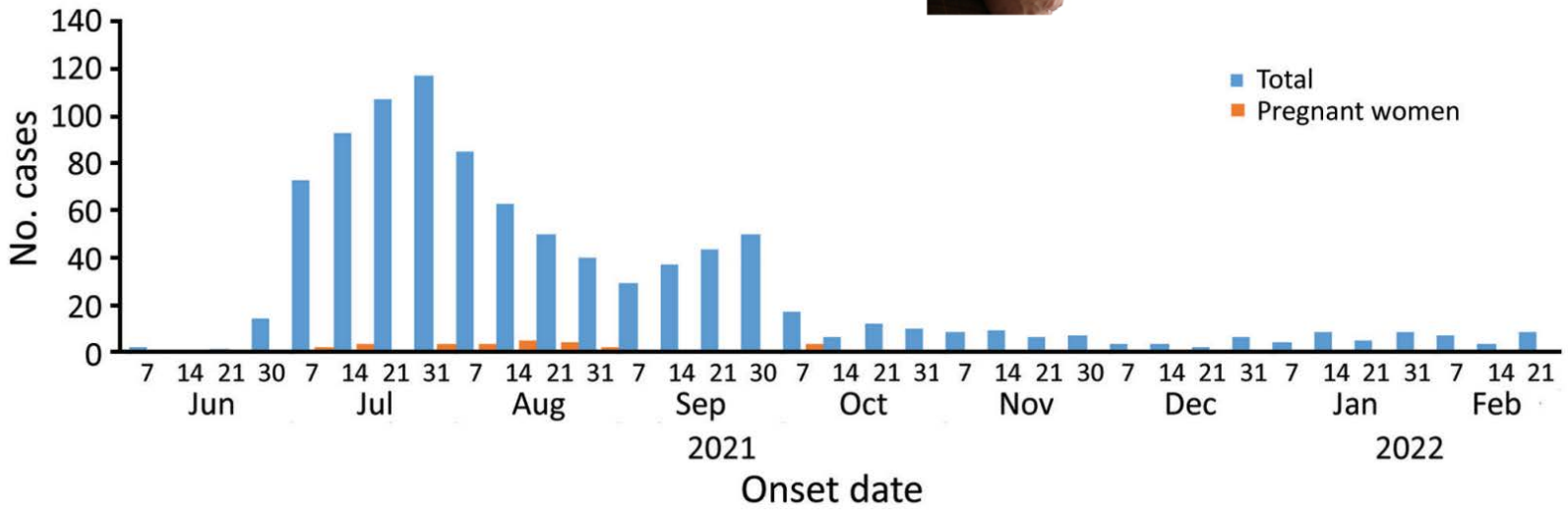


Hakim M et al. Liver International 2016

Hepatitis E Virus Outbreak among Tigray War Refugees from Ethiopia, Sudan

We report hepatitis E virus (HEV) outbreaks among refugees from Ethiopia in Sudan during June 2021–February 2022. We identified 1,589 cases of acute jaundice syndrome and used PCR to confirm HEV infection in 64% of cases. Implementing vaccination, water, sanitation, and hygiene programs might reduce HEV outbreak risk.

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



Ahmed, A et al. Emerging Infectious Diseases 2022:28,

Hepatitis E : a virus with different faces

Genotype 1 and 2

Large outbreaks

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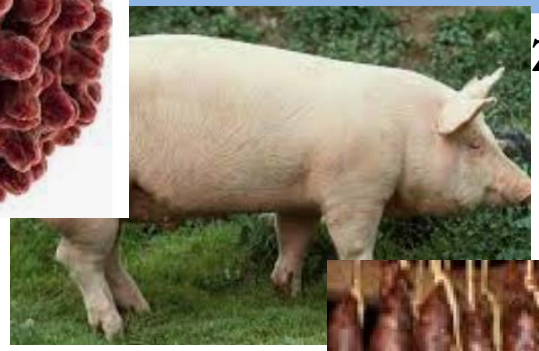
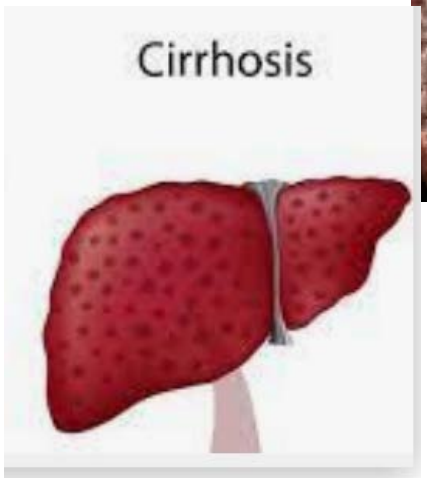
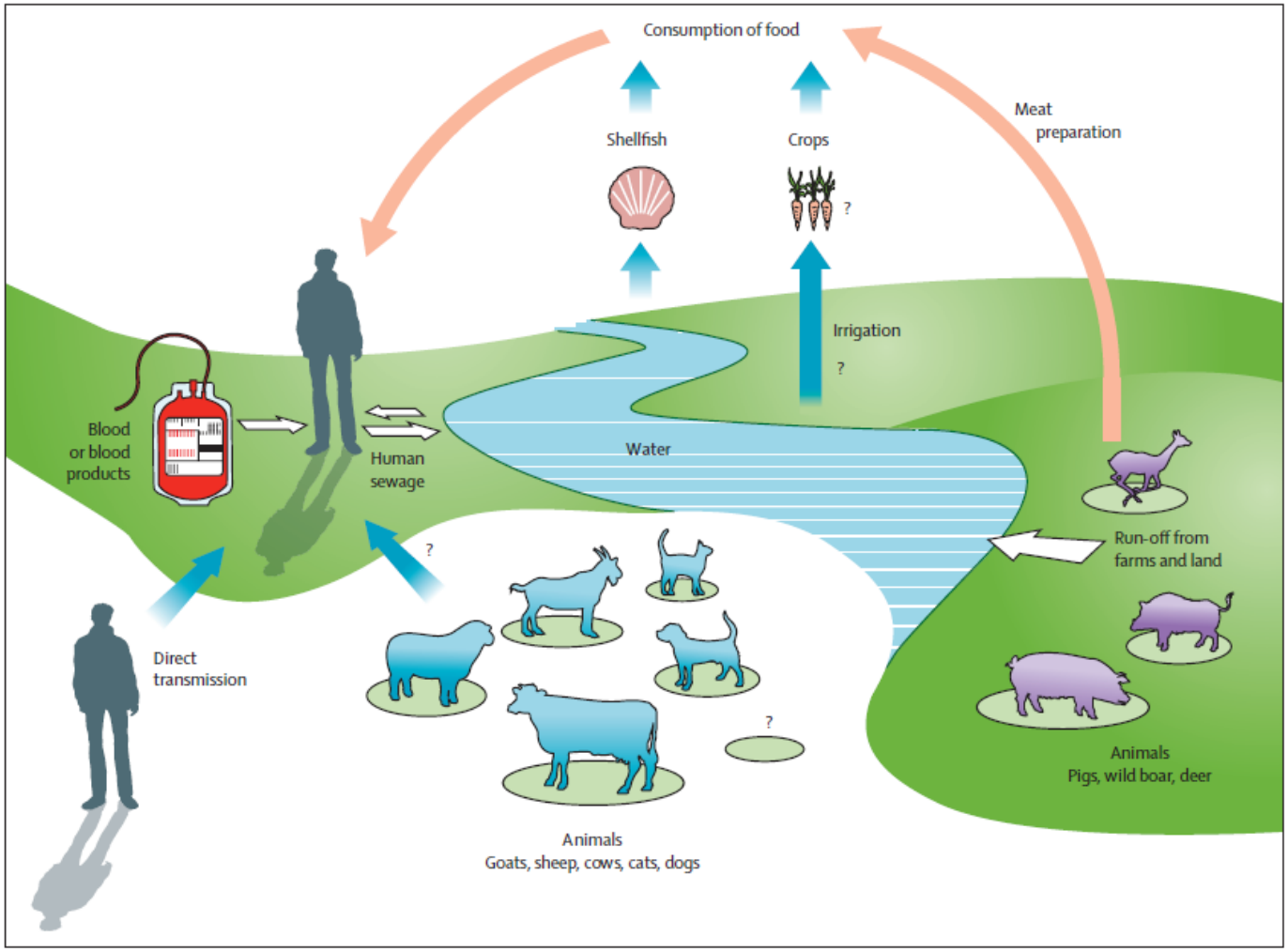
Genotype 3 and 4



Zoonosis

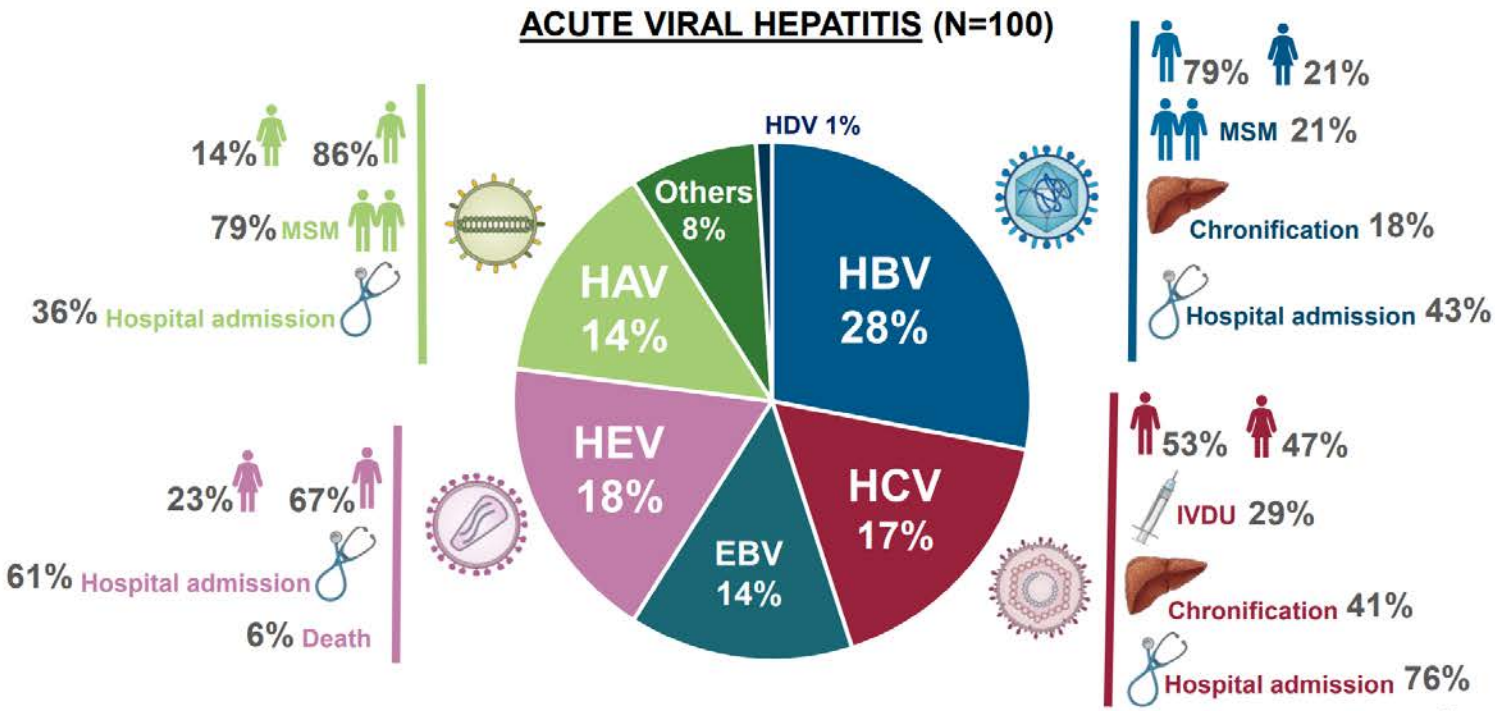


Routes of transmission of Hepatitis E



Kamar N, *et al.* Lancet 2012 30;379(9835):2477-2488

Acute Hepatitis E in Spain



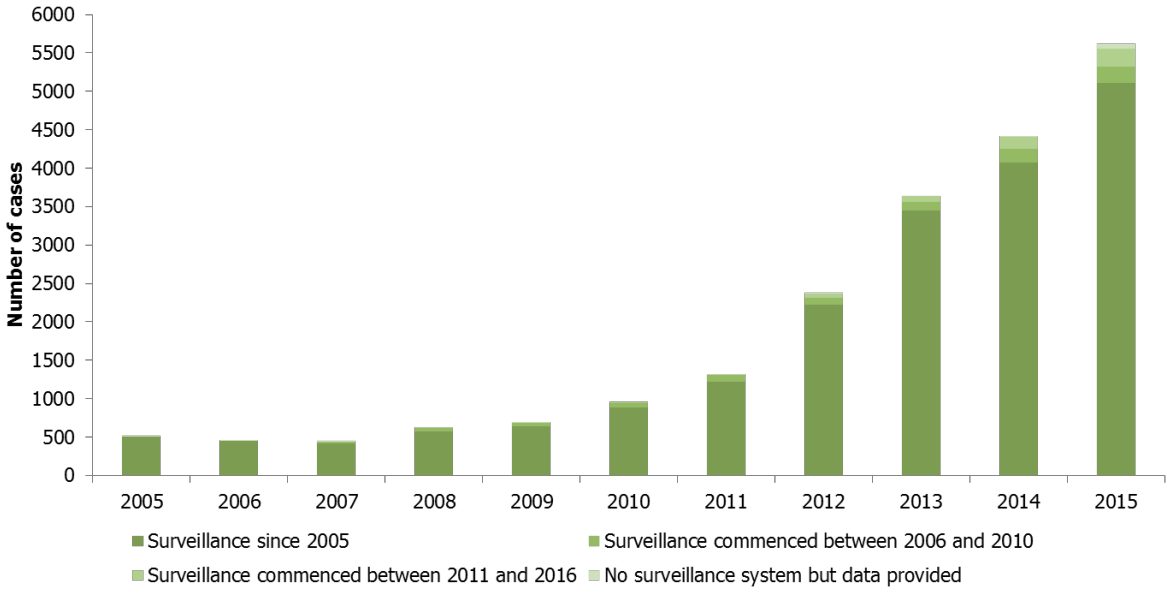
But the majority of acute hepatitis E are asymptomatic

LllanerasJ et al 2020

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

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



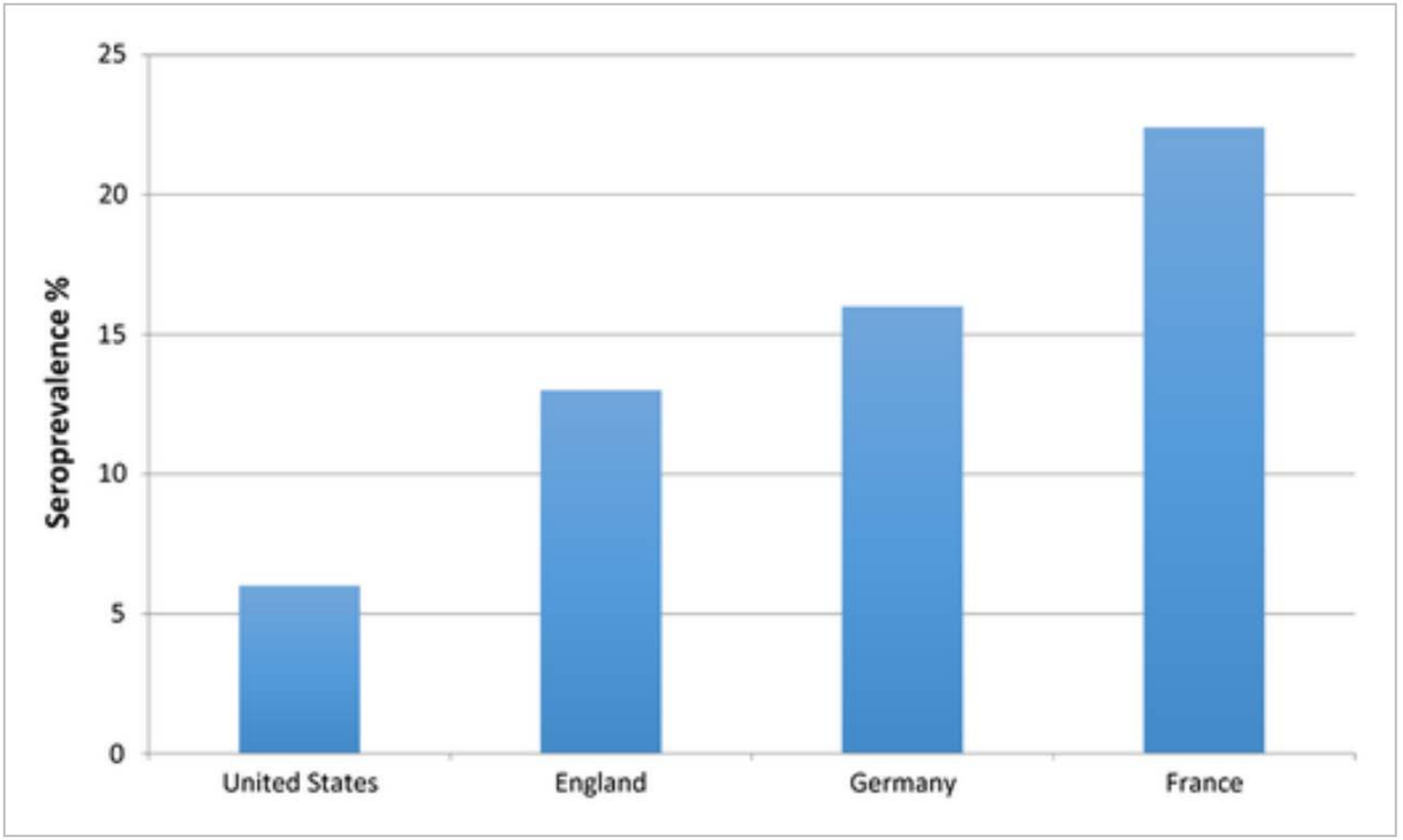
- 10-fold increase 2005–2015 due locally acquired infections
- 78% of cases reported from France, Germany and UK

* 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

Europe vs. US

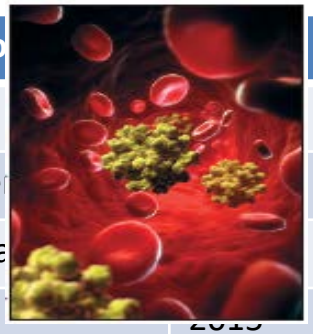

TEAR ACROSS
RESEALABLE 2 LB PACK
TEAR ACROSS
NOW! VALUE PACK
40 PATTIES
Banquet
Brown'N Serve
ORIGINAL
40 FULLY COOKED SAUSAGE PATTIES
MADE with PORK & TURKEY
MICROWAVABLE
KEEP FROZEN
NET WT 32 OZ (2 LB) 907g

HEV seroprevalence



Seth A et al. Clinical Liver Disease

HEV RNA prevalence in blood donors



The Lancet. January 2014

Should we screen blood products for hepatitis E virus RNA ?

Co				
USA				
Nethe				
Germa				
Spain	2013	Sauleda	9998	1/3332
Netherlands	2			1/1321

EASL Clinical Practice Guidelines on hepatitis E virus infection ☆

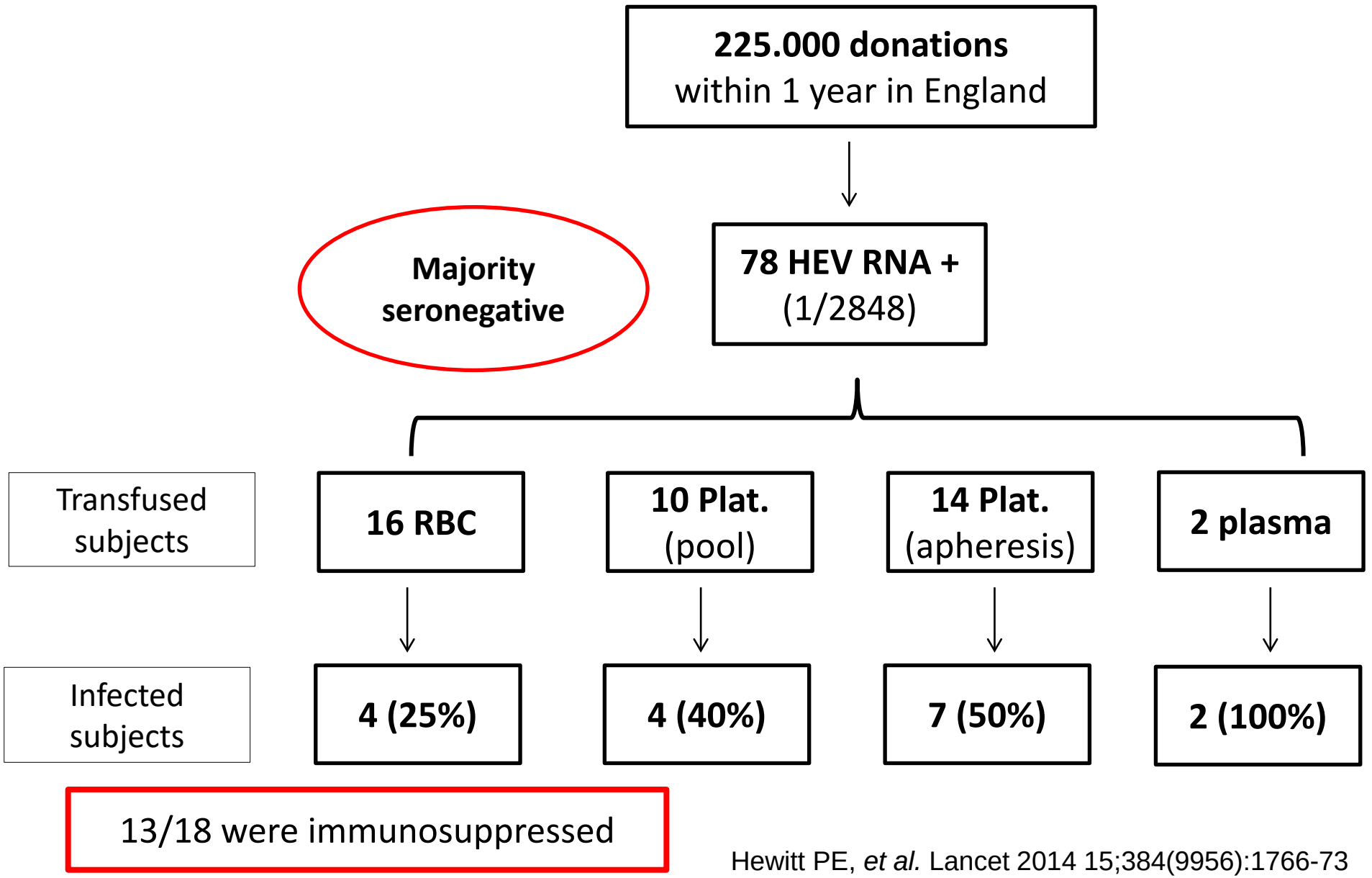
European Association for the Study of the Liver *

Recommendations

- Patients with abnormal LFTs after receiving blood products should be tested for HEV. **(A1)**
- 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)**

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.

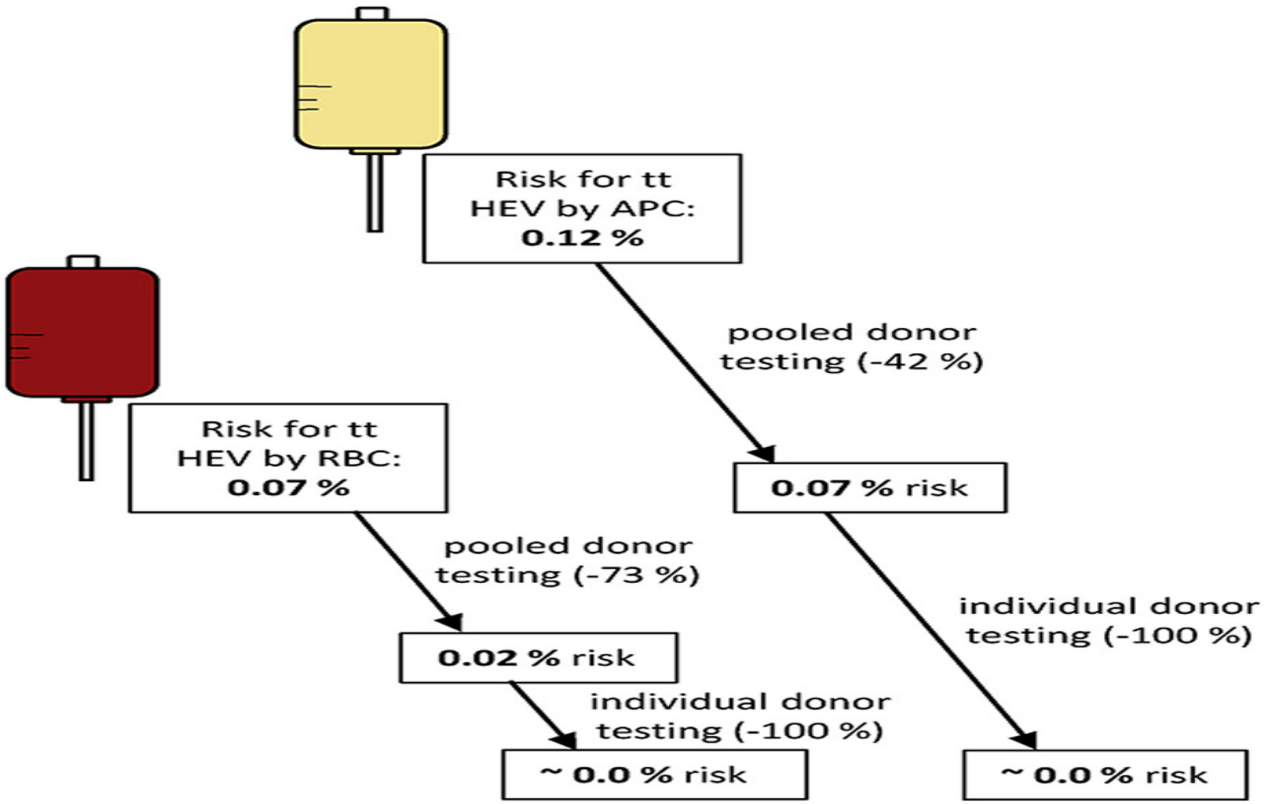
Hepatitis E in blood products



Hewitt PE, *et al.* Lancet 2014 15;384(9956):1766-73

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

Cordes A et al. J Hepatol 2021

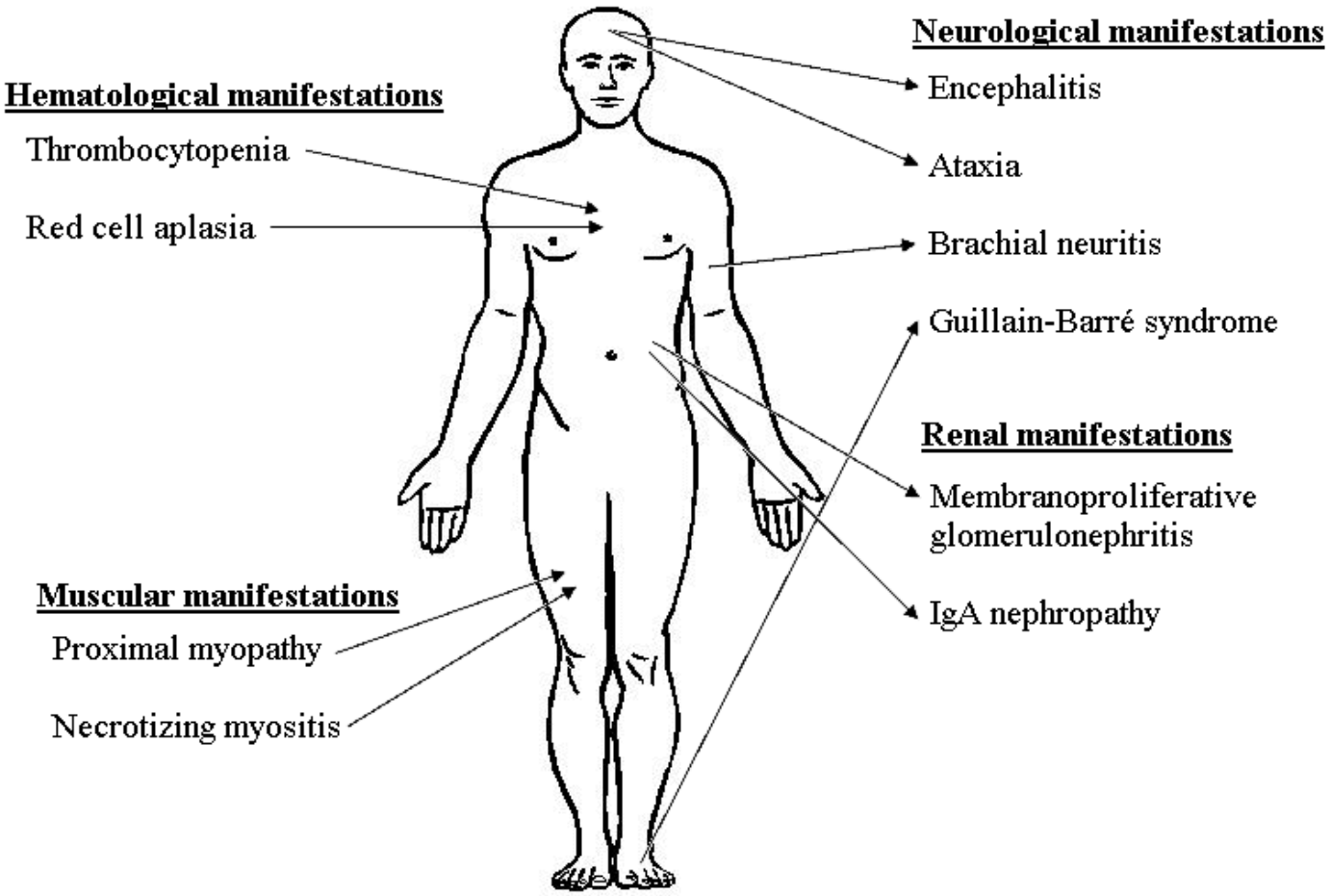
HEV and the blood supply

- 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
Blood donor screening • Blood donor services should screen blood donors for HEV by NAT, informed by local risk assessment and cost-effectiveness studies	A	1

EASL CPG HEV. J Hepatol 2018;doi: 10.1016/j.jhep.2018.03.005 [Epub ahead of print]

Extrahepatic manifestations of HEV

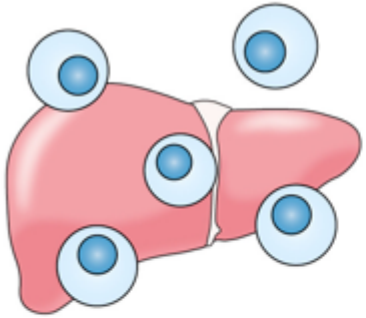


Neurologic manifestations in 200 acute hepatitis E cases (French National Reference Center)

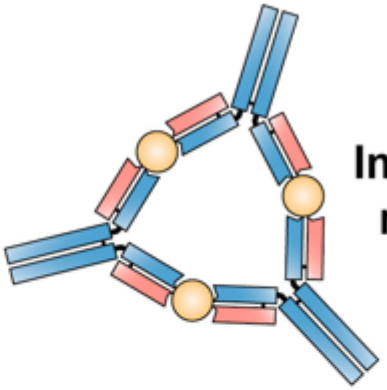
	Immuno Competent N=137	Immuno compromised N=63
Neurological symptoms	**31 (22.6%)**	**2 (3.2%)**
Neuropathic pain	13 (42%)	1 (50%)
Painless sensory disorders	8 (26%)	1 (50%)
Neuralgic amyotrophy	6 (19%)	0 (0%)
Guillain Barre syndrome	1 (3%)	0 (0%)
Meningitis	1 (3%)	0 (0%)
Diplopia	1 (3%)	0 (0%)

Abravanel F, *et al.* J Infect. 2018;77(3):220-226

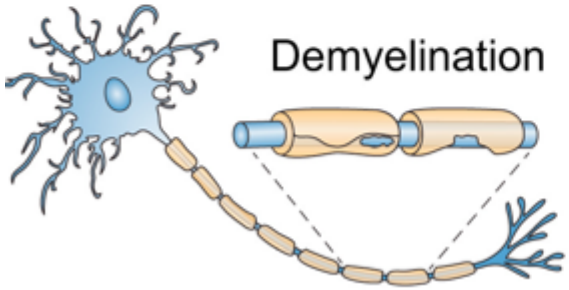
Pathogenesis



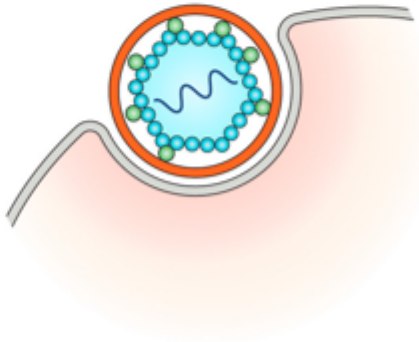
Immune cell-mediated injury



Immune complex-mediated injury

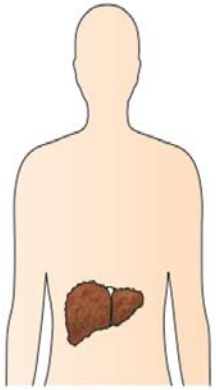


Molecular mimicry

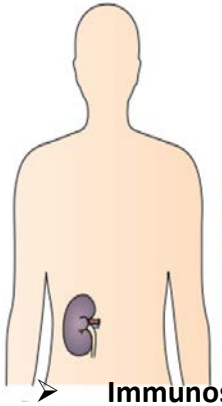


Direct toxicity

Hepatitis E. Risk Factors for complications

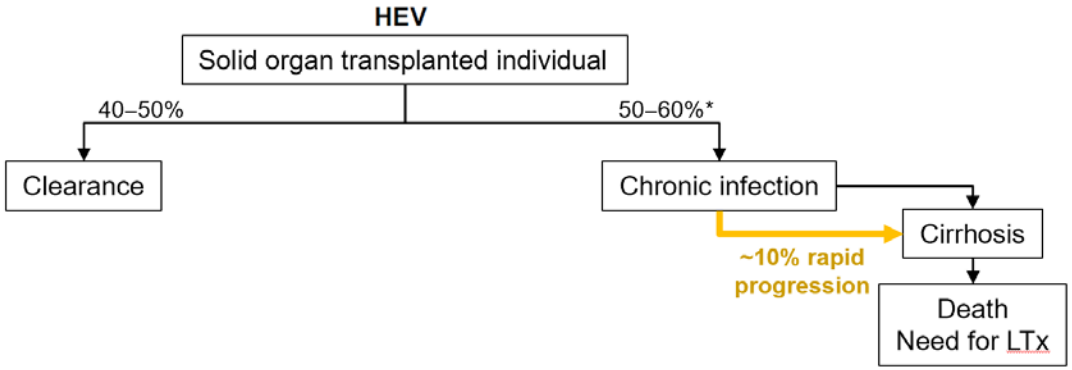


Cirrhosis



Organ transplantation

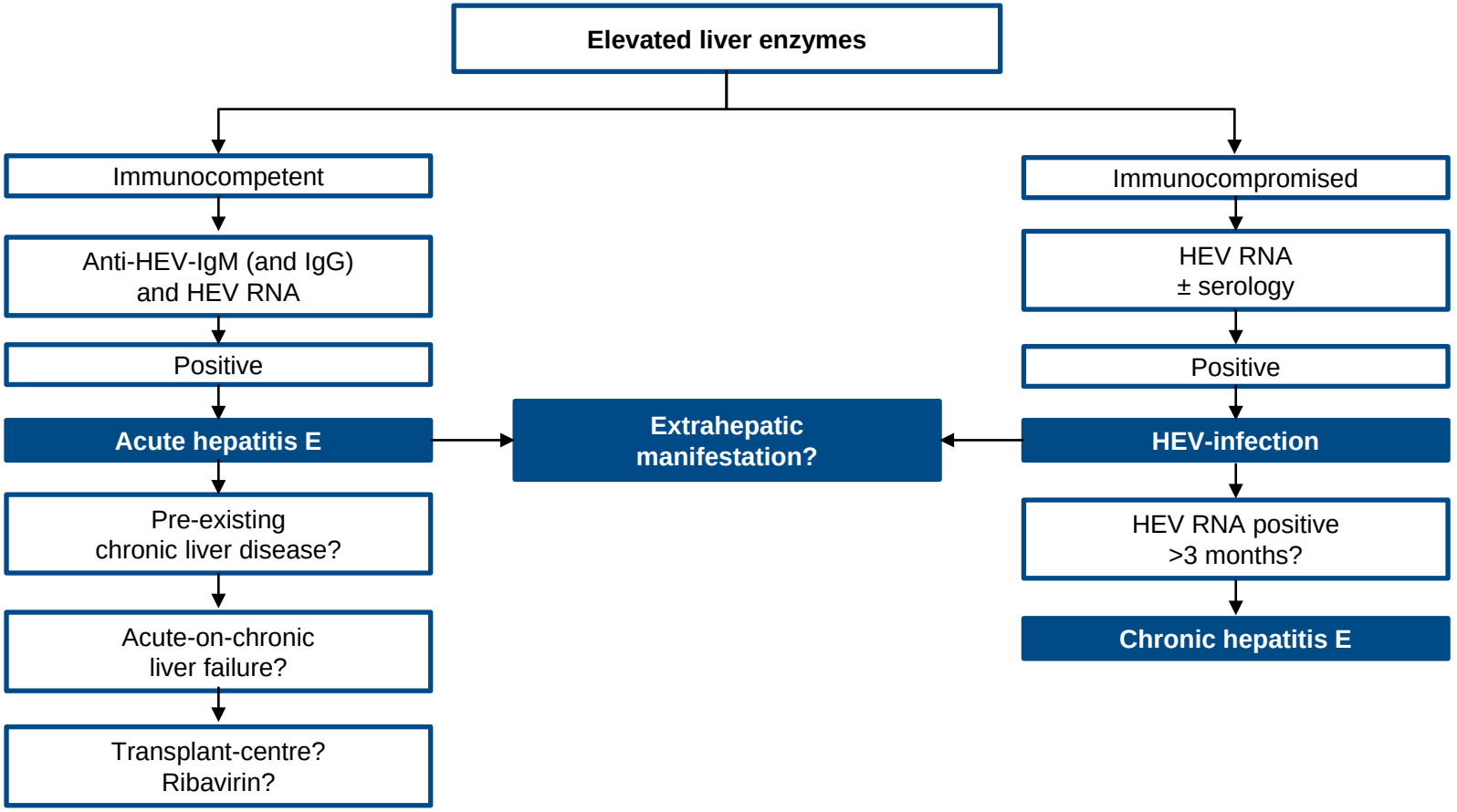
Acute-on-chronic liver failure



- **Immunosuppresion**
  - **HIV infection**
  - **Haematological neoplasm and chemotherapy**
  - **Immunosuppressive therapy**

EASL guidelines hepatitis E
Behrendt P, et al. J Hepatol 2014;61:1418–29

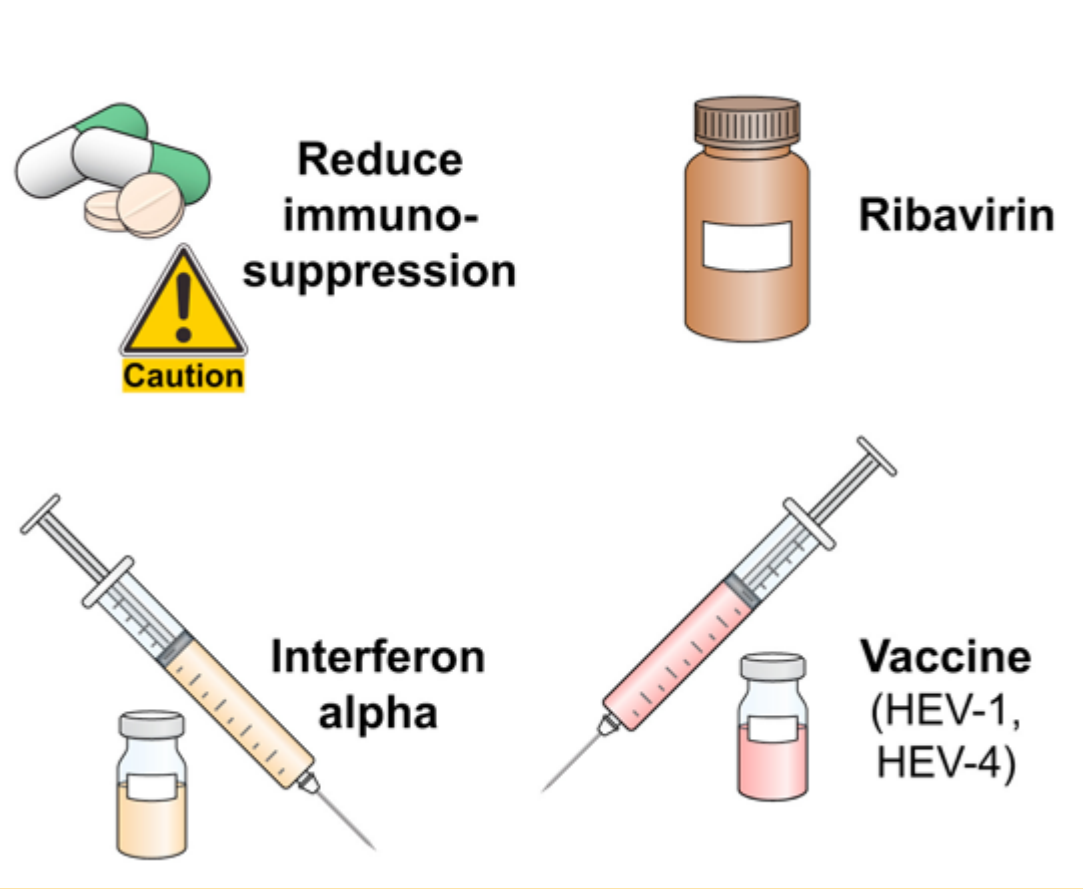
Diagnostic algorithm for HEV infection



Serology and NAT testing are best used in combination, as a negative PCR does not exclude acute infection; serology is sometimes negative in immunosuppressed patients with chronic infection

EASL CPG HEV. J Hepatol 2018;doi: 10.1016/j.jhep.2018.03.005 [Epub ahead of print]

Therapy and Prevention



Treatment of acute HEV infection

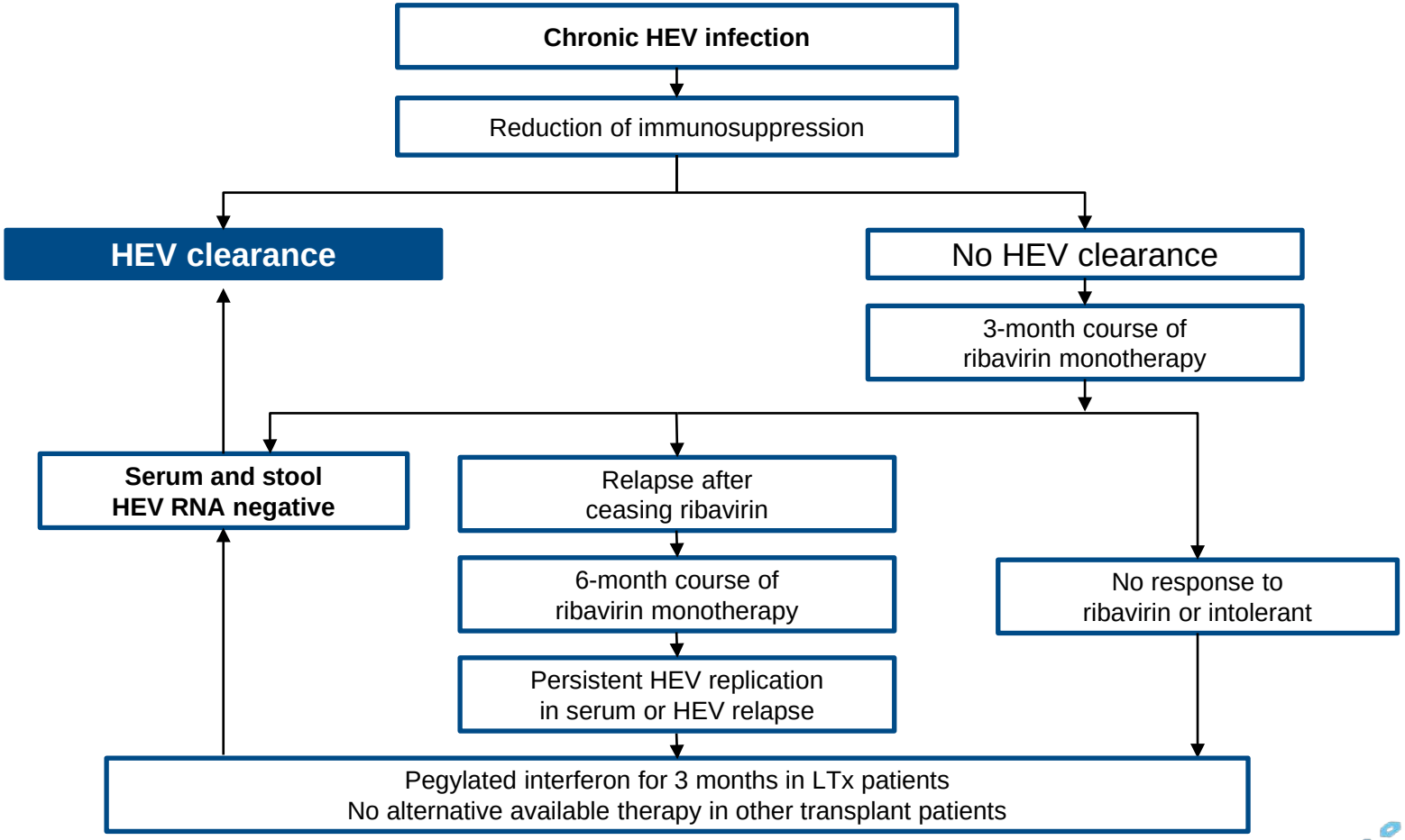
- Acute HEV infection does not usually require antiviral therapy*
- Most cases of HEV infection are spontaneously cleared
  - Some patients may progress to liver failure
  - Ribavirin
    - Early therapy of acute HEV may shorten course of disease and reduce overall morbidity

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

*Grade of evidence A

EASL CPG HEV. J Hepatol 2018;doi: 10.1016/j.jhep.2018.03.005 [Epub ahead of print]

Management of patients not clearing HEV infection



EASL CPG HEV. J Hepatol 2018;doi: 10.1016/j.jhep.2018.03.005 [Epub ahead of print]

Prevention of HEV infection

- 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 ≥70°C	B	2

EASL CPG HEV. J Hepatol 2018;doi: 10.1016/j.jhep.2018.03.005 [Epub ahead of print]

What kind of vaccine is available?

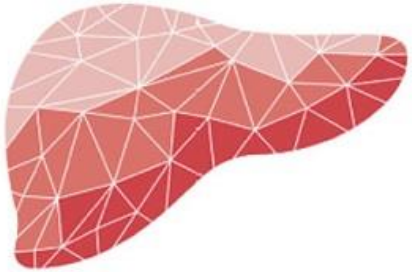
- Vaccine against HEV (HEV 239 vaccine, Hecolin®), based on a genotype 1 HEV strain, has been licensed in China in December 2011 for use in healthy adults aged ≥16 years
- 3 doses schedule at 0, 1 and 6 months
-
- Phase III randomized trial (> 100 000 participants16- 65 years old), the primary (per protocol) analysis revealed 100% vaccine efficacy (95% CI: 72.1%–100)
- Extension of Phase III trial for 4.5 years. Efficacy of 93% (95% CI: 78.6%-97.9%) among participants having received all three doses
- Expected cross protection against other genotypes

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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