PSMU
Department of Microbiology, Virology and Immunology

Hepatitis viruses

For two-way communication

between the lecturer and students during the lecture, please contact the following e-mail address:

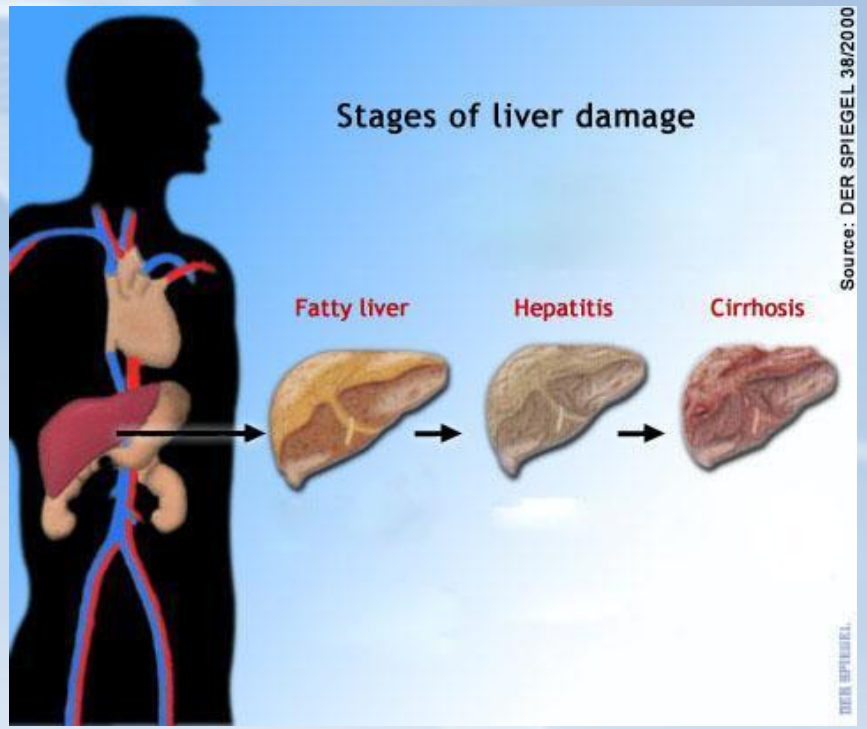
v.fedorchenko@pdmu.edu.ua

Viral Hepatitis

- A group of viruses known as the hepatitis viruses cause most cases of liver damage worldwide. Hepatitis can also be due to toxins (notably alcohol), other infections.
- Common viruses cause hepatitis include A,B,C,D,E. G .....

Viral hepatitis

- **Viral hepatitis - a group of polietiologic antroponotic Viral Diseases of liver accompanied with jaundice and characterized by different modes of pathogens transmission. These are hepatitis A, B, C, D, E, G, F, TT and so on.**



Viral hepatitis

- Social value and economic losses inflicted by viral hepatitis, high enough that defines them as a significant health issue. Every year, for example, hepatitis A sick more than 1 million people, and the number of carriers of hepatitis B virus in the world exceeds 1 billion

Type of Hepatitis

	A	B	C	D	E
Source of virus	feces	blood/ blood-derived body fluids	blood/ blood-derived body fluids	blood/ blood-derived body fluids	feces
Route of transmission	fecal-oral	percutaneous permucosal	percutaneous permucosal	percutaneous permucosal	fecal-oral
Chronic infection	no	yes	yes	yes	no
Prevention	pre/post-exposure immunization	pre/post-exposure immunization	blood donor screening; risk behavior modification	pre/post-exposure immunization; risk behavior modification	ensure safe drinking water

Viral hepatitis

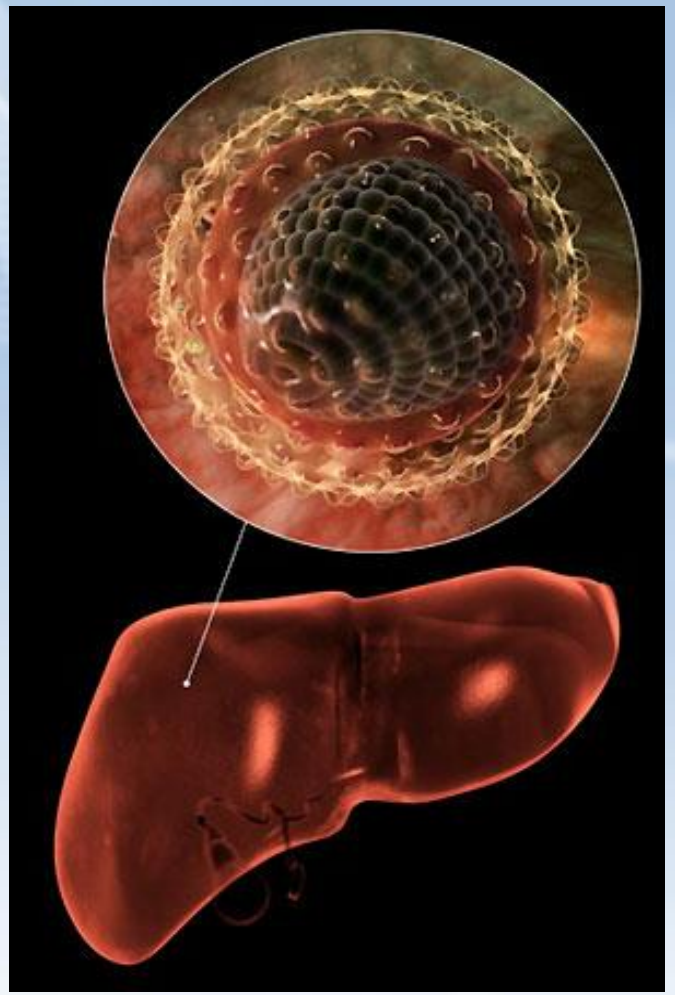
Viruses of hepatitis are invaded by more than ***two billion*** *inhabitants of the Earth. As reported Gather, DATA Such were published by World Health Organization (WHO). The day of combating hepatitis first time will be held on* ***July 28****.*

Viral hepatitis

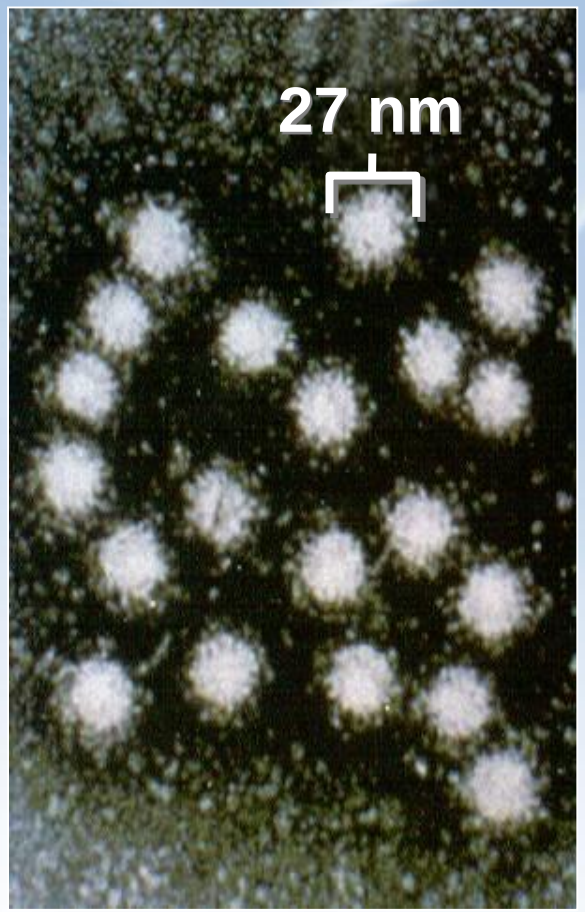
- Viruses with hepatotropic ability belonging to different taxonomic groups, but they can be divided to separate groups according to the following criteria:

- a) the type of nucleic acid - 2 groups:

- - RNA-containing viruses hepatitis - A, C, D, E and G.
- - DNA-containing viruses hepatitis - B and TT.

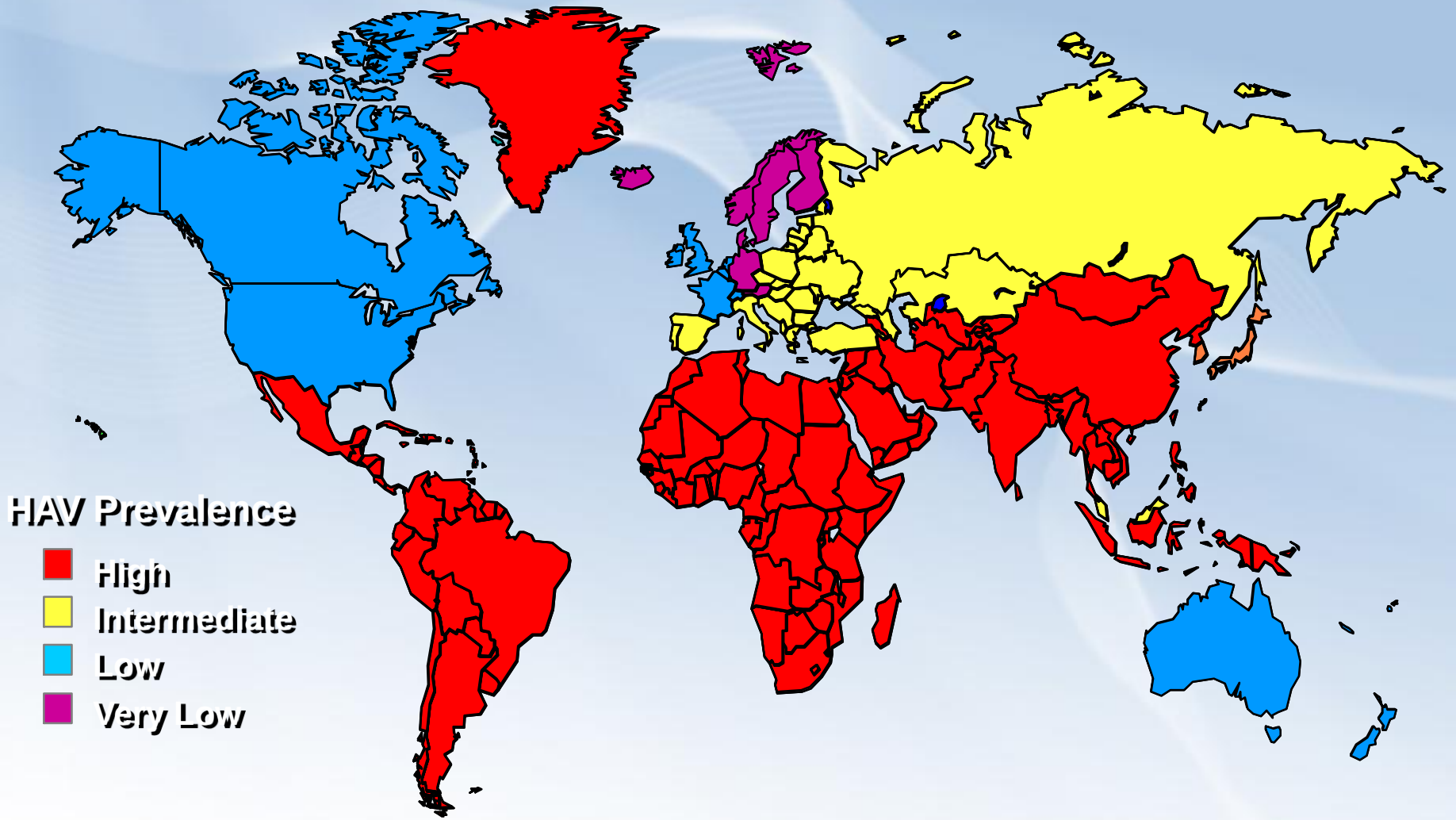


Viral hepatitis A



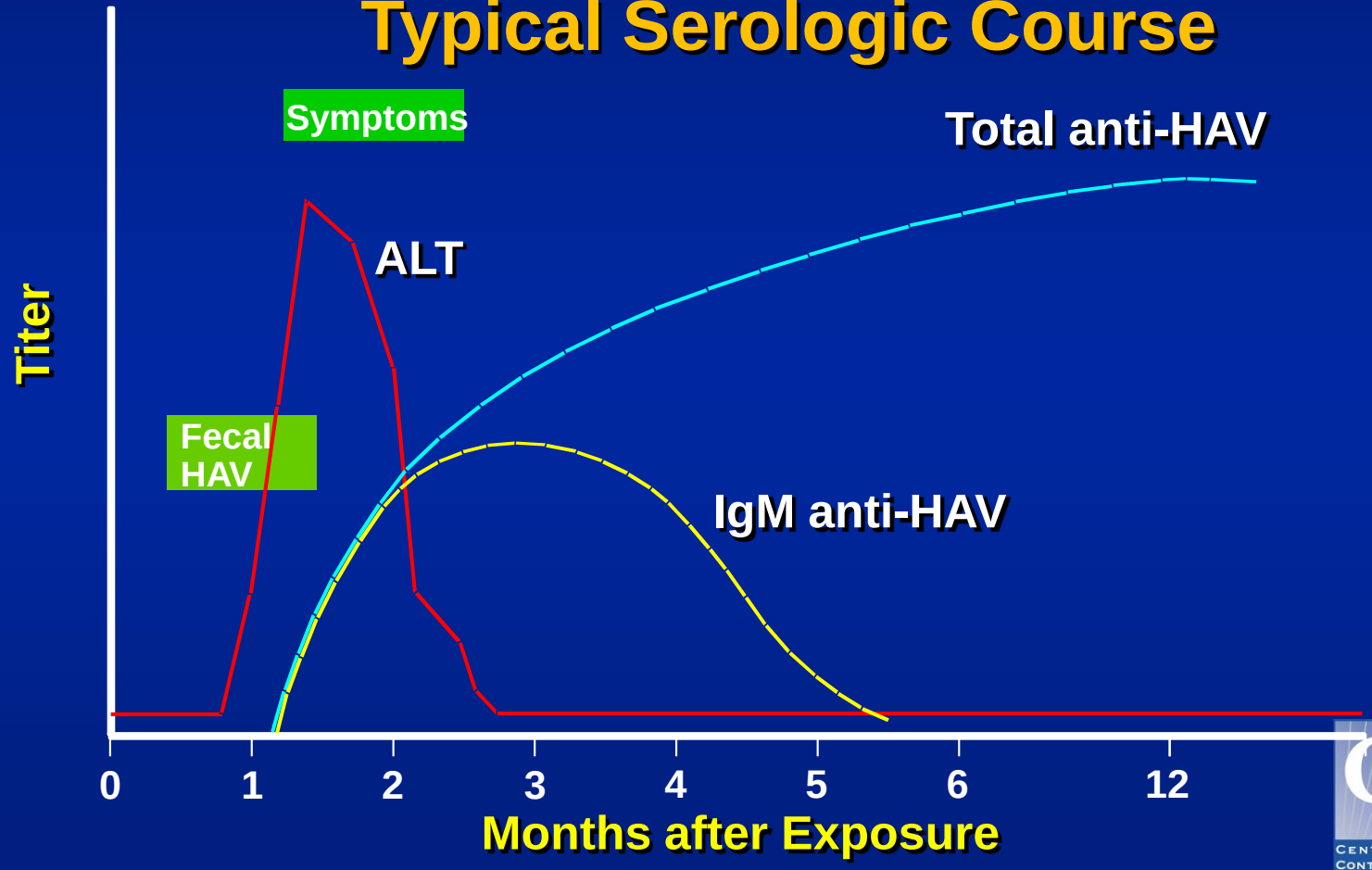
- Transmission route: fecal-oral
- Clinical presentation
  - Jaundice: Adults- 30%, Children- <5%
  - Fulminant: <1%
- Diagnostic tests
  - Acute infection: IgM anti-HAV
  - Chronic infection: Not applicable
- Immunity: IgG anti-HAV
- Case-fatality rate: 0.1 – 2.7%
- Chronic infection: None

Global Prevalence of Hepatitis A Infection



Hepatitis A Virus Infection

Typical Serologic Course

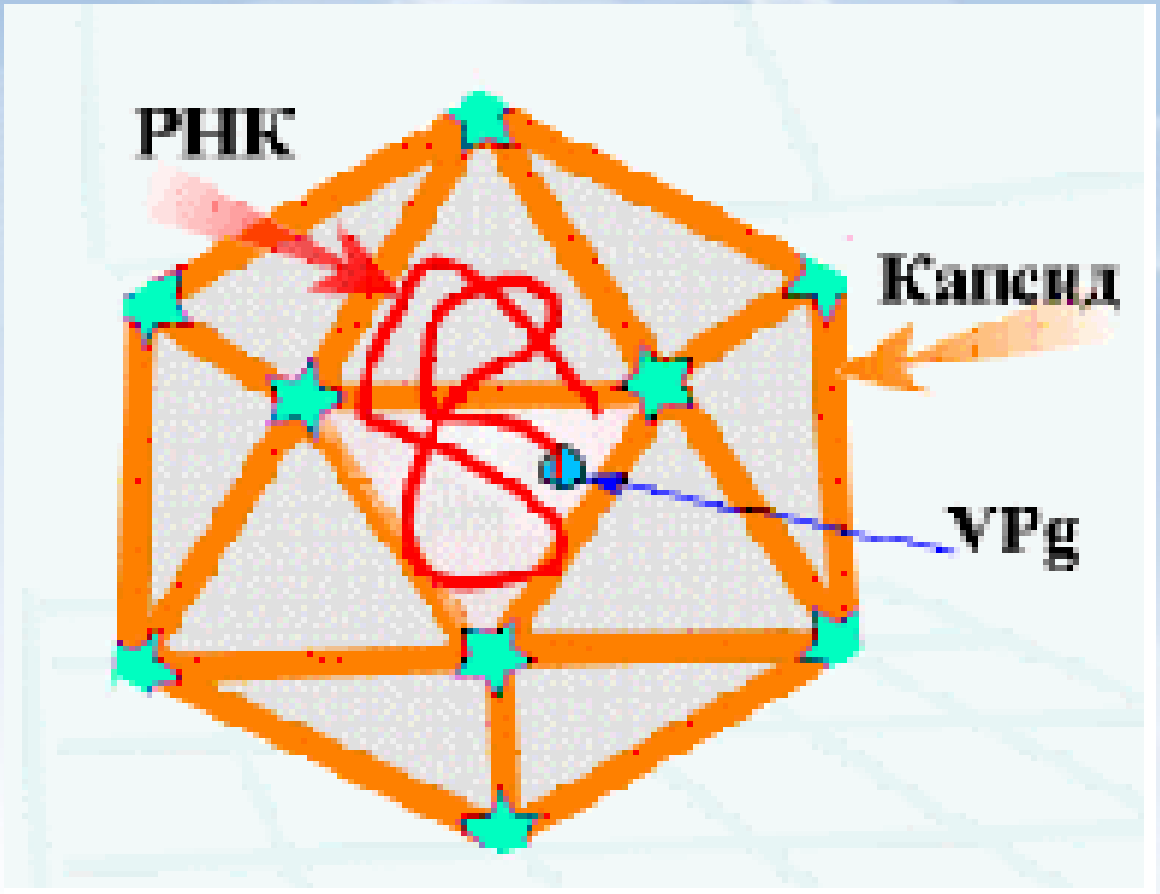


CDC
Centers for Disease Control and Prevention

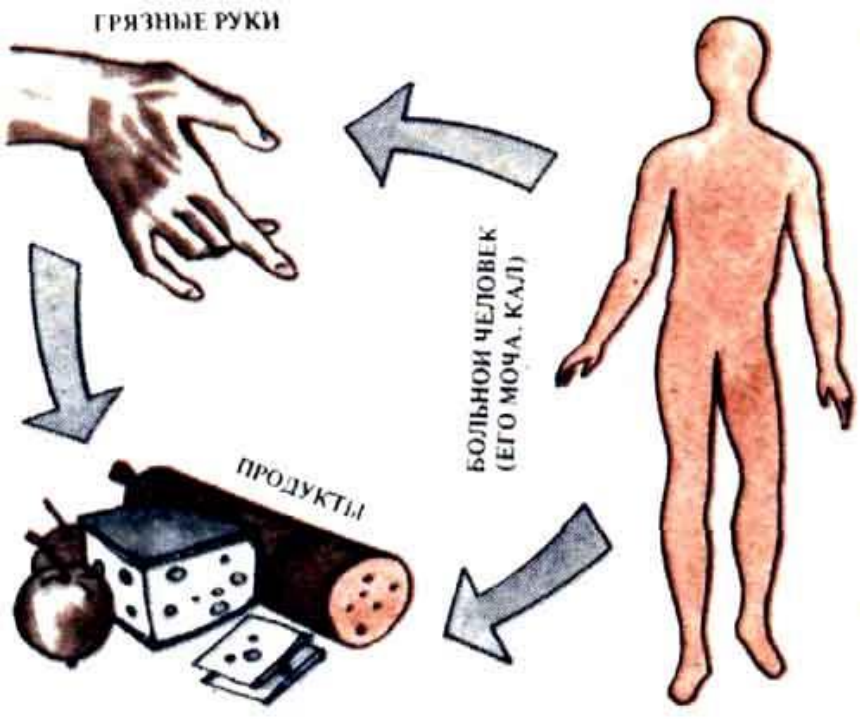
Viral hepatitis A

Family Picornaviridae

genus *Hepatovirus*



Viral hepatitis A
Epidemiology



Viral hepatitis A - ELISA

Hepatitis A Prevention – vaccination

- *Preexposure:*

- ***Formalin-inactivated HAV vaccines,***
- ***Live attenuated vaccines.***

Hepatitis A: Pre-exposure Vaccination

- Persons at increased risk or danger of infection
  - Travelers to intermediate an d high HAV prevalence areas
  - Men having sex with men
  - Injecting drug users
  - Persons with chronic liver disease
- Communities with high rates of hepatitis A (e.g., Alaskan Natives, Native-Americans)
- Routine pre-school childhood vaccination

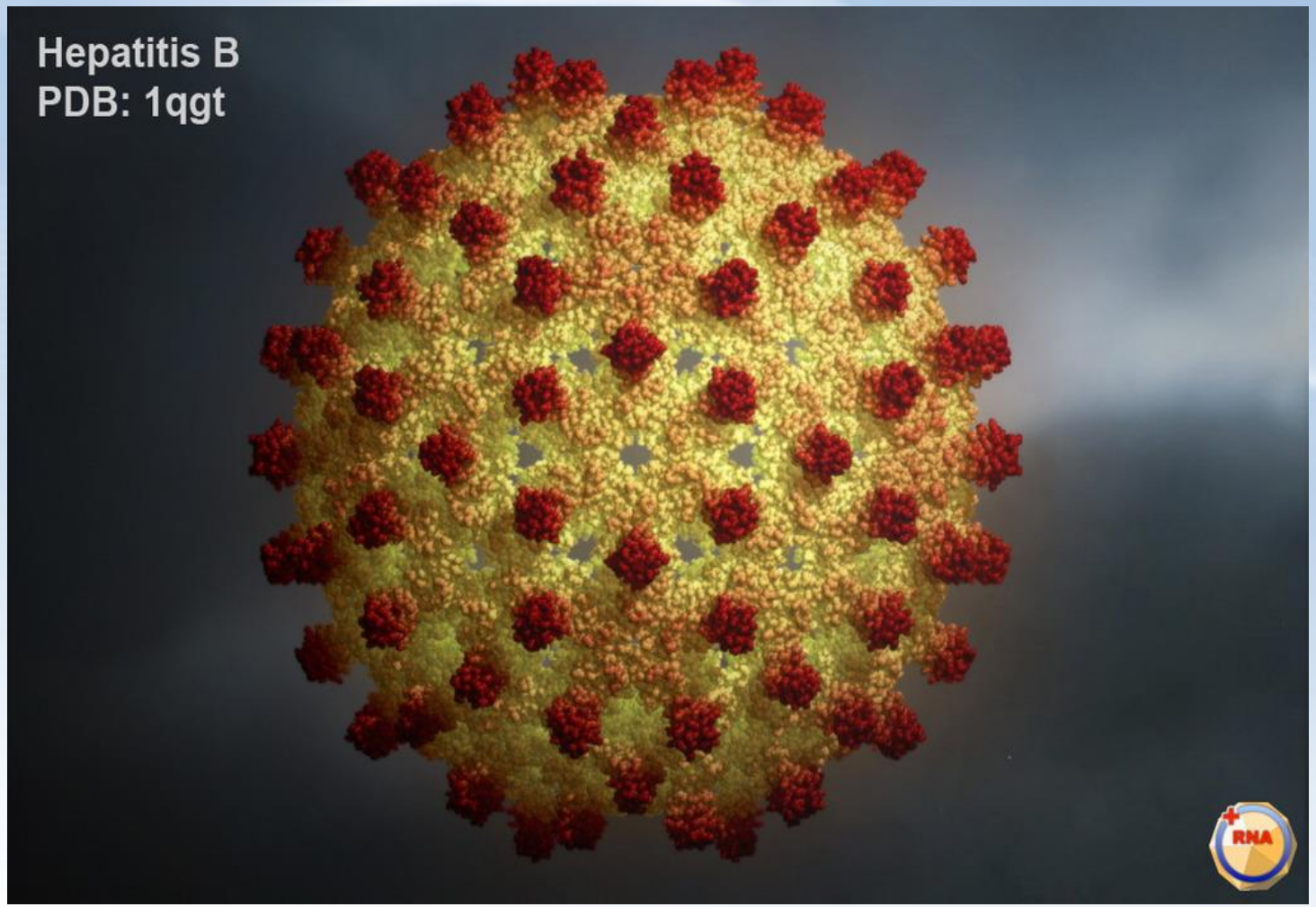
Hepatitis A Prevention – Immune (γ) Globulin (IG)

- Postexposure (within 14 days)
  - Selected situations:
    - Institutions (e.g. daycare centers)
    - Common source exposure (e.g. food prepared by infected food handler)

Hepatitis B

- **Hepatitis B** is a liver disease caused by the hepatitis B virus (HBV). It ranges in severity from a mild illness, lasting a few weeks (acute), to a serious long-term (chronic) illness that can lead to liver disease or liver cancer.

Hepatitis B Virus

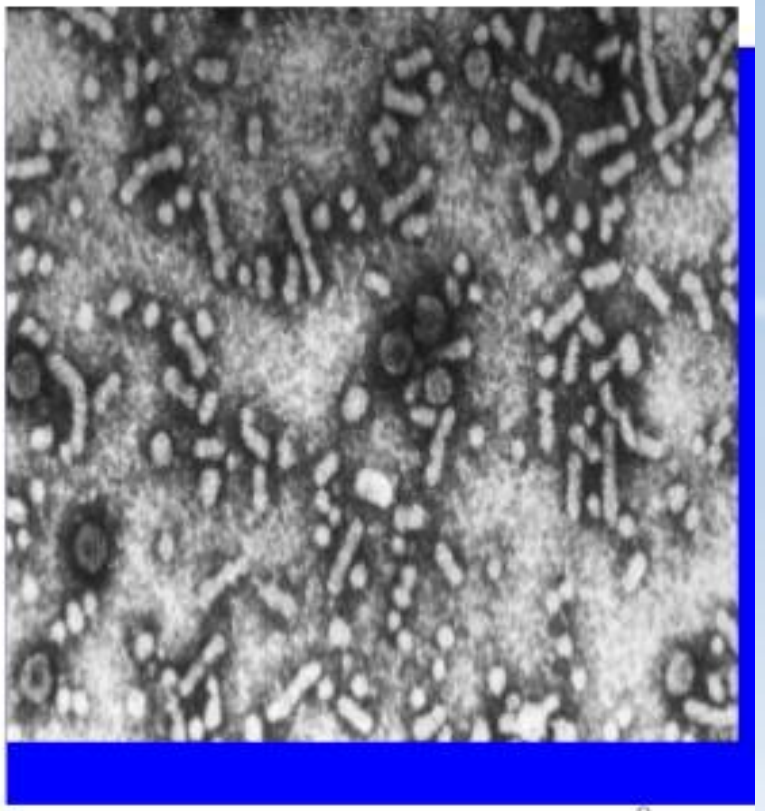


Hepatitis B In the World

- 2 billion people have been infected (1 out of 3 people).
- 400 million people are chronically infected.
- 10-30 million will become infected each year.
- An estimated 1 million people die each year from hepatitis B and its complications.
- Approximately 2 people die each minute from hepatitis B.

Hepatitis B Virus

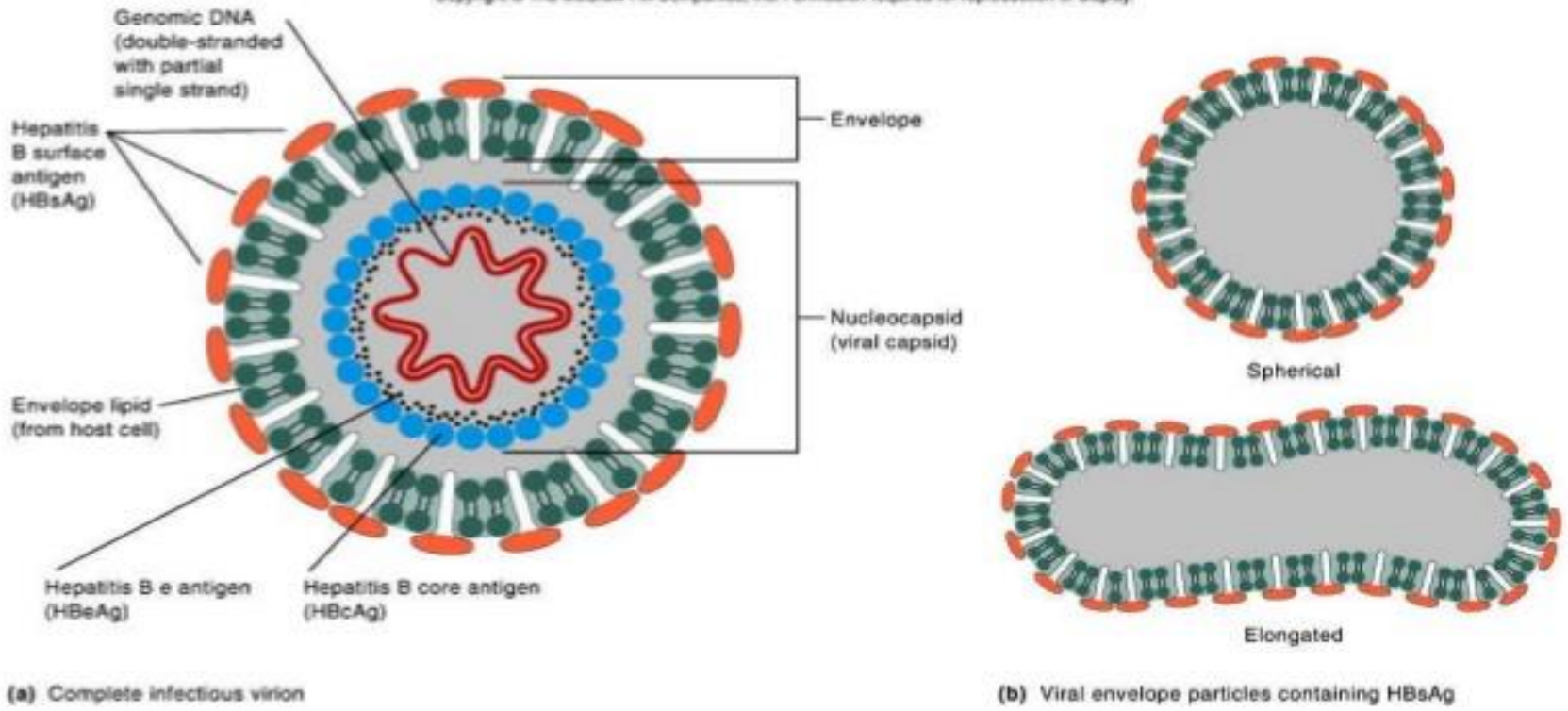
- Blumberg in 1965 discovers, names as Australia antigen.
- 1968 identified with association in serum hepatitis.
- Surface component of HBV called as surface antigen.



Hepatitis B Virus - Virology

- Double stranded DNA virus, the + strand not complete
- Replication involves a reverse transcriptase.
- Complete Dane particle 42 nm, 28 nm electron dense core, containing HBcAg and HBeAg. The coat and the 22 nm free particles contain HBsAg
- At least 4 phenotypes of HBsAg are recognized;
  adw, adr, ayw and ayr.
- The HBcAg is of a single serotype

HBV : Structure



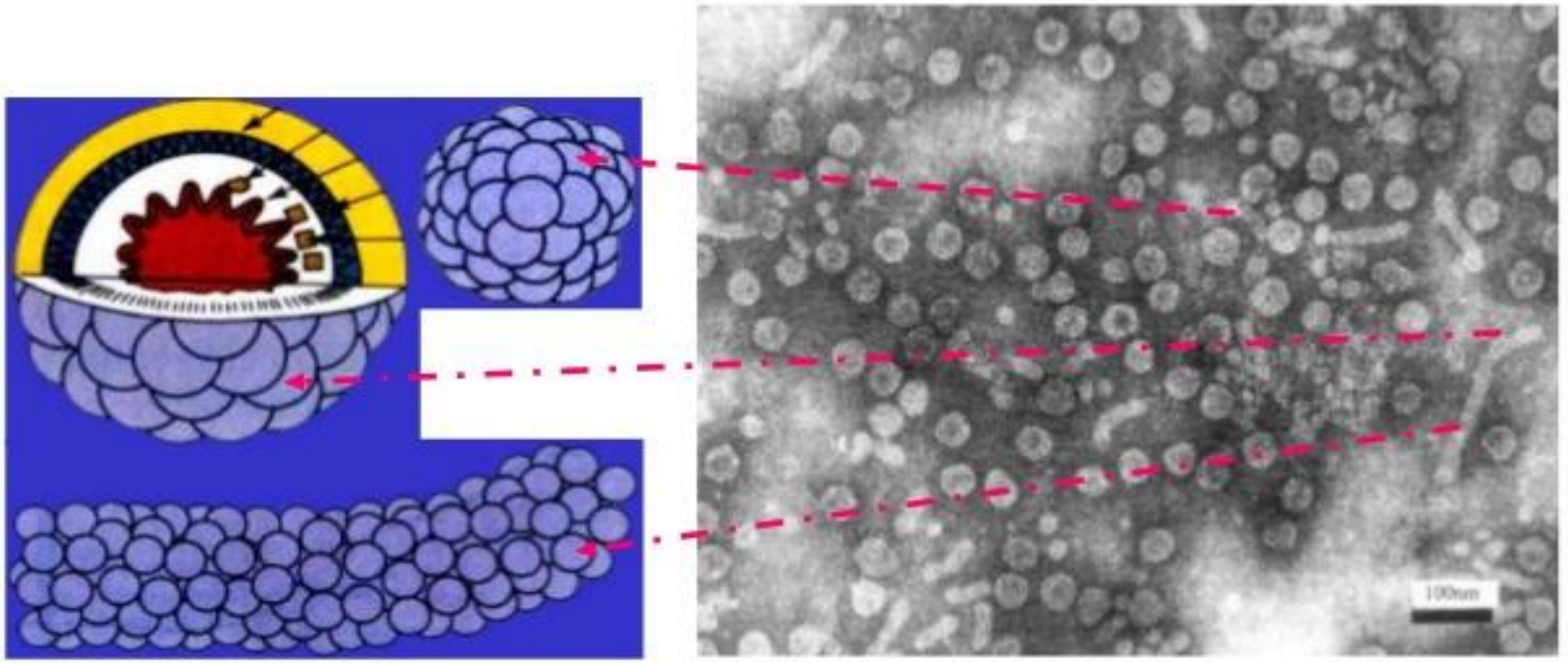
(a) Complete infectious virion

(b) Viral envelope particles containing HBsAg

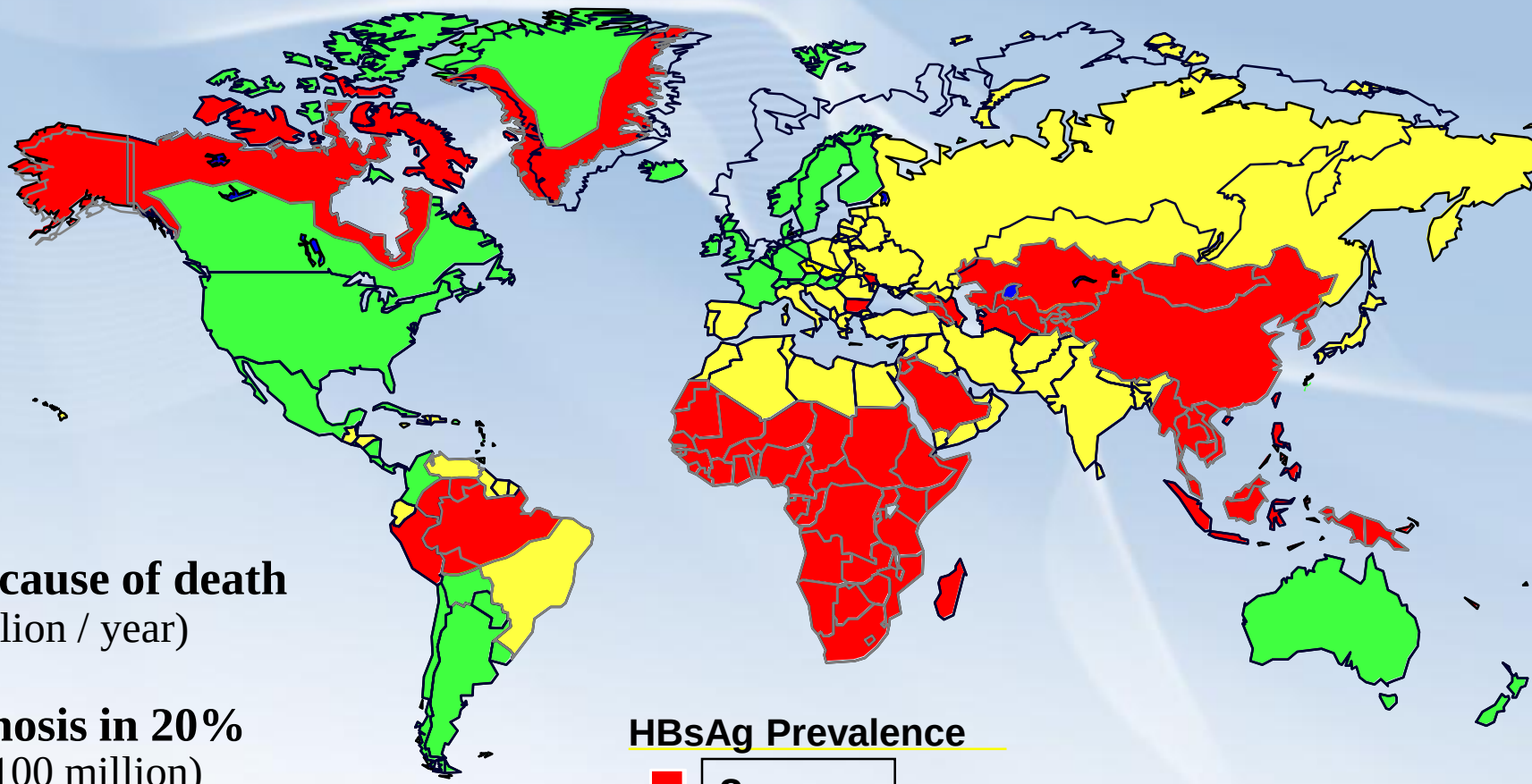
HBV Virology Under Electron Microscope

- Spherical particles 22 nm in diameter
- Filamentous or tubular 22 nm with varying length
- Called as HBs Ag surface components which are produced in excess.
- Third type double walled spherical structure 42 nm diameter called HBV
- **Called as Dane particle**

Hepatitis B Virus



Geographic Distribution of Chronic HBV Infection

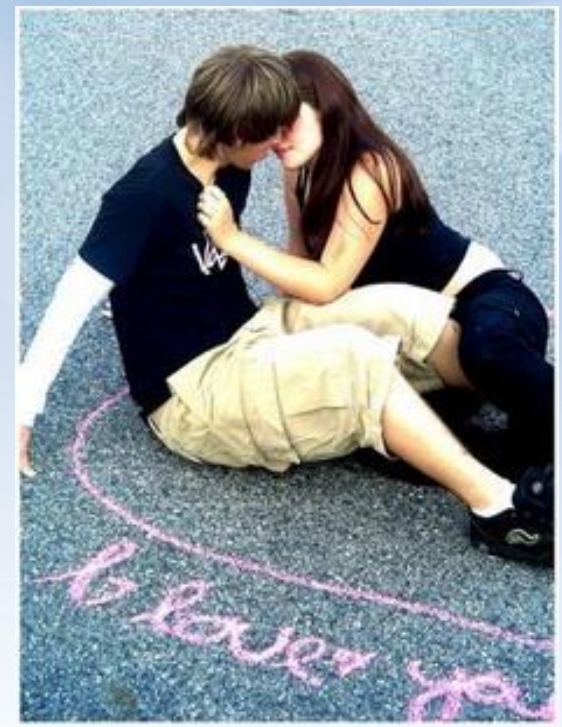


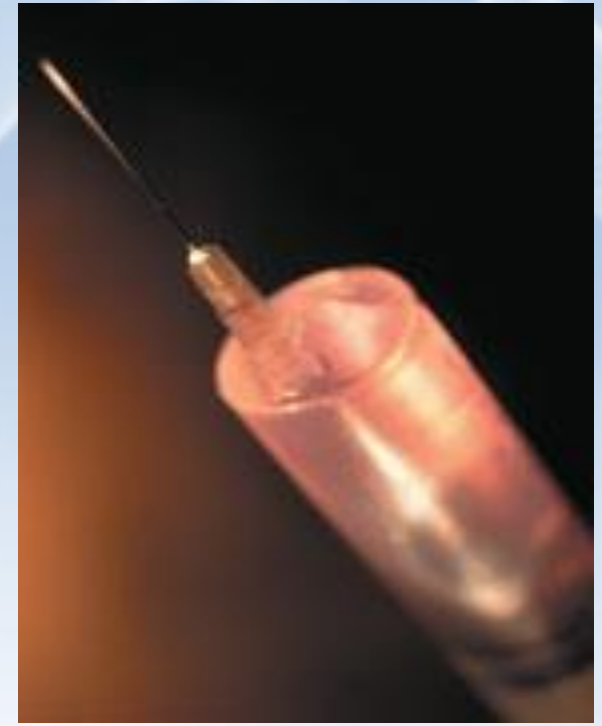
10th cause of death
(1 million / year)

Cirrhosis in 20%
(75 - 100 million)

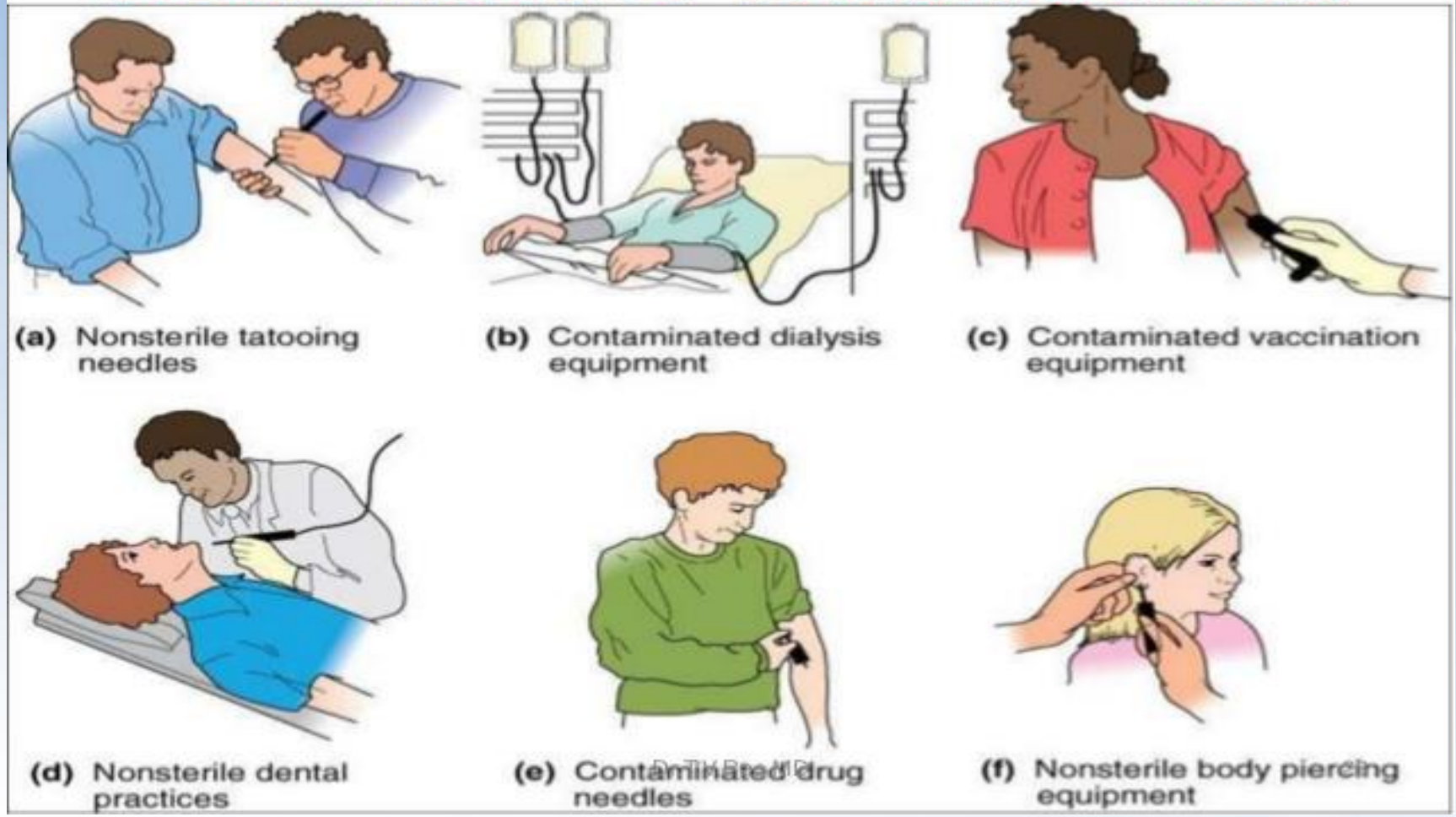
HCC in 5 - 10%
(20 - 40 million)

Epidemiology – Sources Transmission





How the HBV is transmitted



Hepatitis B Virus
Modes of Transmission

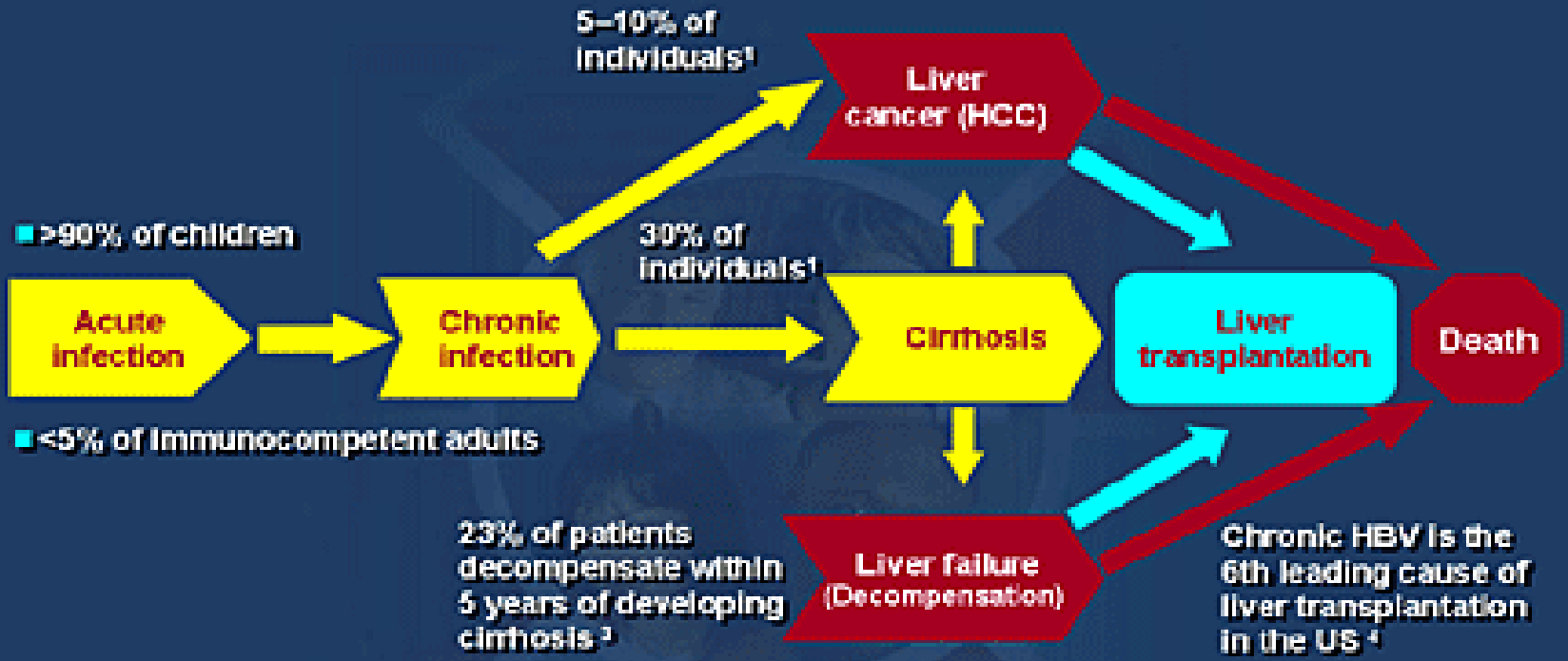
- Sexual - sex workers and homosexuals are particular at risk.
- Parenteral - IVDA, Health Workers are at increased risk.
- Perinatal - Mothers who are HBeAg positive are much more likely to transmit to their offspring than those who are not. Perinatal transmission is the main means of transmission in high prevalence populations.

Epidemiology – risk group

HBV: Clinical Features Are Age-Dependent

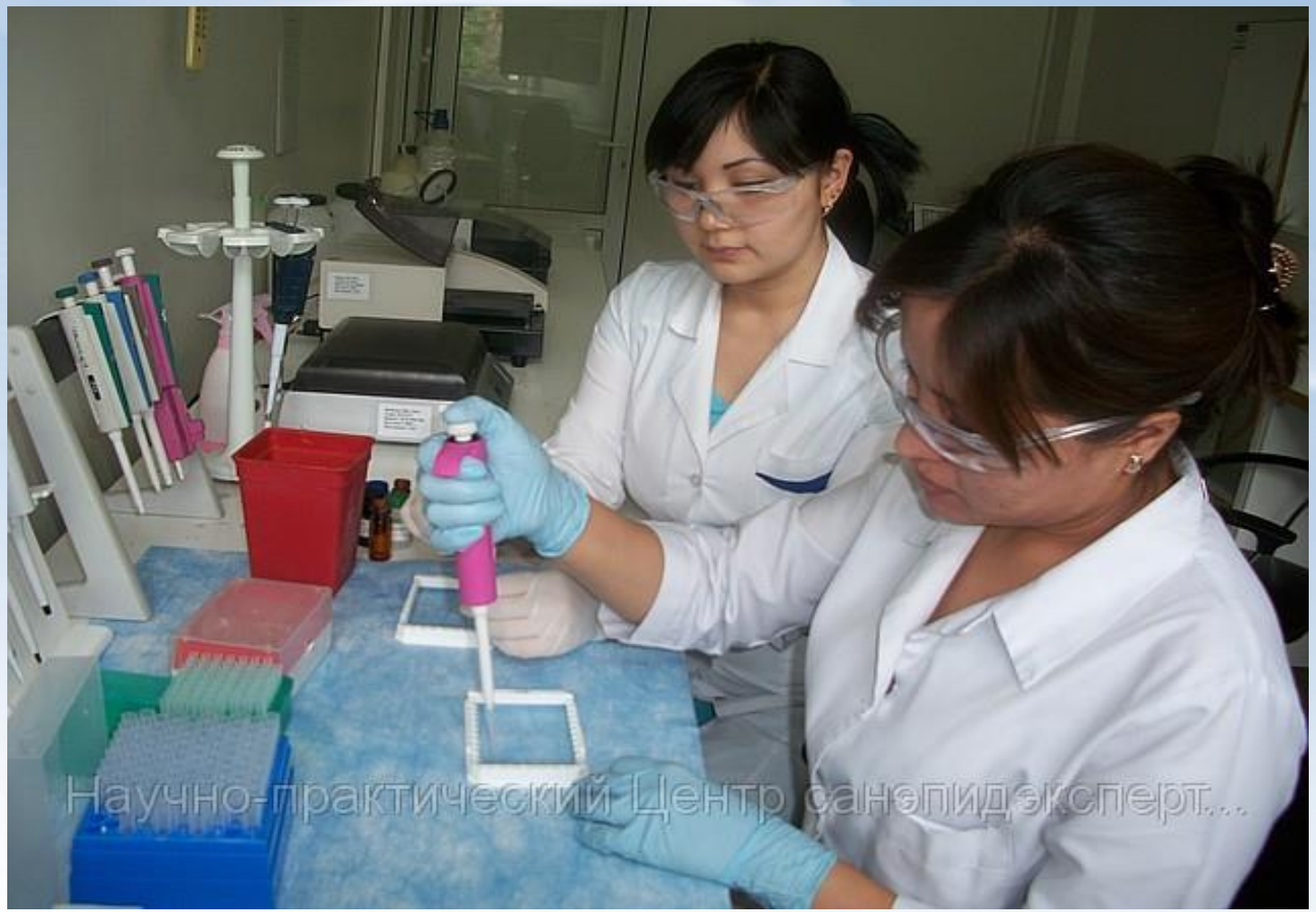
Incubation period	**Average: 60-90 days** **Range: 45-180 days**
Clinical illness (jaundice)	**<5 years: <10%** **>5 years: 30%-50%**
Acute case-fatality rate	**0.5%-1%**
Chronic infection	**<5 years: 30%-90%** **>5 years: 2%-10%**
Premature mortality from chronic liver disease	**15%-25%**

Hepatitis B disease progression



[1]Terrault et al. Gastroenterology 2000; 118(2 suppl. 1): S33
[2]Fattovich et al. Hepatology 1995; 22: 1355
[3]Moyer et al. Am J Prev Med 1954; 10(suppl.): 45
[4]Perrillo et al. Hepatology 2001; 33: 424

Hepatitis B Diagnostics - ELISA



Interpretation of Serologic Markers

	Acute hepatitis B	Recovery from acute hepatitis B	Chronic HBeAg + disease	Chronic HBeAG – disease	Successful Vaccination	Resistance to antiviral agents
HBsAg	✓		✓	✓		
Anti-HBs		✓			✓	
Anti-HBc IgM	✓					
Anti-HBc	✓	✓	✓	✓		
HBeAg	✓		✓			
Anti-HBe		✓ **(in some cases)**		✓		
HBV DNA	✓		✓	✓		✓ **(sequence *pol* region)**

Hepatitis B prevention
Subunit vaccines
(Shanvac, Engerix)

Hepatitis B Vaccine

- Composition Recombinant HBsAg
- Efficacy 95% (Range, 80%-100%)
- Duration of Immunity 20 years or more
- Schedule 3 Doses
- Booster doses not routinely recommended

Hepatitis B prevention

Prevention

- 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.

Goals of Treatment in HBV

- ***Reduce the risk of disease progression.***
- ***Reduce the risk of hepatocellular carcinoma.***
- Loss of HBeAg,
- HBeAg → HBeAb
- Undetectable HBV-DNA
- Normalization of ALT
- Histologic Response
- HBsAg → HBsAb

Treatment

- 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 HBeAg.

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.

Hepatitis D Virus: Morphology and Characteristics

- **Nucleic Acid: 1.7 kb ssRNA**
- **Classification: *unclassified, related to viroids; deltavirus***
- **Transmission: sex, IVDA**
- **Clinical features**
  - **Fulminant: 2 – 7.5%**
  - **Chronic infection**
    - ***Superinfection: 80%***
    - ***Coinfection: < 5%***

Hepatitis D virus (HDV)

- Hepatitis D virus (HDV) is found only in people who carry the hepatitis B virus. HDV may make a recent (acute) hepatitis B infection or an existing long-term (chronic) hepatitis B liver disease worse. It can even cause symptoms in people who carry hepatitis B virus but who never had symptoms.

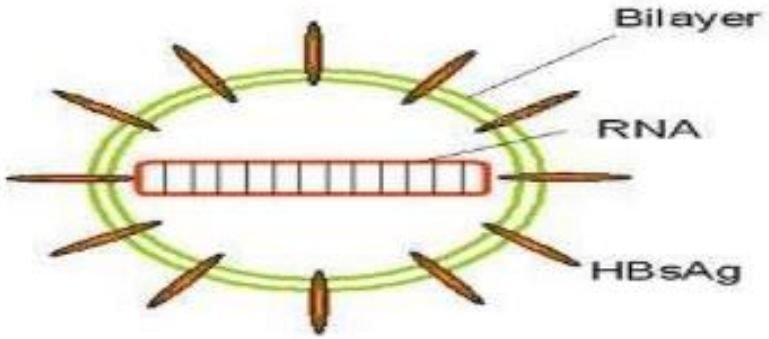
Hepatitis D Virus

- 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

Delta antigen

- In 1977, a previously unrecognized nuclear antigen was detected in hepatocytes of patients with chronic hepatitis B. The antigen resembled hepatitis B core antigen (HBcAg) in its subcellular localization. Its presence was always associated with hepatitis B virus (HBV) infection, but it rarely coexisted with HBcAg. It was termed "delta antigen". Patients with delta antigen develop anti-delta antibodies.

Hepatitis D Infection



Risk factors include:

- Abusing intravenous (IV) or injection drugs
- Being infected while pregnant (the mother can pass the virus to the baby)
- Carrying the hepatitis B virus
- Men having sexual intercourse with other men,

  Receiving many blood transfusions

HDV can lead to fulminant Hepatitis

- HDV infection of chronically infected HBV-carriers may lead to fulminant acute hepatitis or severe chronic active hepatitis, often progressing to cirrhosis.
- Chronic hepatitis D may also lead to the development of hepatocellular carcinoma.

Best Way to Prevent HDV Infection

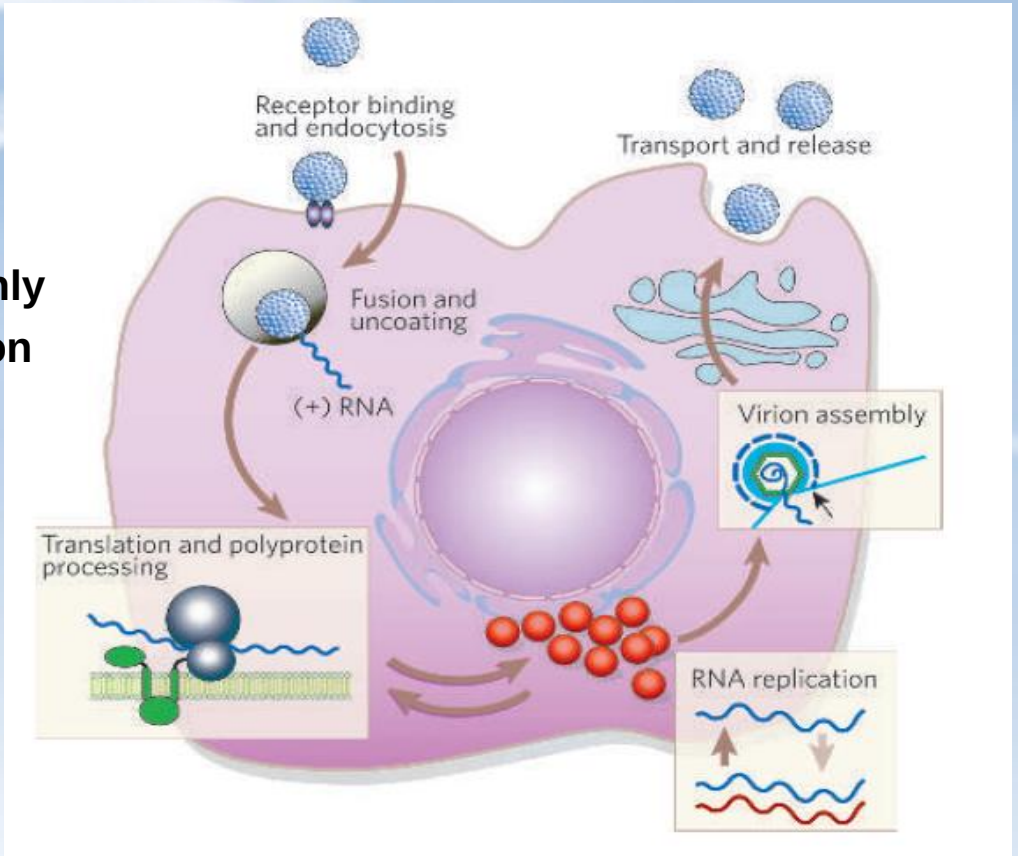
- Control of HDV infection can be achieved by targeting and limiting HBV infections. HBV vaccination is therefore recommended to avoid HBV-HDV confection.

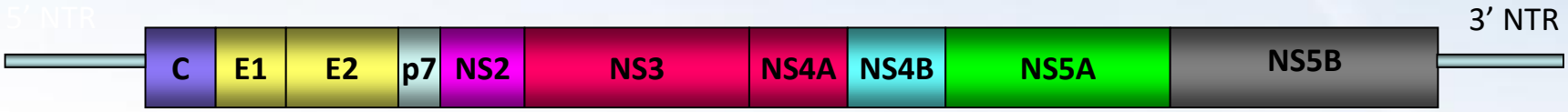
Hepatitis D Diagnostics

- **Diagnostic tests - ELISA**
- **-Acute infection: IgM anti-HDV**
- **-Chronic infection: IgG anti-HDV, HBsAg +**

Hepatitis C Virus

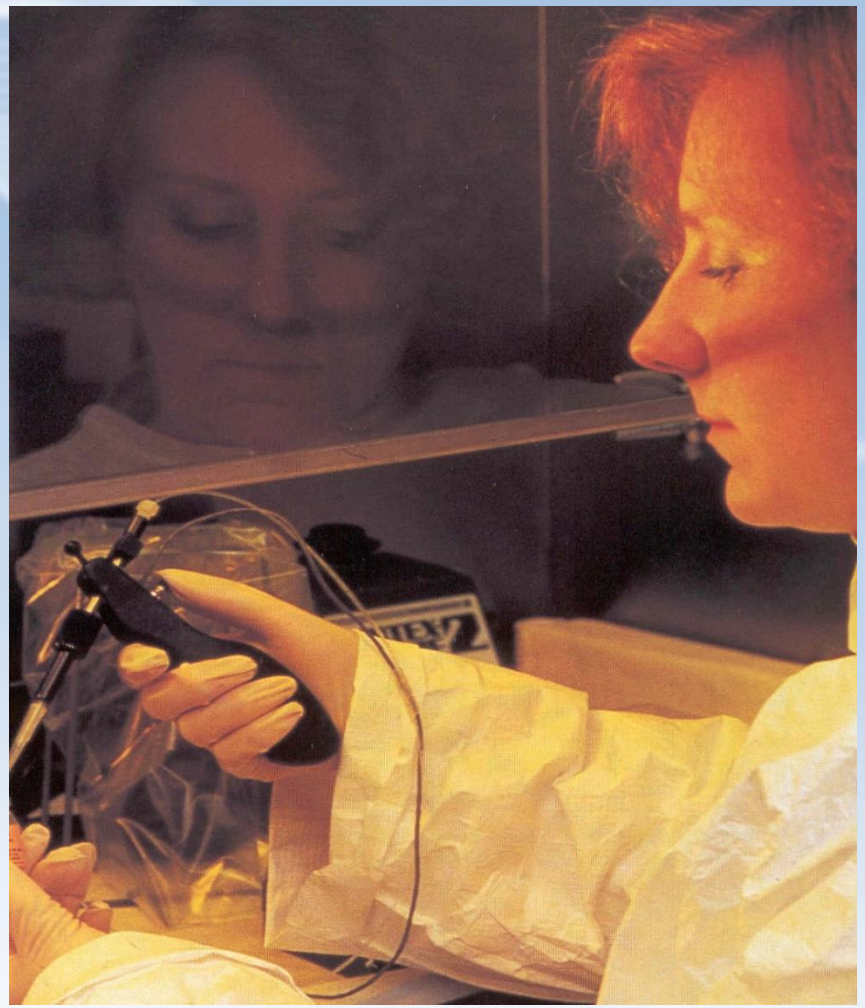
- NANBH
- Discovered in 1989
- Plus-stranded RNA
- 9.6 kb
- Replicates in Hepatocytes mainly
- Causes Persistent Viral Infection



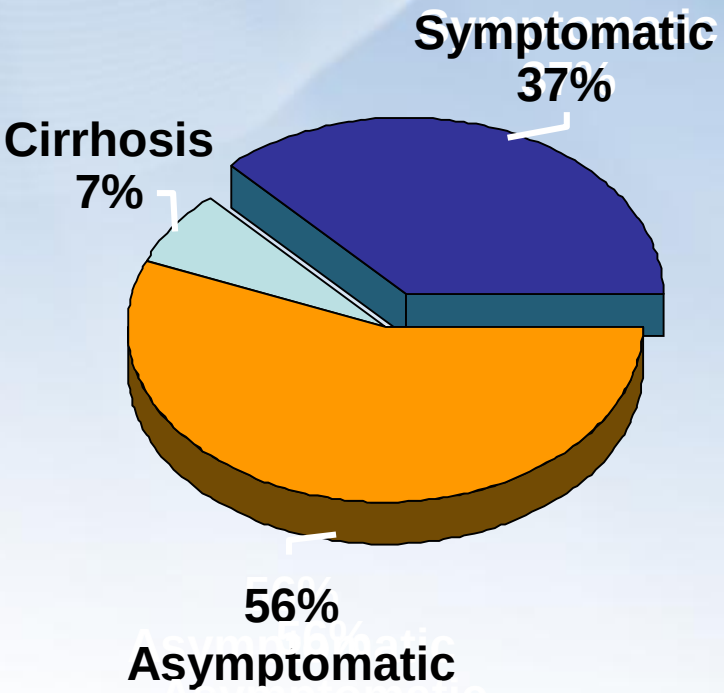


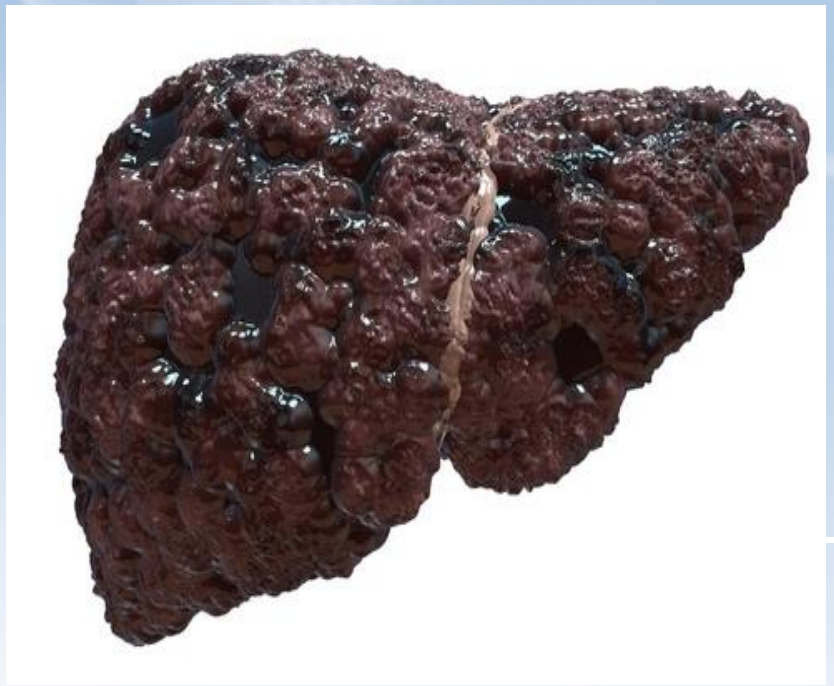
Hepatitis C Diagnostics

- ELISA
- PCR
- IEM



Symptoms, or Lack of, in Chronic HCV Infection



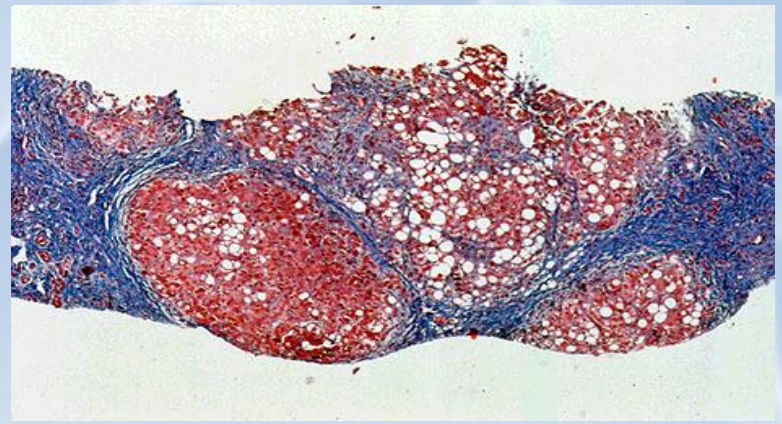


Prevalence of HCV Dependant on Risk Factors

• Hemophilia	74-90%
• *IVDA*	72-89%
• Prison	40%
• HIV	30-40%
• Blood transfusion prior to 90	5-9%
• Infants to HCV+ Mothers	5%
• Sexual Partner	0.5-3%
• General Population	1.8%

HCV: Disease Progression

Time: 20-30 years



HCV infection

60-85%[1]

Chronic HCV

20%-50%[2]

Cirrhosis

~ 20%[3]

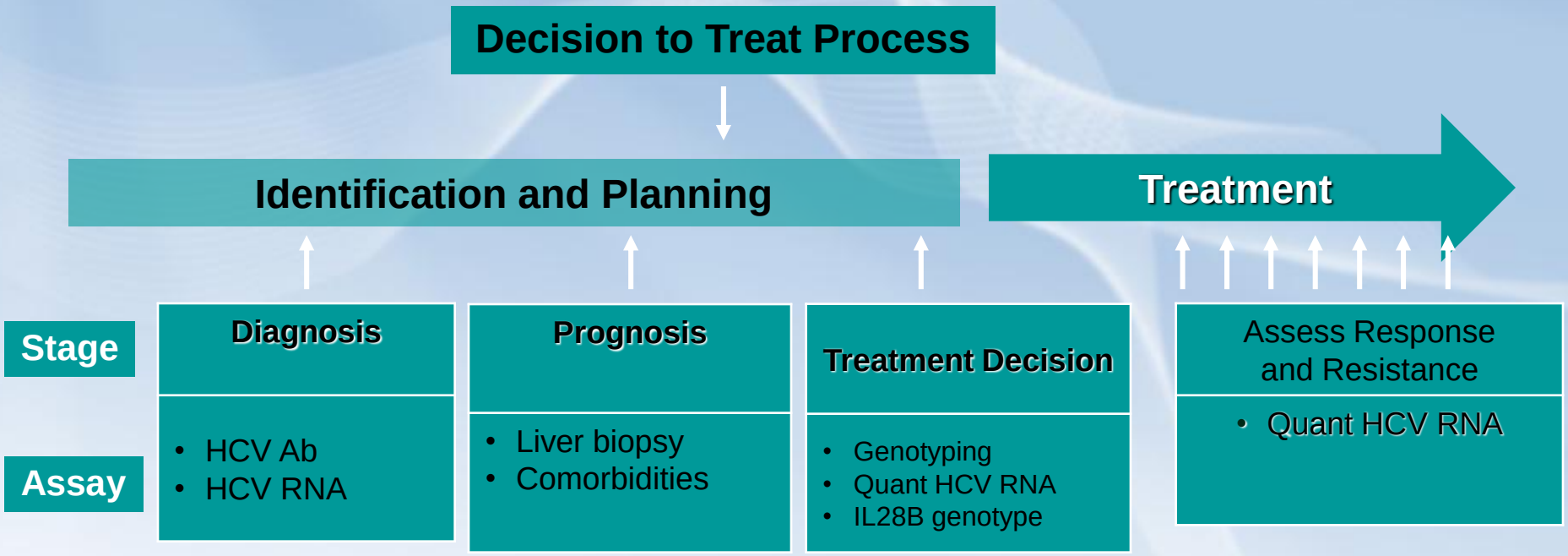
Hepatic Failure

~20%[4]

Liver Cancer

Liver Transplant Candidates

Common Schedule and Type of HCV Testing



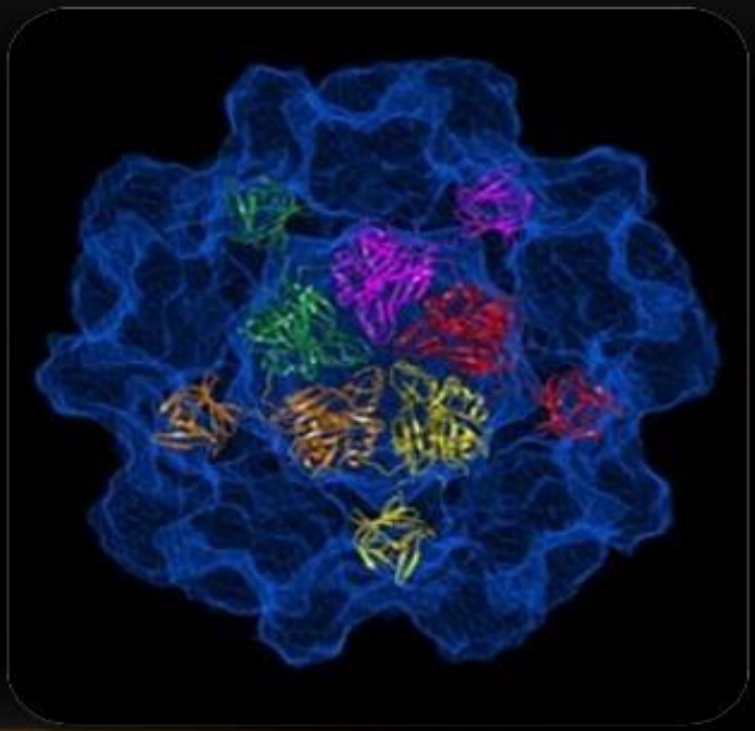
Genotypes: 1-6 associated with response to therapy:

G1: 40-50% SVR

G2/3: 70-80% SVR

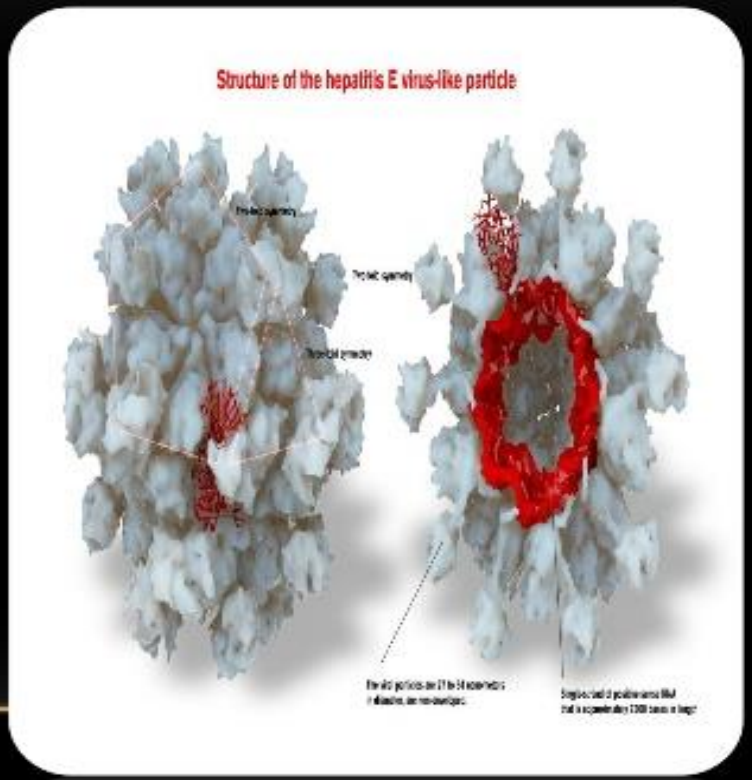
HEPATITIS *E VIRUS* INFECTION

- Hepatitis E (HEV) was not recognized as a distinct human disease until 1980. Hepatitis E is caused by infection with the hepatitis E virus, a non-enveloped, positive-sense, single-stranded RNA virus.
- Although man is considered the natural host for HEV, antibodies to HEV or closely related viruses have been detected in primates and several other animal species



STRUCTURE OF HEPATITIS E VIRUS

- The virus is icosahedral and nonenveloped. It has a diameter of approximately 34 nanometers, and it contains a single strand of RNA approximately 7.5 kilobases in length. Four HEV genotypes exist, and genotype 1 causes human disease.



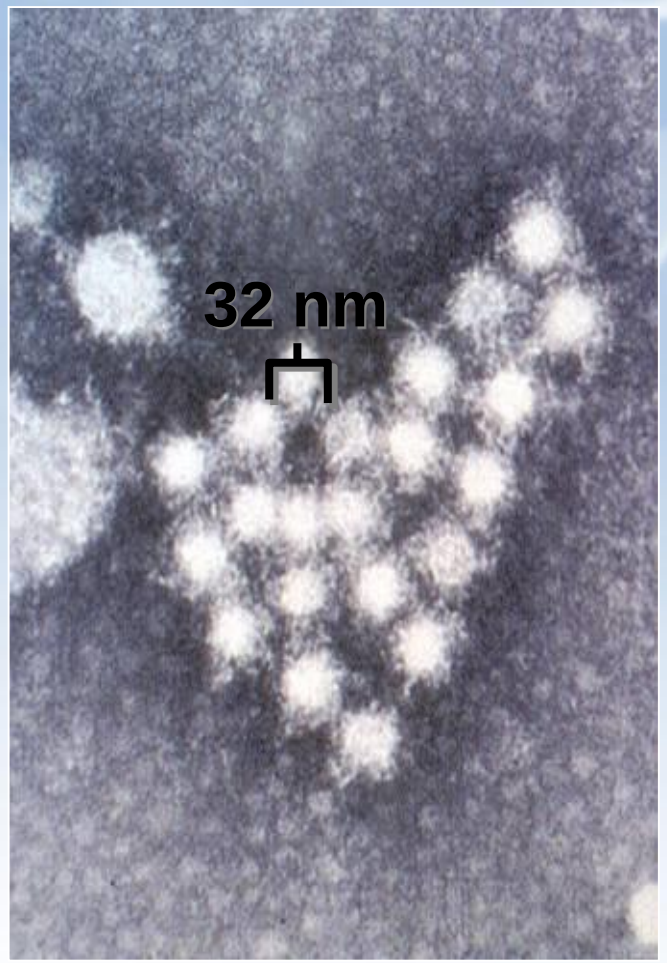
STRUCTURAL CHARACTER OF HEPATITIS E VIRUS

- HEV is an icosahedral, nonenveloped single stranded RNA virus that is approximately 27 to 34 nm in diameter . It has been classified as the single member of the genus herpesvirus in the family Herpesviridae Three large opening reading frames (ORFs) of the **positive-sense RNA of HEV have been described**
- The largest ORF consists of 1693 codons; it codes for nonstructural proteins that are responsible for the processing and replication of the virus.
- The second ORF is composed of 660 codons and codes for structural proteins.
- The third ORF consists of 123 codons; although it may encode for a structural protein, its function remains undetermined.

Hepatitis E - Epidemiologic Features

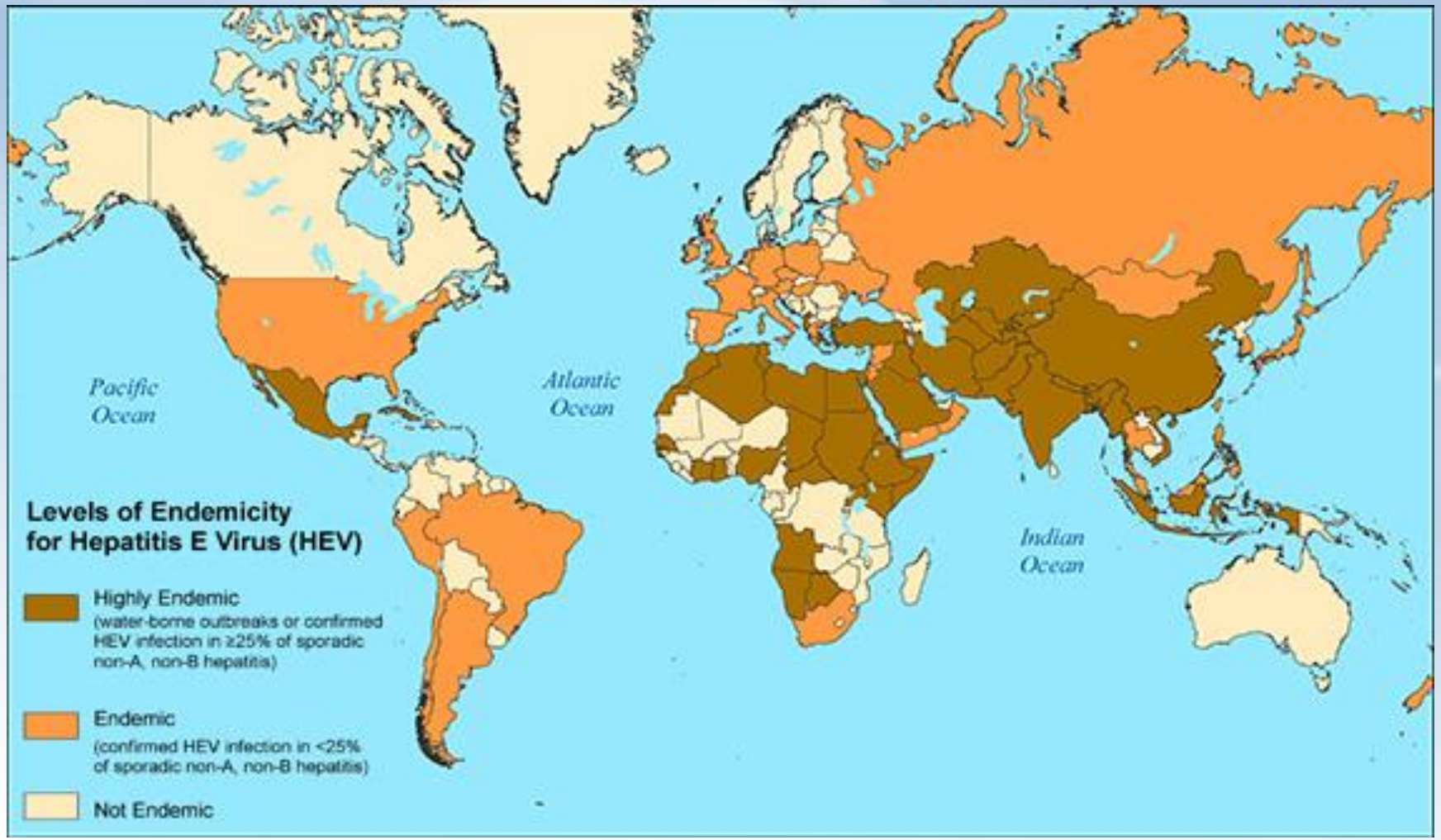
- Most outbreaks associated with faecally contaminated drinking water.
- Several other large epidemics have occurred since in the Indian subcontinent and the USSR, China, Africa and Mexico.
- In the United States and other nonendemic areas, where outbreaks of hepatitis E have not been documented to occur, 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.

Hepatitis E



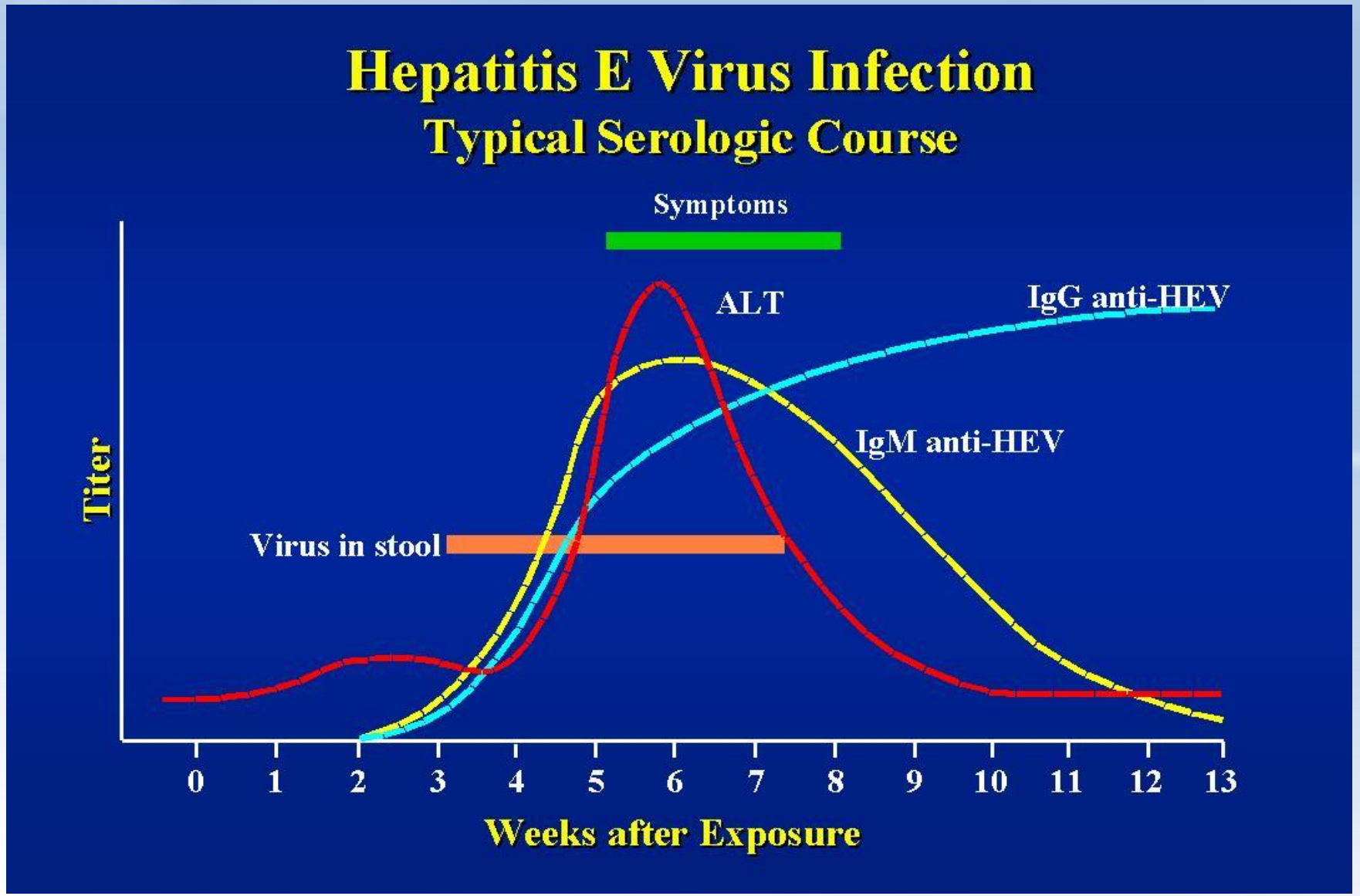
- Fecal-oral transmission (human to human)
- Contaminated water supplies in tropical or subtropical developing countries
- Mainly young adults
- Can infect primates, swine, sheep, rats
- Swine may be reservoir of infection in North America
- Maternal-infant transmission occurs and is often fatal

Hepatitis E


Pacific Ocean
Atlantic Ocean
Indian Ocean
Levels of Endemicity for Hepatitis E Virus (HEV)
Highly Endemic
(water-borne outbreaks or confirmed HEV infection in ≥25% of sporadic non-A, non-B hepatitis)
Endemic
(confirmed HEV infection in <25% of sporadic non-A, non-B hepatitis)
Not Endemic

Hep E: Clinical Characteristics

- Similar to hepatitis A
- Dx: IgG anti-HEV (seroconversion)
- Can cause severe acute hepatitis
- Subclinical infection is common
  - Attenuated virus from animal reservoirs
  - Low-dose infections often asymptomatic
- No chronic infection
- Up to 20% mortality among pregnant women (esp. third trimester)


Hepatitis E Virus Infection
Typical Serologic Course
Symptoms
ALT
IgG anti-HEV
IgM anti-HEV
Virus in stool
Titer
0
1
2
3
4
5
6
7
8
9
10
11
12
13
Weeks after Exposure

Diagnosis of hepatitis E

- To confirm the results of EIA or ELISA tests, Western blot assays to detect IgM and IgG anti-HEV in serum can be used
- PCR tests for the detection of HEV RNA in serum and stool,
- Immunofluorescent antibody blocking assays to detect antibody to HEV antigen in serum and liver,
- Immune electron microscopy to visualize viral particles in faeces