Transmission of HEV by plasmapheresis

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Transmission of HEV by secured plasma

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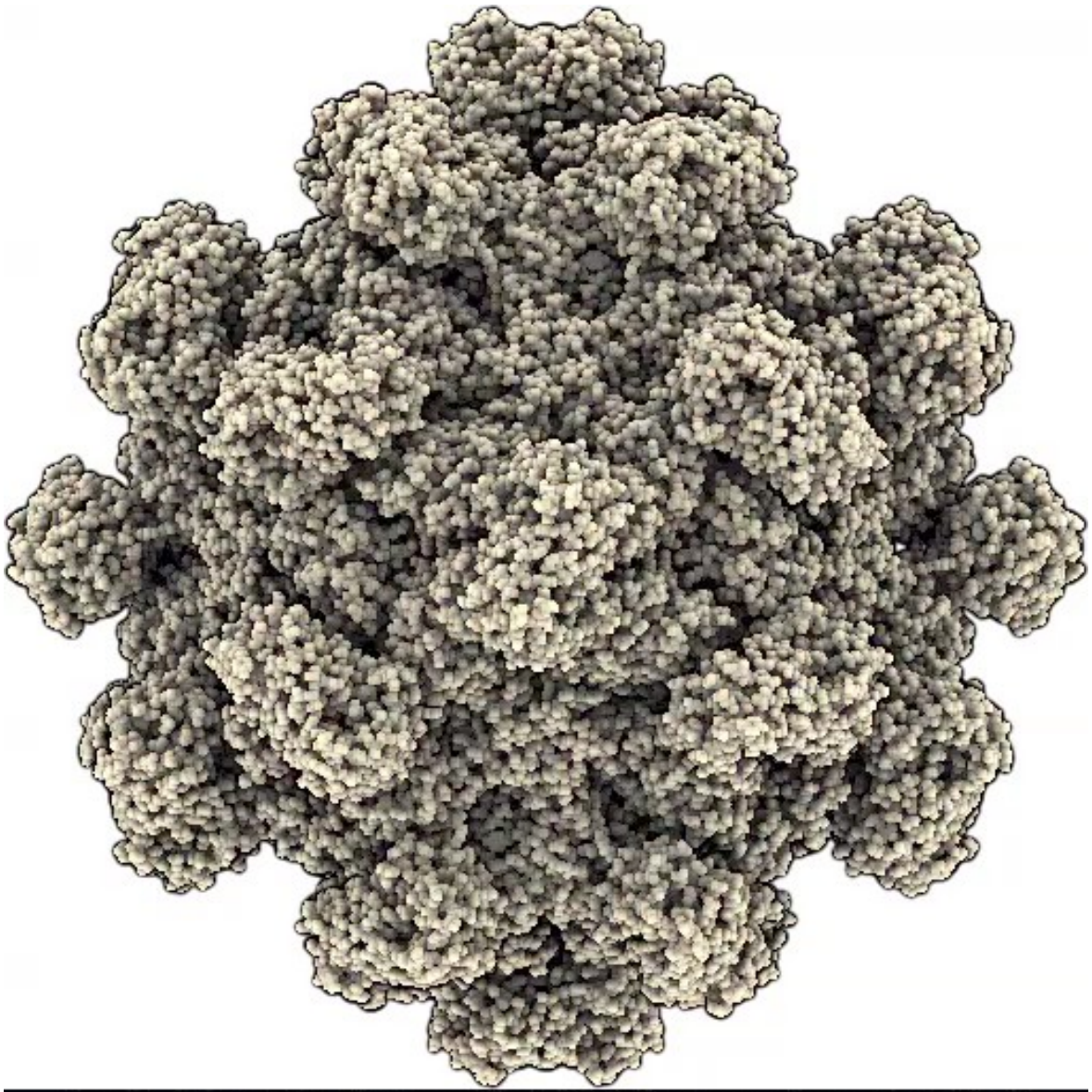


Hepatitis E virus ORF2 (Genotype 3) - PDB 2ZTN - Quttemol image © 2010 JYS

Yamashita, T. et al. Proc.Natl.Acad.Sci.USA 106: 12986-12991

HEV — Milestones

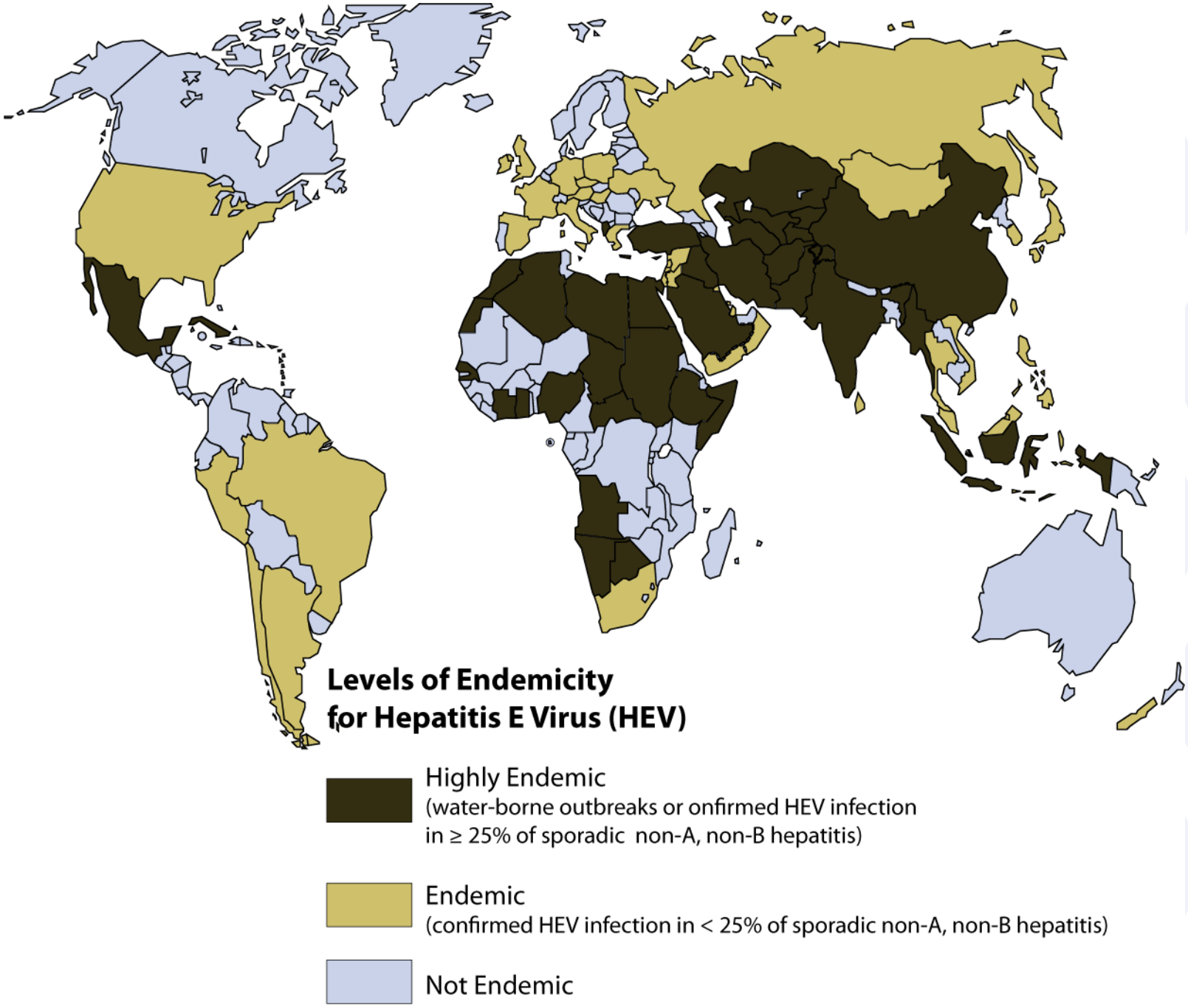
- Balayan MS et al. Intervirology 1983: First observation of viral particles
- Reyes RG et al. Science 1990: Molecular cloning and sequencing of HEV
- Yarbough PO et al. J Virol 1991: First serological test
- Arankalle VA et al. Proc Natl Acad Sci USA 1994: HEV, major ET-hepatitis
- Meng XJ et al. Proc Natl Acad Sci USA 1997: HEV, zoonosis
- Kamar N et al. N Engl J Med. 2008: Chronic HEV
- Yamashita et al. Proc Natl Acad Sci USA 2009: Cristal structure
- Mallet et al. Ann Intern Med 2010: Ribavirin for HEV
- Zhu FC et al. Lancet 2010: Phase 3 trial on recombinant HEV vaccine

Characteristics	HAV	HEV
Family	Picornaviridae	Hepeviridae
Genus	hepatovirus	hepevirus
Diameter (nm)	27 - 32	27 - 34
Genome	1 RNA+ strand	1 RNA+ strand
Nucleotides	7474	7200
Replication	Cytoplasm	Cytoplasm
Serotypes, n	1	1
Genotypes, n	6	5

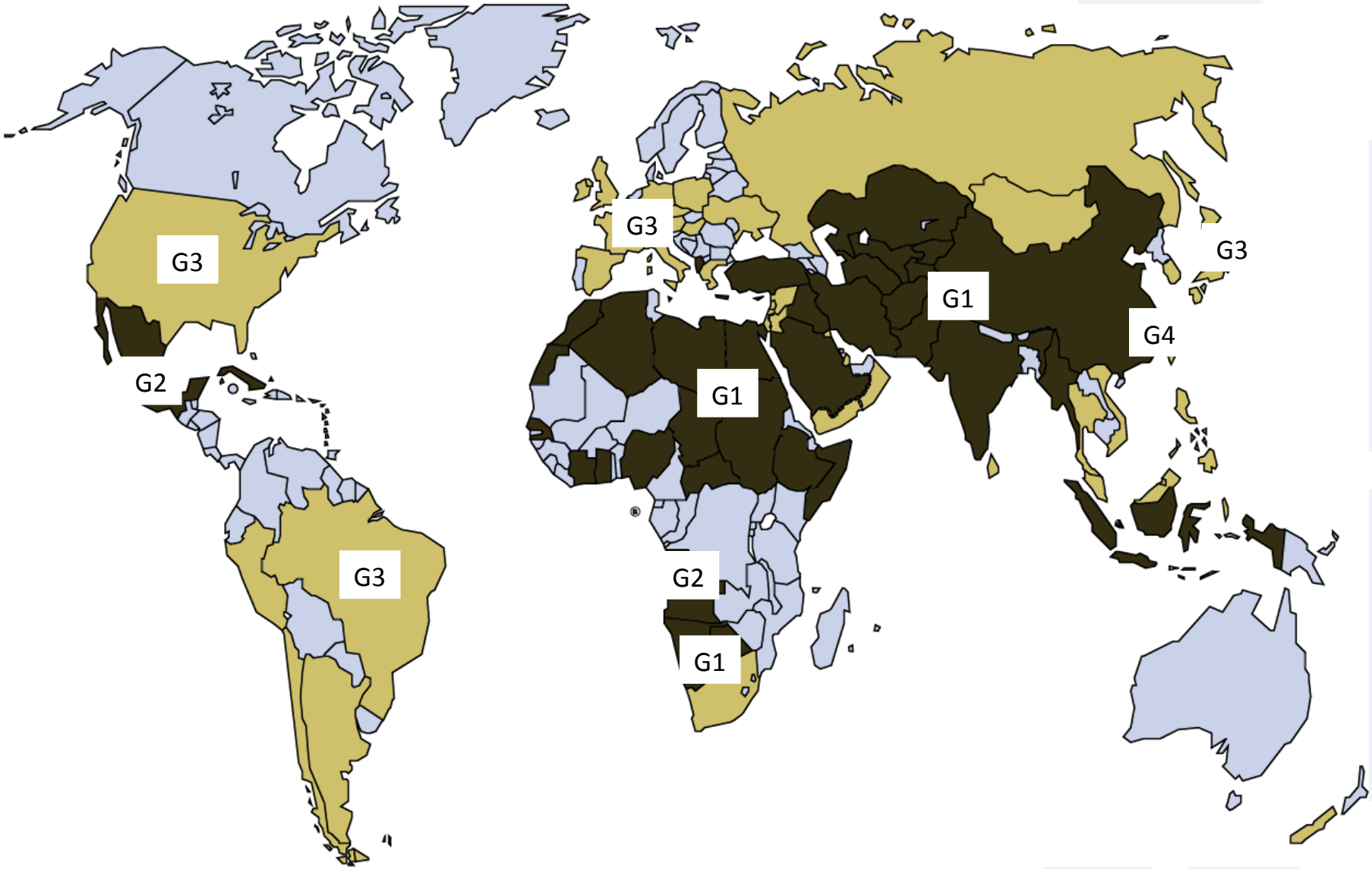
HEV: a universal virus

Animals	Countries	Seroprevalence	Genotypes
Swine	Worldwide	30-80 %	3-4
Wild boars	Japan, France, Deutschland, Italia, Spain, Hungary	5-42 %	3-4
			3-4
Deer	Japan, Hungary	2,6 %	Rabbit
Rabbit	China	57 %	Rat
Rat	India, Brazil, USA	50-80 %	3-4
Mongoose	Japan	8,3 %	
Horse	China, Egypt	13-16,3 %	
Cat	Japan, Spain	11,1-33 %	
Dog	Brazil, China	7-17,8 %	
Cheep	China, Spain	1,9 %	
Goat	China, Spain	0,6-24 %	
Bovine	Brazil, China, India	1,42-6,9 %	
Chicken	USA, Australia, Hungary	20-30 %	
Duck	China	12,8 %	
			Avian

Source N. Pavio



http://www.cdc.gov/hepatitis/HEV/HEVfaq.htm; (January 17, 2011, date last accessed).

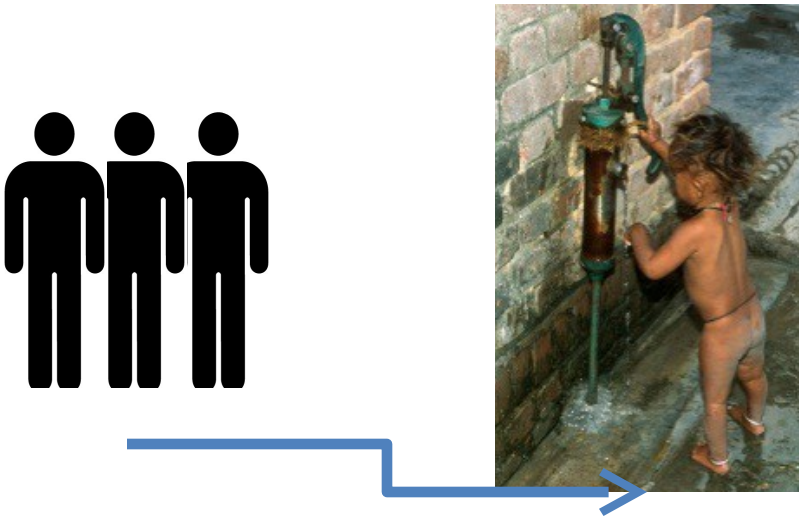


Human HEV

Geographic Distribution of Genotypes

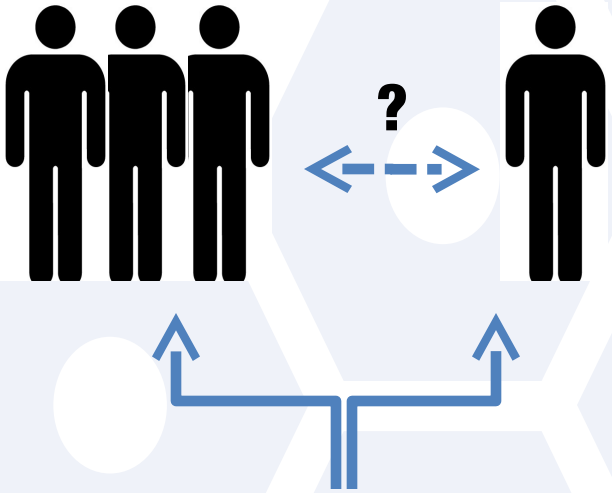
Methods of transmission

- **Highly endemic areas**

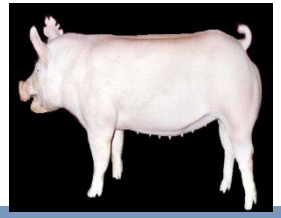


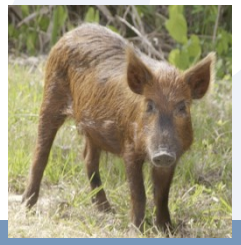
Genotypes 1, 2

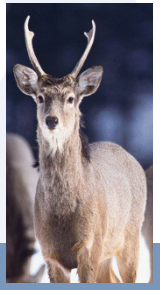
- **Endemic areas**



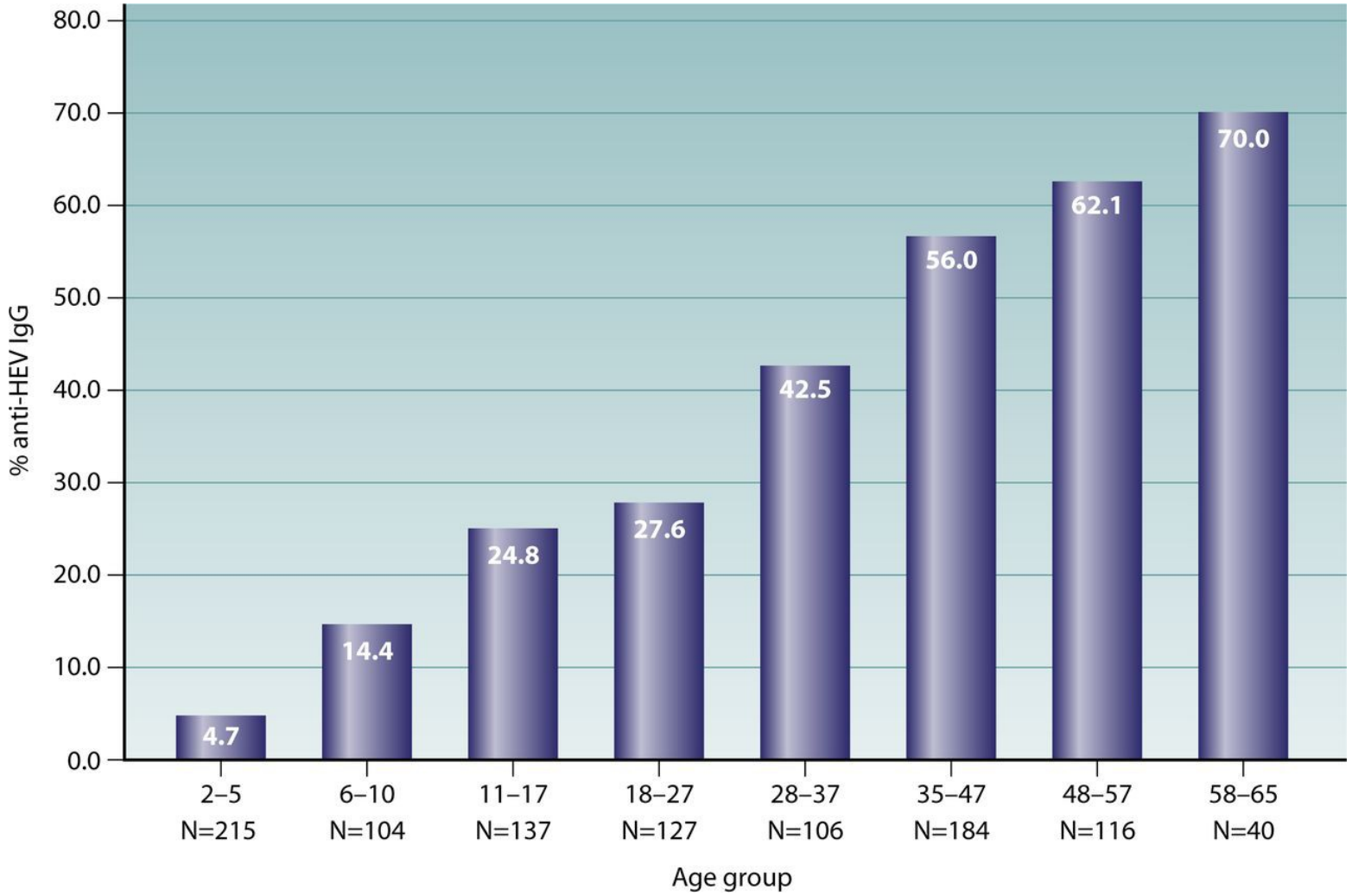
Genotypes 3, 4







Anti-hepatitis E virus IgG distribution in Midi-Pyrenees area of France, according to age.



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

Frequency of HEV detection in donors of blood products in Europe

Country	Percentage of HEV RNA in blood donors (absolute numbers)	Reference
Scottland	0.007%, (3/43560)	Cleland et al 2013
Sweden	0.013%, (12/95835)	Baylis et al. 2012
England	>0.014%, (6/42000)	Ijaz et al. 2011
Germany	0.015% (exploration)	Corman et al. 2013
Germany	0.022%, (4/18100)	Baylis et al. 2012
England	0.035% (79/225000)	Hewitt et al. 2014
Netherlands	0.037%, (17/45415)	Slot et al. 2013
Spain	0.03% (1/3333)	Sauleda et al. 2014

Hepatitis e virus infections in blood donors, france

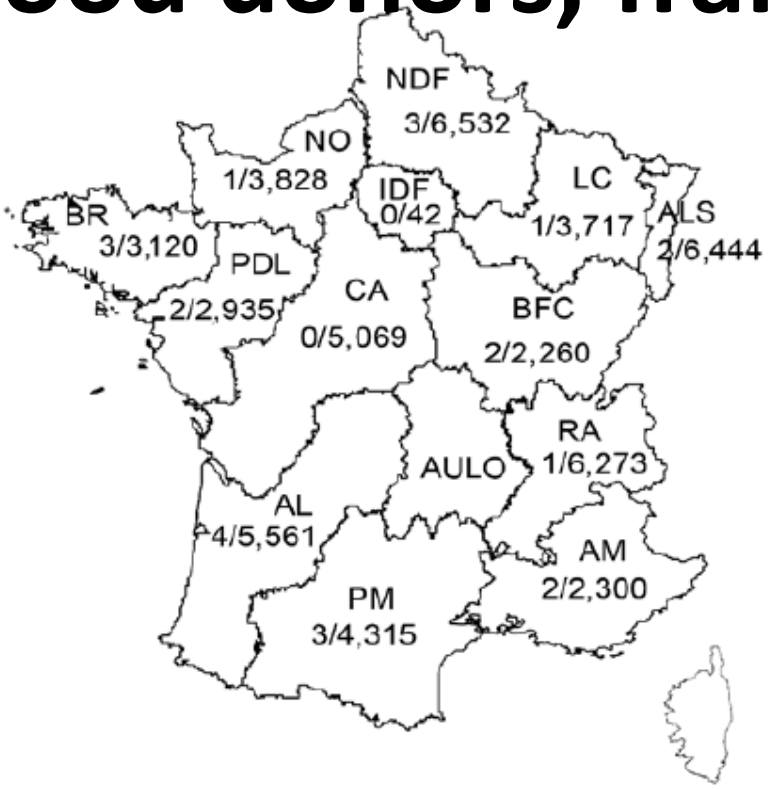


Figure 1. Prevalence (no. samples positive/no. tested) of hepatitis E virus RNA in plasma collected during November 27, 2012–December 1, 2013, at regional establishments of the French Blood Agency, France. Southern France: AL, Aquitaine-Limousin; PM, Pyrénées-Méditerranée; AM, Alpes-Méditerranée (including Corsica). Northern France: NDF, Nord de France; NO, Normandie; IDF, Ile de France; LC, Lorraine-Champagne; ALS, Alsace; BR, Bretagne; PDL, Pays de Loire; CA, Centre Atlantique; BFC, Bourgogne-France [illegible] AULO, Auvergne-Loire; RA, Rhône-Alpes.

Gallian P Emerg Infect Dis 2014

Chronic Hepatitis E in Heart Transplant Recipients

Table 1: Prevalence of HEV antibodies and HEV-RNA in different patient groups in Germany

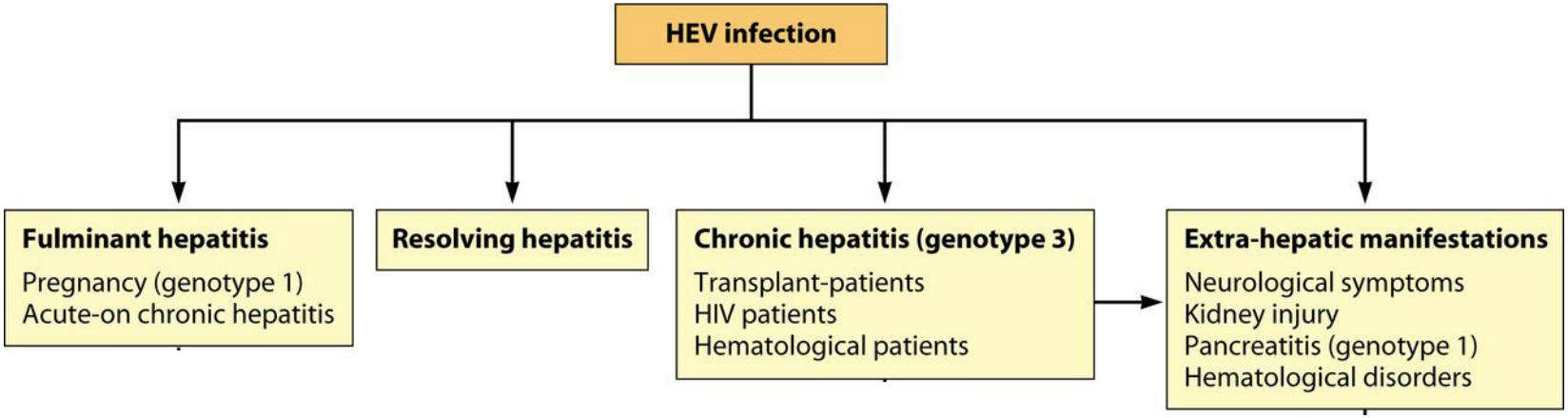
Groups	Number of patients	Anti-HEV-IgG positive n	HEV-RNA positive n	p-Value; seroprevalence rate in comparison to seroprevalence rate in HTR (chi-square)
Heart transplant recipients	274	31 (11.3%)	4 (1.5%)	
Healthy controls (15)	537	11 (2.0%)	0 (0%)*	<0.001
Non transplanted cardiac patients	137	10 (7.3%)	0 (0%)	ns
Liver transplant recipients (9)	226	10 (4.4%)	2 (< 1%)	0.005
Non transplant liver patients (9)	129	4 (3.1%)	0 (0%)	0.006
HIV-infected patients (16)	123	6 (4.9%)	0 (0%)	0.04
Stem cell transplant recipients with strongly elevated transaminases (17)	52	3 (5.8%)	0 (0%)	ns
Patients with common variable immunodeficiency (CVID) (18)	73	0 (0%)	0 (0%)	0.003

*Healthy controls were only tested for HEV-RNA if they tested positive for IgG.

Pischke S, 2012

Presence of anti-HEV antibodies 12 months after kidney transplant in 248 kidney transplant recipients

Different patterns of hepatitis E virus infection.



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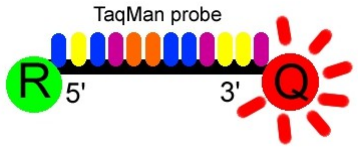
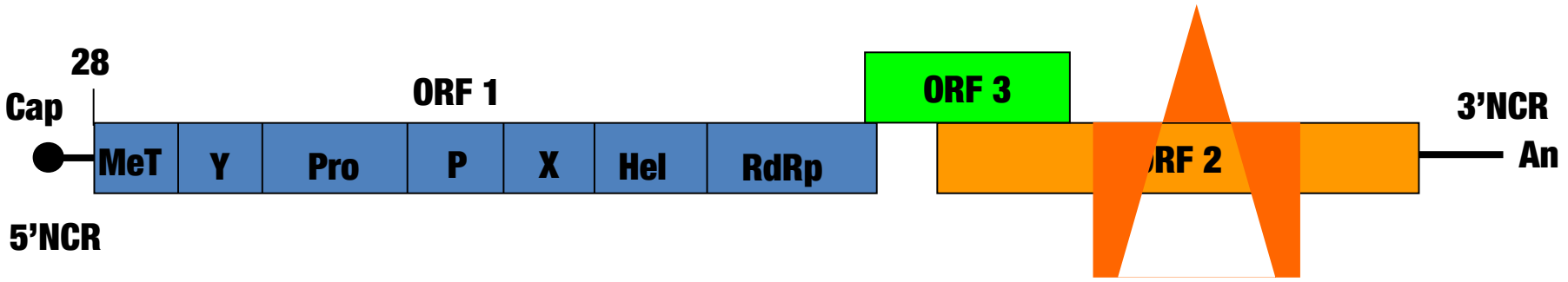
Diagnosis of HEV

- **Detection of anti-HEV antibodies**
  - **Early (IgM) : Sensitivity 82-90%, specificity 99.5-100% (Legrand-Abravanel Clin Vaccine Immunol 2009)**
  - **Late (IgG) : Low sensitivity, especially in immunocompromised (Kamar N Engl J Med 2008)**
- **PCR on ORF 2 in blood, stool, liver… (Mansuy J Clin Virol 2009)**



189 bp product

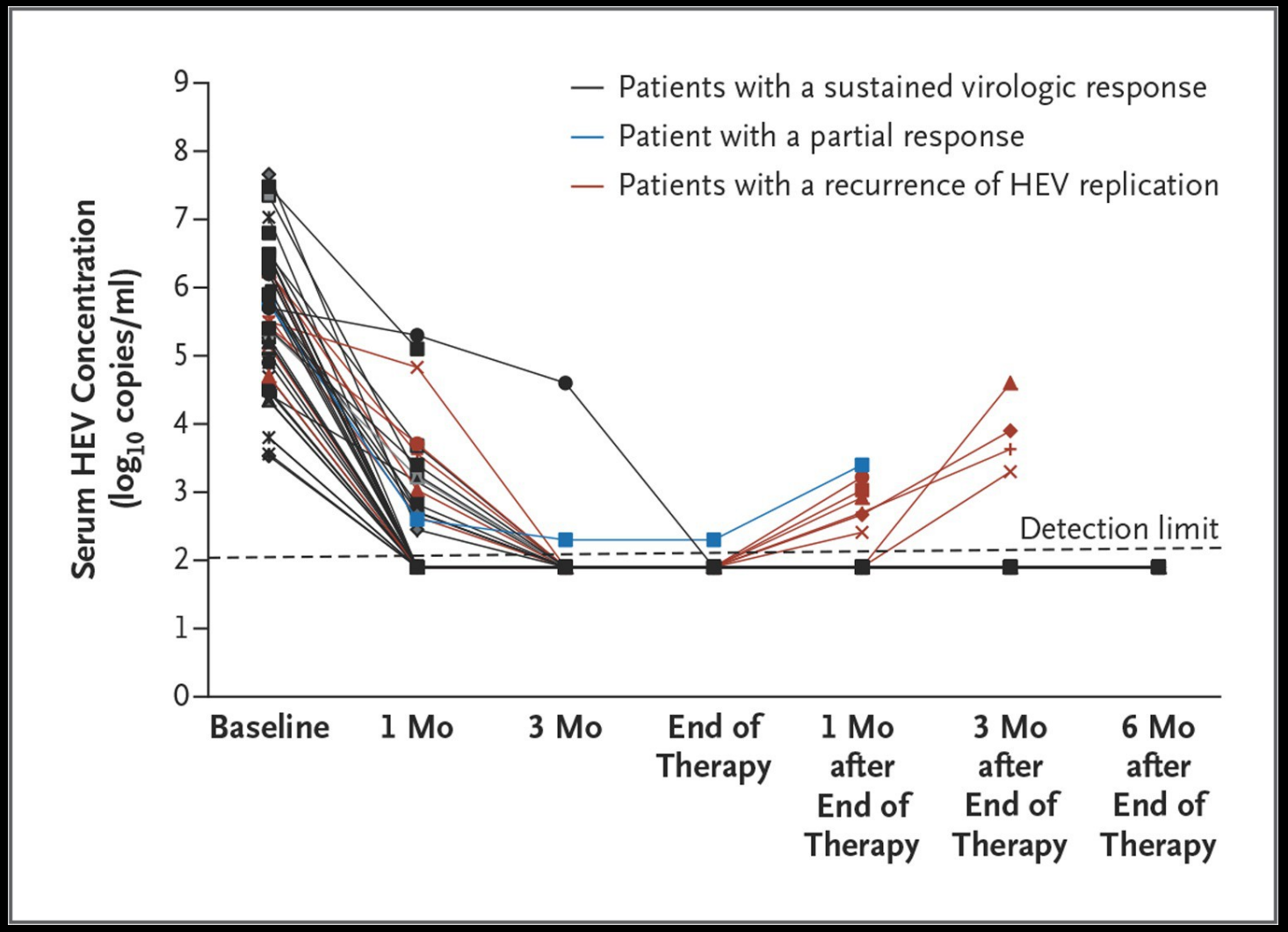


Chronic HEV infection

- Immunocompromised patients
  - Transplant recipients
  - People living with HIV
  - Chemotherapy (lymphoma)
- After HEV infection, the rate of chronicity ranges from 40-60% in solid organ recipients
- HEV clearance is possible after immune restoration or reduction of immune suppressive regimen
- Mild antiviral efficiency of Interferon (risk of graft rejection)

Dalton HR et al. N Engl J Med 2008; Kamar N et al. N Engl J Med 2008; Kamar N et al. Transplantation 2010; Kamar N et al. Clin Infect Dis 2010

- Hepatitis E virus may cause chronic infection in certain patients, such as those who are immunocompromised.
- In this report from France involving 59 solid-organ transplant recipients with persistent HEV viremia, ribavirin was associated with HEV clearance in 78% of patients.

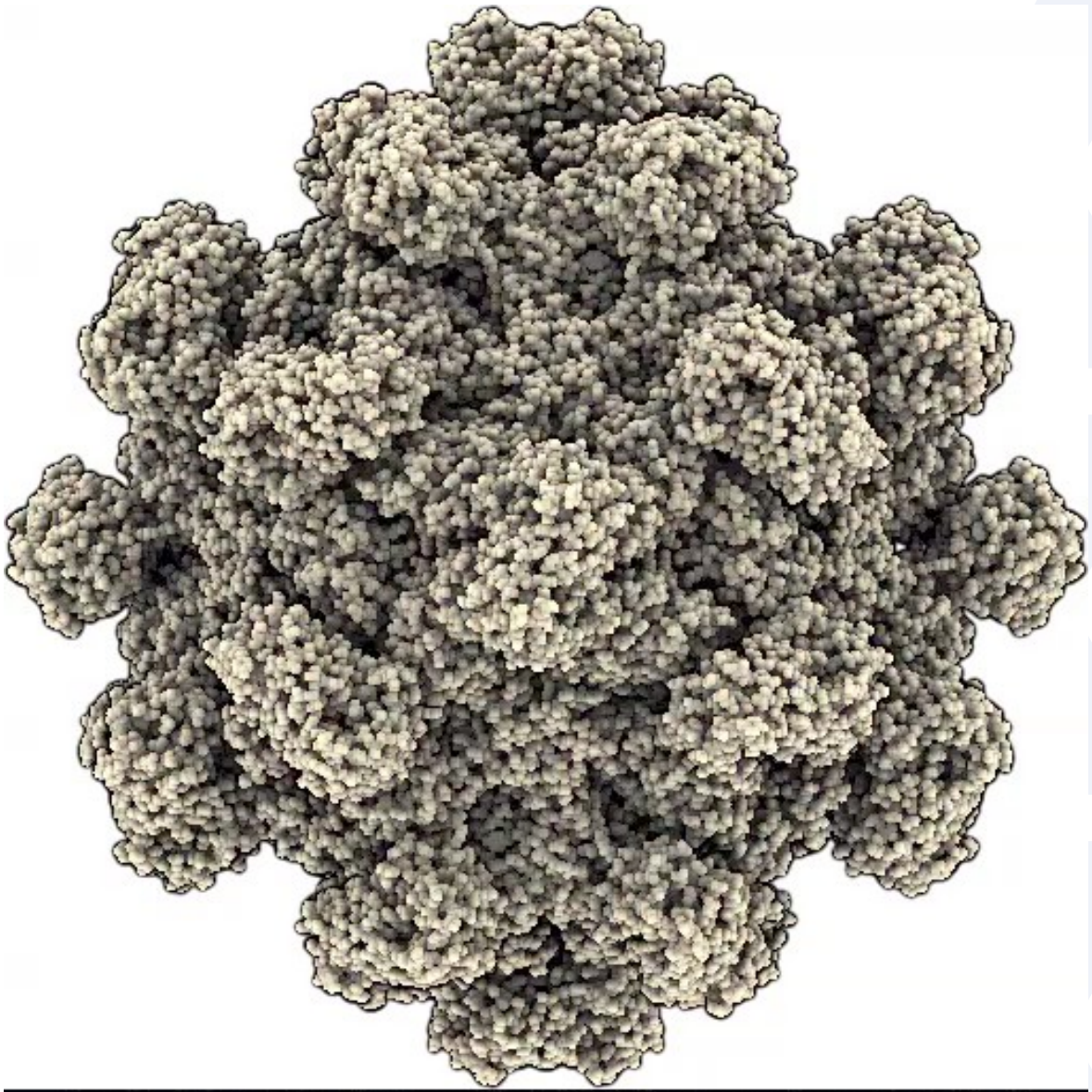


Key messages on HEV

- First cause of acute hepatitis worldwide
- Emerging autochtonous infectious disease
- New cause of chronic liver disease
- HEV should always be searched in the setting of acute/chronic unexplained liver disease
- Use PCR
- Ribavirin is a treatment of HEV
- Plasma exchange is a method of transmission of

Recommendations

- **Compromised patients should be informed about the risks of foodborne transmission of HEV (A III)**
- **For patients with chronic HEV, reduction of immunosuppressive drugs could be considered (B III)**
- **For patients with chronic HEV, antiviral therapy with ribavirin could be considered (B III)**



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