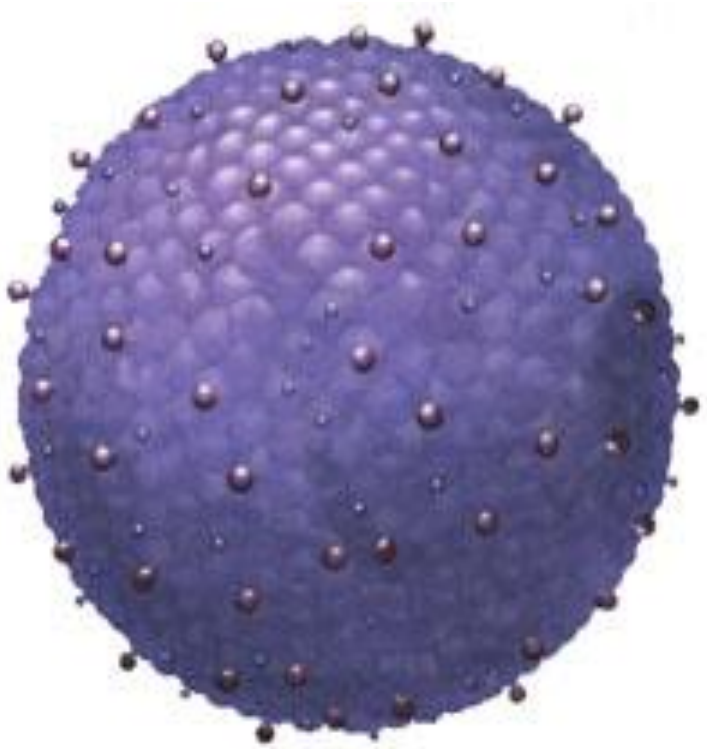
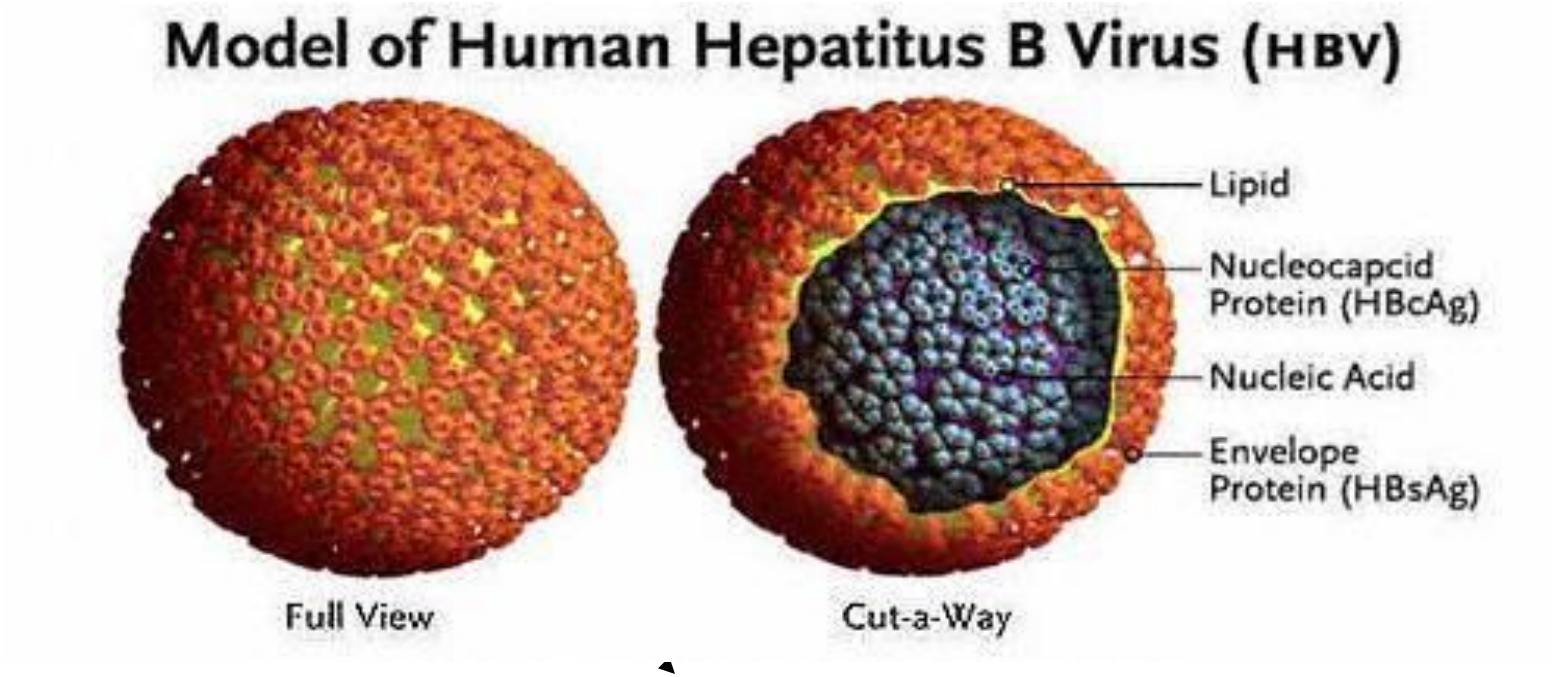
Hepatitis B Virus



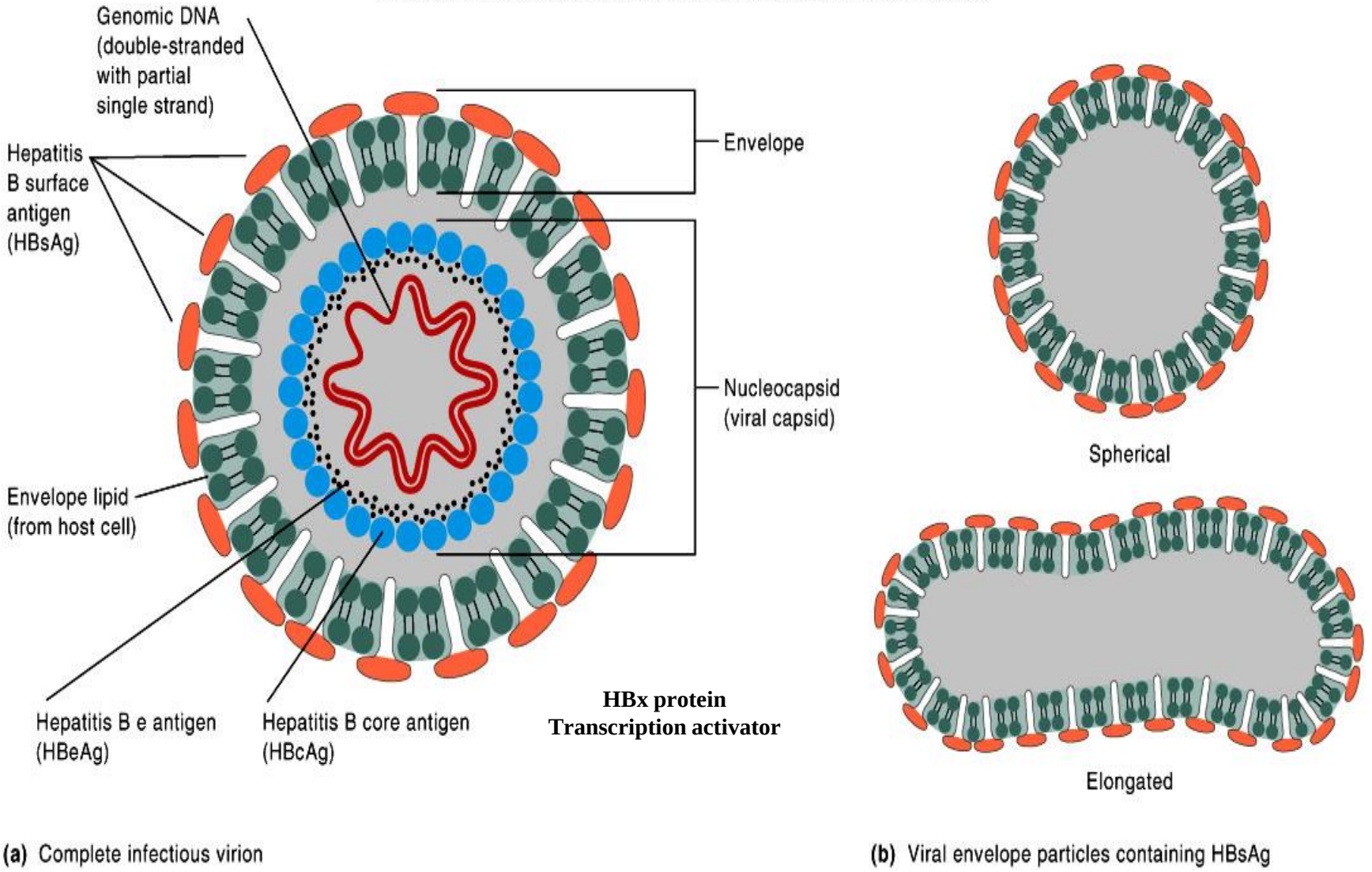
Hepatitis B Virus



Properties of HBV

- a member of the hepadnavirus group
- Enveloped, partially double-stranded DNA viruses, smallest DNA virus
- Replication involves a reverse transcriptase
- endemic in the human population and hyperendemic in many parts of the world.
- 8 genotypes (A-H), type D in middle east
- 4 serotypes
- It has not yet been possible to propogate the virus in cell culture

HBV : Structure



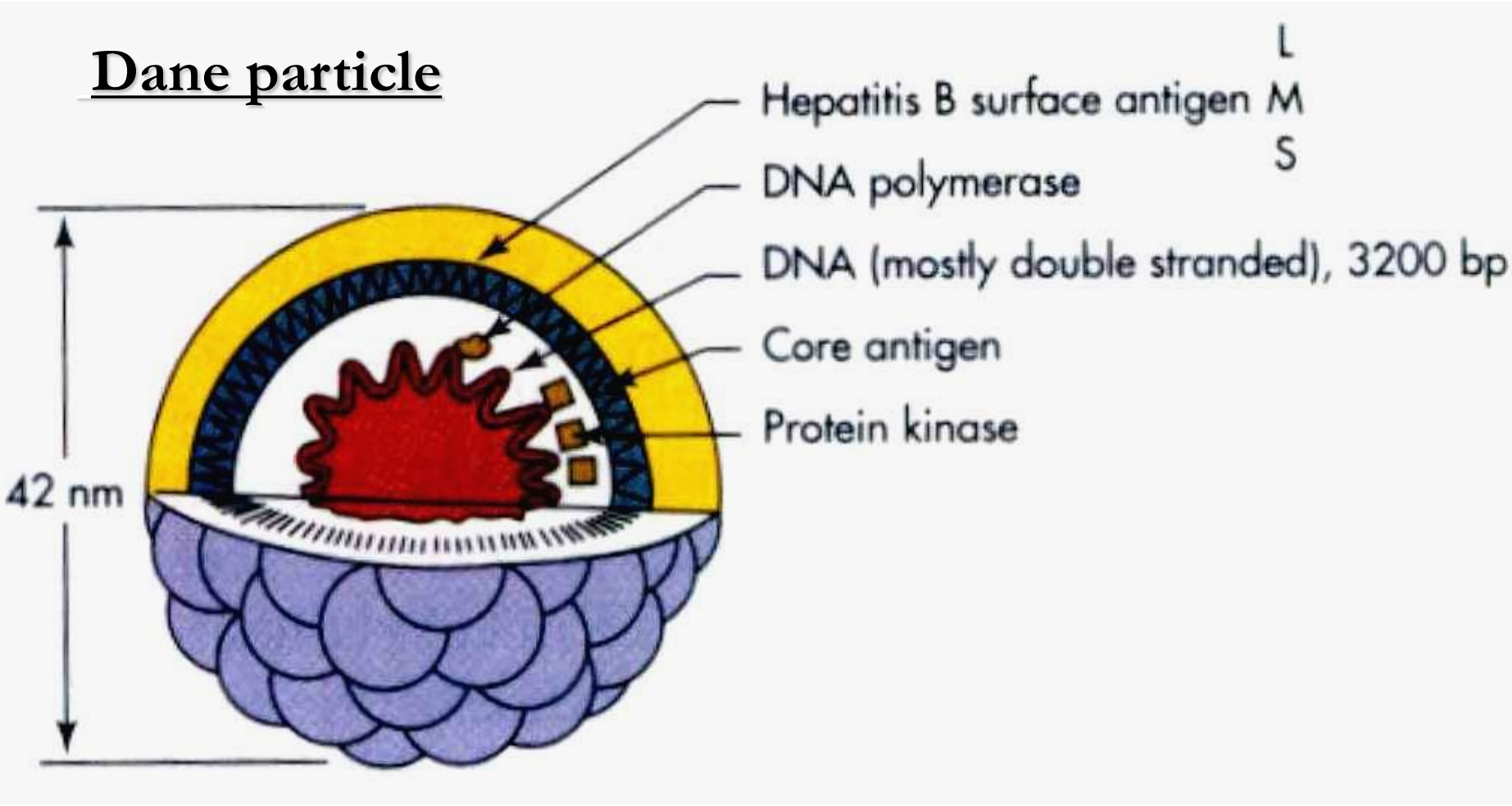
HBV : Structure

- Virion also referred to as Dane particle (ds-tranded DNA)
- 42nm enveloped virus
- Core antigens located in the center (nucleocapsid)

  * Core antigen (HBcAg)

  * e antigen (HBeAg)- an indicator of transmissibility (minor component of the core- antigenically distinct from HBcAg)
- 22nm spheres and filaments other forms- no DNA in these forms so they are not infectious (composed of surface antigen)- these forms outnumber the actual virions

HBV Structure & Antigens



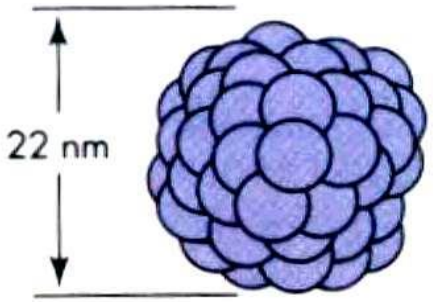
HBsAg = surface (coat) protein (**4 serotypes : adw, adr, ayw and ayr)**

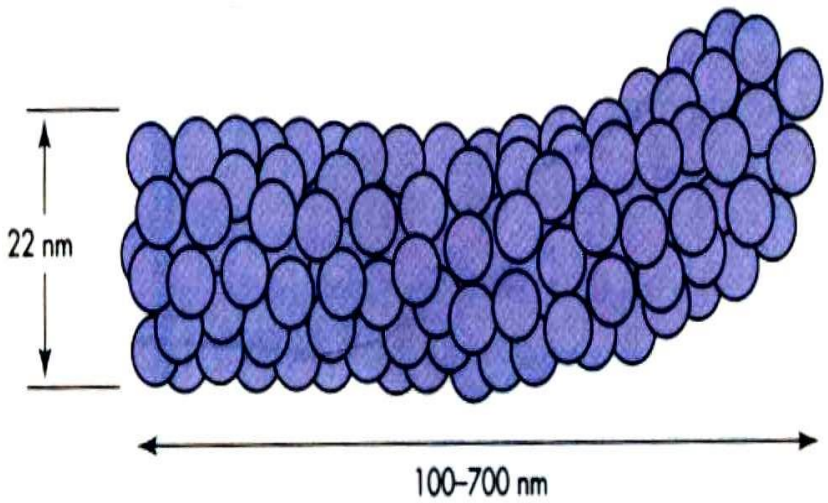
HBcAg = inner core protein (**a single serotype)**

HBeAg = secreted protein; function unknown

Decoy particles

- HBsAg-containing particles are released into the serum of infected people and outnumber the actual virions.
- Spherical or filamentous
- They are immunogenic and were processed into the first commercial vaccine against HBV.



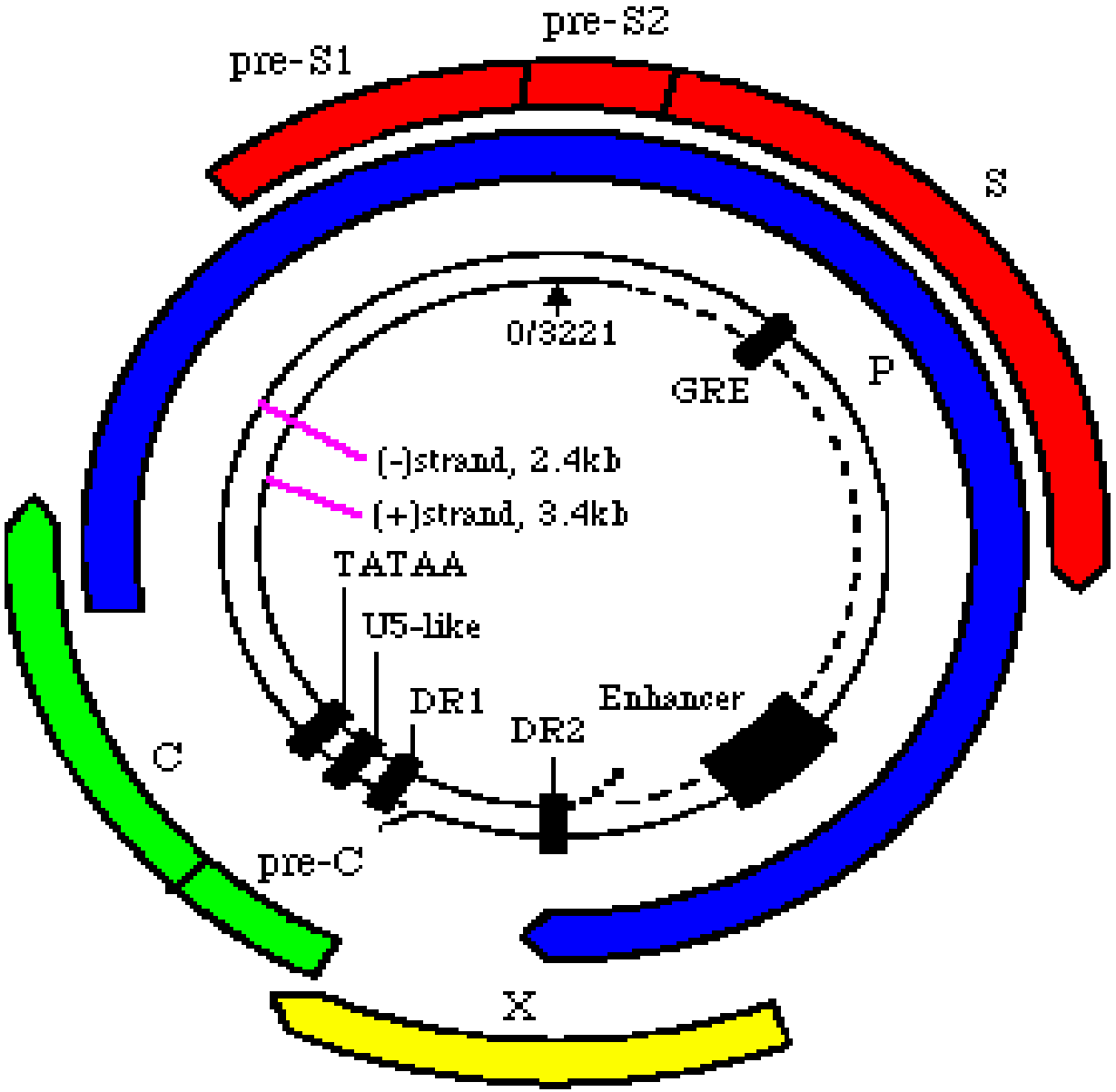


Open Reading Frames

There are 4 open reading frames derived from the same strand (the incomplete + strand)

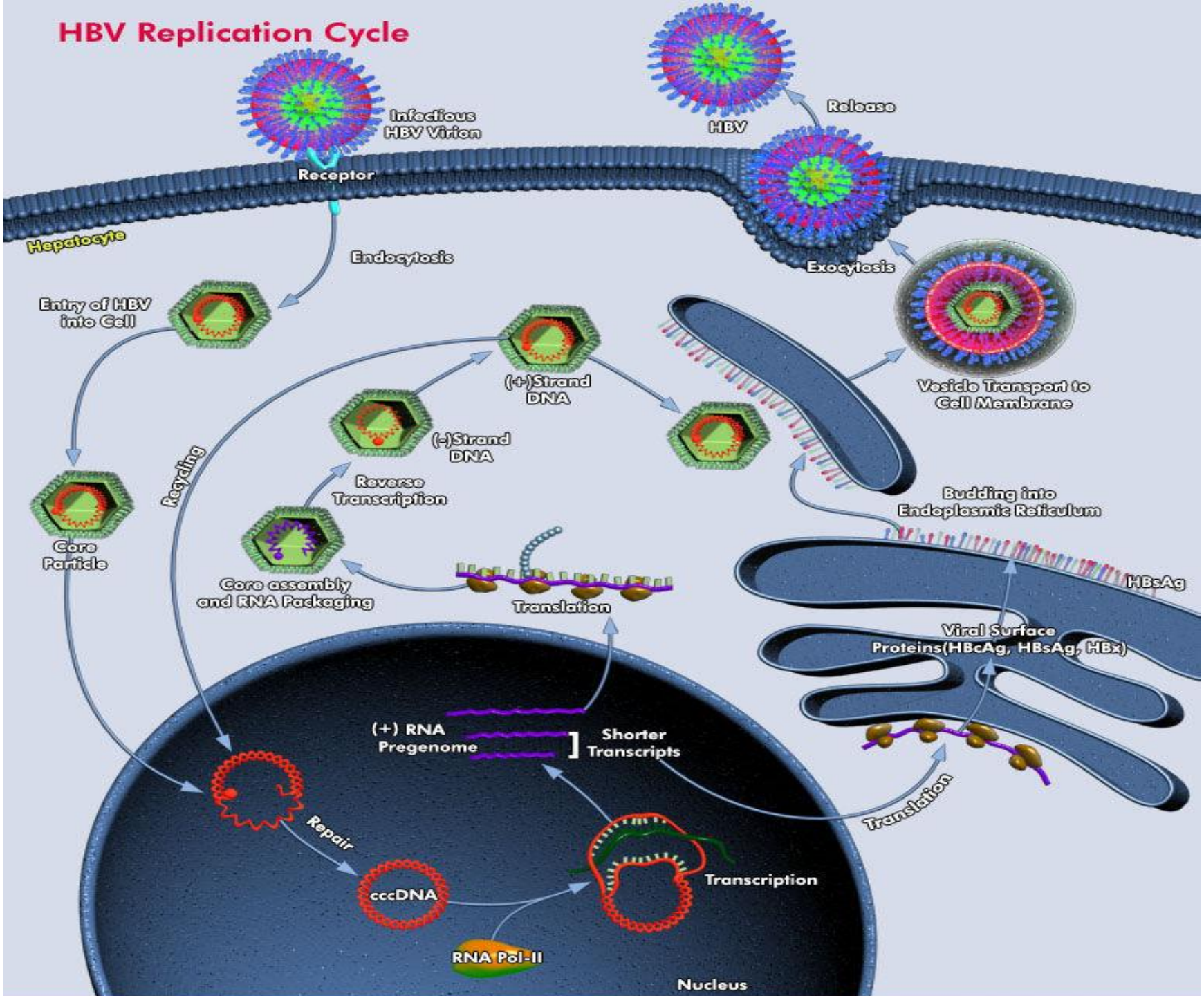
- **S** - the 3 polypeptides of the surface antigen (**preS1, preS2 and S -** produced from alternative translation start sites.
- **C** - Core protein: HBcAg, HBeAg: glycoprotein secreted from infected cells
- **P** - the polymerase: RNase H, RNA-dependent DNA polymerase and DNA-dependent DNA polymerase.
- **X** - a transactivator of viral transcription (and cellular genes). HBx is conserved in all mammalian (but not avian) hepadnaviruses. Though not essential in transfected cells, it is required for infection in vivo.

GENOME


pre-S2
pre-S1
S
0/3221
GRE
P
(-)strand, 2.4kb
(+)strand, 3.4kb
TATAA
U5-like
DR1
DR2
Enhancer
C
pre-C
X

HBV: Replication

- Reverse transcription: one of the mRNAs is replicated with a reverse transcriptase making the DNA that will eventually be the core of the progeny virion
- RNA intermediate: HBV replicates through an RNA intermediate and produces and release antigenic decoy particles.
- Integration: Some DNA integrates into host genome causing carrier state


HBV Replication Cycle
Infectious HBV Virion
Receptor
HBV
Release
Hepatocyte
Endocytosis
Exocytosis
Entry of HBV into Cell
(+)Strand DNA
Vesicle Transport to Cell Membrane
(-)Strand DNA
Reverse Transcription
Recycling
Budding into Endoplasmic Reticulum
Core Particle
Core assembly and RNA Packaging
Translation
HBsAg
Viral Surface Proteins(HBcAg, HBsAg, HBx)
(+) RNA Pregenome
Shorter Transcripts
Translation
Repair
cccDNA
Transcription
RNA Pol-II
Nucleus

Epidemiology

- 350,000,000 carriers worldwide

  - the carrier rate can exceed 10%

  -15 to 25% of chronically infected patients will die from chronic liver disease

- 50% of children born to mothers with chronic HBV in the US are Asian American

HBV: Modes of Transmission

- Parenteral - IV drug abusers, health workers are at increased risk.
- Sexual (50%)- sex workers and homosexuals are particular at risk.
- Perinatal (**Vertical) –** mother →infant. Does not cross placenta
- HCC associated with high virus load and integrated virus infections; activate cellular oncogene

Concentration of Hepatitis B Virus in Various Body Fluids

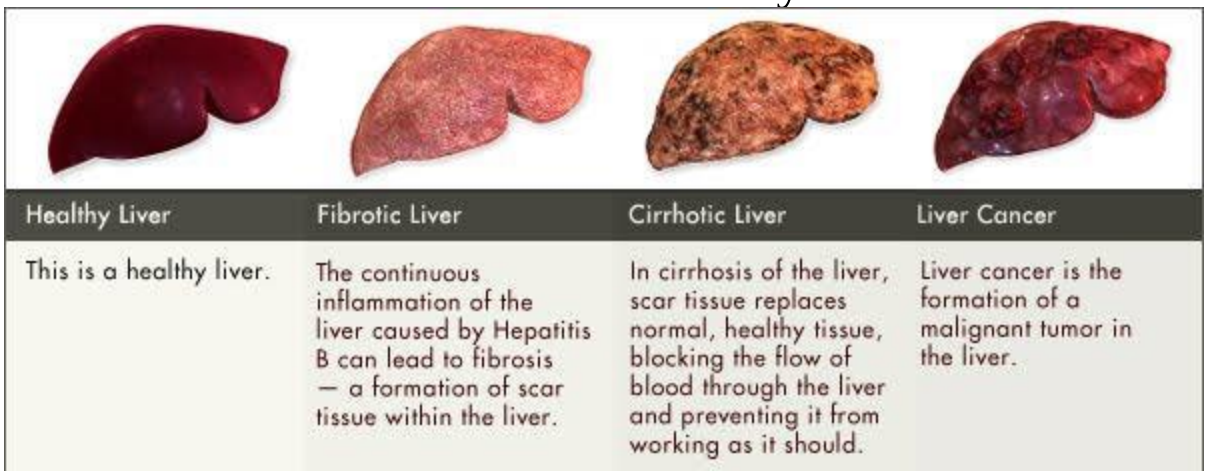
High	Moderate	Low/Not Detectable
blood	semen	urine
serum	vaginal fluid	feces
wound exudates	saliva	sweat
		tears
		Breast milk

High-risk groups for HBV infection

- People from endemic regions
- Babies of mothers with chronic HBV
- Intravenous drug abusers
- People with multiple sex partners
- Hemophiliacs and other patients requiring blood and blood product treatments
- Health care personnel who have contact with blood
- Residents and staff members of institutions for the mentally retarded

Pathogenesis & Immunity

- Virus enters hepatocytes via blood
- HBsAg found in blood, semen and cervical fluid
- 1ul of infectious blood has produced infection
- Serum sickness-like rash and arthritis may precede symptoms; immune complexes and complement activation
- Immune response (cytotoxic T cell) to viral antigens expressed on hepatocyte cell surface responsible for clinical syndrome
- 5-10% become chronic carriers (HBsAg> 6 months)
- Higher rate of hepatocellular ca in chronic carriers, especially those who are “e” antigen positive
- Hepatitis B surface antibody likely confers lifelong immunity (anti-HBs)
- Hepatitis B e Ab indicates low transmissibility



Clinical Features

- Incubation period: Average 60-90 days
  Range 30-180 days
- Gradual onset of fatigue, loss of appetite, nausea, pain and fullness in the right upper abdominal quadrant.
- Early in the disease the pt. might have joint pain and rash
- Liver damage associated with cholestasis, and hence clay-colored stool, dark urine and jaundice. Symptoms may persist for months before resolving
- Acute hepatitis B symptoms are more severe and prolonged than hepatitis A
- Anicteric disease and asymptomatic infection may occur
- Infection to disease ratio 3:1

Clinical illness (jaundice): <5 yrs, <10%
≥ 5 yrs, 30%-50%
1/3 adults-no symptoms

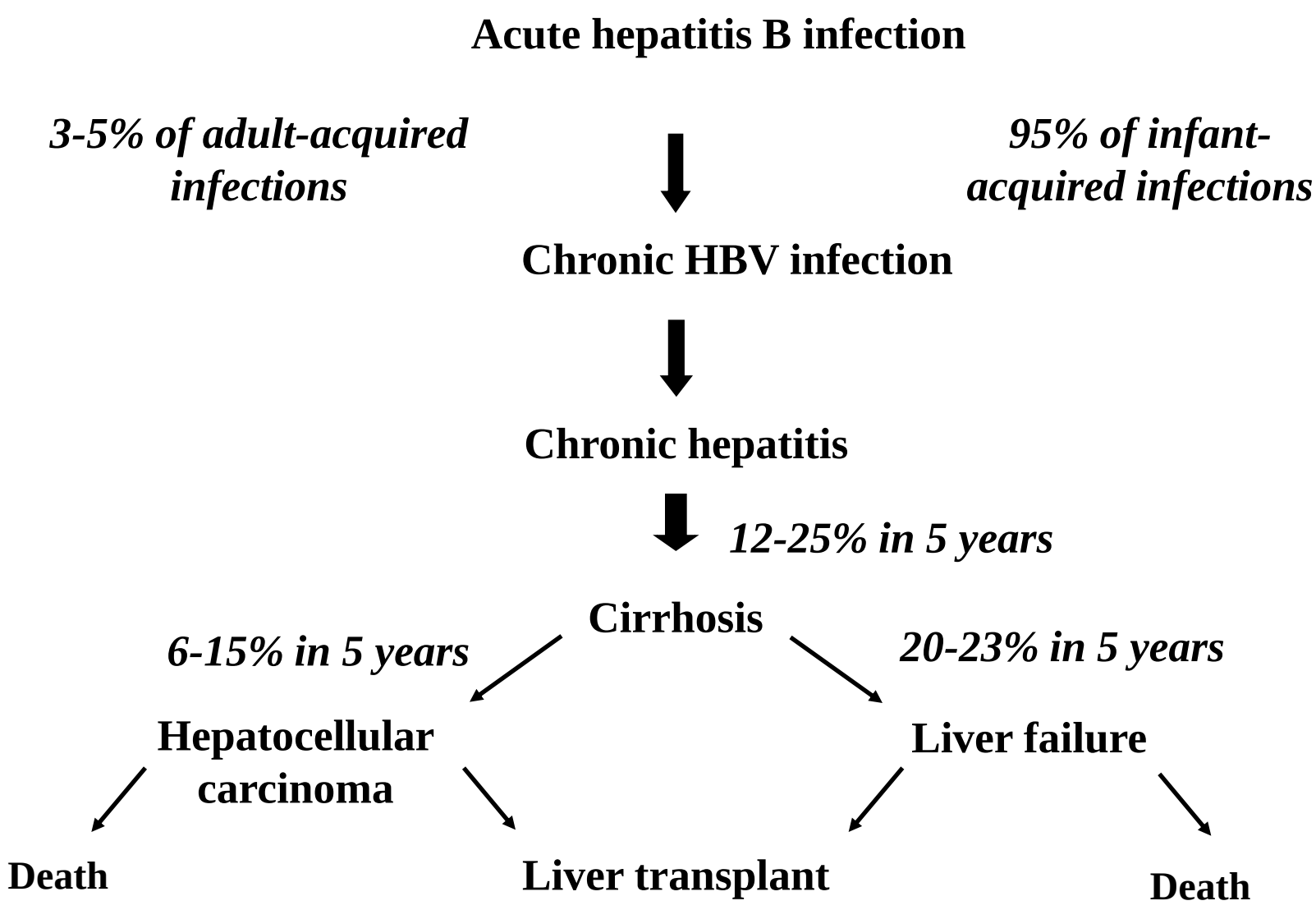
Clinical Illness at presentation 10%

Acute case-fatality rate: 0.5%-1%

Chronic infection: < 5 yrs, 30%-90%
≥ 5 yrs, 2%-10%
More likely in asymptomatic infections

Premature mortality from chronic liver disease: 15%-25%

Possible Outcomes of HBV Infection

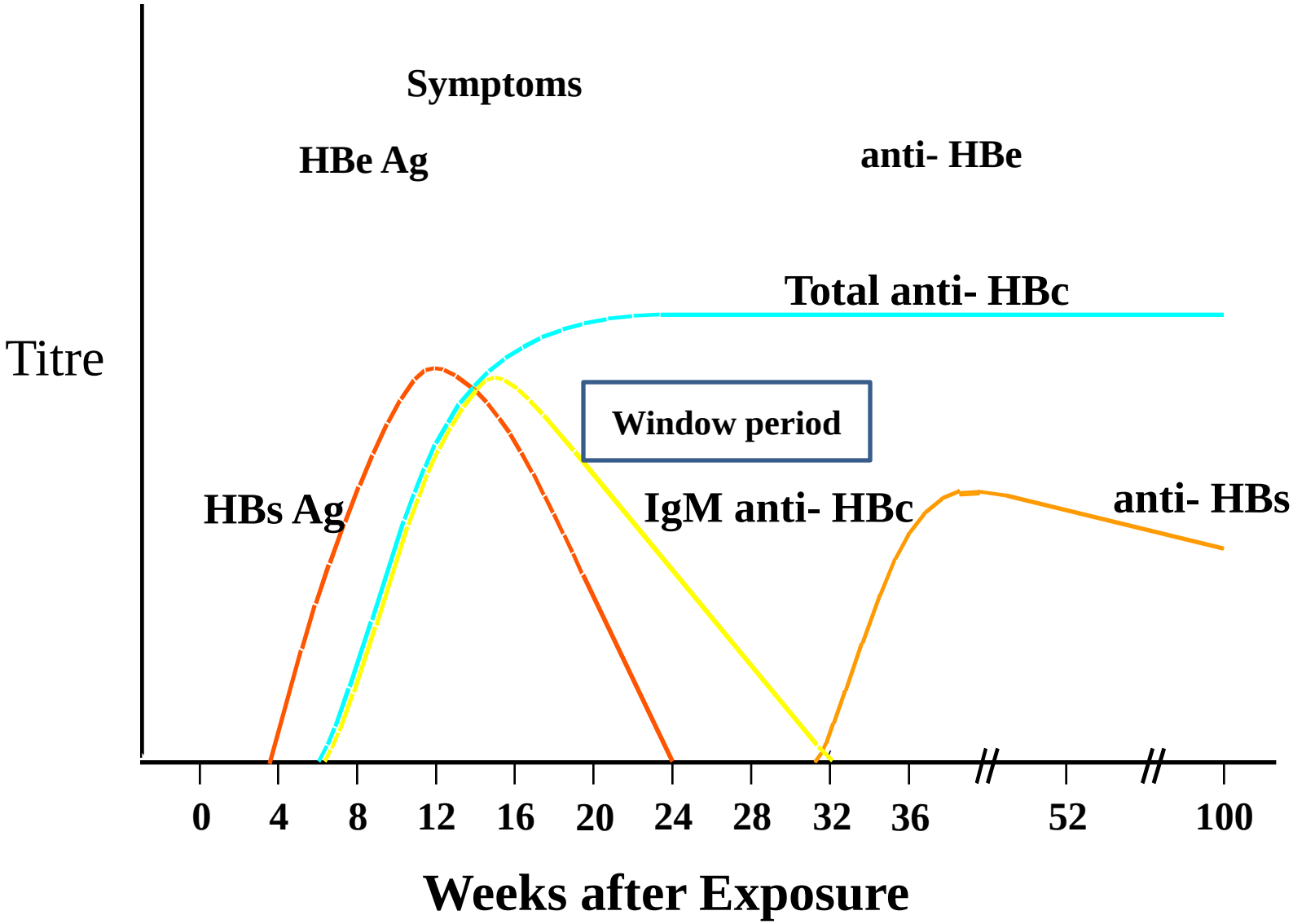


Diagnosis

- A battery of serological tests are used for the diagnosis of acute and chronic hepatitis B infection.
- HBsAg - used as a general marker of infection.
- HBsAb - used to document recovery and/or immunity to HBV infection.
- anti-HBc IgM - marker of acute infection.
- anti-HBcIgG - past or chronic infection.
- HBeAg - indicates active replication of virus and therefore infectiveness.
- Anti-HBe - virus no longer replicating. However, the patient can still be positive for HBsAg which is made by integrated HBV.
- HBV-DNA - indicates active replication of virus, more accurate than HBeAg especially in cases of escape mutants. Used mainly for monitoring response to therapy.

Acute Hepatitis B Virus Infection with Recovery

Typical Serologic Course



Laboratory Diagnosis

Serologic Markers for the Different Phases of Acute and Chronic Hepatitis B Virus Infection

HBsAg	HBeAg	IgM anti-HBc	IgG anti-HBc	Anti-HBs	Anti-HBe	HBV DNA	Interpretation
Acute HBV infection							
+	+	+				+	Early phase
		+				±	Window phase
			+	+	+	-	Recovery phase
Chronic HBV infection							
+	+		+			+	Replicative phase
+			+		+	-	Low, nonreplicative phase
+	±	+				+	Flare-up of chronic HBV
+					+	+	Precore/core promoter mutants

Hep B markers

- HBsAg –ve
- Anti HBc -ve
- Anti HBs –ve

- HBsAg –ve
- Anti HBc +ve
- Anti HBs +ve

- HBsAg –ve
- Anti HBc -ve
- Anti HBs +ve

- HBsAg +ve
- Anti HBc (IgM)+ve
- Anti HBs –ve

- HBsAg +ve
- Anti HBc +ve
- IgM anti HBc -ve
- Anti HBs -ve

- HBsAg –ve
- Anti HBc (IgM)+ve
- Anti HBs -ve

Treatment

- Interferon - for HBeAg +ve carriers with chronic active hepatitis. Response rate is 30 to 40%.
  - alpha-interferon 2b (original)
  - alpha-interferon 2a (newer, claims to be more efficacious and efficient)
- Lamivudine - a nucleoside analogue reverse transcriptase inhibitor. Well tolerated, most patients will respond favorably. However, tendency to relapse on cessation of treatment. Another problem is the rapid emergence of drug resistance.
- Adefovir – less likely to develop resistance than Lamivudine and may be used to treat Lamivudine resistance HBV. However more expensive and toxic
- Entecavir – most powerful antiviral known, similar to Adefovir
- Successful response to treatment will result in the disappearance of HBsAg, HBV-DNA, and seroconversion to anti-HBeAg.

Prevention

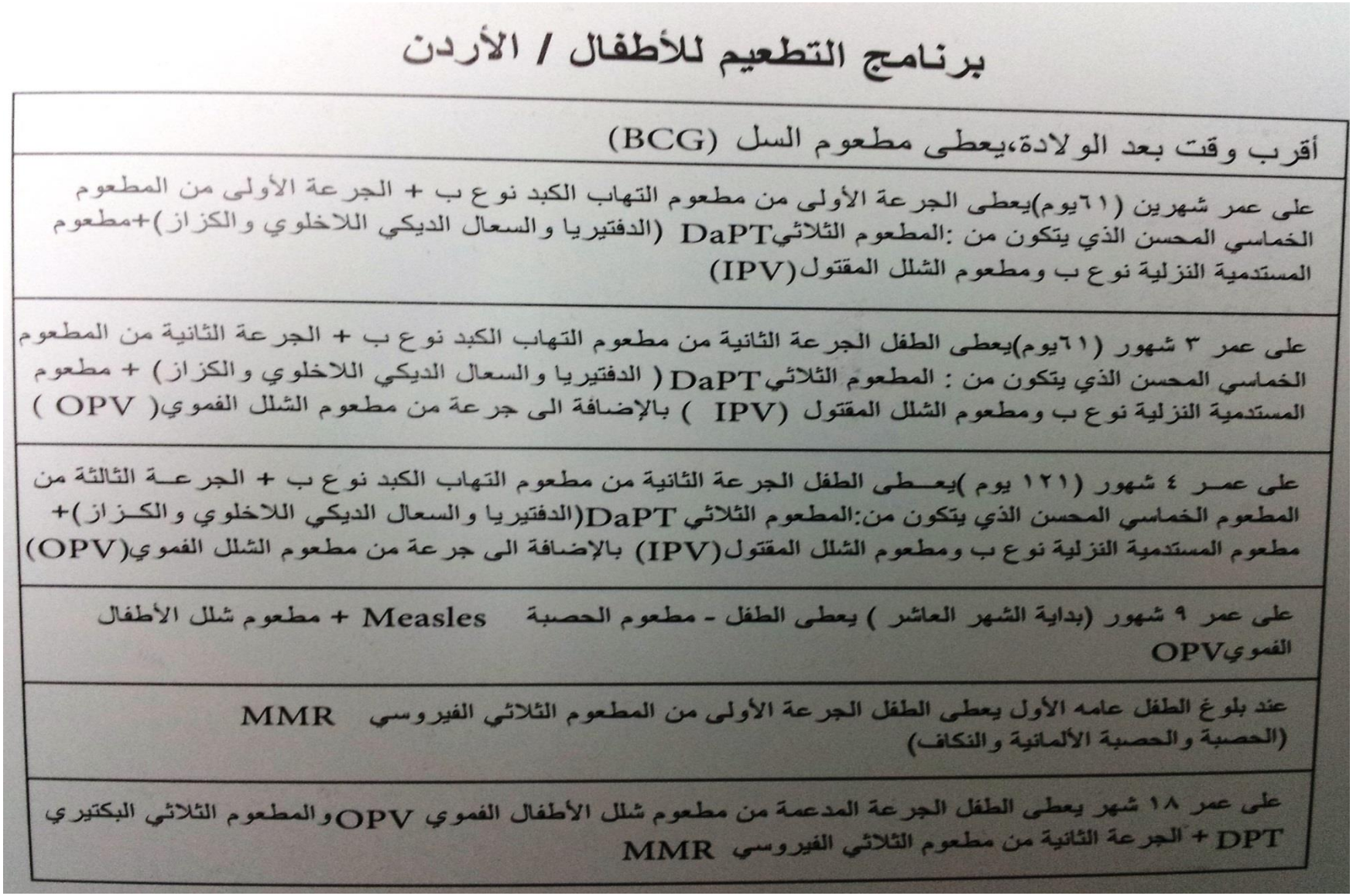
- Vaccination - highly effective recombinant vaccines are now available. Vaccine can be given to those who are at increased risk of HBV infection such as health care workers. It is also given routinely to neonates as universal vaccination in many countries.
- Hepatitis B Immunoglobulin - HBIG may be used to protect persons who are exposed to hepatitis B. It is particular efficacious within 48 hours of the incident. It may also be given to neonates who are at increased risk of contracting hepatitis B i.e. whose mothers are HBsAg and HBeAg positive.
- Other measures - screening of blood donors, blood and body fluid precautions.

Hepatitis B Vaccine

- Infants: several options that depend on status of the mother
  - If mother HBsAg negative: birth, 1-2m,6-18m
  - If mother HBsAg positive: vaccine and Hep B immune globulin within 12 hours of birth, 1-2m, <6m
- Adults

  * 0,1, 6 months
- Vaccine recommended in
  - All those aged 0-18
  - Those at high risk

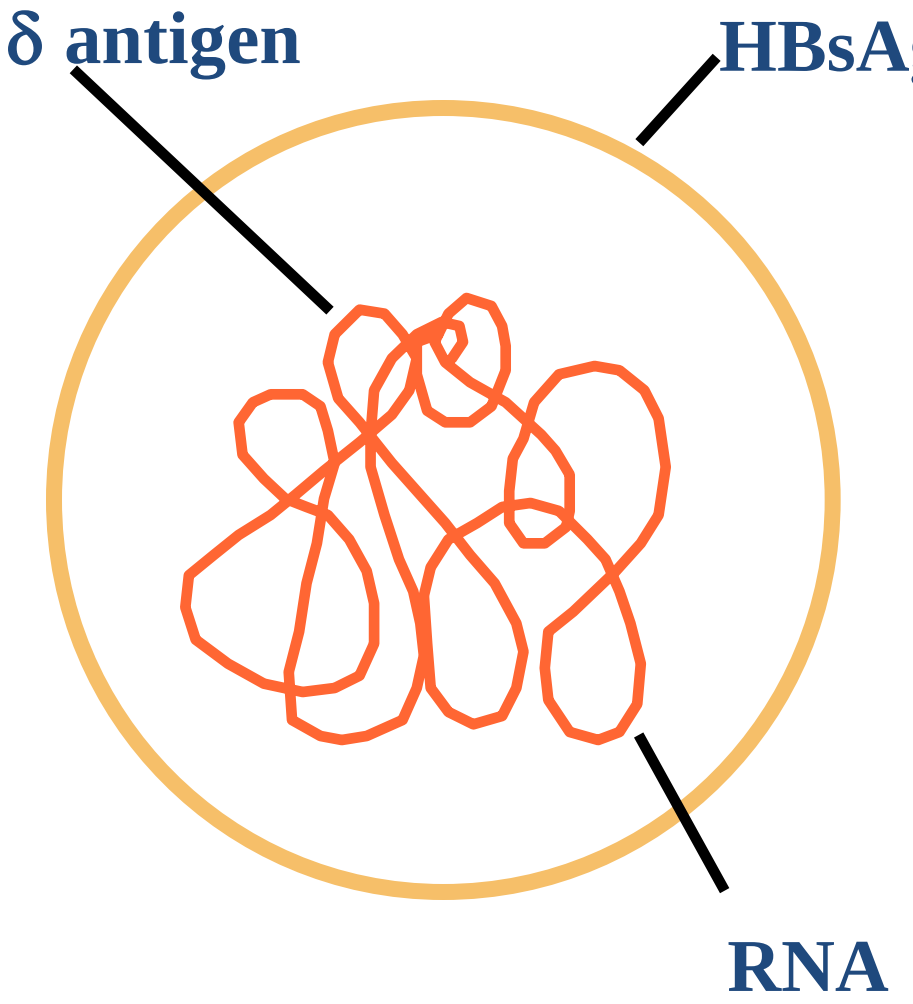
National vaccination program



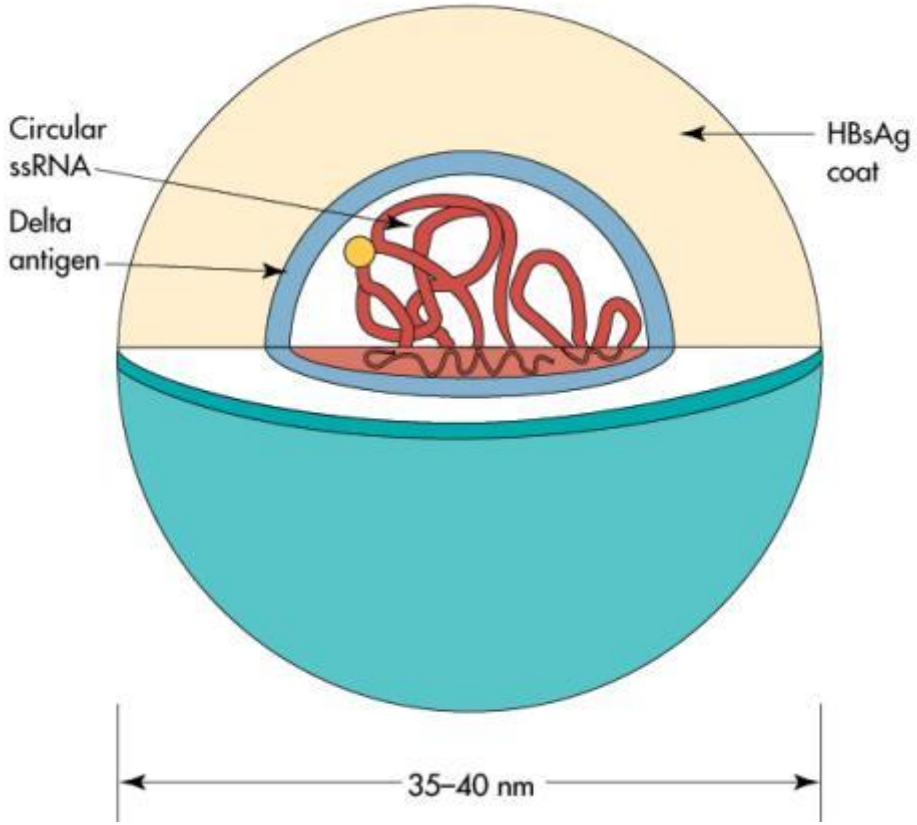
برنامج التطعيم للأطفال / الأردن

أقرب وقت بعد الولادة،يعطى مطعوم السل (BCG)
على عمر شهرين (٦١يوم)يعطى الجرعة الأولى من مطعوم التهاب الكبد نوع ب + الجرعة الأولى من المطعوم الخماسي المحسن الذي يتكون من :المطعوم الثلاثيDaPT (الدفتيريا والسعال الديكي اللاخلوي والكزاز)+مطعوم المستدمية النزلية نوع ب ومطعوم الشلل المقتول(IPV)
على عمر ٣ شهور (٦١يوم)يعطى الطفل الجرعة الثانية من مطعوم التهاب الكبد نوع ب + الجرعة الثانية من المطعوم الخماسي المحسن الذي يتكون من : المطعوم الثلاثيDaPT (الدفتيريا والسعال الديكي اللاخلوي والكزاز) + مطعوم المستدمية النزلية نوع ب ومطعوم الشلل المقتول (IPV) بالإضافة الى جرعة من مطعوم الشلل الفموي(OPV)
على عمر ٤ شهور (١٢١ يوم)يعطى الطفل الجرعة الثانية من مطعوم التهاب الكبد نوع ب + الجرعة الثالثة من المطعوم الخماسي المحسن الذي يتكون من:المطعوم الثلاثي DaPT(الدفتيريا والسعال الديكي اللاخلوي والكزاز)+ مطعوم المستدمية النزلية نوع ب ومطعوم الشلل المقتول(IPV) بالإضافة الى جرعة من مطعوم الشلل الفموي(OPV)
على عمر ٩ شهور (بداية الشهر العاشر) يعطى الطفل - مطعوم الحصبة Measles + مطعوم شلل الأطفال الفموي OPV
عند بلوغ الطفل عامه الأول يعطى الطفل الجرعة الأولى من المطعوم الثلاثي الفيروسي MMR (الحصبة والحصبة الألمانية والنكاف)
على عمر ١٨ شهر يعطى الطفل الجرعة المدعمة من مطعوم شلل الأطفال الفموي OPV والمطعوم الثلاثي البكتيري DPT + الجرعة الثانية من مطعوم الثلاثي الفيروسي MMR

Hepatitis D (Delta) Virus

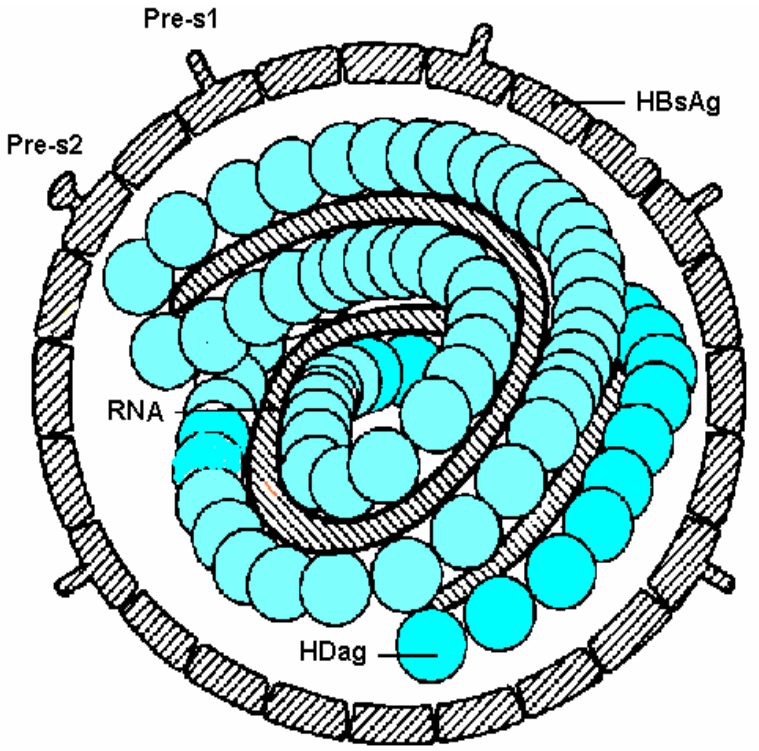


Hepatitis Delta Virion



HEPATITIS D VIRUS (HDV, DELTA AGENT)

VIRION: spherical, 36-38 nm, HBV capsid, HDV nucleoprotein
NUCLEIC ACID: (-) ss RNA, circular
Satellite virus : replicates only in the presence of HBV

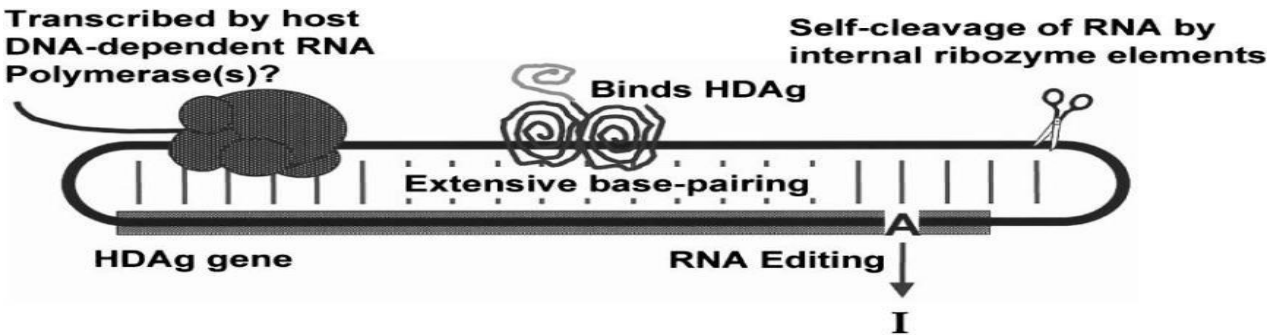


Hepatitis D Virus

- The delta agent is a defective virus which shows similarities with the viroids in plants.
- The agent consists of a particle 35 nm in diameter consisting of the delta antigen surrounded by an outer coat of HBsAg.
- The genome of the virus is very small and consists of a single-stranded RNA
- HDV genome is not capable of encoding an RNA polymerase
- Replicates in the nucleus using the cellular machinery

Hepatitis D Virus replication

- Entry of HDV into hepatocytes
- Lacks RNA polymerase; uses cellular RNA polymerase II to synthesis mRNA and RNA genome in the nucleus
- It is unique for an RNA virus to replicate in the nucleus without encoding its own RNA polymerase
- The extensive base-pairing in some regions of the HDV genome allows the cellular RNA polymerase to bind the base-paired RNA sequences, as RNA polymerase binds to DNA sequences, and to transcribe HDV mRNA.
- The RNA genome further forms a ribozyme structure that allows self-cleaving of the RNA genome to generate mRNA.
- The delta capsid antigens are synthesized and associate with HDV circular RNA genomes followed by acquiring an envelope from endoplasmic reticulum or Golgi apparatus containing HBsAg.
- The presence of HBsAg is essential for assembly of HDV virions.



Hepatitis D Virus-Epidemiology

- It is most prevalent in groups with high risk for developing hepatitis B
- It is most common in the Middle East, parts of Africa and South America
- Modes of Transmission
  - Percutaneous exposures
  - Injecting drug use
  - Permucosal exposures sex contact
  - Vertical transmission can also occur

Hepatitis D - Clinical Features

- Coinfection

  Severe acute disease indistinguishable from acute hepatitis A and B, but may manifest as second rise in liver enzymes (AST, ALT).

  Low risk of chronic infection.

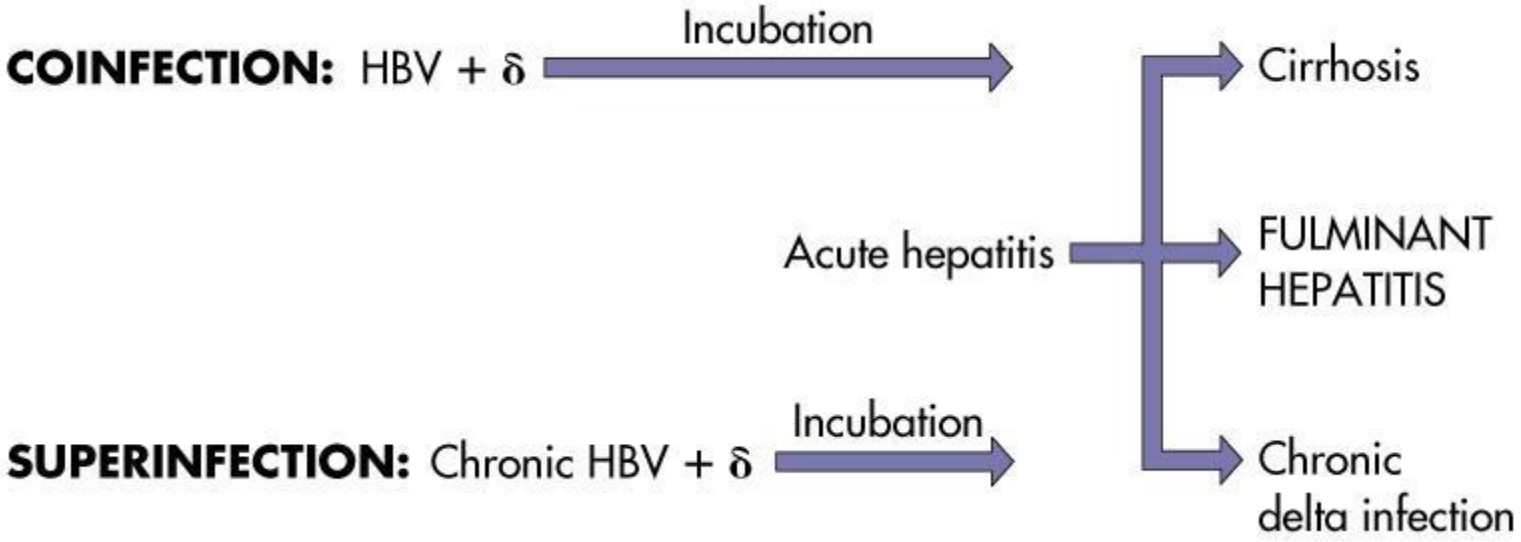
- Superinfection

  Relapse of jaundice

  Usually develop chronic HDV infection.

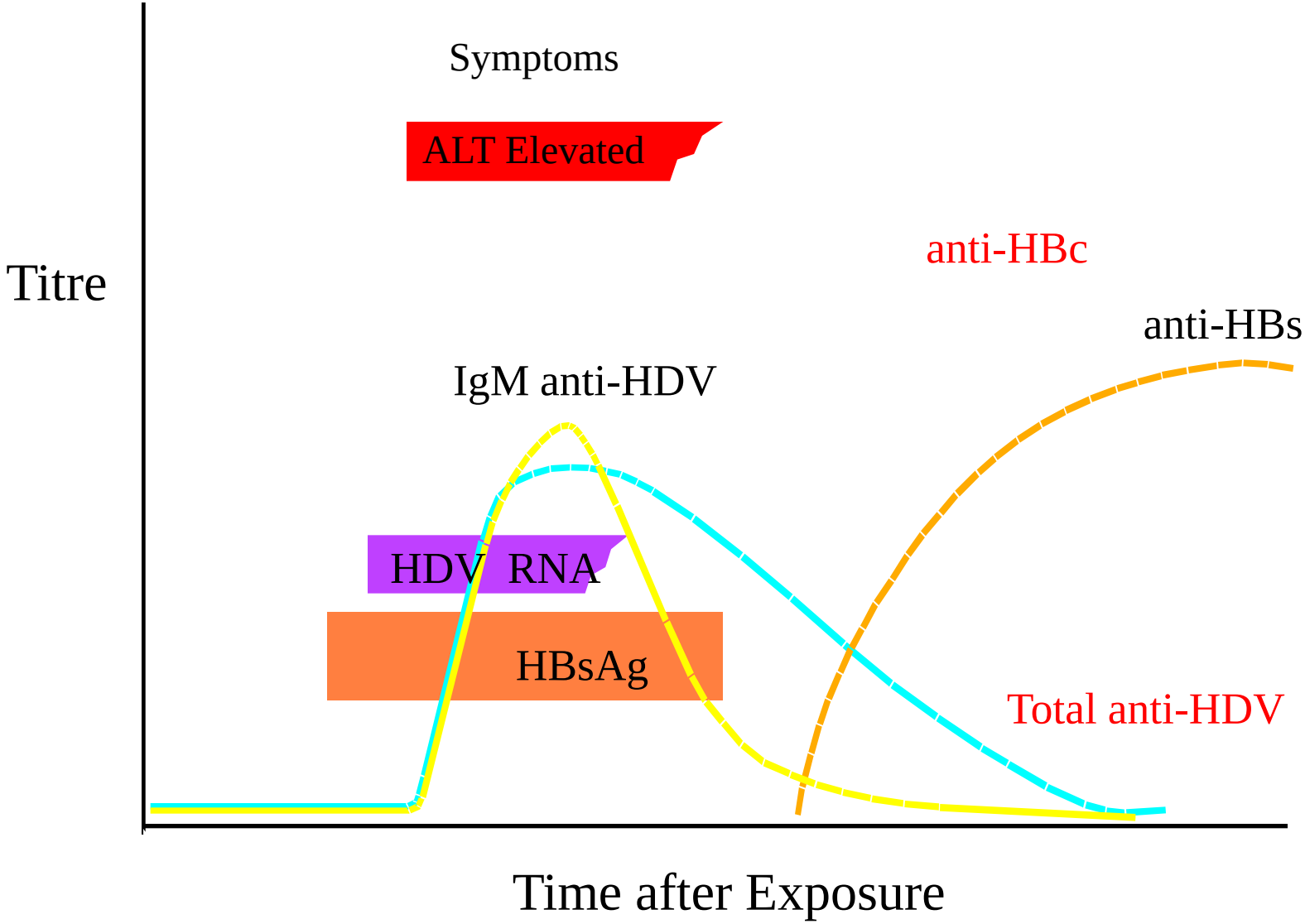
  High risk of severe chronic liver disease with 20% mortality.

Consequences of hepatitis B and delta virus infection



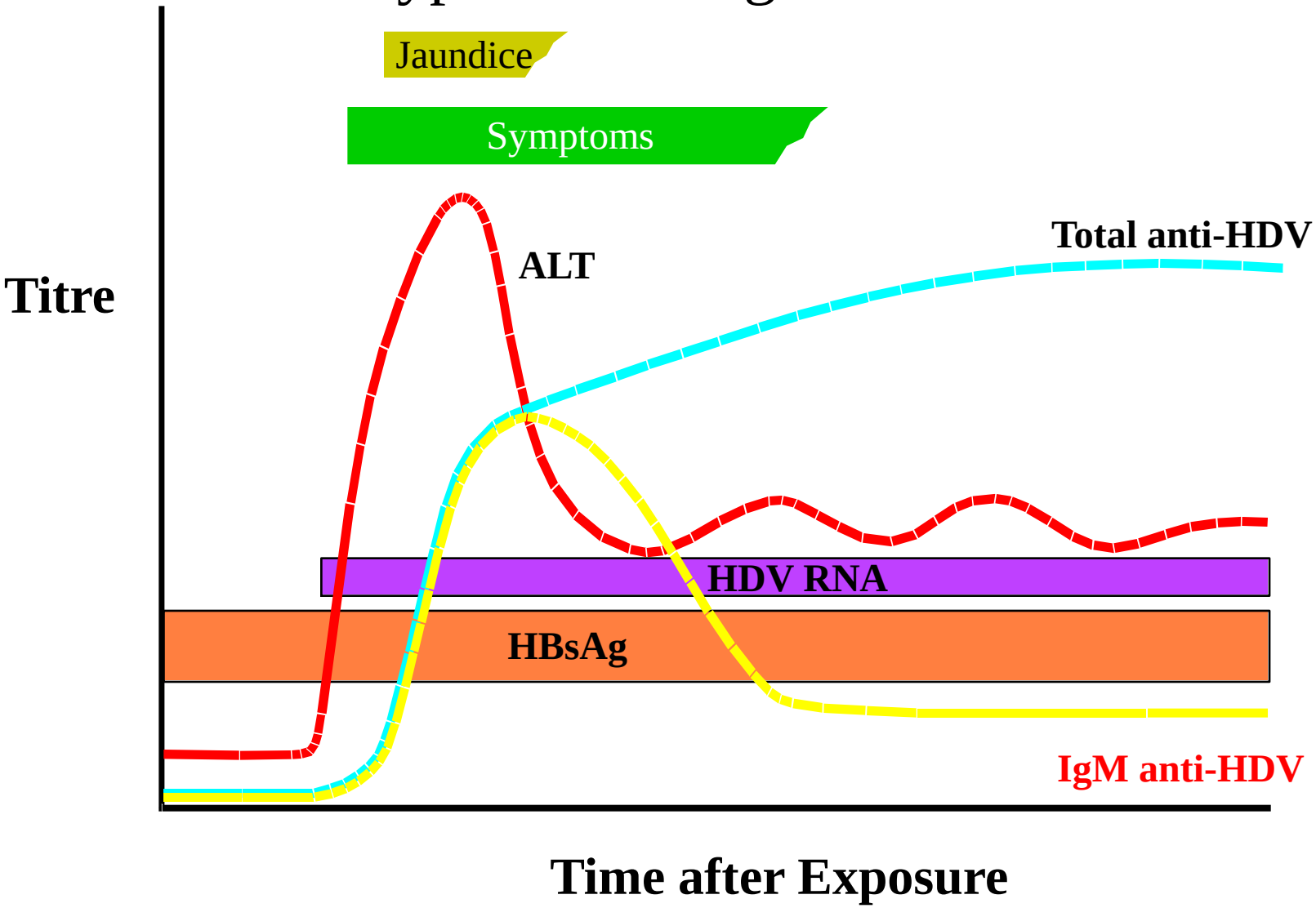
HBV - HDV Coinfection

Typical Serologic Course



HBV – HDV Superinfection

Typical Serologic Course



Treatment and Prevention

- Interferon and anti-HBV drugs are not active against hepatitis D
- HBV-HDV Coinfection

  Pre or post exposure prophylaxis to prevent HBV infection.
- HBV-HDV Superinfection

  Education to reduce risk behaviors among persons with chronic HBV infection:
  - Blood, organ and tissue donation prohibited
  - Safe sex
  - decrease use of contaminated needles and use of needle safety devices by health care workers.