An idea about hepatitis E

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HepatitisE

Mortality **25%**

HEV misdiagnosed as Drug-induced liver injury (DILI)

13% of patients with DILI have HEV3

Dalton et al AP The rap 2007

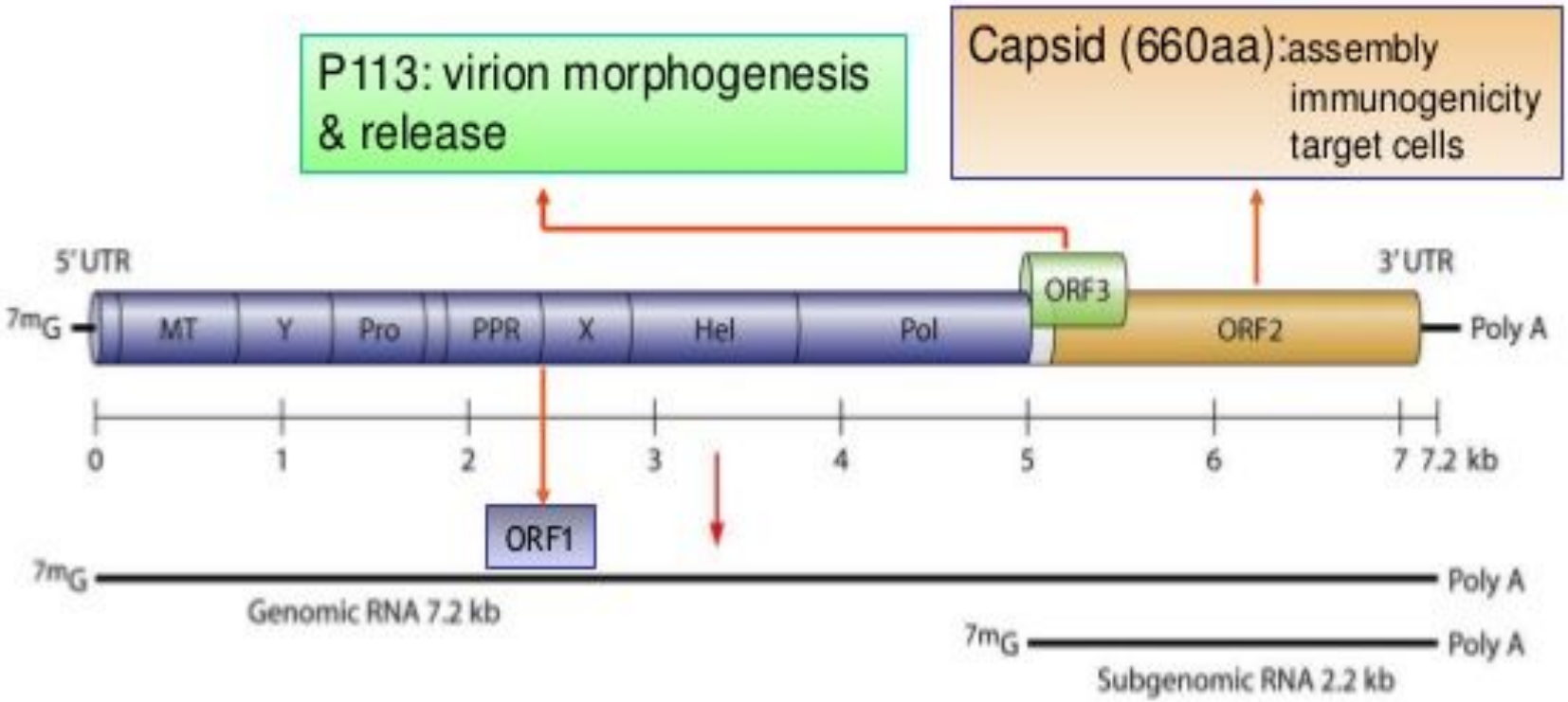
- Diagnosis of DILI not secure without testing for HEV

Hepatitis E: A True Story

- In 1983, Dr. Balayan was investigating an outbreak of non-A, non-B hepatitis among Soviet soldiers in Afghanistan. Though he wanted to bring samples back to his Moscow laboratory, he lacked refrigeration. So he made a shake of yogurt and an infected patient's stool, drank it, went back to Moscow, and waited until a few weeks later when he developed symptoms of hepatitis.
- He then started collecting and analyzing his own samples. In these he found a new virus, similar to HAV by EM, that produced liver injury in laboratory animals. Dr. Balayan already had antibodies against the HAV which did not protect him from the infection.

Balayan MS, et al. *Intervirology* 1983;20:23–31.

Hepatitis E Virus Genome



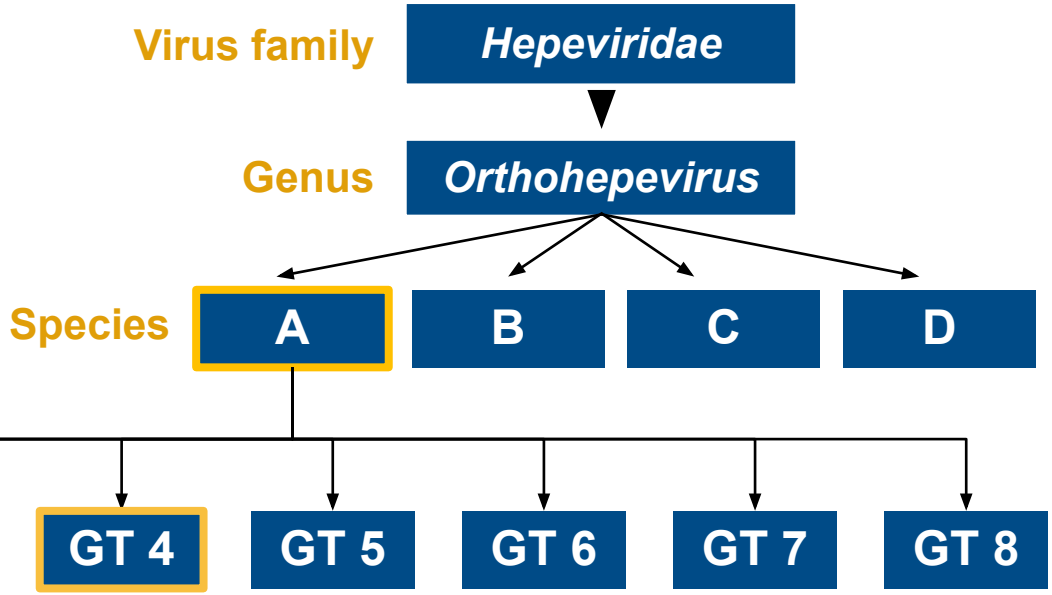
Kamar N et al. *Clin. Microbiol. Rev.* 2014;27:116-138

Virology of HEV

Hepeviridae viruses infect mammals, birds and fish

Strains infecting humans belong to the *Orthohepevirus* genus, species A

Species A comprises **8 genotypes**



- Only infect humans
- **Faecal–oral spread** via contaminated water
- Large **outbreaks**
- Brief, **self-limiting**
- Never chronic
- High mortality in **pregnancy** (25%)

- **Endemic** in animal species; eg, pigs and wild boar
- **Zoonotic** infections in humans
- **High-income countries**
- China: GT 4 most common
- S. America: GT 3 only

- Have only been reported in wild boar

- GT 7 identified in patient regularly consuming camel meat and milk
- Have since been identified in camels

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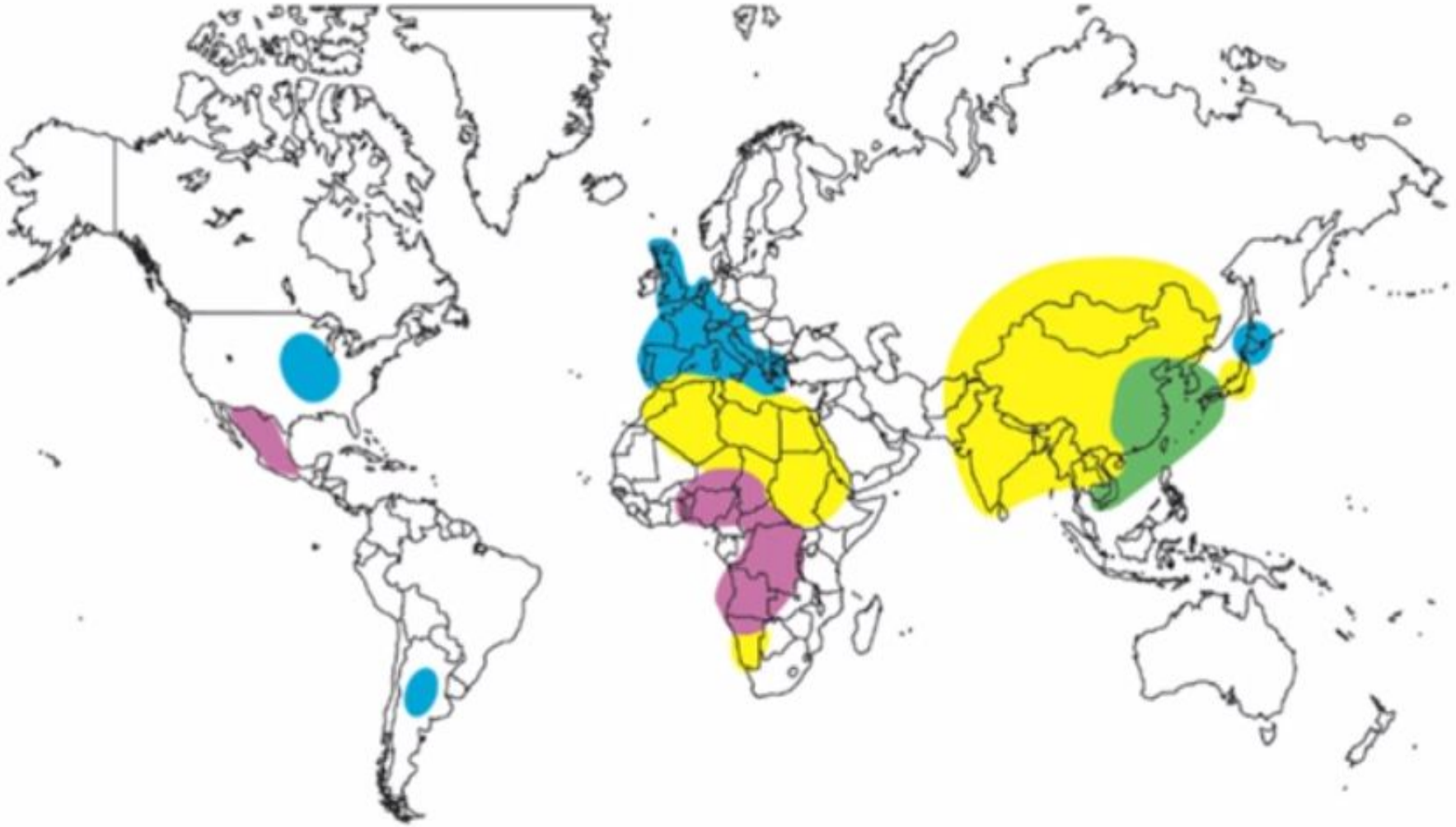
EASL CPG HEV. J Hepatol 2018;doi: 10.1016/j.jhep.2018.03.005 [Epub ahead of print]

HEV genotypes in humans: distribution

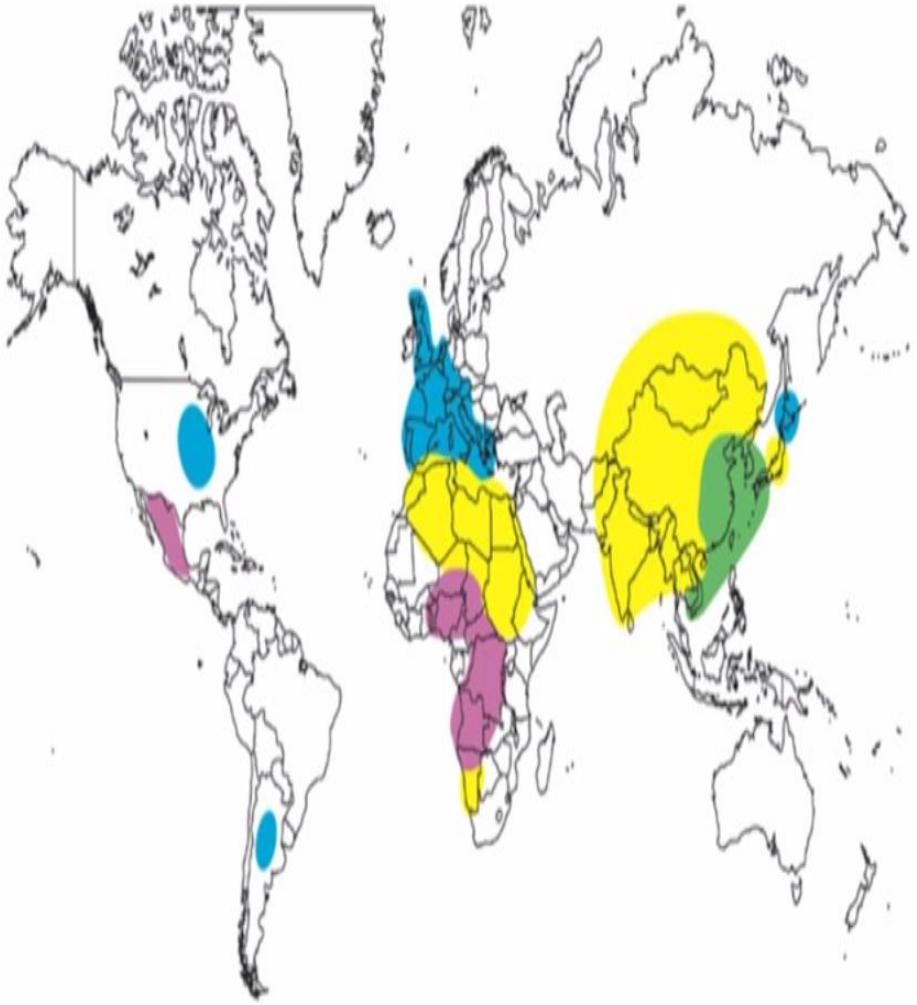


Purcell. J Hepatol 2011; 48: 494.

HEV genotypes in swine: distribution

Purcell. J Hepatol 2011; 48: 494.

HEV genotypes in humans: distribution

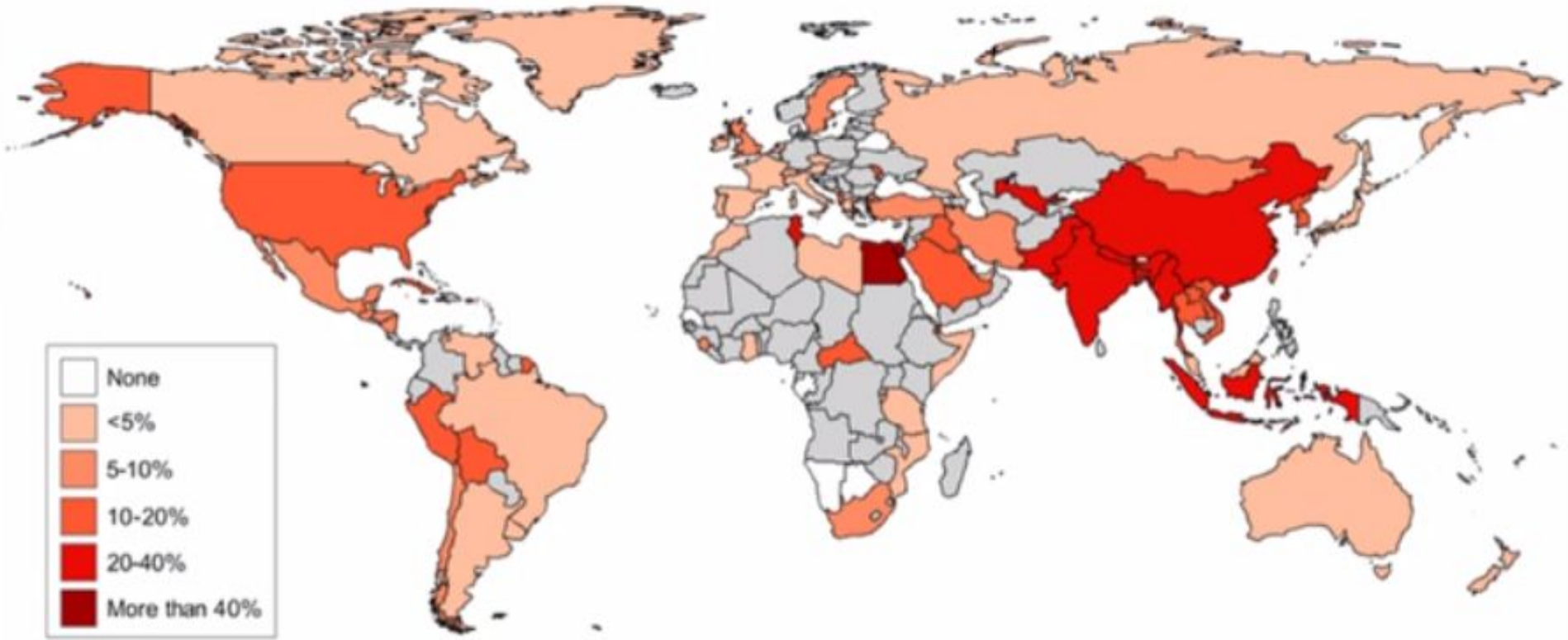


Purcell. J Hepatol 2011; 48: 494. **Genotype:** 1 2 3 4

HEV genotypes in swine: distribution

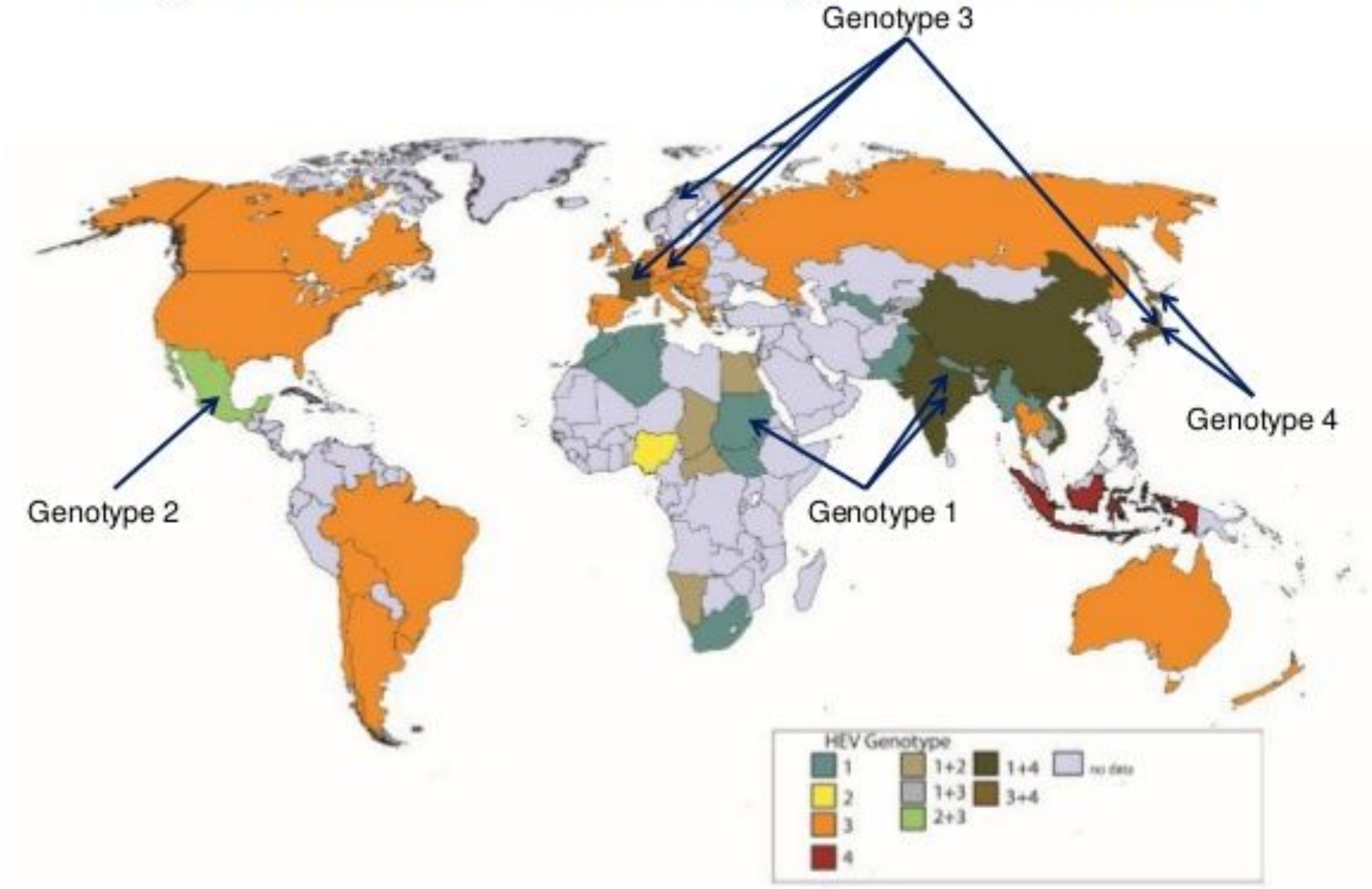
Purcell. J Hepatol 2011; 48: 494. **Genotype:** 3 4

Anti-HEV antibodies: Seroprevalence



Aggarwal R. http://whqlibdoc.who.int/hq/2010/WHO_IVB_10.14_eng.pdf

Origin of WHO HEV Genotype Panel Strains

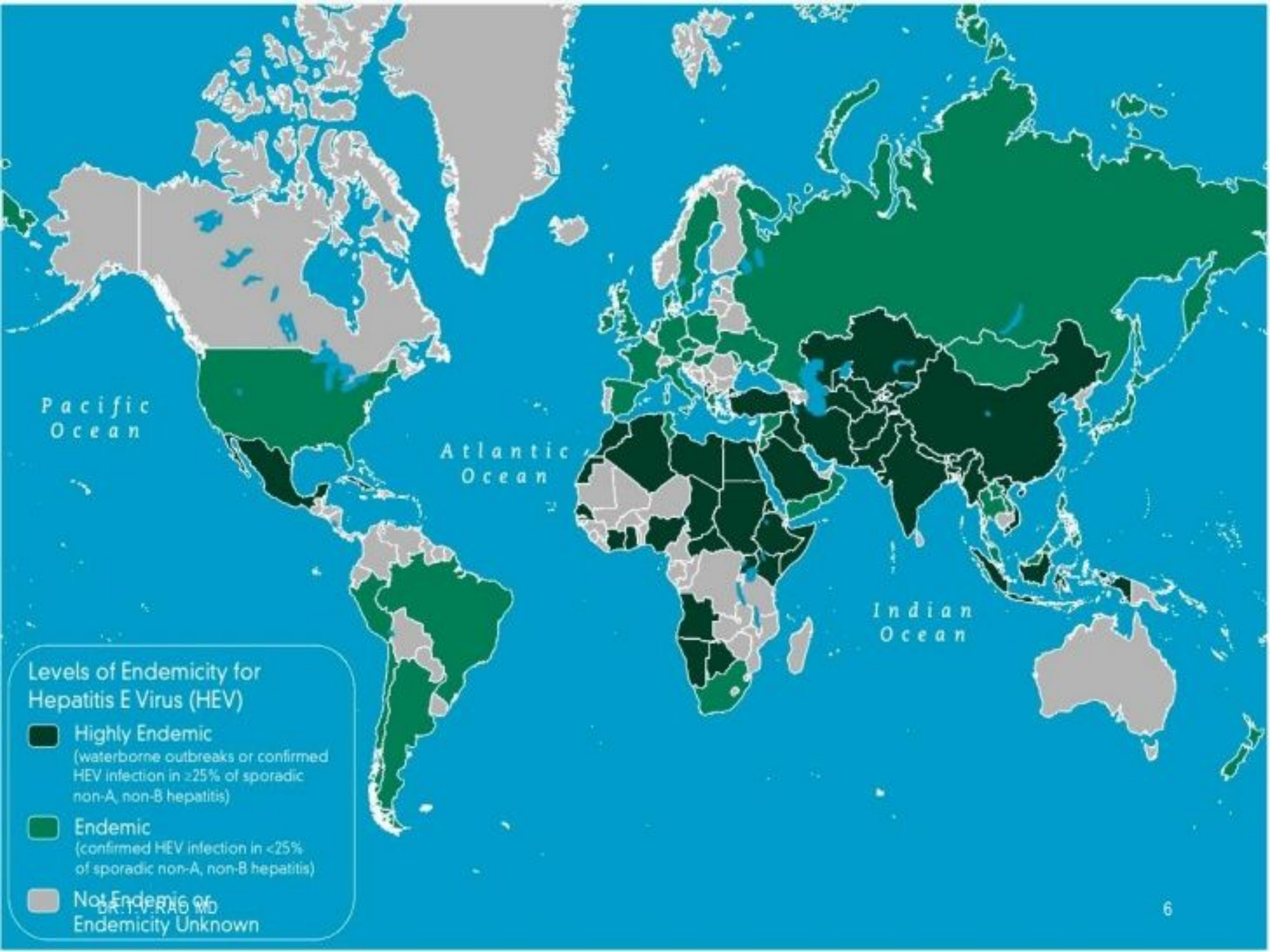


Worldwide prevalence of HEV

Endemic regions of hepatitis E

where >25% of acute viral hepatitis is due to HEV

Wedemeyer H et al. Gastroenterology 2012 ; 142 : 1388 – 1397.


Pacific Ocean
Atlantic Ocean
Indian Ocean
Levels of Endemicity for Hepatitis E Virus (HEV)
Highly Endemic
(waterborne outbreaks or confirmed HEV infection in ≥25% of sporadic non-A, non-B hepatitis)
Endemic
(confirmed HEV infection in <25% of sporadic non-A, non-B hepatitis)
Not Endemic or Endemicity Unknown

WWHO2019

Key facts

Hepatitis E is a liver disease caused by infection with a virus known .as hepatitis E virus (HEV)

Every year, there are an *estimated 20 million HEV* infections worldwide, leading to an estimated 3.3 million symptomatic cases of .hepatitis E (1)

WHO estimates that hepatitis E caused approximately 44 000 deaths .in 2015 (accounting for 3.3% of the mortality due to viral hepatitis)

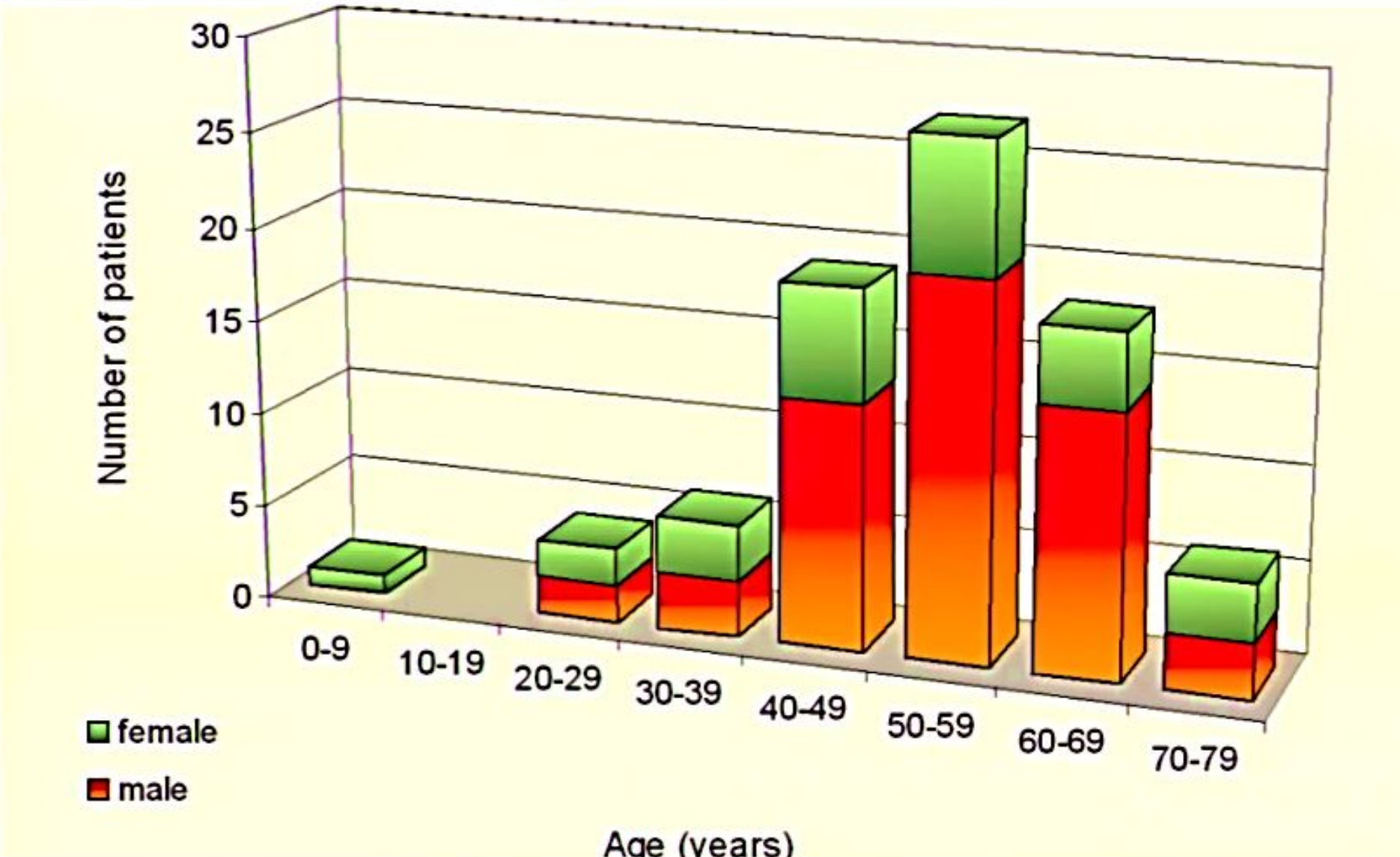
The virus is transmitted via the fecal-oral route, principally via .contaminated water

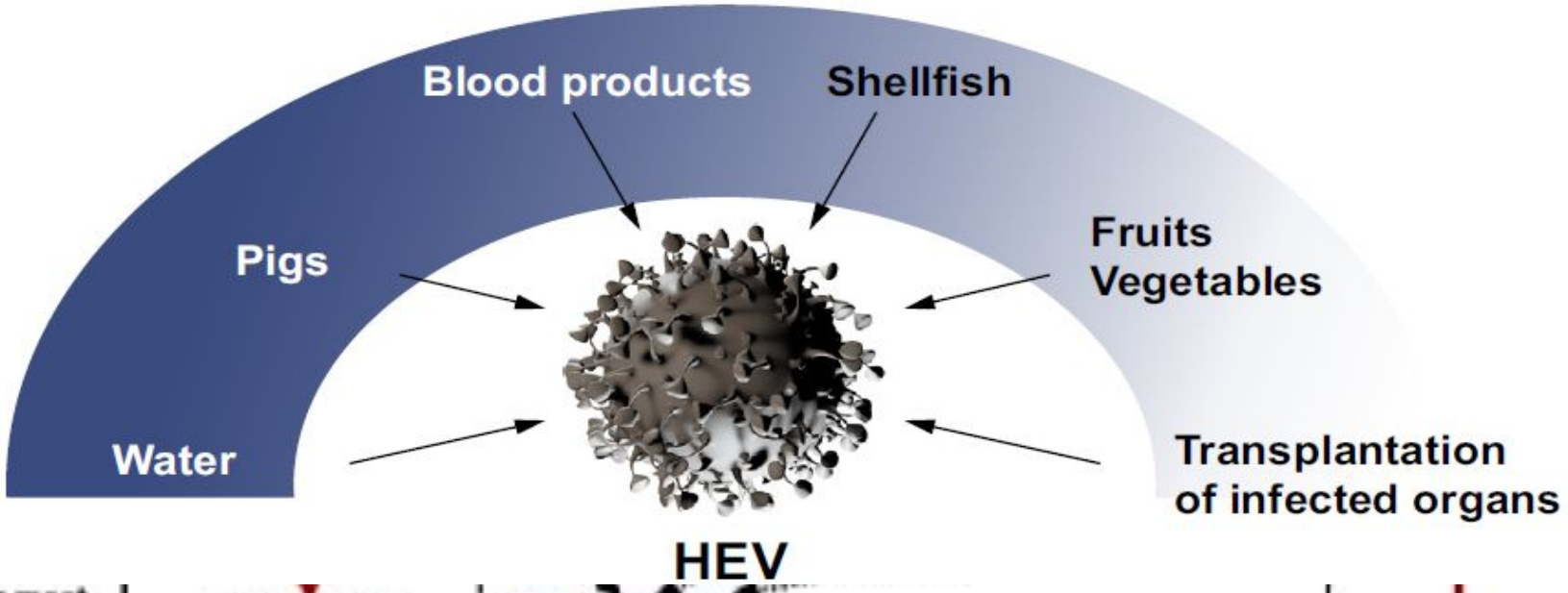
Hepatitis E is found worldwide, but the disease is most common in .East and South Asia

A vaccine to prevent hepatitis E virus infection has been developed .and is licensed in China, but is not yet available elsewhere

Age and sex distribution Acute HEV

H.Zaaijer et al, data submitted.





Sika D

Ingesti
underc
Sika deer meat

- Waterborne : genotypes 1 & 2 in developing countries
  - ➔ Outbreaks and sporadic cases

- Zoonotic : genotypes 3, 4 & 7
  - ➔ Autochtonous infection through consumption of un or under cooked meat

Genotype 4 in milk in China

Blood
Transfusion

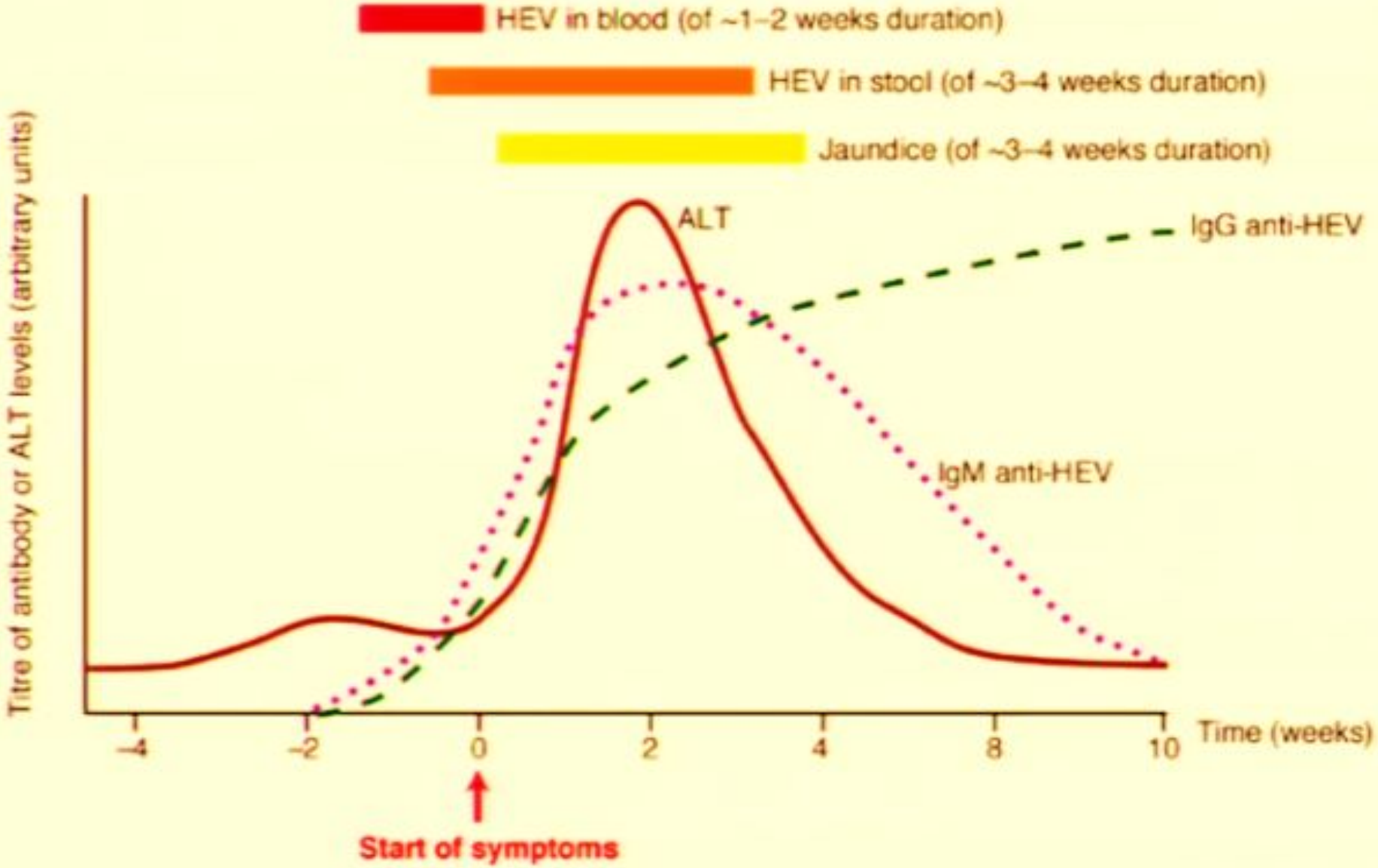
Other mammals

HEV infections according to genotype

Characteristic	Genotypes 1 and 2 Epidemic	Genotypes 3 and 4 Autochthonous
Distribution	Developing countries	Developing & developed countries
Pattern of spread	Epidemic & sporadic	Sporadic
Species	Human	Swine, human
Mode of spread	Waterborne	Foodborne
Icteric illness	High	Low
Age	Adolescents & young	older
Se		
M		
Ex		
Ch		essed patients
Therapy	None known	Ribavirin, PEG-IFN
Prevention	Vaccine	Vaccine

Recommendations		
• **Travellers** with hepatitis returning **from areas endemic** for HEV GT 1 or 2 **should be tested** for HEV	A	1
• **Pregnant women** with HEV GT 1 or 2 **should be cared for in a high-dependency setting**, and transferred to a liver transplant unit if liver failure occurs	A	1

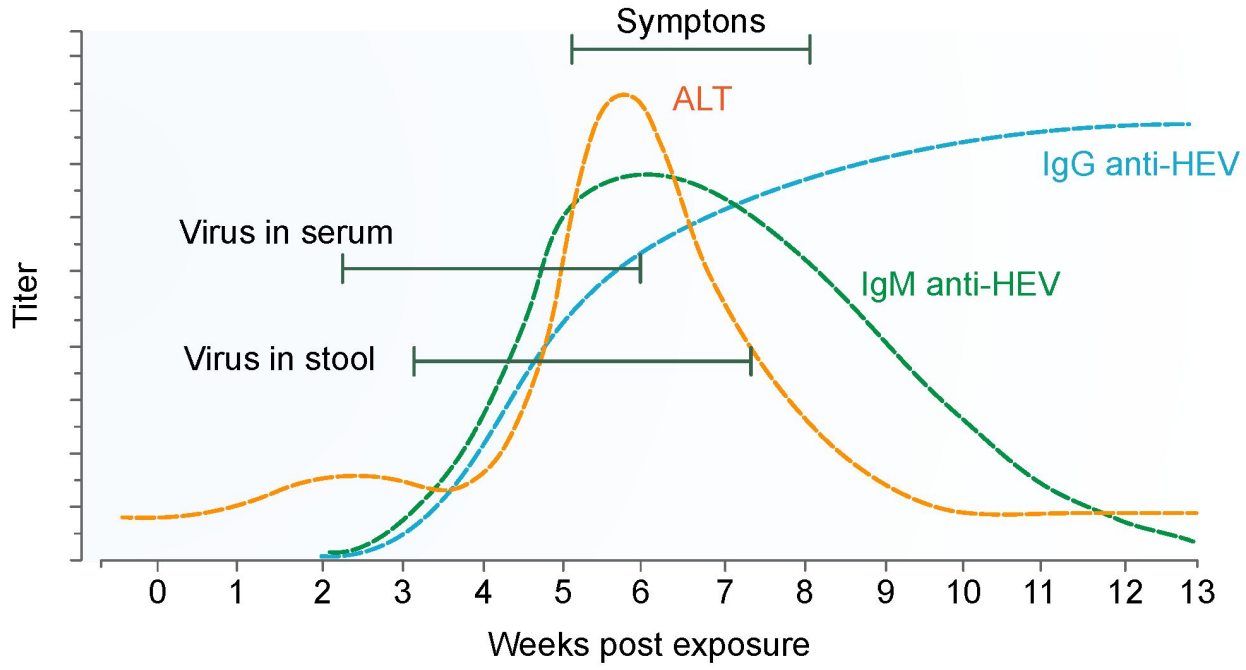
Hoofnagle JH et al. N Engl J Med 2012 ; 367 : 1237 – 44 .



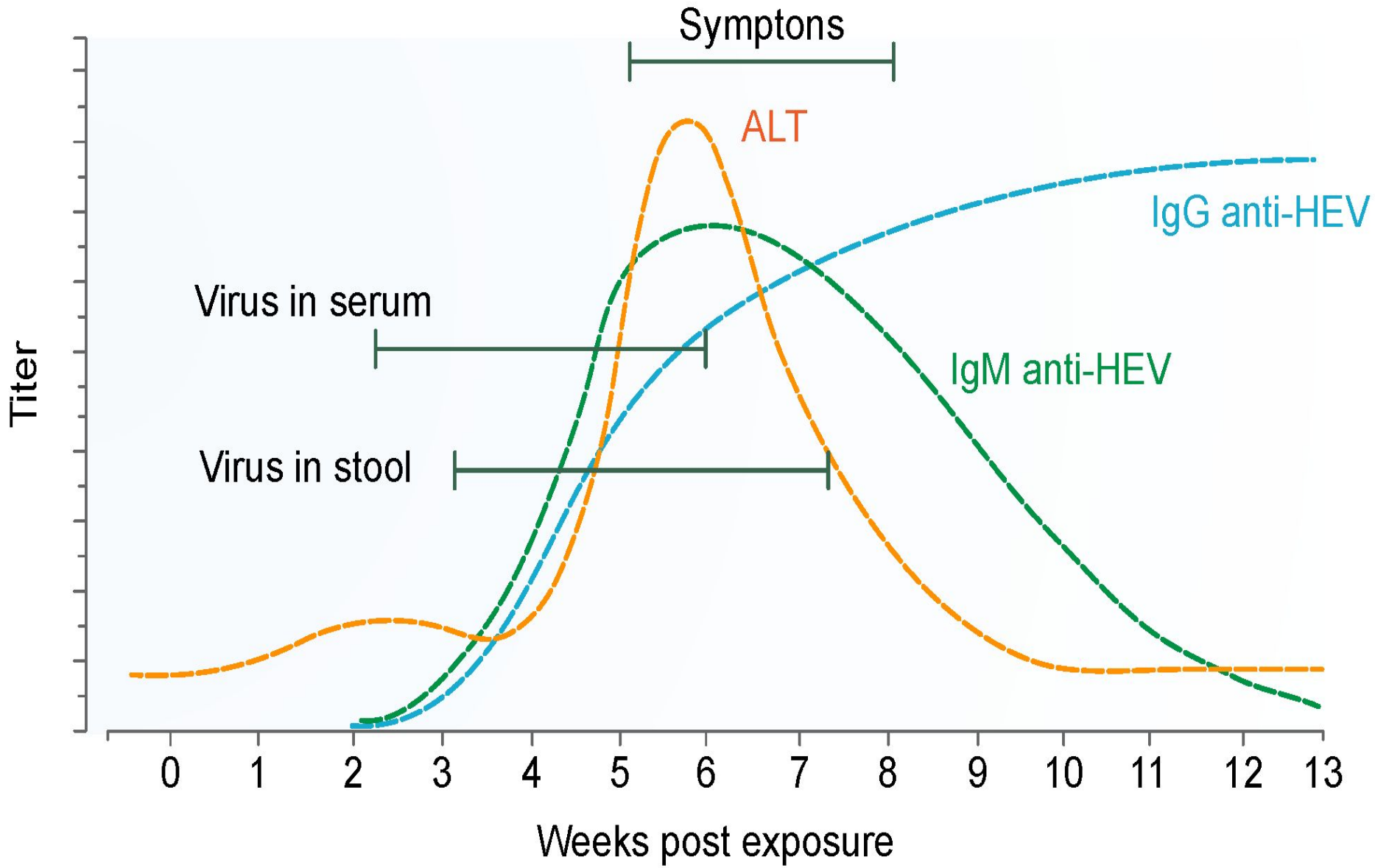
Time course of hepatitis E virus infection

Laboratory diagnosis of HEV infection

- Incubation period for HEV is ~15–60 days
  - HEV RNA is detected ~3 weeks post-infection in blood and stool
    - Shortly before onset of symptoms
- At clinical onset biochemical markers become elevated
  - First IgM followed by IgG



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


Symptons
ALT
IgG anti-HEV
Virus in serum
IgM anti-HEV
Virus in stool
Titer
0
1
2
3
4
5
6
7
8
9
10
11
12
13
Weeks post exposure

Animal HEV

- Discovered in 1997 ('swine' HEV)
- Ubiquitous among pigs ≥3 mo of age in midwestern US
- Found in all parts of the world
- Viremia, viral excretion, mild microscopic hepatitis, no clinical illness
- Found in several mammalian species e.g. pigs, deer, wild boars, sheep
- Genotype 3/4

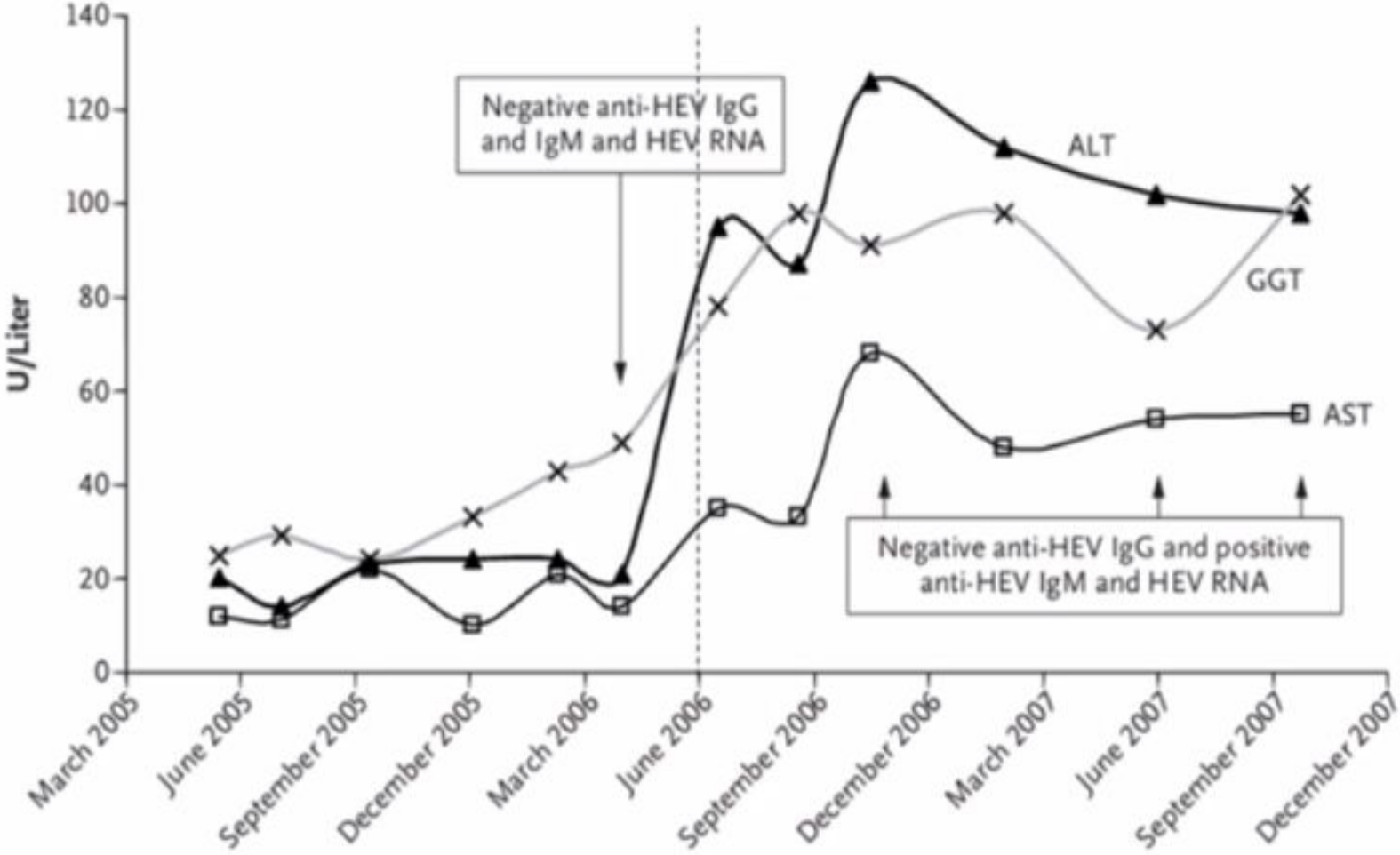
Meng et al. Proc Natl Acad Sci USA 1997;94:9860-5

VHE NRC networks 2002-2015

Nb patients tested	209	155	233	327	583	1012	1700	2150	2549	3429	17566	35416	44382	67000

➔ *A less and less neglected virus*

Chronic hepatitis E



Gerolami R et al. New Engl J Med 2008; 358: 859-60.

Hepatitis E : The new threat ?

Marc Bourliere , MD

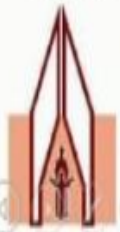
Hôpital Saint Joseph

Marseille, France

UEG week

15-19 October 2016

Vienna



Clinical aspects: chronic infection

- Immunosuppressed patients can fail to clear HEV infection
  - Progression to chronic hepatitis*
- Immunosuppressed groups include:
  - Solid organ transplant recipients
    - ~50–66% of HEV-infected organ transplant recipients develop chronic hepatitis
  - Patients with haematological disorders
  - Individuals living with HIV
  - Patients with rheumatic disorders receiving heavy immunosuppression
- Most patients are asymptomatic and present with mild and persistent LFT abnormalities

Chronic HEV has mainly been described in the solid organ transplant setting

Recommendations	Grade of evidence	Grade of recommendation
Should test for HEV in: • All immunosuppressed patients with unexplained abnormal LFTs	A	1

*Persistence of HEV replication for 3 months. In rare cases, spontaneous clearance has been observed between 3 and 6 months

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

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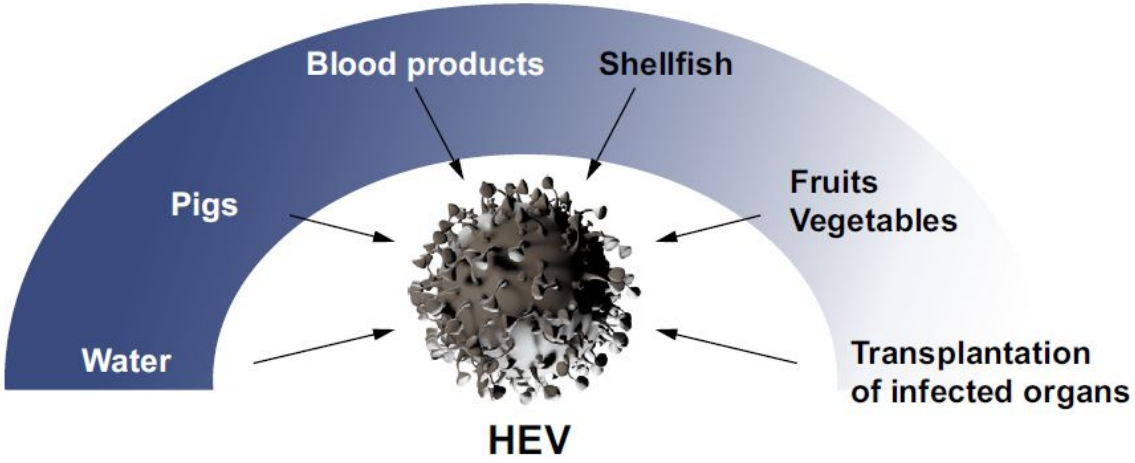
Transmission and disease progression in transplanted individuals



Solid organ transplanted individual

40−50%

50−60%*

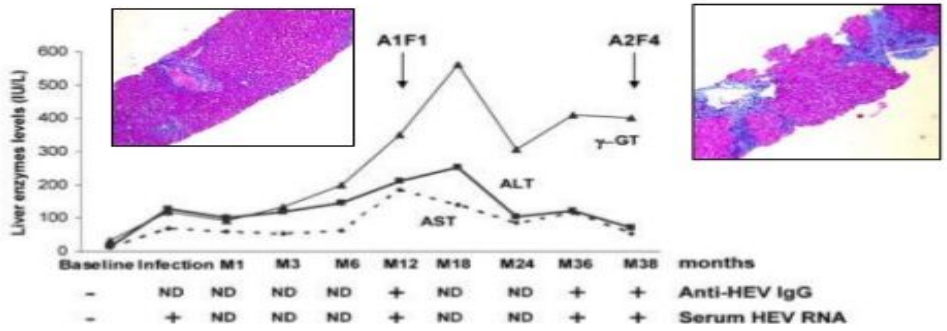
Rapid Progression of Hepatitis E to Cirrhosis after Solid Organ Transplantation

hronic infection

~10% rapid progression

Cirrhosis

Death
Need for LTx



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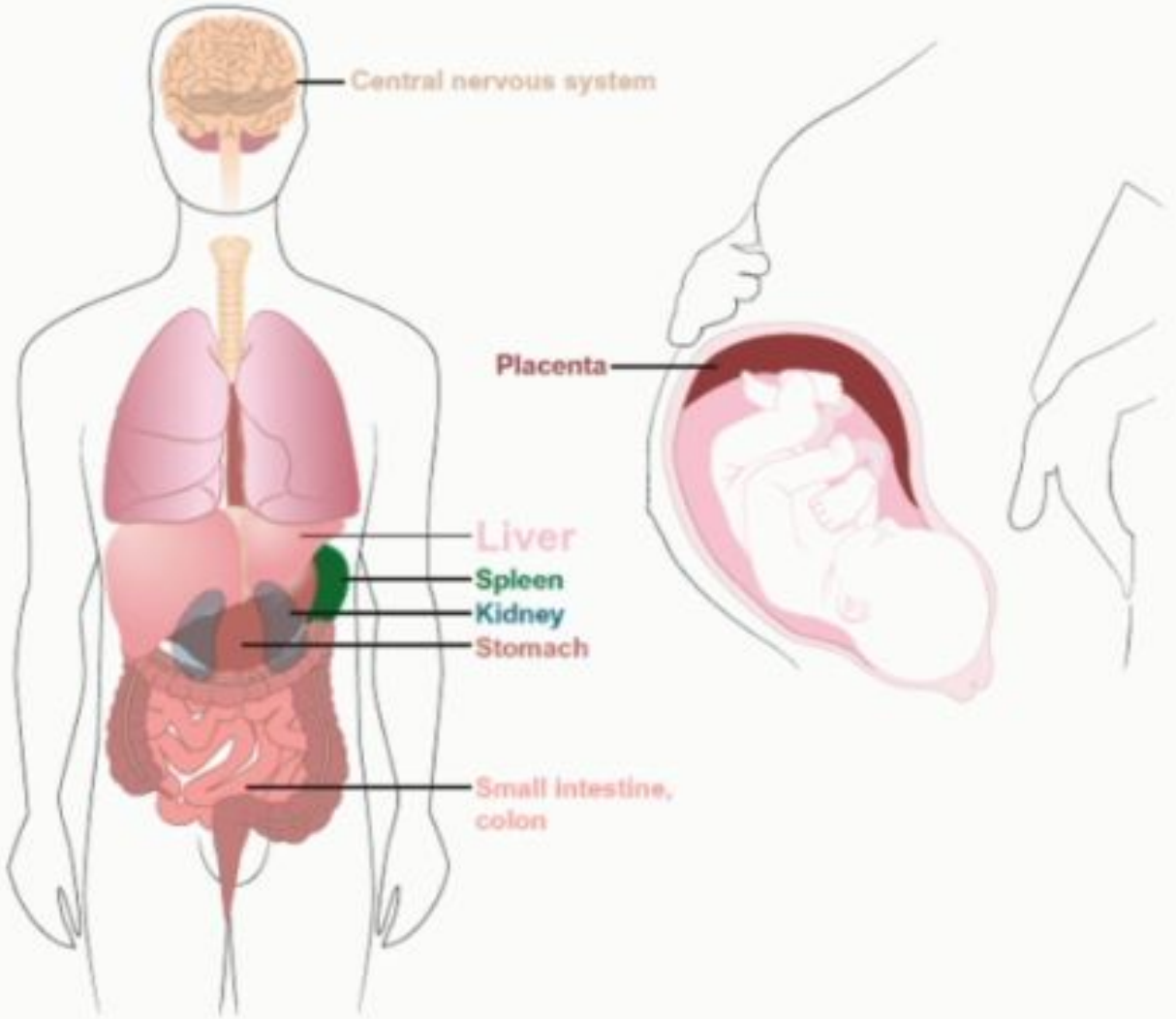
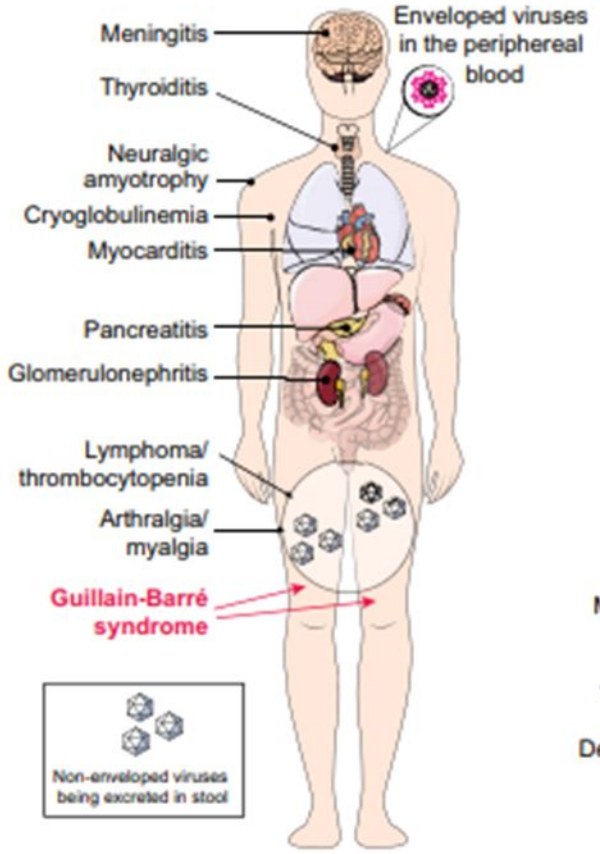
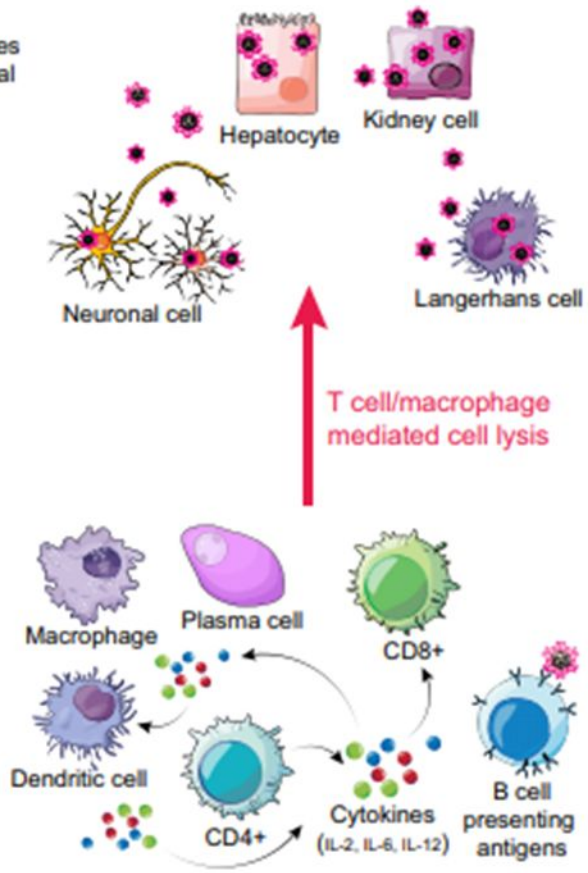
Reported sites of HEV replication



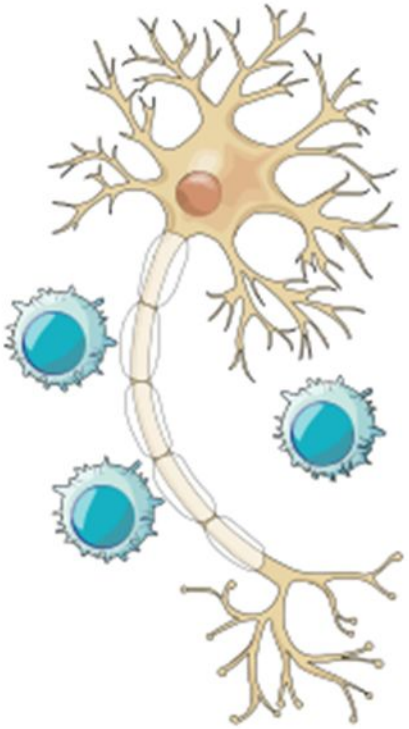
Debing Y et al. J Hepatol 2016; 65: 200-212



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



Possible mechanisms of extrahepatic symptoms in the context of HEV replication



Possible mechanisms of neurological manifestations in the absence of HEV replication

Extrahepatic manifestations

- Extrahepatic manifestations of HEV are increasingly recognized

Organ system	Clinical syndrome	Notes
Neurological	• Neuralgic amyotrophy* • Guillain–Barré syndrome* • Meningoencephalitis* • Mononeuritis multiplex • Myositis • Bell's palsy, vestibular neuritis and peripheral neuropathy	• ~150 cases of neurological injury (in HEV GT 3); mainly Europe • Most (>90%) cases in the immunocompetent **Most important**
Renal*	• Membranoproliferative and membranous glomerulonephritis • IgA nephropathy	• Mainly immunosuppressed GT 3-infected patients • Renal function improves and proteinuria levels decrease following HEV clearance
Haematological	• Thrombocytopenia • Monoclonal immunoglobulin • Cryoglobulinaemia • Aplastic anaemia† • Haemolytic anaemia†	• Mild thrombocytopenia is common; occasionally severe • Reported in 25% of cases of acute HEV in UK study • Occurs mainly in association with renal disease
Other	• Acute pancreatitis • Arthritis† • Myocarditis† • Autoimmune thyroiditis†	• 55 cases worldwide. HEV GT 1 only; usually mild

*There is good evidence to support a causal role for HEV and these associated conditions. For the other extrahepatic manifestations, causality remains to be established; †Case reports only

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

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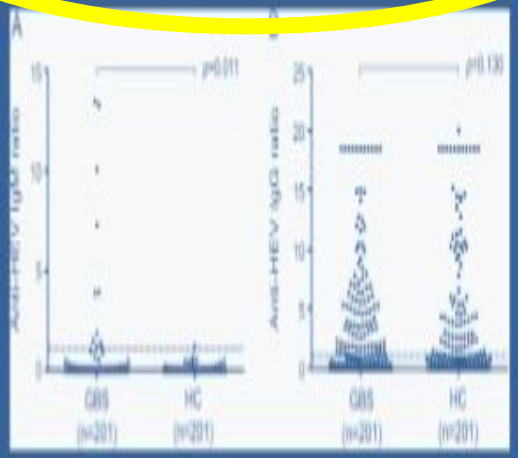
HEV & Guillain-Barré syndrome

Case control study of Dutch patients with GBS (n=201)

- 5% of GBS have HEV infection (10/201, p=0.01 vs controls)



van den Berg et al Neurology 2014

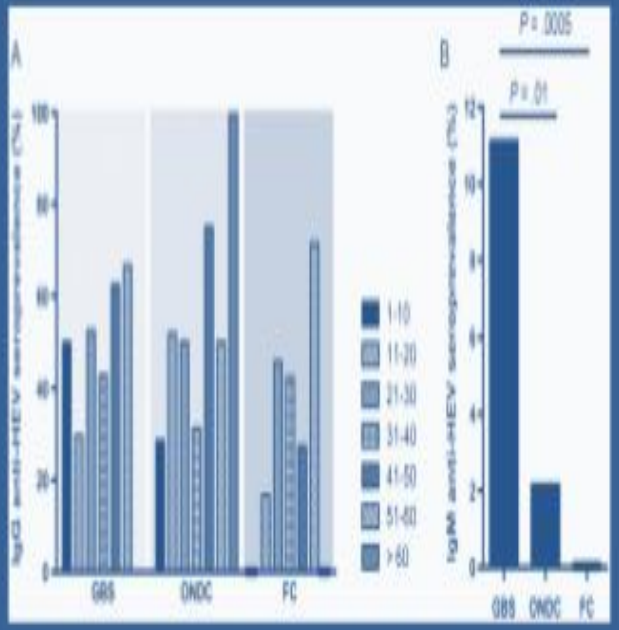
- Mildly abnormal LFT's:
  - normal bilirubin
  - ALT: 70 (range 26-921); abnormal n=7
- Outcome:
  - 1 required ventilation, 7 have significant disability at 6 months
- Some patients are viraemic (HEV3) at presentation
  - ?role for early therapy with ribavirin

HEV & Guillain-Barré syndrome

Case control study of Bangladeshi patients with GBS (n=100)

- 11% of GBS have HEV infection (genotype 1, n=1)

Geurtsvankessel et al Clin Infect Dis 2013



Worldwide HEV & GBS: n=36

- Age 2-73 years, 72% male
- All but one: immunocompetent

Dalton et al Nature Rev Neurol, in press

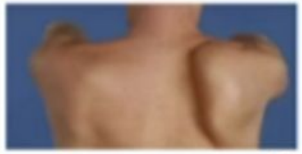
Extra hepatic manifestations

✓ Neurological complications :

- Guillain-Barré sd: frequent, immune-mediated process, 201 GBS
  5% HEV IGM Ab (10 times higher than control group)

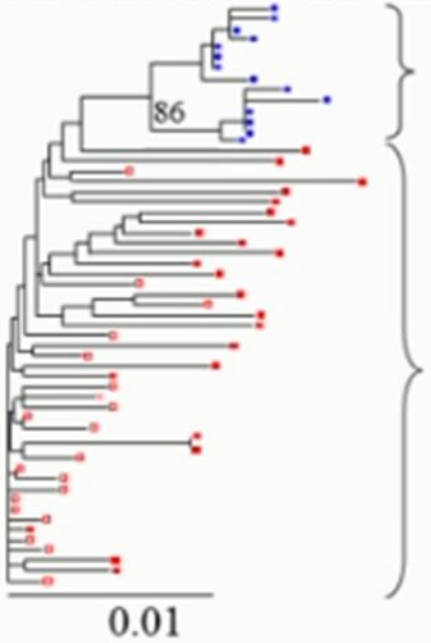
Van den Berg et al Neurology 2014; 82: 491

- Neuralgic amyotrophy (Parsonage-Turner sd); 30 cases reported ,
  prevalence of HEV in 47 NA patients (10%,)



Van Eijik JJ et al. Neurology 2014; 82:498-503

- CNS infection : 12 cases reported



HEV sequences in CSF

HEV sequences in blood

Existence of neurotropic HEV variants
And possible active viral replication in the CNS

Kamar, *Am J Transplant* 2010: 10; 1321-1324

Extrahepatic manifestations

- Existence of extrahepatic manifestations of HEV means that testing is warranted in a number of patient populations

Recommendations	Grade of evidence	Grade of recommendation
Testing for HEV recommended in:*		
• Patients with neuralgic amyotrophy	B	1
• Patients with Guillain–Barré syndrome	B	1
Testing for HEV suggested in: • Patients with encephalitis/myelitis	C	2
Testing for proteinuria suggested in: • HEV-infected patients	C	2
• Patients with acute or chronic HEV infection who develop new-onset proteinuria may be considered for a renal biopsy	C	2
Treatment • Antiviral treatment suggested for patients with chronic HEV infection and associated glomerular disease	C	2

*Irrespective of LFT results

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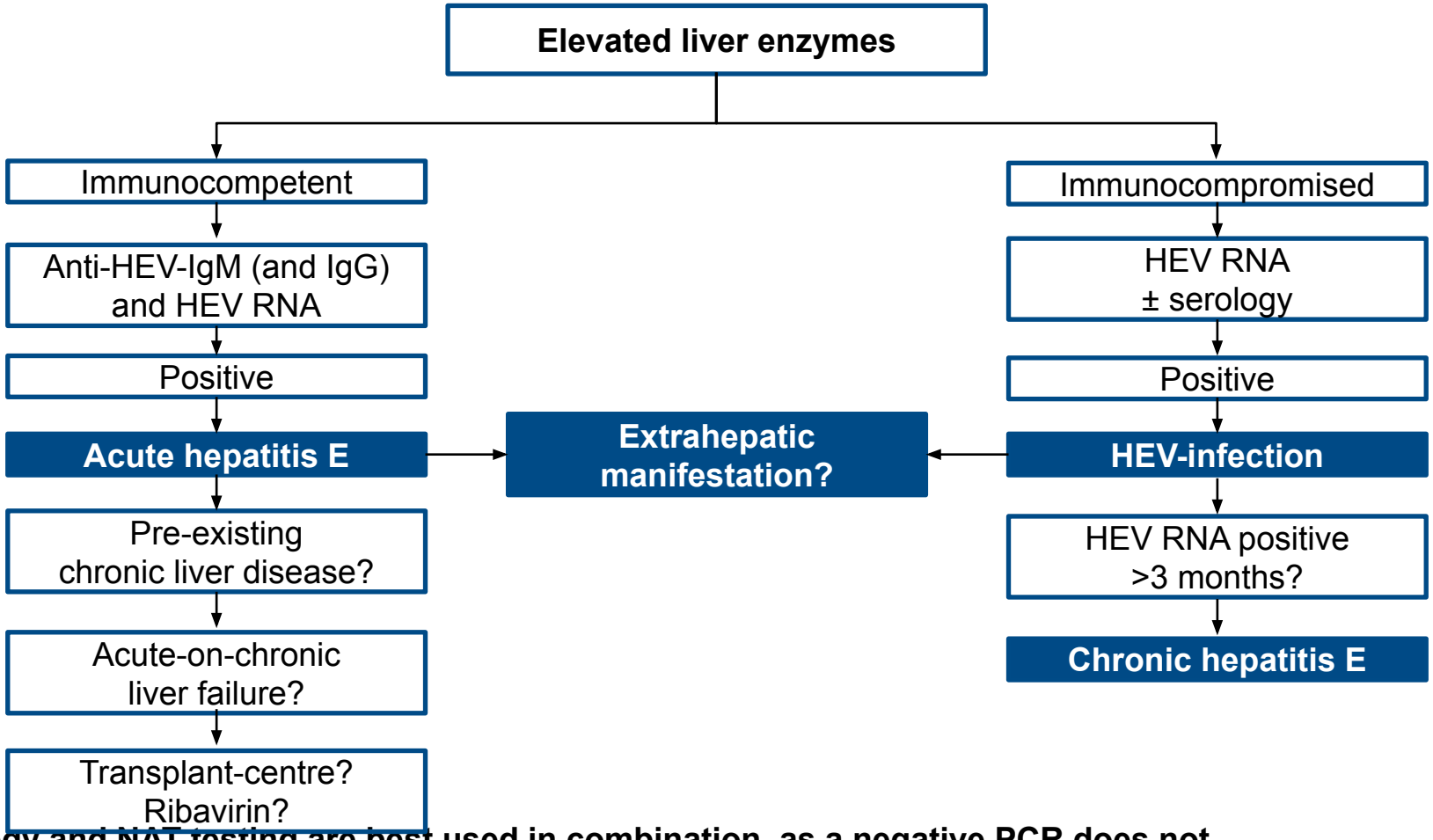
Diagnostic algorithm for HEV infection



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
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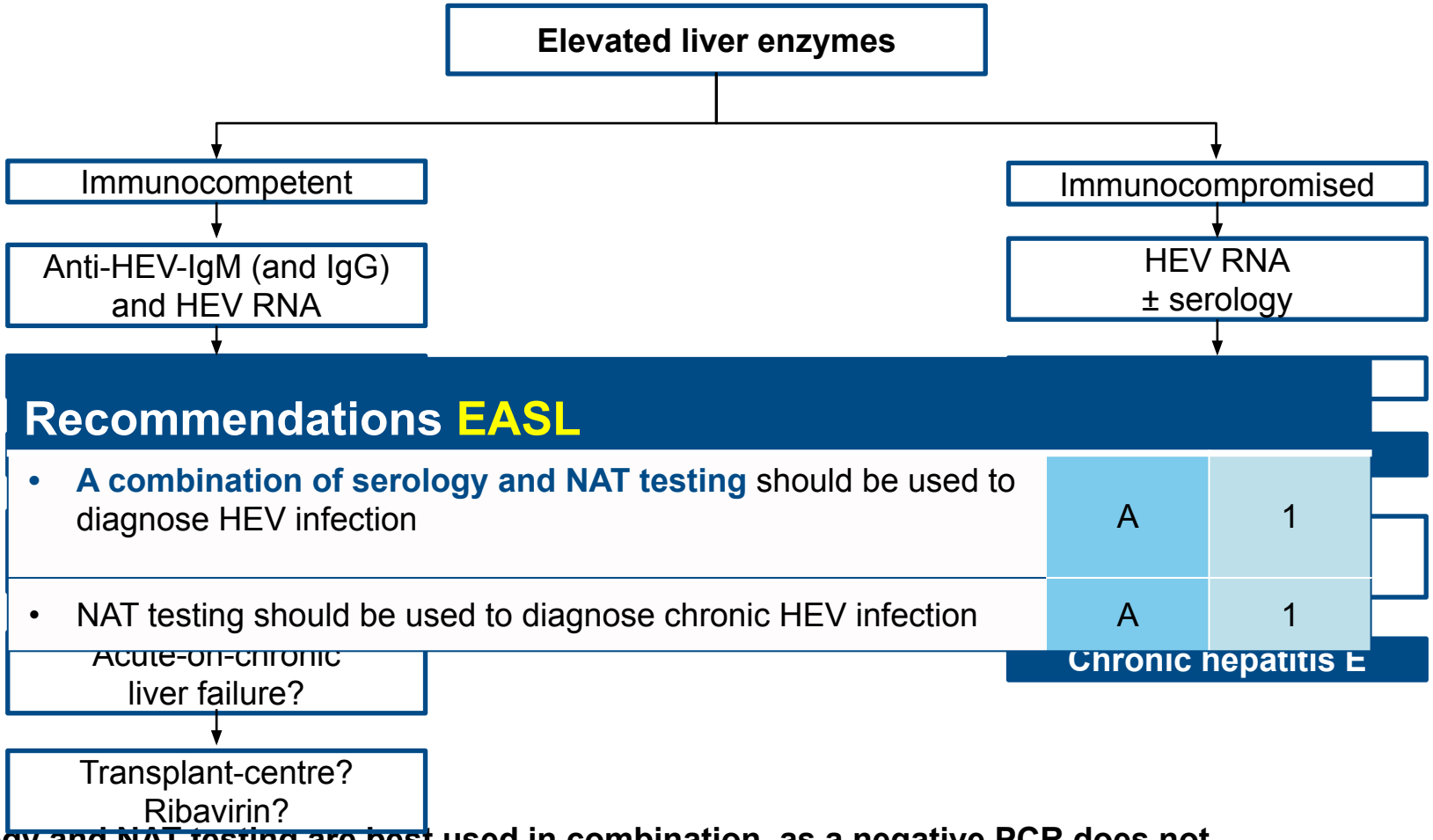
Diagnostic algorithm for HEV infection



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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

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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

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Ribavirin treatment for acute hepatitis E ?

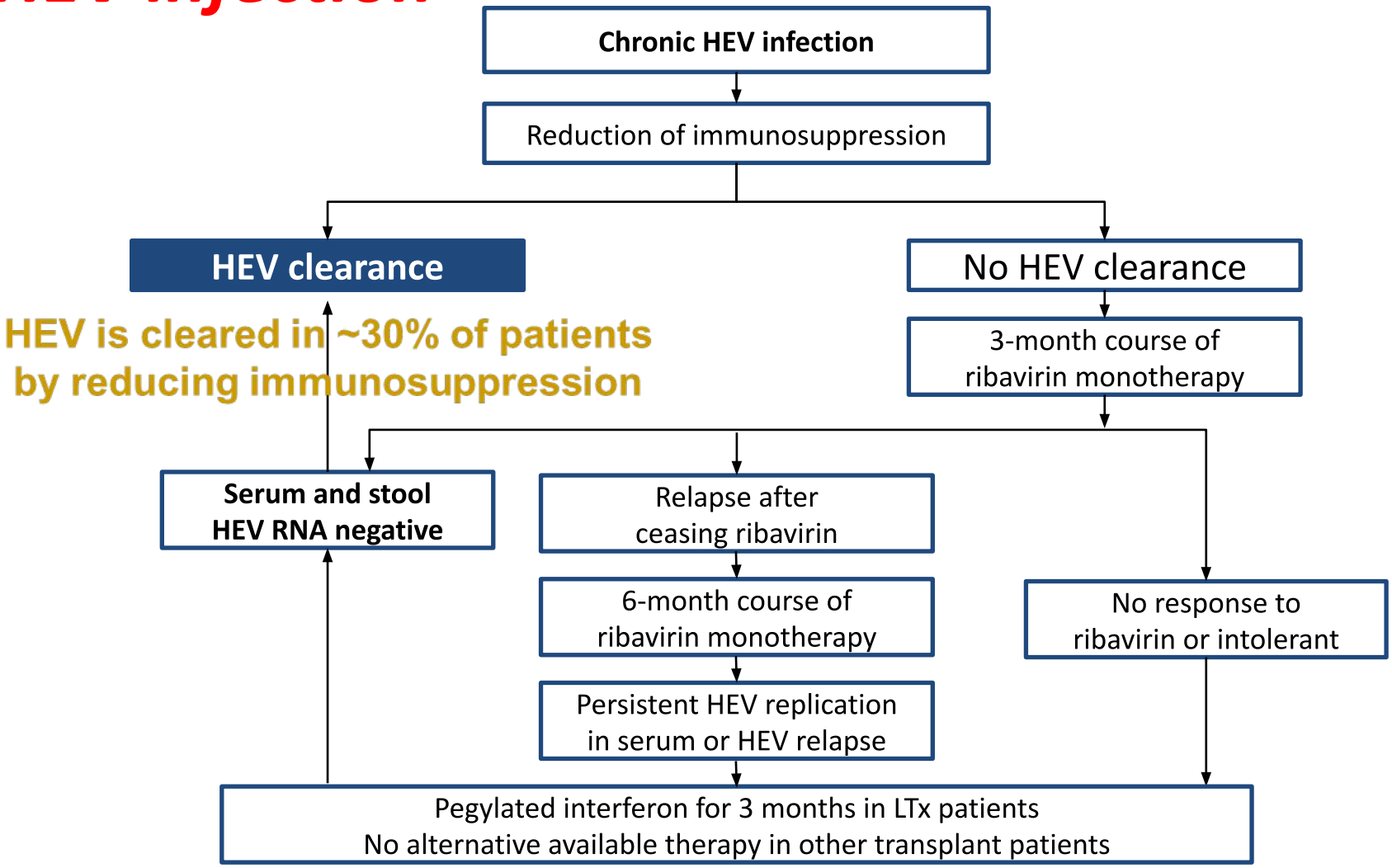
- 21 patients with acute symptomatic HEV infection either at risk of developing acute liver failure or receiving immunosuppressive therapy for autoimmune disease or undergoing chemotherapy

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

- All patients had undetectable HEV RNA in a median time of 29 days

Peron JM et al . Liver Int 2015; 36: 328-333.

Management of patients not clearing HEV infection



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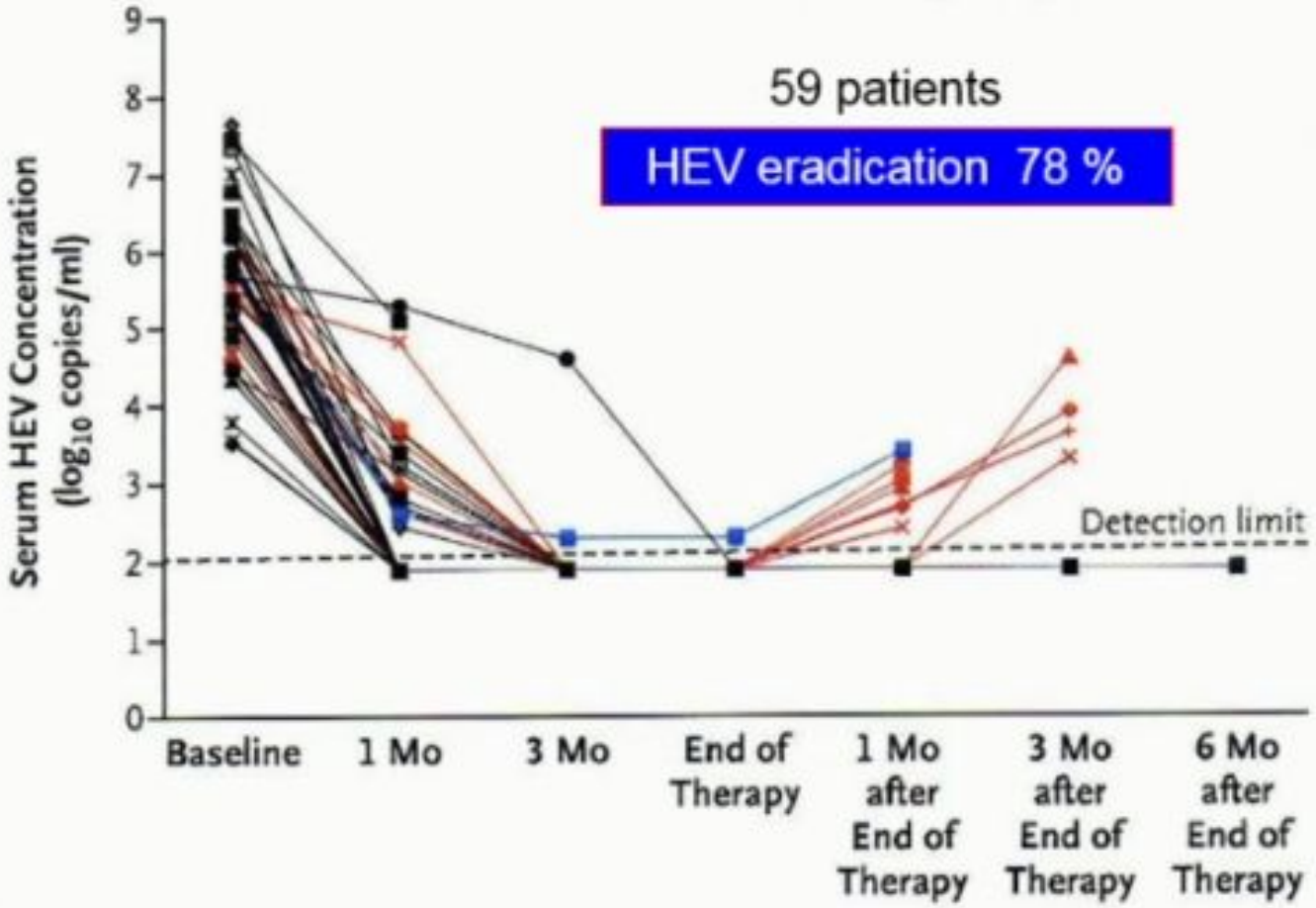
Ribavirin treatment



Kamar, *New Engl J Med* 2014

Factors associated with response to ribavirin treatment

- ✓ Viral kinetics on treatment
  - → ≥ 0.5 log c/ml decrease at D7

Kamar, *Transplantation* 2015

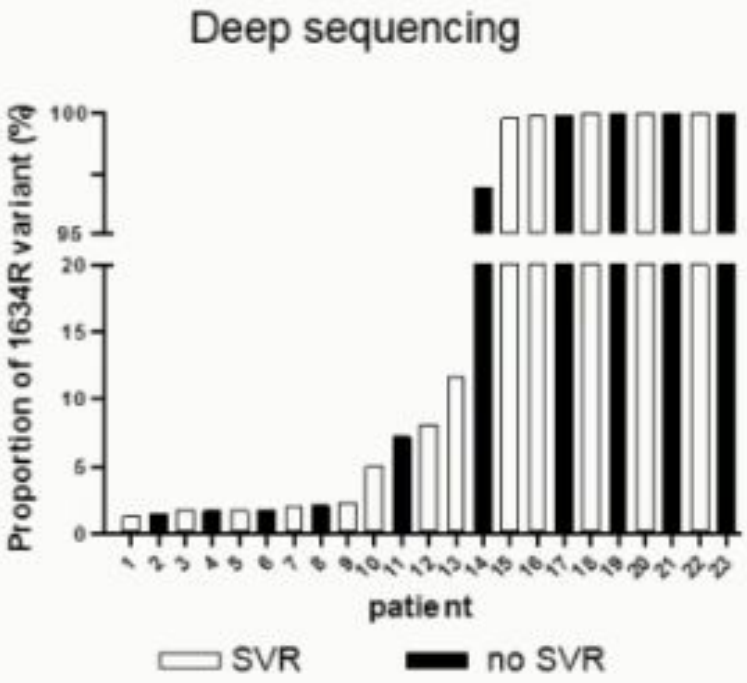
- ✓ Detection of HEV RNA in stools after 3 months of treatment is always associated with relapse

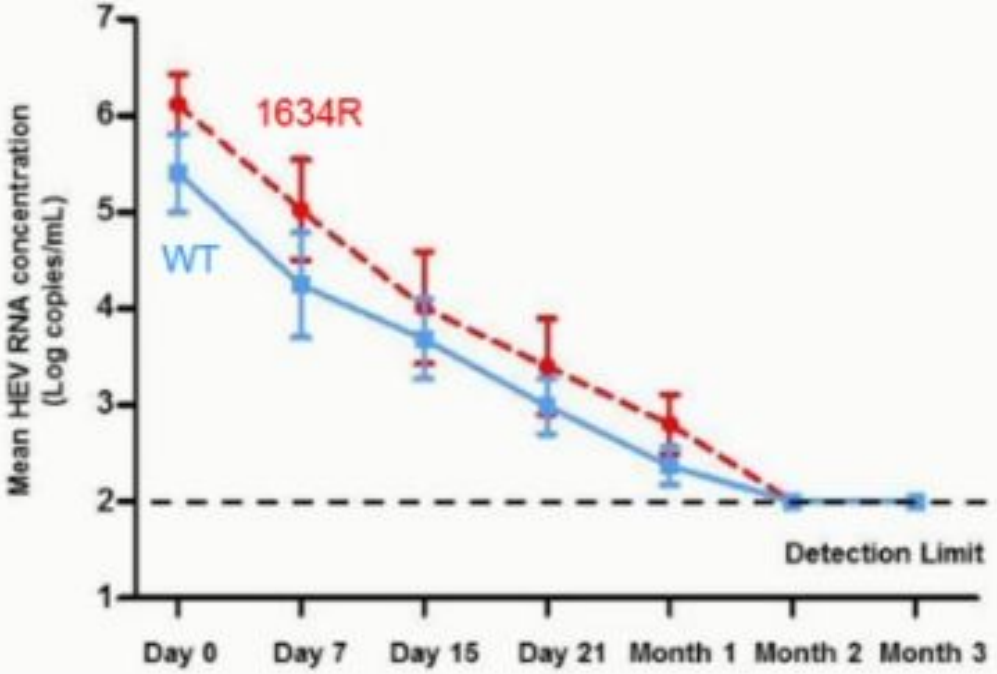
Abravanel, *Clin Infect Dis* 2015

- ✓ No role of ribavirin blood concentration

1634R polymerase mutation & HEV ribavirin resistance

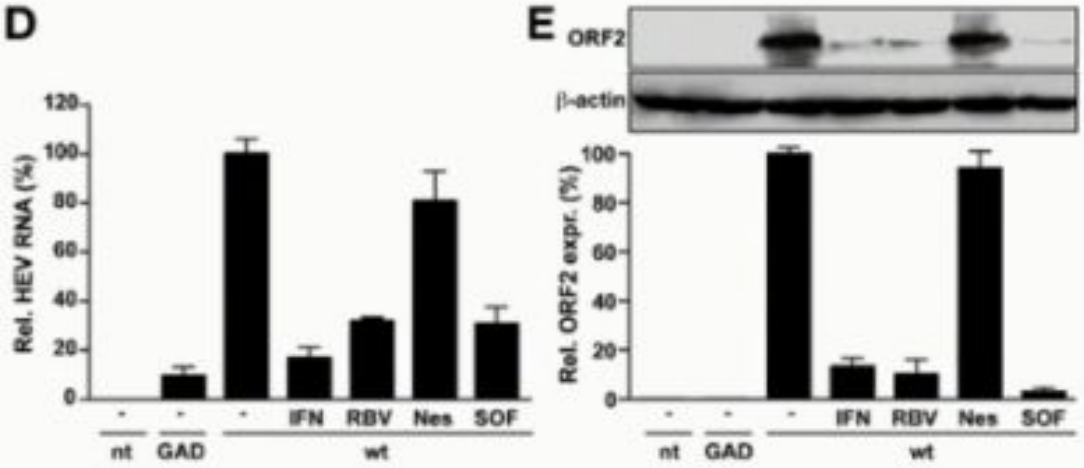
- ✓ *In vitro* : ↑ replication capacity of HEV
  Debing, *Gastroenterology* 2014; 147: 1008-1011
- ✓ *In vivo* : No role on SVR
  Lhomme, *Antimicrobial Agents Chemotherapy* 2016; 60: 1608-1614





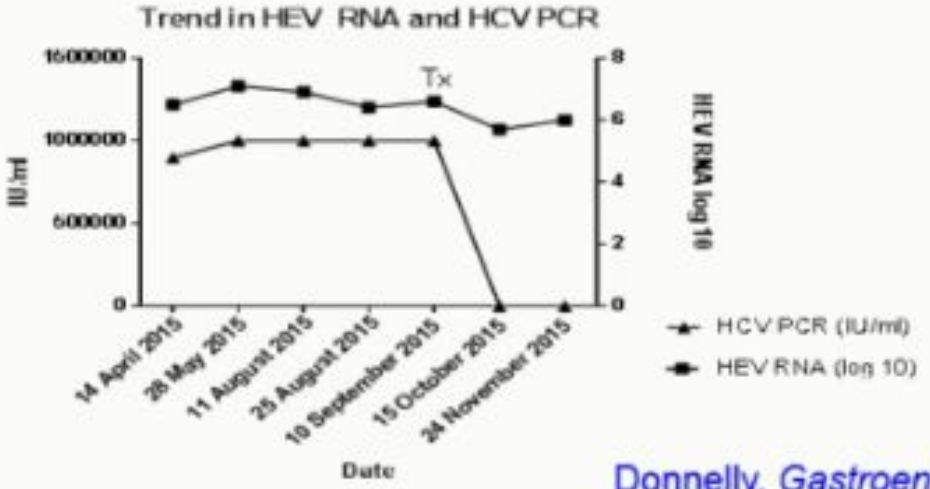
Sofosbuvir efficacy?

- ***In Vitro***



Dao Thi, *Gastroenterology, 2015*

- ***In Vivo***



Donnelly, *Gastroenterology*, sous presse

Although developed as treatment for hepatitis C, it has been reported that sofosbuvir has some activity against HEV RNA replication in vitro and has an additive antiviral effect with ribavirin[30]. However, when a hepatitis C/HEV co-infected patient received a 12-week course of *sofosbuvir* and daclatasvir, they did not achieve virologic clearance of HEV[31]. Therefore, it remains unknown if the observations made in vitro will translate into clinical efficacy in vivo.

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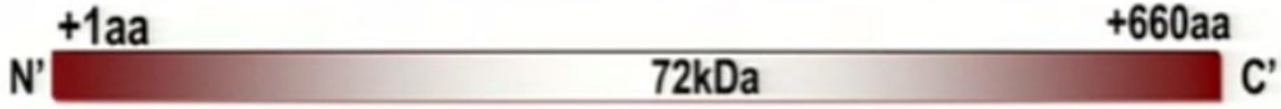
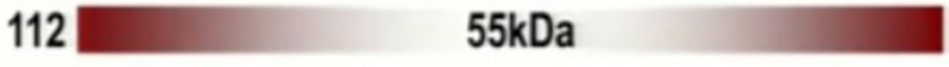
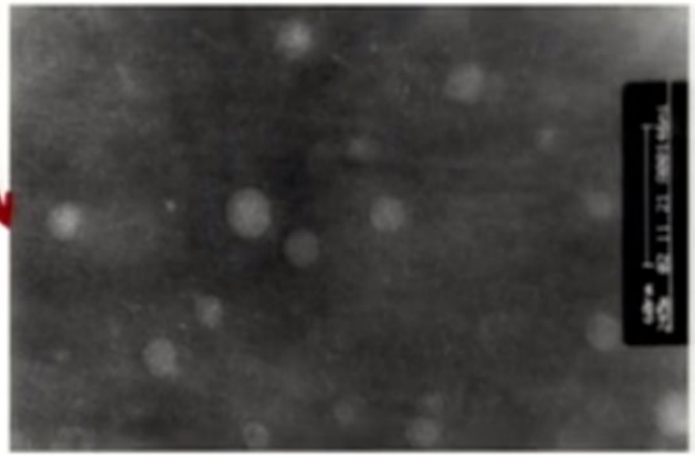
HEV proteins used as human vaccines





- Expressed in insect cells
- Virus-like particles (VLPs)
- Alum adjuvanted



- Expressed in *E coli*
- 26 nm; HPLC: >500 kDa
- Alum adjuvanted

Tsarev et al. Vaccine 1997; 15: 1834-8.
Li et al. Vaccine 2005: 23: 2893-901.

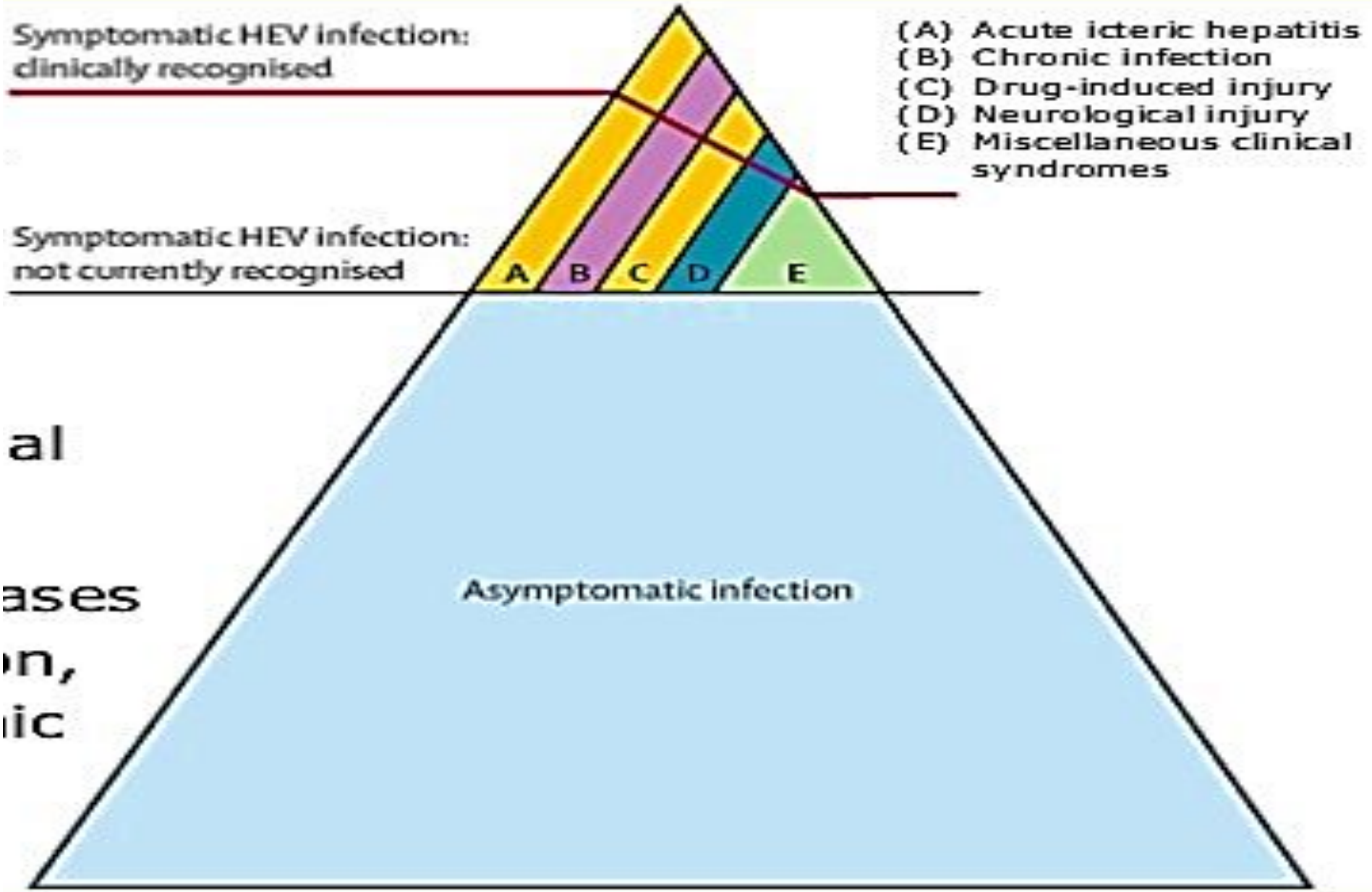
Vaccines

- HEV 239 Vaccine:
  - Hecolin®
  - The only experimental vaccine at clinical trial stage in humans that has been developed and manufactured.
  - Currently only licensed in China
  - Licensed for use in people 16-65 years of age who are at high risk for HEV infection based on occupation/lifestyle
    - Those involved in animal husbandry, food handling, students, army personnel, young women, travellers

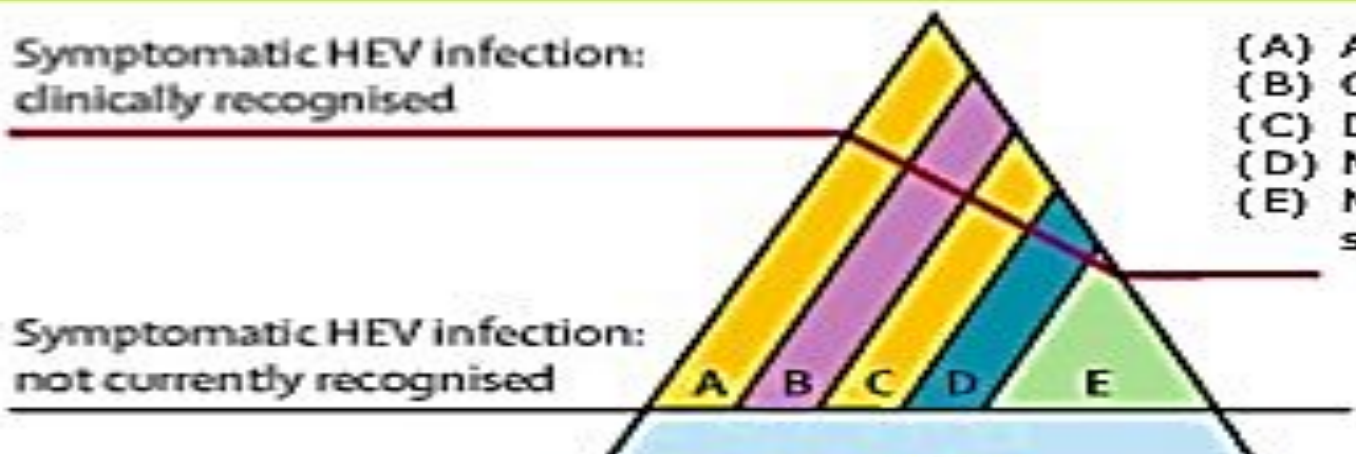
WHO Position

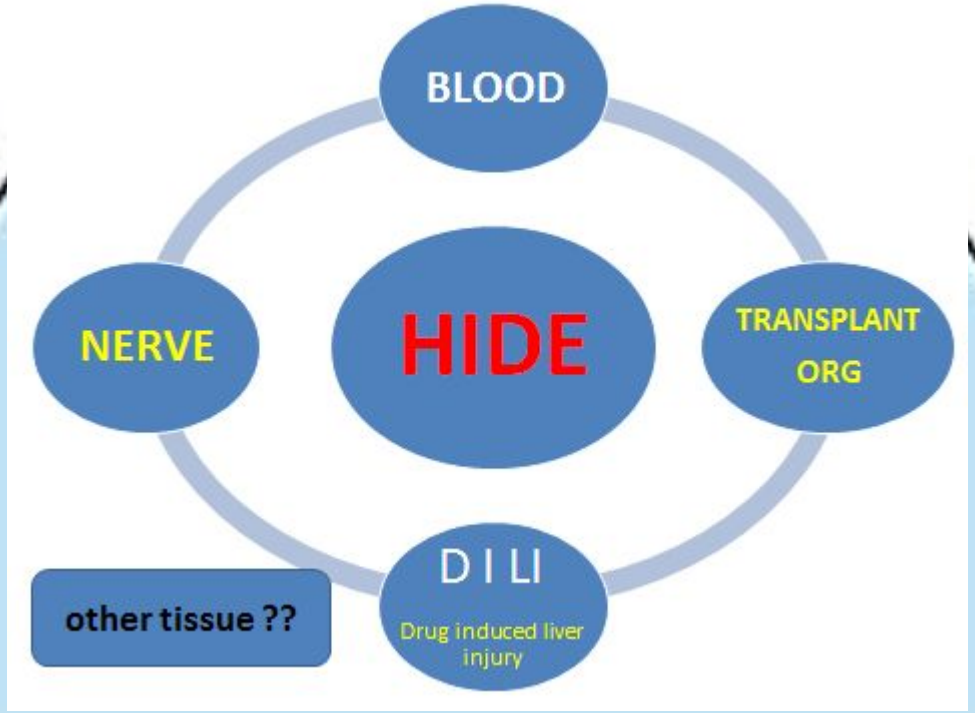
- Hepatitis E recognized as an important public health problem in developing countries
  - Especially among special populations: pregnant women, displaced individuals living in camps, outbreak situations.

- In the absence of sufficient information, the WHO does not:
  - make a recommendation on the introduction of the vaccine for routine use in national programmes in populations where epidemic and sporadic hepatitis E disease is common. However, national authorities may decide to use the vaccine based on the local epidemiology.
  - Recommend routine use of vaccine in the following groups in endemic areas:
    - Children below age of 16 years
    - Pregnant women
    - Patients with chronic liver disease
    - Patients on organ transplant wait lists
    - Travellers



Kamar et al. *Lancet* 2012; 379: 2477–88





Kamar et al. *Lancet* 2012; 379: 2477–88

ECDC- HEV-Exp meeting , Stockholm, 9,10 Dec 2015

Table 1. Who should we test for HEV?.

Immunological status	Criteria for testing
Immunocompetent patients	• ALT > 300 IU/L • Clinical suspicion of DILI • Decompensated chronic liver disease (regardless of LFT results) • Guillain-Barré syndrome (regardless of LFT results) • Neuralgic amyotrophy (regardless of LFT results) • Patients with unexplained acute neurology and a raised ALT
Immunocompromised patients	• As above • Persistently elevated ALT • Annual PCR screening

Testing algorithm for HEV (adapted from Wallace, et al.[115]) ALT, alanine transaminase; DILI, drug-induced liver injury; HEV, hepatitis E virus; LFT, liver function test.

Therapeutic Advances in Infectious Disease

Hepatitis E: an underestimated emerging threat

Glynn W. Webb, Harry R. Dalton

First Published April 3, 2019 | Review Article | Check for updates

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Abstract

Hepatitis E virus (HEV) is the most common cause of viral hepatitis in the

conclusion

- Understanding of HEV infection has changed dramatically in the last decade
- Infection with HEV represents an important global public health problem and is a cause of significant morbidity and mortality worldwide
- There are still many knowledge gaps
- CPGs will require amendment in a few years' time with further research and evolving evidence
- We must be awarness to HEV hepatitis in our country

The agora of Dionysias

Suwayda's City aerial view October 2011

Thank you

Dr Saleem Sray Aldeen gastroenterologist Swaida SYRIA December 2019