# HEPATITIS VIRUSES

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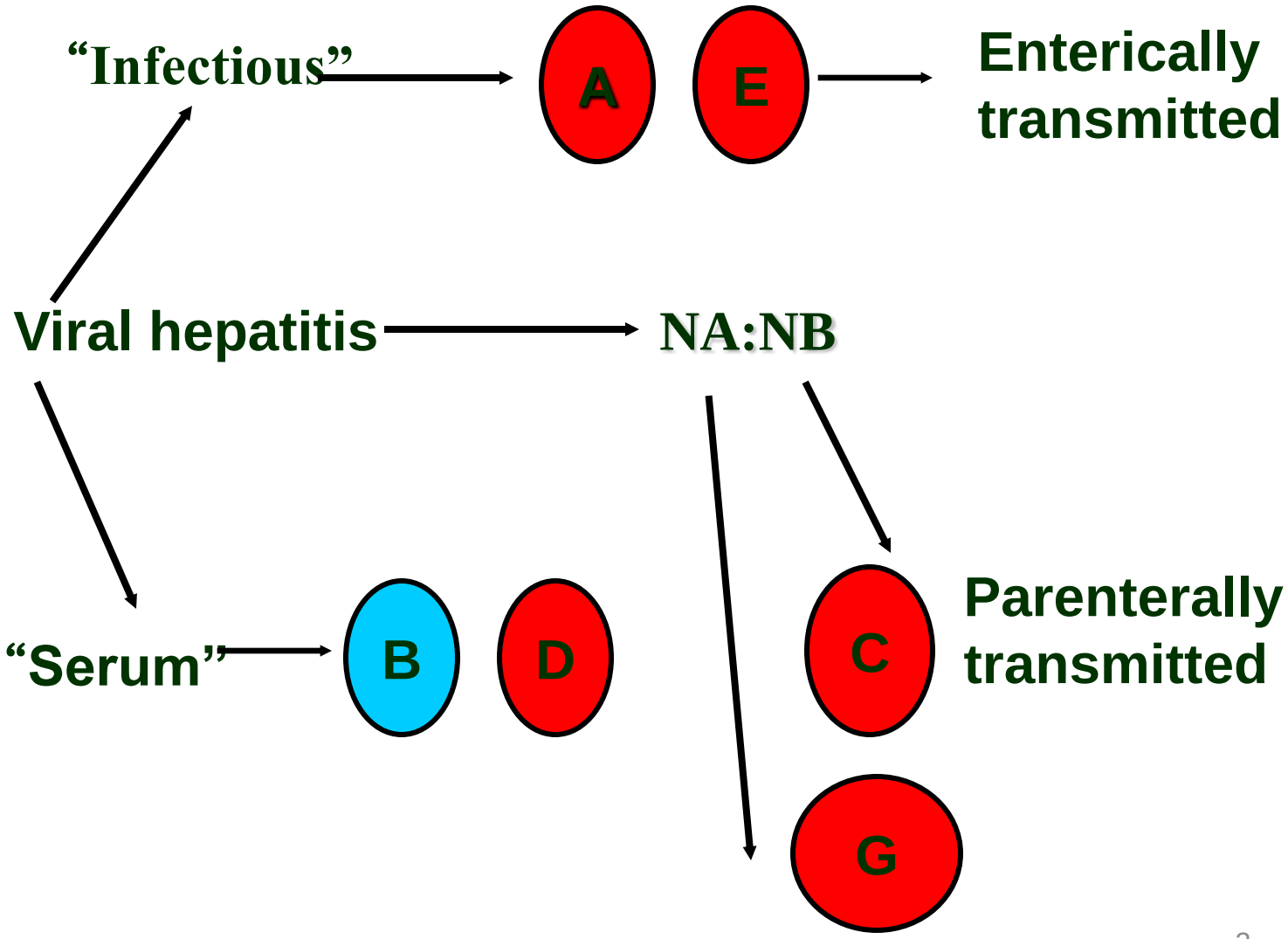
- **Hepatitis A (HAV) Picornaviridae (1973)**
- **Hepatitis B (HBV) Hepadnaviridae (1970)**
- **Hepatitis C (HCV) Flaviviridae (1988)**
- **Hepatitis D (HDV) ? (1977)**
- **Hepatitis E (HEV) (Caliciviridae) (1983), Hepeviridae**
- **Hepatitis G (HGV) Flaviviridae (1995)**

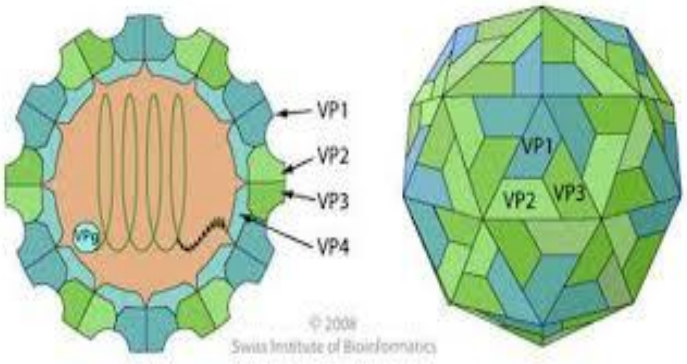
# Viral Hepatitis - Historical Perspectives



| | A | B | C | D | E |
|---|---|---|---|---|---|
| Type | SS RNA | DS DNA | RNA | SS RNA | RNA |
| Source of virus | Feces | Blood<br>Blood derived<br>Body fluids | Blood<br>Blood derived<br>Body fluids | Blood<br>Blood derived<br>Body fluids | Feces |
| onset | Usually sudden | Usually slow | variable | Insidious | |
| Incubation Period | 15-45 | 1-6 months mean 60-90 | 1-5 months mean 50 | 30-45 | 21-60 |
| Transmission | FO,P | S, P | S, P | S, P | FO |
| Age | Children, young adults | All ages | All ages | All ages | Young adults |
| Chronic Infection | No | Yes | Yes | Yes | No |
| Carrier state | No | 10 | 85 | 50-70 | No |
| Prevention | Pre Post Exposure Immunization | Pre Post Exposure Immunization Blood donor Screening | Blood donor screening | Pre Post Exposure Immunization | Ensure Safe Drinking water |
| Vaccine | Y | Y | N | Y | N |

# Hepatitis A Virus

- Naked +ve sense, single stranded RNA virus with icosahedral symmetry




- Related to enteroviruses, formerly known as Enterovirus 72, now put in its own family: picornaviridae; genus: hepatovirus

- One stable serotype only

- Difficult to grow in cell culture: primary marmoset cell culture and also in vivo in chimpanzees and marmosets

- 4 genotypes exist, but in practice most of them are group 1

# PATHOGENESIS - HAV

Cause subacute disease in children & young adults.

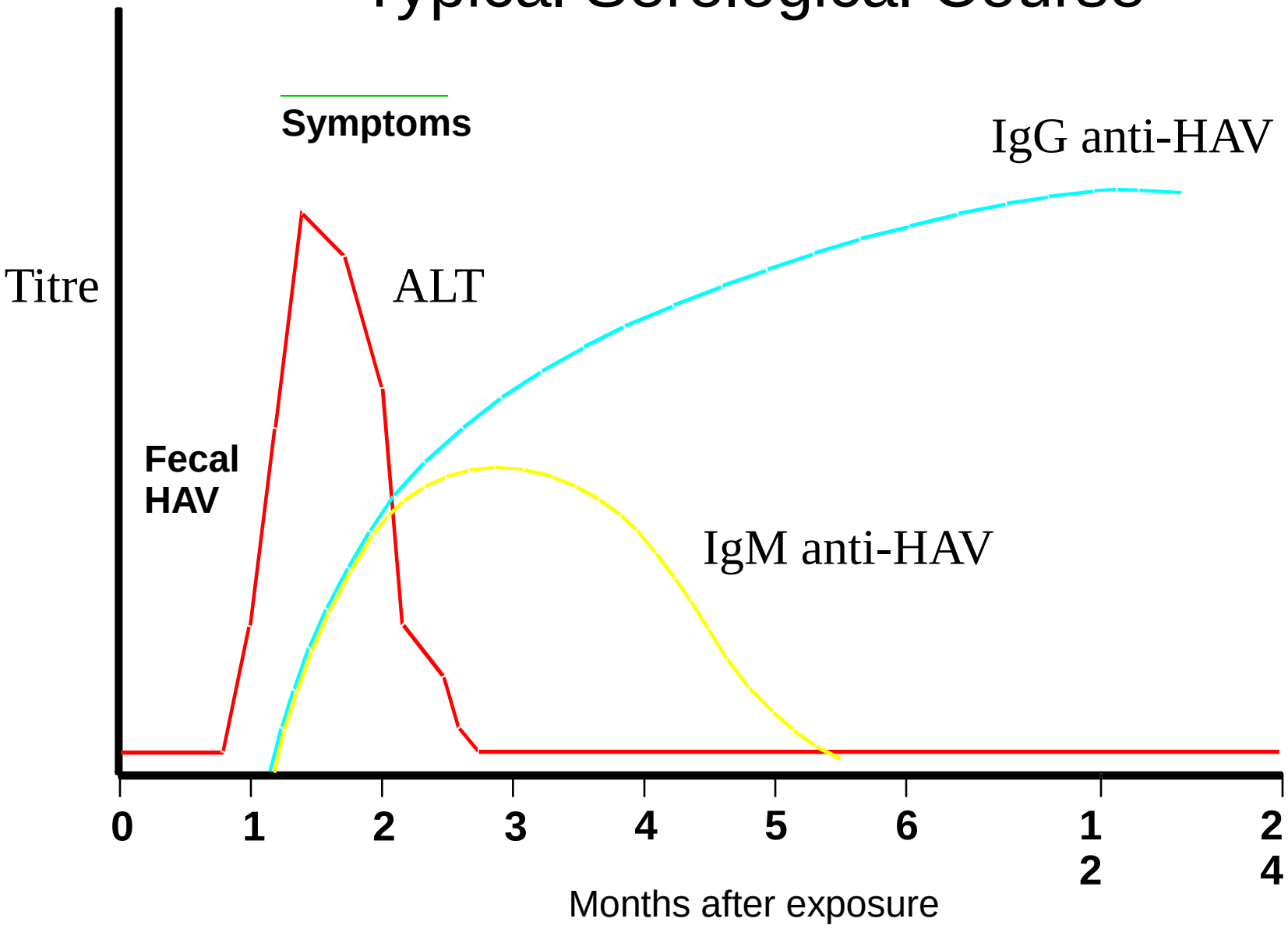
HAV invade into human body by fecal-oral route, multiplies in the intestinal epithelium & reaches the liver by hematogenous spread.

After one week, the HAV reach liver cells replicate within.Then enter intestine with bile and appear in feces.

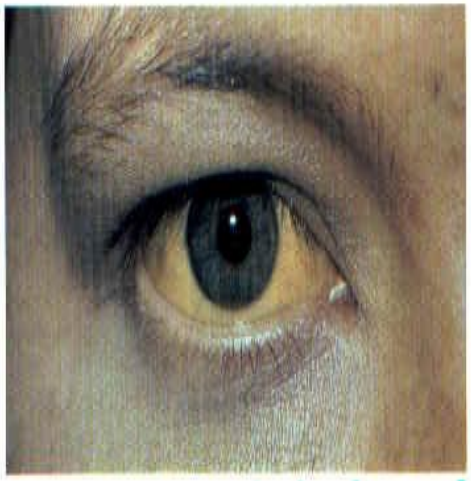
Incubation Period : 2 to 6 weeks.

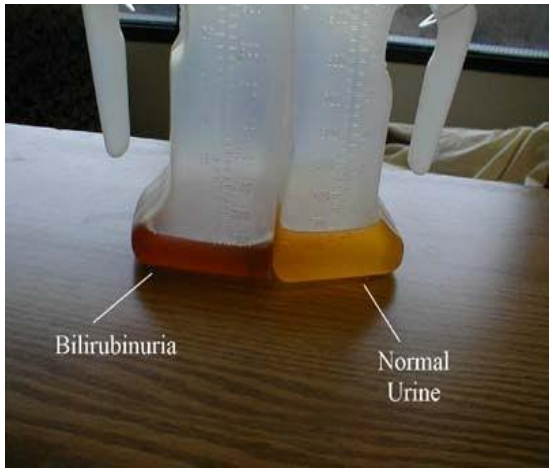
# Hepatitis A Infection

## Typical Serological Course



Prodromal or Preicteric phase :
(symptoms: fatigue, joint- and abdominal pain, malaise, vomiting, lack of appetite, hepatomegaly)
Icteric phase: Icterus: jaundice (skin, sclera, mucous membranes,
cause: elevated bilirubin level,
bilirubinuria: dark urine, pale stool)



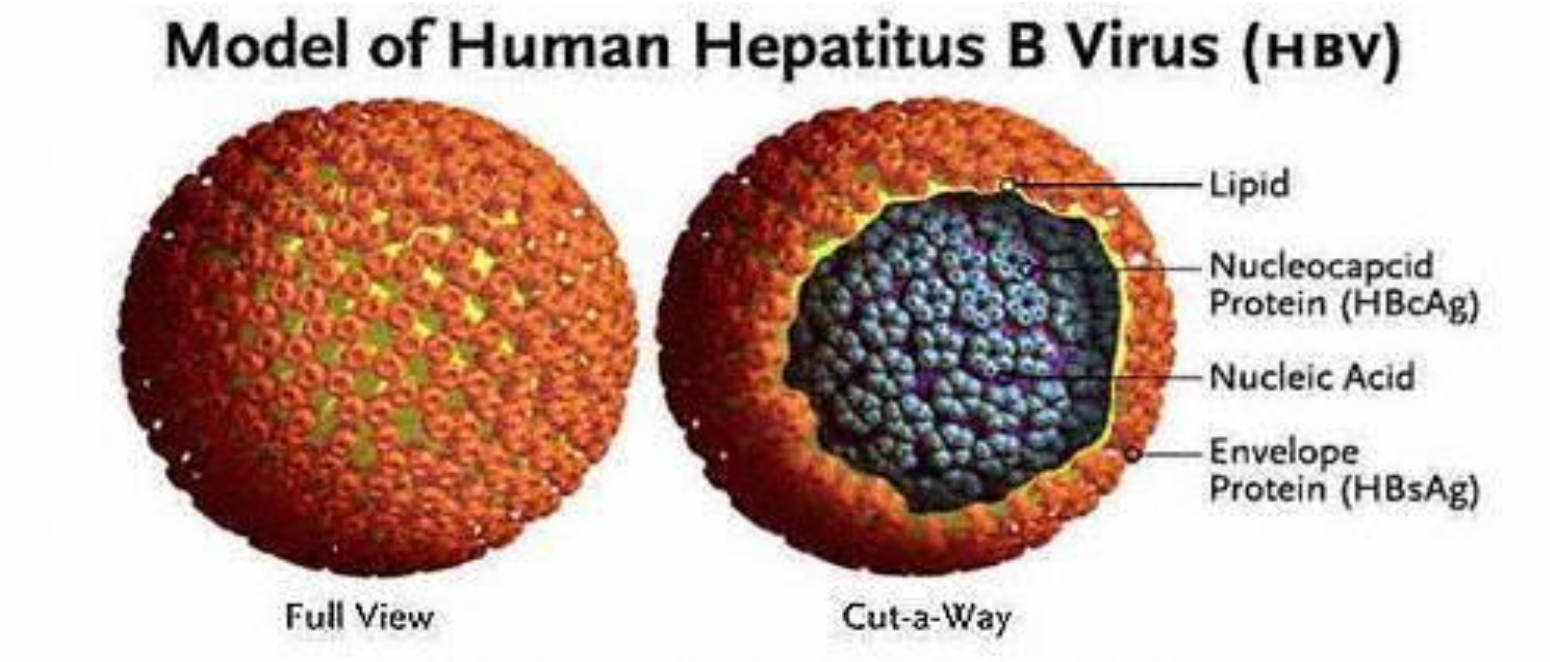



# Treatment and prevention

- No specific treatment
- Supportive: adequate nutrition and rest

- Passive immunization (ISG)
  - Protective if given before or during incubation period
- Active immunization
  - Formalin killed HAV
  - 100% protective
  - 2 doses 6-12 months apart

# Hepatitis B Virus

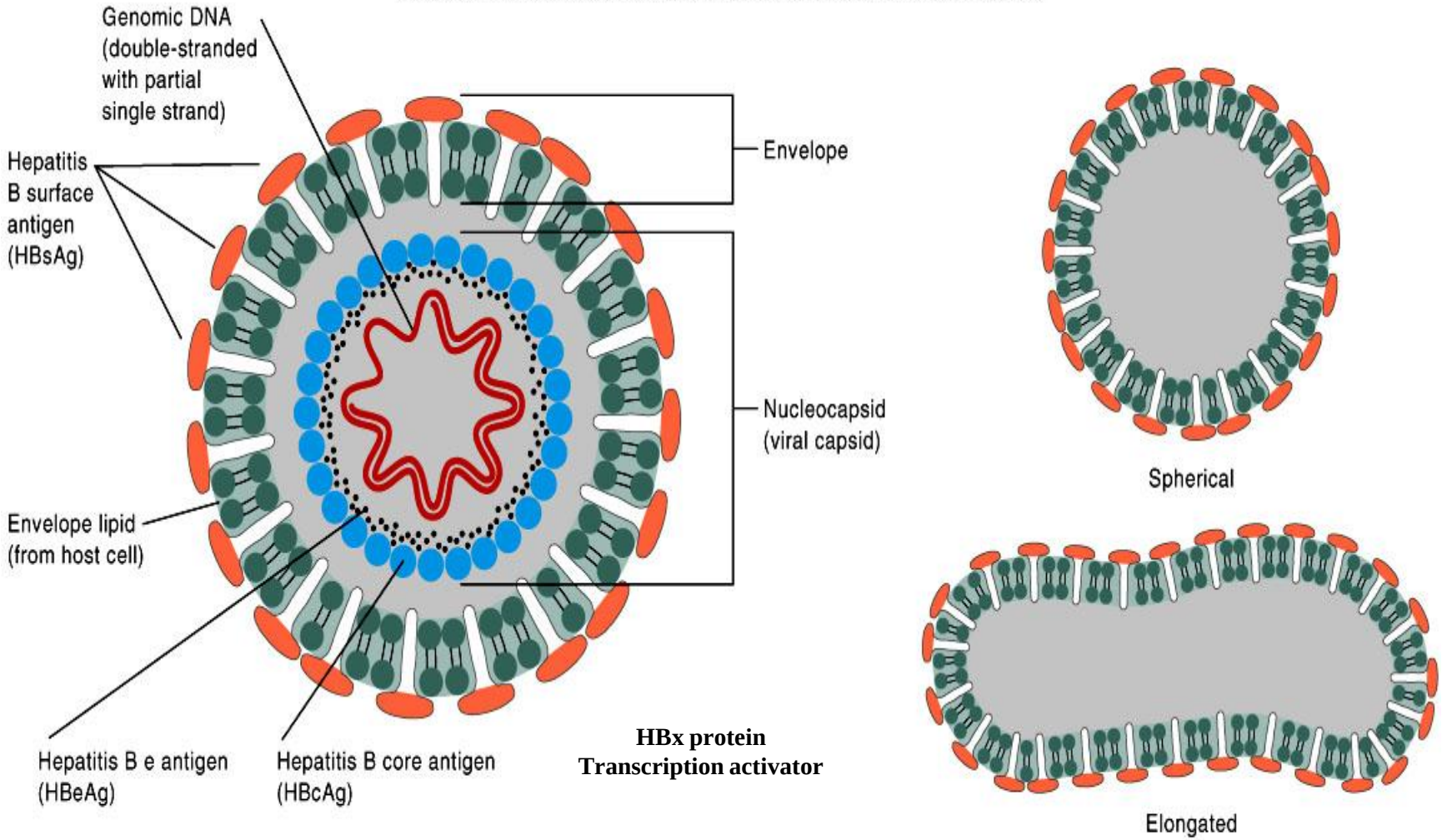


# Properties of HBV

- 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

# 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

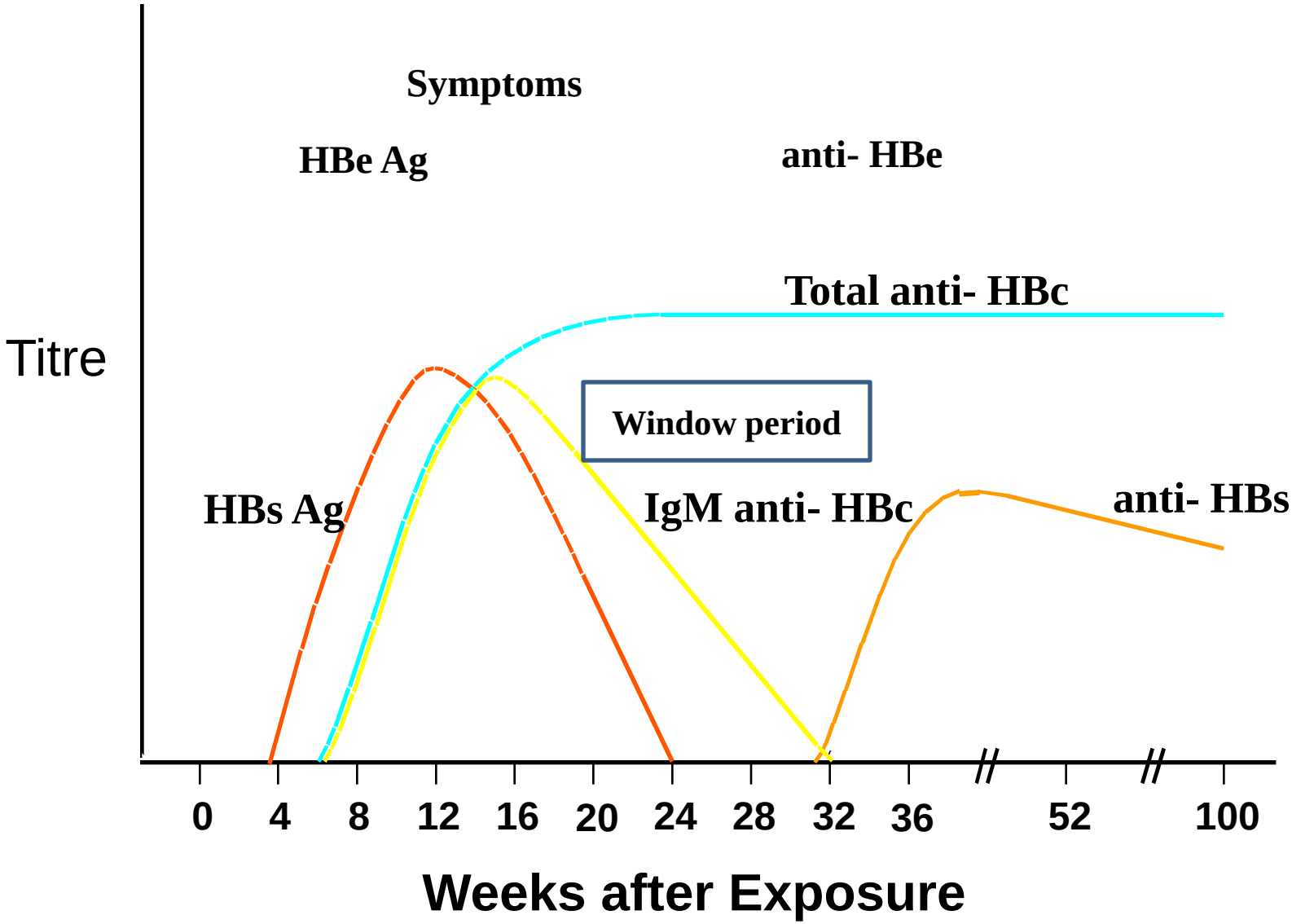
- 50% of children born to mothers with chronic HBV in the US are Asian American

# Pathogenesis & Immunity

- Virus enters hepatocytes via blood
- Immune response (cytotoxic T cell) to viral antigens expressed on hepatocyte cell surface responsible for clinical syndrome
- 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 (IgG anti-HBs)
- Hepatitis B e Ab indicates low transmissibility

# Acute Hepatitis B Virus Infection with Recovery

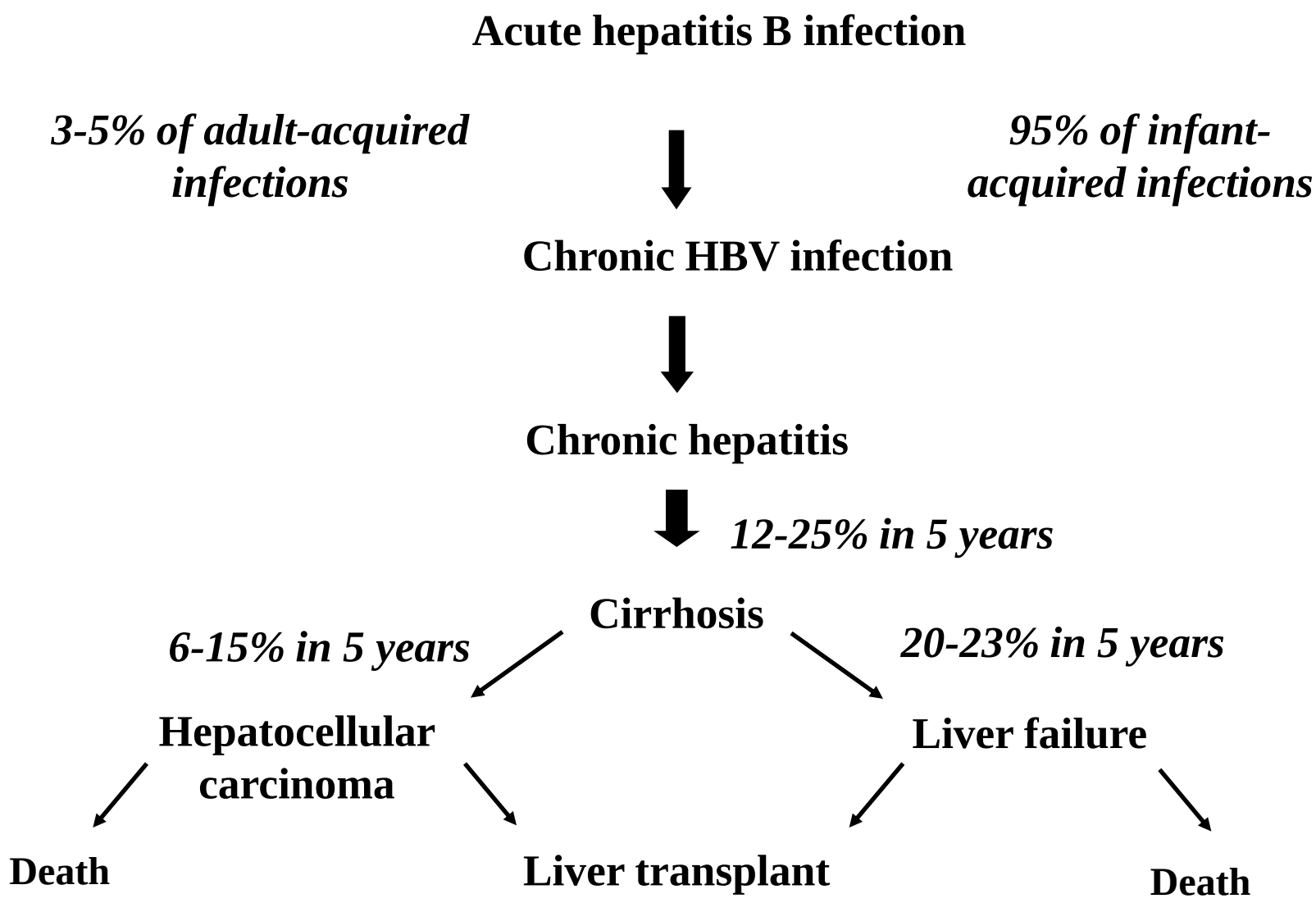
## Typical Serologic Course



# 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.

# Possible Outcomes of HBV Infection



# 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 |

# 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

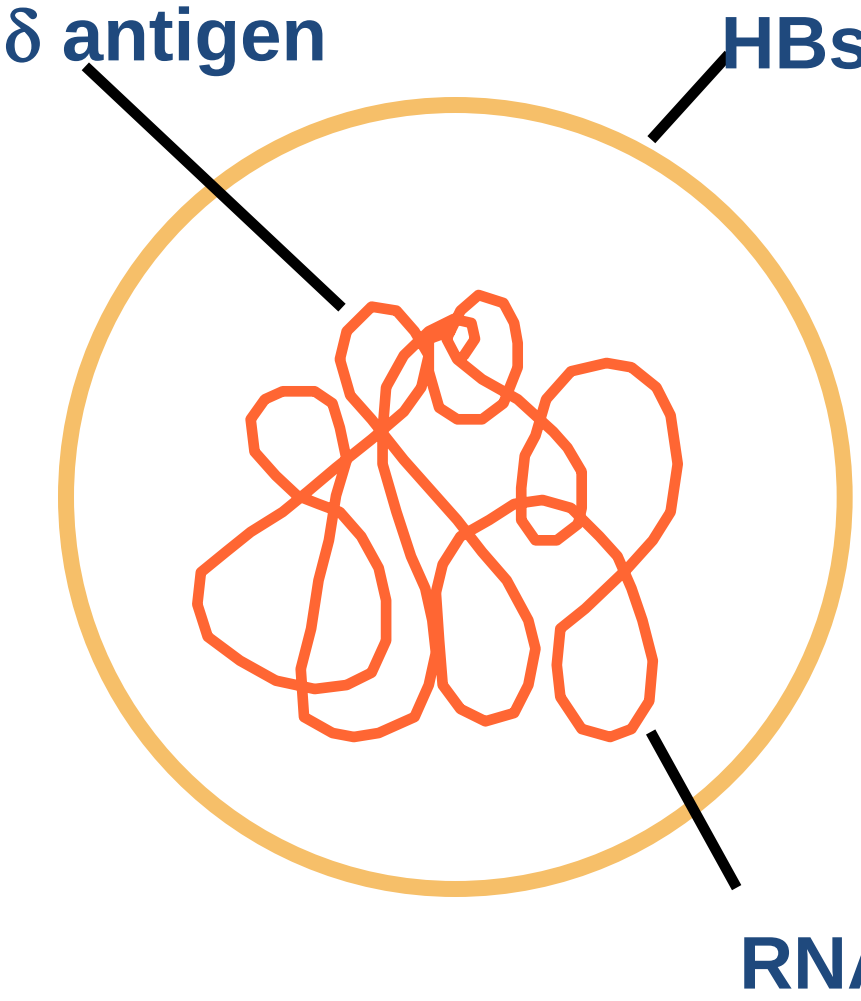
- Vaccination - highly effective recombinant vaccines are now available. Vaccine can be given to those who are at increased risk of HBV infection such as health care workers. It is also given routinely to neonates as universal vaccination in many countries.
- Hepatitis B Immunoglobulin - HBIG may be 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

# Hepatitis D (Delta) Virus




# 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
- Replicates in the nucleus using the cellular machinery

# Hepatitis D - Clinical Features

- Coinfection

  severe acute disease.

  low risk of chronic infection.

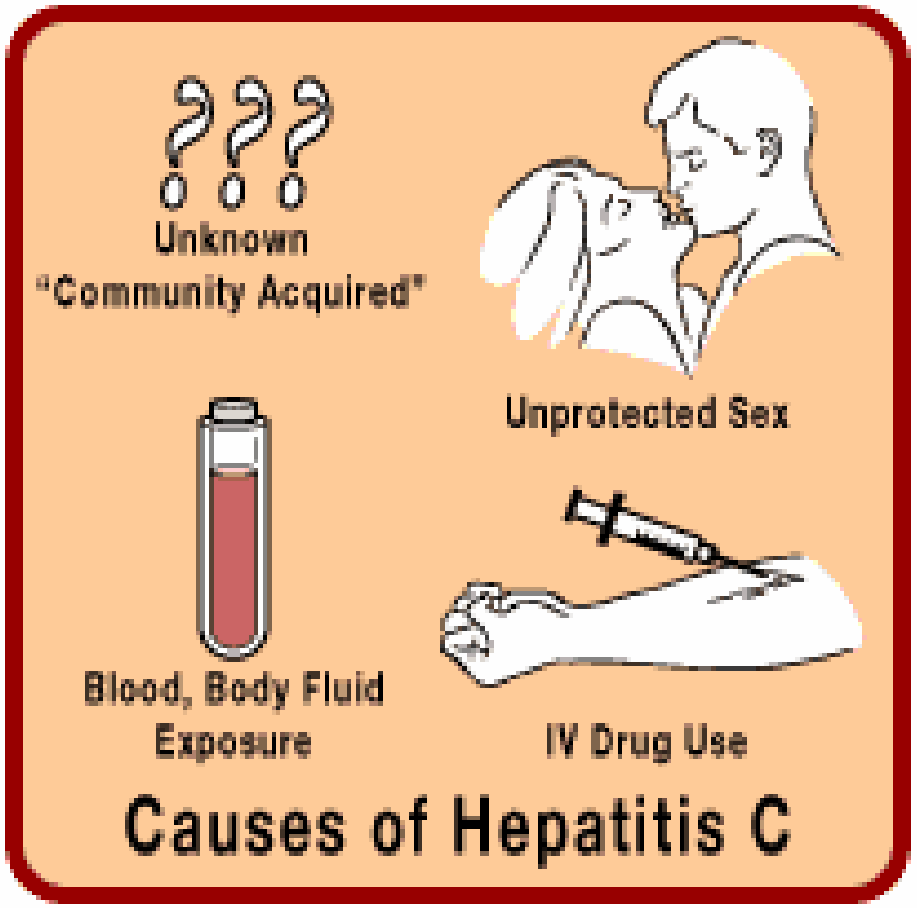
- Superinfection

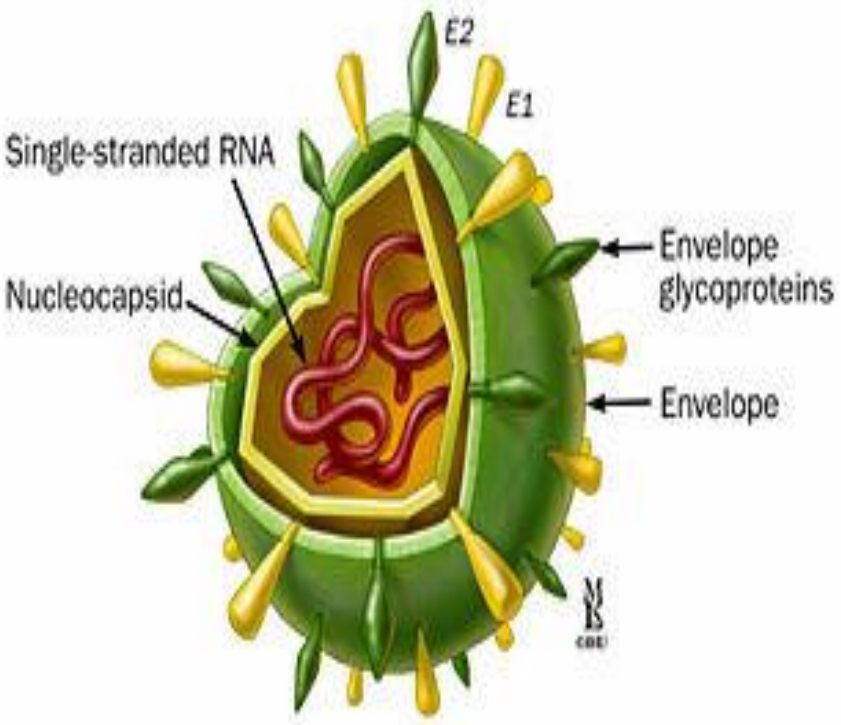
  usually develop chronic HDV infection.

  high risk of severe chronic liver disease.

  may present as an acute hepatitis.

# HEPATITIS C VIRION: spherical, icosahedral, NUCLEIC ACID: ss (+) RNA



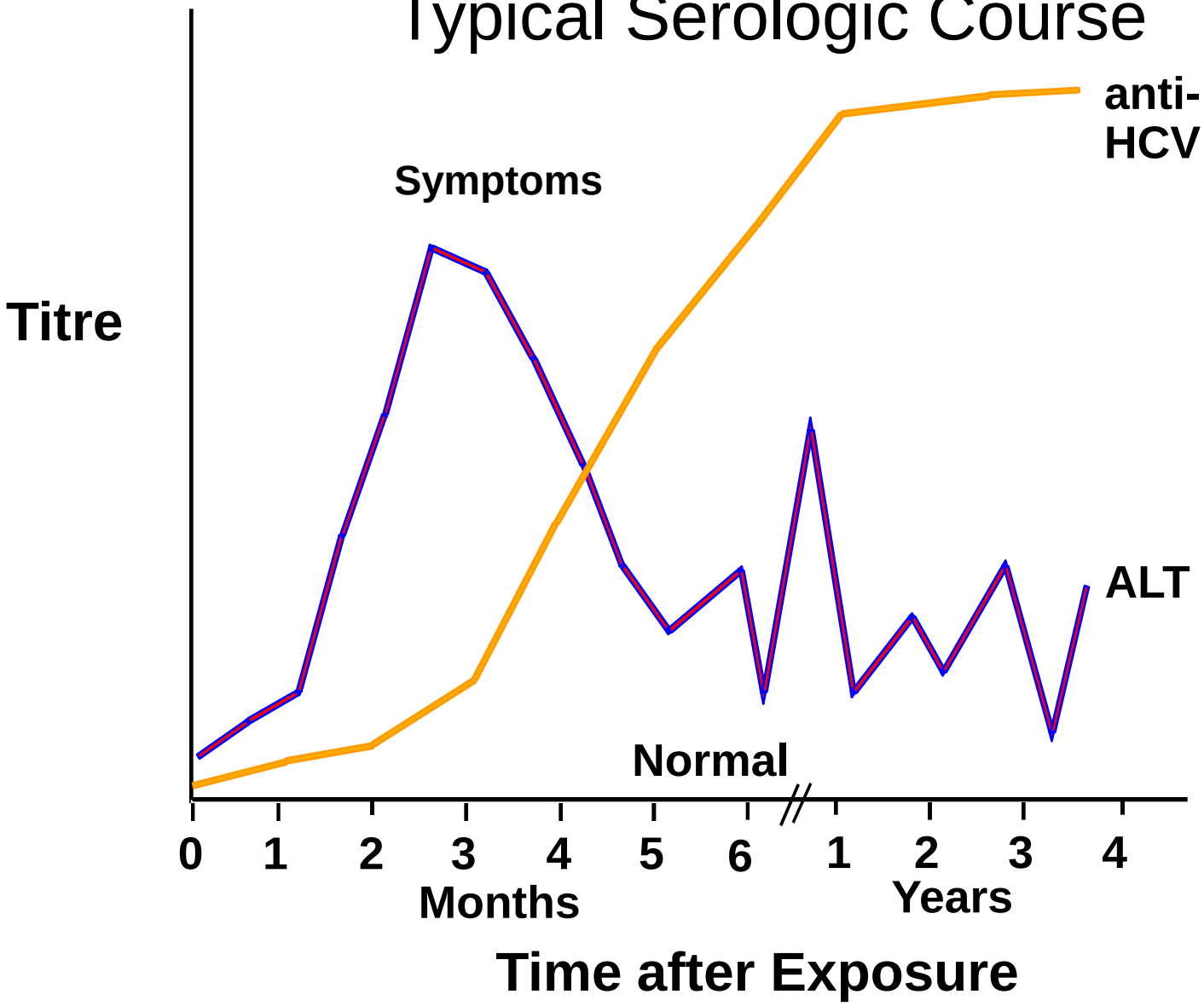
# Chronic Hepatitis C Infection

- The spectrum of chronic hepatitis C infection is essentially the same as chronic hepatitis B infection.

- All the manifestations of chronic hepatitis B infection may be seen, albeit with a lower frequency i.e. chronic persistent hepatitis, chronic active hepatitis, cirrhosis, and hepatocellular carcinoma.

# Hepatitis C Virus Infection

## Typical Serologic Course



# Laboratory Diagnosis

- HCV antibody - generally used to diagnose hepatitis C infection. Not useful in the acute phase as it takes at least 4 weeks after infection before antibody appears.

- HCV-RNA - various techniques are available e.g. PCR and branched DNA. May be used to diagnose HCV infection in the acute phase. However, its main use is in monitoring the response to antiviral therapy.

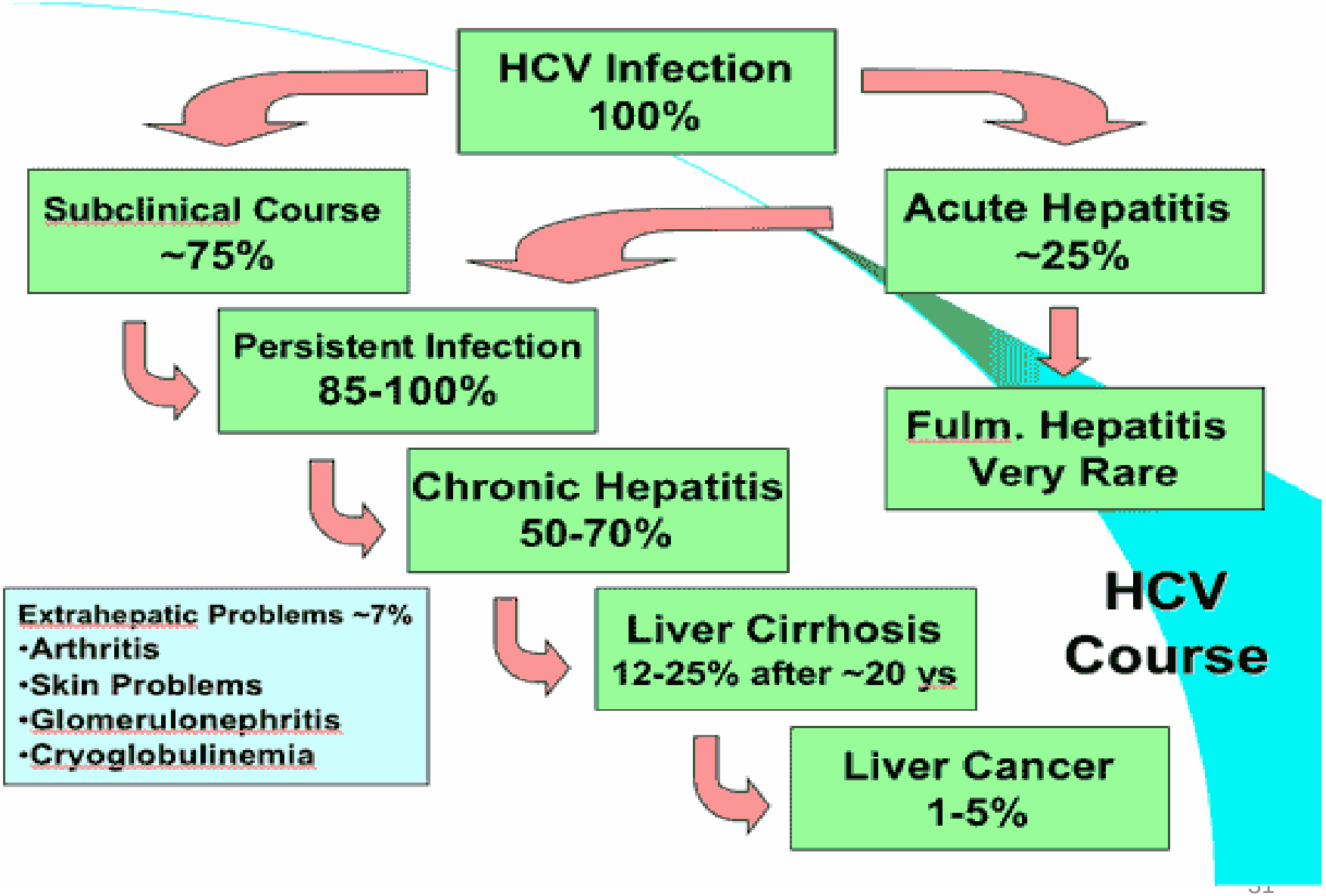
- HCV-antigen - an EIA for HCV antigen is available. It is used in the same capacity as HCV-RNA tests but is much easier to carry out.

# Treatment

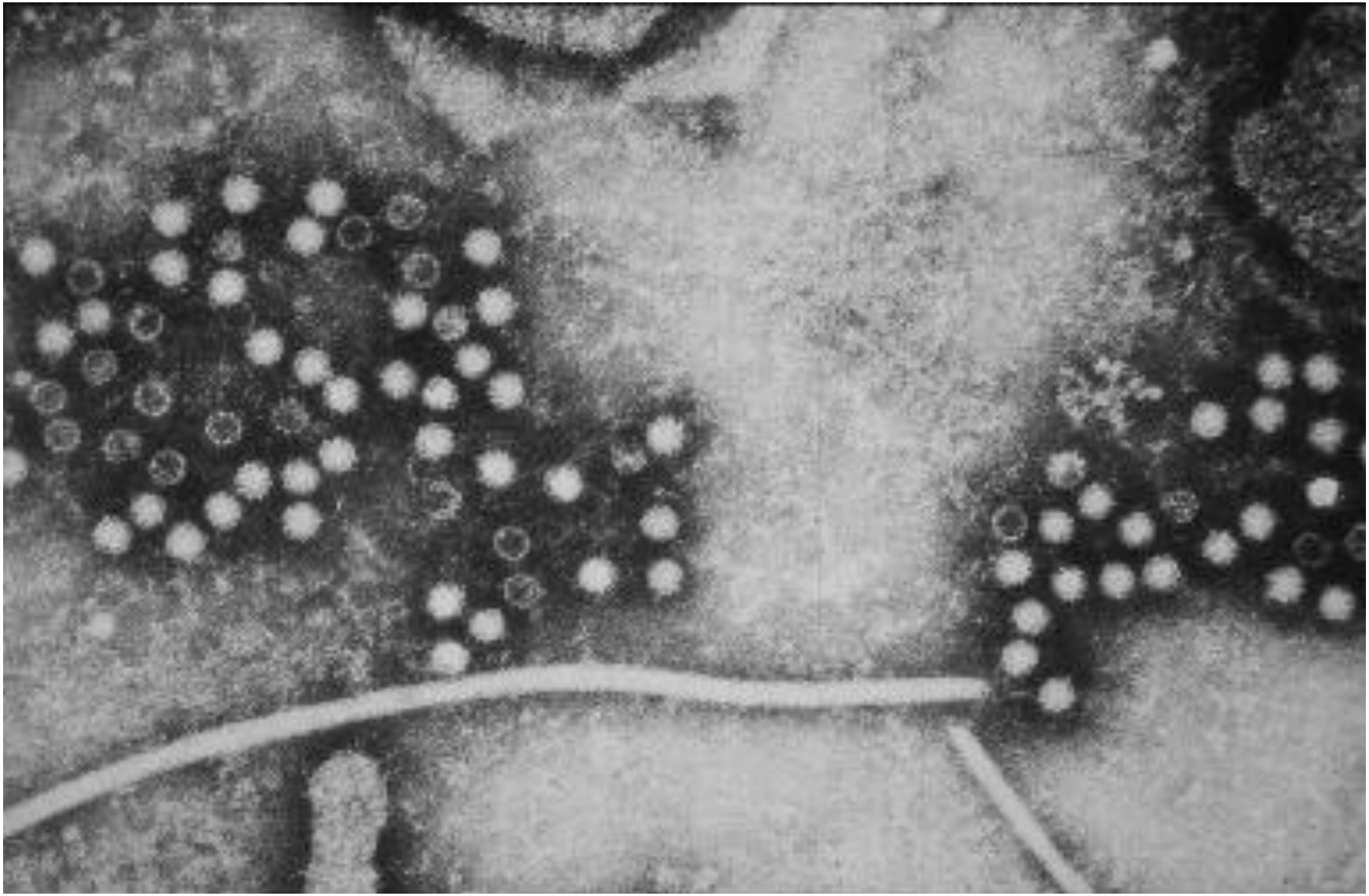
- Interferon - may be considered for patients with chronic active hepatitis. The response rate is around 50% but 50% of responders will relapse upon withdrawal of treatment.

- Ribavirin - there is less experience with ribavirin than interferon. However, recent studies suggest that a combination of interferon and ribavirin is more effective than interferon alone.

# OUTCOMES of HCV hepatitis



# Hepatitis E Virus

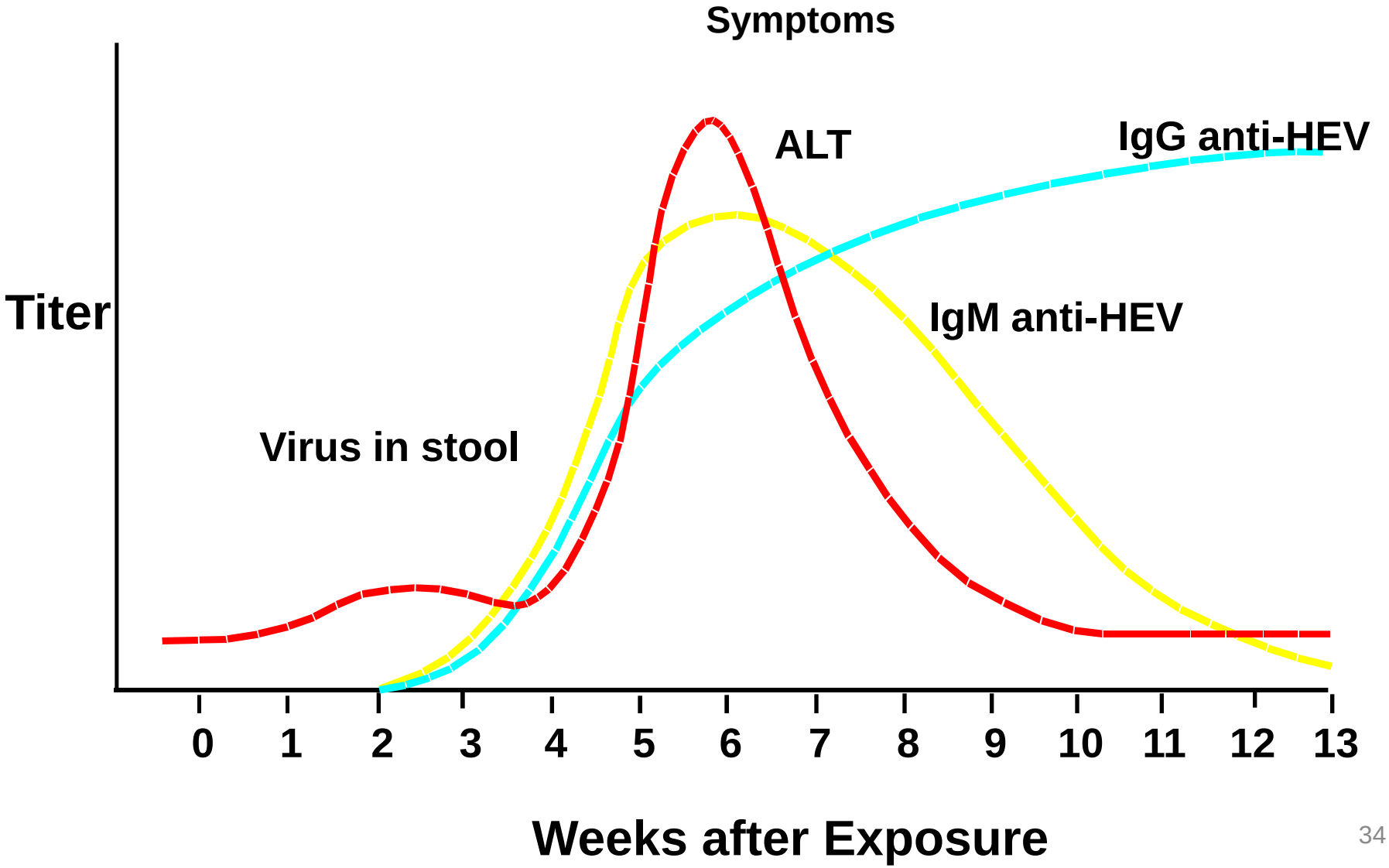


# Hepatitis E Virus

- Calicivirus-like viruses
- unenveloped RNA virus, 32-34nm in diameter
- +ve stranded RNA genome, 7.6 kb in size.
- very labile and sensitive
- Was cultured only recently

# Hepatitis E Virus Infection

## Typical Serologic Course



# 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.

# Prevention and Control Measures for Travelers to HEV-Endemic Regions

- Avoid drinking water (and beverages with ice) of unknown purity, uncooked shellfish, and uncooked fruit/vegetables not peeled or prepared by traveler.
- Unknown efficacy of IG prepared from donors in endemic areas.
- No Vaccine

# HEPATITIS G VÍRUS

FLAVIRUS: similar morphology and genome

◊ in risk groups: acute, chronic and fulminant hepatitis
• 10-20% infected HCV also infected with HGV

◊ transmission: blood (mother- newborn babies)

◊ prevalence is higher in HCV infected people