HEV: update epidemiologico-clinico

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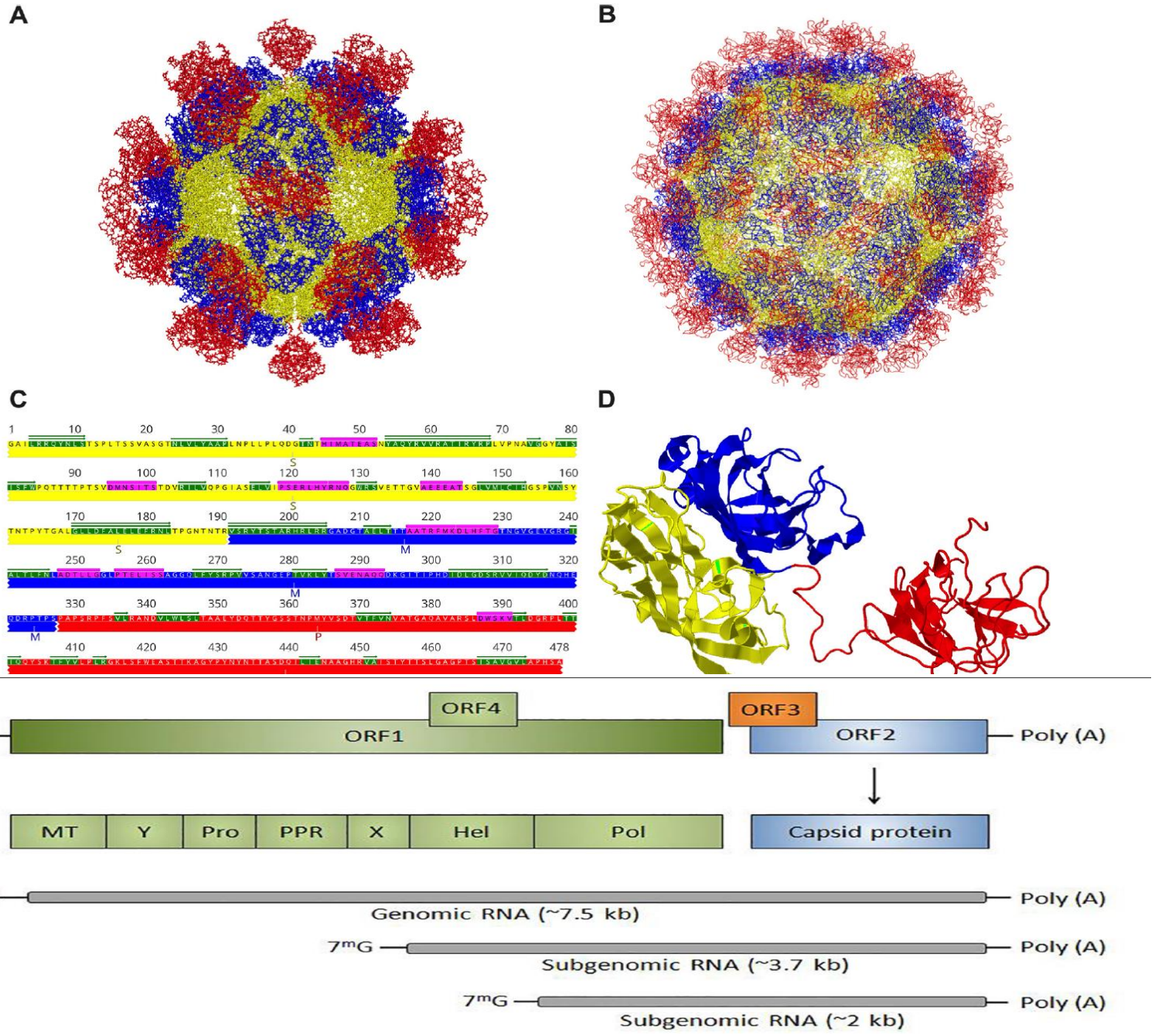
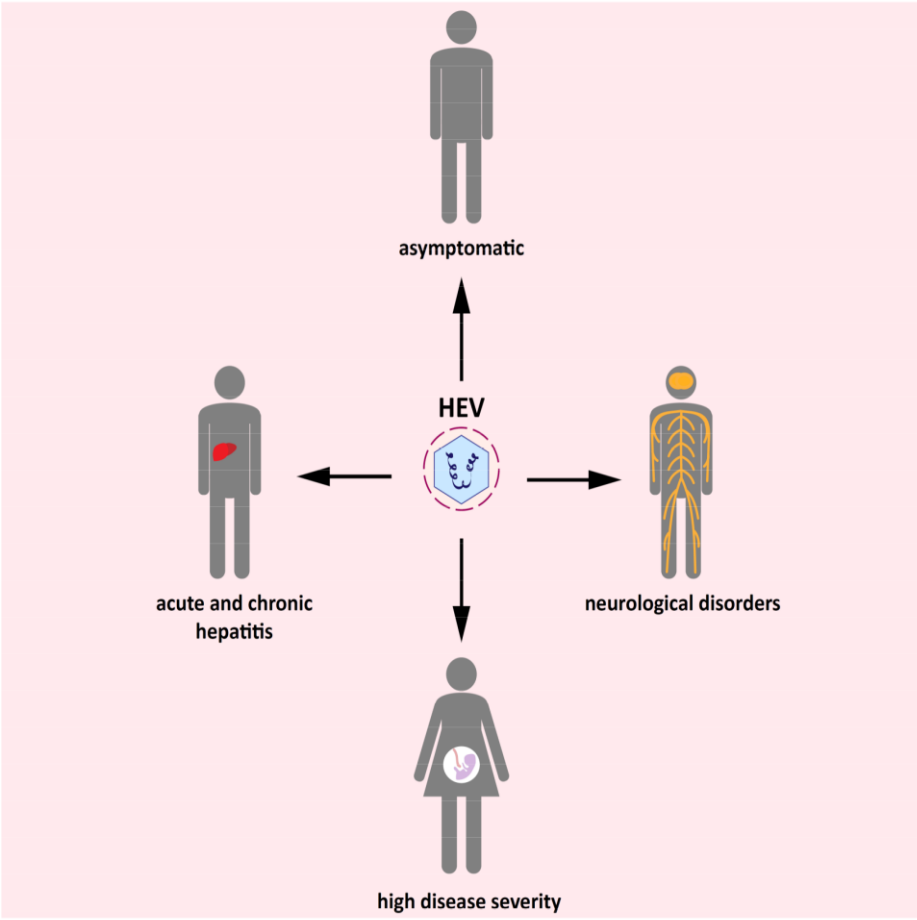

A
B
C
D
ORF4
ORF3
ORF1
ORF2
7mG
Poly (A)
MT
Y
Pro
PPR
X
Hel
Pol
Capsid protein
Genomic RNA (~7.5 kb)
Subgenomic RNA (~3.7 kb)
Subgenomic RNA (~2 kb)


HEV


asymptomatic
HEV
acute and chronic hepatitis
neurological disorders
high disease severity

A Year in History: Timeline of 1983 Event

- HEV: the first time in 1983 in stool samples.
- HEV is common in low- middle-income countries with limited access to water, sanitation, hygiene and health services.
- The outbreaks follow periods of faecal contamination of drinking water supplies, may affect several hundred to thousand persons.
- The first HEV-outbreak: **1955-1956** in New Delhi, India (water), though it was to be attributed to HAV. It took until 1994 to identify HEV as cause for this outbreak.
- **Outbreaks: in areas of conflict and humanitarian emergencies.**

Table 1. Reported HEV outbreaks.

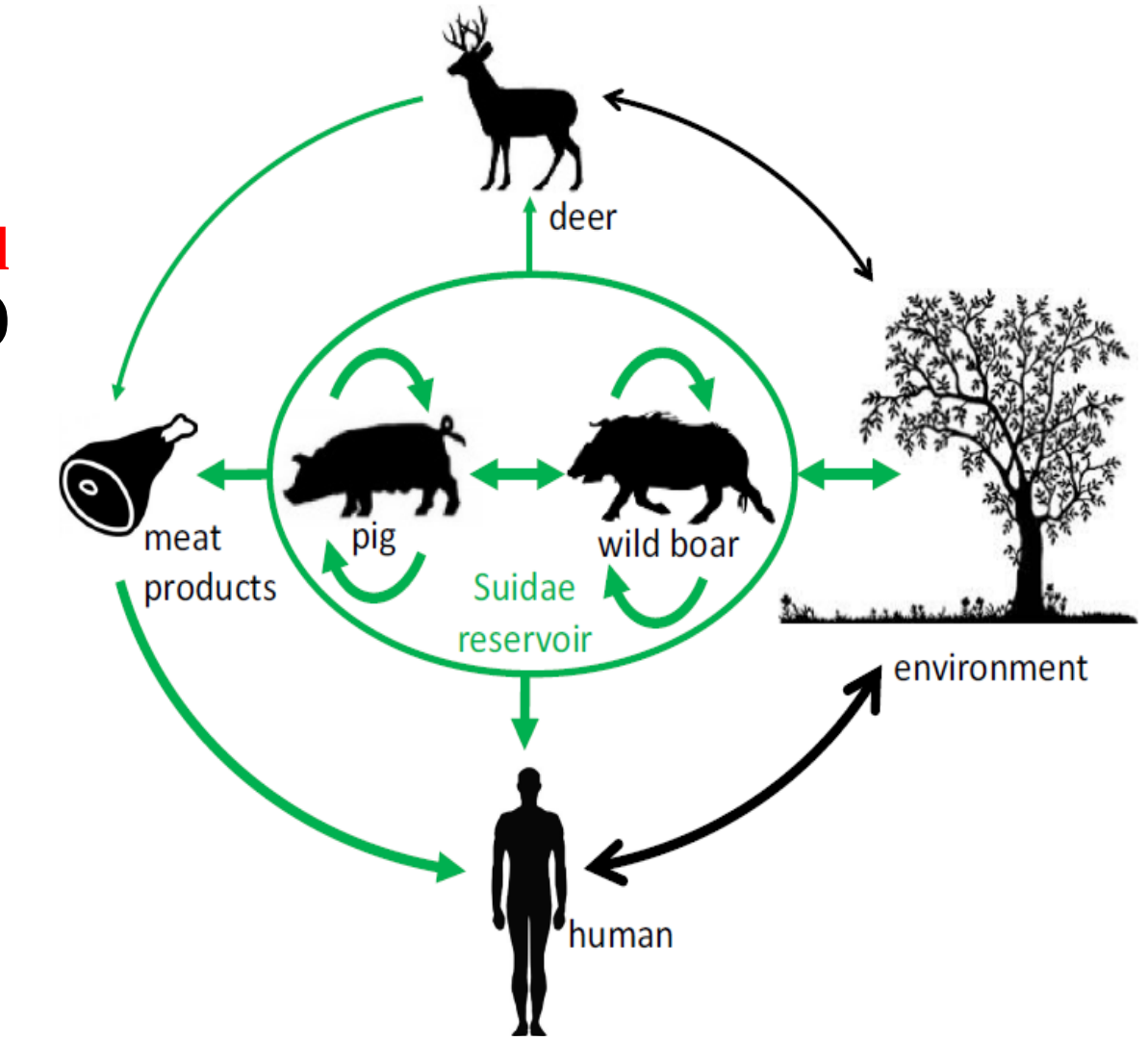
Year(s)	Country	Mode of Transmission	Reported
1955–1956	India	Waterborne	29,300
1978–1979	Kashmir	Waterborne	>270
1980–1981	Algeria	Sewage contamination—river water	788
1982	Myanmar	Waterborne	399
1983	Namibia	Waterborne	hundreds
1983–1984	Cote d'Ivoire	Waterborne	623
1985	Turkmenistan	Waterborne	16,175
1985	Botswana	Fecal contamination of water	273
1986	Mexico	Contaminated well water	>200
1988	Somalia	Waterborne	106
1988–1989	India	Contaminated drinking water	53
1988–1989	Ethiopia	After monsoon rains	>750
1989	Myanmar	Contamination—water supply by feces	93
1991	India	Contaminated river water (Ganges)	79,000 [1]

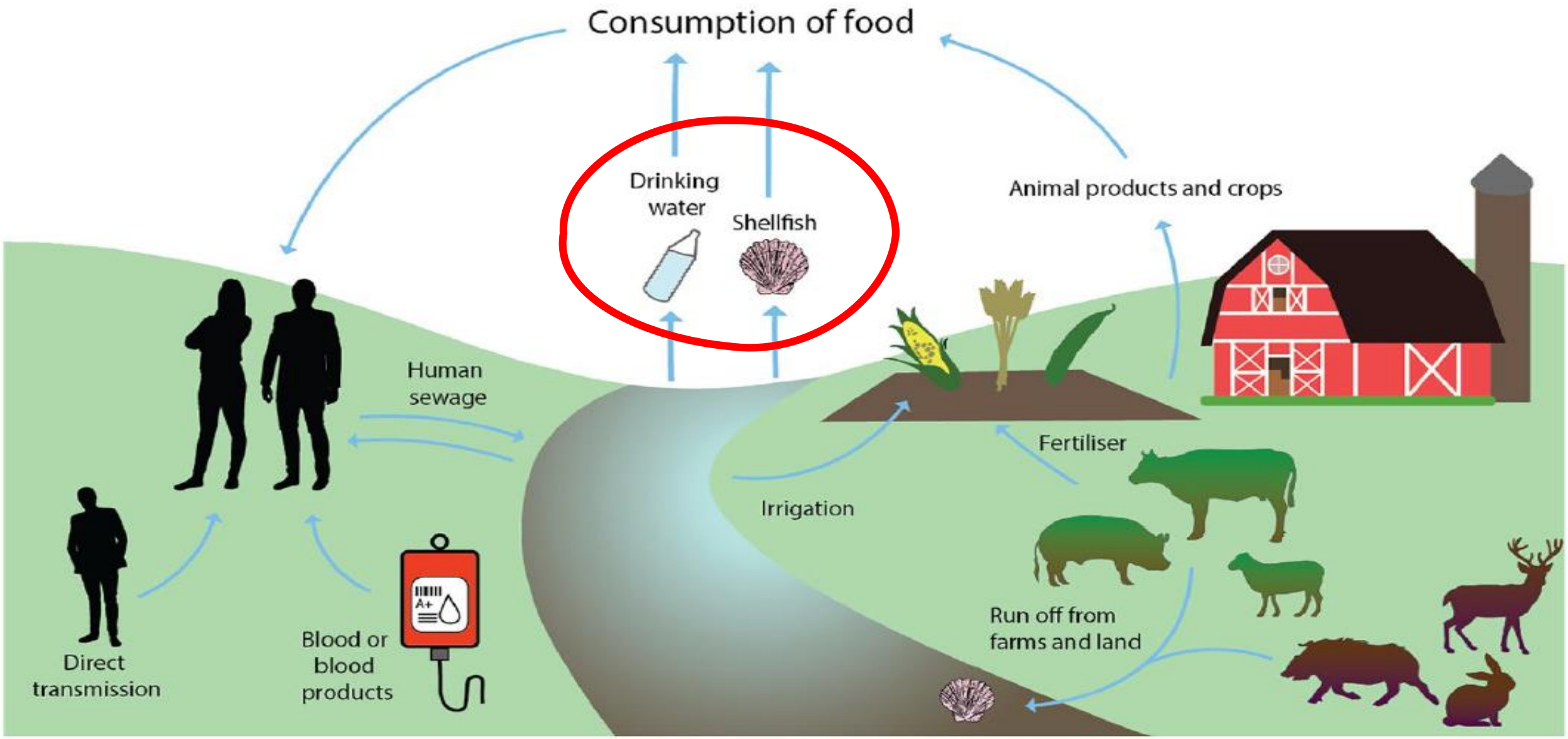
Year(s)	Country	Mode of Transmission	Reported
1991	China	Waterborne	119,000
1991	Indonesia	Waterborne	1688 [1]
1993–1994	Pakistan	Waterborne	3827
1994	Vietnam	After heavy rains	>300
1994	Morocco	Fecal contamination of drinking water	73
1995–1996	Namibia	Waterborne	>600
1998	India	Waterborne	82
1998	Indonesia	Waterborne	472
1998	Pakistan	Fecal contamination—water system	104
2002	India	Contaminated water	185
2004	Central African Republic	Rainy season	213
2004	Sudan	Safe water insufficient	>2600
2004	India	Drinking untreated raw river water	538
2004	Chad	Waterborne	1442 [1]
2005	Iraq	Waterborne	268 [1]
2005	India	Contaminated drinking water	429
2006	Sudan	Waterborne	2621
2007–2008	India	Fecal contamination of water resources	64
2007–2008	Egypt	Waterborne	28
2007–2009	Uganda	Waterborne	146
2008	India	Sewage contamination of the river	23,915 [1]
2008	Uganda	Substantial person-to-person	>10,000
2008–2009	Bangladesh	Sewage contamination—municipal water	4751 [1]
2009–2012	Uganda	Contaminated water	987
2010	Bangladesh	Waterborne	200
2010	India	Waterborne	102
2005–2010	India	Waterborne	442
2010–2011	Sudan	Waterborne	39
2012	India	Fecal contamination of drinking water	180
2012	Kenya	Waterborne	131
2008–2012	Central African Republic	Waterborne	745
2012–2013	South Sudan	Waterborne	5080 [1]
2013	India	Sewage contamination of drinking water	240

Year(s)	Country	Mode of Transmission	Reported
2013	Cameroon	Waterborne	33
2014–2015	Bangladesh	Waterborne	103
2014–2016	India	Waterborne	17
2016–2017	Chad	Waterborne	1293
2017–2018	Nigeria	Contamination of drinking water	1376
2014–2017	Bangladesh	Waterborne	661
2018	Central African Republic	Waterborne	149
2018	South Sudan	Waterborne	161
2019	Pakistan	Waterborne	300
2017–2020	Namibia	Waterborne	7247

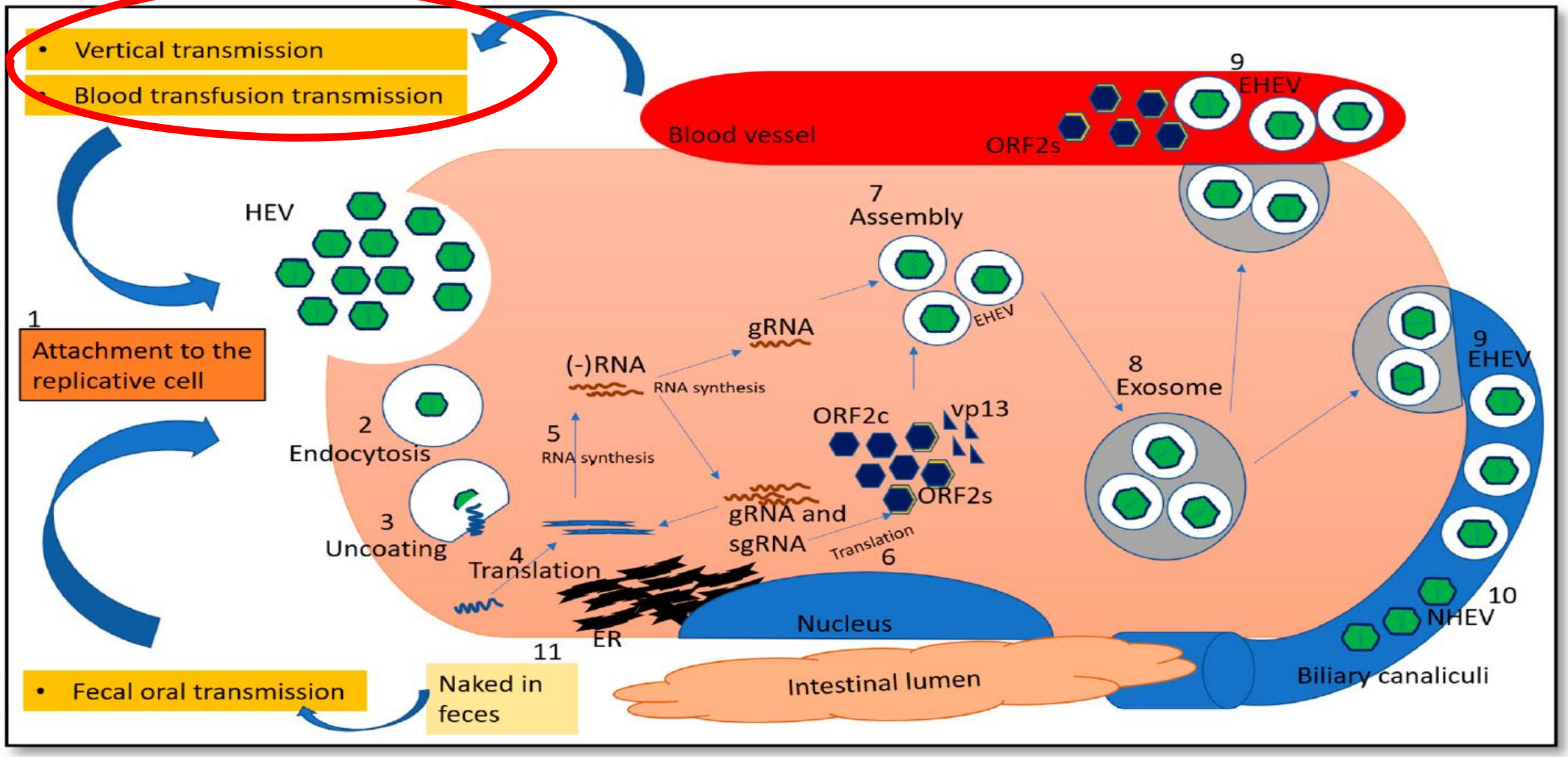
Transmission

- **HEV: worldwide, most common in East South Asia, Africa and Central America. HEV transmitted via fecal-oral (contaminated water).**
- **In Europe, HEV is mainly zoonotic disease (pigs primary reservoir HEV3). Contaminated food products (undercooked pork, game meat)**
- **Occupationally group: slaughterhouse, forestry workers, hunters, farmers, veterinarian.**
- **The differences in seroprevalence between/within countries reflect different exposure to HEV, lower or higher endemicity within source population pigs, different consumer habits (raw pig liver).**





HEV1 and 2 spread by fecal-oral route via contaminated water.
HEV3 and 4 infect humans, pigs, animal species, responsible for sporadic cases



ORF1 translation. RdRp synthesizes negative strand RNA (- RNA), followed by synthesis of genomic RNA (gRNA) and sub-genomic RNA (sgRNA). Translation of structural proteins occurs followed by assembly and egress. The released HEV is enveloped (EHEV), however when released into biliary canaliculi, envelope becomes degraded, and naked (NHEV) virions are released into intestines and excreted in feces. The EHEV is also released into the blood vessels. Furthermore, ORF2s (secreted form) is glycosylated and secreted into the blood stream. When such blood is transfused to naive patients or if the woman is pregnant, HEV transmission happens, which is referred as blood-borne transfusion or vertical transmission, respectively. Number 1 to 11 represents the step-by-step process occurring in the life cycle. ER—Endoplasmic reticulum.

Transfusion or transplantation transmitted HEV have sporadically, asymptomatic infection among blood donors is widespread.

- **In last decade, increasing incidence HEV3-donations in European countries.**
- **England, Ireland: selective or universal screening of blood donations. Other countries are considering similar screening.**

TABLE

Prevalence of hepatitis E virus RNA positive donations, population of transplanted patients at risk, reported cases of transfusion-transmitted hepatitis E virus and screening of blood donations in 11 European countries

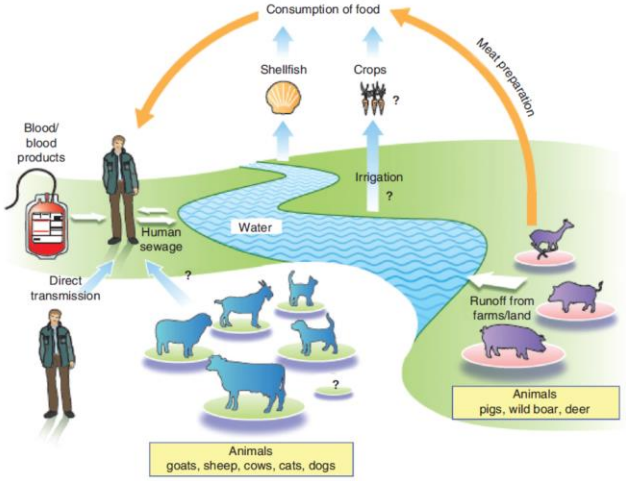
Country	HEV RNA positive donations	Population at risk		Reported TT HEV infections	Screening of blood donations			
		allo-HSCT [51] AN (AR/p1omp)	SOT [52] AN (AR/pmp)		Implemented	Under Consideration	In evaluation	Not recommended
Denmark	1:2,331(2016) [16]	144 (201 – 300)	356 (63.6)					x
France	1:2,218 (2012–3) [18]	1,724 (201 – 300)	5,141(79.6)	x		x[a]		
Germany	1:1,241 (2012) [24]	2,892 (›300)	3,710 (44.9)	x		x[b]		
Greece	NA	169 (151 – 200)	171 (15.4)				x	
Ireland	1:2,778 (2016)	77(151 – 200)	246 (52.3)		x[c]			
Italy	NA	1,625 (201 – 300)	3,252 (53.2)				x	
The Netherlands	1: 726 (2016) [7]	1175 (›300)	1,315 (78.3)			x [d/e]		
Portugal	NA	137 (101 – 150)	739 (69.7)				x	
Spain	1:3,333 (2014) [53]	1,072 (201 – 300)	4,247 (90.2)	x			x	
Switzerland	NA	191 (201 – 300)	504 (61.5)			x		
United Kingdom	1:1,340–5,000 (2016)	1,602 (201 – 300)	4,561 (71.8)	x	x[e/f]			

allo-HSCT: allogeneic haematopoietic stem cell transplant patients; AN: annual number; AR: annual rate; HEV: hepatitis E virus; NA: not

EUROROUNDUP

Hepatitis E and blood donation safety in selected European countries: a shift to screening?

D Domanović [1], R Tedder [2], J Blümel [3], H Zaaijer [4], P Gallian [5], C Niederhauser [6], S Sauleda Oliveras [7], J O'Riordan [8], F Boland [8], L Harritshøj [9], MSJ Nascimento [10], AR Ciccaglione [11], C Politis [12], C Adlhoch [1], B Flan [13], W Oualikene-Gonin [14], G Rautmann [15], P Strengers [16], P Hewitt [17]



ITALIA

HEV-seroprevalence in Italian general population in 6/20 regions:1.5-2.9%. (before 1999)

- **2007-2016: 144 cases of AHE to Italian Surveillance System AVH: 122 (84.7%) M, mean age 40 yrs, 81 (56.6%) Italian.**
- **2004-2016 virological surveillance of 139 AVH non-A, non-B, non-C: 48 (34.5%) HEV. HEV1 55% (22/40), HEV3 45% (18/40).**
- **2014 HEV-ab blood donor: Abruzzo 48.9% (153/313), Lazio 9.0% (9/100). In Lazio in donor population is higher than general population (2.6% in 1996, 2.9% in 2007)**
- **Seroprevalence increased with age and associated with raw dried pork liver sausages. Among 153 IgG positive blood donors in Abruzzo, 2 (1.3%) with IgM, and 2 (1.3%) HEV RNA; HEV3c.**

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Transfusion. 2019 March ; 59(3): 1024–1034. doi:10.1111/trf.15140.

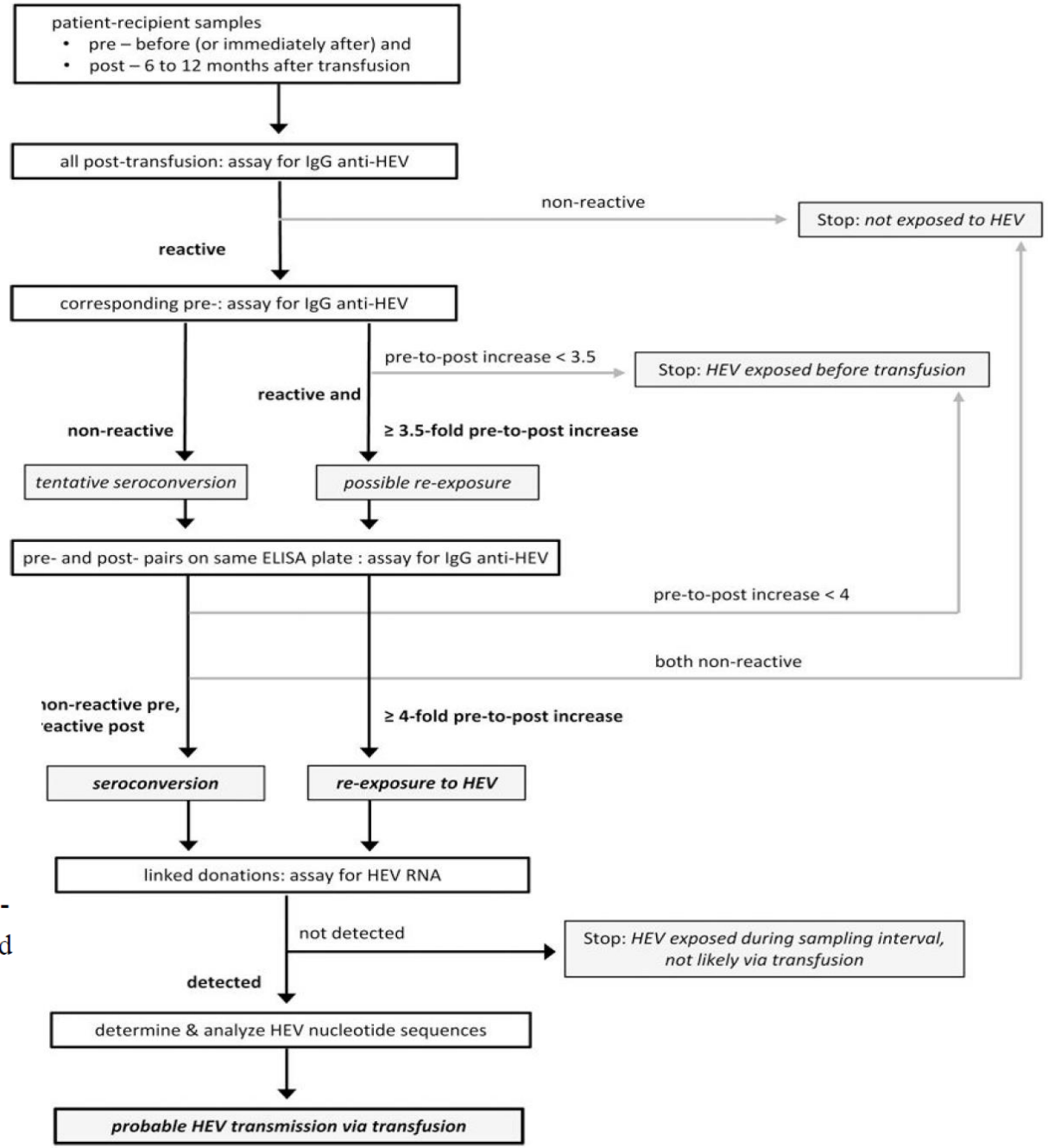
Probable Transmission of Hepatitis E Virus (HEV) via Transfusion in the United States

John R Ticehurst[1,4,6], Nora Pisanic[2], Michael S Forman[6], Carly Ordak[2], Christopher D Heaney[2,1,3], Edgar Ong[8,*], Jeffrey M Linnen[8,†], Paul M Ness[7,5], Nan Guo[1,‡], Hua Shan[9], and Kenrad E Nelson[1,4]

We assayed post-transfusion specimens for IgG anti-HEV and, for those with reactive results, tested corresponding pre-transfusion specimens in subsequent assay-runs. Each specimen-pair that yielded preliminary evidence of HEV exposure during the sampling interval, as manifested by seroconversion or by ≥ 3.5-fold increase in IgG anti-HEV S/CO value, was re-assayed on single ELISA plate. We then assayed for HEV RNA in donations that were linked to patients who had single-plate confirmed seroconversion or ≥ 4-fold increase of IgG anti-HEV concentration. we determined and analyzed partial nucleotide sequences of any detected HEV RNA in donation samples

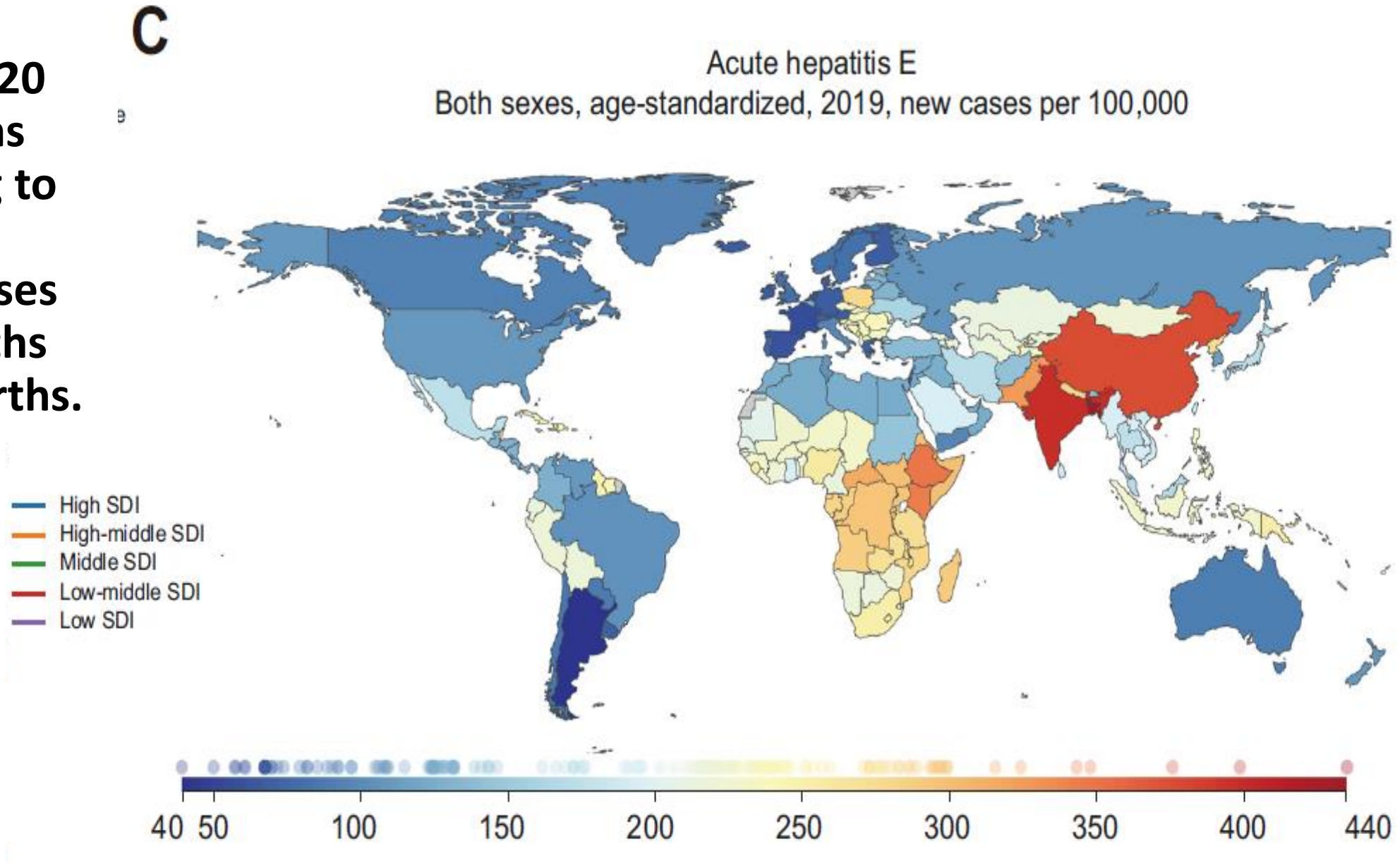
STUDY DESIGN AND METHODS: To identify donations that contained HEV RNA and were linked to patient-recipients with antibody evidence of HEV exposure, we assayed samples from the Retrovirus Epidemiology Donor Study (REDS) Allogeneic Donor and Recipient repository that represents 13,201 linked donations and 3384 transfused patients. Post-transfusion samples, determined to contain IgG anti-HEV by ELISA, were re-assayed along with corresponding pre-transfusion samples for seroconversion (incident exposure) or ≥4-fold IgG anti-HEV increase (re-exposure). HEV-exposed patients were linked to donations in which HEV RNA was then detected by RT-qPCR, confirmed by Transcription Mediated Amplification (TMA), and phylogenetically analyzed as sub-genomic cDNA sequences.

Testing algorithm for patient-recipient and donation samples



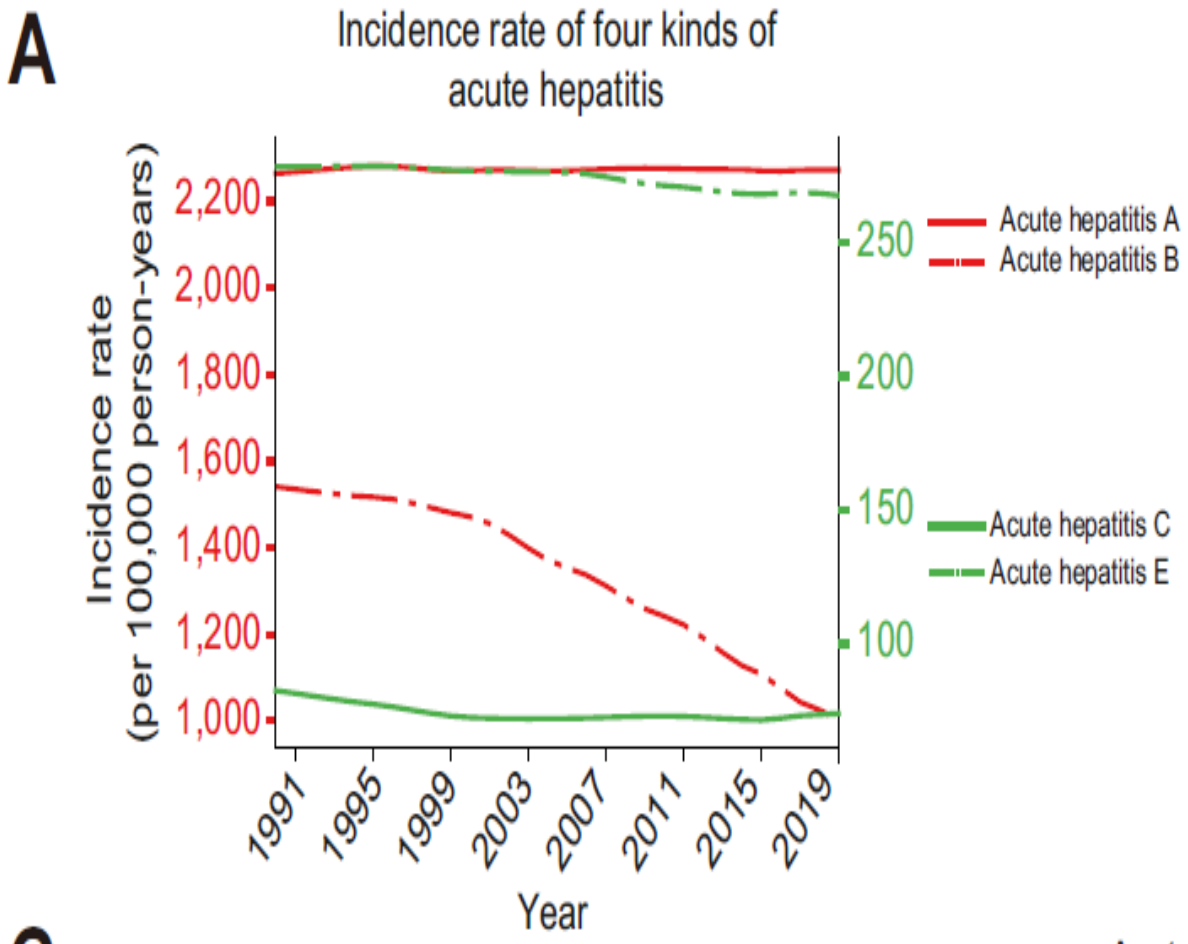
Global burden of acute viral hepatitis and its association with socioeconomic development status, 1990–2019

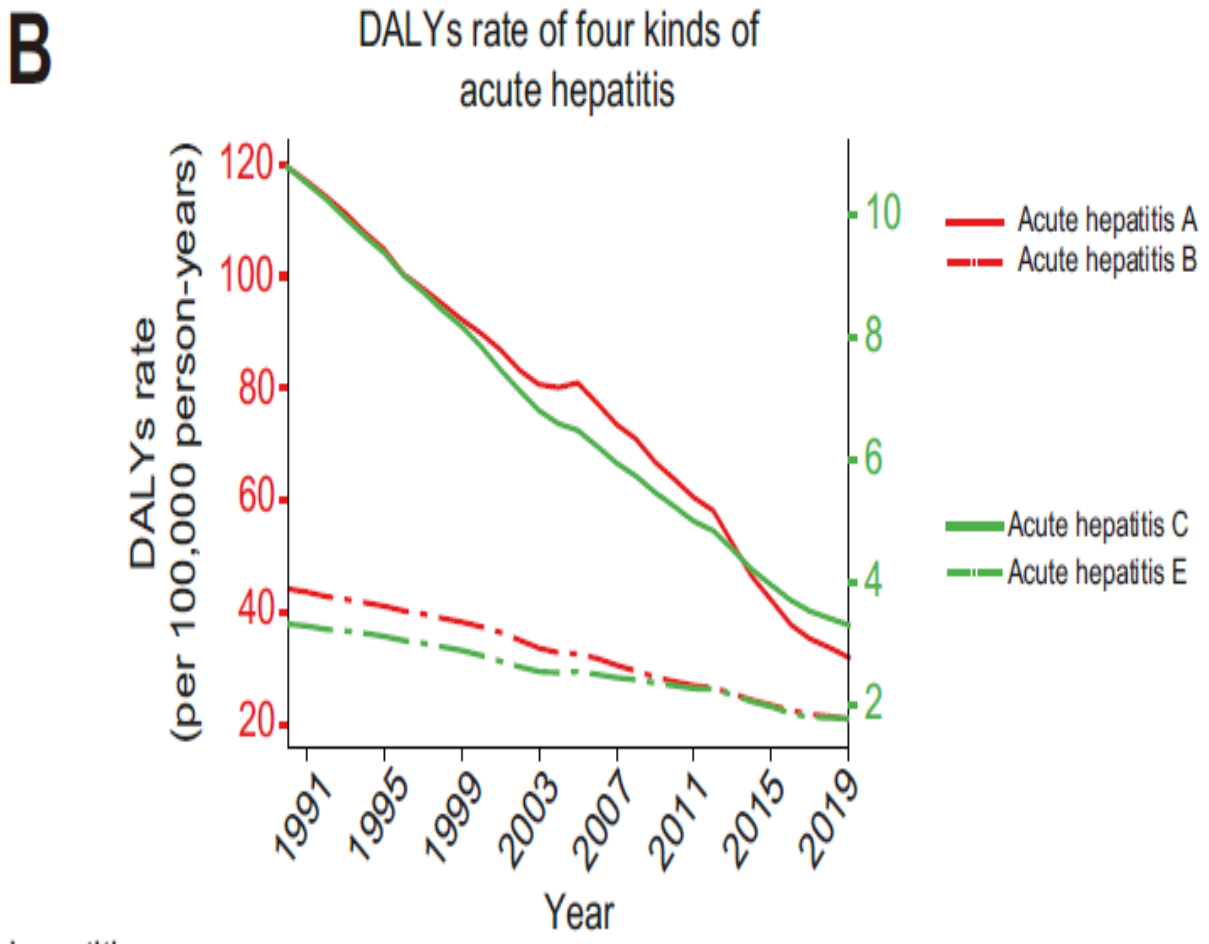
HEV: estimated 20 million infections per year leading to 3.4 million symptomatic cases and 70,000 deaths plus 3000 stillbirths.



Global burden of acute viral hepatitis and its association with socioeconomic development status, 1990–2019

JOURNAL OF HEPATOLOGY





C

Acute hepatitis

Sociodemographic index (SDI), disability-adjusted life year (DALY)

Burden of acute HEV

East and South Asian regions shoulder the heaviest burden of AHE.

highest incidence rates: Bangladesh (435.3 [353.6–518.4] per 100,000 p-y), followed India, China.

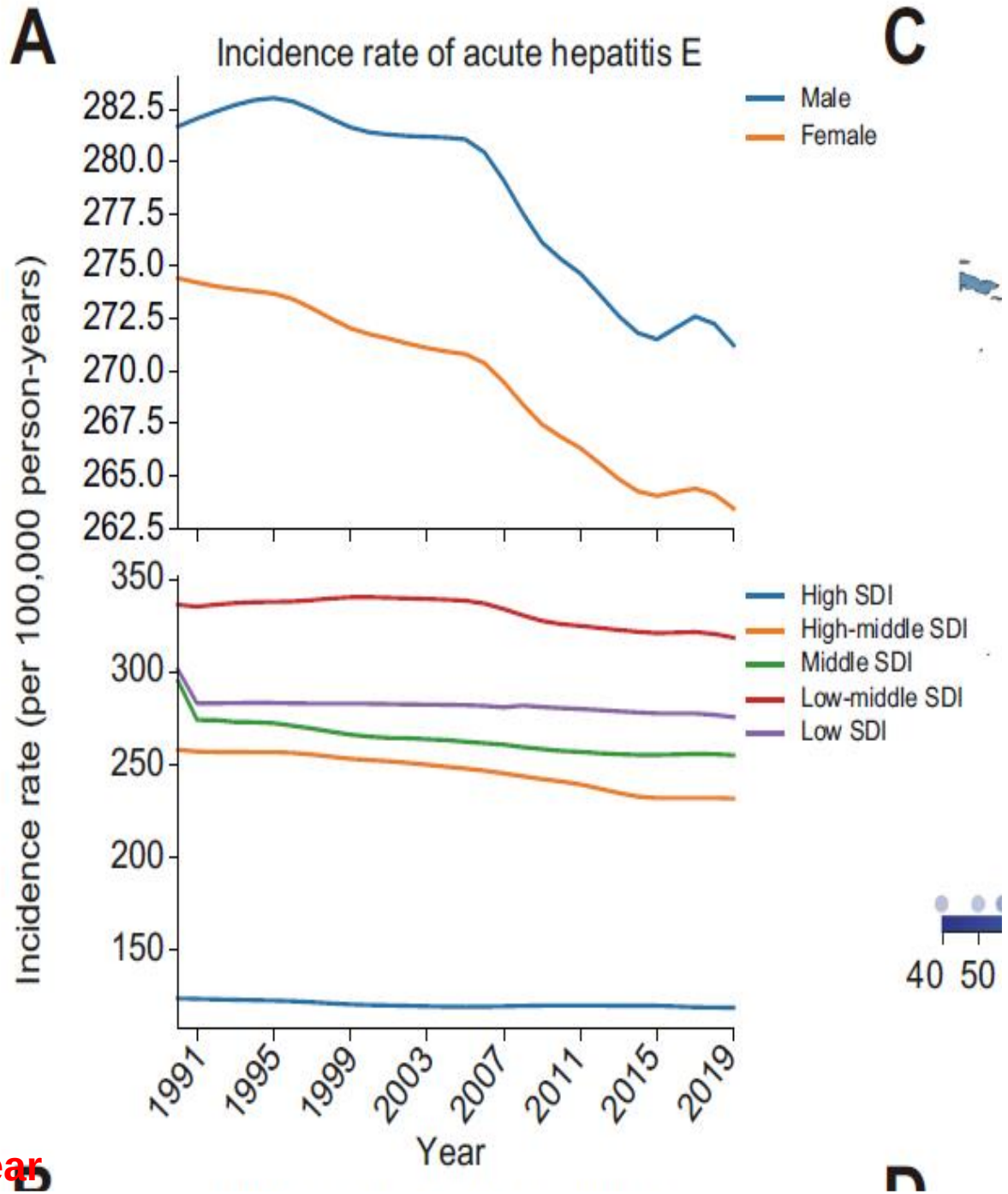
highest DALY rates: Tonga (8.1 [4.4–13.4] per 100,000 p-y), followed Zimbabwe, India.

the lowest age-standardized incidence rate: Argentina, San Marino, France.

lowest DALY rates: Austria, Switzerland, Israel.

the dominant circulating genotype in China has shifted from HEV1 to HEV4, reflect improvement in sanitary infrastructure since HEV1 are obligate human pathogens spread by fecal-oral route via contaminated water.

Sociodemographic index (SDI), disability-adjusted life year (DALY)



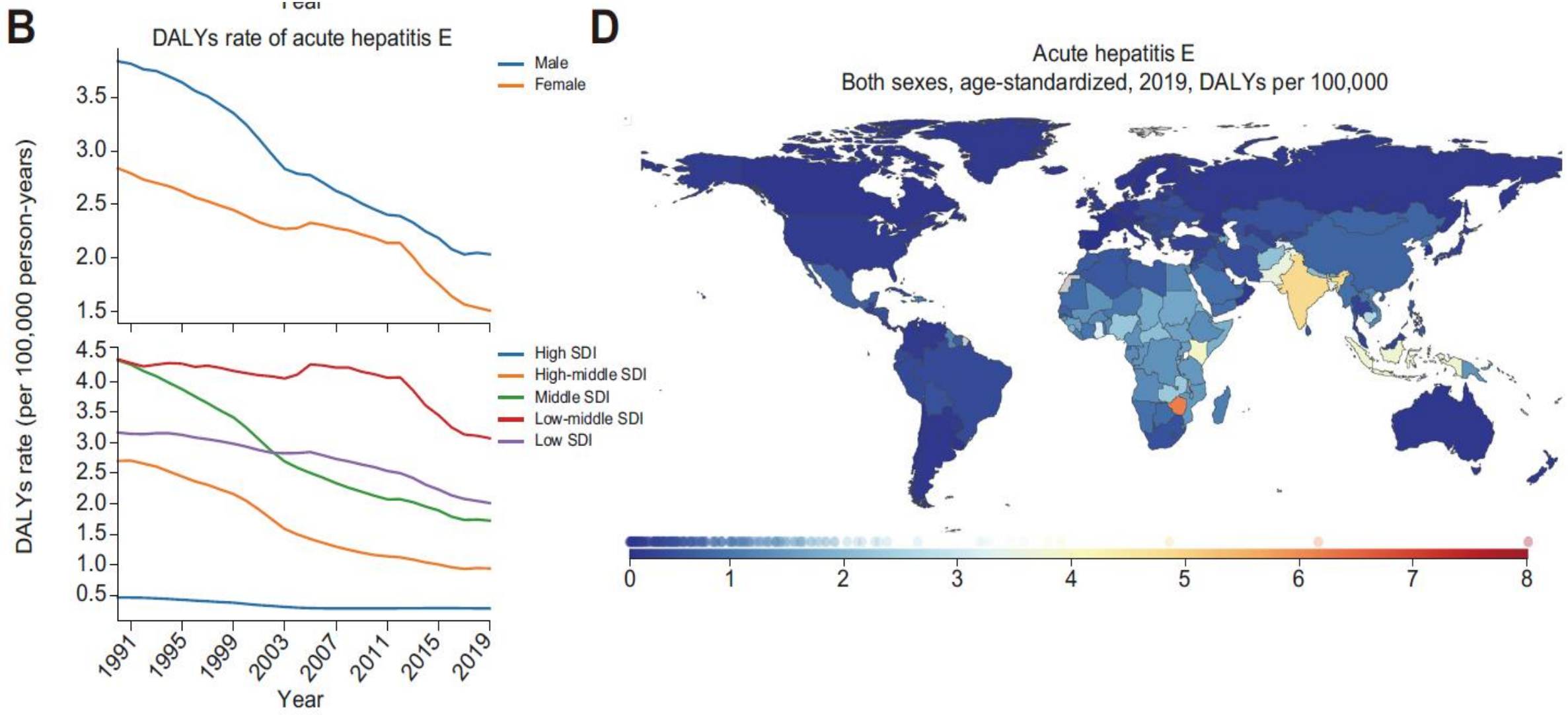


Fig. 5. Burden of AHE for 204 countries and territories. Age-standardized (A) incidence and (B) DALY rates of AHE per 100,000 population from 1990 through 2019 categorized according to country and territory, stratified by sex or SDI. Age-standardized (C) incidence and (D) DALY rates of AHE per 100,000 person-years by country and territory, in 2019. The maps in (C) and (D) were generated by the GBD 2019 tool. AHE, acute hepatitis E; DALY, disability-adjusted life year; GBD, Global Burden of Disease; SDI, socio-demographic index.

Sociodemographic index (SDI), disability-adjusted life year (DALY)

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REVIEW PAPER

The Foodborne Transmission of Hepatitis E Virus to Humans

Samantha Treagus[1,3] · Conal Wright[2] · Craig Baker-Austin[3] · Ben Longdon[1] · James Lowther[3]

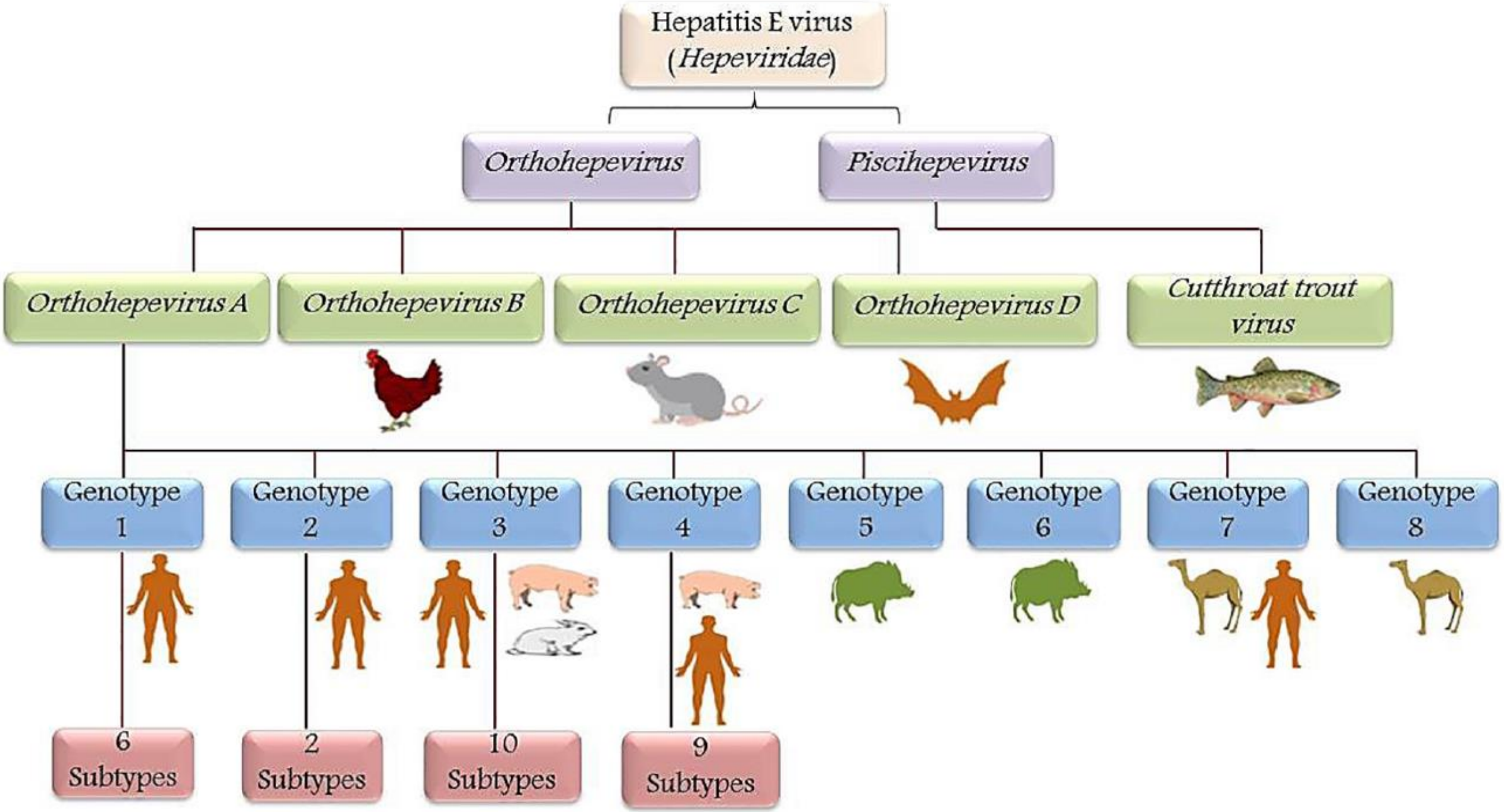
Table 1 Pattern of infection for the different genotypes of HEV, adapted from Centers for Disease Control and Prevention (2020)

Genotype	Transmission in humans?	Transmission routes	Geographical distribution pattern	Extrahepatic manifestations	Age groups at higher risk	Gender more commonly affected	Lethality
1	Yes	Faecal-oral; waterborne; blood transfusion; organ donation	Economically developed and developing countries	Pancreatic	Differs by country[a,b]	Differs by country[a,b]	0.5–1%[c]; 20% in pregnant women[d,e,f]
2	Yes	Faecal-oral; waterborne; blood transfusion; organ donation	Economically developing countries	Unknown	Young adults	Unknown	0.5–1%[c]
3	Yes	Foodborne; blood transfusion; organ donation	Economically developed and developing countries	Chronic infections in immune-compromised patients. Neurological, haematological, immunological and renal manifestations[g]	Older adults (>40 years)	Males	0.5–1%[c]
4	Yes	Foodborne; blood transfusion; organ donation	Economically developed and developing countries	Unknown	Young adults	Possibly males (limited data)[h]	0.5–1%[c]
5	No	Faecal-oral	Unknown	Unknown	Unknown	Unknown	Unknown
6	No	Faecal-oral	Unknown	Unknown	Unknown	Unknown	Unknown
7	Yes	Foodborne; Faecal-oral; blood transfusion?	Unknown	Unknown	Unknown	Unknown	Unknown
8	No	Faecal-oral	Unknown	Unknown	Unknown	Unknown	Unknown

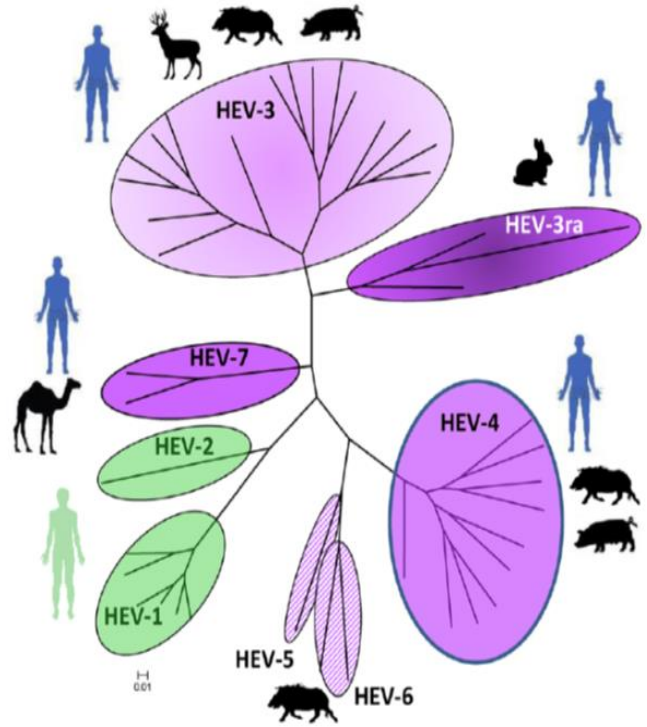
Table 2 Summary of HEV host species by genotype adapted from Kenney (2019)

Genotype	Hosts identified (common names)	Species infected
1	Humans, Chimpanzees, Monkeys, Horses	*Homo sapiens, Pan troglodytes, Chlorocebus sabaeus*[a], *Chlorocebus pygerythrus*[a], *Erythrocebus patas*[a], *Macaca mulatta, Macaca radiata, Macaca fascicularis, Semnopithecus entellus, Aotus trivirgatus*[a], *Saguinus mystax mystax*[a], *Saimiri sciureus*[a], *Equus caballus ferus*
2	Humans, Monkeys	*Homo sapiens, Chlorocebus pygerythrus*[a], *Erythrocebus patas*[a], *Macaca mulatta, Macaca fascicularis, Aotus trivirgatus*[a], *Saguinus mystax mystax*[a], *Saimiri sciureus*[a]
3	Humans, Monkeys, Hares and Rabbits, Rats, Minks, Mongooses, Pigs, Goats and Sheep, Deer, Dolphins, Horses, Vultures	*Homo sapiens, Erythrocebus patas, Macaca mulatta, Macaca fascicularis, Macaca fuscata, Lepus europaeus, Oryctolagus cuniculus domesticus, Rattus norvegicus, Neovison vison, Herpestes javanicus, Sus scrofa, Sus scrofa domestica, Capra hircus aegagrus, Ovis aries orientalis, Cervus elaphus, Cervus nippon, Capreolus, Tursiops truncatus, Equus africanus, Equus caballus ferus, Gyps himalayensis*
4	Humans, Monkeys, Gerbils, Dogs, Bears, Leopards, Pigs, Cows, Goats, Deer, Cranes, Pheasants	*Homo sapiens, Macaca fascicularis, Macaca mulatta, Meriones unguiculatus*[a], *Canis lupus familiaris, Ursus thibetanus, Neofelis nebulosa, Sus scrofa, Sus scrofa domesticus, Bos taurus primigenius, Bos grunniens, Capra hircus aegagrus, Ovis aries orientalis, Cervus nippon, Elaphodus cephalophus, Muntiacus reevesi, Balearica regulorum, Lophura nycthemera*
5	Monkeys, Pigs	*Macaca fascicularis, Sus scrofa*
6	Pigs	*Sus scrofa*
7	Humans, Camels	*Homo sapiens, Camelus dromedarius,*
8	Camels	*Camelus bactrianus*

[a]Infections instigated through experimental conditions


Hepatitis E virus
(Hepeviridae)
Orthohepevirus
Piscihepevirus
Orthohepevirus A
Orthohepevirus B
Orthohepevirus C
Orthohepevirus D
Cutthroat trout virus
Genotype 1
Genotype 2
Genotype 3
Genotype 4
Genotype 5
Genotype 6
Genotype 7
Genotype 8
6 Subtypes
2 Subtypes
10 Subtypes
9 Subtypes

Genotype [1] (Subtypes)	Host	Transmission Route	Global Distribution [1]
HEV-1 (1a–1g)	Human, primates	Fecal–oral via contaminated drinking water	Mainly resource poor regions in India, Pakistan, Bangladesh, Myanmar, China, Mongolia, Morocco, Chad, Nigeria
HEV-2 (2a, 2b)	Human, primates	Fecal–oral via contaminated drinking water	Mainly resource poor regions in Mexico, Nigeria
HEV-3 (3a–3m, 3ra)	Human, pig, wild boar, deer, mongoose, rabbit (3ra), hare (3ra), rodents	Zoonotic via consumption or contact of/with contaminated foodstuffs; parenteral via contaminated blood donations	Mainly in industrialized countries such as USA, Canada, China, Japan, South Korea, India, Singapore, UK, Germany, France, Italy, Spain, Sweden, Switzerland, Netherlands, Denmark, Hungary



Genotype [1] (Subtypes)	Host	Transmission Route	Global Distribution [1]
HEV-4 (4a–4i)	Human, pig, wild boar, cow, goat, yak, Rhesus monkey	Zoonotic via consumption or contact of/with contaminated foodstuffs; parenteral via contaminated blood donations	Mainly in Asian countries such as China, Mongolia, Japan, South Korea, Taiwan, Cambodia, India
HEV-5 (5a)	Wild boar	Unavailable	Japan
HEV-6 (6a)	Wild boar	Unavailable	Japan
HEV-7 (7a)	Human, dromedary camel	Zoonotic, likely via consumption of camel meat	UAE
HEV-8 (8a)	Bactrian camel	Unavailable	China

[1] Information according to the International Committee on Taxonomy of Viruses (ICTV) as of September 2020 and Smith et al. 2020 [10].

The Global Threat–Epidemiological Aspects of HEV

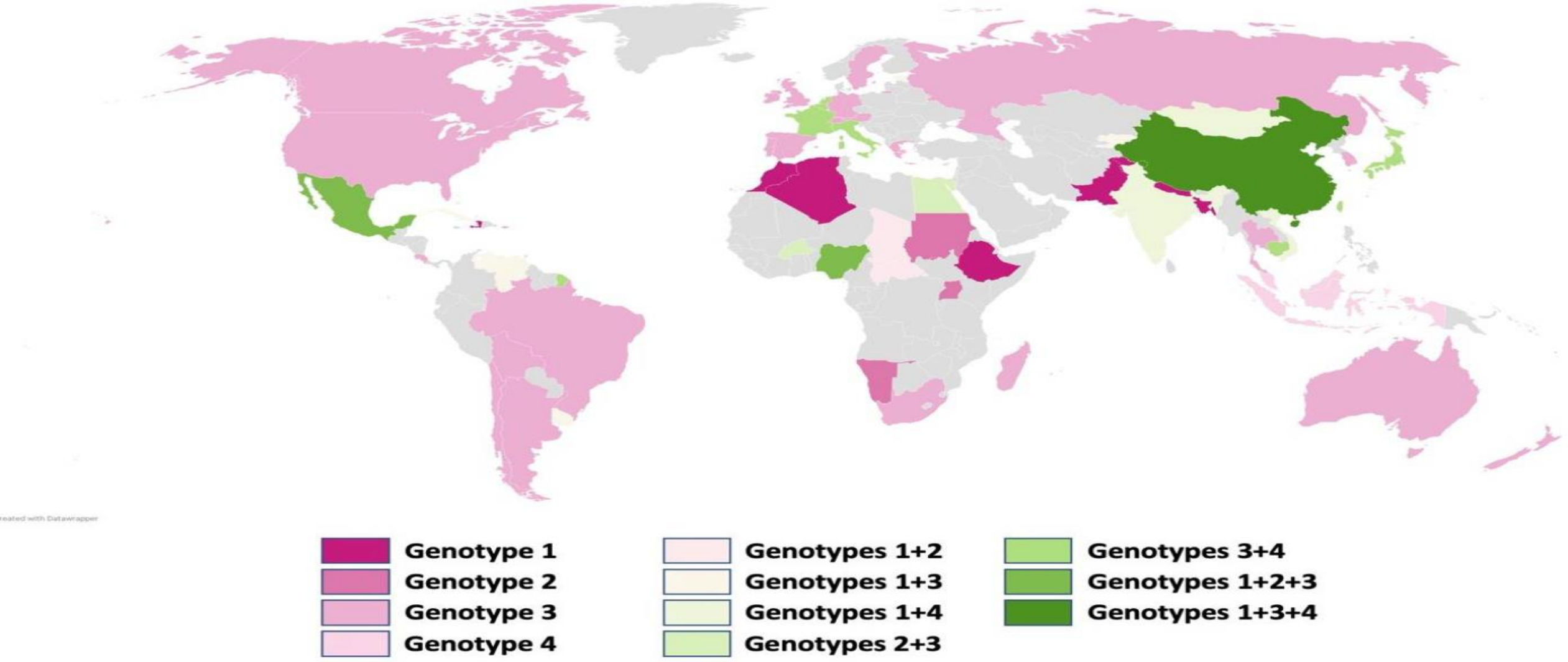


Figure 1. Map with the geographical distribution of the four major human pathogen HEV genotypes. Data adapted from WHO and map generated with Datawrapper, Berlin, Germany.

HEV genotype

Characteristics	Genotype 1	Genotype 2	Genotype 3	Genotype 4
Geographic Location	Africa and Asia	Mexico, West Africa	Developed Countries	China, Taiwan, Japan
Transmission route	Waterborne fecal-oral person-to-person	Waterborne fecal-oral	Food-borne	Food-borne
Groups at high risk for infection	Young Adults	Young Adults	Older Adults (>40 years) and males, immunocompromised persons	Young Adults
Zoonotic transmission	No	No	Yes	Yes
Chronic Infection	No	No	Yes	No
Occurrence of Outbreaks	Common	Smaller scale outbreaks	Uncommon	Uncommon

chttps://www.cdc.gov/hepatitis/hev/hevfaq.htm#section1

Table 3 A list of the seroprevalence levels of anti-HEV antibodies in pigs and the percentage of pork products found to be HEV positive by RT-PCR in those locations

Location	Pig sample population anti-HEV antibody seroprevalence	Percentage of tested foodstuffs HEV positive by RT-PCR
Brazil	63.6% of 357 pigs (Vitral et al. 2005)	1.7% of 118 slaughterhouse livers (Gardinali et al. 2012)
Canada	59.4% of 998 pigs (Yoo et al. 2001)	8.8% of 283 livers, 1.0% of 599 pork chops (Wilhelm et al. 2014)
		47.0% of 76 pork pâtés and 10.5% of 19 retail raw pork livers (Mykytczuk et al. 2017)
France	31.0% of 6565 pigs (Rose et al. 2011); 60% of 1034 pigs (Feurer et al. 2018)	4.0% of 3715 slaughterhouse livers (Rose et al. 2011)
		2.8% of 1034 slaughterhouse livers (Feurer et al. 2018)
		30.0% of 140 figatelli and fitone, 29.0% of 169 liver sausages, 25.0% of 55 quenelles or quenelle paste, 3.0% of 30 dried salted livers (Pavio et al. 2014)
		58.3% of 12 raw liver sausage (Colson et al. 2010)
Germany	49.8% of 1072 pigs (Baechlein et al. 2010)	4.0% of 200 retail livers (Wenzel et al. 2011)
		20.0% of 70 raw sausages and 22.0% of 50 liver sausages (Szabo et al. 2015)
Italy	45.1% of 2700 pigs (Mughini-Gras et al. 2017)	20.8% of 48 slaughterhouse livers (Di Bartolo et al. 2011)
		6.0% of 33 slaughterhouse livers (Di Bartolo et al. 2012)
		13.3% of 15 fresh liver sausages, 7.1% of 14 dried liver sausages (Di Bartolo et al. 2015)
Japan	57.9% of 2500 pigs (Takahashi et al. 2003)	1.9% of 363 retail livers (Yazaki et al. 2003)
Netherlands	89.0% of 417 organic pigs, 72% of 265 conventionally farmed pigs, 76% of 164 free range pigs (Rutjes et al. 2014)	6.5% of 62 commercial pork livers (Bouwknegt et al. 2007)
		12.7% of 79 livers, 70.7% of 99 liver sausages, 68.9% of 90 liver pâté samples (Boxman et al. 2019)
Spain	20.4% of 1441 pigs (de Oya et al. 2011)	6.0% of 93 sausages, 3.0% of 39 slaughterhouse livers (Di Bartolo et al. 2012)
Switzerland	62.3% of 1001 pigs in 2006, 53.8% of 999 pigs in 2011 (Burri et al. 2014)	1.3% of 160 slaughterhouse livers (Müller et al. 2017)
		11.8% of 102 raw liver sausages (Giannini et al. 2017)
		11.7% of 90 pork liver and raw meat sausages (Moor et al. 2018)
UK	92.8% of 629 pigs, with 20.5% viraemic at slaughter (Grierson et al. 2015)	10.0% of 63 sausages, 3.0% of 40 slaughterhouse livers (Berto et al. 2012)
USA	21.9% of 182 pigs (Owolodun et al. 2013)	11.0% of 127 retail liver (Feagins et al. 2007)

Table 8 The presence of HEV in shellfish in different countries

Location	Study	Percentage of shellfish HEV positive
China	Gao et al. (2015)	17.5% of 126 shellfish samples[a] of various species from production areas
Denmark	Krog et al. (2014)	0% of 29 mussel samples[a] from 19 production areas
France	Grodzki et al. (2014)	0% of 286 shellfish samples[a] of various species from two production areas
Italy	La Rosa et al. (2018)	2.6% of 384 shellfish samples[a] of various species from production areas
Japan	Li et al. (2007)	6.3% of 32 Yamato-Shijimi clam samples[a]
Scotland	Crossan et al. (2012)	85.4% of 48 individual wild mussels
	O'Hara et al. (2018)	2.9% of 310 retail shellfish samples[a] (mussels and oysters)
Spain	Mesquita et al. (2016)	14.8% of 81 mussel samples[a] from a production area
	Rivadulla et al. (2019)	24.4% of 164 mussel, clam, and cockle samples[a]

[a]Where the study states that samples of shellfish were tested, it was either stated or assumed in each publication that each "sample" would have been formed by ten or more shellfish individuals and is therefore technically a pooled sample

Thermal inactivation treatments for HEV in non-food matrix samples

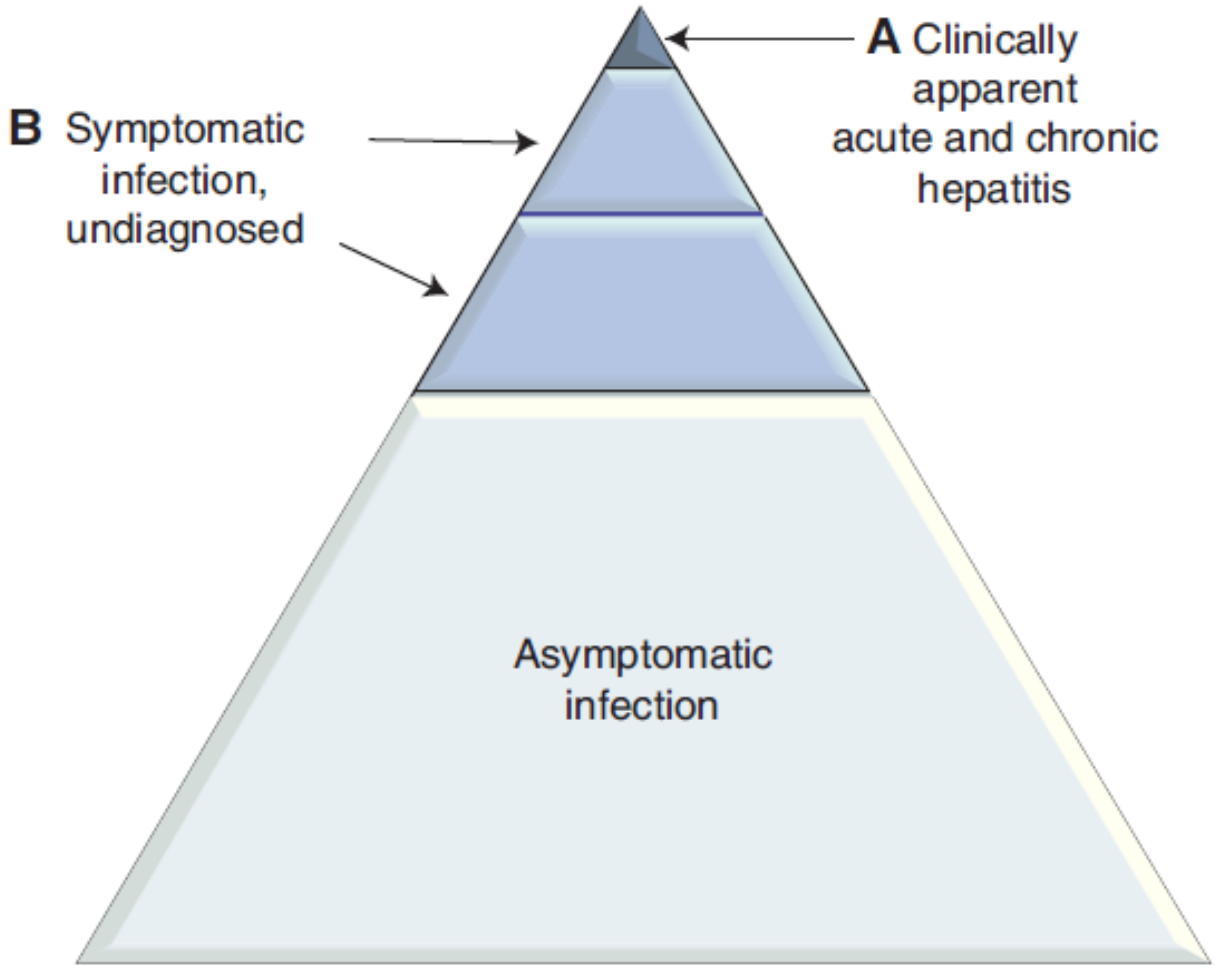
Study	Cell culture or molecular detection?	Genotype	Heat treatment		Growth period	Inactivation/reduction
			Temperature (°C)	Time (min)		
Emerson et al. (2005)	Cell culture, HepG2/C3A cells	1 (strain Akluj[a])	56	60	5–6 days	> 80% reduction
		1 (strain SAR55[b])	56	60	5–6 days	~ 50% reduction
		2 (strain Mex14[c])	60	60	5–6 days	96% reduction
Huang et al. (1999)	Cell culture, A549 cells	3 (strains G93-1*, G93-2*, G93-3*, G93-4*)	56	30	72 h	< 1.0 (TCID50/0.025 ml)
Johne et al. (2016)	Cell culture, A549/D3 cells	3 (strain 47832c[f])	55	1	35 days	~ 1 log reduction in focus forming units
			70	2		"No infectious virus"
Schielke et al. (2011)	Molecular detection	3 (strain wbGER27[e])	56	15	N/A	74.07% reduction
		3 (strain wbGER27[e])	56	60	N/A	99.90% reduction
Tanaka et al. (2007)	Cell culture, PLC/PRF/5 cells	3 (strain JE03-1760F[d])	70	10	35 days	"No infectious virus"
		3 (strain JE03-1760F[d])	56	30	50 days	"Still infectious"

thermal inactivation treatments for HEV in foodstuffs

Study	Food stuff	Cooking method	Temperature (°C)	Time (min)	Measurement of inactivation	HEV inactivated?
Barnaud et al. (2012)	Pâté preparation (spiked with 10^8 HEV genome copies)	Water bath	62	5	Intravenous administration to pigs	No
				20		No
				120		No
			68	5		No
				10		No
				20		No
			71	5		No
				10		No
				20		Yes
Feagins et al. (2008)	Pig liver (naturally infected)	Incubation	56	60	Oral administration to pigs	No
		Boiling	≥ 71 (internal)	5		Yes
		Stir fry	≥ 71 (internal)	5		Yes
Imagawa et al. (2018)	Minced meat (spiked with 10^{10} HEV genome copies)	Boiling or roasting	63	1	Cell culture	No
				5		No
				30		Yes
			65	1		No
				5		Yes
			70	1		No
				5		Yes

HEV Presentazione Clinica

- **Il periodo di incubazione**: 2-10 wks, (media 5-6 wks).
- Le persone infette espellono HEV da pochi giorni prima fino a 3-4wks dopo l'insorgenza della malattia.
- Il rapporto tra infezione sintomatica e asintomatica varia da 1:2 a 1:13.
- Più del 90% di HEV3 e 4 sono asintomatici. Una piccola minoranza di pazienti (maschi più anziani) sviluppa epatite sintomatica (A).
-

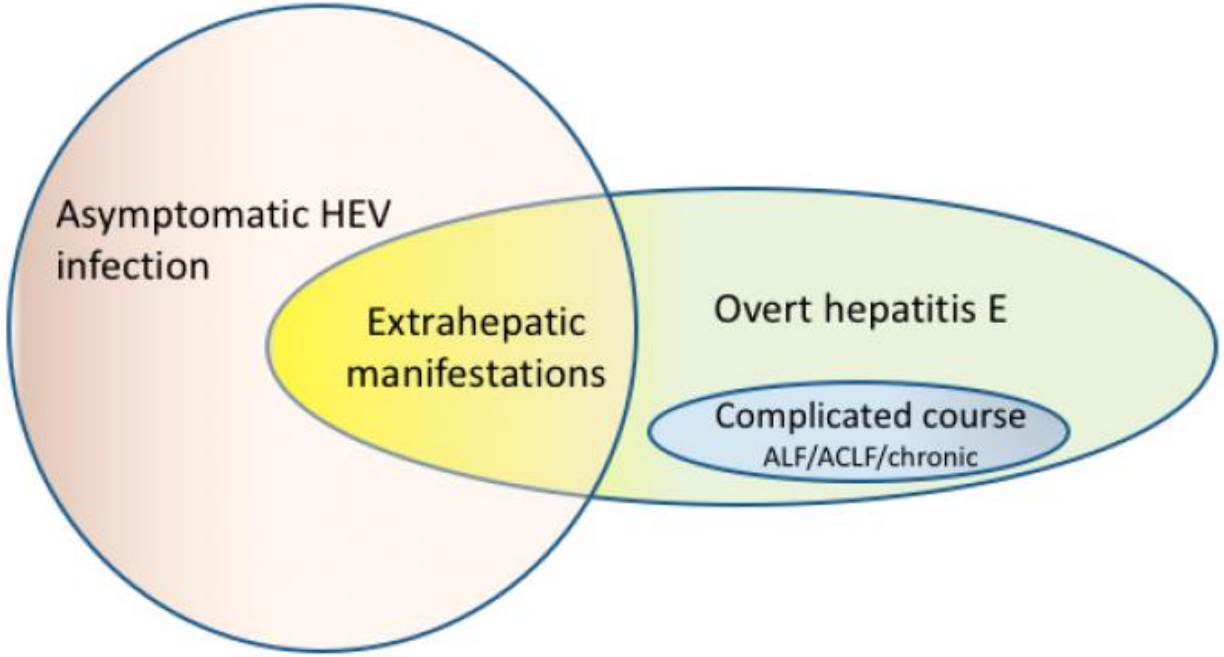


H.R. Dalton and J. Izopet

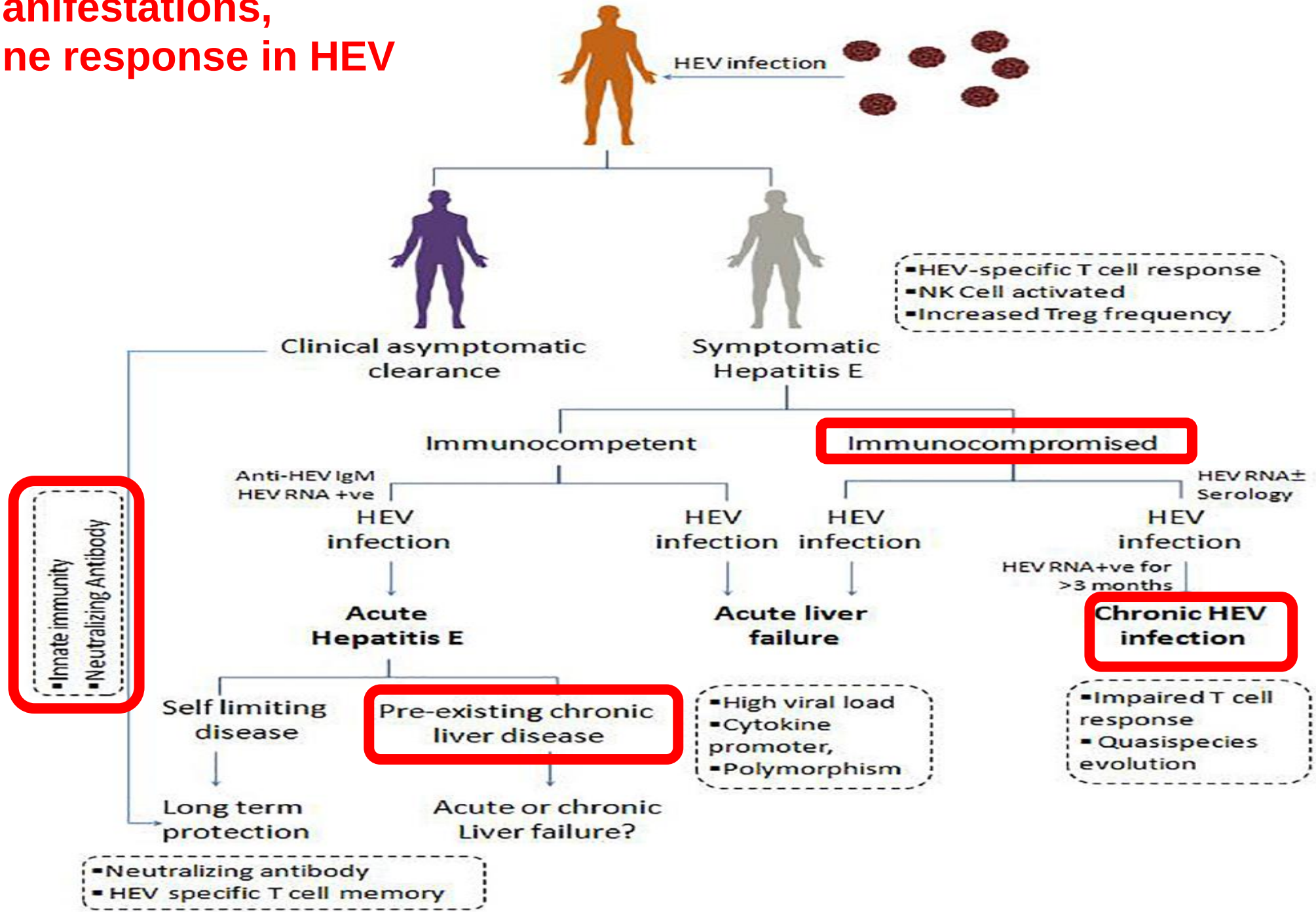
Sintomi

- **L'AHE è una malattia autolimitante con un basso tasso di mortalità.**
- **Aree endemiche l'infezione sintomatica è più comune a 15-40 anni; nei bambini asintomatica o lieve senza ittero.**
- **Segni e sintomi di AHE: febbre lieve, anoressia, nausea e vomito per alcuni giorni; dolore addominale, prurito, eruzione cutanea o dolori articolari; ittero urine scure e feci pallide; e epatomegalia.**

Nei pazienti immunocompromessi (SOT HEV3 o 4) presenza di HEV RNA per più di 3 mesi si traduce in CHE (evoluzione HEV-quasi-specie e dalla compromissione della risposta delle cellule T).



Clinical manifestations, and immune response in HEV



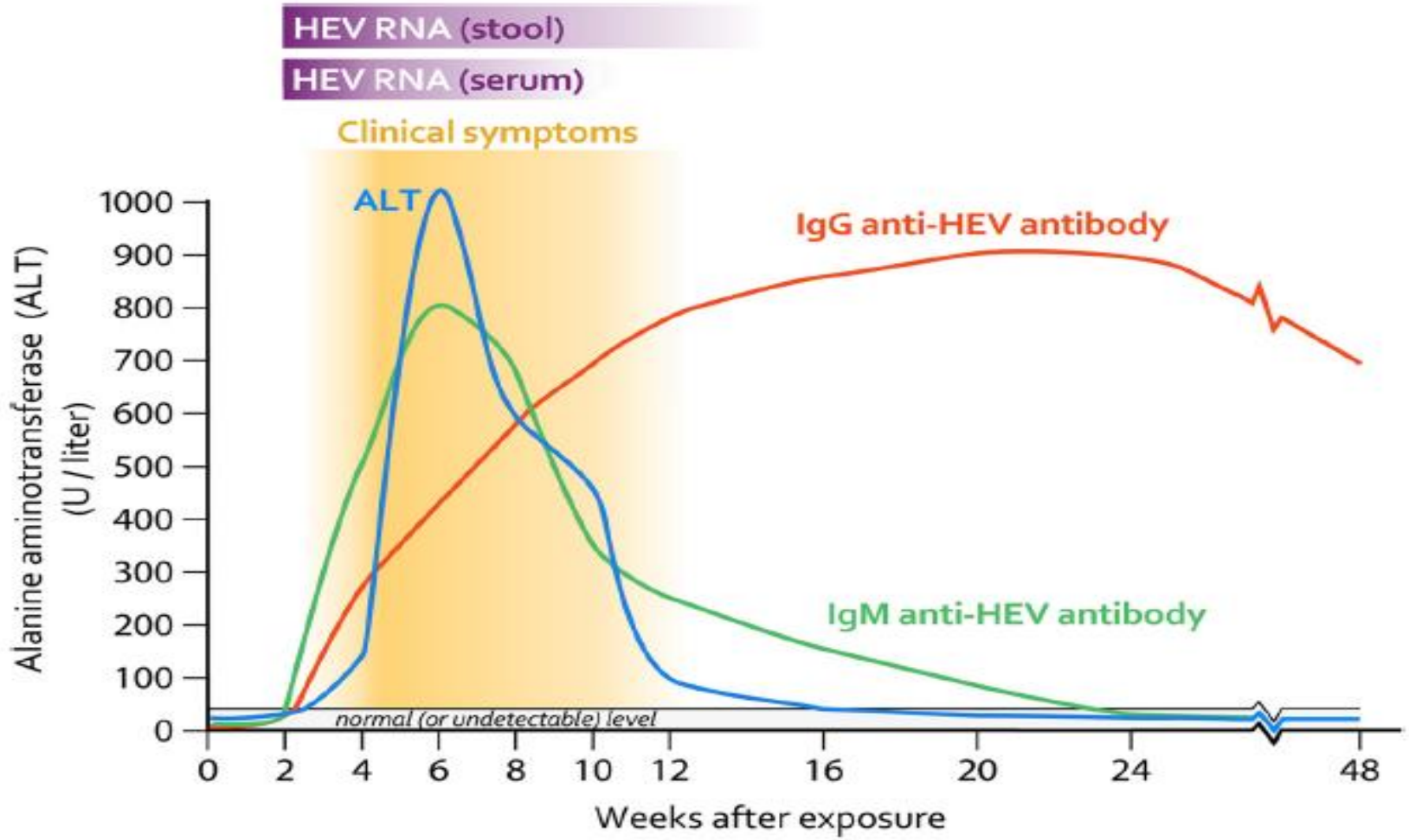


FIG 3 Course of acute hepatitis E virus (HEV) infection. Acute hepatitis E is characterized by symptoms such as fever, anorexia, vomiting, and jaundice, with onset several weeks after initial exposure. The onset of clinical symptoms coincides with a sharp rise in serum alanine transaminase (ALT) levels. Symptoms may persist for a few weeks to a month or more. ALT levels return to normal during convalescence. HEV RNA may be detected in both serum and stool early in the course of infection, but serum viremia may be difficult to detect by the time cases come to clinical attention. Anti-HEV IgM titers increase rapidly and then wane over the weeks following infection, while anti-HEV IgG antibody titers continue to rise more gradually during the convalescent period, and detectable anti-HEV IgG may persist for months to years. (Adapted from Fig. 2 of reference 170, with permission of the publisher [copyright 2012 Massachusetts Medical Society].)

HEV for High-Risk Patients

- **CHE is mainly seen in immunocompromised patients. Ankcorn et al. investigated CHE-patients lover long period of time and SOT was present in 60% of the patients.**
- **In 2 of 3 immunocompromised SOT-recipients, AHE leads to CHE, and in 10% to liver cirrhosis.**

TABLE 3 Prevalence of anti-HEV IgG and HEV RNA among transplant patients

Study	No. of patients	Transplanted organ(s)[a]	Serology test	Prevalence (%)	
				Anti-HEV IgG	HEV RNA
Abravanel et al. (286)	88	SCT	Wantai	36	
Buti et al. (236)	108	KT, LT	Biokits	2.3	
Haagsma et al. (237)	285	LT	Genelabs	3.5	1.75
Kamar et al. (13)	217[b]	KT, LT, SPK	Abbott		6.5
Knoenecke et al. (285)	52	SCT	Abbott	5.3	0
Legrand-Abravanel et al. (188)	700	KT, LT, SPK	Adaltis	12.7	3.2
Moal et al. (238)	1,350	KT	Adaltis		1.2
Moal et al. (242)	160[b]	KT	Adaltis	14	4.3
Pas et al. (239)	1,200	SOT	Wantai		1
Pischke et al. (227)	274	HT	Genelabs	11.3	1.5
Pischke et al. (240)	226	LT	Abbott	4.4	0.9
Riezebos-Brilman et al. (241)	468	Lung transplantation			2.1

[a] SCT, stem cell transplantation; KT, kidney transplantation; LT, liver transplantation; SPK, simultaneous kidney-pancreas transplantation; SOT, solid organ transplantation; HT,

Donor-Derived Genotype 4 Hepatitis E Virus Infection, Hong Kong, China, 2018

Siddharth Sridhar, Vincent C.C. Cheng, Shuk-Ching Wong, Cyril C.Y. Yip, Shusheng Wu, Anthony W.I. Lo, Kit-Hang Leung, Winger W.N. Mak, Jianpiao Cai, Xin Li, Jasper F.W. Chan, Susanna K.P. Lau, Patrick C.Y. Woo, Wai-Ming Lai, Tze-Hoi Kwan, Timmy W.K. Au, Chung-Mau Lo, Sally C.Y. Wong, Kwok-Yung Yuen

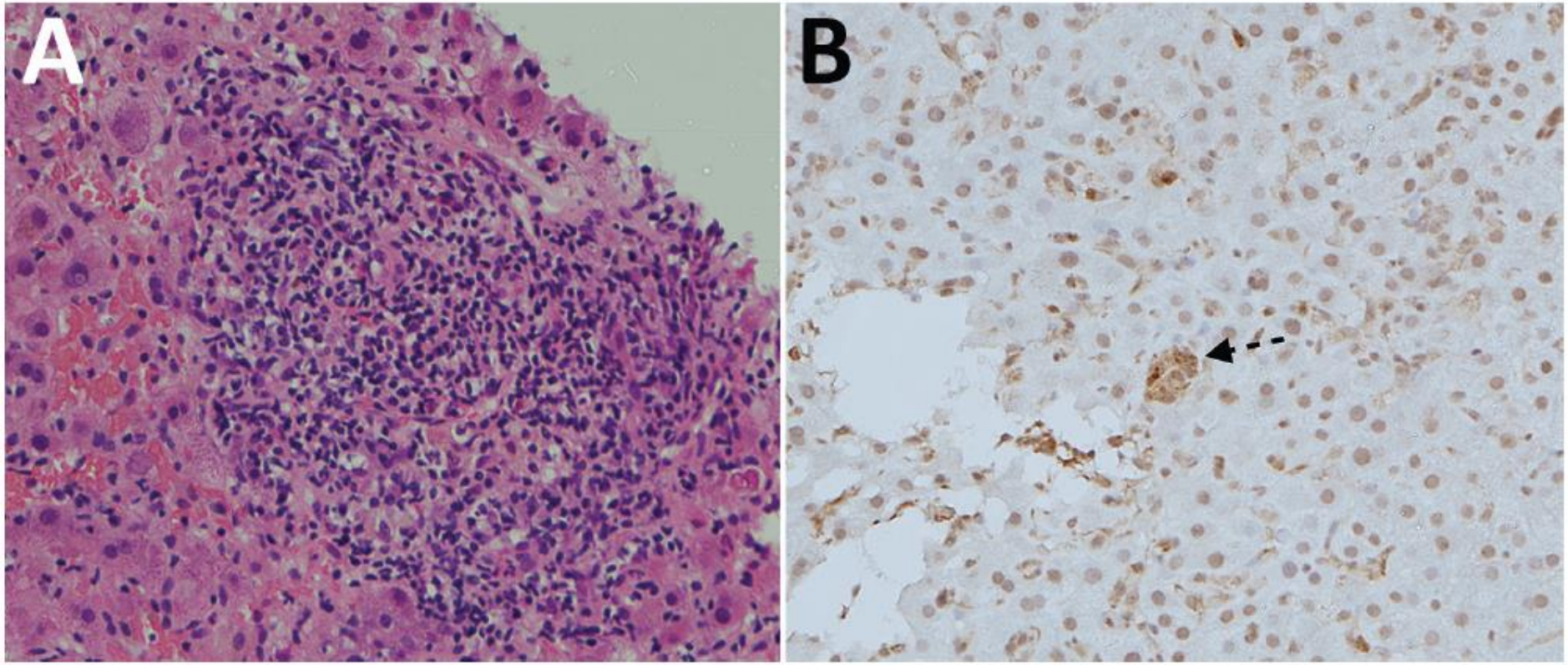
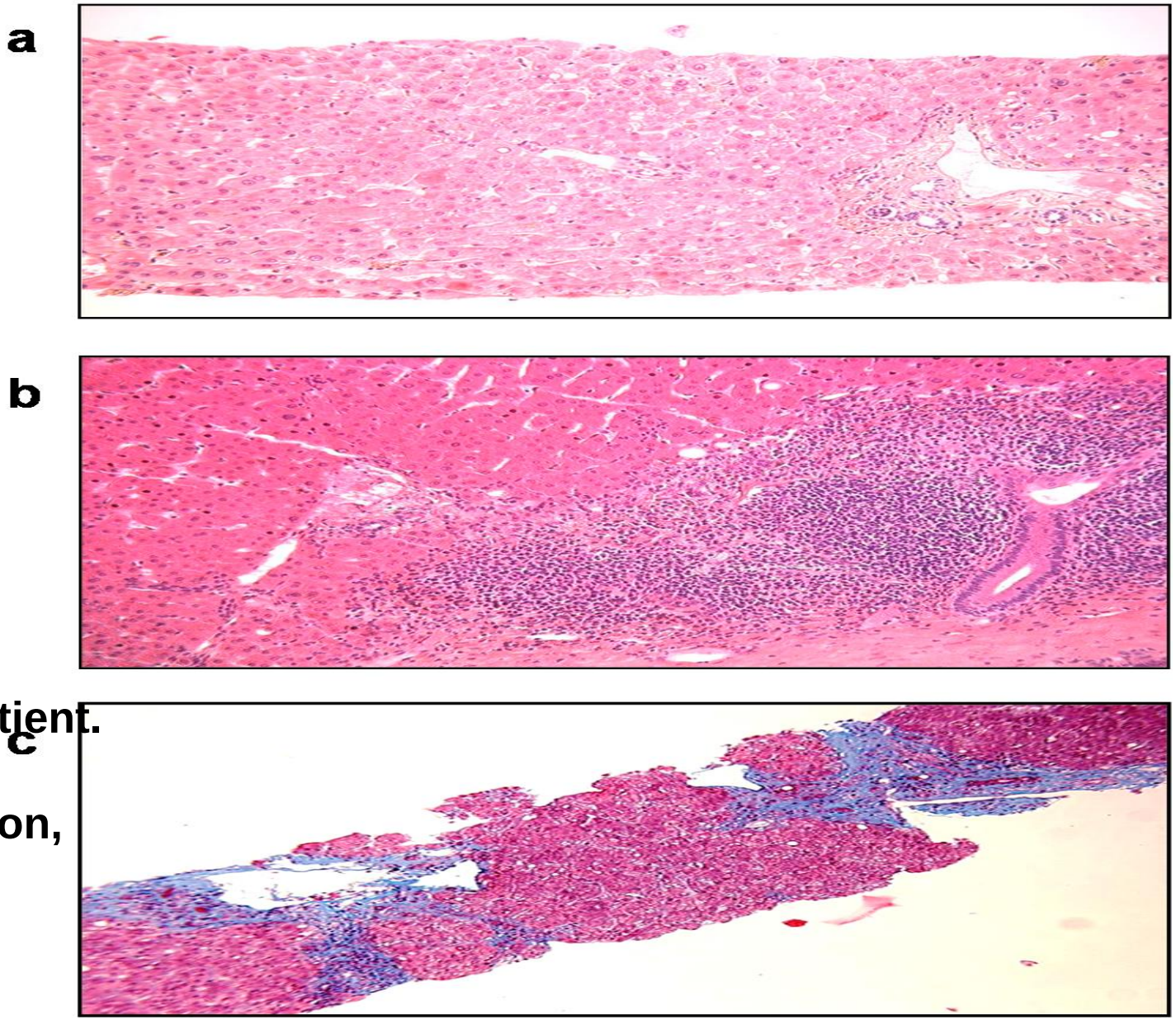


Figure 3. Histology of tissue from liver graft of hepatitis E virus case-patient 1, a 66-year-old man, on posttransplantation day 122. A) Hematoxylin and eosin staining showing moderate (grade 2) inflammation. B) Immunohistochemical staining (using hepatitis E virus monoclonal antibody); arrow indicates small groups of hepatocytes with positive cytoplasmic signals. Original magnification ×200.

Nearly 10% of HEV-SOT patients develop cirrhosis within 3 to 5 years after primary infection

CHE have more aggressive variants (recombinant HEV-host variants).

PPR regions of recombinant variants included fragments of human genes of varying origin (inter alpha trypsin inhibitor (ITI-H2), ribosomal genes S17 or S19 and tyrosine aminotransferase). Variants harboring S17, S19 or ITI fragment had replicative advantage. Duplications and insertions of HEV genome were described.



Histology of liver biopsies from a CHE- patient.
(a) Initial liver biopsy,
(b) inflammation after 15 months of infection,
(c) Cirrhosis after 38 months of infection
(Masson's trichrome, magnification 100).

CHE in SOT

- **L'epatite fulminante HEV non è riportata nei pazienti sottoposti a trapianto.**
- **HEV-Incidenza in SOT: 0,9-3,5%, (HEVRNA pos), HEV prevalence in LT patients is 20%.**
- **oltre il 60% dei pazienti con HEV abbia sviluppato CHE in trapianto di cuore .**
- **AHE diventano CHE in 21- 60%.**
- L'attivazione della via di segnalazione IFN non porta alla clearance di HEV. L'aumento dell'espressione degli ISG in CHE-pts favorisce la persistenza del virus, la via di segnalazione IFN diventi refrattaria.
- I pazienti immunocompetenti non producono una tale risposta immunitaria, suggerendo che i pazienti SOT mobilitano una frazione maggiore della loro immunità a causa del trattamento farmacologico

- **Strong therapeutical immunosuppression to prevent rejection, SOT-pts can develop opportunistic infections.**

- **Risk factors in development of CHE-SOT: low platelet count, choice of immunosuppressant, liver cirrhosis and HIV infection.**

SOT: Il regime immunosoppressivo può anche influenzare lo sviluppo di un'infezione cronica.

- **HEV3-Suini trattati con ciclosporina, azatioprina e prednisolone sviluppano CHE.**
- **HEV ha maggiori probabilità di persistere nei SOT trattati con tacrolimus rispetto a ciclosporina.**
- **Tacrolimus: fattore di rischio per il suo effetto immunosoppressivo più elevato rispetto alla ciclosporina A.**

Solo l'acido micofenolico (MFA) era associato alla clearance HEV. MFA deve essere presa in considerazione in HEV-SOT

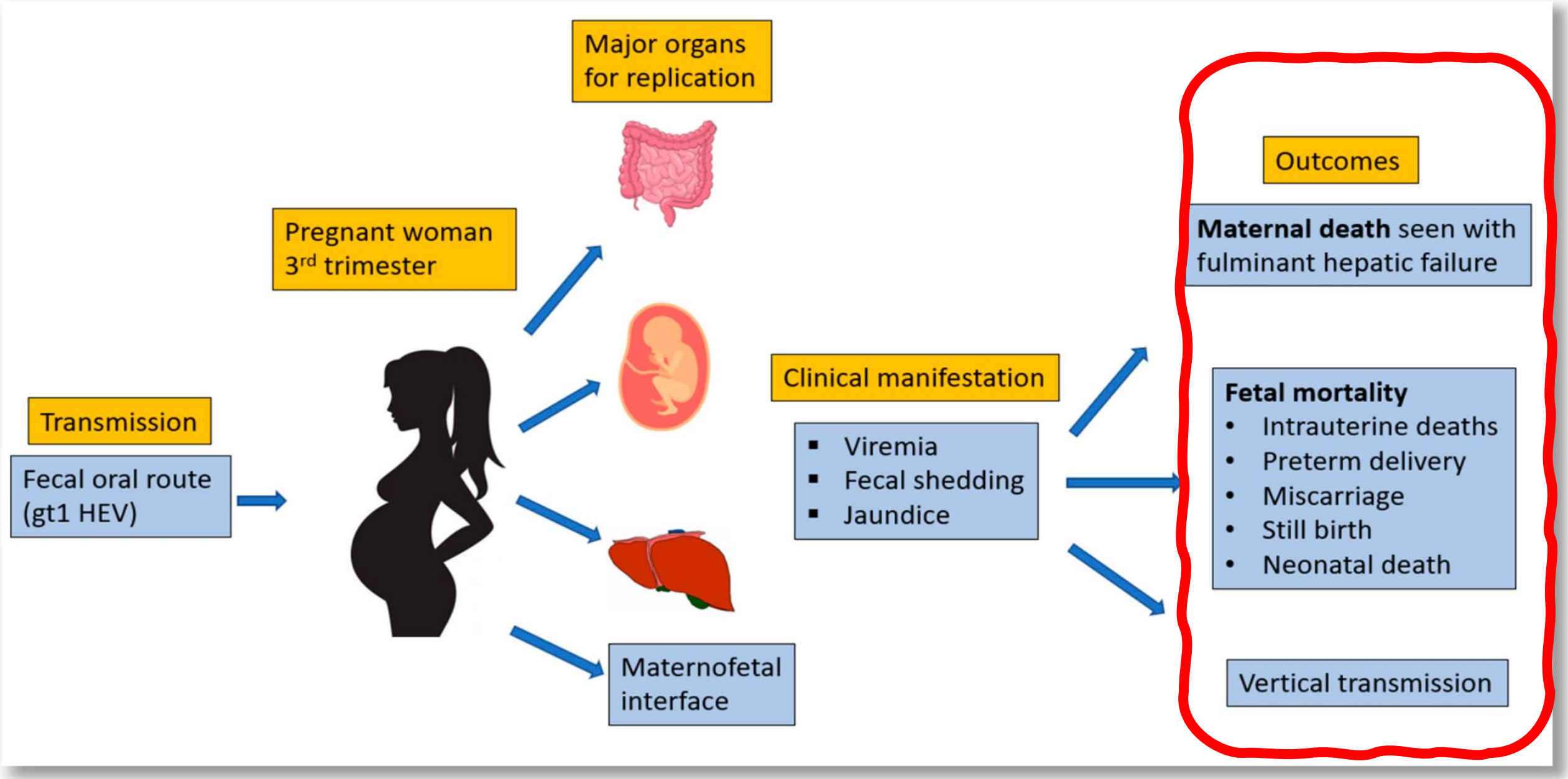
Rapamicina ed everolimus promuovono la replicazione dell'HEV.

Severe Hepatitis in Pregnant Women (PW)

HEV-PW nel 2 o 3 trimestre hanno aumentato rischio di insufficienza epatica acuta, perdita fetale e mortalità. 20-30% mortalità se HEV contratto nel 3 trimestre nei paesi in via di sviluppo. HEV1 si replica in placenta con gravi danni ai tessuti (aumenta apoptosi e necrosi all'interfaccia materno-fetale con alterazioni della barriera placentare) rispetto a HEV3. HEV1 produce più virioni infettivi e innesca la produzione di citochine pro-infiammatorie (IL-6, chemochine)).

Table 1. HEV outbreaks (serologically confirmed) in pregnant women in different countries.

No.	Country	Year	Total cases	Deaths	References
1	Nepal	1987	73	18	54
2	India	1987	19	3	55
3	India	1988	30	2	56
4	Somalia	1988–1989	346	48	57
5	Indonesia	1991	19	5	58
6	Kenya	1991	28	4	59
7	India	1991	48	12	24
8	Djibouti	1991–1993	3	1	60
9	Pakistan	1993–1994	35	4	61
10	Central African Republic	2002	7	1	62
11	Sudan	2004	61	19	63
12	Uganda	2007–2009	189	13	64
13	Bangladesh	2008–2009	21	4	65
14	Bangladesh	2010	12	3	66
15	Sudan	2010–2011	39	11	67



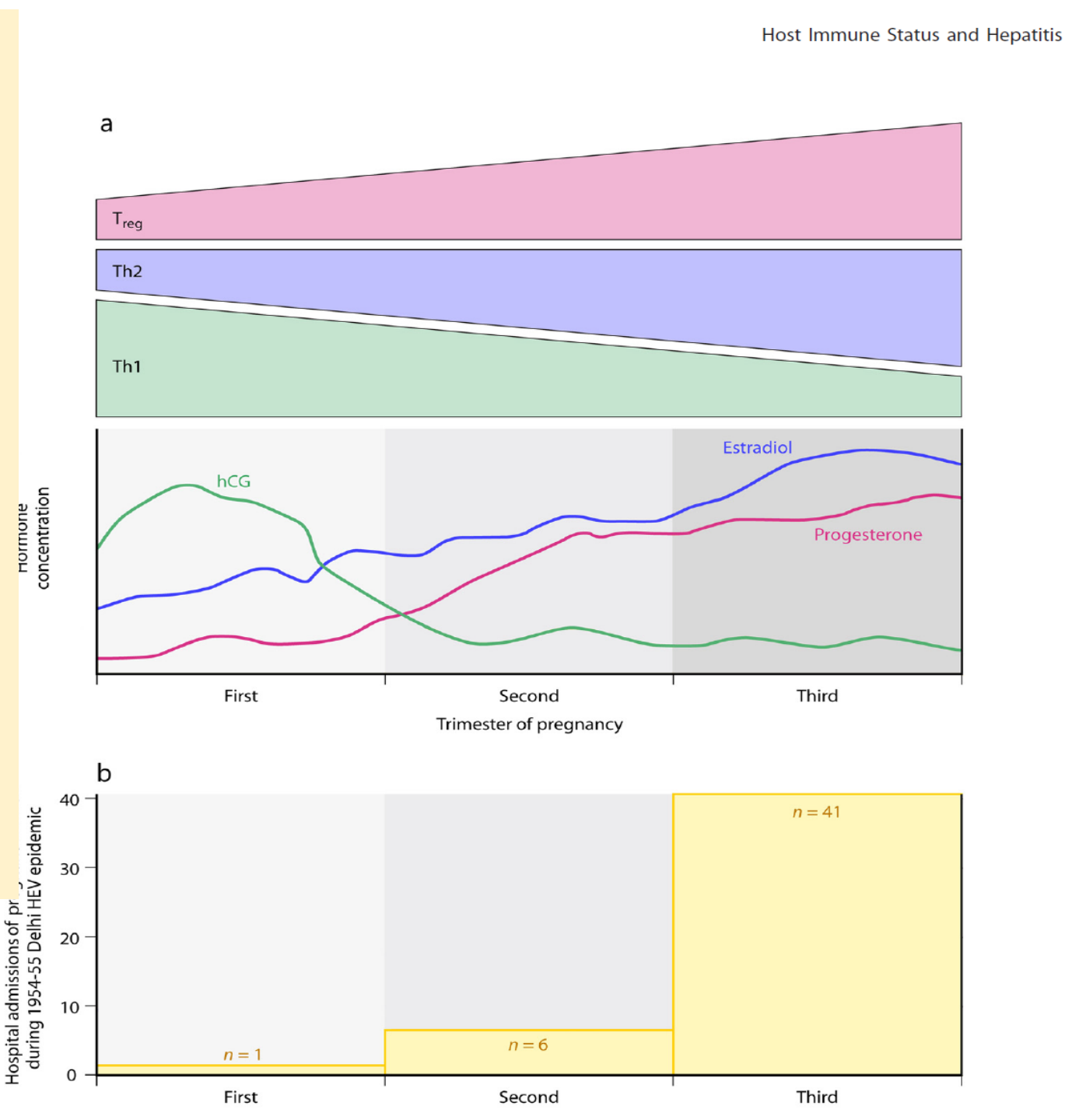
- **Non sono disponibili regimi terapeutici stabiliti per le donne in gravidanza. (RBV teratogeno)**

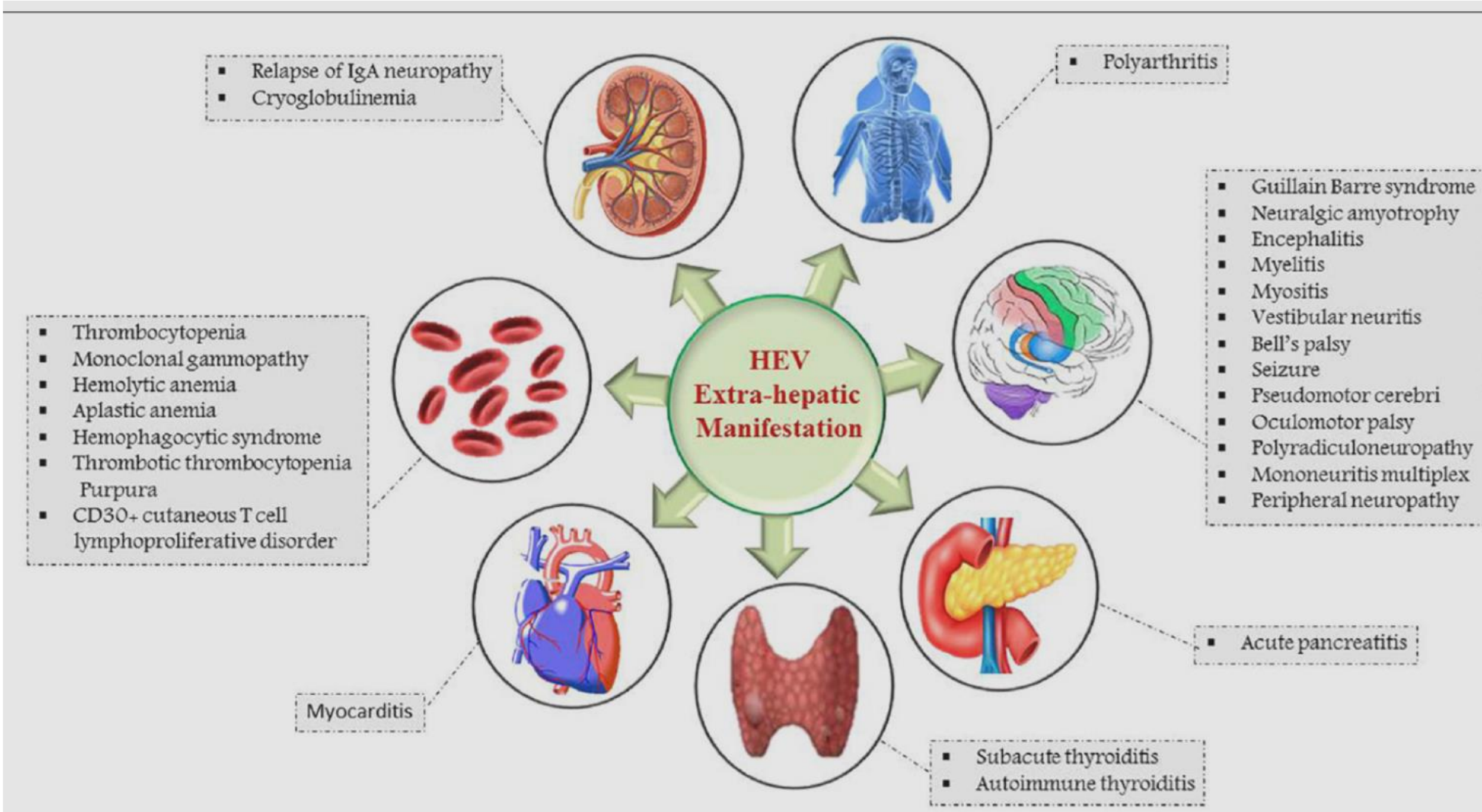
PW: Con il progredire della gravidanza, risposta immunitaria adattativa diminuisce e il numero e funzione delle cellule T e NK diminuiscono costantemente.
La risposta immunitaria si allontana dalla risposta infiammatoria Th1, diminuiscone le cellule B. barriera immunitaria è rafforzata dall'aumento della fagocitosi e dell'attività dei granulociti.

Le alterazioni degli ormoni svolgono un ruolo dominante. Fino 3 trimestre, aumentano estrogeni e progesterone. All'inizio della gravidanza, estrogeno aumenta la risposta Th1 e immunità dipendente dalle cellule. Con concentrazioni di estrogeni più elevate la risposta Th2 ha maggiori probabilità di essere supportata insieme alla risposta umorale.

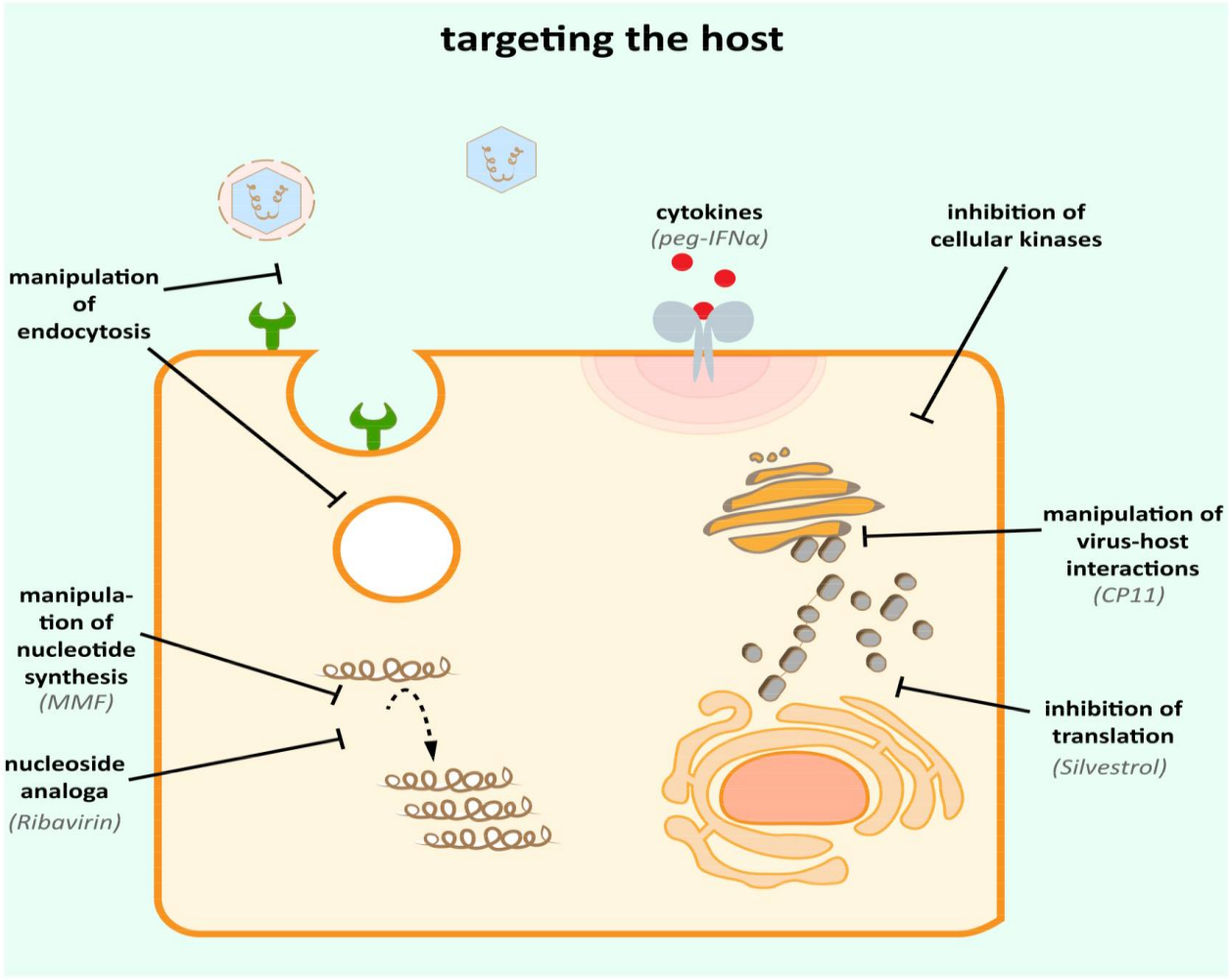
Alte concentrazioni di progesterone sopprimono la risposta immunitaria materna e influenzano l'interazione tra Th1 e Th2. **livelli elevati di estrogeni promuovono la HEV-replicazione**.

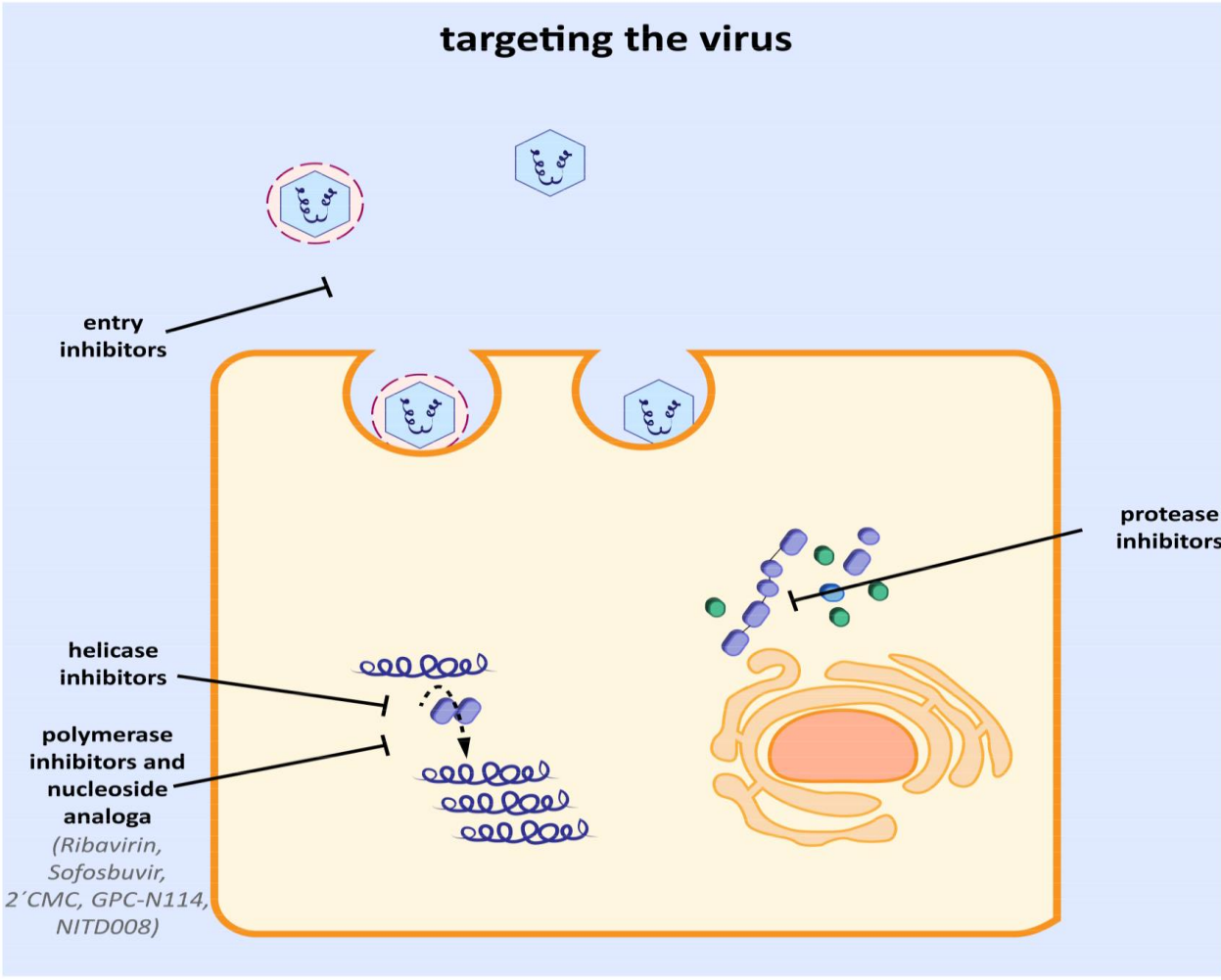
Portano al parto pretermine e mortalità fetale nei pazienti con HEV per la disfunzione placentare




Relapse of IgA neuropathy
Cryoglobulinemia
Polyarthritis
Guillain Barre syndrome
Neuralgic amyotrophy
Encephalitis
Myelitis
Myositis
Vestibular neuritis
Bell's palsy
Seizure
Pseudomotor cerebri
Oculomotor palsy
Polyradiculoneuropathy
Mononeuritis multiplex
Peripheral neuropathy
Thrombocytopenia
Monoclonal gammopathy
Hemolytic anemia
Aplastic anemia
Hemophagocytic syndrome
Thrombotic thrombocytopenia Purpura
CD30+ cutaneous T cell lymphoproliferative disorder
HEV Extra-hepatic Manifestation
Acute pancreatitis
Myocarditis
Subacute thyroiditis
Autoimmune thyroiditis

Potential host and viral targets of antiviral drugs

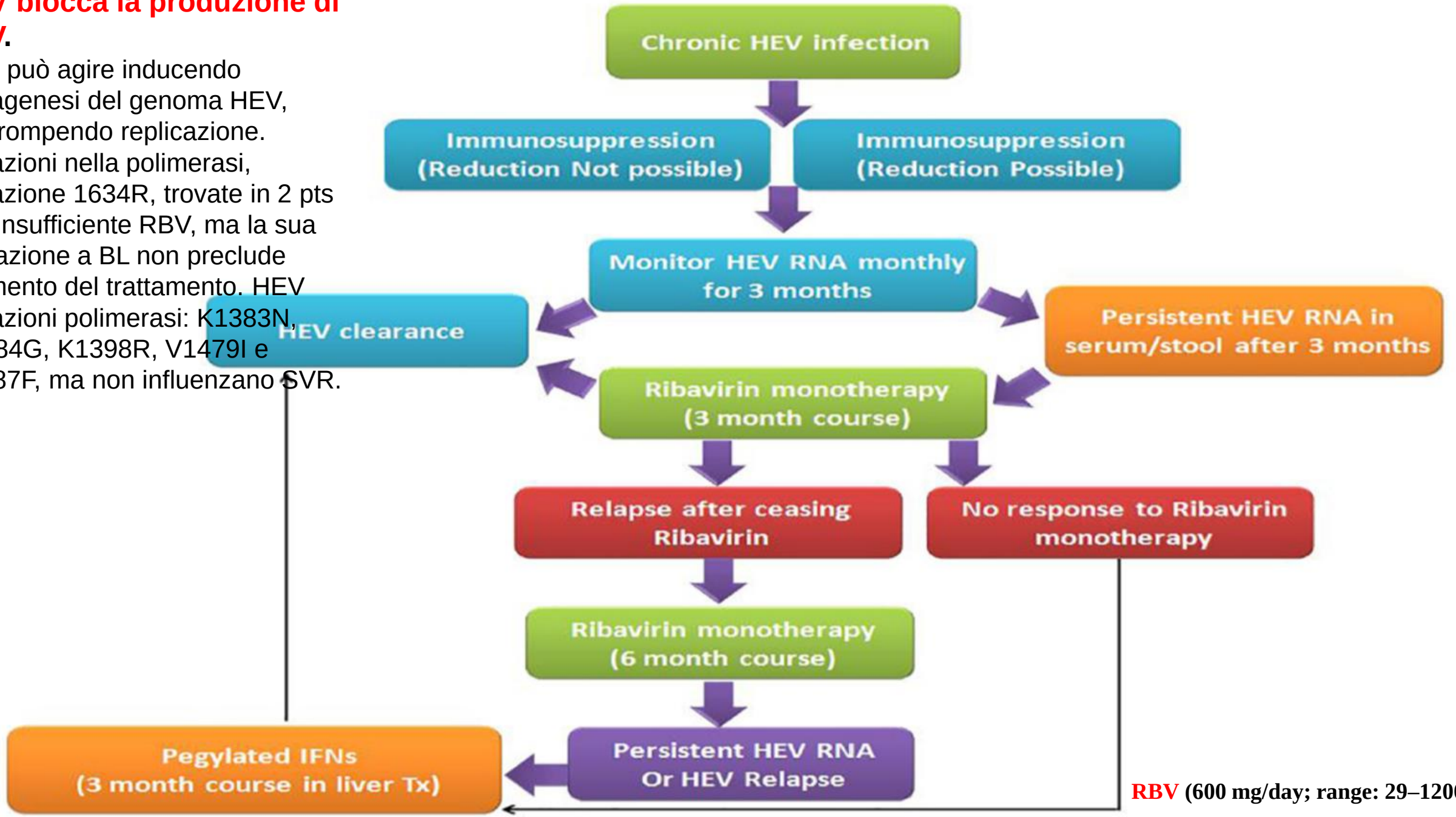




Antiviral therapy against HEV can rely on inhibition and manipulation of host components, which are important for HEV life cycle. Direct acting antiviral specifically can target viral enzymes (helicase, polymerase, protease) without affecting host components. RBV is reported to exert antiviral effects by targeting both virus and host

RBV blocca la produzione di HEV.

RBV può agire inducendo mutagenesi del genoma HEV, interrompendo replicazione. Mutazioni nella polimerasi, mutazione 1634R, trovate in 2 pts con insufficiente RBV, ma la sua rilevazione a BL non preclude fallimento del trattamento. HEV mutazioni polimerasi: K1383N, D1384G, K1398R, V1479I e Y1587F, ma non influenzano SVR.



RBV (600 mg/day; range: 29–1200)

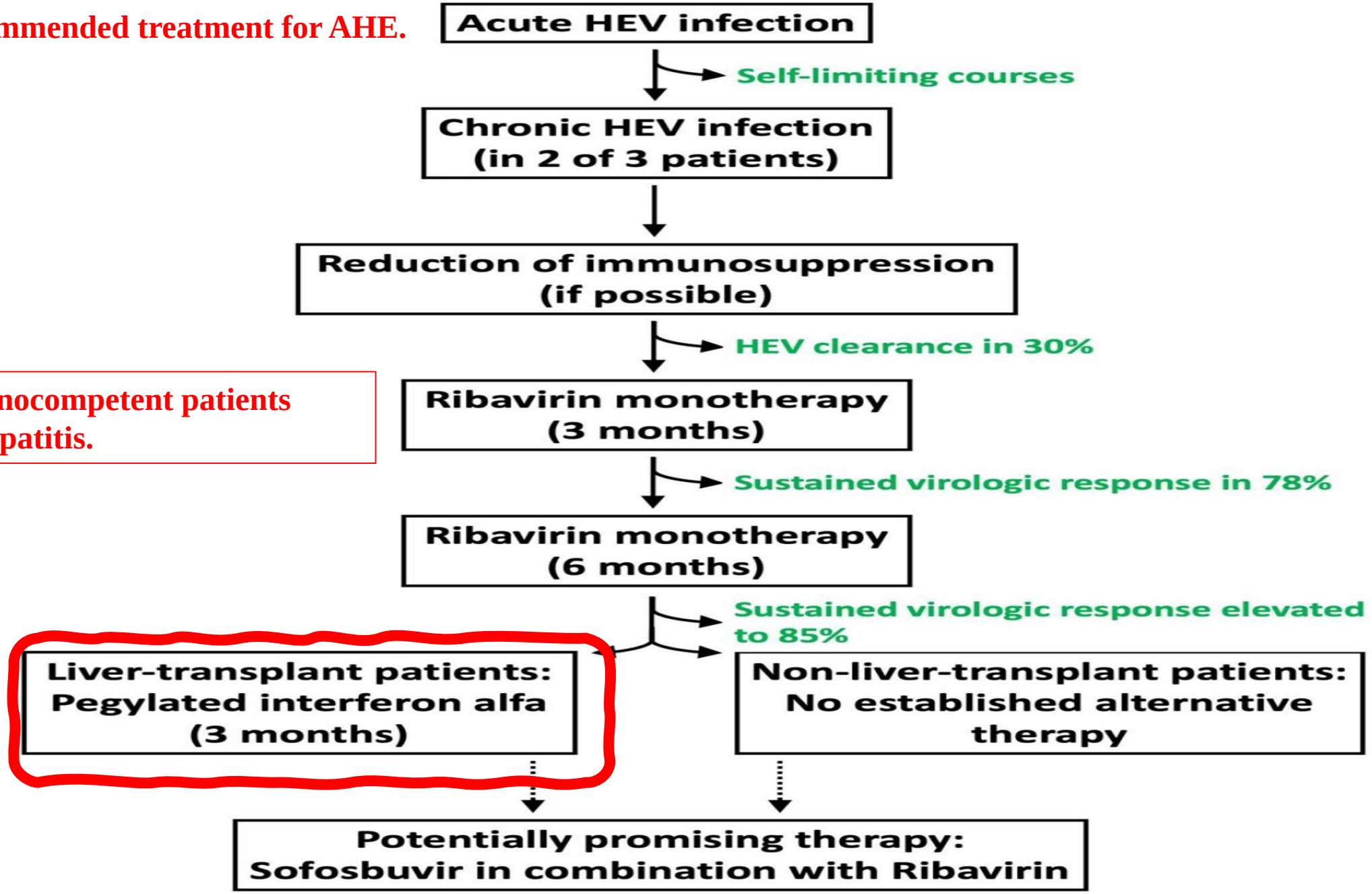
Immunocompromised SOT-recipients

The first treatment of SOT is reduction of immunosuppressive (to clear HEV in 30%)

Balance between infection and rejection (elevated risk of organ rejection)

- **The standard of care for patients unable to clear HEV is RBV 3-month.**
- **RBV for 3 months in 59 CHE-SOT recipients decrease HEV-replication (SVR 78%). Relapse patients retreated with RBV for 6 months cleared HEV with SVR 85%.**
- **CHE-LT and hemodialysis pts with Peg-INF-alfa 3 month results in HEV clearance (risk acute rejection). INF is contraindicated in kidney, pancreas, heart, lung transplant recipients because it increases risk of acute rejection.**
- **In vitro, sofosbuvir inhibits HEV replication and additive effect combination with RBV. CHE treated with sofosbuvir monotherapy showed decreased HEV replications but did not achieve viral clearances.**
- **In CHE adding sofosbuvir to RBV led to temporary HEV eradication.**

There is no recommended treatment for AHE.

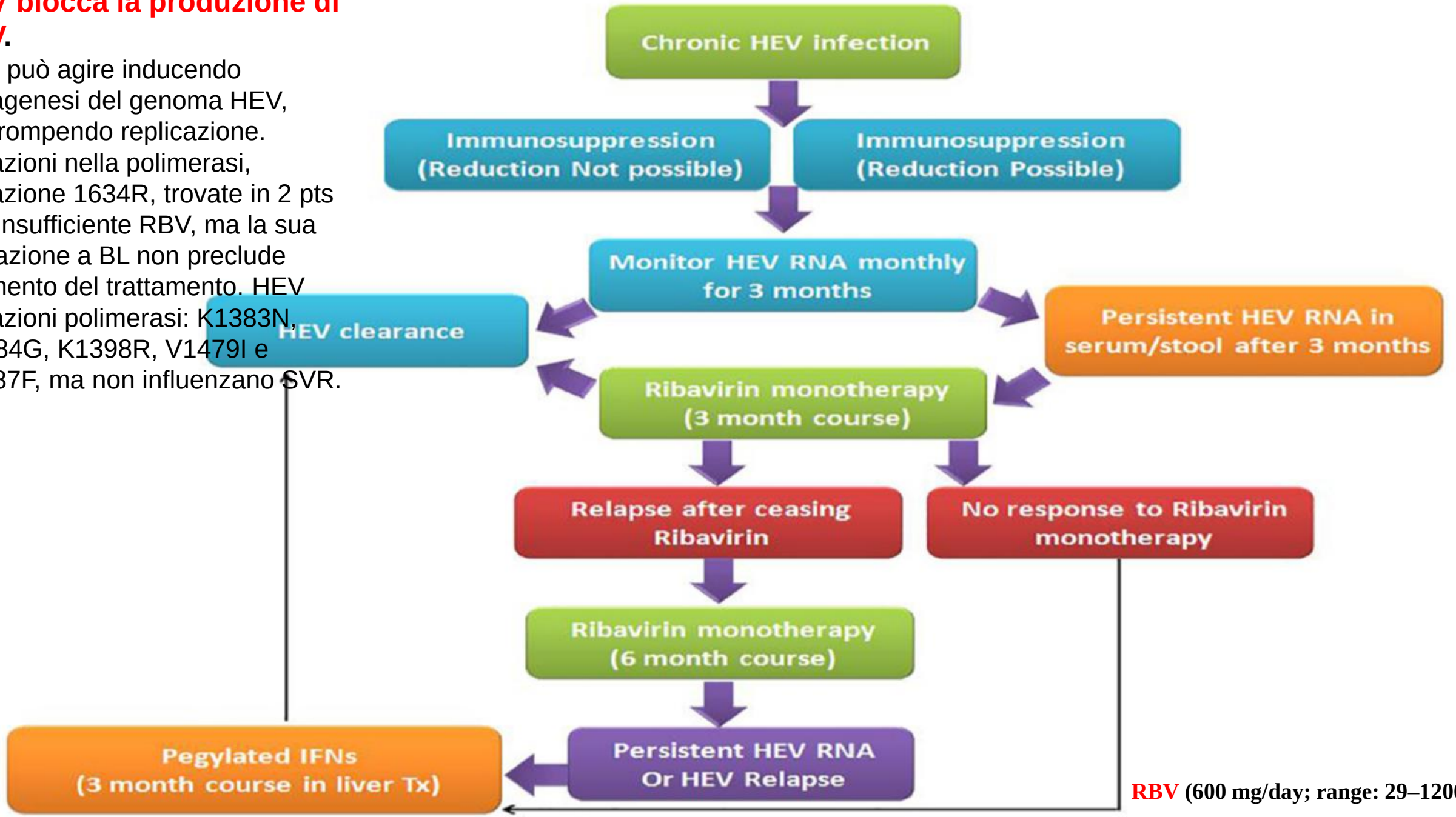


RBV in immunocompetent patients with severe hepatitis.

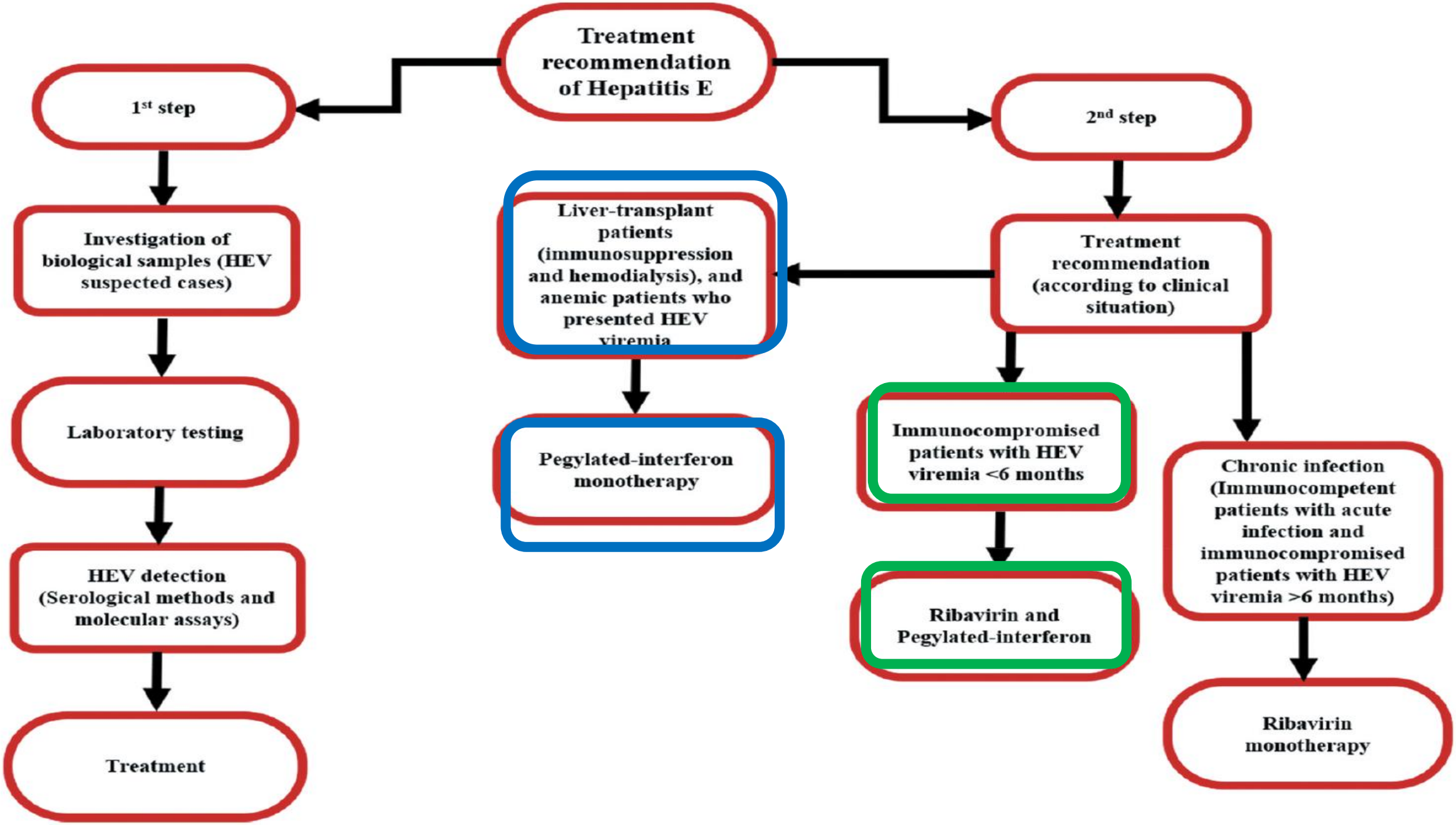
Figure 2. Therapy algorithm for chronic HEV-infected immunosuppressed patients.

RBV blocca la produzione di HEV.

RBV può agire inducendo mutagenesi del genoma HEV, interrompendo replicazione. Mutazioni nella polimerasi, mutazione 1634R, trovate in 2 pts con insufficiente RBV, ma la sua rilevazione a BL non preclude fallimento del trattamento. HEV mutazioni polimerasi: K1383N, D1384G, K1398R, V1479I e Y1587F, ma non influenzano SVR.



RBV (600 mg/day; range: 29–1200)


Treatment recommendation of Hepatitis E
1st step
Investigation of biological samples (HEV suspected cases)
Laboratory testing
HEV detection (Serological methods and molecular assays)
Treatment
2nd step
Treatment recommendation (according to clinical situation)
Liver-transplant patients (immunosuppression and hemodialysis), and anemic patients who presented HEV viremia
Pegylated-interferon monotherapy
Immunocompromised patients with HEV viremia <6 months
Ribavirin and Pegylated-interferon
Chronic infection (Immunocompetent patients with acute infection and immunocompromised patients with HEV viremia >6 months)
Ribavirin monotherapy

Ulteriori gruppi di pazienti immunocompromessi

- **Più del 10% di CHE.**
- L'infezione da HIV CD4+ inferiore a 200 cellule/mm3 è il principale fattore di rischio per CHE. Trattare con RBV, peg-INF alfa, o una combinazione di entrambi. La normalizzazione della conta dei CD4+ da sola non porta alla risoluzione dell'HEV stesso.
- Malattie reumatiche Il metotrexato ha molteplici effetti sulle cellule T. Alcuni pazienti che ricevono metotrexato raggiunto HEV-SVR dopo la riduzione dell'immunosoppressione.
- Gli inibitori del TNF CHE richiede la riduzione della terapia. La produzione di citochine pro-infiammatorie come il TNF svolge un ruolo nel controllo delle infezioni da HEV.

Patients with Hematological Diseases

- Immune insufficiency due to underlying disease or CT, stem cell transplantation has been implicated as a cause of prolonged HEV.
- HEV prevalence is higher in patients with malignant hematological disease than in the general population (severe or 28% prolonged HEV disease courses).
- HEV is mainly associated with NHL.
- During rituximab was observed rising transaminases and HEV markers by reducing rituximab dosing alone.
- Early RBV administration is preferable, as reduction of immunosuppression was associated with increased mortality.

Screening to identify new anti-HEV drugs: NITD008, broad-spectrum chain-terminating adenosine nucleoside analogue (dengue), GPC-N114, which binds to RNA channels of picornavirus polymerases.

T cell-based immunotherapy based on cytotoxic T cells targeting specific antigens. Soon et al. identified several HEV-specific T cell receptors that could be a potential candidates in therapy of CHE.

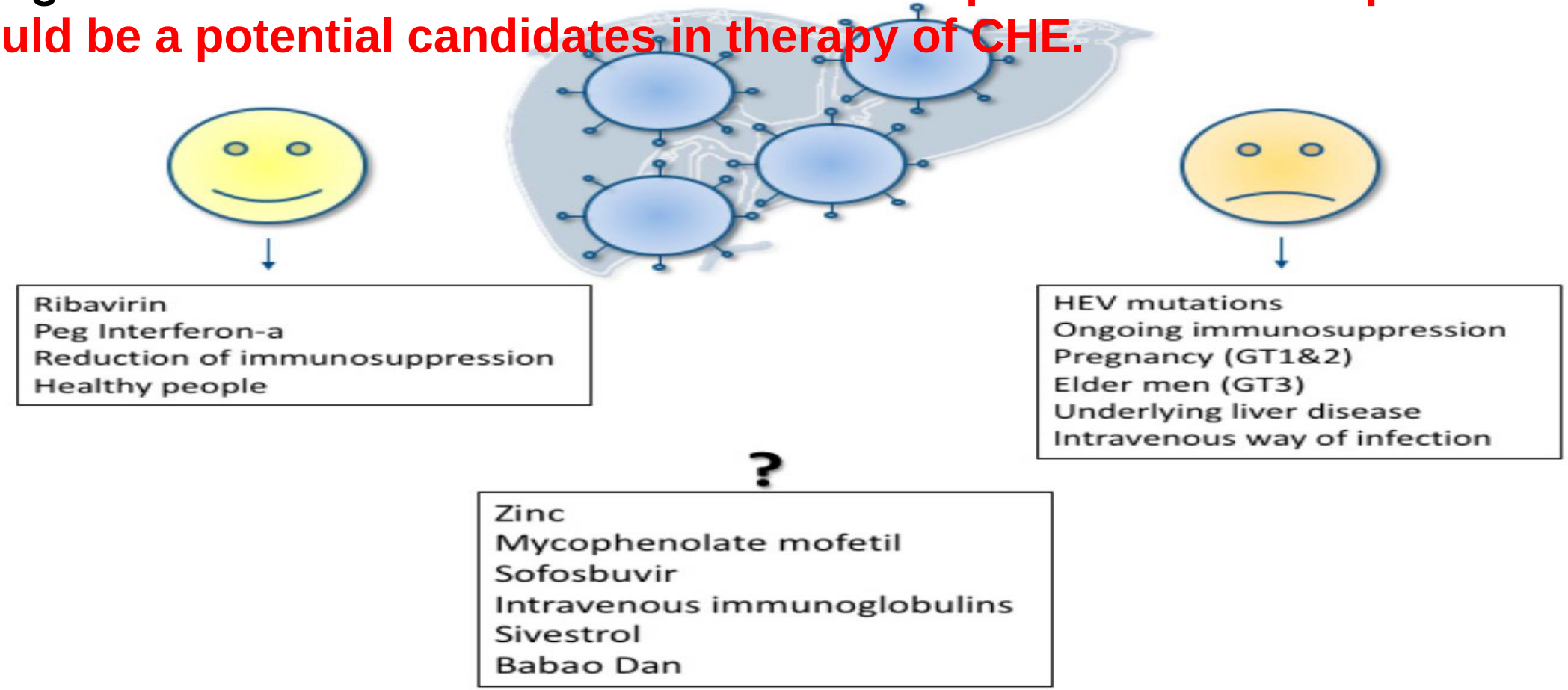
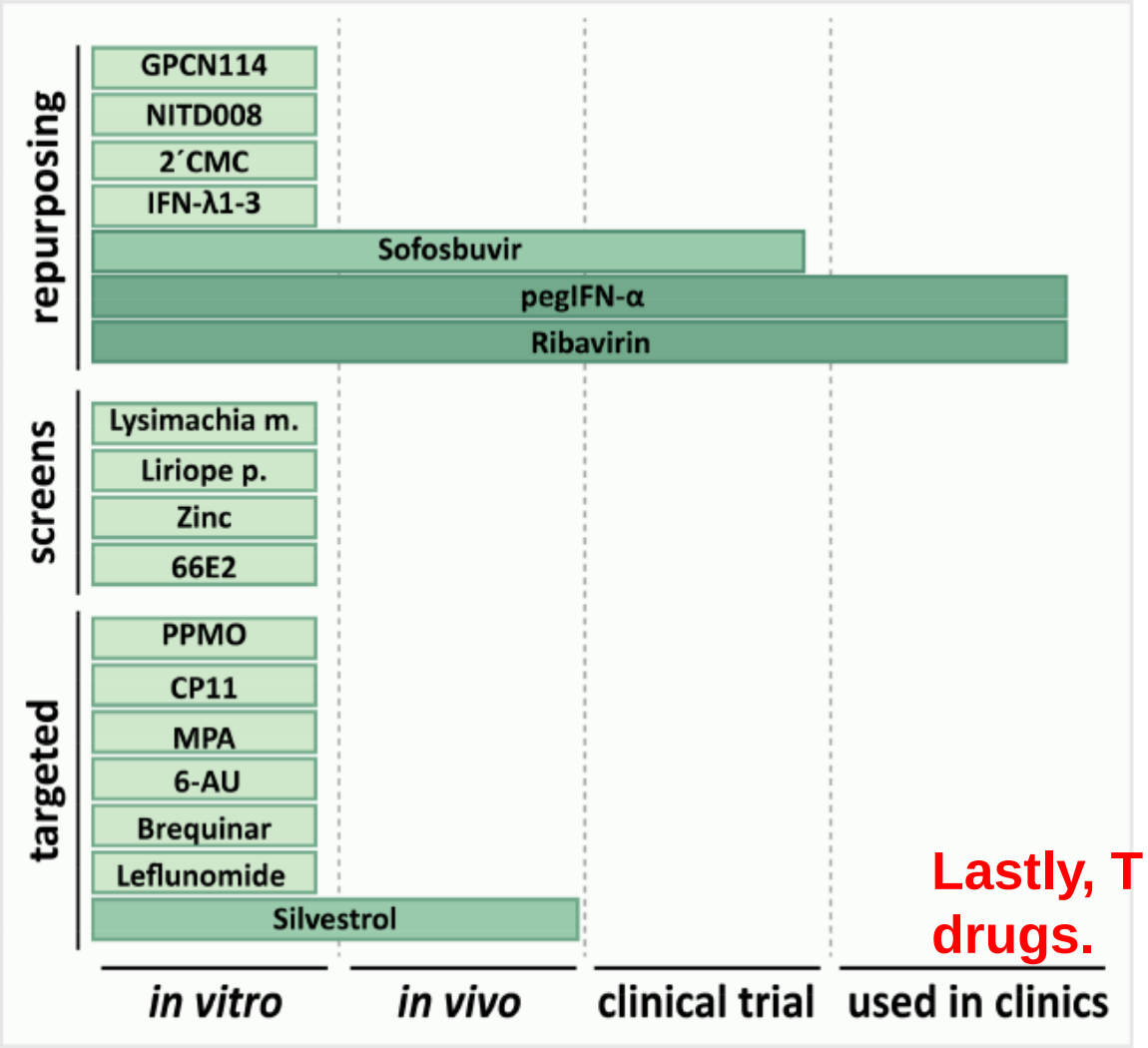


Figure 2. Different factors influencing HEV infection: Protective and beneficial factors on the left hand; unfavorable and risk factors on the right hand; not yet clarified factors in the lower middle.



The risk of HEV reinfection is unclear

Although minimum protective concentration of Ab remains to be determined, an Ab concentration of 2.5 WHO units/mL was found to be protective. In vaccine study SOT recipients can be re-infected when Ab concentration is below 7 WHO units/mL

Lastly, T cell therapy may be an alternative to drugs.

Figure 3. Overview of molecules/extracts with antiviral activity against HEV. The depicted molecules/extracts are classified according to the strategy that was used to identify them. So far, the antiviral activity against HEV of only four drugs (Sofosbuvir, pegIFN-α, Ribavirin and silvestrol) was approved in experimental settings beyond in vitro cell culture systems. Both drugs in the clinics are used off-label and therefore have not been tested in clinical trials against HEV.

2’-C-Methylcytidine

2'-C-metilcitidina (2-CMC), NM107, analogo nucleosidico (NA) contro HEV in vitro, composto ha dimostrato effetto inibitorio contro la replicazione dell'HEV (IC50 di 22 M/L). Insieme a RBV ha moderato effetto antagonistico, suggerendo meccanismo convergente di inibizione. Nel trattamento dell'HCV, è stata riportata biodisponibilità orale insufficiente. Il profarmaco NM283 sviluppo è stato interrotto per effetti tossici avversi.

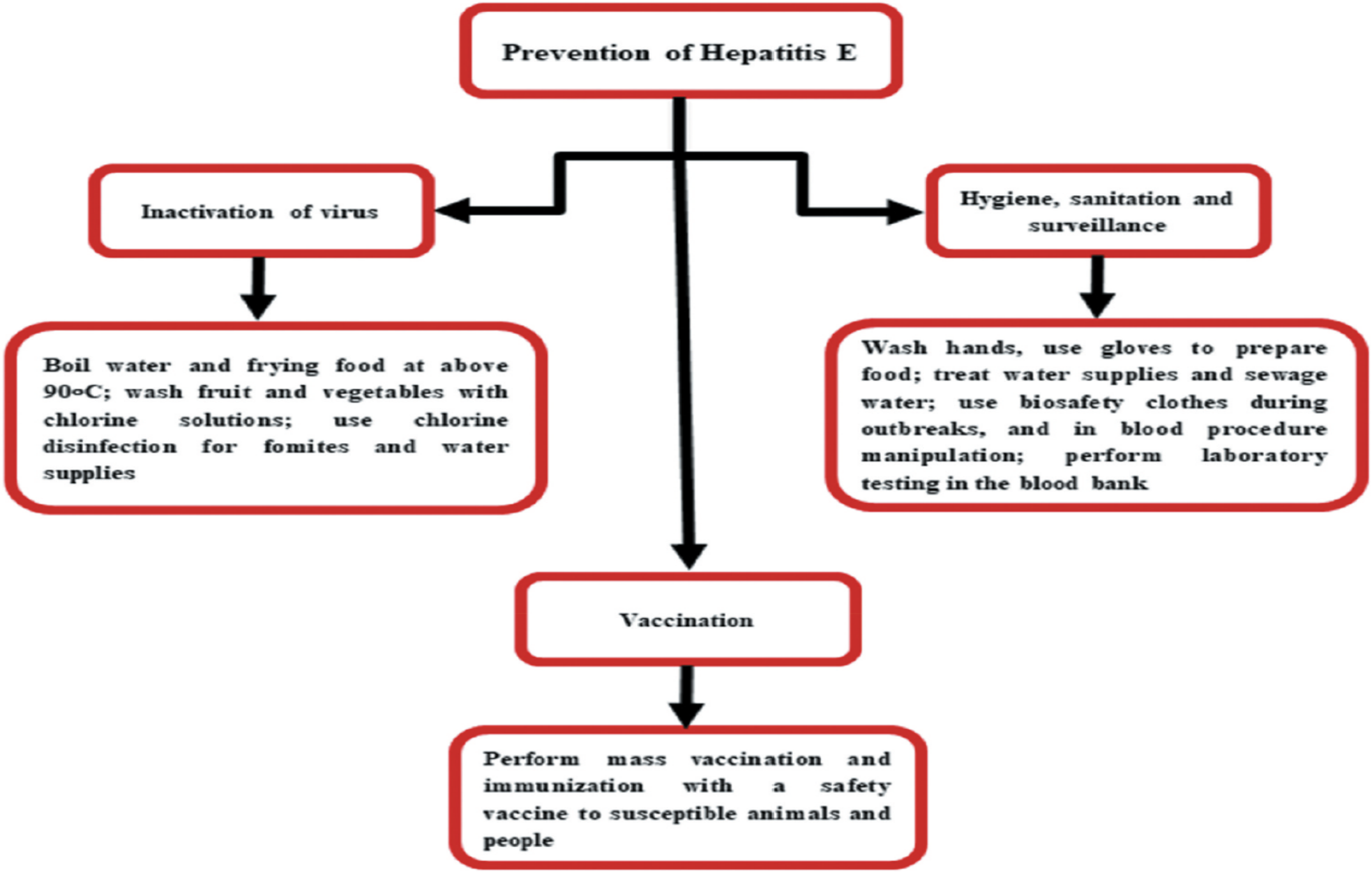
Zinc salts can block HEV replication in vitro by inhibiting RNA polymerase. 2 F CHE-transplant-recipients did not respond to RBV despite having elevated intra-erythrocyte zinc concentrations. The natural compound silvestrol blocks HEV replication in vitro, and HEV RNA concentrations in feces of treated mice rapidly decreased. has a similar action in humans …

NITD008 and GPC-N114

GPC-N114 e NITD008, inibendo replicone subgenomico derivato da GT1. GPC-N114 aveva concentrazione efficace semi-massima (EC50) di 1,07 M e indice terapeutico (TI) di >93 (GPC-N114) mentre NITD008 aveva EC50 0,03 M e TI >3333. GPC-N114 è stato descritto come NNI di RdRP di più generi all'interno della famiglia Picornaviridae. NITD008 agisce come antivirale su HCV, West Nile Virus o Zika. NITD008 ha mostrato tossicità in vivo.

Ciprofloxacin and IFN-

- Nishiyama et al hanno utilizzato farmaci per lo screening in vitro contro un ceppo GT3 contenente Gaussia luciferase reporter. Ciprofloxacina (CPFX) e IFN-1-3 hanno mostrato la migliore attività contro il genoma del reporter.
- Tutti i sottotipi IFN-, ma non CPFX, hanno mostrato una robusta riduzione dell'HEV RNA.


Prevention of Hepatitis E
Inactivation of virus
Boil water and frying food at above 90∘C; wash fruit and vegetables with chlorine solutions; use chlorine disinfection for fomites and water supplies
Hygiene, sanitation and surveillance
Wash hands, use gloves to prepare food; treat water supplies and sewage water; use biosafety clothes during outbreaks, and in blood procedure manipulation; perform laboratory testing in the blood bank
Vaccination
Perform mass vaccination and immunization with a safety vaccine to susceptible animals and people

Increasing the coverage of HEV vaccination will be key to minimizing the burden of AHE.

- (Hecolin®) vaccine developed in China elicits protective antibodies to all HEV genotypes (HEV1,4) and has been licensed in China since 2012 (Zhu 2010). This vaccine is 97% effective (3 dose course) in preventing symptomatic AHE (Zhang 2015).

- not been licensed and approved in any other country.
- It is not recommended by WHO in children aged under 16 years, PW, chronic liver disease, organ transplant waiting lists, and travellers .

There is no recommended treatment for AHE.

- **The optimal duration of treatment has still to be determined.**
- **Treatment should be continued for further 3 months if HEV RNA is detected in stool at EOT.**

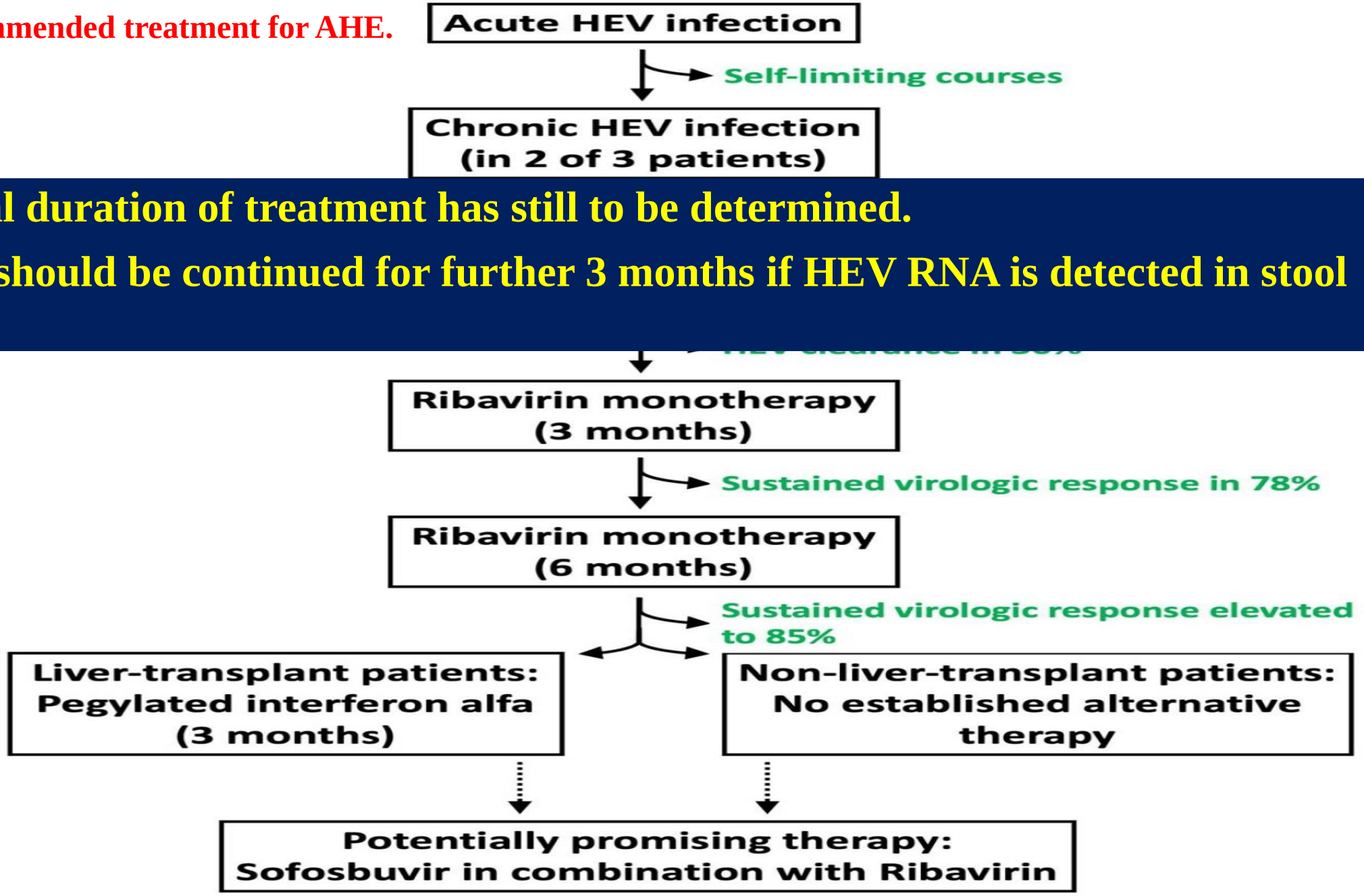


Figure 2. Therapy algorithm for chronic HEV-infected immunosuppressed patients.

Table 1. Histopathological evaluation of liver tissue and results of IHC, serology and real-time PCR in HEV-positive wild boar.

Animal	Sex	Age	Real-time PCR HEV		Liver HEV viral load (copies/mL)	IHC HEV	Ab HEV	Hepatocellular necrosis	Lymphoplasmacytic aggregates	Sinusoidal congestion	Bile pigment accumulation
			Liver	Serum							
1	Female	Subadult	+	-	532	+	-	/	◆	▲	/
2	Female	Subadult	+	-	478	+	-	□	◆	▲	●
3	Female	Juvenile	+	-	107	+	-	/	◆	▲▲	/
4	Female	Adult	+	+	426	+	-	/	◆◆	▲▲▲	●

Real-time PCR hepatitis E virus (HEV), immunohistochemistry (IHC) HEV and antibodies (Ab) HEV: (-) negative; (+) positive.

Hepatocellular necrosis:(/) absence; (□) <10 cells per total section of 1cm^2 approx.

Lymphoplasmacytic aggregates: (/) absence; (◆) ≤3 small aggregates; (◆◆) 4–7 small or medium-sized aggregates.

Sinusoidal congestion: (▲) very scarce presence of erythrocytes; (▲▲) ≈30% of sinusoids contain moderate amounts of erythrocytes; (▲▲▲) 30–80% of lobules are highly congested.

Bile pigment accumulation (extracellular (canalicular cholestasis) and intracellular): (/) absence; (●) multifocal and in low amounts.

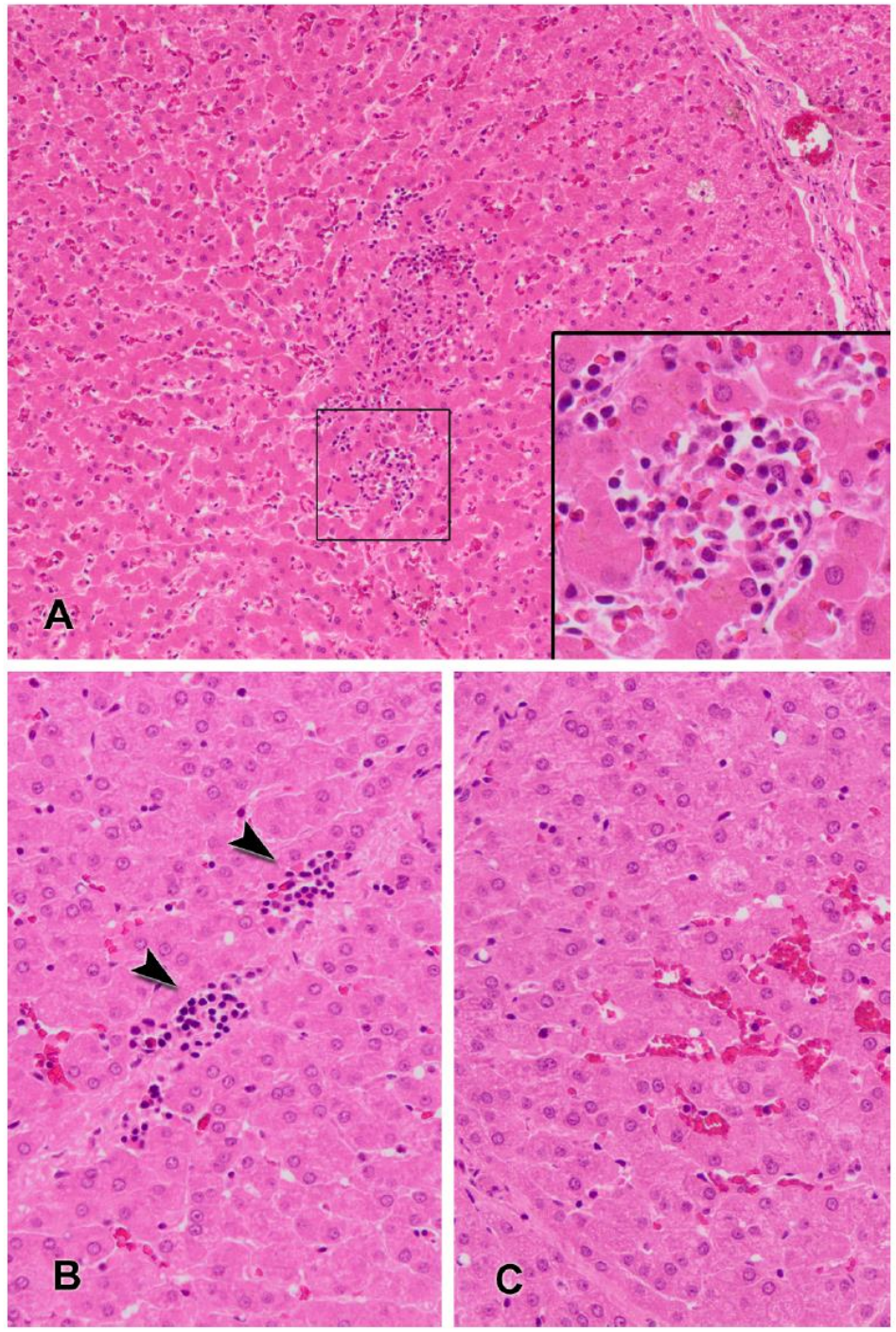
Treatment

- **Sofosbuvir was shown to have antiviral activity against HEV in vitro but had limited efficacy in HEV-patients. A pilot study of 9 patients (7 RBV previously failed) given sofosbuvir (400 mg/day) for 24 wks found that their HEV viremia decreased, but was not cleared. Sofosbuvir alone is not cure for HEV.**
- **Zinc salts can block HEV replication in vitro by inhibiting RNA polymerase. 2 F CHE-transplant-recipients did not respond to RBV despite having elevated intra-erythrocyte zinc concentrations. The natural compound silvestrol blocks HEV replication in vitro, and HEV RNA concentrations in feces of treated mice rapidly decreased. has a similar action in humans …**

Histopathologic lesions in wild boar naturally infected with HEV

- The livers of the 4 animals with naturally occurring HEV infection displayed only mild diffuse lymphoplasmacytic infiltrates (Fig 1A and 1B), with one of them also showing slight signs of hepatocyte necrosis. One of these animals also had a high degree of congestion in the hepatic sinusoids (Fig 1C).

- Fig 1A: liver with presence of mild intralobular lymphoplasmacytic aggregates in the hepatic parenchyma. Inset showing a lymphoplasmacytic aggregate at higher magnification (hematoxylin and eosin, HE).
- Fig 1B: liver showing slight perilobular infiltrations of lymphocytes (arrowheads) (HE).
- Fig 1C: hepatic lobule with moderate
- hyperemia of liver sinusoids (HE).



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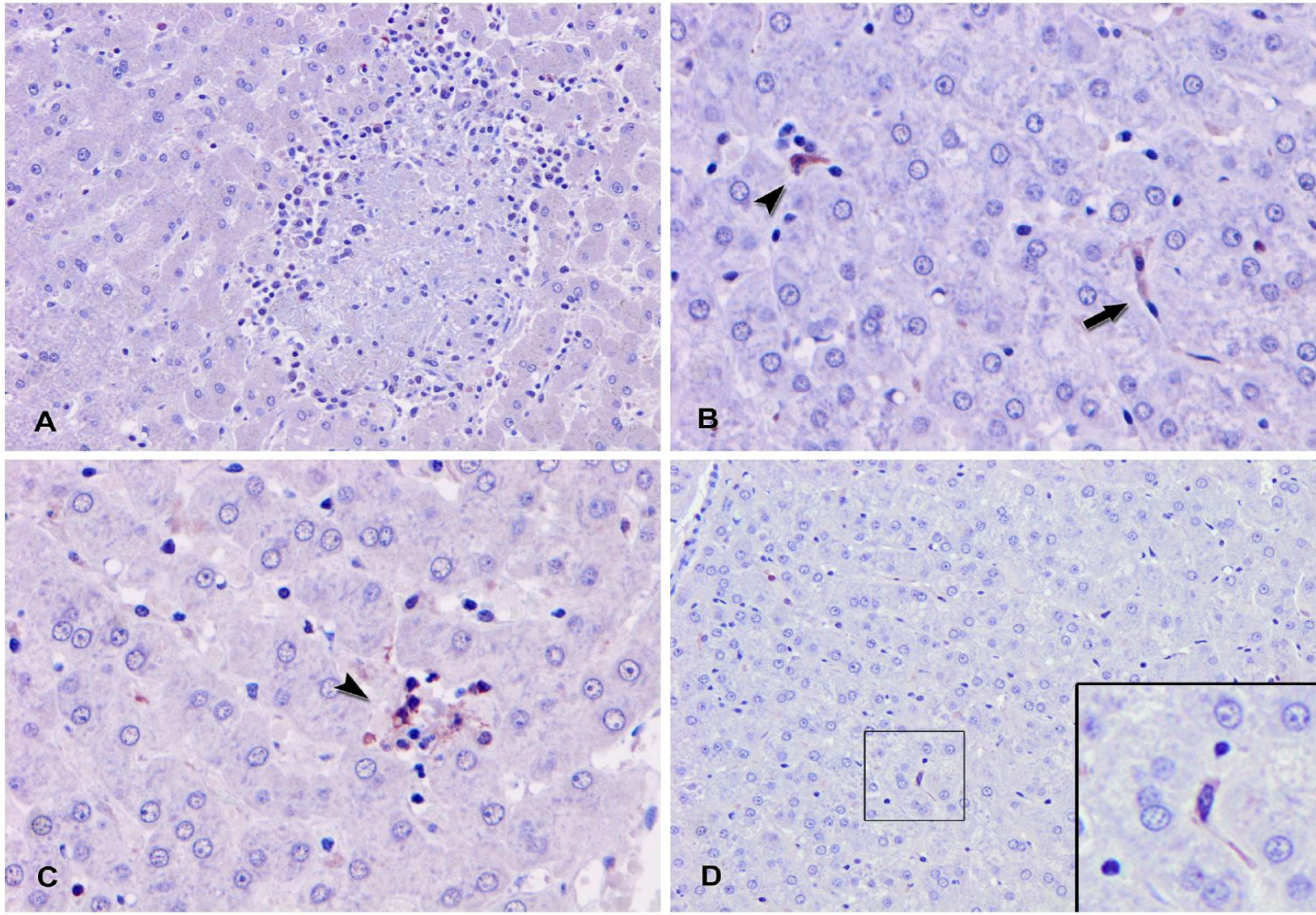
Representative photomicrographs of liver sections from 3 wild boar naturally infected with HEV

- Fig 2A: liver with absence of association of HEV antigen inside lymphoplasmacytic aggregates (Immunohistochemistry (IHC) with avidin-biotin-peroxidase complex (ABC) method counterstained with hematoxylin).
- Fig 2B: HEV immunolabeling in cytoplasm of Kupffer cells (arrowhead) and sinusoidal endothelial cells (arrow) (IHC ABC method).
- Fig 2C: HEV immunostaining of light lymphoplasmacytic infiltrate (arrowhead) (IHC ABC method).
- Fig 2D: liver showing slight labeling for HEV antigen in hepatic parenchyma, which is appreciable in Kupffer cells (inset) (IHC ABC method).



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2’-C-Methylcytidine

- La 2'-C-metilcitidina (2-CMC), NM107, analogo nucleosidico (NA) contro HEV in vitro, il composto ha dimostrato un effetto inibitorio contro la replicazione dell'HEV (IC50 di 22 M/L).
- Applicandolo insieme a RBV ha prodotto un moderato effetto antagonistico, suggerendo un meccanismo convergente di inibizione.
- Quando valutato per il trattamento dell'HCV, è stata riportata una biodisponibilità orale insuciente. è stato sviluppato un profarmaco NM283, lo sviluppo è stato interrotto a causa di effetti tossici avversi.
-

The risk of HEV reinfection is unclear.

Although the minimum protective concentration of antibodies remains to be determined, an antibody concentration of 2.5 World Health Organization (WHO) units/mL was found to be protective in a vaccine study SOT recipients can be re-infected when the antibody concentration is below 7 WHO units/mL

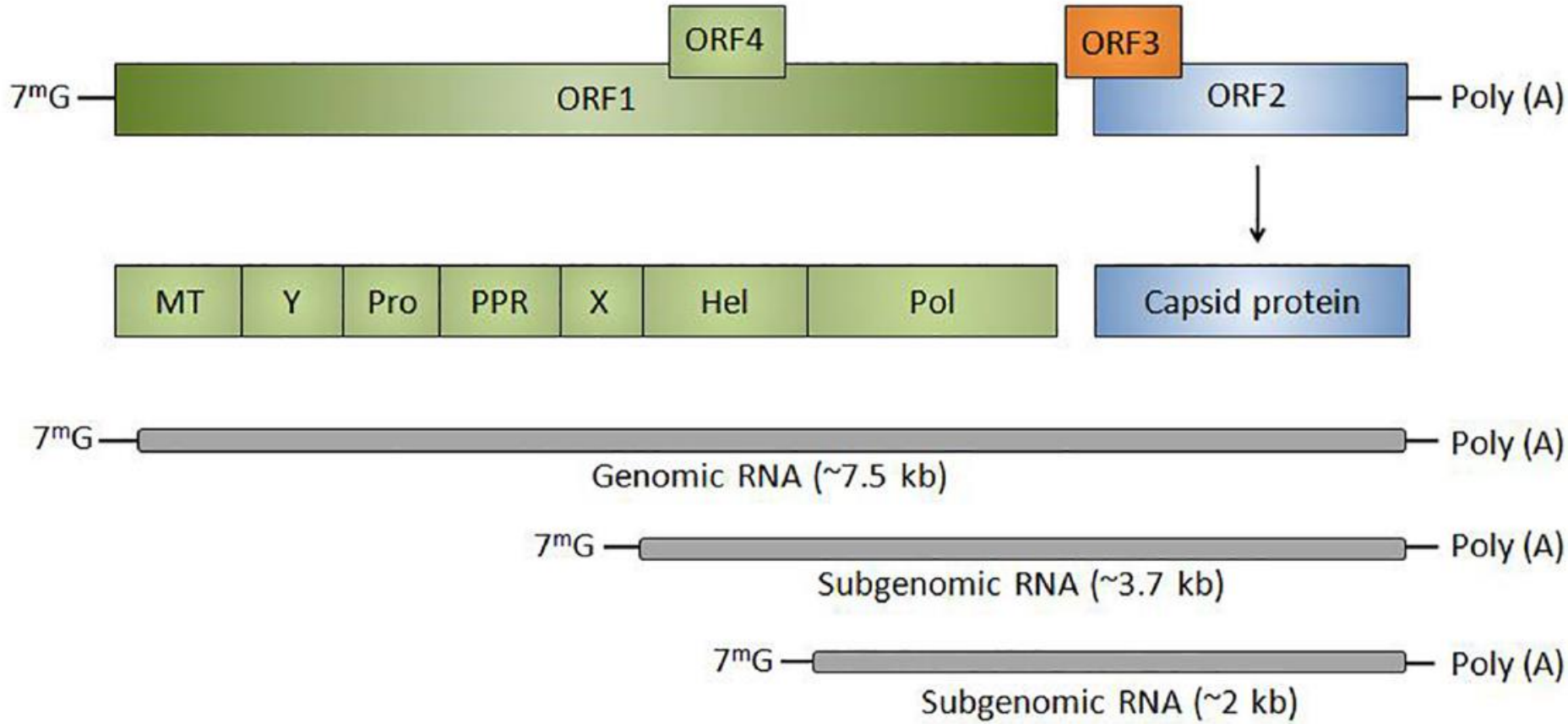


FIGURE 1 | Genomic organization of HEV: Classically divided into three ORFs (ORF1, ORF2, and ORF3) except genotype-1 having an additional ORF4. HEV RNA is transcribed into subgenomic RNA of ~3.7 and ~2 kb. The 5′ non-coding region is capped with 7-methylguanosine (7mG) and 3′ is polyadenylated [poly(A)]. ORF1 encodes for non-structural proteins including MT, regions of unknown function (Y, PPR, and X), Pro, Hel, and Pol or RdRp. ORF2 codes for capsid protein and ORF3 is a multifunctional protein that helps in the release of virions from the infected cell.

Sofosbuvir

- Sofosbuvir è un profarmaco nucleotidico, che può essere incorporato nell'HCV RNA dal RdRp NS5B che agisce come terminatore di catena. Il suo potenziale antivirale contro HEV è stato dimostrato utilizzando i repliconi HEV GT3 nelle cellule Huh7 e HepG2. I valori IC50 erano in un intervallo micromolare basso, da 1 a 2 ordini di grandezza meno potenti rispetto ai repliconi HCV. Sofosbuvir ha mostrato un effetto additivo insieme a RBV. L'effetto inibitorio è stato confermato dallo stesso gruppo in cellule staminali pluripotenti indotte derivate da epatociti (iPSC-HLC) per tutti e quattro i GT comuni e in coltura cellulare per GT1 e GT3 da altri gruppi. è stato descritto che sia i repliconi GT1 e GT3 che il virus GT3 a lunghezza intera non erano inibiti nelle cellule HEK293T, U-87MG e Huh7. Li et al. hanno riferito che un ceppo GT5 è stato moderatamente inibito a 200 M da un estere isopropilico di Sofosbuvir, PSI 7977.
- L'efficacia di Sofosbuvir in vivo è stata inconcludente. 3case ha dichiarato che Sofosbuvir non è riuscito a eliminare l'HEV quando somministrato insieme a RBV, mentre 3 ha riportato un trattamento di successo insieme a RBV. Uno studio multicentrico di fase II Sofosbuvir in monoterapia (400 mg una volta al giorno 24 settimane) in 9 pazienti precedentemente falliti RBV. Nessuno dei pazienti ha eliminato il virus, sebbene abbia ridotto i livelli di HEV RNA. potrebbe essere ulteriormente studiato in combinazione con RBV.
-

Conclusions

- The pathogenesis of HEV infection involves a complex interplay between the virus and the host immune response. While the clinical phenotype of an HEV infection is primarily hepatological, the range and incidence of HEV-associated clinical symptoms is much broader, including neurological and renal disorders. Ribavirin is currently the treatment of choice for chronically infected patients but there is an urgent need to find other compounds with which to treat patients who fail to clear HEV after ribavirin therapy.

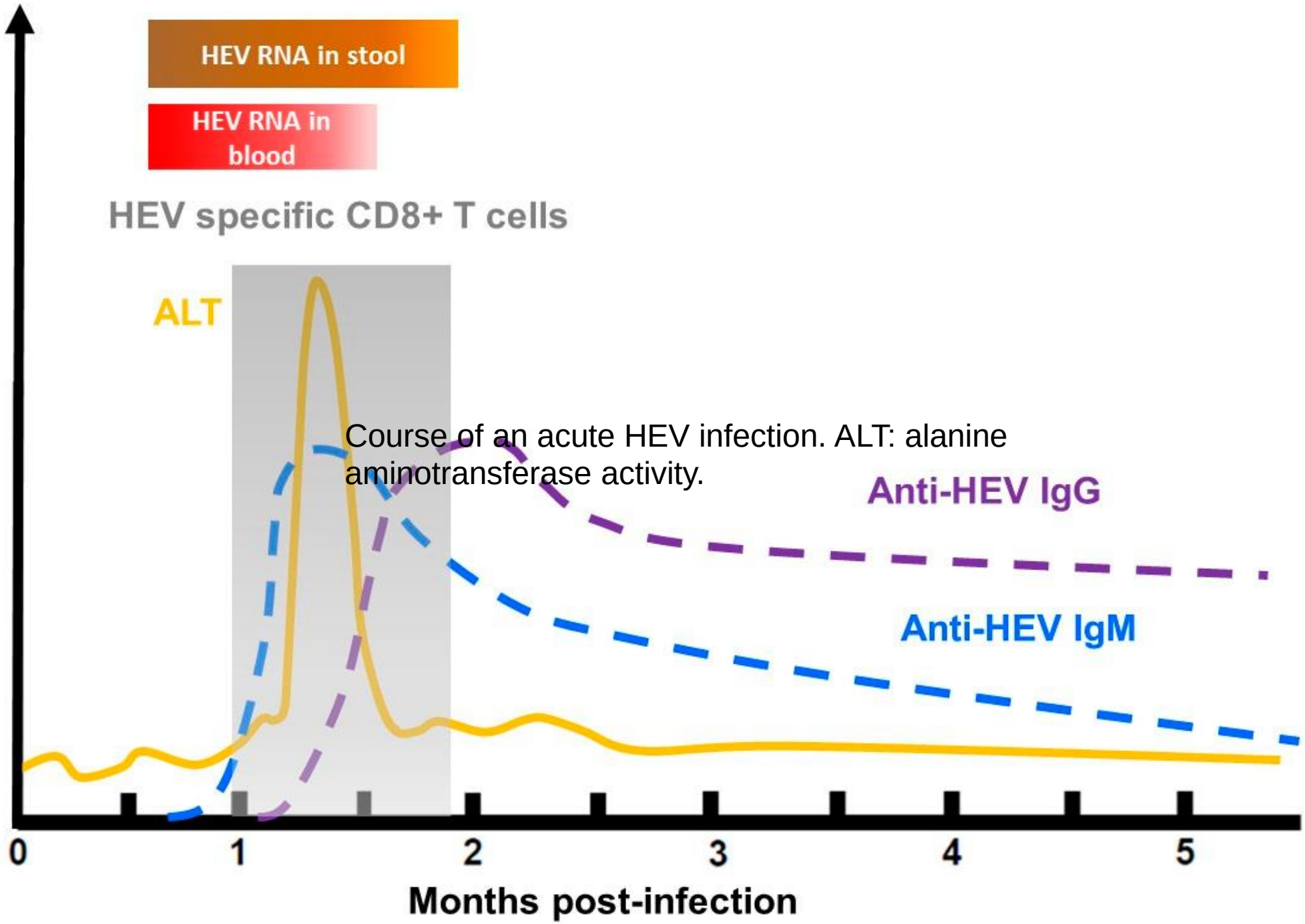
Public health control measures

- In December 2011, the first HEV recombinant subunit vaccine (Hecolin®) was registered in China for the prevention of HEV infection and HEV-related diseases in humans. So far, it has not been licensed and approved in any other country. Although randomized controlled trials have shown a high efficiency and very low number of SAEs following HEV vaccination, it is not recommended by WHO for routine use in under 16 years, pregnant women, people with chronic liver disease, people on organ transplant waiting lists, and travellers .
- The WHO position concerning routine vaccination programs should not preclude the use of the vaccine in specific situations such as outbreaks where the risk of hepatitis E or of its complications or mortality is particularly high.

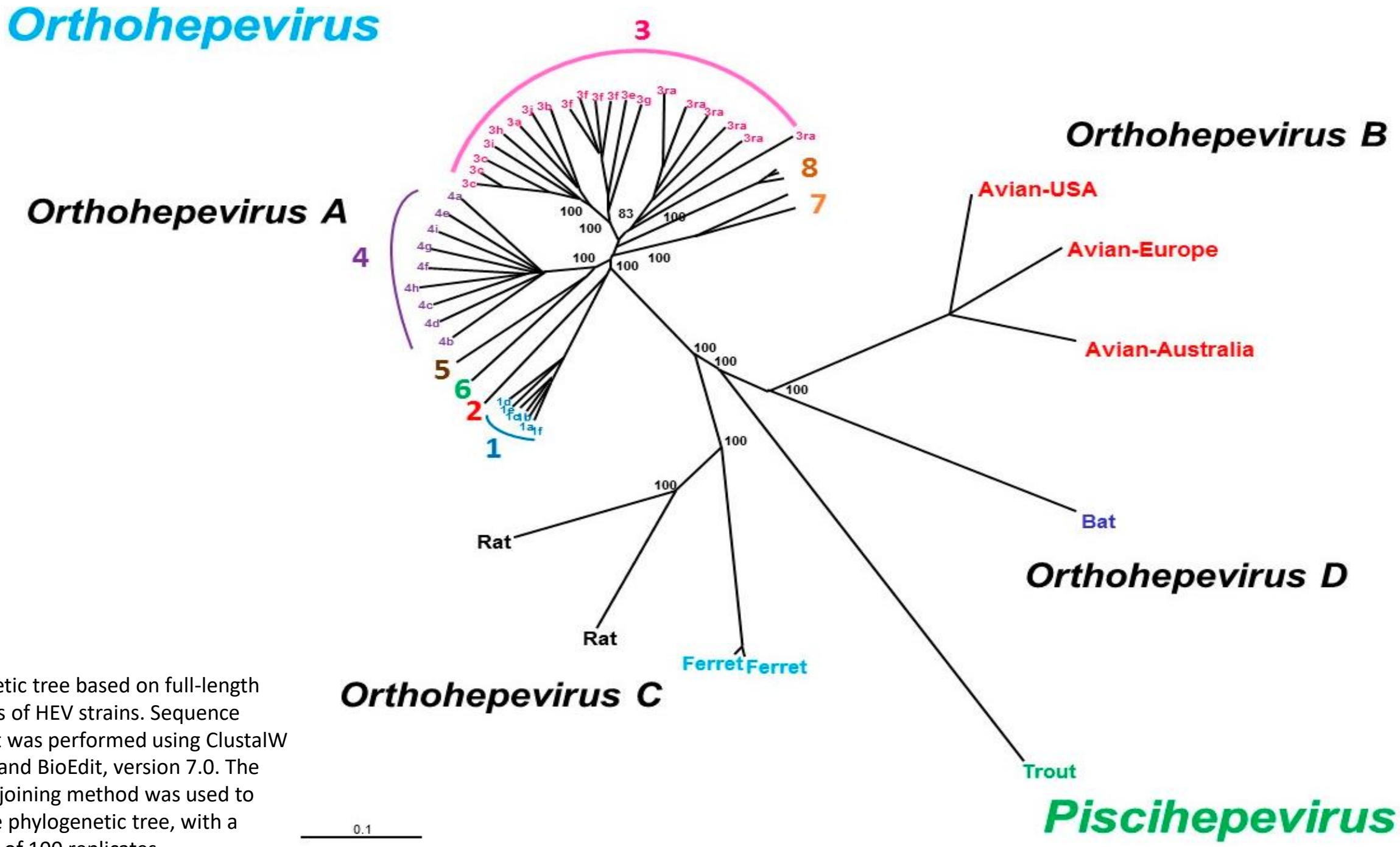
Infection control, personal protection and prevention of infection

- Consumption of raw or undercooked pig meat and shellfish should be avoided in all parts of the world. It is important to make sure that processed food containing pig meat is well cooked.
- When travelling to countries with poor sanitation, it is advisable to boil all drinking water, including water used for brushing teeth.
- Wearing working gloves and boots might reduce HEV infection in those workers with occupational exposure to HEV-infected animals.

- Transfusion or transplantation-related HEV transmission events have been described and the conduction of risk assessment is recommended for each product with special consideration of risk groups. Some assessments stated that transfusion-transmitted infection plays a minor role as source of infection in the risk group of solid-organ recipients and risk factors have been identified to be consumption of pork or game meat.



Course of an acute HEV infection. ALT: alanine aminotransferase activity.



Phylogenetic tree based on full-length sequences of HEV strains. Sequence alignment was performed using ClustalW (MEGA5) and BioEdit, version 7.0. The neighbor-joining method was used to create the phylogenetic tree, with a bootstrap of 100 replicates.

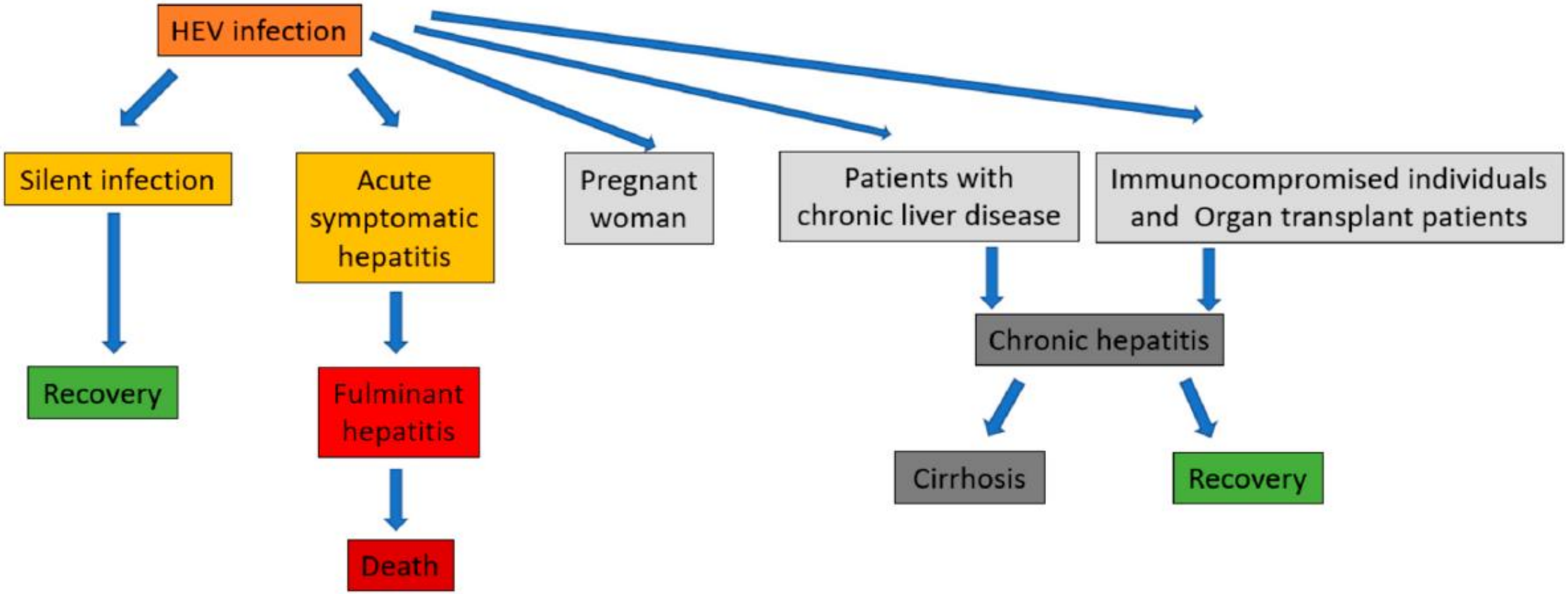
Year(s)	Country	Mode of Transmission	Reported
2013	Cameroon	Waterborne	33
2014–2015	Bangladesh	Waterborne	103
2014–2016	India	Waterborne	17
2016–2017	Chad	Waterborne	1293
2017–2018	Nigeria	Contamination of drinking water	1376
2014–2017	Bangladesh	Waterborne	661
2018	Central African Republic	Waterborne	149
2018	South Sudan	Waterborne	161
2019	Pakistan	Waterborne	300
2017–2020	Namibia	Waterborne	7247

[1] Numbers based on reported estimates.

Diagnostica

- Diagnosi AHE: IgM anti-HEV nel siero e/o HEV RNA nel siero o feci.
- Genoma HEV: PCR generica o RT-PCR.
- Metodi basati su Ab (Western blot o immunoassay enzimatici) CHE: IgG anti-HEV
- L'infettività dell'HEV è determinata nell'inoculazione sperimentale di animali o con tecniche di coltura cellulare.
-

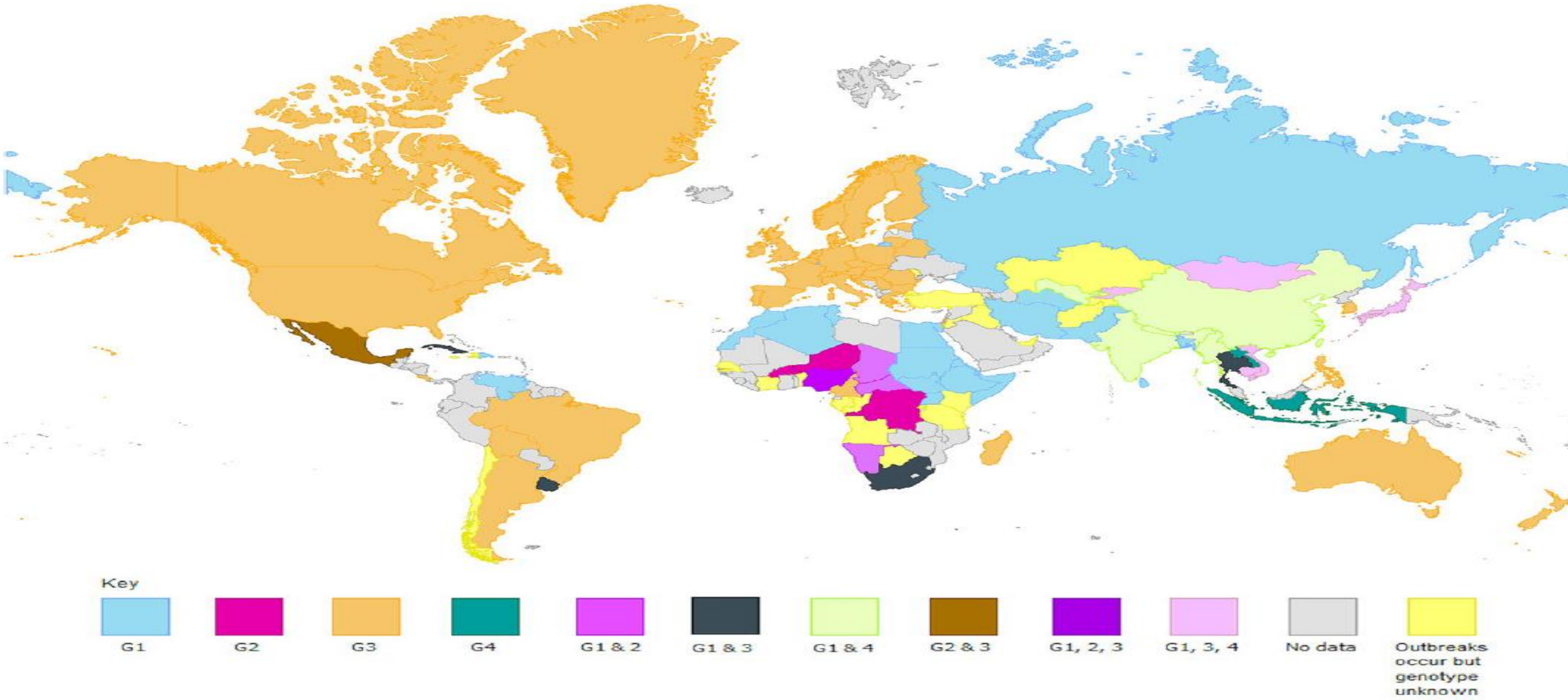
Different disease scenarios seen with HEV.



Legame clinico tra compromissione delle cellule linfoidi ed esito hev

- Pazienti dopo SOT
- Tacrolimus:f attore di rischio per il suo effetto immunosoppressivo più elevato rispetto alla ciclosporina A. Entrambi avevano un potere molto potente nel colpire le cellule T.
- oltre il 60% dei pazienti con HEV abbia sviluppato CHE in trapianto di cuore .
- solo l'acido micofenolico (MFA) era associato alla clearance HEV. MFA inibisce HEV.
- MFA mostra effetti antivirali diretti sulla replicazione dell'HEV; L'AMF deve essere presa in considerazione nei pazienti con HEV-SOT quando possibile, sebbene gli effetti specifici richiedano ulteriori indagini.
-

The geographical distribution of HEV 1–4



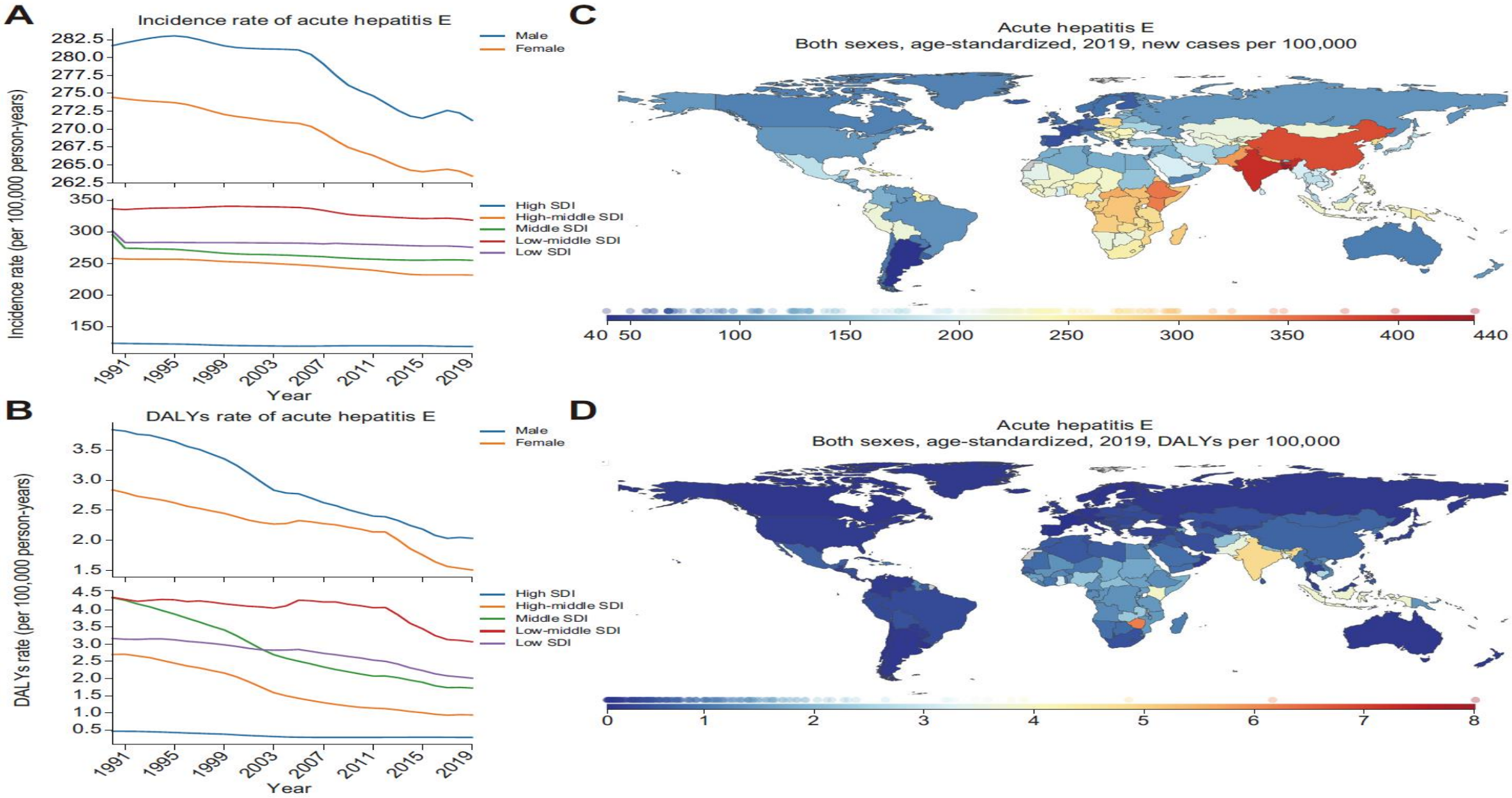


Fig. 5. Burden of AHE for 204 countries and territories. Age-standardized (A) incidence and (B) DALY rates of AHE per 100,000 population from 1990 through 2019 categorized according to country and territory, stratified by sex or SDI. Age-standardized (C) incidence and (D) DALY rates of AHE per 100,000 person-years by country and territory, in 2019. The maps in (C) and (D) were generated by the GBD 2019 tool. AHE, acute hepatitis E; DALY, disability-adjusted life year; GBD, Global Burden of Disease; SDI, socio-demographic index.