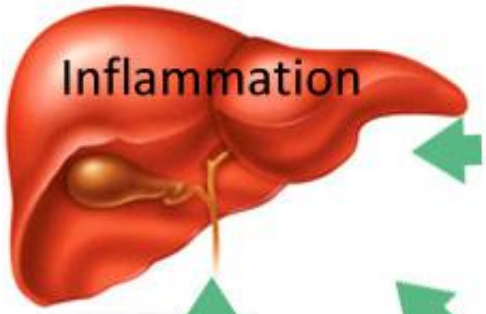
Gent.mi studenti
E' stata attivata la rilevazione delle Opinioni Studenti [OPIS]. In tale frangente il questionario OPIS è stato implementato con alcune domande sull'erogazione dell'insegnamento a distanza.
Il codice OPIS da utilizzare per il corso di Microbiologia (Antonelli) è il seguente: **EPR3P0KB**
Esso riguarda l'intero insegnamento; pertanto le valutazioni riguarderanno l'intero insegnamento anche se avrete la possibilità nello spazio dedicato di inserire vostri commenti personali.
Nel raccomandare la compilazione del questionario perchè di notevole importanza per Sapienza, vi ringrazio e vi invio i saluti più cordiali
GA

HEPATITIS - inflammation of the liver tissue



Toxic Damage
Alcohol
Drugs
Poisons/Chemicals

Immunologic Damage

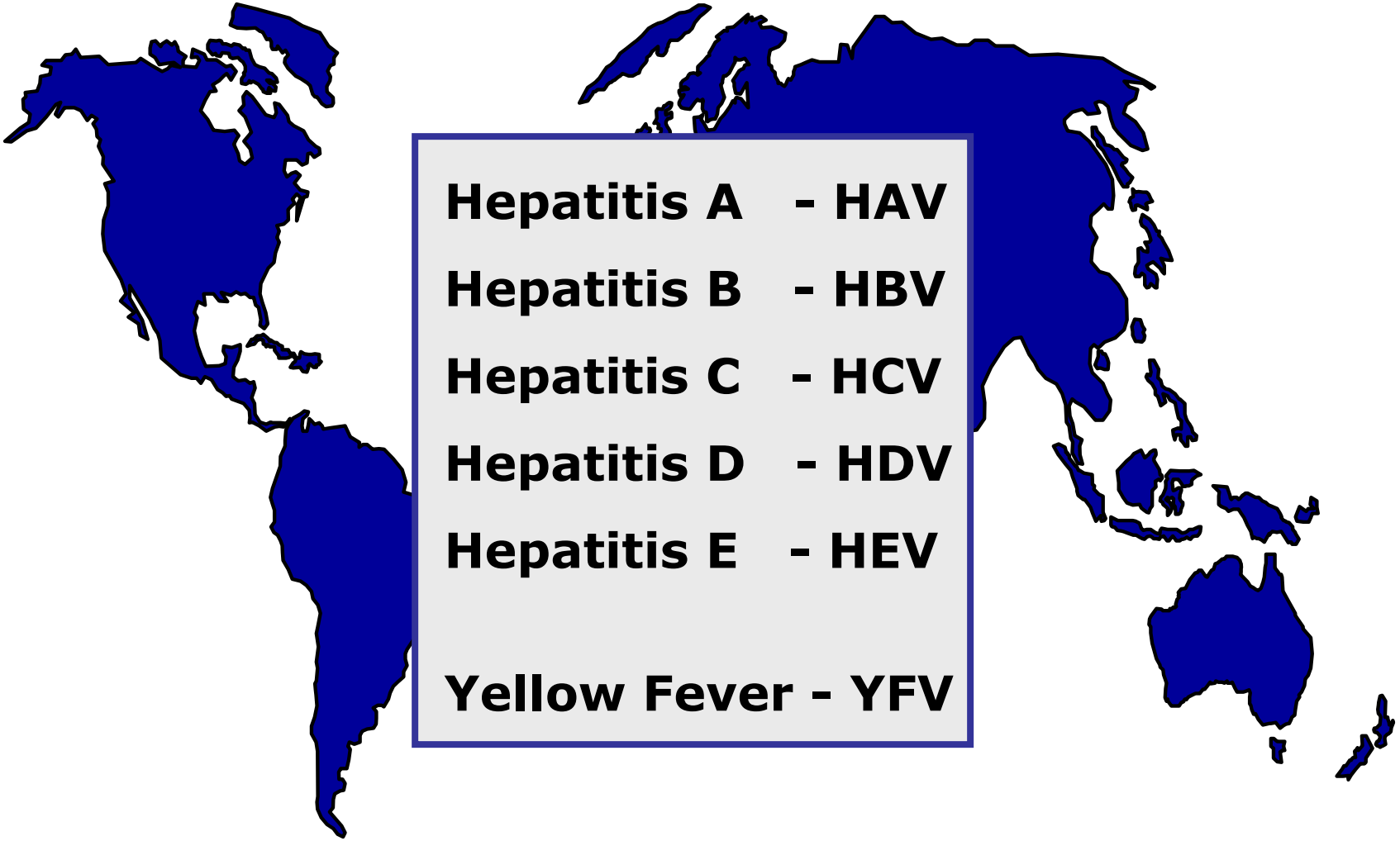
Infections
Viruses
Bacteria
Fung
Protozoa

- **Hepatitis A - HAV**
- **Hepatitis B - HBV**
- **Hepatitis C - HCV**
- **Hepatitis D - HDV**
- **Hepatitis E - HEV**

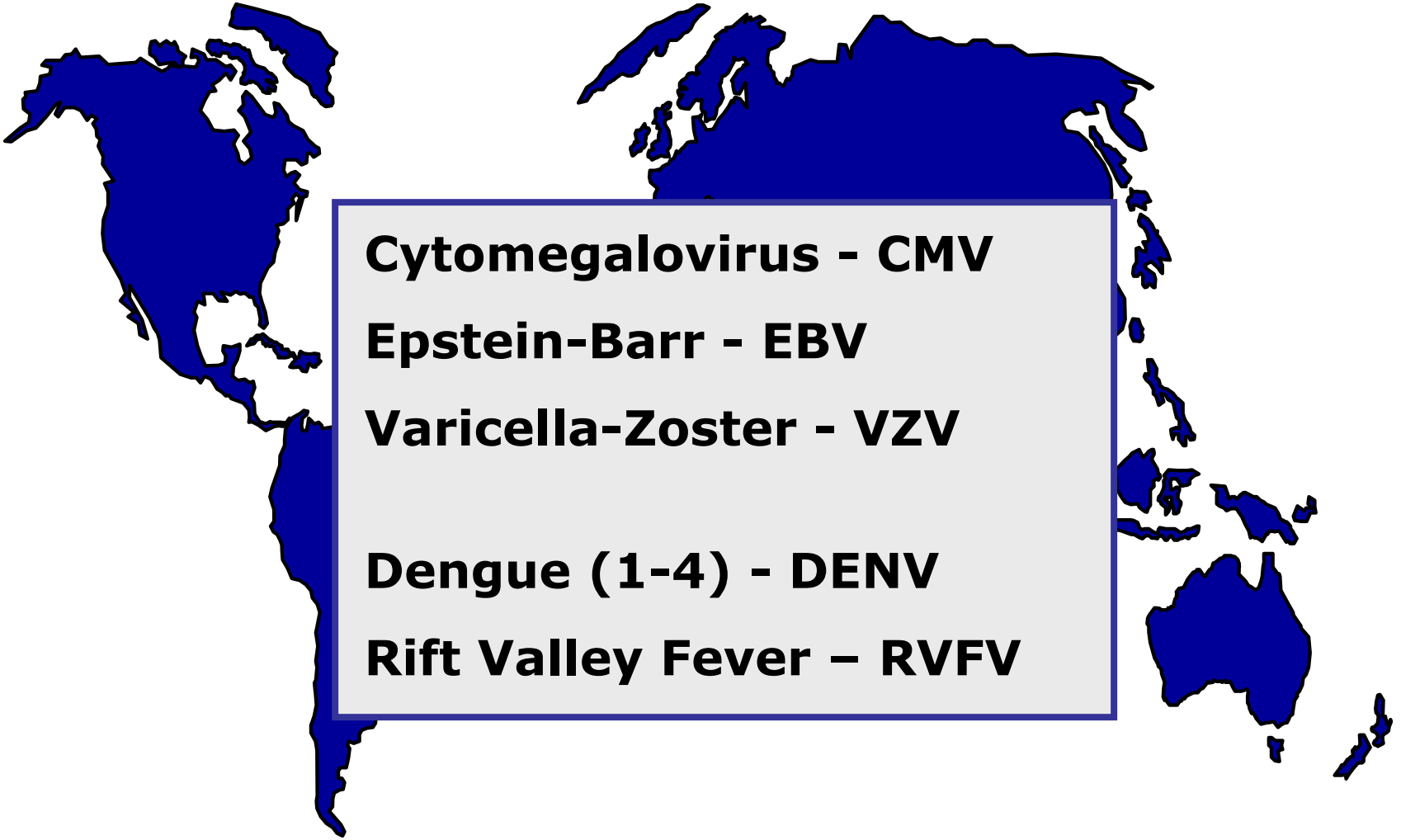
Differential Diagnosis of Acute Hepatitis

Infectious	*Noninfectious*
Epstein-Barr virus	Drug-induced hepatitis
Cytomegalovirus	Autoimmune hepatitis
Herpes simplex virus	Ischemic hepatitis
Yellow fever	Acute fatty liver of pregnancy
Leptospirosis	Acute Buddy-Chiari syndrome
Q fever	Wilson's disease
HIV	
Brucellosis	
Lyme disease	
Syphilis	

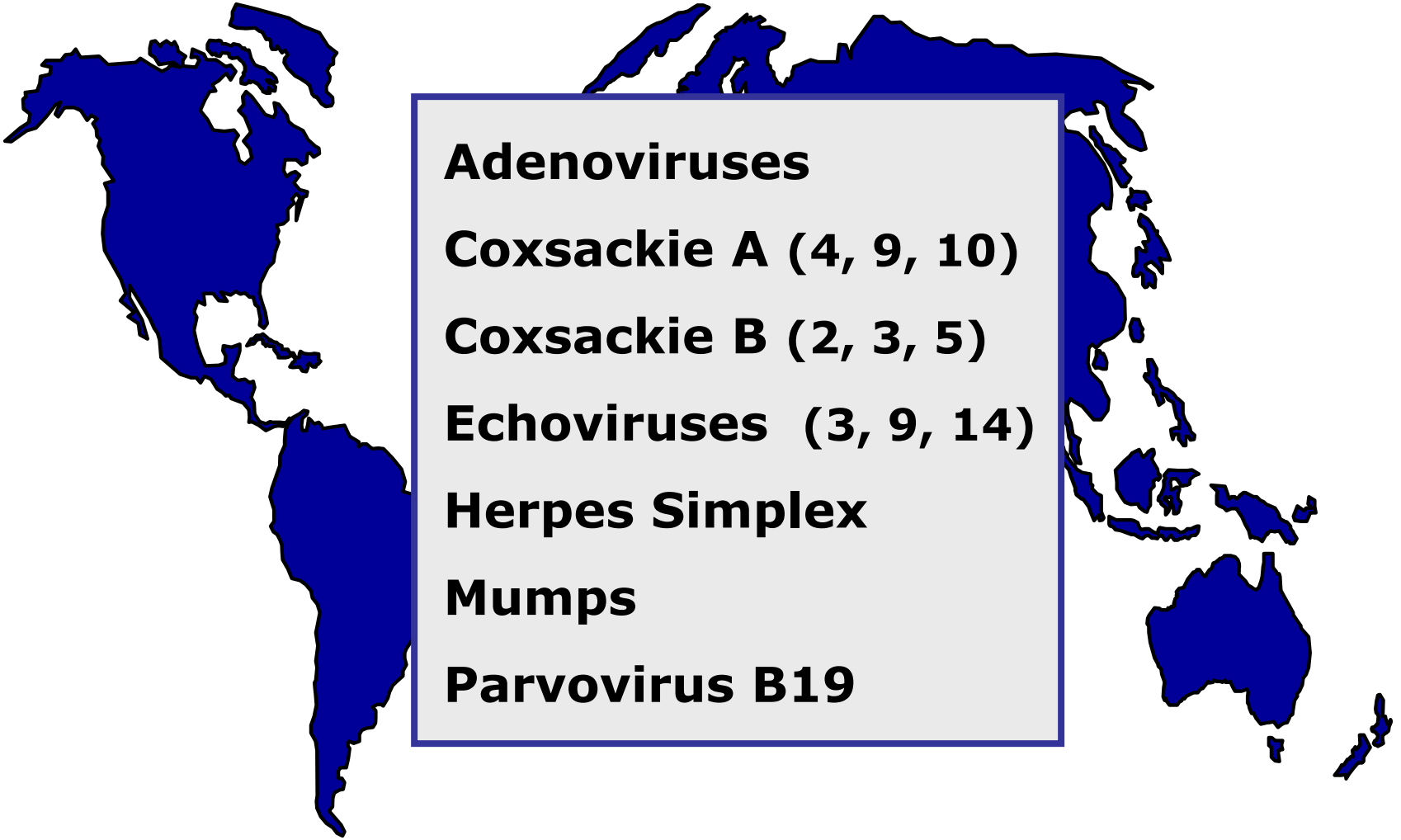
HEPATOTROPISM: broad



HEPATOTROPISM: FREQUENT



HEPATOTROPISM: SPORADIC



Adenoviruses

Coxsackie A (4, 9, 10)

Coxsackie B (2, 3, 5)

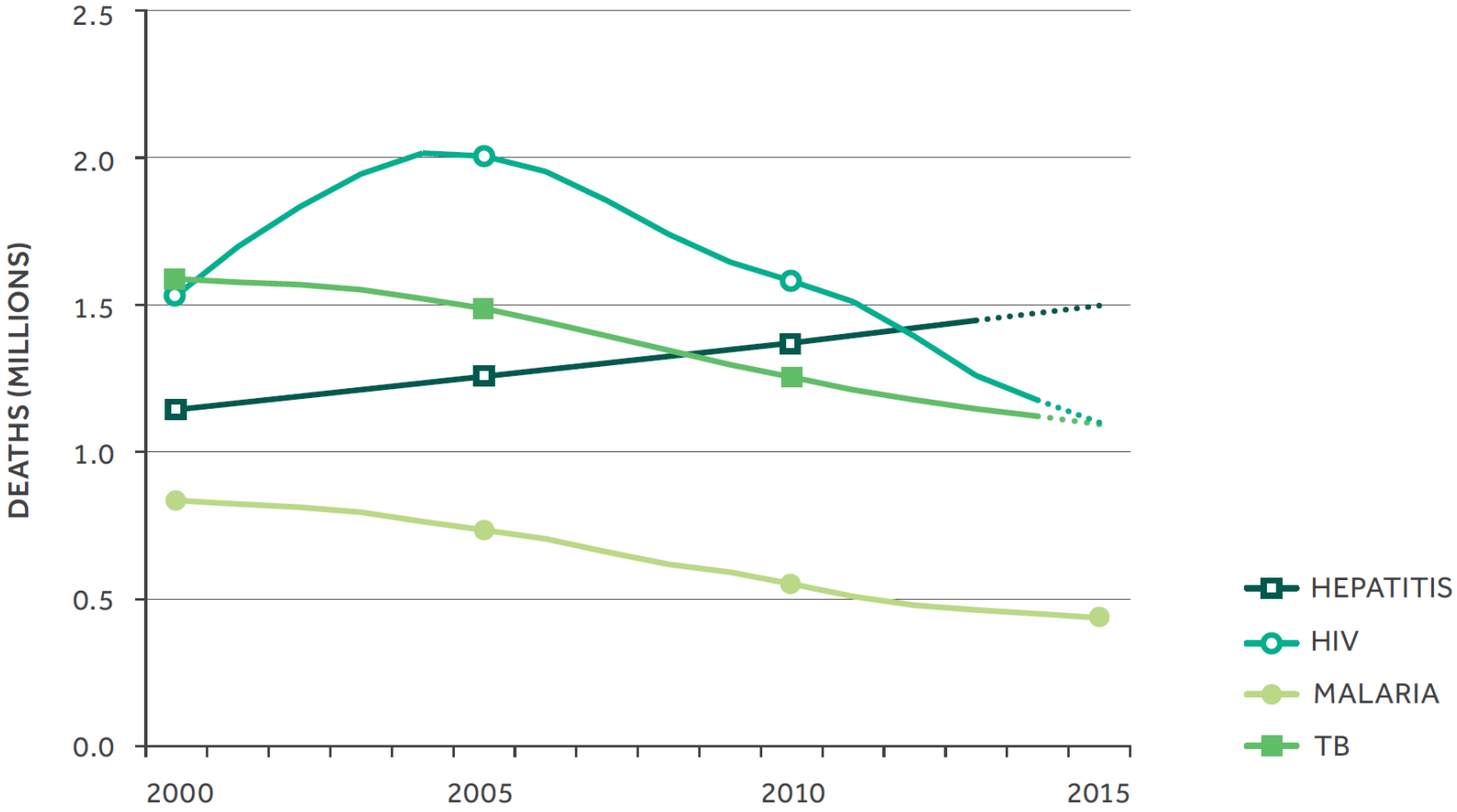
Echoviruses (3, 9, 14)

Herpes Simplex

Mumps

Parvovirus B19

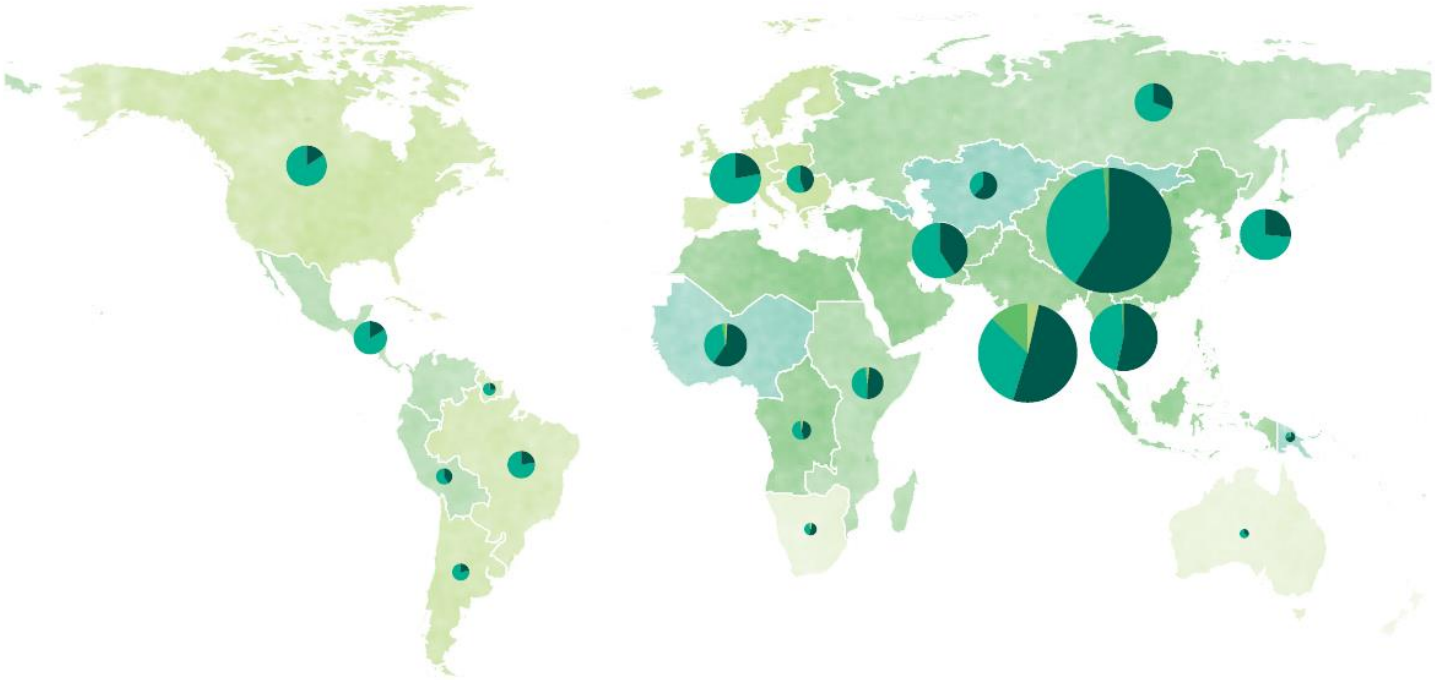
Figure 2. Estimated global number of deaths due to viral hepatitis, HIV, malaria and TB, 2000–2015



Source: Global Burden of Disease and WHO/UNAIDS estimates, see http://ihmeuw.org/3pms, http://ihmeuw.org/3pmt (accessed 2 April 2016).

World Health Organization

Figure 3. Regional distribution of viral hepatitis deaths



MORTALITY RATE (PER 100,000 PY)

- <10
- 10 - 14.9
- 15 - 22.49
- 22.5 - 33.49
- 33.5 +

PROPORTION ATTRIBUTABLE TO EACH VIRUS

The area of each pie is proportional to the number of hepatitis-attributable deaths in that region: each wedge represents the proportion of those deaths attributable to a given virus

- Hepatitis A
- Hepatitis B
- Hepatitis C
- Hepatitis E

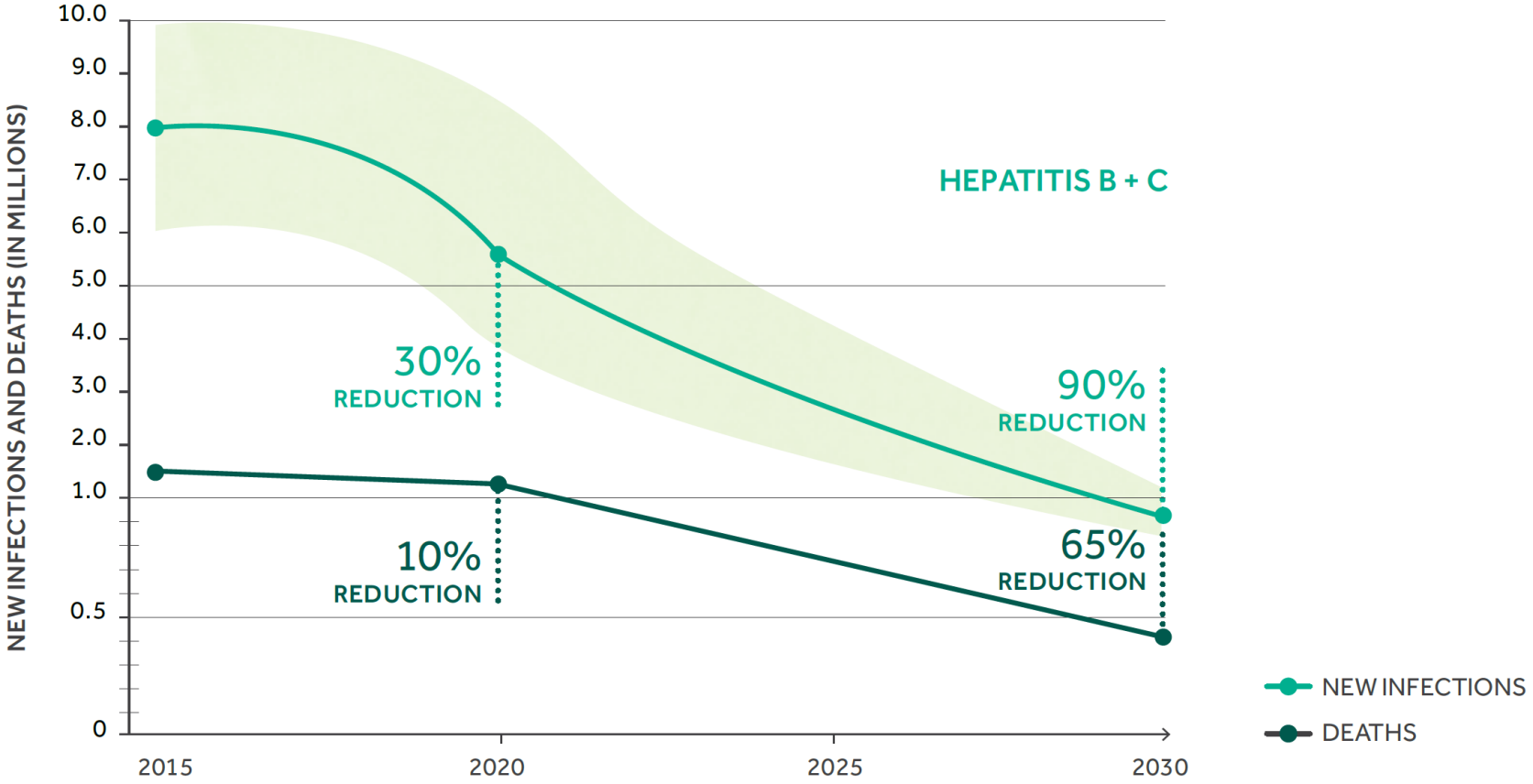
Global Service Coverage

	HIV[a]	Viral hepatitis	Sexually transmitted infections[d]
Screening and diagnosis	29.8 million people, or 79% of people living with HIV know their HIV status (2018)	27 million (10%) people living with hepatitis B knew their hepatitis B status (2016)[b] 13.1 million (19%) of the people living with hepatitis C knew their hepatitis C status (2017)[c]	66% of pregnant women screened for syphilis during antenatal care (2016)
Treatment	23.3 million people, or 62% of those living with HIV, received antiretroviral therapy (2018) 20.0 million people, or 53% of the people living with HIV have suppressed viral loads (2018)	4.5 million (17%) of the people diagnosed with hepatitis B received treatment (2016)[b] 5.0 million of the people diagnosed with hepatitis C received treatment (2017)[c]	78% of pregnant women who tested positive for syphilis in antenatal care received treatment (2016)

Sources:

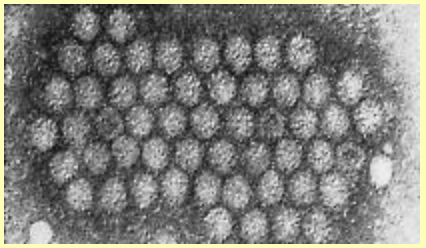
[a] UNAIDS/WHO estimates, 2019.

Figure 6. Targets for reducing new cases of and deaths from chronic viral hepatitis B and C infection

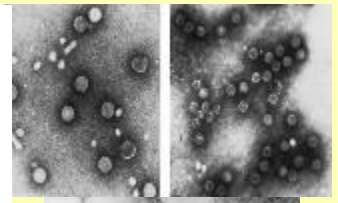


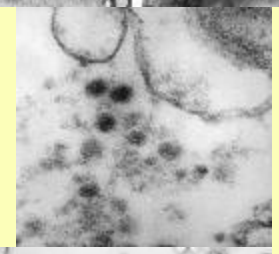
MAJOR HEPATITIC VIRUS

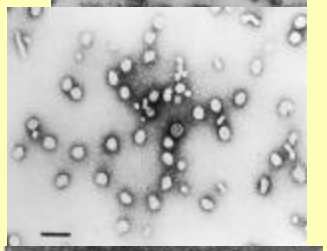
Name	Family	genome
Hepatitis A virus	*Picornaviridae*	RNA +
Hepatitis B virus	*Hepadnaviridae*	DNA
Hepatitis C virus	*Flaviviridae*	RNA+
Hepatitis delta virus	*Deltavirus*	RNA –
Hepatitis E virus	*Caliciviridae*- *Hepevirus*	*RNA* +

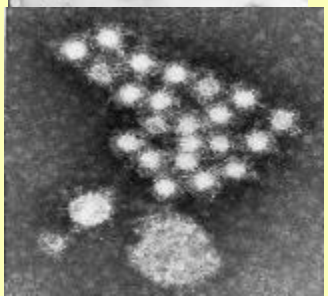


HCV

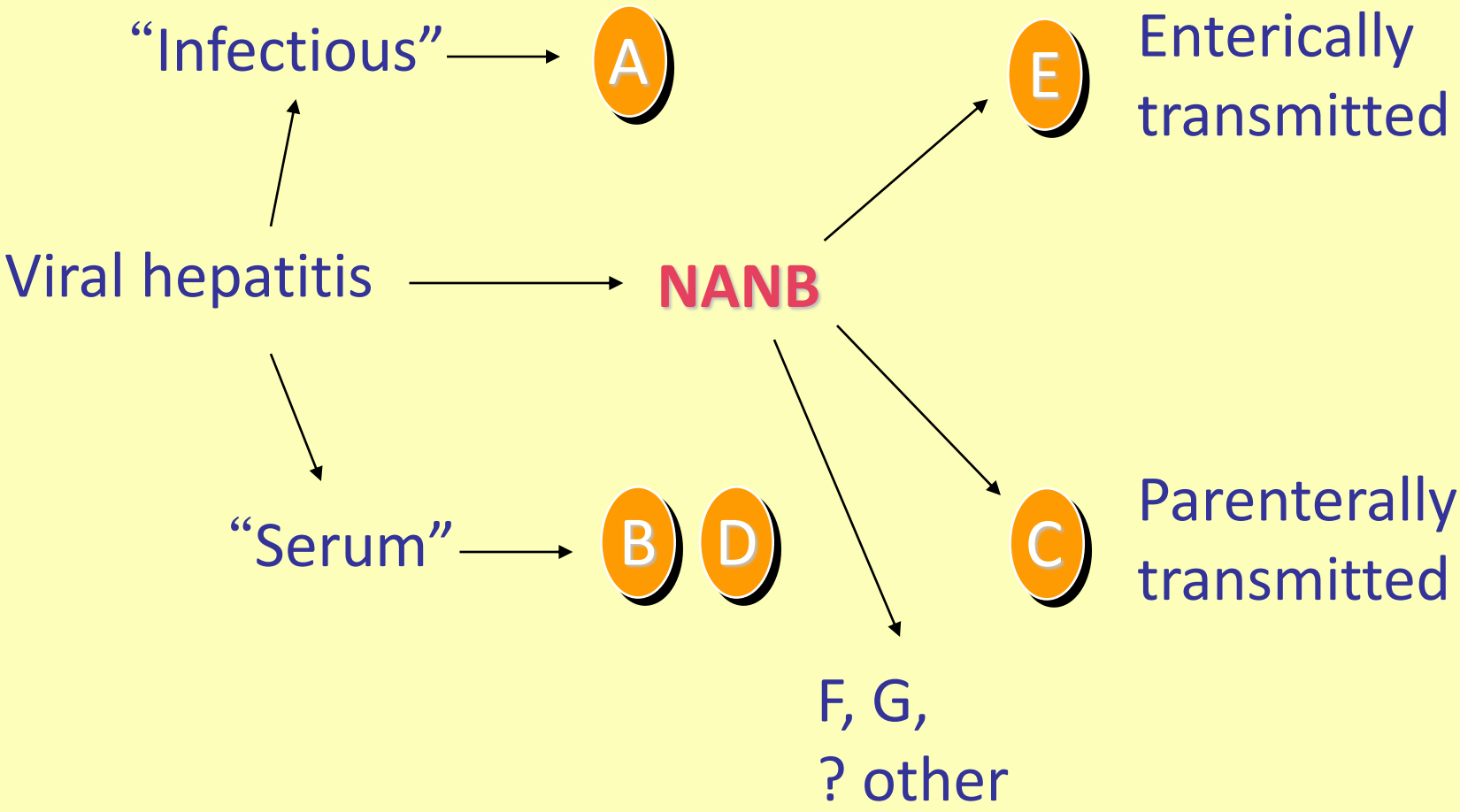




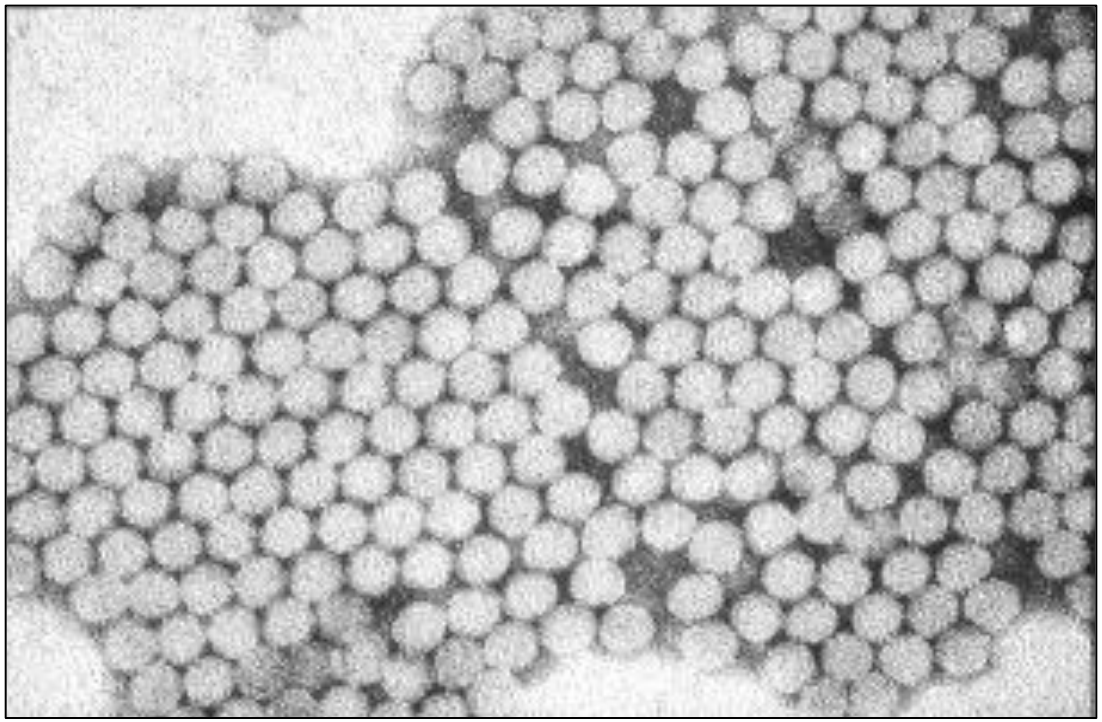




Viral Hepatitis - Historical Perspectives



HEPATITIS A VIRUS



The *Picornaviridae* is a family of small, icosahedral viruses with single-stranded, highly diverse positive-sense RNA genomes.

The family comprises 47 genera containing 110 species, but many viruses are presently awaiting classification.

Picornaviruses may cause subclinical infections of humans and animals or conditions ranging from mild febrile illness to severe diseases of heart, liver and the central nervous system.

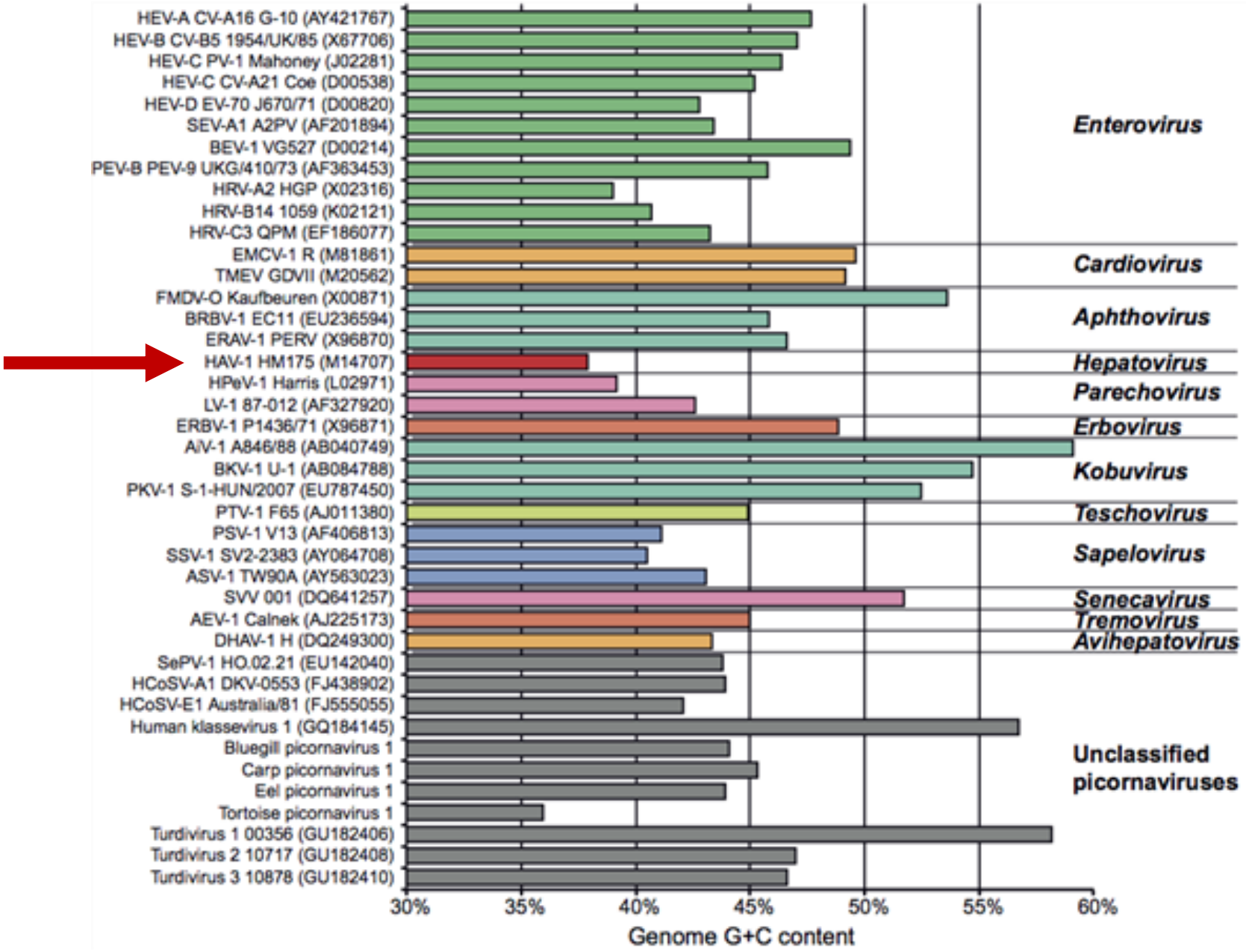
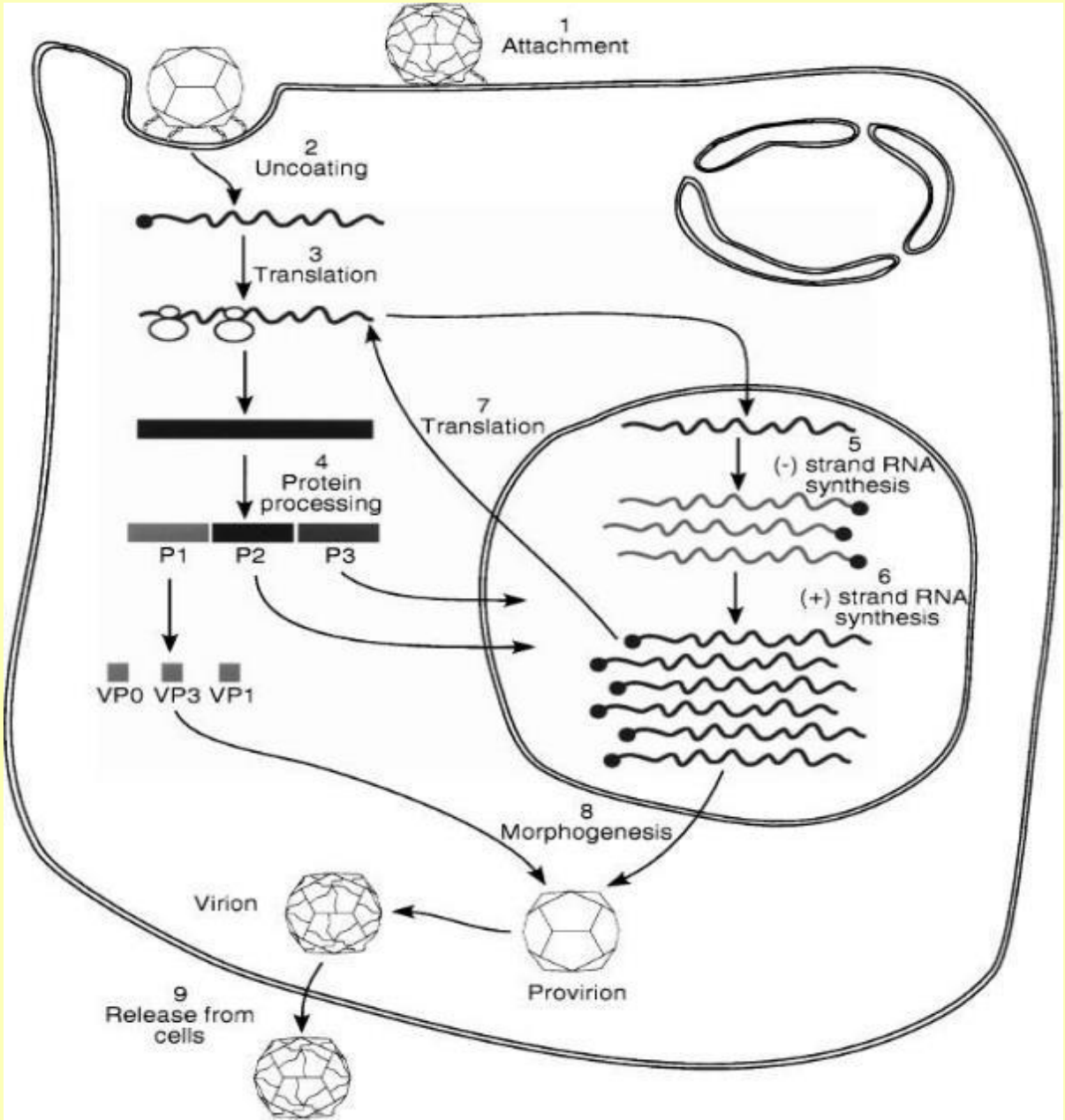

HEV-A CV-A16 G-10 (AY421767)
HEV-B CV-B5 1954/UK/85 (X67706)
HEV-C PV-1 Mahoney (J02281)
HEV-C CV-A21 Coe (D00538)
HEV-D EV-70 J670/71 (D00820)
SEV-A1 A2PV (AF201894)
BEV-1 VG527 (D00214)
PEV-B PEV-9 UKG/410/73 (AF363453)
HRV-A2 HGP (X02316)
HRV-B14 1059 (K02121)
HRV-C3 QPM (EF186077)
EMCV-1 R (M81861)
TMEV GDVII (M20562)
FMDV-O Kaufbeuren (X00871)
BRBV-1 EC11 (EU236594)
ERAV-1 PERV (X96870)
HAV-1 HM175 (M14707)
HPeV-1 Harris (L02971)
LV-1 87-012 (AF327920)
ERBV-1 P1436/71 (X96871)
AiV-1 A846/88 (AB040749)
BKV-1 U-1 (AB084788)
PKV-1 S-1-HUN/2007 (EU787450)
PTV-1 F65 (AJ011380)
PSV-1 V13 (AF406813)
SSV-1 SV2-2383 (AY064708)
ASV-1 TW90A (AY563023)
SVV 001 (DQ641257)
AEV-1 Calnek (AJ225173)
DHAV-1 H (DQ249300)
SePV-1 HO.02.21 (EU142040)
HCoSV-A1 DKV-0553 (FJ438902)
HCoSV-E1 Australia/81 (FJ555055)
Human klassevirus 1 (GQ184145)
Bluegill picornavirus 1
Carp picornavirus 1
Eel picornavirus 1
Tortoise picornavirus 1
Turdivirus 1 00356 (GU182406)
Turdivirus 2 10717 (GU182408)
Turdivirus 3 10878 (GU182410)
Enterovirus
Cardiovirus
Aphthovirus
Hepatovirus
Parechovirus
Erbovirus
Kobuvirus
Teschovirus
Sapelovirus
Senecavirus
Tremovirus
Avihepatovirus
Unclassified picornaviruses
30%
35%
40%
45%
50%
55%
60%
Genome G+C content

Table 1.*Picornaviridae.* Characteristics of members of the family *Picornaviridae*.

Characteristic	Description
Typical member	poliovirus 1 Mahoney (V01149), species *Enterovirus C,* genus *Enterovirus*
Virion	Non-enveloped, 30–32 nm virions comprising 60 protomers
Genome	6.7–10.1 kb of positive-sense, non-segmented RNA with a poly(A) tail
Replication	RNA synthesis occurs in reorganized cytoplasmic replication organelles containing non-structural proteins derived from the 2BC-P3 region of the encoded polyprotein; RNA structures at the 5′ and 3′ ends of the genome direct initiation of RNA synthesis and uridylated 3B serves as primer for synthesis of both RNA strands
Translation	Directly from genomic RNA containing an internal ribosomal entry site (IRES)
Host range	Vertebrates (at least five of the seven classes)
Taxonomy	Realm *Riboviria*, order *Picornavirales*; 47 genera containing 110 species

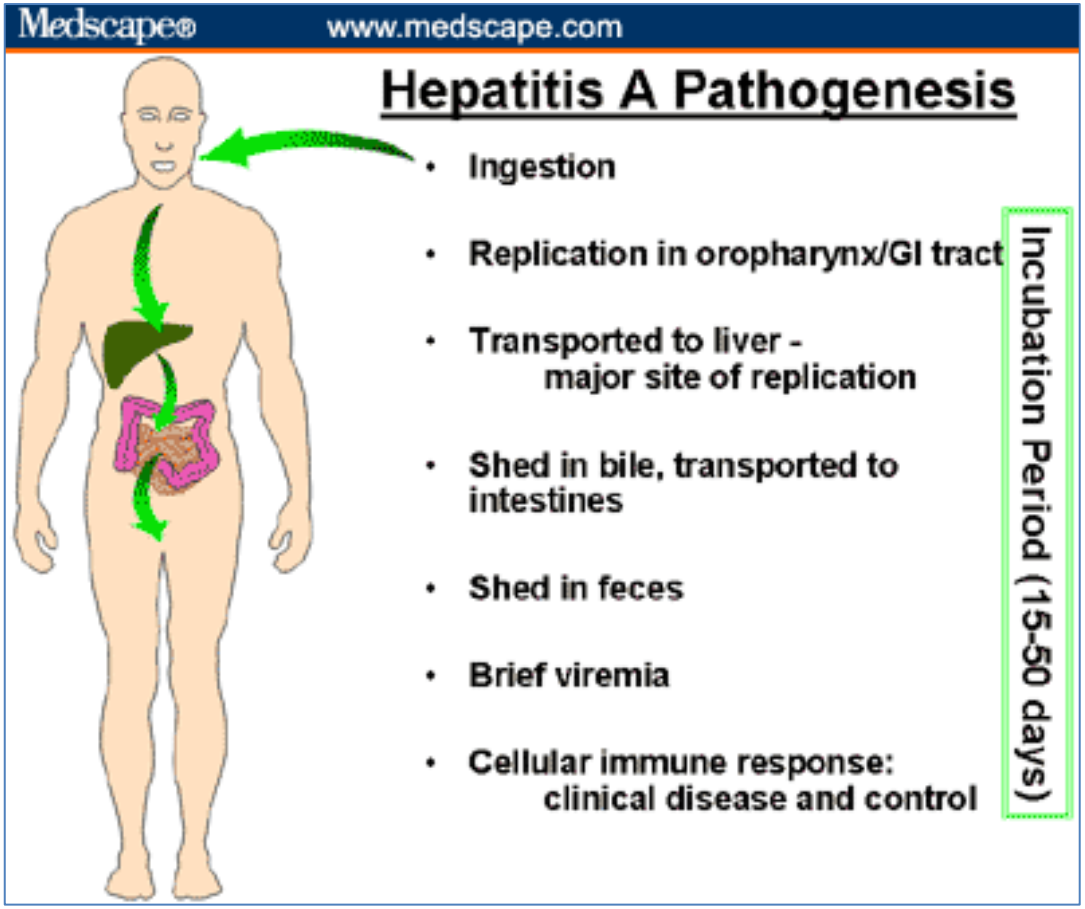
HEPATITIS A VIRAL LIFE CYCLE



HAV is most commonly contracted via ingestion; after that, the primary sites of virus replication are postulated to be the oropharynx and gastrointestinal tract.

The virus is then transported to the major site of replication, the liver, where shedding into the bile occurs with subsequent passage to the intestines and feces.

A brief viremia precedes the appearance of the virus in the stool and liver.



HEPATITIS A VIRUS

Picornaviridae

- Single serotype
- Endemic worldwide
- Acute disease and asymptomatic infection

Oro-fecal transmission

No chronic infection

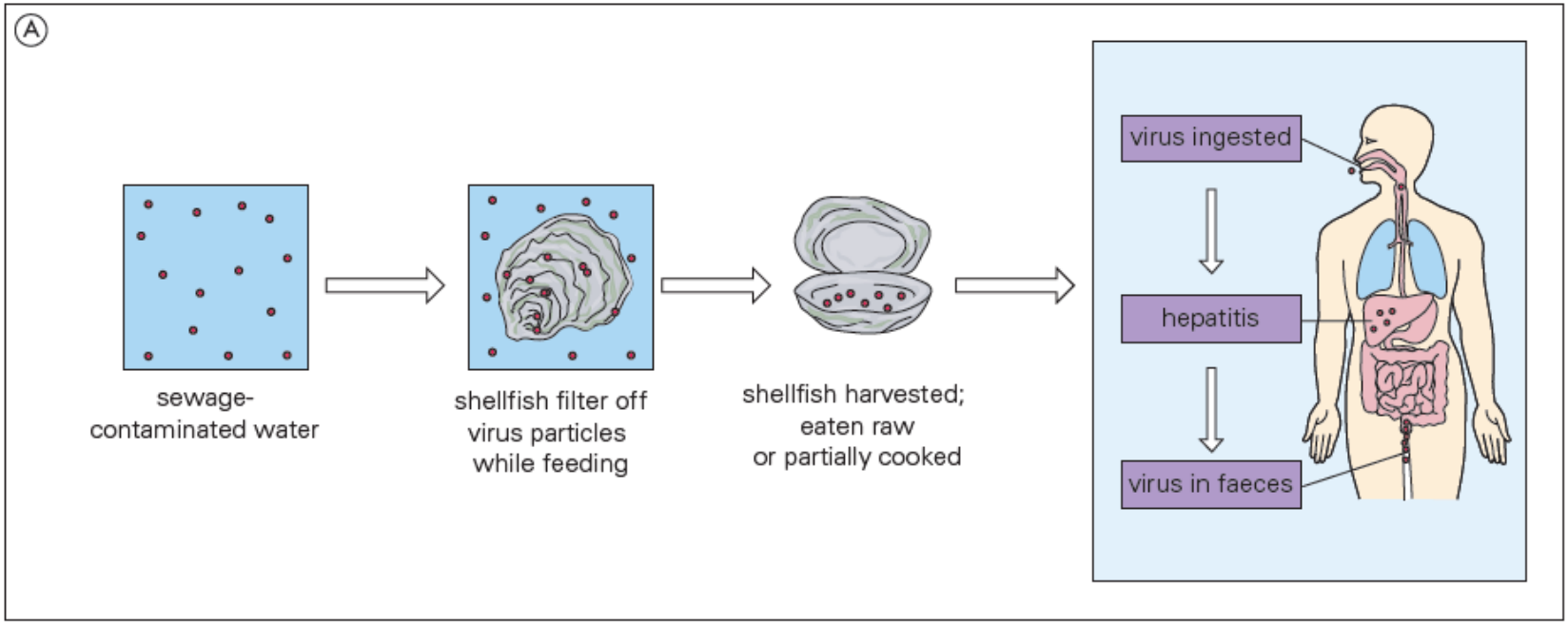
- Protective antibodies develop in response to infection - confer lifelong immunity

HEPATITIS A VIRUS - CLINICAL FEATURES

•Jaundice by age group:	<6 yrs	<10%
	6-14 yrs	40%-50%
	>14 yrs	70%-80%
•Rare complications:	Fulminant hepatitis Cholestatic hepatitis Relapsing hepatitis	
•Incubation period:	30 days on average Range: 15-50 days	
•Chronic sequelae:	None	

HAV Transmission

- ✓ Close personal contact *(e.g., household contact, sex contact, child day-care centers)*
- ✓ Contaminated food, water *(e.g., food handlers)*
- ✓ Blood exposure *(e.g., injection drug use, transfusion)*



Hepatitis A Vaccination Strategies
Epidemiologic Considerations
-Purified inactivated hepatitis A vaccine-

- Many cases occur in community-wide outbreaks
  - no risk factor identified for most cases
  - highest attack rates in 5-14 year olds
  - children serve as reservoir of infection

- Persons at increased risk of infection
  - travelers
  - homosexual men
  - injecting drug users

Hepatitis A Prevention - Immune Globulin

- Pre-exposure
  - travelers to intermediate and high HAV-endemic regions
- Post-exposure (within 14 days)

  Routine
  - household and other intimate contacts

  Selected situations
  - institutions (e.g., day care centers)
  - common source exposure (e.g., food prepared by infected food handler)

HAV Transmission

- ✓ Close personal contact *(e.g., household contact, sex contact, child day-care centers)*
- ✓ Contaminated food, water *(e.g., food handlers)*
- ✓ Blood exposure *(e.g., injection drug use, transfusion)*

Prevention

- ✓ Hygiene *(e.g., hand washing)*
- ✓ Sanitation *(e.g., sources of clean water)*
- ✓ Hepatitis A vaccine *(pre-exposure)*
- ✓ Immunoglobulin *(pre- and post-exposure)*

HAV Diagnosis

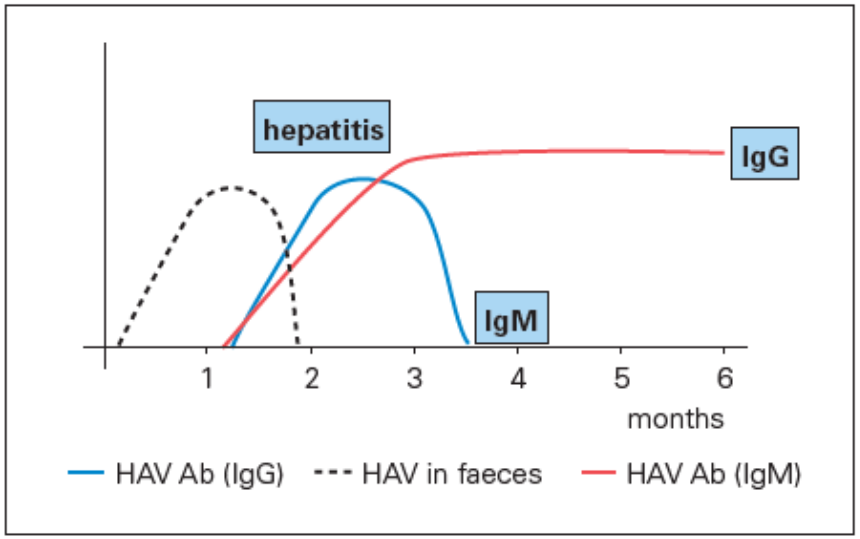
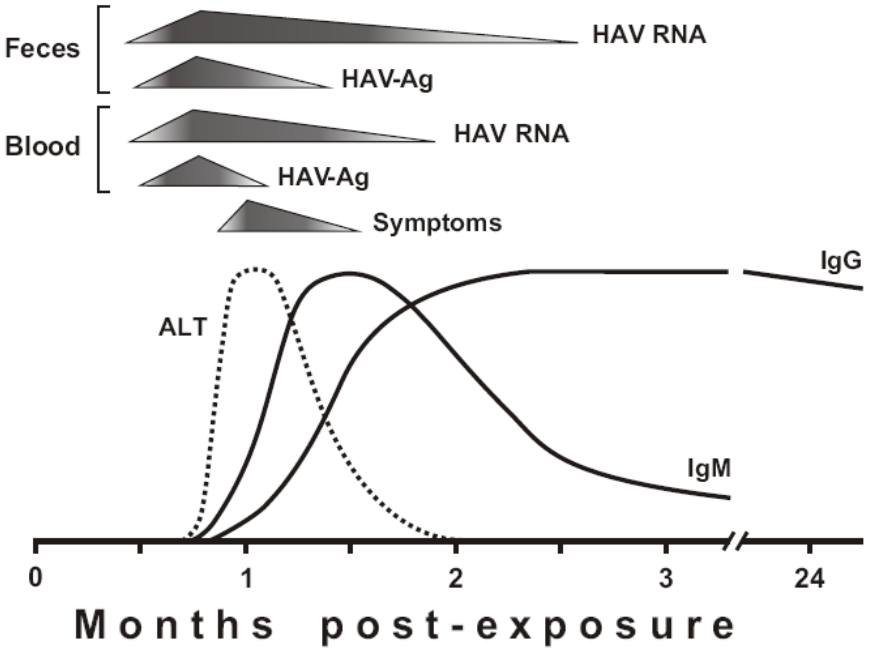


Figure 23.43 The clinical and virological course of hepatitis A virus (HAV). Ab, antibody; Ig, immunoglobulin.

The best laboratory method for the diagnosis of acute infection is the detection of HAV-specific IgM in serum



Bendinelli, Pistello *et al*., **Manual of Clinical Laboratory Immunology**, Rose et al. eds, American Society for Microbiology, VIIth ed., *in press*.

HEPATITIS B VIRUS

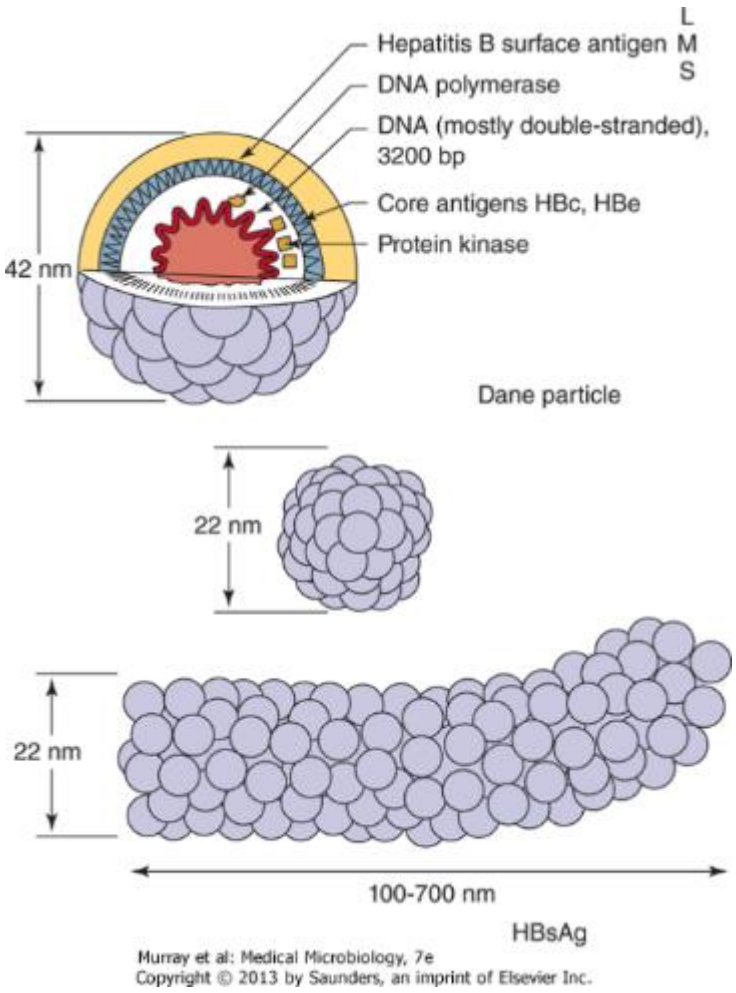
Hepatitis B

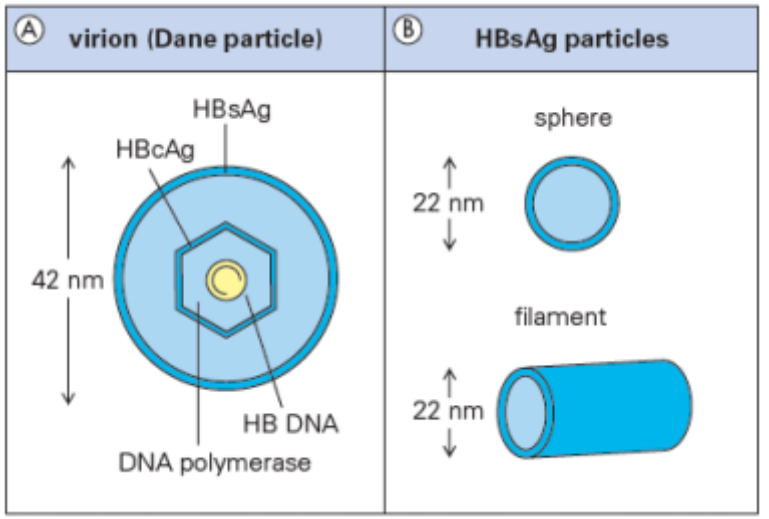
18 July 2019

Key facts

- Hepatitis B is a viral infection that attacks the liver and can cause both acute and chronic disease.
- The virus is most commonly transmitted from mother to child during birth and delivery, as well as through contact with blood or other body fluids.
- WHO estimates that in 2015, 257 million people were living with chronic hepatitis B infection (defined as hepatitis B surface antigen positive).
- In 2015, hepatitis B resulted in an estimated 887 000 deaths, mostly from cirrhosis and hepatocellular carcinoma (i.e. primary liver cancer).
- As of 2016, 27 million people (10.5% of all people estimated to be living with hepatitis B) were aware of their infection, while 4.5 million (16.7%) of the people diagnosed were on treatment.
- Hepatitis B can be prevented by vaccines that are safe, available and effective.

Hepatitis B Virus





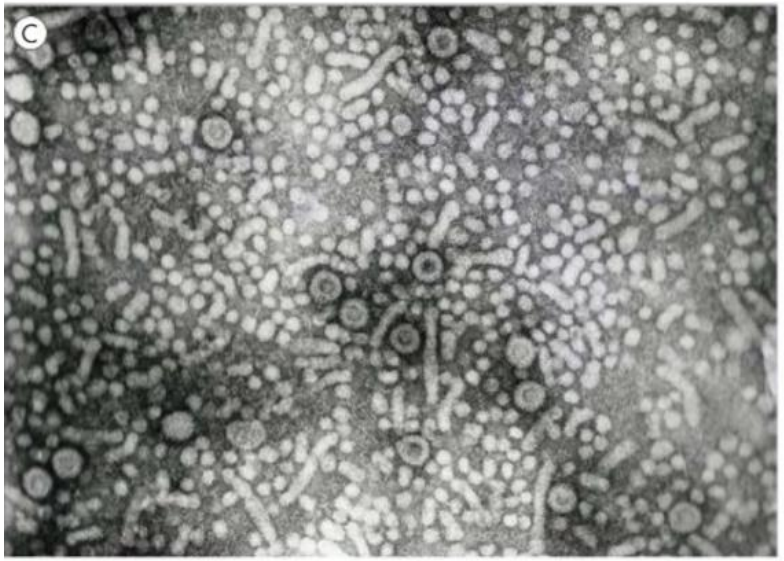
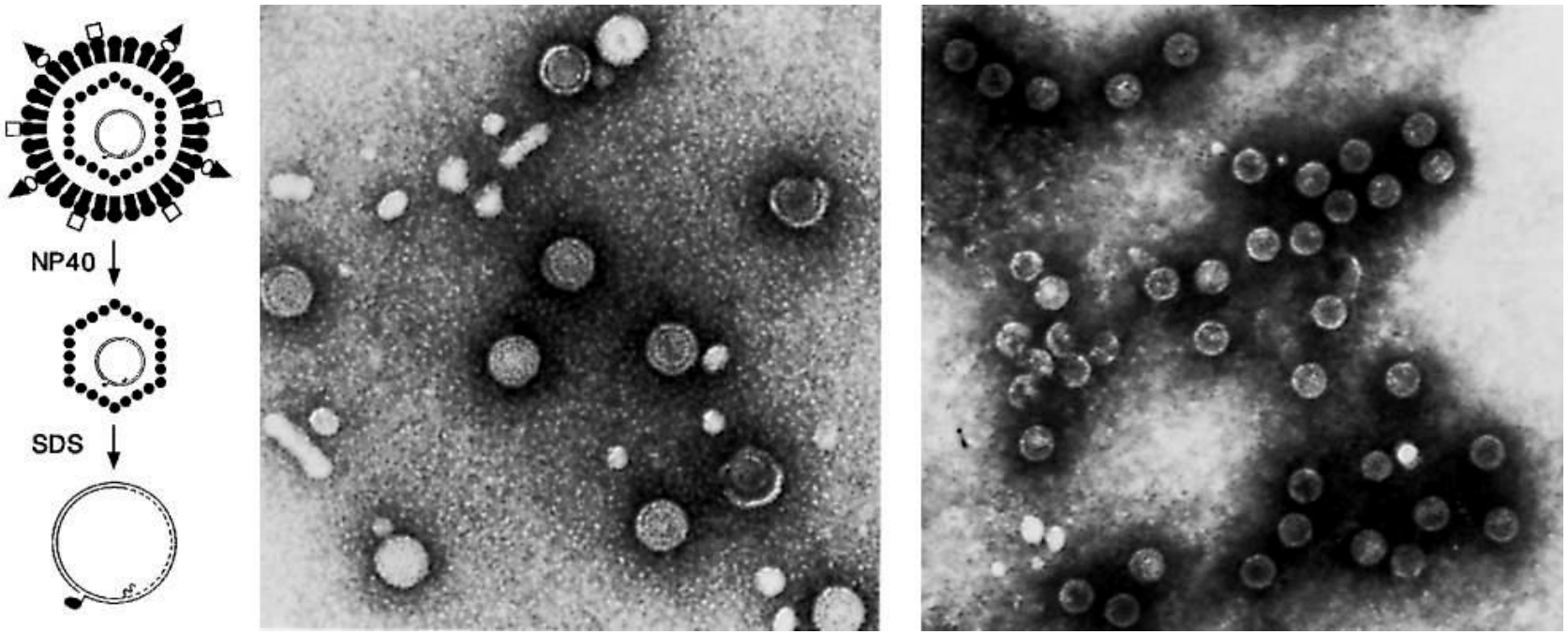


Figure 23.44 During acute infection, and in some carriers there are 10^6–10^7 infectious (Dane) particles/mL of serum (A), and as many as 10^{12} hepatitis B surface antigen (HBsAg) particles/mL (B). (C) Electron micrograph showing Dane particles and HBsAg particles.

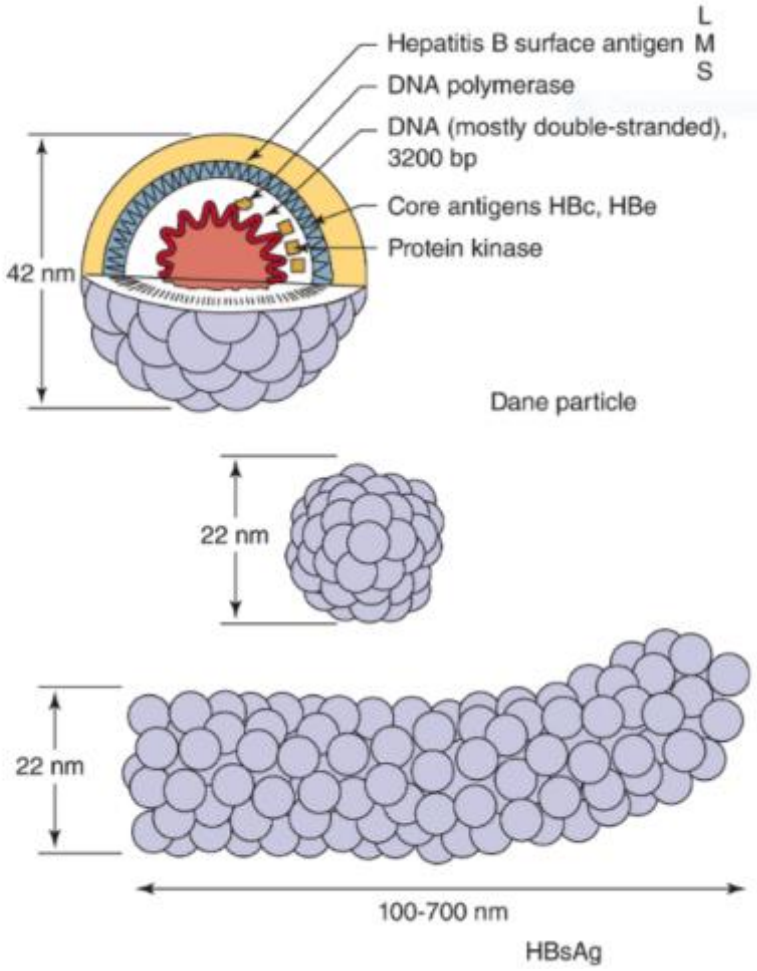
Hepatitis B Virus



The structure of hepadnaviral virions and subviral particles. Left: Schematic depiction of virion (top), core particle (middle), and virion DNA (bottom). The outer envelope of the virion contains three related surface glycoproteins (L, M, and S); the inner nucleocapsid contains a single capsid protein (C). The viral DNA contains a terminal protein (oval) attached to the negative strand and a short RNA (wavy line) attached to the positive strand. Dashes indicate single-stranded gap region on virion DNA. Center: Electron micrograph of hepatitis B virus particles, including virions, 20-nm spheres, and filaments. Right: Electron micrograph of virion cores produced by detergent (NP40) treatment of virions.

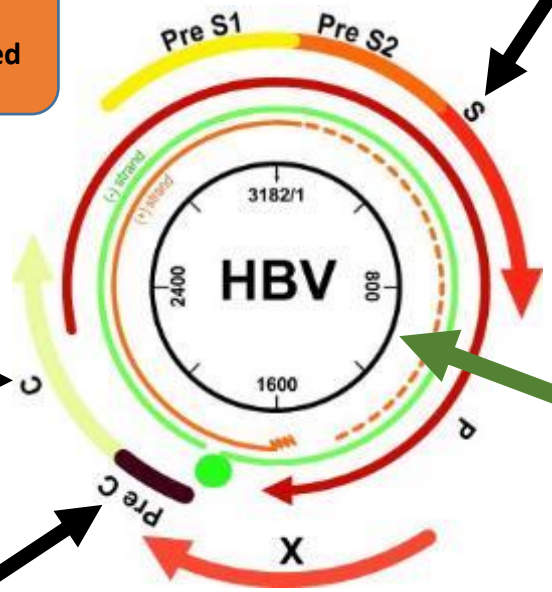
Unique Features of Hepadnaviruses

Virus has enveloped virion containing partially double-stranded, circular DNA genome.
Replication is through a circular RNA intermediate.
Virus encodes and carries a reverse transcriptase.
Virus encodes several proteins (HBsAg [L, M, S]; HBe/HBc antigens) that share genetic sequences but with different in-frame start codons.
HBV has a strict tissue tropism to the liver.
HBV-infected cells produce and release large amounts of HBsAg particles lacking DNA.
The HBV genome can integrate into the host chromosome.


L
M
S
Hepatitis B surface antigen
DNA polymerase
DNA (mostly double-stranded), 3200 bp
Core antigens HBc, HBe
Protein kinase
42 nm
Dane particle
22 nm
22 nm
100-700 nm
HBsAg

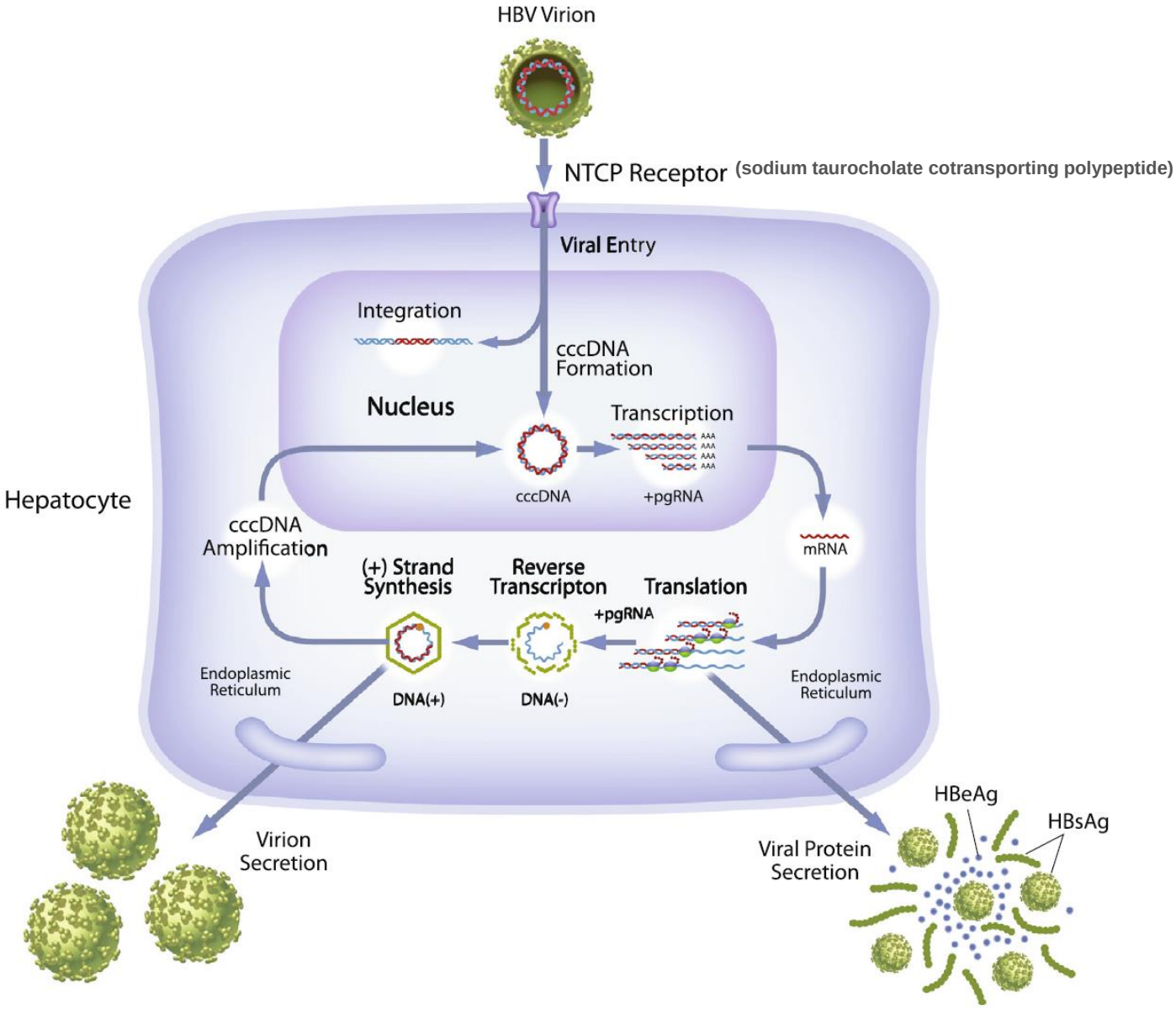
The Hepatitis surface antigen (HbsAg) and the related antibody (Anti-Hbs)

The particulate nucleocapsid antigen (HbcAg) and the related antibody (Anti-HbC)



HBV DNA

The antigen structurally related to HbcAg, namely hepatitis B e antigen (HBeAg) and the related antibody (Anti-Hbe)


HBV Virion
NTCP Receptor (sodium taurocholate cotransporting polypeptide)
Viral Entry
Integration
cccDNA Formation
Nucleus
Transcription
cccDNA
+pgRNA
Hepatocyte
cccDNA Amplification
(+) Strand Synthesis
Reverse Transcripton
Translation
mRNA
+pgRNA
Endoplasmic Reticulum
DNA(+)
DNA(-)
Endoplasmic Reticulum
Virion Secretion
HBeAg
HBsAg
Viral Protein Secretion

Key role of HBV covalently closed circular (ccc) DNA in viral persistence and chronic hepatitis B

- cccDNA is the template for viral RNAs and subsequent generation of progeny virions
- A few copies of cccDNA per liver can (re)initiate full-blown infection.
- ***HBV persistence is mediated by an intranuclear, episomal form of cccDNA***
- ***cccDNA is not targeted by current treatments and a cure of chronic hepatitis B requires elimination of cccDNA***

Transmission of HBV

Body fluids - HBV concentration :

- **High**: *blood, serum, wound exudates*
- **Medium**: *saliva, semen, and vaginal secretions*
- **Low/not detectable**: *urine, feces, sweat, tears, breastmilk*

- Perinatal – *transplacental transmission (70-90% risk if mother HBsAg+/HBeAg+ , 2-5% risk if HBsAg+/HBeAg-)*

Sexual transmission – *unprotected sex*

Percutaneous transmission – *sharing of injection drug use equipment, needle stick injury, body piercing, tattooing, inadequate sterilization of medical equipment, scarification*

Household and interhousehold transmission – *shared toothbrushes, razors, combs, washcloths*

Institutionalized settings – *risks of biting, sexual abuse*

HBV - Clinical Features

Incubation period:	Average 60-90 days Range 45-180 days
Clinical illness (jaundice):	<5 yrs, <10% >5 yrs, 30%-50%
Acute case-fatality rate:	0.5%-1%
Chronic infection:	<5 yrs, 30%-90% >5 yrs, 2%-10%
Premature mortality from chronic liver disease:	15%-25%

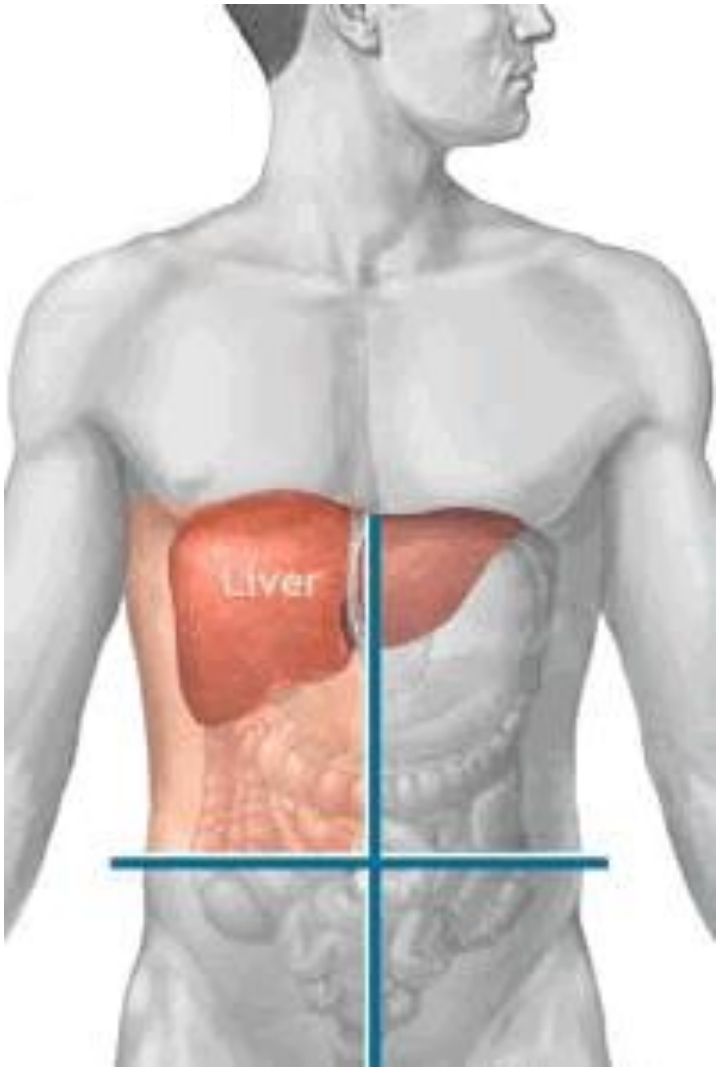
Signs and Symptoms

Symptoms

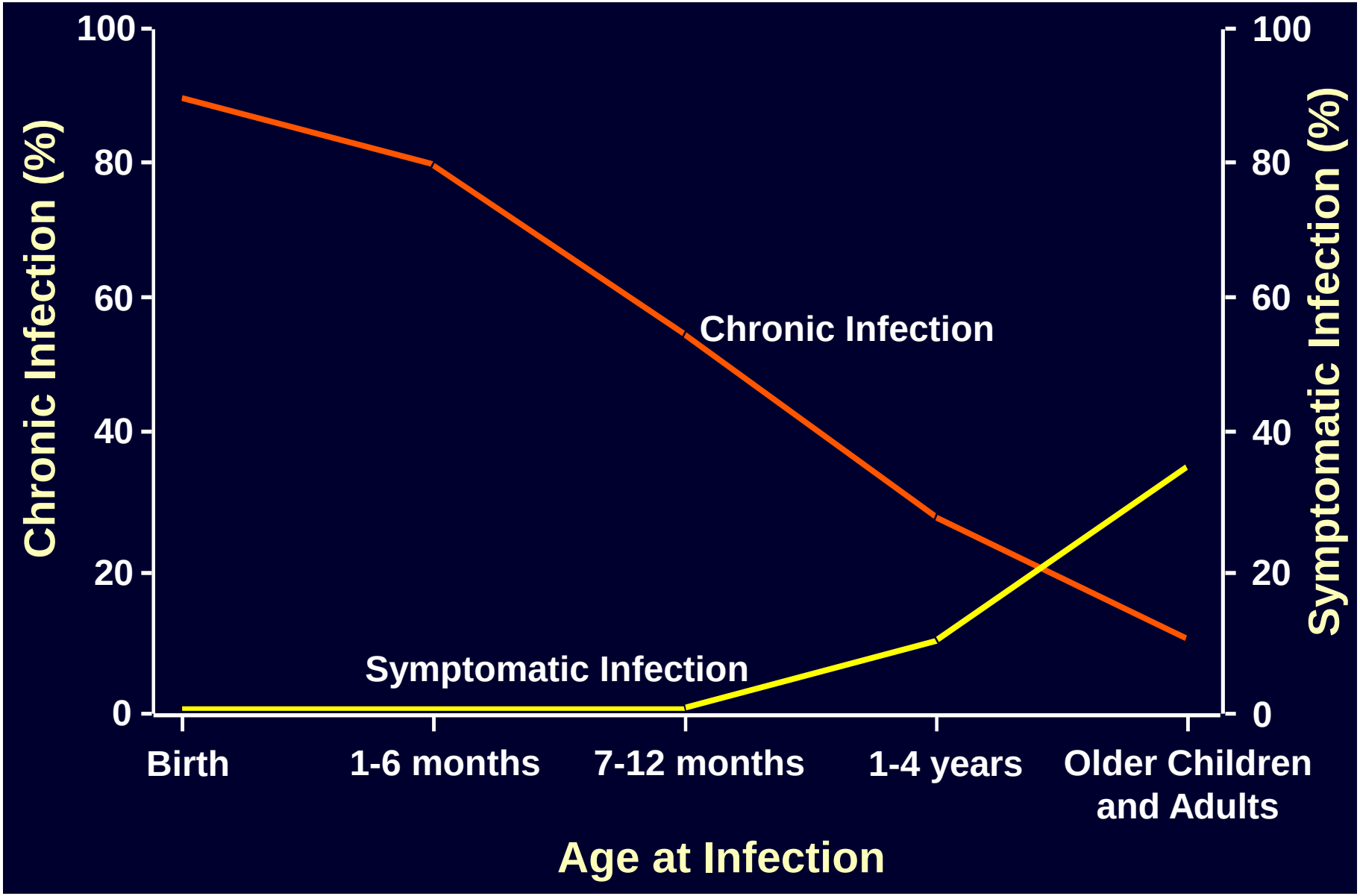
- There may be none
- Pain in the upper right quadrant of abdomen
- Loss of appetite
- Nausea and vomiting
- Abdominal pain
- Arthralgia
- Fatigue
- Itching

Signs

- There may be none
- Jaundice
- Fever
- Dark urine



Outcome of Hepatitis B Virus Infection by Age at Infection



Outcome of Hepatitis B Virus Infection by Age at Infection

Age at initial infection	Outcome	Relative frequency (%)
Normal adults	Inapparent or anicteric disease	65–80
	Icteric disease	20–35
	Mortality	0.2–0.5
	Complete spontaneous recovery and viral clearance	90–98
	Viral persistence and chronic hepatitis	2–10
Newborn infants	Inapparent, with icteric or anicteric disease	10–30
	Icteric disease	<5
	Complete spontaneous recovery and viral clearance	10–30
	Viral persistence and high risk of hepatocellular carcinoma	70–90

TABLE 16.5 Course of infection with hepatitis B virus (HBV). The substantial frequency of spontaneous recovery and viral clearance suggests that persistent HBV infection might be a good candidate for therapy
After Hollinger B, Liang TJ. Hepatitis B virus, chapter 87 in Knipe DM, Howley PM (eds), *Fields Virology*, 4th edn, 2001, with permission.

Hepatocellular Carcinoma – HCC

HBV leads to liver cancer

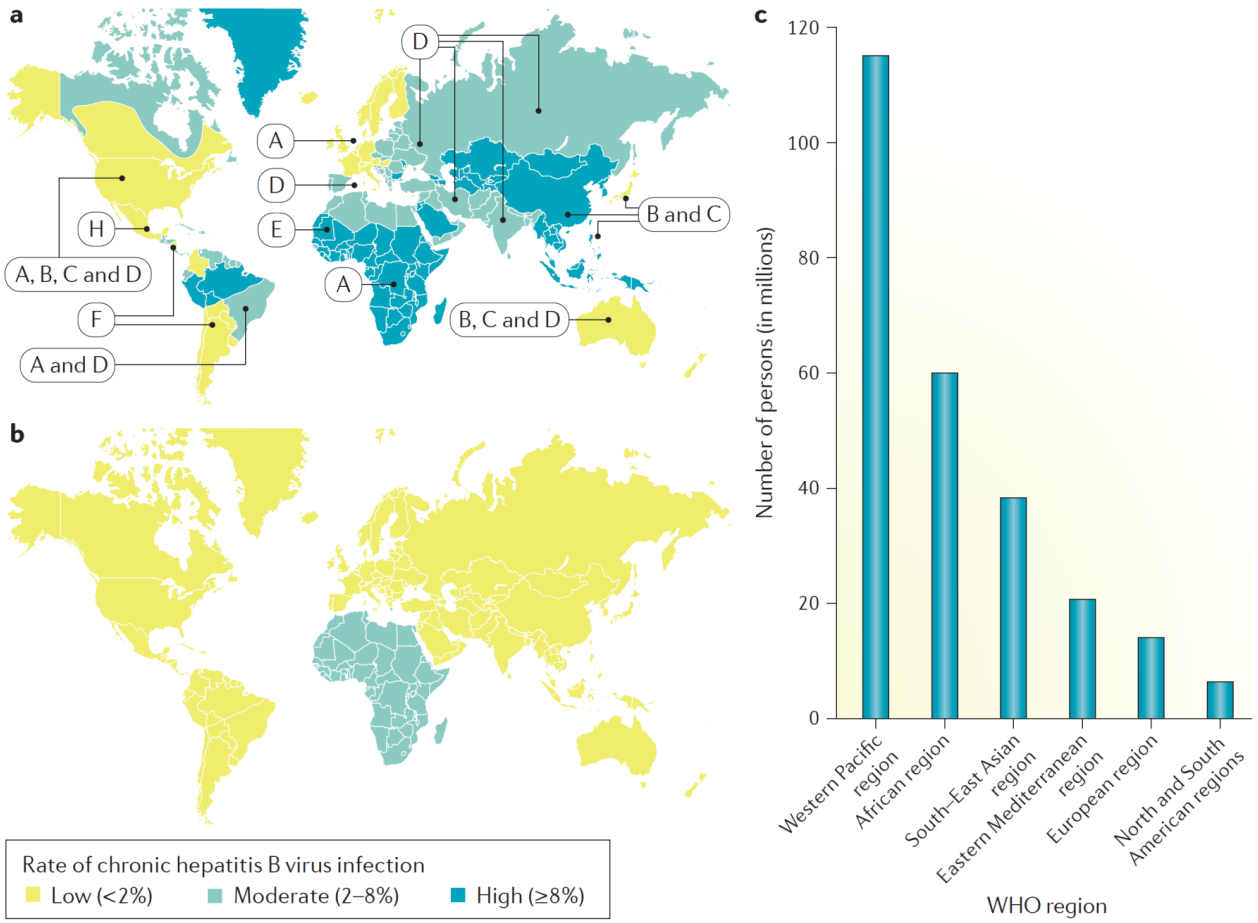
- epidemiologic correlation in many populations
- risk for HCC is 12-300 times greater in HBsAg+ persons
- HBV DNA is incorporated into DNA of hepatoma cells

Incidence

- peak incidence is in 40-60 yr olds
- in Taiwan, #1 cause of death for men >40 yrs
- 0.25-1 million deaths/year in the world
- over 1500 persons die/yr in the U.S. from HCC
- HCC is 3-4x more common in HBsAg+ men than women

5-year survival rate is 2.3%

HBV - Chronic infection

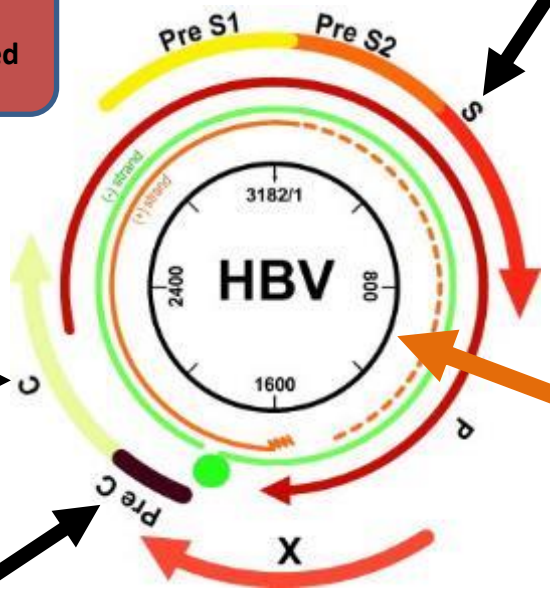


doi:10.1038/nrdp.2018.35
Published online 7 Jun 2018

Figure 2 | **Global distribution of chronic hepatitis B infection and viral genotypes.** Regions with different population prevalence of chronic hepatitis B infection, categorized as high (>8%), moderate (2–8%) and low (<2%), are depicted in part **a**. High prevalence of chronic hepatitis B infection is found in the Western Pacific and Africa. Prevailing genotypes (letters) in different countries are also depicted in part **a**. Part **b** illustrates the global prevalence of chronic hepatitis B infection in children <5 years old. There has been a substantial reduction of prevalence of chronic hepatitis B infection in children as a result of a successful vaccination programme, for example, in Asian countries. Part **c** shows the exact population size of chronic hepatitis B carriers in different WHO regions.

The Hepatitis surface antigen (HbsAg) and the related antibody (Anti-Hbs)

The particulate nucleocapsid antigen (HbcAg) and the related antibody (Anti-HbC)



HBV DNA

The antigen structurally related to HbcAg, namely hepatitis B e antigen (HBeAg) and the related antibody (Anti-Hbe)

HBV - Diagnosis

Characteristics of hepatitis B virus antigens (Ag) and antibodies (Ab)

HBsAg	Envelope (surface) antigen of HBV particle also occurs as free particles (spheres and filaments) in blood; indicates infectivity of blood
HBsAb	Antibody to HBsAg; post-hepatitis B vaccine response; appears late after resolved HBV infection (not in carriers)
HBcAb (total)	Antibody to HB core antigen; appears early; includes HB core IgM
HBc IgM	Appears in acute HBV infection; can last for 3 months and is a marker of acute HBV infection if it has resolved; seen in HBeAg-positive carriers with high viral replication; seen in HBeAg HBeAb reversion
HBeAg	Antigen derived from HBV core; indicates high transmissibility
HBeAb	Antibody to the HBV core

HBV - Diagnosis

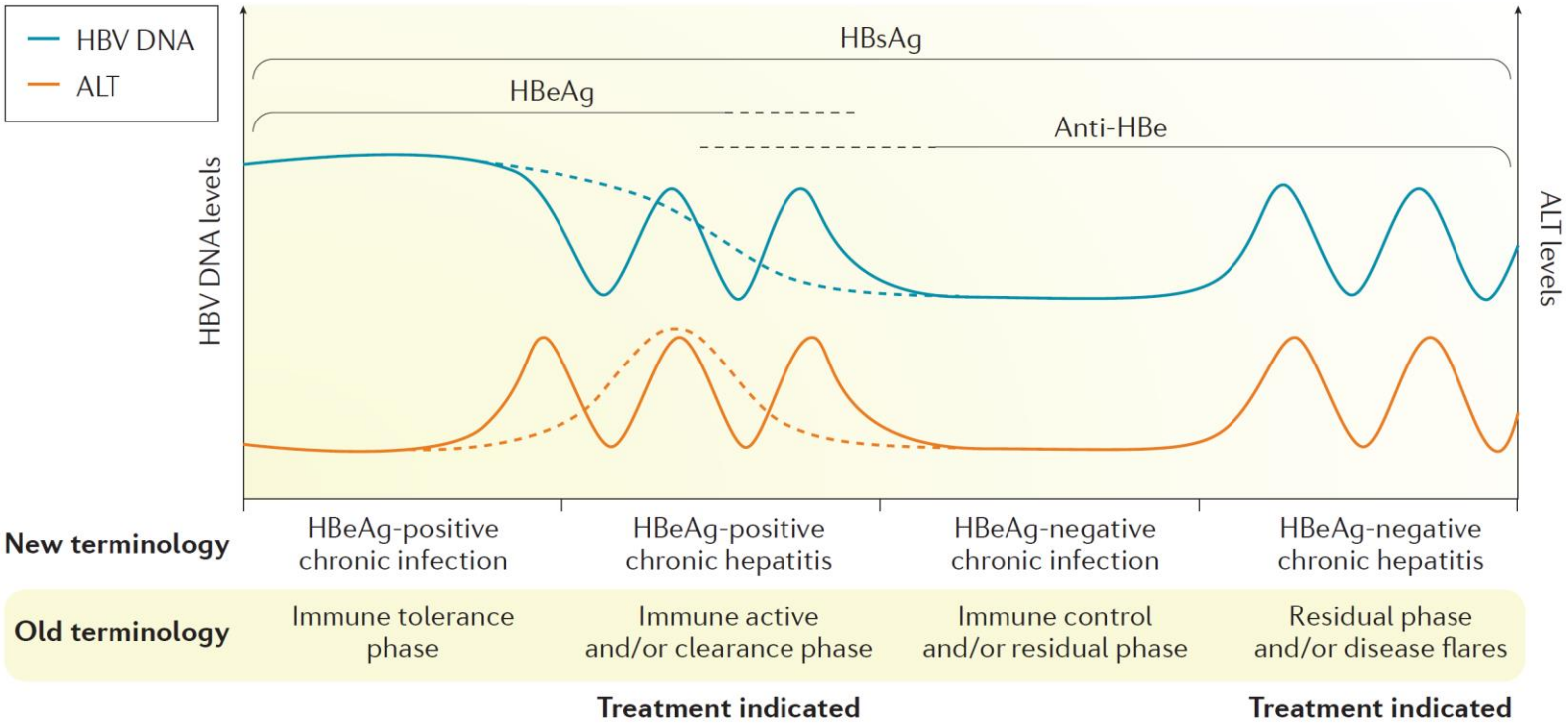


Figure 6 | **Hepatitis B disease phases and treatment indications.** Diagram showing the relationship between hepatitis B virus (HBV) DNA and alanine transaminase (ALT) levels and the relation of these levels to different phases of chronic HBV infection using new and old terminology. Some patients (solid lines) experience intermittent flares in HBV DNA and ALT levels before achieving HBeAg seroconversion, whereas other patients (dashed line) may have a less frequent flares. Treatment is indicated when the HBV DNA levels are >2,000 or >20,000 international units (IU) per litre and ALT levels are higher than one or two times the upper limit of normal according to different regional guidelines. anti-HBe, antibodies against HBeAG; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen.

doi:10.1038/nrdp.2018.35
Published online 7 Jun 2018

HBV - Diagnosis

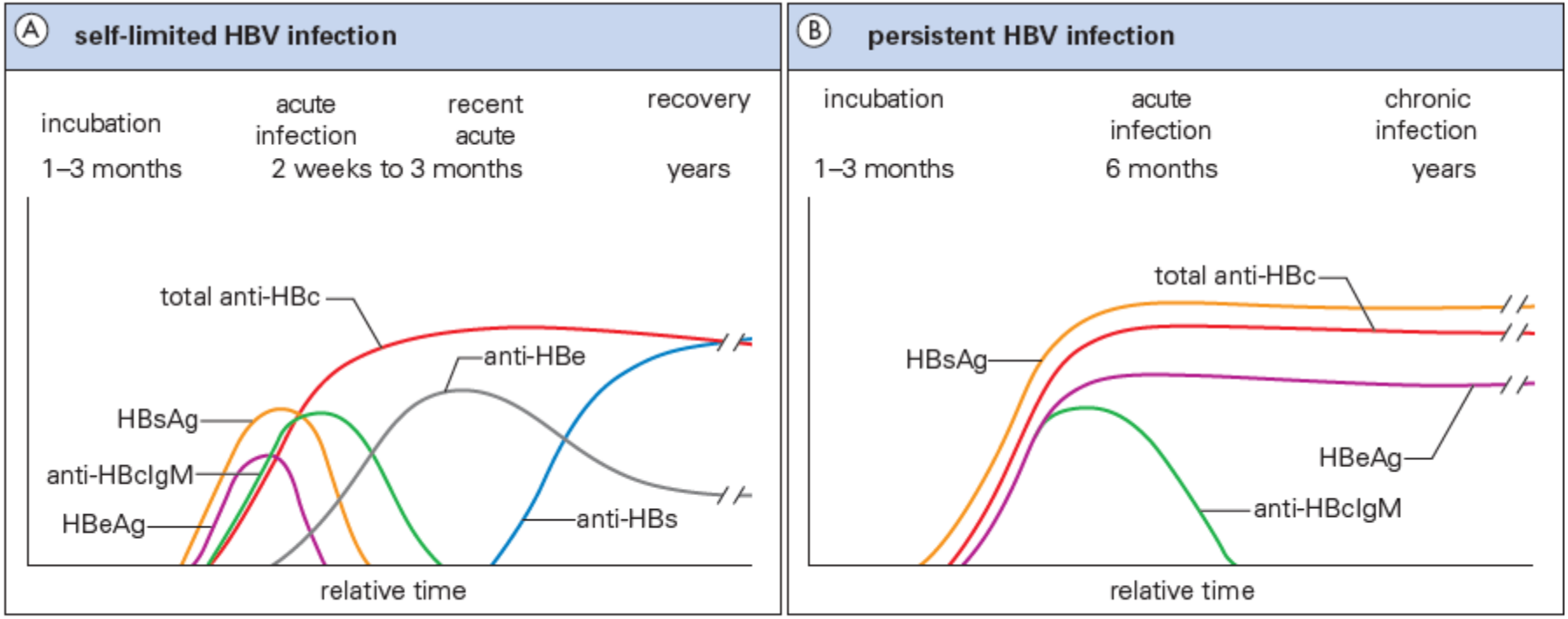
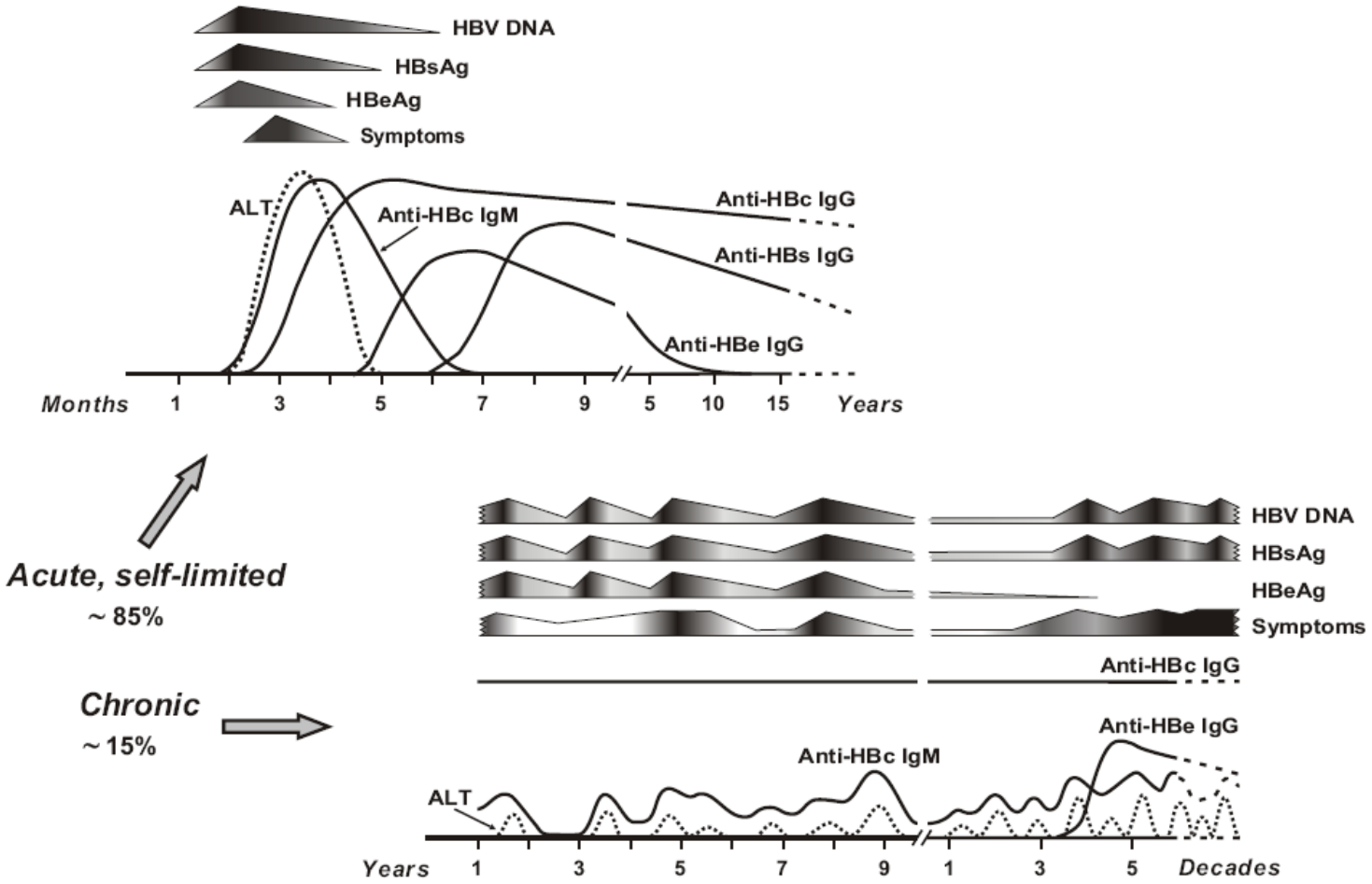


Figure 23.45 (A) Clinical and virological course of hepatitis B virus (HBV) infection, with recovery. (B) Clinical and virological course in a carrier of hepatitis B.

HBV - Diagnosis



Bendinelli, Pistello *et al*., **Manual of Clinical Laboratory Immunology**, Rose et al. eds, American Society for Microbiology, VIIth ed., *in press*.

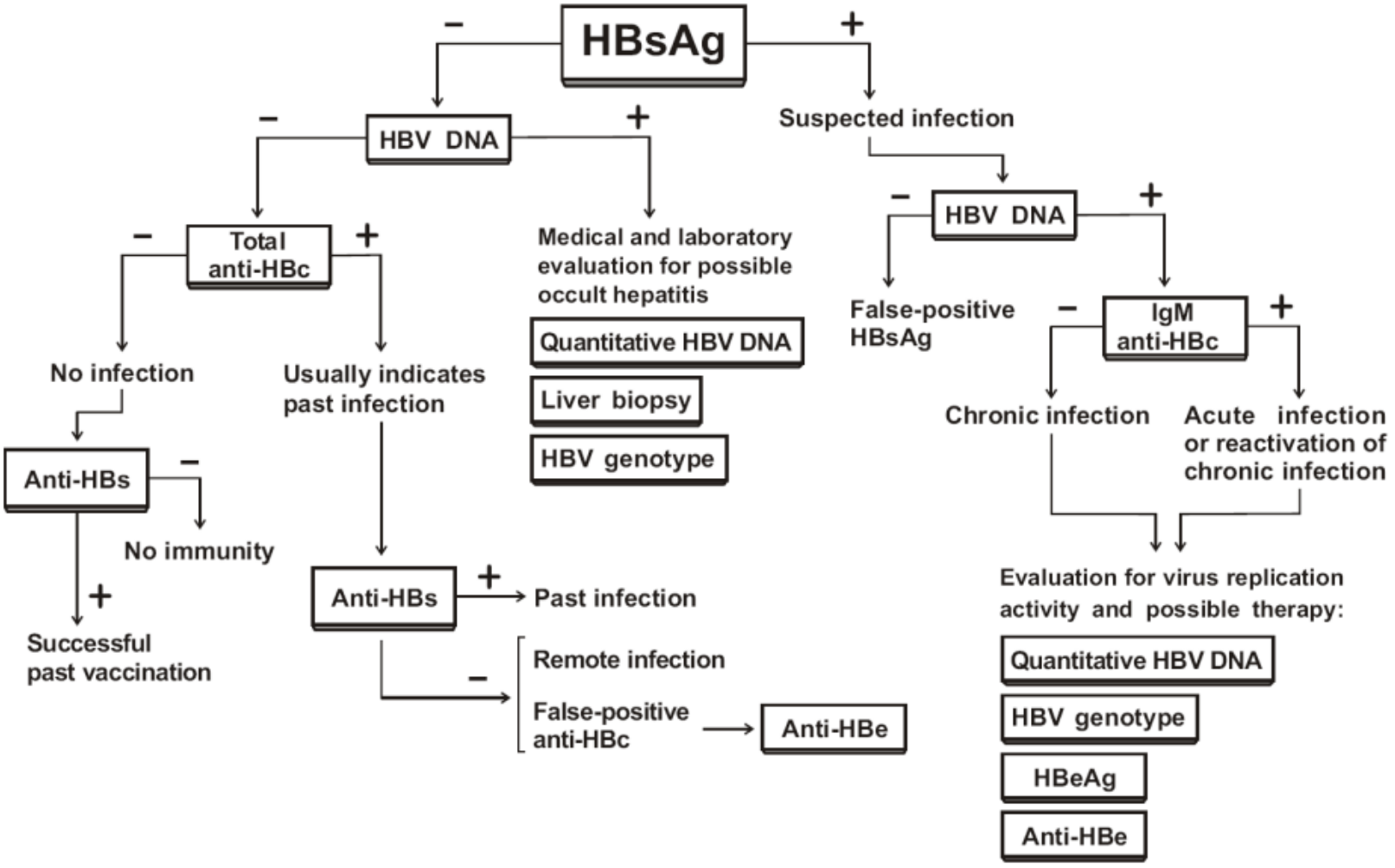
HBV - Diagnosis

INTERPRETATION OF SEROLOGICAL RESULTS

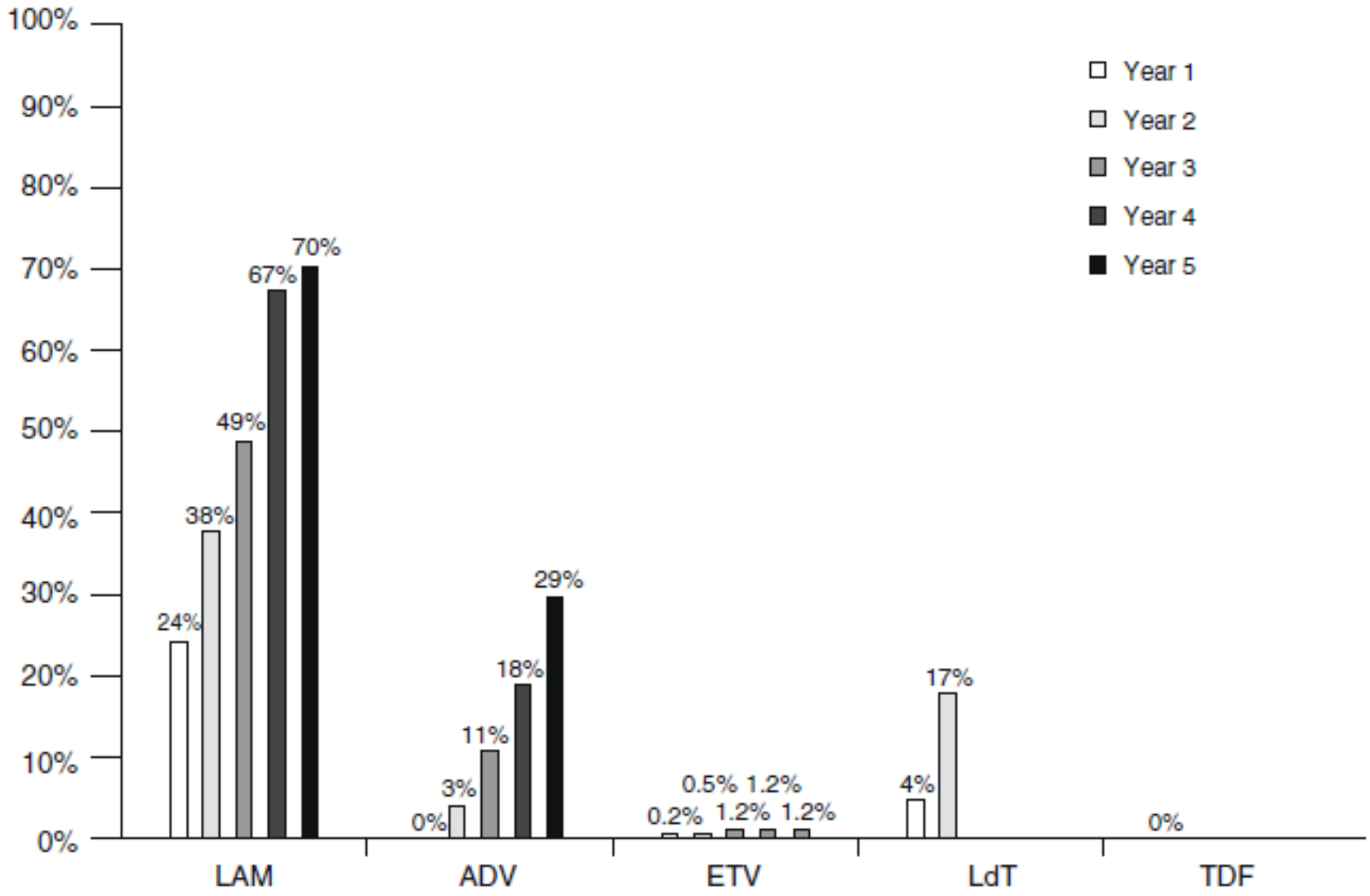
	Acute hepatitis B	Hepatitis B carrier	Hepatitis B carrier	Past hepatitis B virus infection[b]	Hepatitis B vaccine response
HBsAg[a]	+	+	+	–	–
HB core antibody (total)	+	+	+	+	–
HB core IgM	+	–	–	–	–
HBe antibody	–	+	–	+	–
HBe antigen	+	–	+	–	–
HB surface antibody	–	–	–	+	+

[a]Always confirm by neutralization if positive.
[b]Or passively acquired antibody having received blood products from someone with a history of past HBV infection.

HBV - Diagnosis



Bendinelli, Pistello *et al*., **Manual of Clinical Laboratory Immunology**, Rose et al. eds, American Society for Microbiology, VIIth ed., *in press*.



Cumulative incidence of HBV resistance to lamivudine (LAM), adefovir (ADV), entecavir (ETV), telbivudine (LdT) and tenofovir (TDF) in published pivotal trials in NUC-naive patients. For method of calculation, see [61]. These trials included different populations, used different exclusion criteria and different follow-up endpoints

Hepatitis B infection can be prevented by immunization

A **RECOMBINANT HEPATITIS B SURFACE ANTIGEN VACCINE** was first licensed in the USA in 1986, the first vaccine produced using genetic engineering. Recombinant HBV vaccines produced in yeast have an efficacy of 80–100% against infection or clinical hepatitis, with immunity lasting >20 years after three vaccine doses.

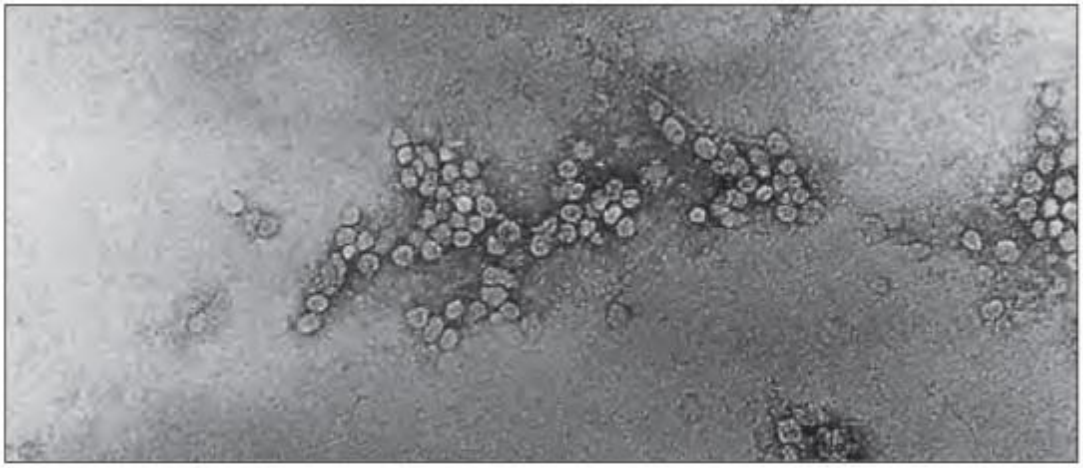


Figure 35.12 Electron micrograph of purified 22 nm hepatitis B surface antigens expressed in yeast cells. (Courtesy of J.R. Pattison.)

Main features of all antiviral vaccines commercially available (2)

Virus	Type of vaccine	Route of administration	Protocols for administration	Effectiveness	Duration of protection	Possible adverse events
JEV	inactivated	intramuscular	3 doses given on days 0, 7 , 30 before travel to endemic areas	80% after 2 doses 99% after 3 doses	(?)	Fever, headache, nausea, abdominal pain, myalgia, dizziness, neurological complications, skin rashes
VZV	attenuated	subcutaneous	1 dose in children up to 12 years old, 2 doses in older individuals	>90%	(?)	Local: redness, swelling, tenderness General: fever with skin rash
Smallpox	attenuated	subcutaneous	single administration	>95%	3-5 years	Fever, hypersensitivity, cutaneous manifestations, cardiac abnormalities and abnormalities of CNS
HBV	recombinant	intramuscular	3 dosi in the 1st year of life (3-5-12 months)	50-99%	3-5 years	Local:pain General: headache
Rabies virus	inactivated	intramuscular	Pre-exposure: 3 doses given on days 0-7-21 or 28 Post-exposure: 5 doses given on days 0-3-7-14-28 with hyperimmune globulins	100%	>2 years	Headache, dizziness, myalgia, abdominal pain, hypersensitivity, rare neurological complications

Legend: MMR:measles-mumps-rubella; HAV: hepatitis A virus; JEV: Japanese encephalitis virus; VZV: varicella-zoster virus; HBV: hepatitis B virus; HPV: human papilloma virus; LAIV: live attenuated influenza vaccine.

G. Antonelli, M. Clementi, G. Pozzi, G.M. Rossolini
Principi di Microbiologia Medica, II edizione. Copyright 2017 C.E.A. Casa Editrice Ambrosiana

DELTA HEPATITIS - HEPATITIS D VIRUS

Hepatitis D

5 May 2020

Key facts

- Hepatitis D virus (HDV) is a virus that requires hepatitis B virus (HBV) for its replication. HDV infection occurs only simultaneously or as super-infection with HBV.
- The virus is most commonly transmitted from mother to child during birth and delivery, as well as through contact with blood or other body fluids.
- Vertical transmission from mother to child is rare.
- Hepatitis D virus (HDV) affects globally nearly 5% of people who have a chronic infection with hepatitis B virus (HBV).
- Several geographical hotspots of high prevalence of HDV infection exist, including Mongolia, the Republic of Moldova, and countries in Western and Middle Africa.
- Populations that are more likely to have HBV and HDV co-infection include people who inject drugs, indigenous populations and recipients of hemodialysis.
- Worldwide, the overall number of HDV infection has decreased since 1980s. This trend is mainly due to a successful global HBV vaccination programme.
- HDV-HBV co-infection is considered the most severe form of chronic viral hepatitis due to more rapid progression towards liver-related death and hepatocellular carcinoma.
- Currently, treatment success rates are generally low.
- Hepatitis D infection can be prevented by hepatitis B immunization.

I viroidi

I viroidi sono i più piccoli agenti patogeni conosciuti e agenti causali di malattie delle piante.

La forma extracellulare del viroide consiste semplicemente di molecole di RNA nude, ovvero non racchiuse da un rivestimento proteico protettivo.

Tali agenti infettanti non codificano proteine.

Un viroide è quindi solo una piccola molecola di RNA circolare arrotolata su se stessa a creare un esteso segmento a doppio filamento.

Essi posseggono vaste regioni a doppio filamento che sono resistenti alla distruzione da parte delle ribonucleasi.

I viroidi

Le modalità con cui i viroidi eseguono la sintesi dell'RNA è un evento molto complesso. L'RNA dei viroidi infettanti viene replicato da una RNA polimerasi dell'ospite che può sintetizzare l'RNA usando un RNA stampo. Tali enzimi sono comuni nelle piante ma non lo sono negli animali e nei batteri non infetti. Il processo di replicazione viene attuato usando l'RNA circolare come stampo e formando una copia, complementare ad esso, spostandosi tutto intorno al cerchio; questo meccanismo di replicazione a cerchio rotante viene usato anche da alcuni virus a DNA e dai plasmidi.

Il risultato di tale operazione non consiste in una singola copia dello stampo, ma in una lunga serie di copie ripetute in tandem (come un rotolo di carta non svolto).

Per produrre viroidi, questa lunga molecola deve essere scissa in segmenti di dimensioni adeguate. Questo può essere fatto in uno dei due seguenti modi: in alcuni viroidi, lo stesso RNA presenta un'attività enzimatica, ossia è un **ribozima**, ed è quindi capace di tagliare la lunga catena in singole copie; in altri viroidi il taglio viene eseguito da una endonucleasi dell'ospite.

I viroidi - HDV

Il solo agente infettante umano simile al viroide è detto erroneamente virus dell'epatite D (HDV); in realtà tale particella è qualcosa di intermedio fra un virus e un viroide e quindi un'altra possibile denominazione potrebbe essere quella di "virusoide". In effetti, , HDV consiste di RNA nudo che differisce dai viroidi delle piante in quanto codifica per proteine. Tuttavia, a differenza dei veri e propri virus, l'agente dell'epatite D non codifica per il proprio capside, mentre le proteine che esso codifica sembrano svolgere un ruolo importante nell'impacchettamento delle particelle.

L'agente dell'epatite D utilizza il capside di un virus autentico, ossia il virus dell'epatite B (HBV), per essere assemblato. Questo particolare tipo di infezione doppia comporta l'insorgenza di una malattia più grave di quella indotta dalla sola infezione da virus dell'epatite B.

HEPATITIS D (Delta) VIRUS

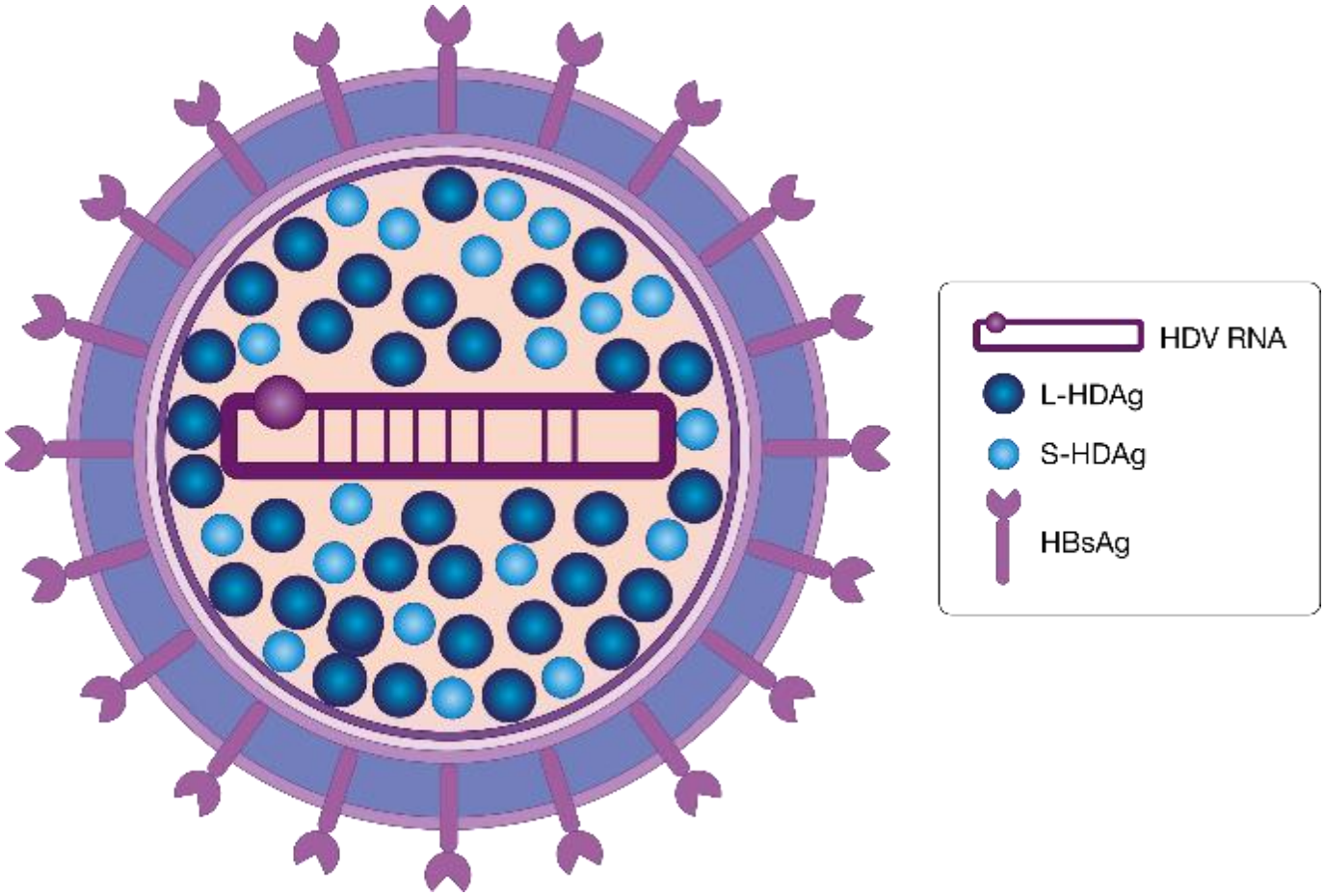


Figura 65.1 **Rappresentazione schematica del virus dell'epatite D (delta, HDV).**

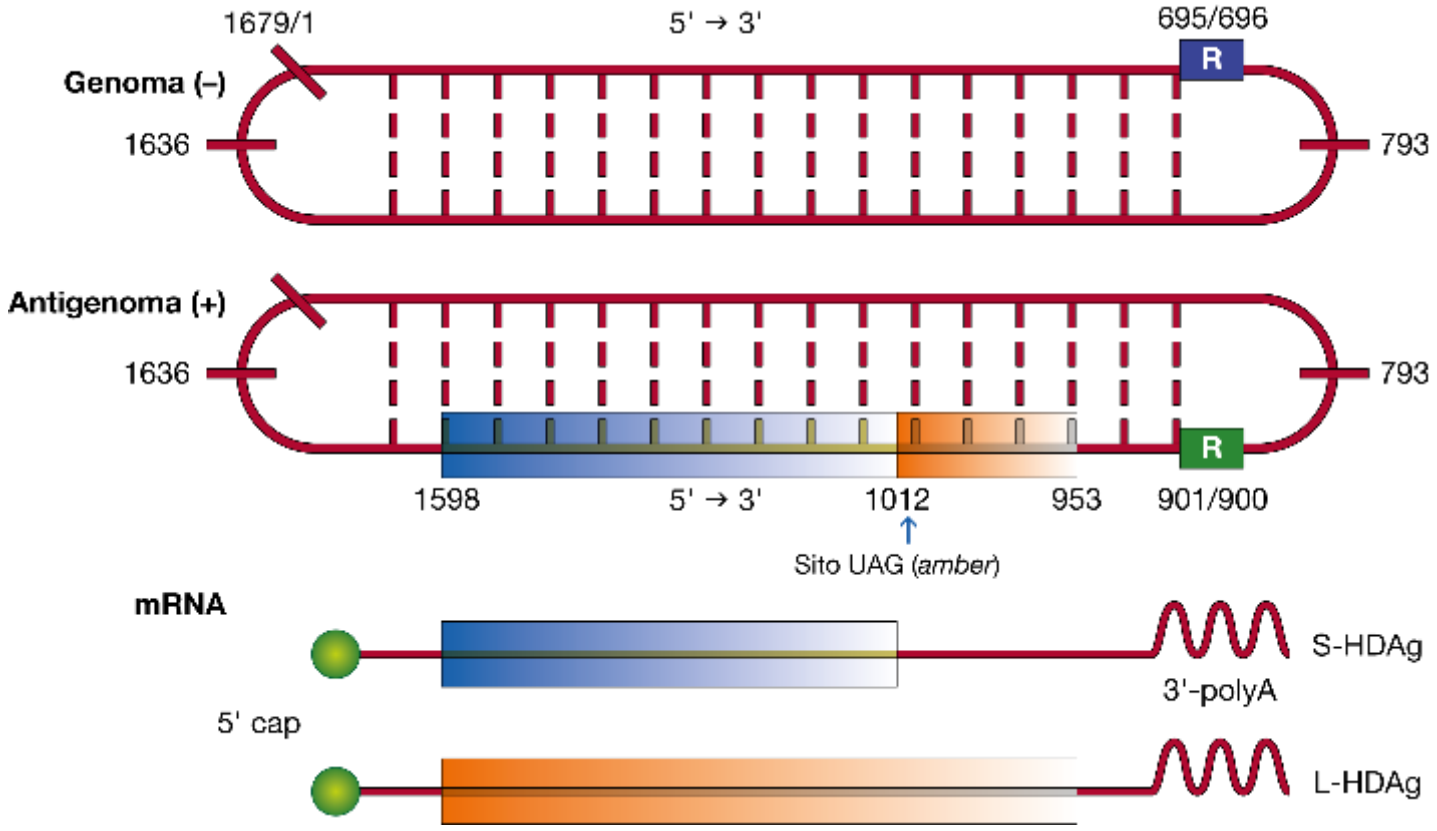


Figura 65.2 **Organizzazione strutturale e funzionale del genoma di HDV.**

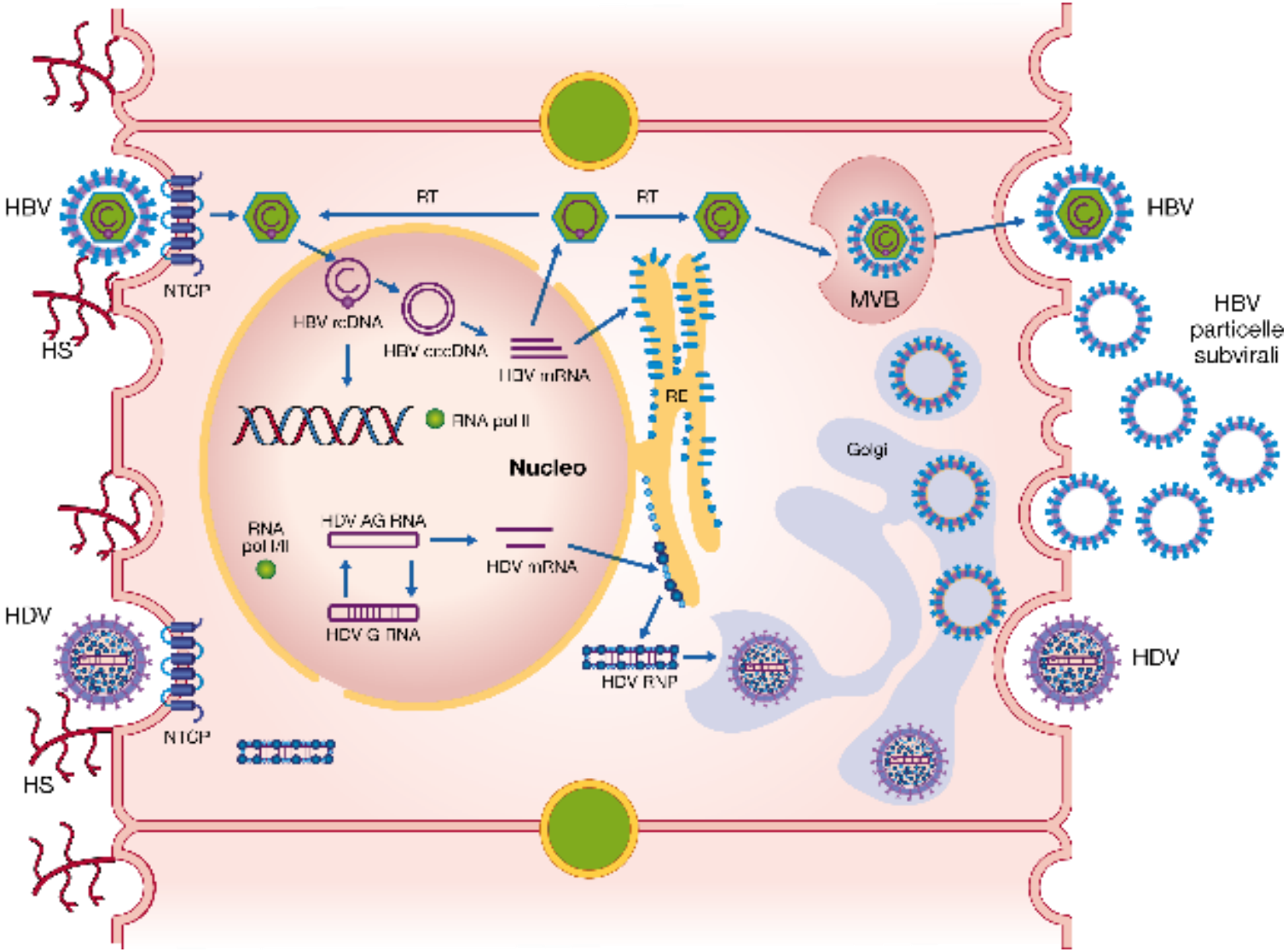


Figura 65.3 **Rappresentazione schematica del ciclo vitale di HDV e HBV.**

Hepatitis D - Clinical Features

Coinfection

- severe acute disease
- low risk of chronic infection

Superinfection

- usually develop chronic HDV infection
- high risk of severe chronic liver disease

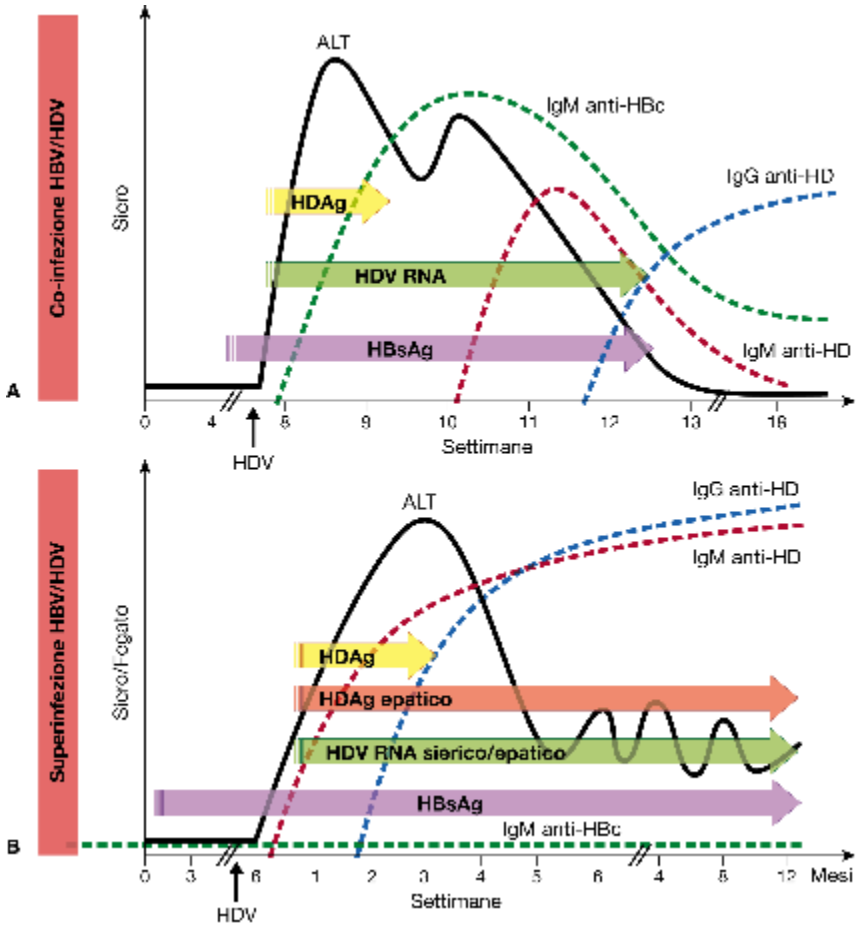


Figura 65.4 Profilo dei marcatori sierologici e molecolari di HDV nella co-infezione (A) e nella superinfezione (B).

HDV Transmission

Percutanous exposures - *injecting drug use*

Permucosal exposures - *sex contact*

Prevention

HBV-HDV Coinfection - *pre or postexposure prophylaxis to prevent HBV infection*

HBV-HDV Superinfection - *reduce risk behaviors among persons with chronic HBV infection*

HEPATITIS C VIRUS

Hepatitis C

9 July 2019

Key facts

- Hepatitis C is a liver disease caused by the hepatitis C virus (HCV): the virus can cause both acute and chronic hepatitis, ranging in severity from a mild illness lasting a few weeks to a serious, lifelong illness.
- Hepatitis C is a major cause of liver cancer.
- The hepatitis C virus is a bloodborne virus: the most common modes of infection are through exposure to small quantities of blood. This may happen through injection drug use, unsafe injection practices, unsafe health care, transfusion of unscreened blood and blood products, and sexual practices that lead to exposure to blood.
- Globally, an estimated 71 million people have chronic hepatitis C virus infection.
- A significant number of those who are chronically infected will develop cirrhosis or liver cancer.
- WHO estimated that in 2016, approximately 399 000 people died from hepatitis C, mostly from cirrhosis and hepatocellular carcinoma (primary liver cancer).
- Antiviral medicines can cure more than 95% of persons with hepatitis C infection, thereby reducing the risk of death from cirrhosis and liver cancer, but access to diagnosis and treatment is low.
- There is currently no effective vaccine against hepatitis C; however, research in this area is ongoing.

Table 1.*Flaviviridae*. Characteristics of the family *Flaviviridae*.

Characteristic	Description
Typical member	yellow fever virus-17D (X03700), species *Yellow fever virus*, genus *Flavivirus*
Virion	Enveloped, 40–60 nm virions with a single core protein (except for genus *Pegivirus*) and 2 or 3 envelope glycoproteins
Genome	9.0–13 kb of positive-sense, non-segmented RNA
Replication	Cytoplasmic, in membrane vesicles derived from the endoplasmic reticulum (ER); assembled virions bud into the lumen of the ER and are secreted through the vesicle transport pathway
Translation	Directly from genomic RNA containing a type I cap (genus *Flavivirus*) or an internal ribosome entry site (other genera)
Host range	Mammals (all genera); most members of genus *Flavivirus* are arthropod-borne
Taxonomy	Four genera containing 89 species

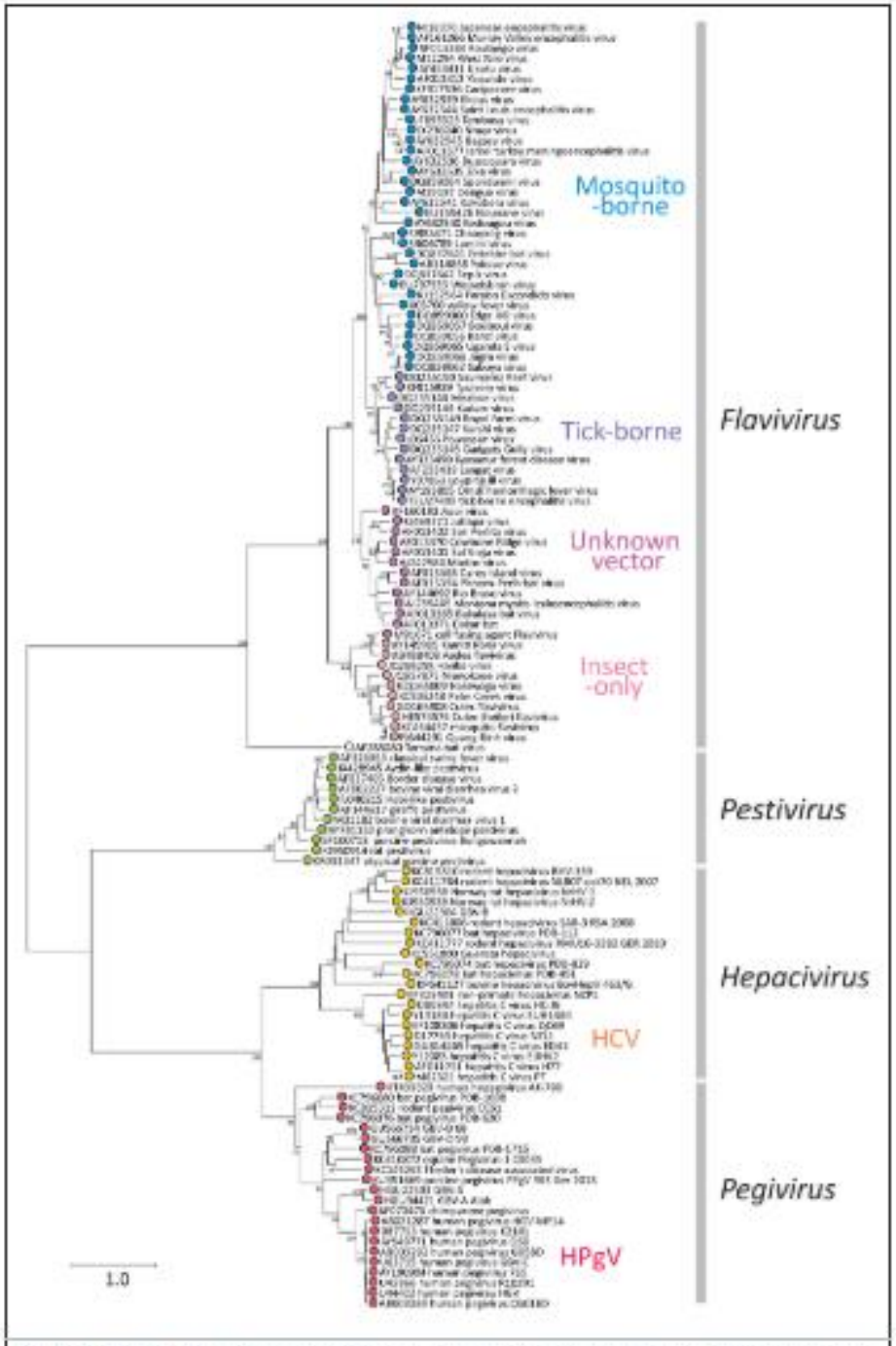


Figure 1. ***Flaviviridae***. Phylogeny of conserved amino acid sequences in the RdRP (NS5 or NS5B)

A number of clades are recognized for *Hepatitis C virus*. Examples are listed below.

Species names are in green italic script; strain names and synonyms are in black roman script; tentative species names are in blue roman script. Sequence accession numbers, and assigned abbreviations ( ) are also listed.

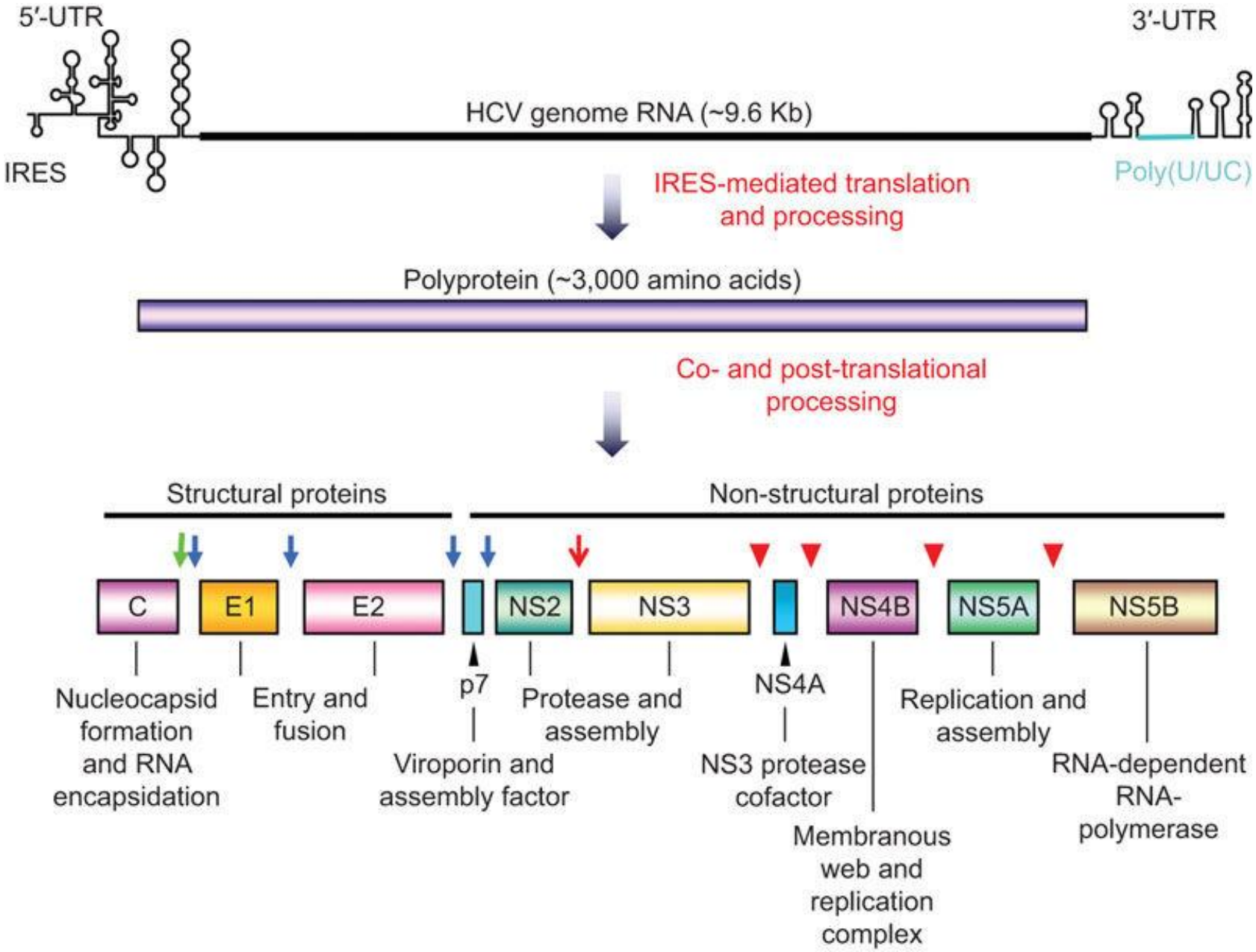
SPECIES IN THE GENUS

Hepatitis C virus

HCV clade 1		
HCV genotype 1a	[M62321]	(HCV-1)
HCV genotype 1b	[D90208]	(HCV-J)
HCV clade 2		
HCV genotype 2a	[D00944]	(HCV-J6)
HCV genotype 2b	[D01221]	(HCV-J8)
HCV clade 3		
HCV genotype 3a	[D17763]	(HCV-NZL1)
HCV genotype 10	[D63821]	(HCV-JK049)
HCV clade 4		
HCV genotype 4a	[Y11604]	(HCV-ED43)
HCV clade 5		
HCV genotype 5a	[Y13184]	(HCV-EVH1480)
HCV clade 6		
HCV genotype 6a	[Y12083]	(HCV-EUHK2)
HCV genotype 11	[D63822]	(HCV-JK046)

TENTATIVE SPECIES IN THE GENUS

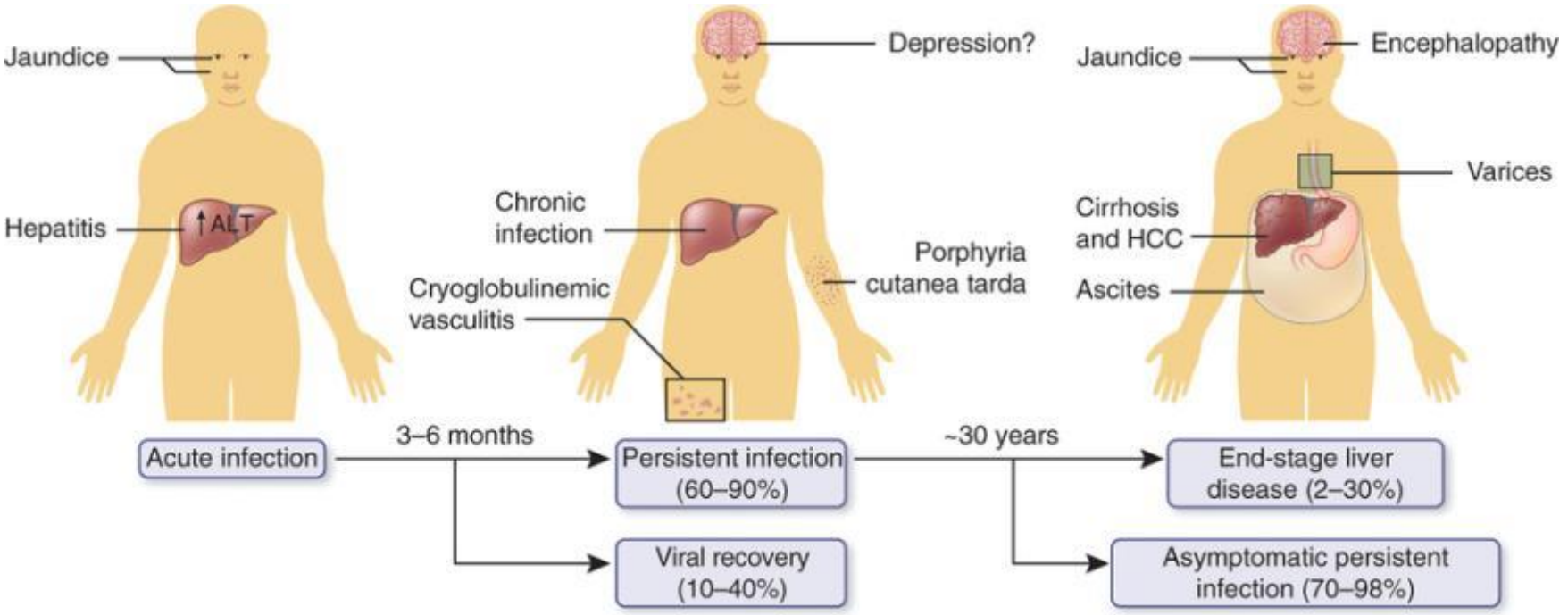
GB virus B	[U22304; AF179612]	(GBV-B)


5′-UTR
3′-UTR
HCV genome RNA (~9.6 Kb)
IRES
Poly(U/UC)
IRES-mediated translation and processing
Polyprotein (~3,000 amino acids)
Co- and post-translational processing
Structural proteins
Non-structural proteins
C
E1
E2
p7
NS2
NS3
NS4A
NS4B
NS5A
NS5B
Nucleocapsid formation and RNA encapsidation
Entry and fusion
Viroporin and assembly factor
Protease and assembly
NS3 protease cofactor
Membranous web and replication complex
Replication and assembly
RNA-dependent RNA-polymerase

Features of HCV Infection

Incubation period	Average 6-7 weeks Range 2-26 weeks
Acute illness (jaundice)	Mild ($\leq$20%)
Case fatality rate	Low
Chronic infection	60%-85%
Chronic hepatitis	10%-70% (most asx)
Cirrhosis	<5%-20%
Mortality from CLD	1%-5%

Outcome and exitus of HCV infection



Risks factors associated with faster fibrosis progression in chronic hepatitis C

Disease State Factors

- Fibrosis stage
- HCV onset after 40 years of age
- Persistently elevated ALT

Host Factors

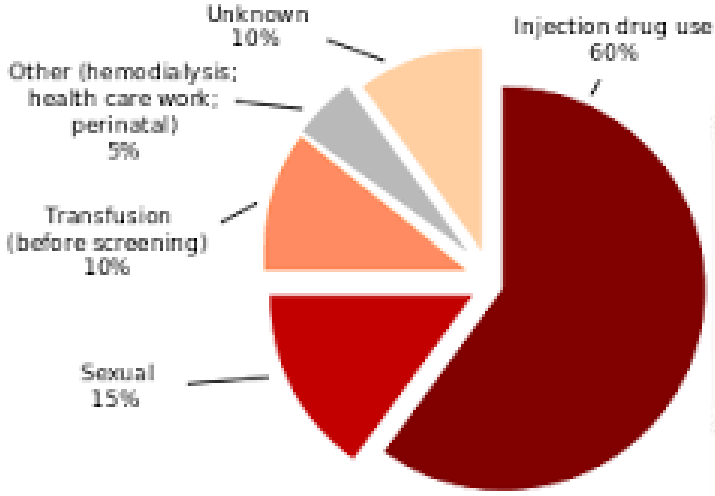
- Male gender
- Age
- Obesity
- Diabetes
- HIV, HBV coinfection
- Immune system compromise
- Steatosis
- Iron overload

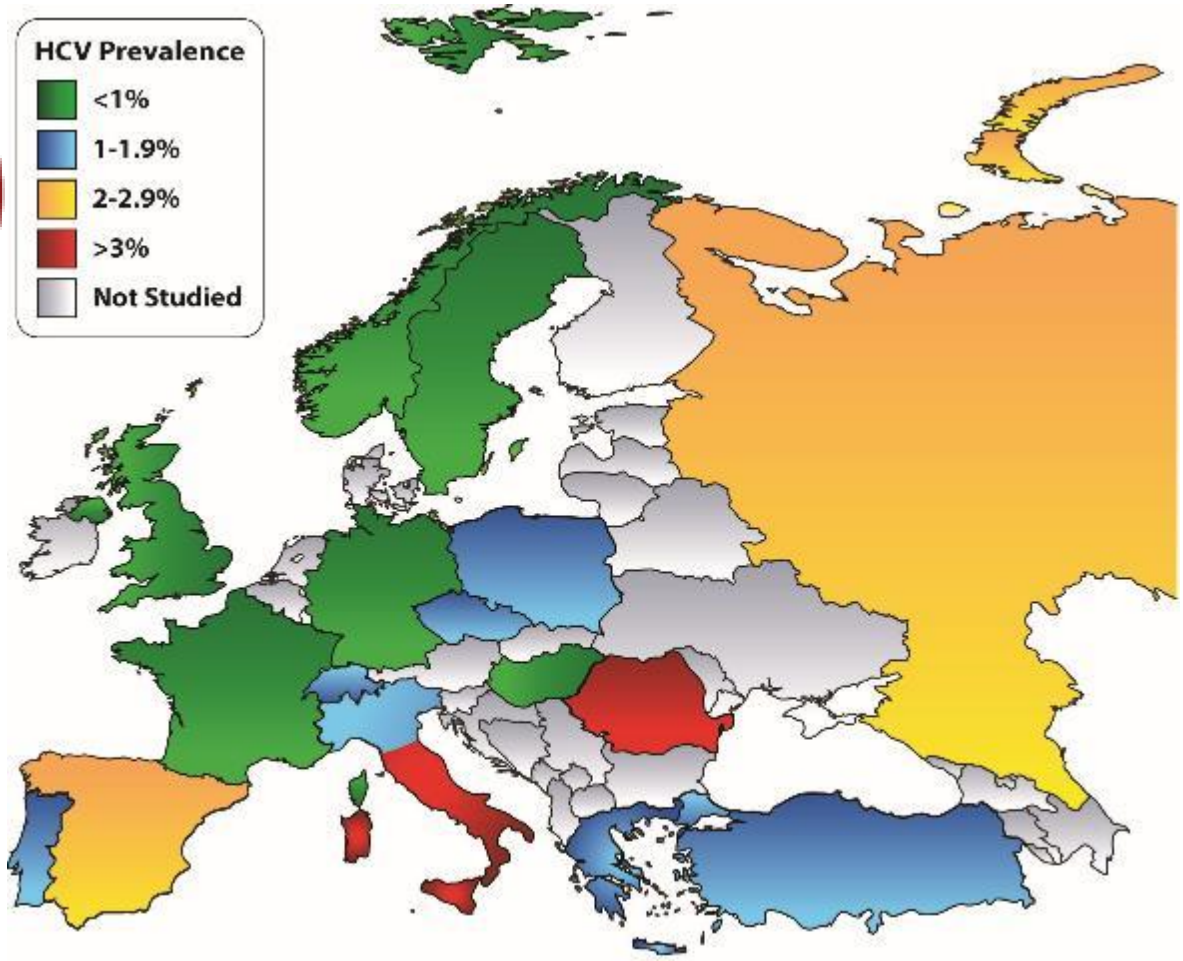
Lifestyle Factors

- Heavy alcohol consumption
- Cannabis use
- Tobacco use

Poynard A. *Antivir Ther*. 2010;15:281-91.
Poynard, et al. *Lancet* .1997;349:825-32.

Sources and incidence of HCV infection





Source: *Center for Disease Analysis*

Practices to reduce or eliminate the risk of acquiring HCV infection

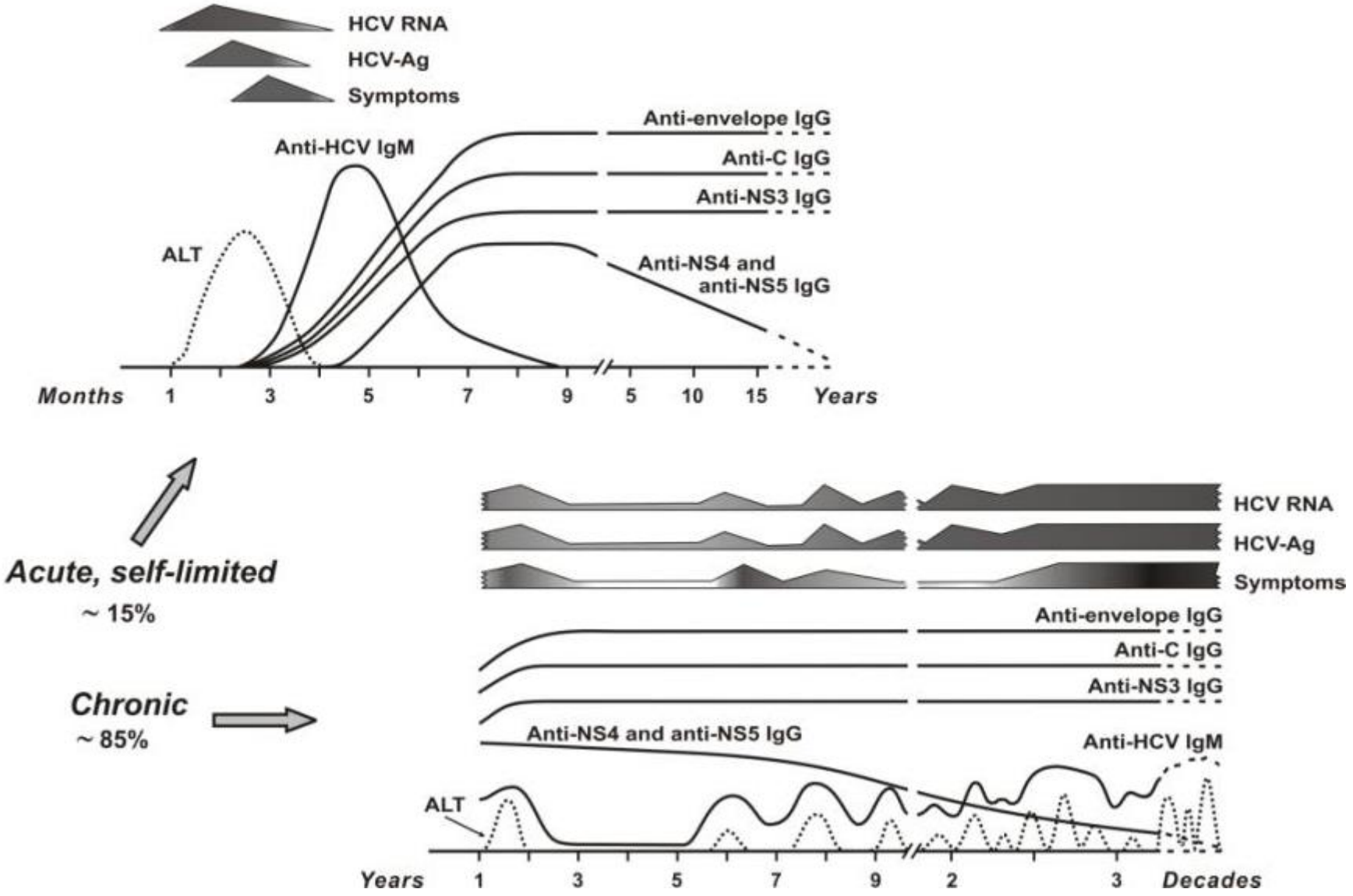
Screening of blood, organ, tissue donors

Virus inactivation of plasma-derived products

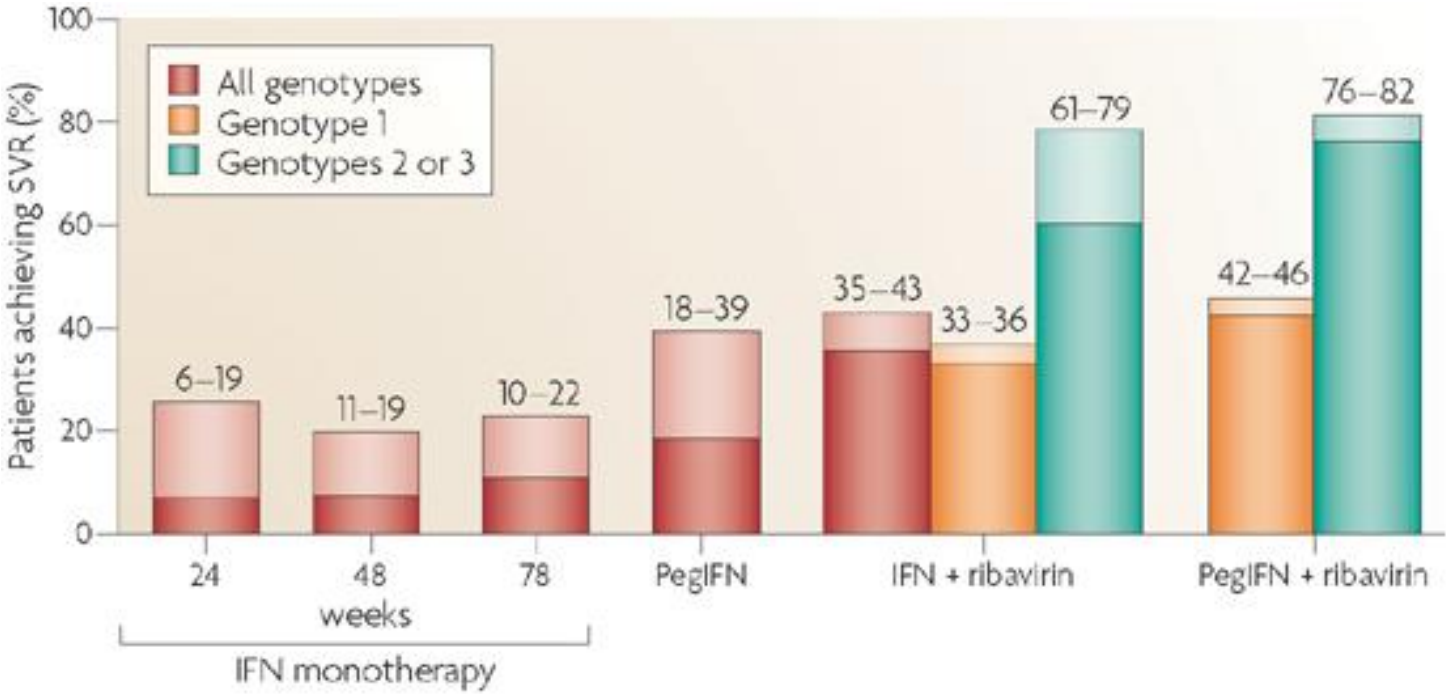
Risk-reduction counseling and services

- Obtain history of high-risk drug and sex behaviors
- Provide information on minimizing risky behavior, including referral to other services
- Vaccinate against hepatitis A and/or hepatitis B

Safe injection and infection control practices



Bendinelli, Pistello *et al*., **Manual of Clinical Laboratory Immunology**, Rose et al. eds, American Society for Microbiology, VIIth ed., *in press*.



Nature Reviews | Drug Discovery

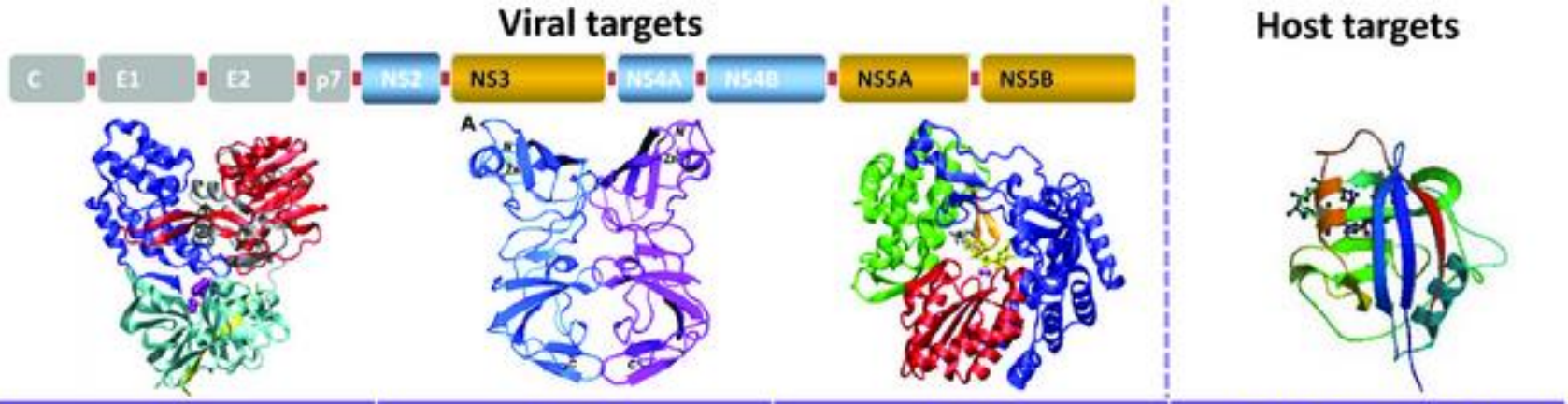
Complications of IFN

Hematologic *(neutropenia, thrombocytopenia)*
Neuropsychiatric *(memory, concentration and visual disturbances, headaches, depression, irritability)*
Metabolic *(hypothyroidism, hyperthyroidism, low-grade fever)*
Gastrointestinal *(nausea, vomiting, weight loss)*
Dermatologic *(alopecia)*
Pulmonary *(interstitial fibrosis)*

Complications of ribavirin

Hematologic *(hemolytic anemia)*
Reproductive *(birth defects)*
Metabolic *(gout)*

Current targets of HCV therapy / 1



NS3	NS5A	NS5B	Cyclophilin A
The NS3/4A serine protease	Multifunctional phosphoprotein, component of the HCV-RNA replication complex	RNA-dependent RNA polymerase	Host protein interacting with NS5A and the NS5B
Boceprevir **Telaprevir** ABT-450/r, ACH-1625 Asunaprevir, TMC-435 (Simeprevir), BI-201335 Danoprevir/r, GS-9451 MK-5172	Daclatasvir GS-5885 ABT-267 PPI-668 MK	<u>Nucleos(t)ide analogue</u> GS-7977 (Sofosbuvir), Mericitabine, IDX-184 <u>Non-nucleoside analogue</u> BI-207127, ABT-333 ABT-072, BMS-791325 Tegobuvir, Setrobuvir VX-222, Filibuvir	Alisporivir SCY-635

HEPATITIS E VIRUS

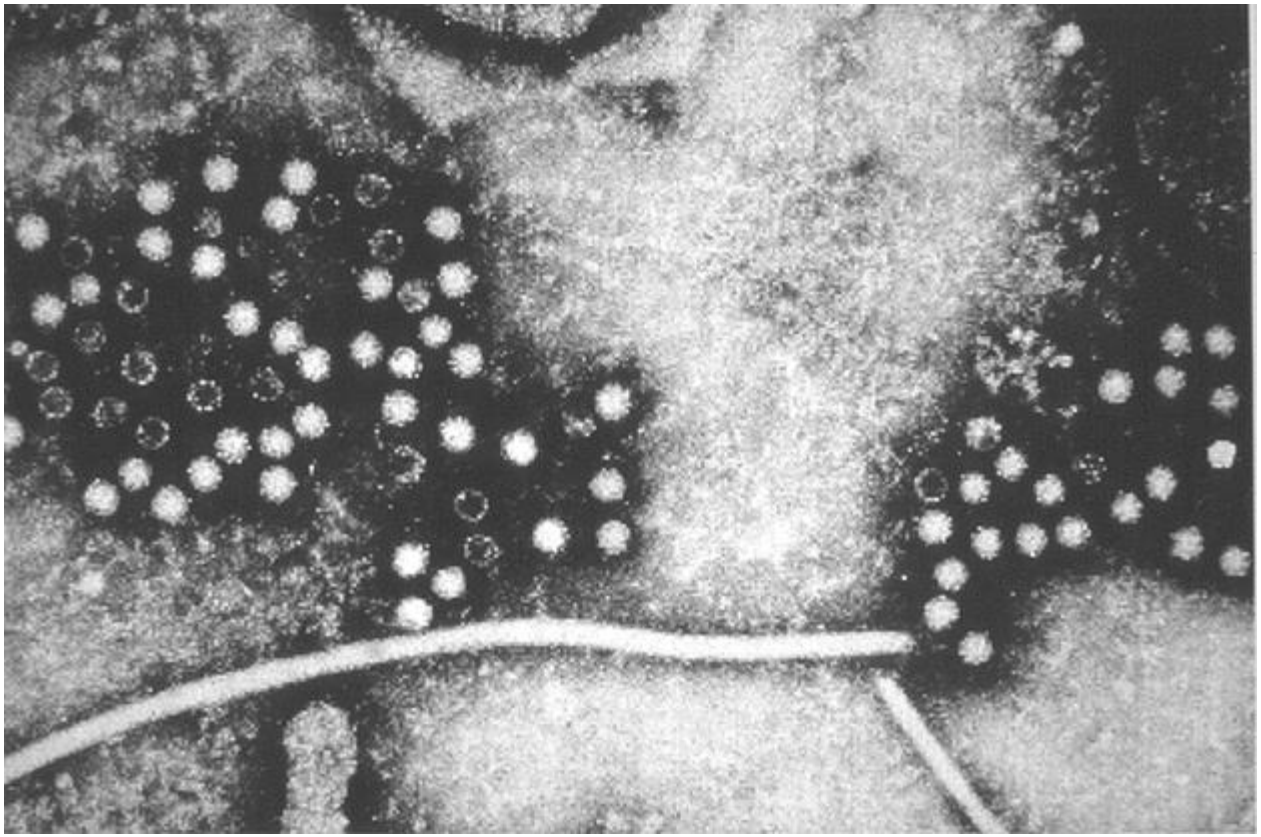


Figura 60.1 Immunoelettromicrografia del virus dell'epatite E. Per dimostrare la trasmissione interumana del virus dell'epatite E un ricercatore russo incaricato di studiare un'epidemia di epatite sviluppatasi nel 1980 in una guarnigione di soldati russi di stanza sul fronte afgano si infettò volontariamente ingerendo materiale virale estratto dalle feci di soldati malati e sviluppò l'epatite 36 giorni dopo la somministrazione dell'inoculo, quindi dimostrò che il virus presente nelle sue feci reagiva con il siero dei soggetti convalescenti e poteva essere osservato mediante immunomicroscopia elettronica.

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Hepatitis E

8 July 2019

Key facts

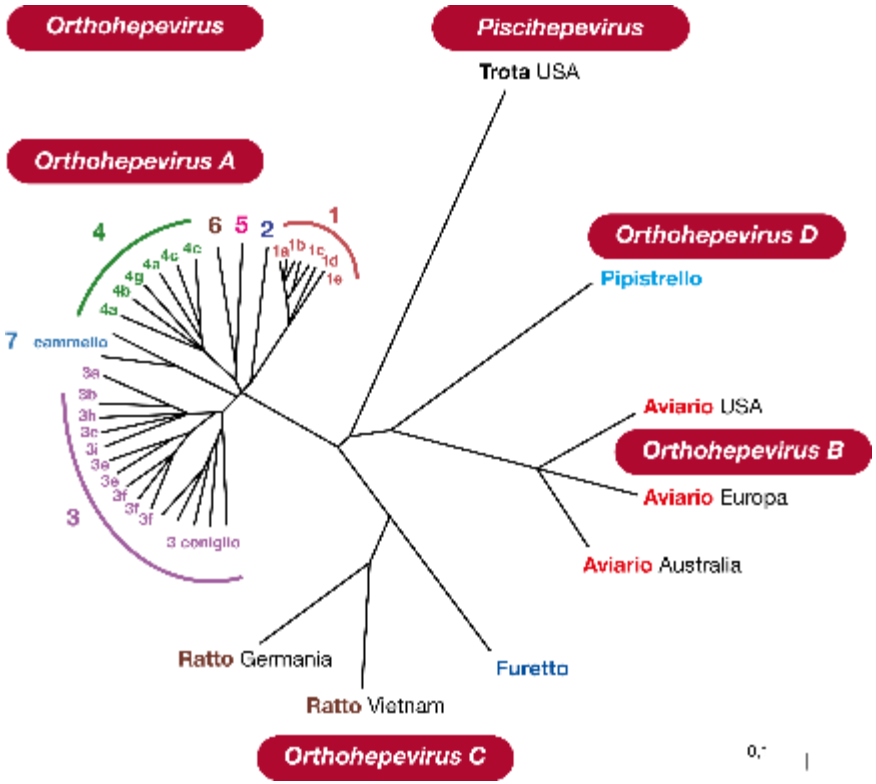
- Hepatitis E is a liver disease caused by infection with a virus known as hepatitis E virus (HEV).
- Every year, there are an estimated 20 million HEV infections worldwide, leading to an estimated 3.3 million symptomatic cases of hepatitis E (1).
- WHO estimates that hepatitis E caused approximately 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.

Hepatitis E virus (HEV) infection is being increasingly recognized in medical research as HEV infection has reached industrialized countries.
Although HEV was discovered in 1983 and subsequent experimental analyses were initiated since 1990/1991 on HEV isolates , there exists a considerable lack of understanding and knowledge of transmission routes, life-cycle, pathogenesis, genome variability and viral evolution.

HEV is a small RNA, non-enveloped virus, 32–34 nm in diameter and belonging to the genus Orthohepevirus of the Hepeviridae family
The HEV genome is a positive-sense single-stranded RNA molecule of 7.2 kb containing three open reading frames (ORF1, ORF2, and ORF3), 5′- and 3′-untranslated regions (UTRs), and a polyA-tract at the 3′-end

Table 1.*Hepeviridae*. Characteristics of the family *Hepeviridae*.

Characteristic	Description
Typical member	hepatitis E virus Burma (M73218), species *Orthohepevirus A*, genus *Orthohepevirus*,
Virion	Non-enveloped, 27–34 nm diameter with a single capsid protein
Genome	6.4-7.2 kb capped positive-sense monopartite RNA containing 3 open reading frames
Replication	Occurs in association with the host endoplasmic reticulum.
Translation	From genomic (ORF1) and subgenomic (ORF2 and ORF3) capped RNA
Host range	Mammals (*Orthohepevirus A*, *C* and *D*), birds (*Orthohepevirus B*) and trout (*Piscihepevirus*)
Taxonomy	two genera



Genotipo 1 (Pakistan Sar55 strain—M80581) and genotipo 2 (Mexican strain—M74506) infettano sostanzialmente solo l'uomo

Figura 60.2 Ricostruzione filogenetica di sequenze genomiche complete di virus dell'epatite E isolati da ospiti diversi. Il genere *Piscihepevirus* include pochissimi ceppi isolati da trote del continente nordamericano. La specie degli *Orthohepevirus A* rappresenta la specie di principale interesse per la patologia umana, include 7 genotipi e svariati sottotipi.

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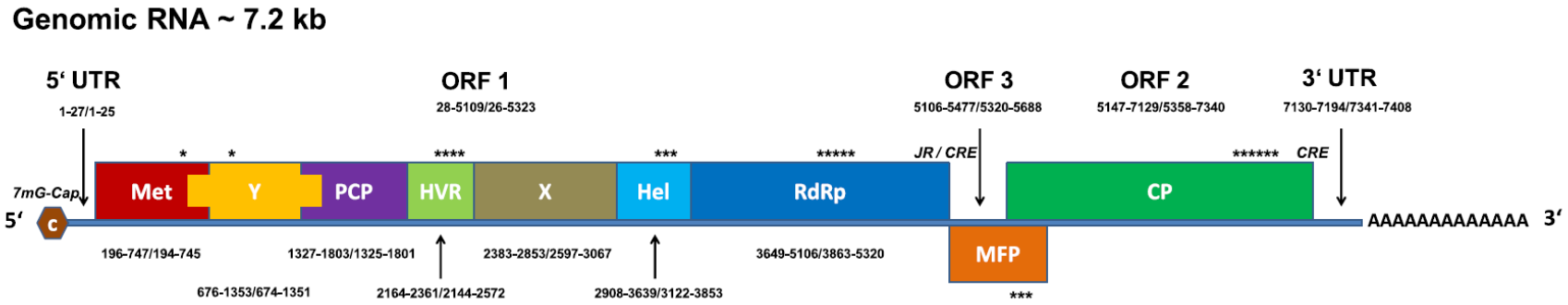
Tabella 60.1 **Distribuzione geografica dei genotipi di HEV che infettano l'uomo e caratteristiche cliniche/epidemiologiche.**

Caratteristiche	Genotipo 1	Genotipo 2	Genotipo 3	Genotipo 4
Localizzazione geografica	Africa e Asia	Messico e Africa	Paesi industrializzati	Cina e Giappone
Via di trasmissione	Acqua contaminata; fecale-orale; raramente contatto tra persone	Acqua contaminata; fecale-orale	Alimenti contaminati mangiati crudi o poco cotti; contatto con animali infetti	Alimenti contaminati mangiati crudi o poco cotti; contatto con animali infetti
Trasmissione zoonotica	No	No	Sì	Sì
Gruppi a rischio d'infezione	Giovani adulti	Giovani adulti	Adulti (> 40 anni) maschi; pazienti immunocompromessi	Giovani adulti
Decessi in gravidanza	Sì	Sì	No	No
Prognosi in pazienti con patologia epatica preesistente	Severa	Severa	Severa	Severa
Infezione cronica	No	No	Sì	No

The HEV genome is a **positive-sense single-stranded R**NA molecule of 7.2 kb containing three open reading frames (ORF1, ORF2, and ORF3), 5'- and 3'-untranslated regions (UTRs), and a polyA-tract at the 3'-end



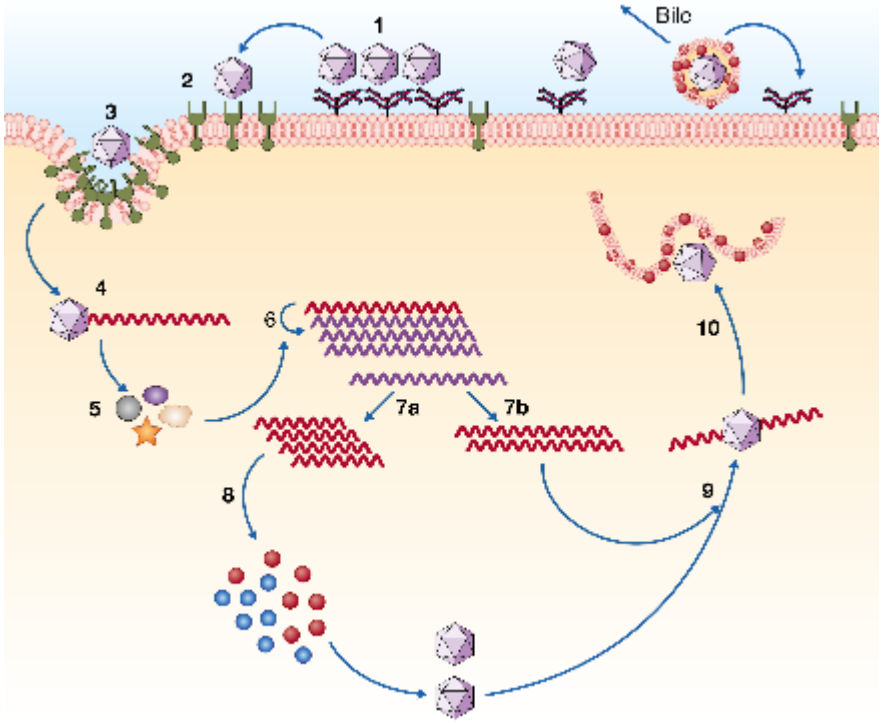


Figura 60.5 Ciclo di replicazione virale. Il virus è intercettato da molecole di eparan-solfato (1) e si lega a un recettore specifico non ancora caratterizzato; (2) viene quindi internalizzato mediante endocitosi (3). In seguito allo scapsidamento l'RNA genomico (linea ondulata rossa) viene rilasciato nel citoplasma (4) e immediatamente tradotto (5); si ottengono le 4 proteine non strutturali, che includono l'enzima per la replicazione, il quale trascrive l'RNA genomico (6); si ottiene così l'intermedio replicativo o antigenoma (linee ondulate viola), che serve come stampo per la sintesi di RNA subgenomici di 2200 basi (7a) e di nuovi RNA genomici di 7200 basi (7b). Gli RNA subgenomici vengono tradotti (8) nelle proteine ORF2 e ORF3. Proteine ORF2 si assemblano tra loro e impacchettano l'RNA genomico formando nuovi virus (9), le proteine ORF3 interagiscono con proteine cellulari e si associano con le membrane cellulari favorendo l'uscita dei virioni attraverso un processo di esocitosi (10). Studi recenti suggeriscono che le particelle rilasciate dall'epatocita sono rivestite di membrana lipidica associata a ORF3; entrambe queste strutture vengono rimosse a livello biliare, per cui il virus nelle feci risulta nudo. Le particelle "quasi-rivestite" sono comunque in grado, sebbene con minore efficienza, di rientrare nell'epatocita attraverso un vacuolo rivestito di clatrina/dinamina 2, come descritto in figura 60.4.

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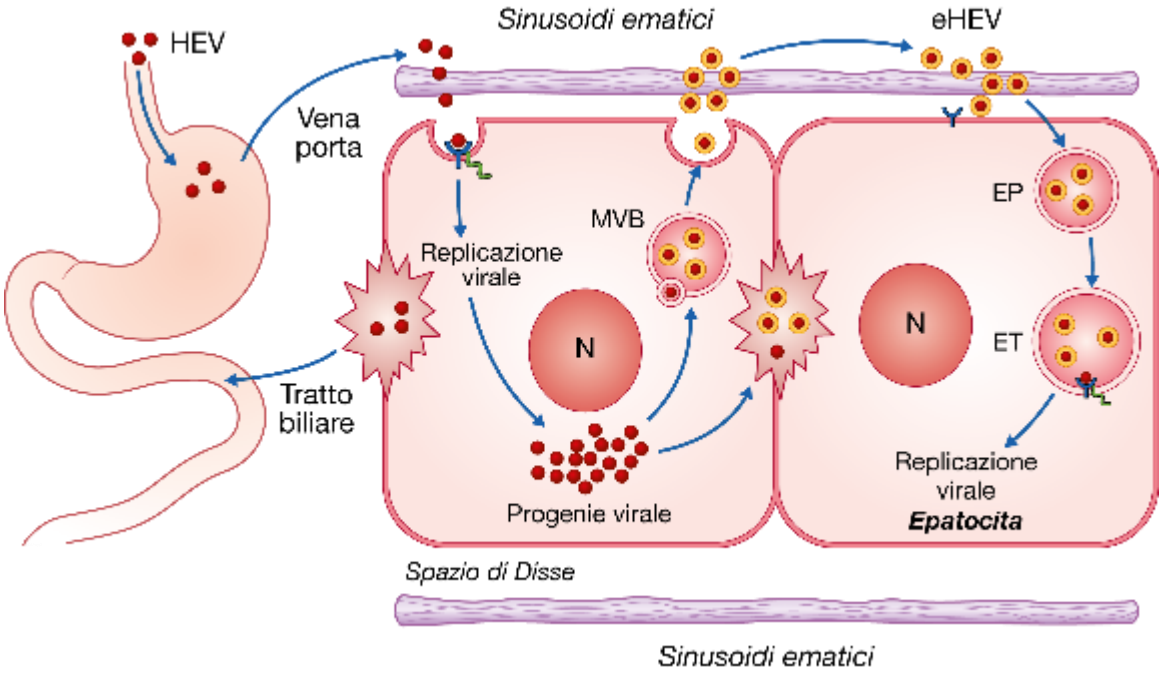

Figura 60.4 Modello proposto per l'ingresso e per la diffusione di HEV nella cellula epatica. L'infezione inizia attraverso l'ingestione di virioni nudi presenti nelle acque o negli alimenti contaminati. Non è chiaro attraverso quale modalità il virus passi nel sangue, è verosimile una fase replicativa a livello intestinale, da dove il virus raggiunge il fegato attraverso la vena porta. La penetrazione è conseguente all'attacco a molecole di eparan-solfato e a un recettore non ancora identificato che media la formazione di un vacuolo; il genoma viene liberato nel citoplasma, segue la replicazione virale e la formazione di nuovi virioni che acquisiscono una membrana lipidica in seguito all'interazione di ORF3 con proteine cellulari coinvolte nel processo di gemmazione; questo promuove la gemmazione di virioni dotati di membrana lipidica associata a ORF3 all'interno di corpi multivescicolari (MVB). Segue il trasporto esocitosico e il rilascio dei virioni in seguito a fusione della membrana dei corpi vescicolari con la membrana plasmatica. I nuovi virioni "quasi-rivestiti" possono essere rilasciati dalla superficie basolaterale degli epatociti, finendo nello spazio di Disse e nei sinusoidi ematici che fiancheggiano gli epatociti. Questa progenie virale "quasi-rivestita" è in grado di entrare, sebbene con minore efficienza, negli epatociti circostanti attraverso la formazione di un vacuolo endocitosico (endosoma precoce, EP); la membrana lipidica viene degradata in seguito all'acidificazione dell'endosoma tardivo (ET) e il genoma viene rilasciato dopo l'interazione del capside con il recettore specifico presente sulla membrana dell'endosoma, dando così inizio a un nuovo ciclo di infezione. I virioni possono anche essere rilasciati dalla superficie apicale degli epatociti infetti, finendo nei canalicoli biliari nei quali si esplica un'azione detergente dalla bile sulle membrane lipidiche. Il virus, che attraverso il tratto biliare arriva

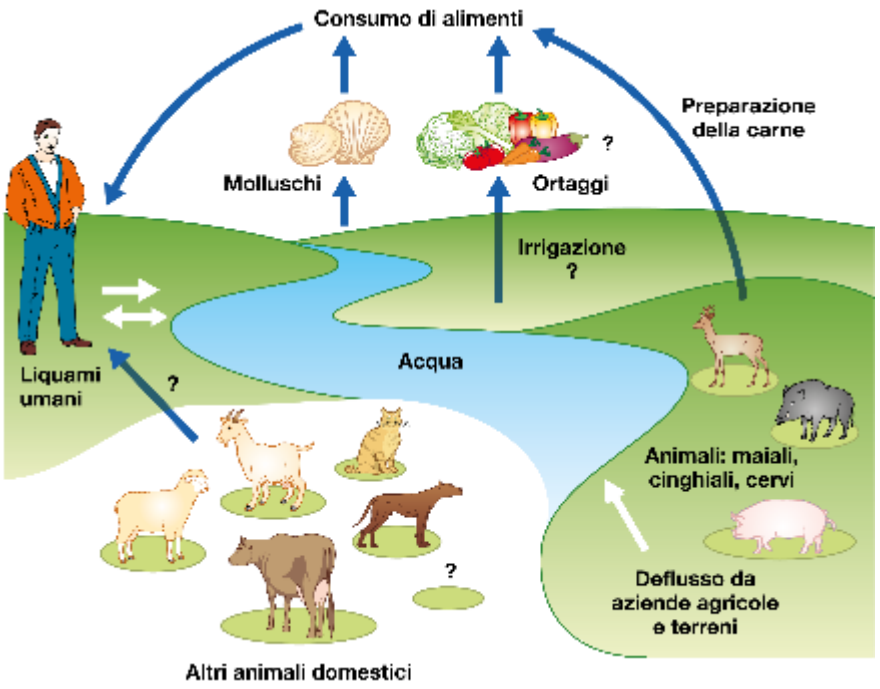

Figura 60.7 Principali modalità di trasmissione del virus dell'epatite E. La grande maggioranza delle infezioni nel mondo avviene in seguito al consumo di acqua contaminata da liquami umani; nei Paesi industrializzati l'infezione è acquisita per il consumo di alimenti contaminati da virus di origine animale; si tratta prevalentemente di prodotti carnei di suini allevati o selvatici e di cervi, mangiati crudi o poco cotti. Recentemente sono state descritte infezioni umane con ceppi di coniglio e cammello e si può ipotizzare che il reservoir animale possa essere più ampio. Acque reflue di allevamenti suinicoli usate per l'irrigazione o defluite al mare possono inoltre contaminare ortaggi o frutti di bosco ed essere filtrate da molluschi, dunque anche questi alimenti che vengono consumati crudi possono essere responsabili di infezione con HEV. La trasmissione tra uomini per contatto diretto è anche possibile come del resto quella attraverso trasfusioni/trapianti.

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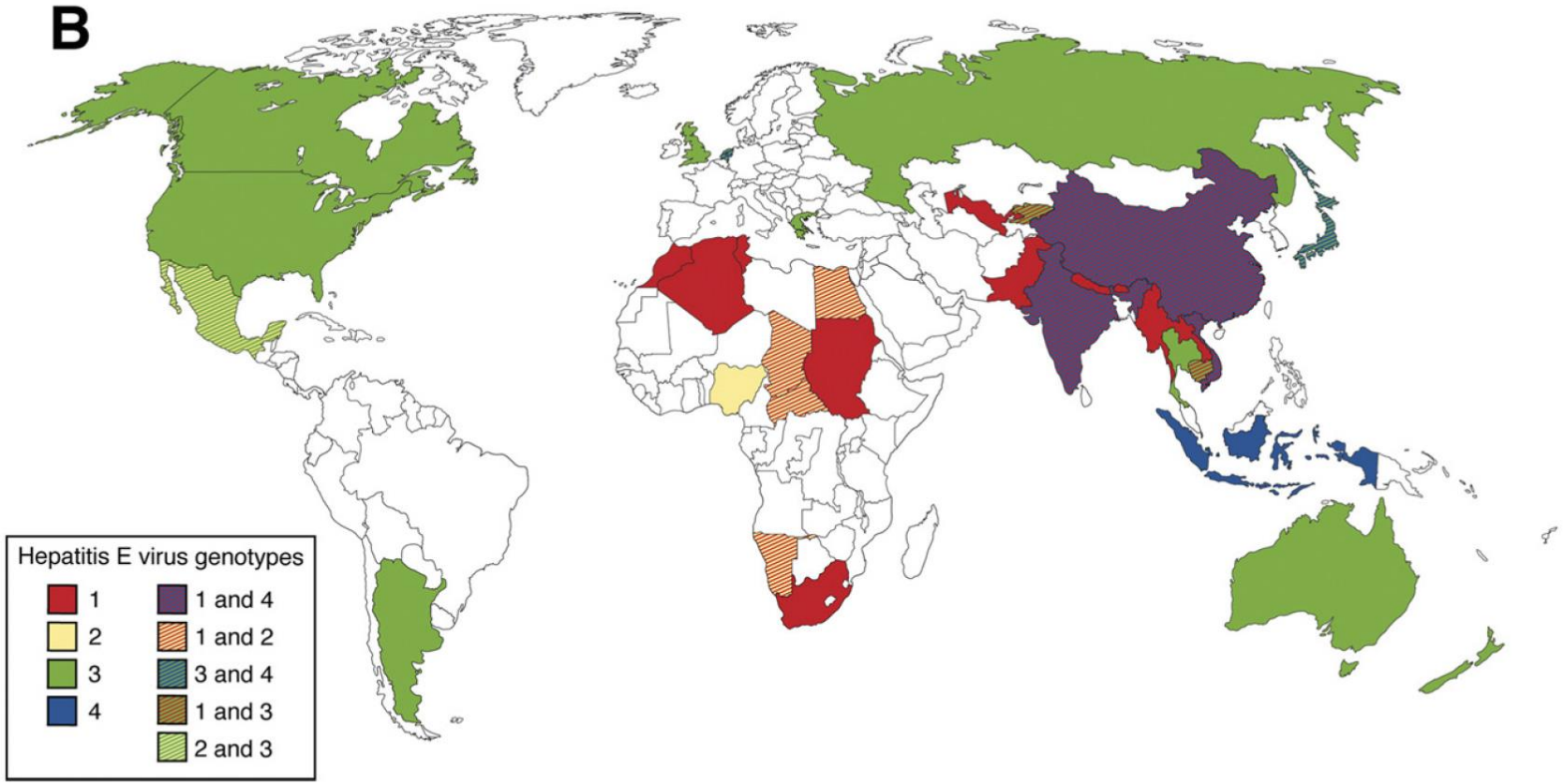

Figure 2. (*A*) Worldwide prevalence of HEV and (*B*) the geographic distribution of the different HEV genotypes.

Hepatitis E - Epidemiologic Features

- Most outbreaks associated with faecally contaminated drinking water.
- Several other large epidemics have occurred since in the Indian subcontinent and the USSR, China, Africa and Mexico.
- In the United States and other nonendemic areas, where outbreaks of hepatitis E have not been documented to occur, a low prevalence of anti-HEV (<2%) has been found in healthy populations. The source of infection for these persons is unknown.
- Minimal person-to-person transmission.

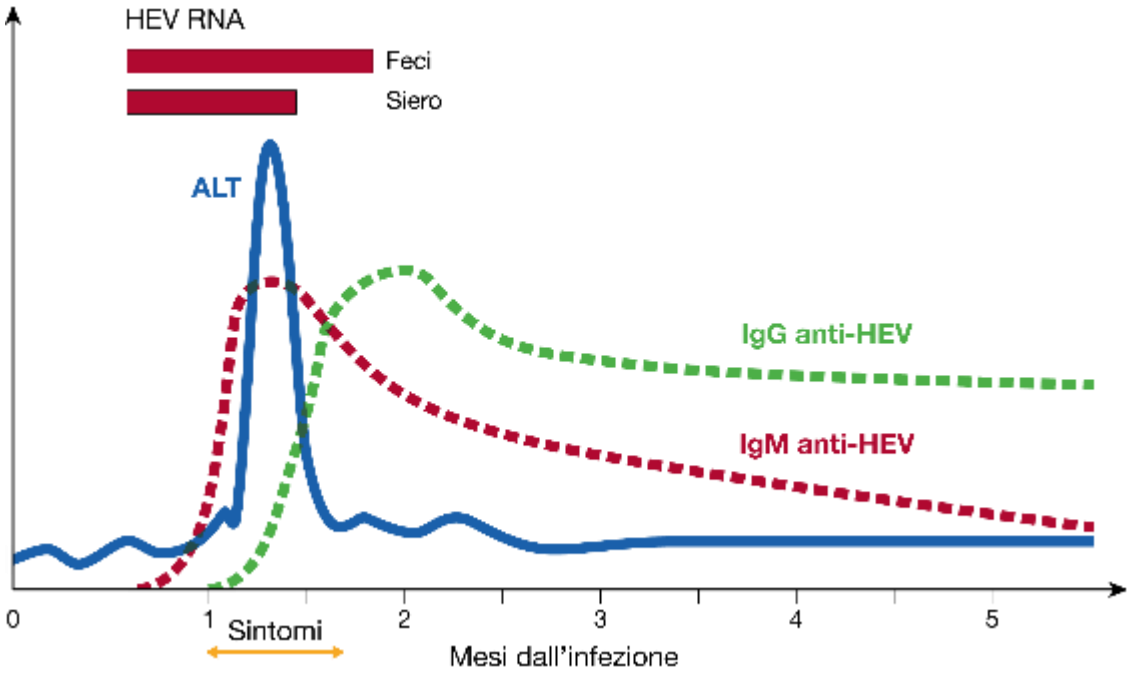

Figura 60.6 Decorso di un'infezione acuta da virus dell'epatite E. Le barre rosse indicano la presenza del virus nelle feci e nel sangue. Le variazioni di concentrazione nel siero di alanina amino transferasi (ALT) e di anticorpi anti-HEV specifici di classe IgM e IgG sono mostrate dalle relative curve. La doppia freccia indica la durata dei sintomi.

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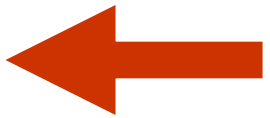
Hepatitis E - Clinical Features

Incubation period: Average 40 days
Range 15-60 days

Case-fatality rate: Overall, 1%-3%
Pregnant women, 15%-25%

Illness severity: Increased with age

Chronic sequelae: None identified



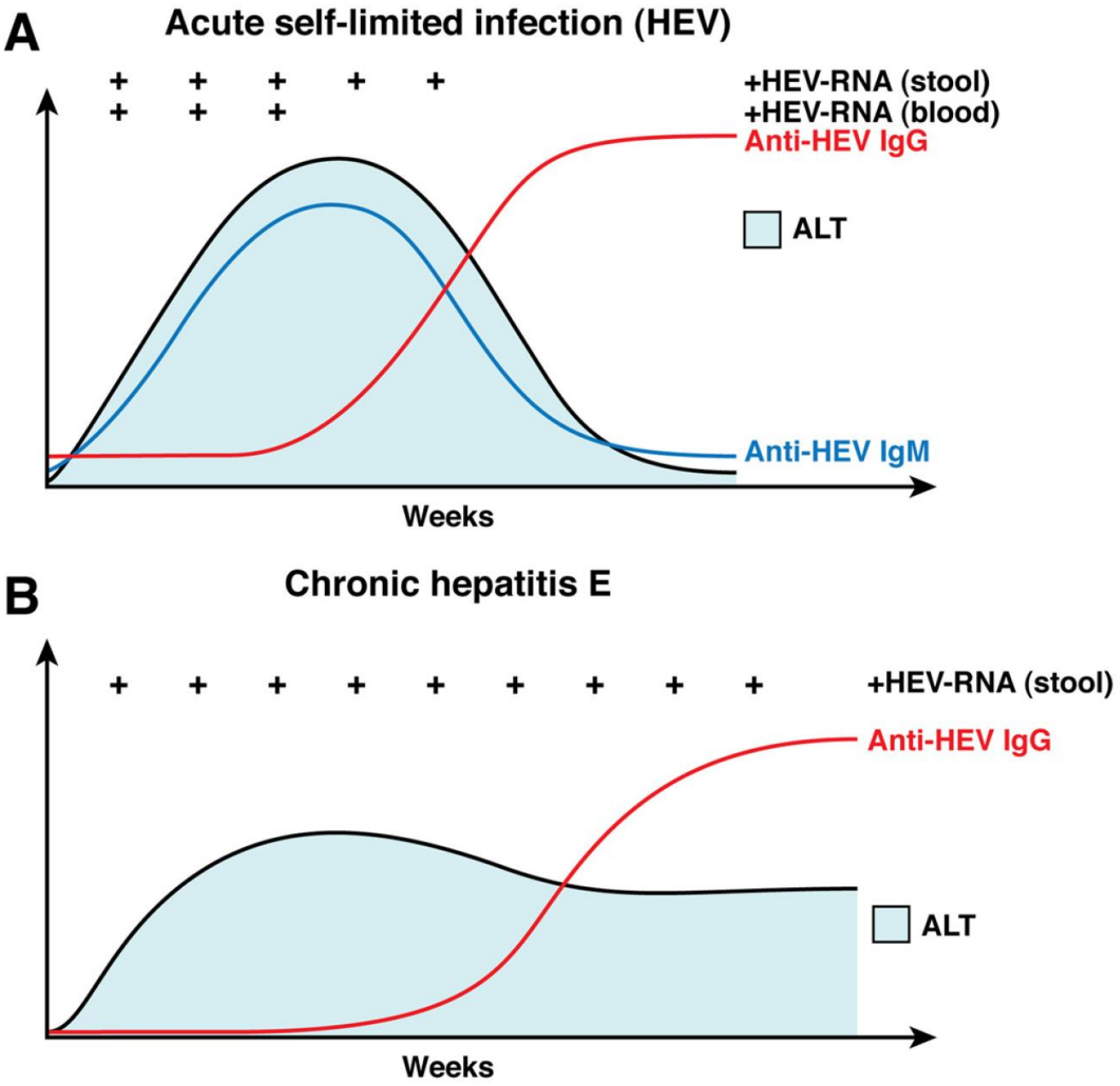
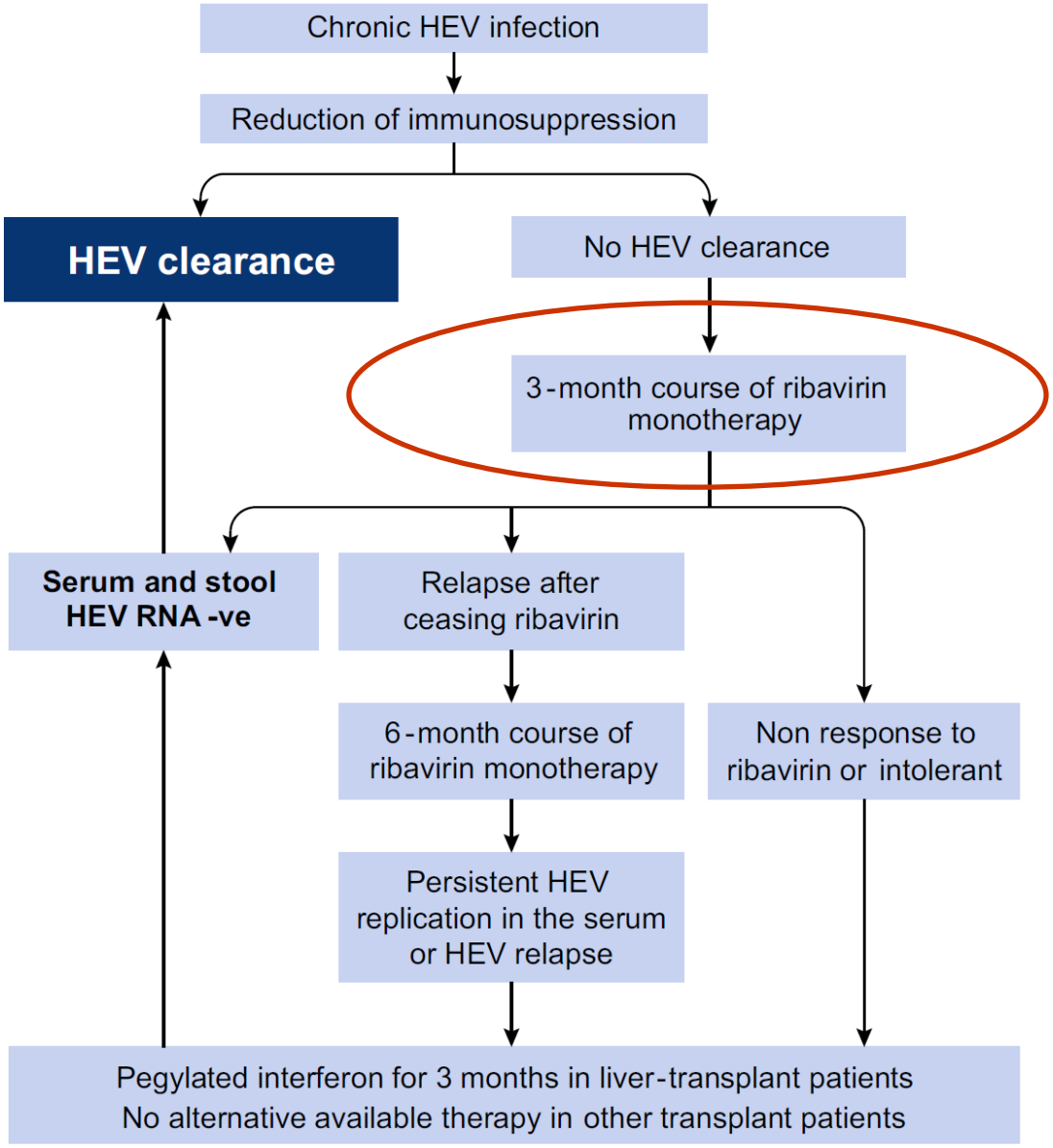

A
Acute self-limited infection (HEV)
+HEV-RNA (stool)
+HEV-RNA (blood)
Anti-HEV IgG
ALT
Anti-HEV IgM
Weeks
B
Chronic hepatitis E
+HEV-RNA (stool)
Anti-HEV IgG
ALT
Weeks

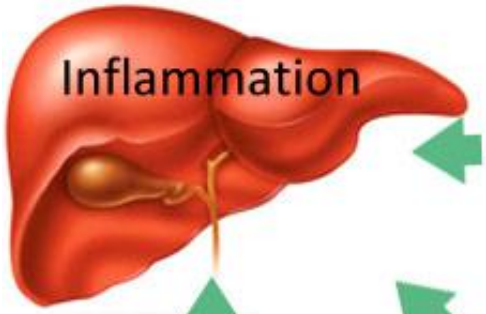
Table 3. Laboratory diagnosis of HEV infection.

Infection status	Positive markers
Current infection - acute	• HEV RNA • HEV RNA + anti-HEV IgM • HEV RNA + anti-HEV IgG* • HEV RNA + anti-HEV IgM + anti-HEV IgG • Anti-HEV IgM + anti-HEV IgG (rising) • HEV antigen
Current infection - chronic	• HEV RNA (± anti-HEV) ≥3 months • HEV antigen
Past infection	• Anti-HEV IgG

*Patients with re-infection are typically anti-HEV IgM negative, but IgG and PCR positive. HEV, hepatitis E virus.


Chronic HEV infection
Reduction of immunosuppression
HEV clearance
No HEV clearance
3-month course of ribavirin monotherapy
Serum and stool HEV RNA -ve
Relapse after ceasing ribavirin
Non response to ribavirin or intolerant
6-month course of ribavirin monotherapy
Persistent HEV replication in the serum or HEV relapse
Pegylated interferon for 3 months in liver-transplant patients
No alternative available therapy in other transplant patients

HEPATITIS - inflammation of the liver tissue



Toxic Damage
Alcohol
Drugs
Poisons/Chemicals

Immunologic Damage

Infections
Viruses
Bacteria
Fung
Protozoa

- **Hepatitis A - HAV**
- **Hepatitis B - HBV**
- **Hepatitis C - HCV**
- **Hepatitis D - HDV**
- **Hepatitis E - HEV**

Differential Diagnosis of Acute Hepatitis

Infectious	*Noninfectious*
Epstein-Barr virus	Drug-induced hepatitis
Cytomegalovirus	Autoimmune hepatitis
Herpes simplex virus	Ischemic hepatitis
Yellow fever	Acute fatty liver of pregnancy
Leptospirosis	Acute Buddy-Chiari syndrome
Q fever	Wilson's disease
HIV	
Brucellosis	
Lyme disease	
Syphilis	