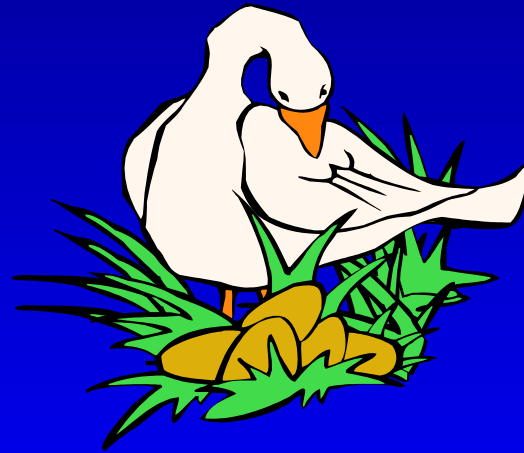


Viral Hepatitis



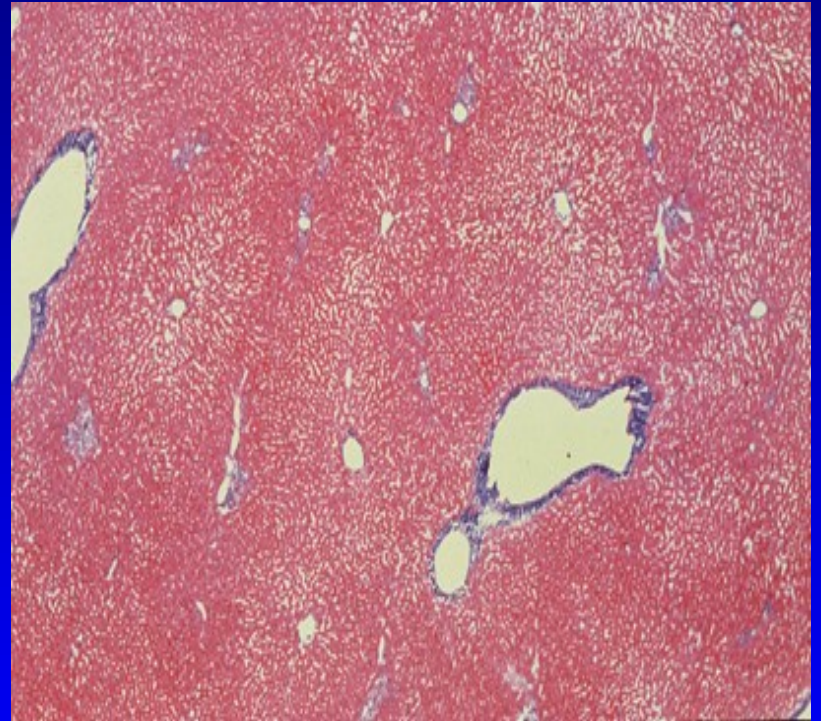
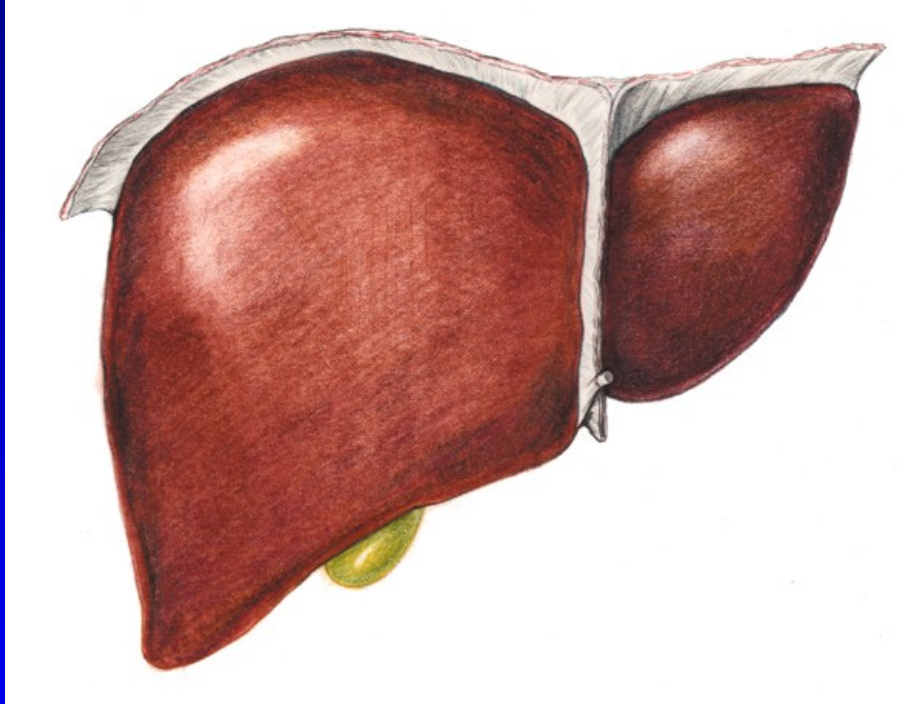
Prof. MUDr. Petr Husa, CSc.

Klinika infekčních chorob, FN Brno

Viral Hepatitis

1. Enterically transmitted – no chronic stage
 - VH A
 - VH E – extremely rare (IS)
2. Parenterally transmitted – possible chronic stage
 - VH B
 - VH C
 - VH D

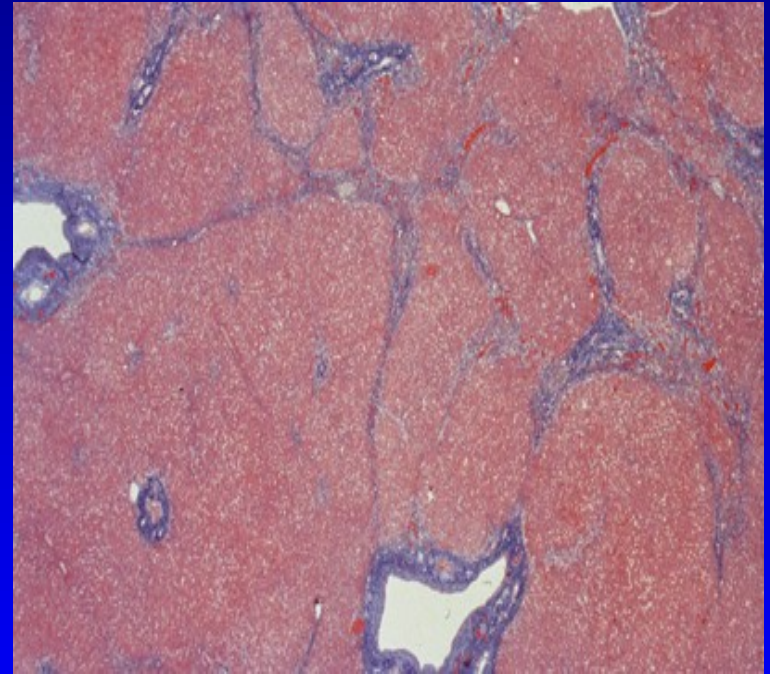
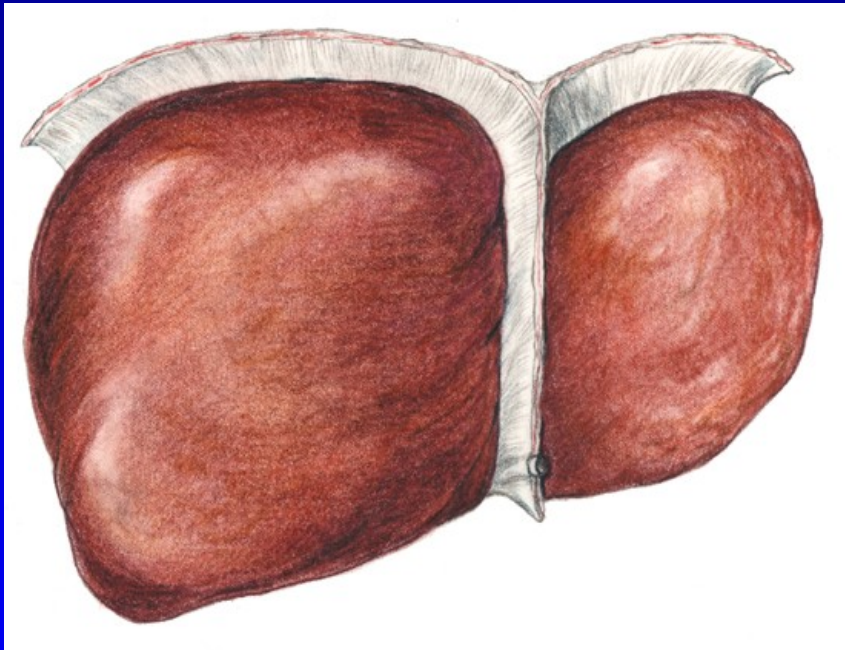
Healthy liver



Normal Biopsy



Liver fibrosis



Mild Fibrosis

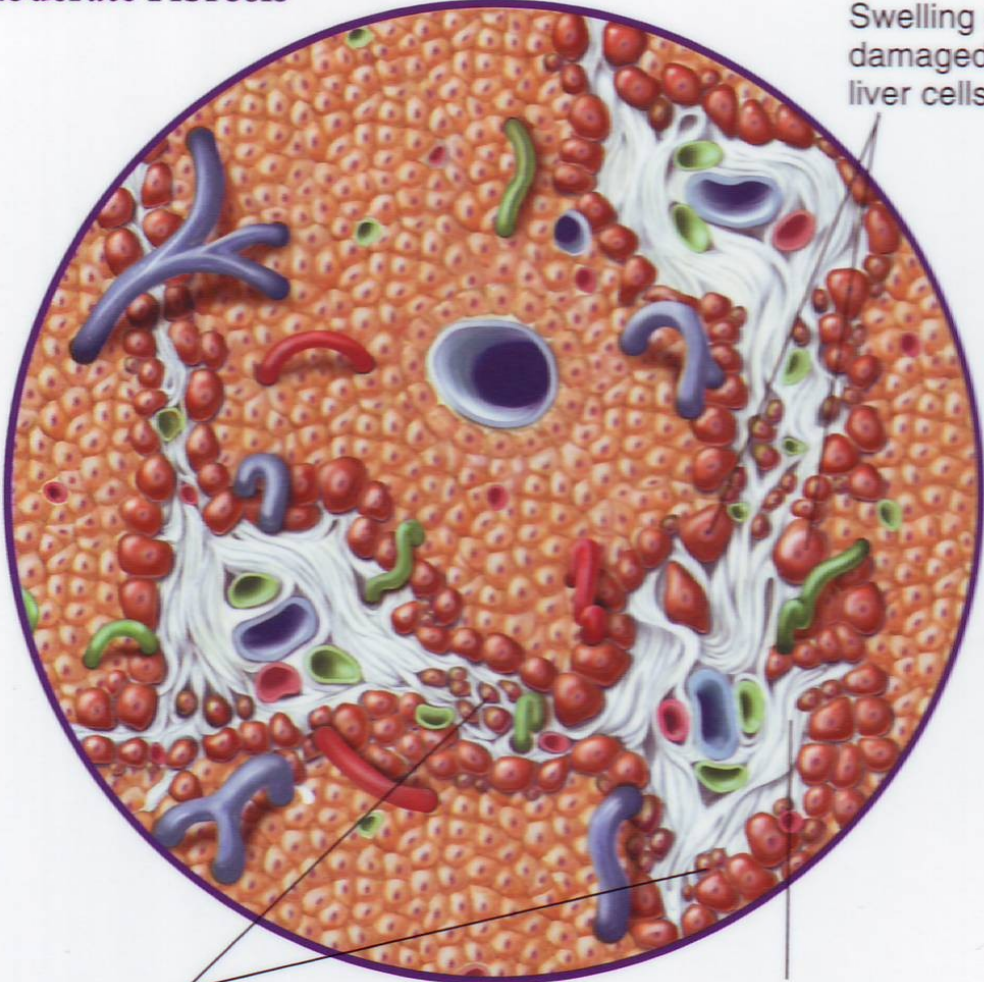
Mild swelling and inflammation of
damaged liver cells around portal areas

Development of
scar tissue (fibrosis)



Normal hepatocytes
(liver cells)

Moderate Fibrosis

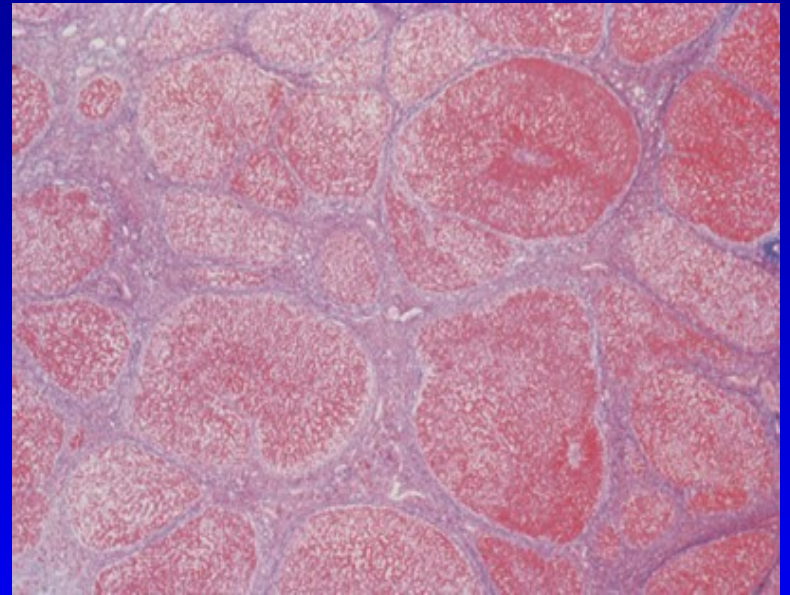
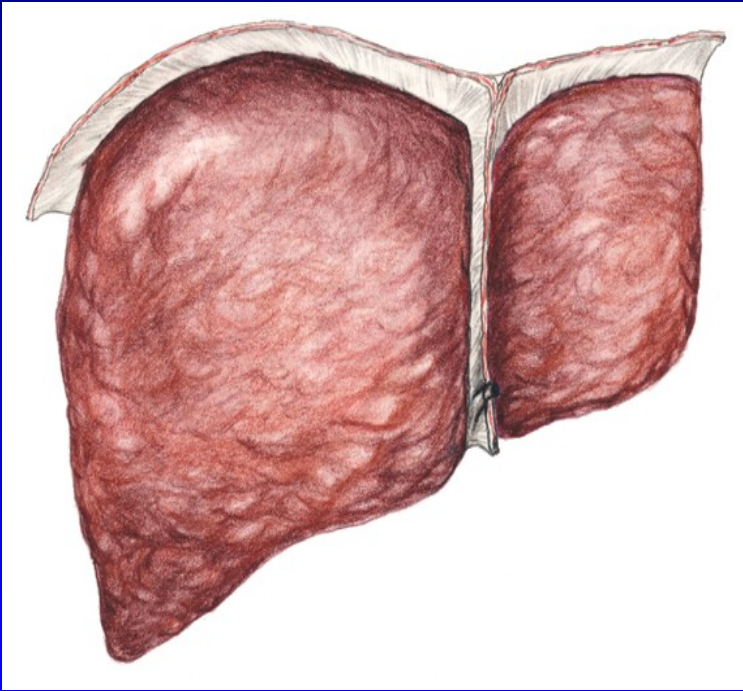


Swelling of damaged liver cells

Necrosis of liver cells

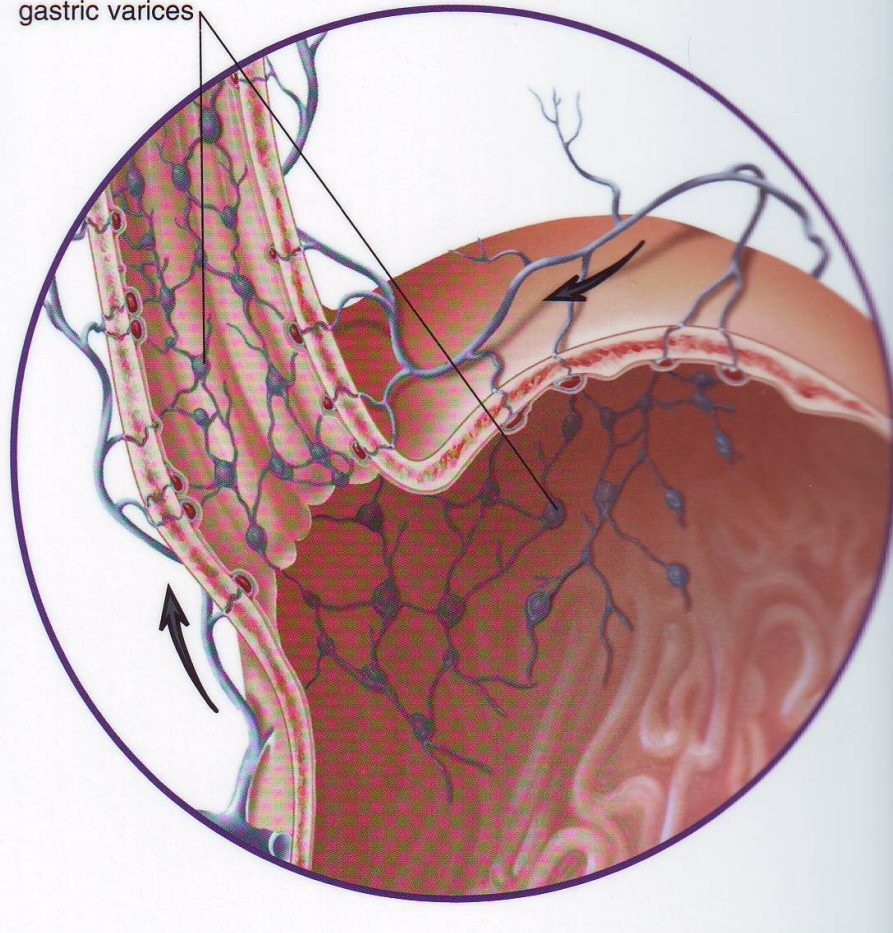
Fibrosis extending between portal areas

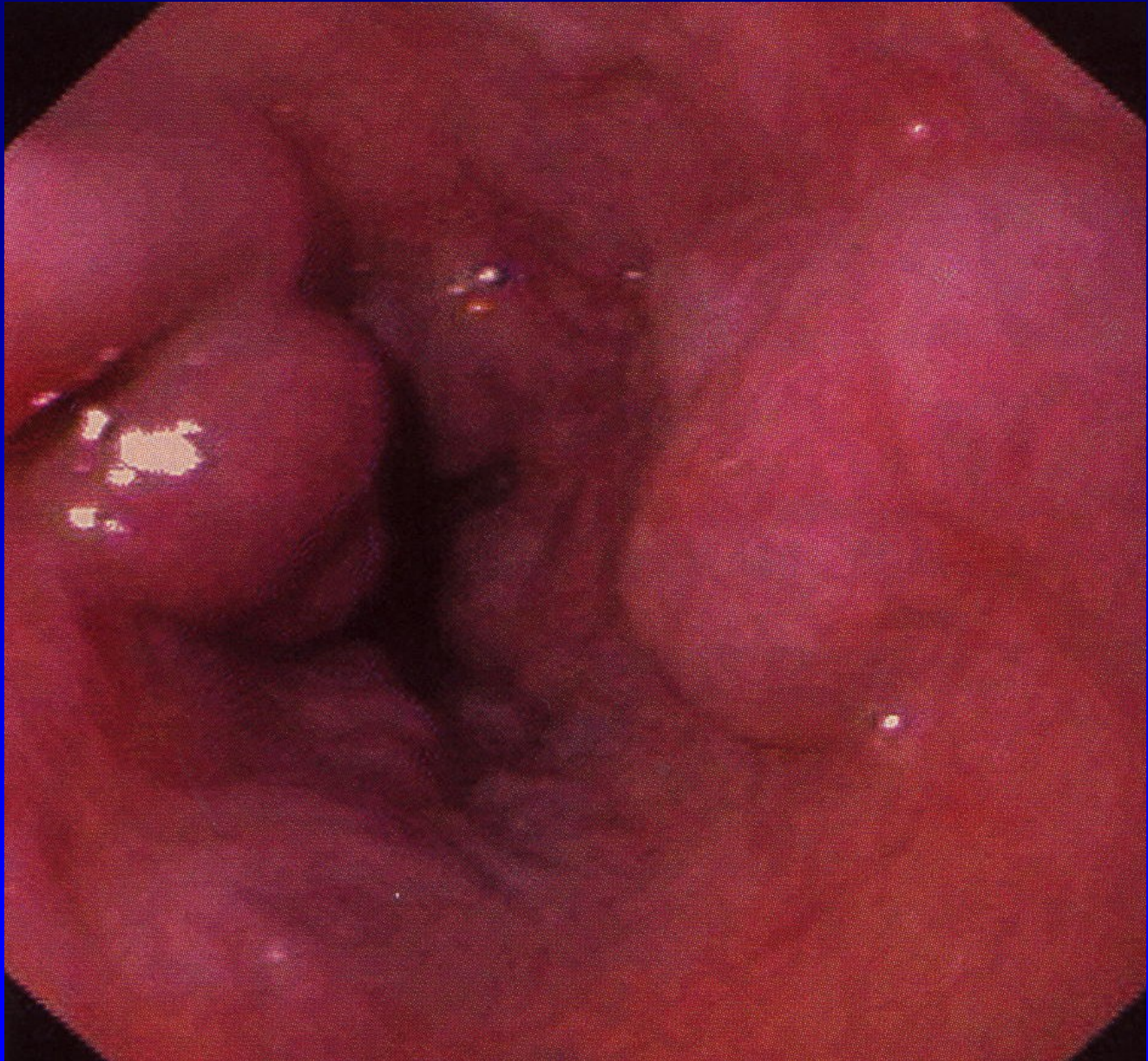
Liver cirrhosis

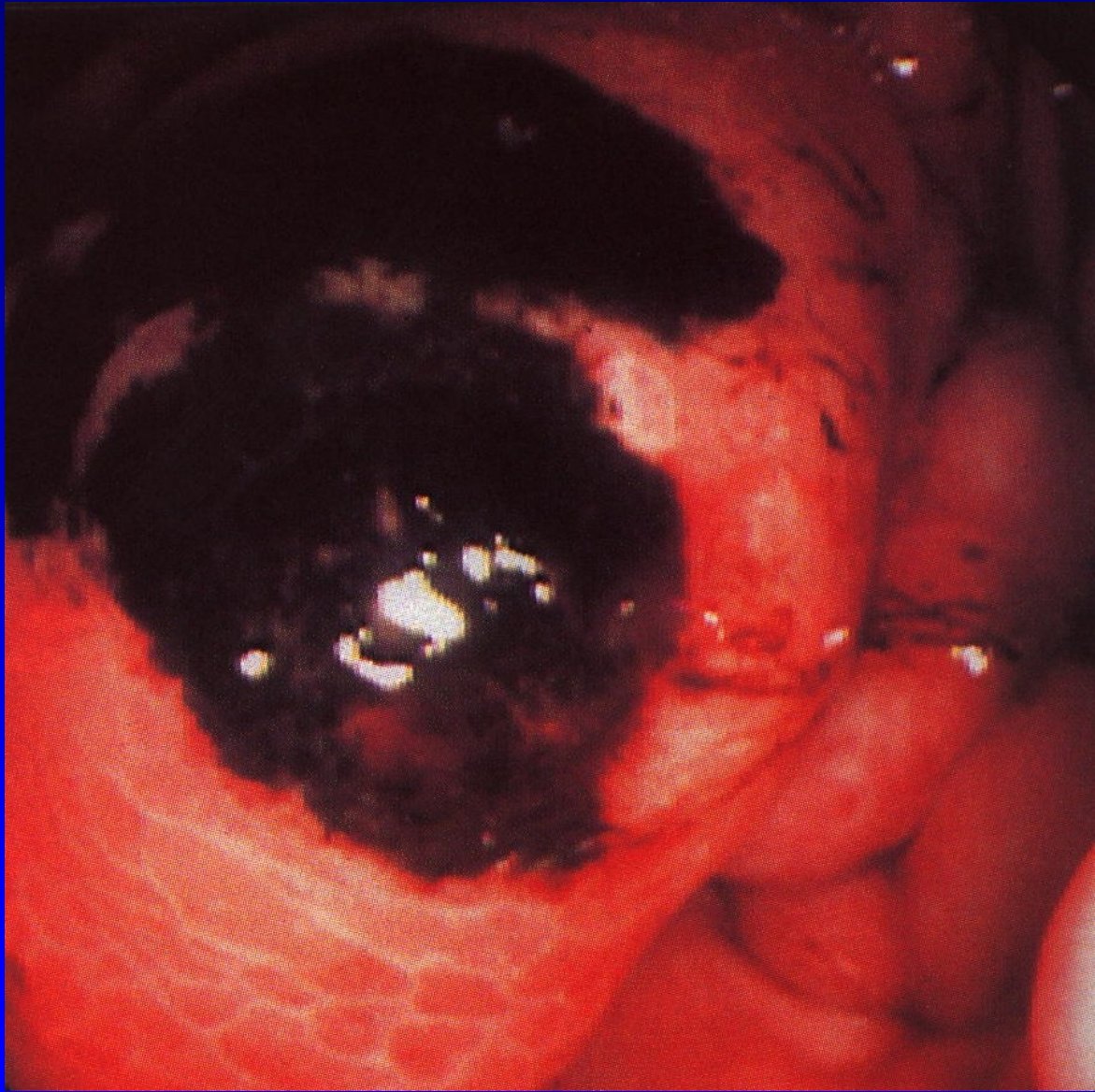


Development of Varices

Esophageal and gastric varices





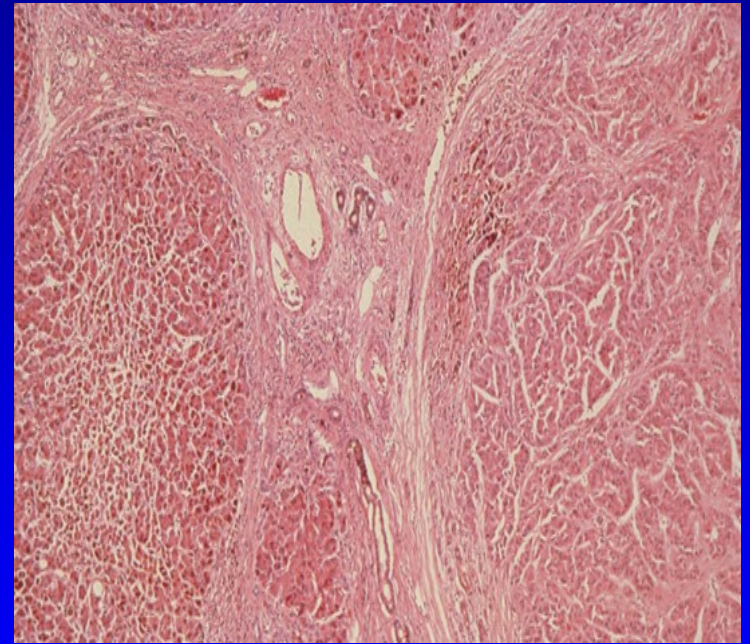
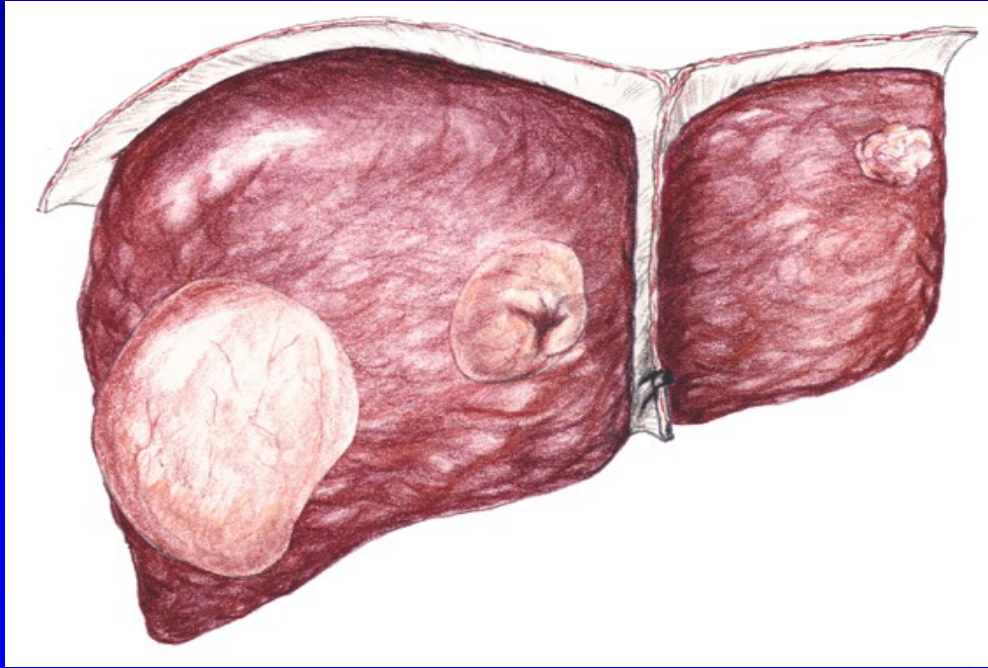








Hepatocellular carcinoma



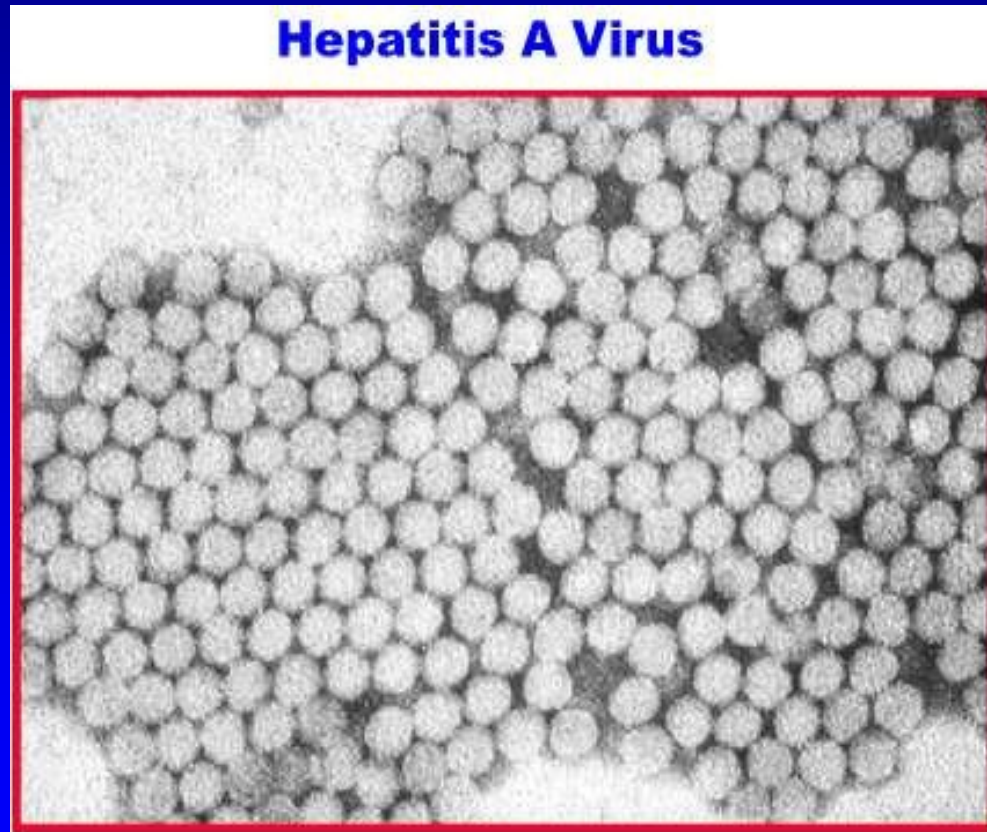


Viral Hepatitis in CR 2004-2013

| | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 |
|------|------|------|------|------|------|------|------|------|------|------|
| VH A | 70 | 322 | 132 | 128 | 1648 | 1104 | 862 | 264 | 284 | 348 |
| VH B | 392 | 361 | 307 | 307 | 306 | 247 | 244 | 192 | 154 | 133 |
| VH C | 868 | 844 | 1022 | 980 | 974 | 836 | 709 | 812 | 794 | 873 |
| VH E | 36 | 37 | 35 | 43 | 65 | 99 | 72 | 163 | 258 | 218 |

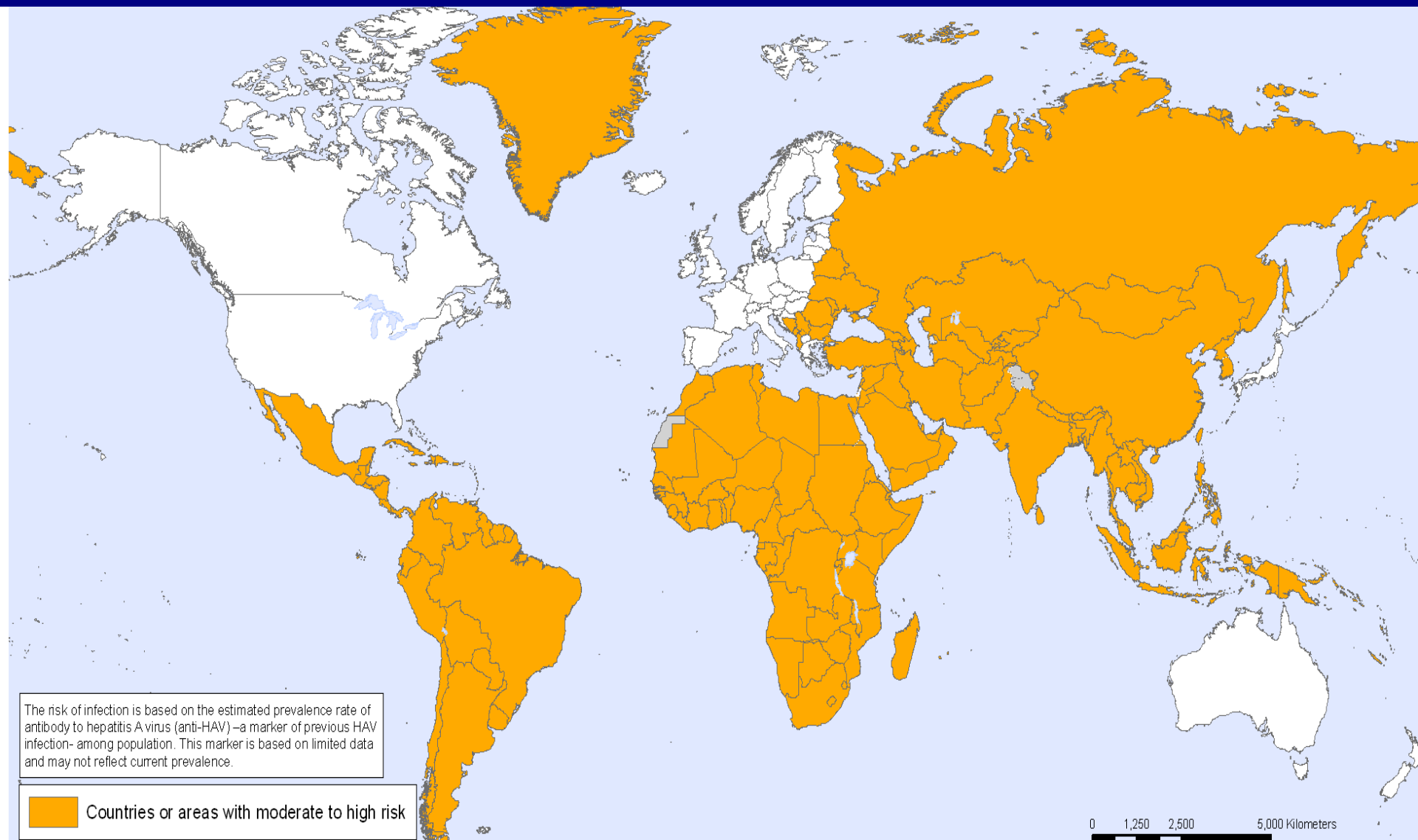
| | A | B | C | D | E |
|--------------------|----------|----------|----------|----------|-----------|
| Genom | RNA | DNA | RNA | RNA | RNA |
| Incubation | 15-50 | 30-180 | 15-180 | 30-180 | 15-60 |
| Enteral | Yes | No | No | No | Yes |
| Parenteral | Rare | Yes | Yes | Yes | No |
| Sexual | Rare | Yes | Rare | Yes | Rare |
| Vertical | No | Yes | Rare | Yes | Yes |
| Chronicity | No | Yes | Yes | Yes | Very rare |
| Vaccination | Yes | Yes | No | VH B | No |
| Imunoglob. | Yes | Yes | No | VH B | No |

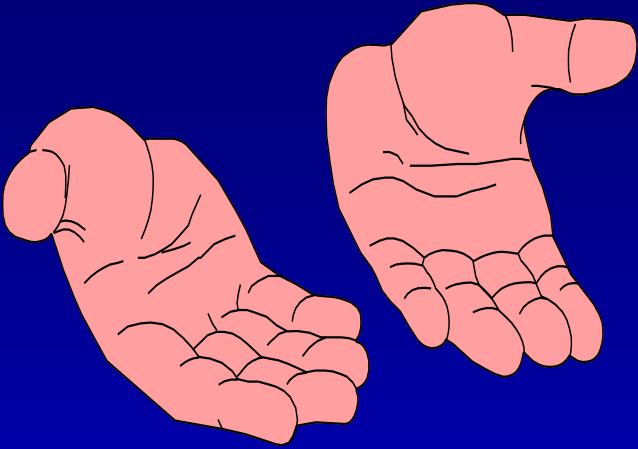
Hepatitis A



family *Picornaviridae*, genus *Hepatovirus* – non-enveloped RNA, 27 nm

Hepatitis A

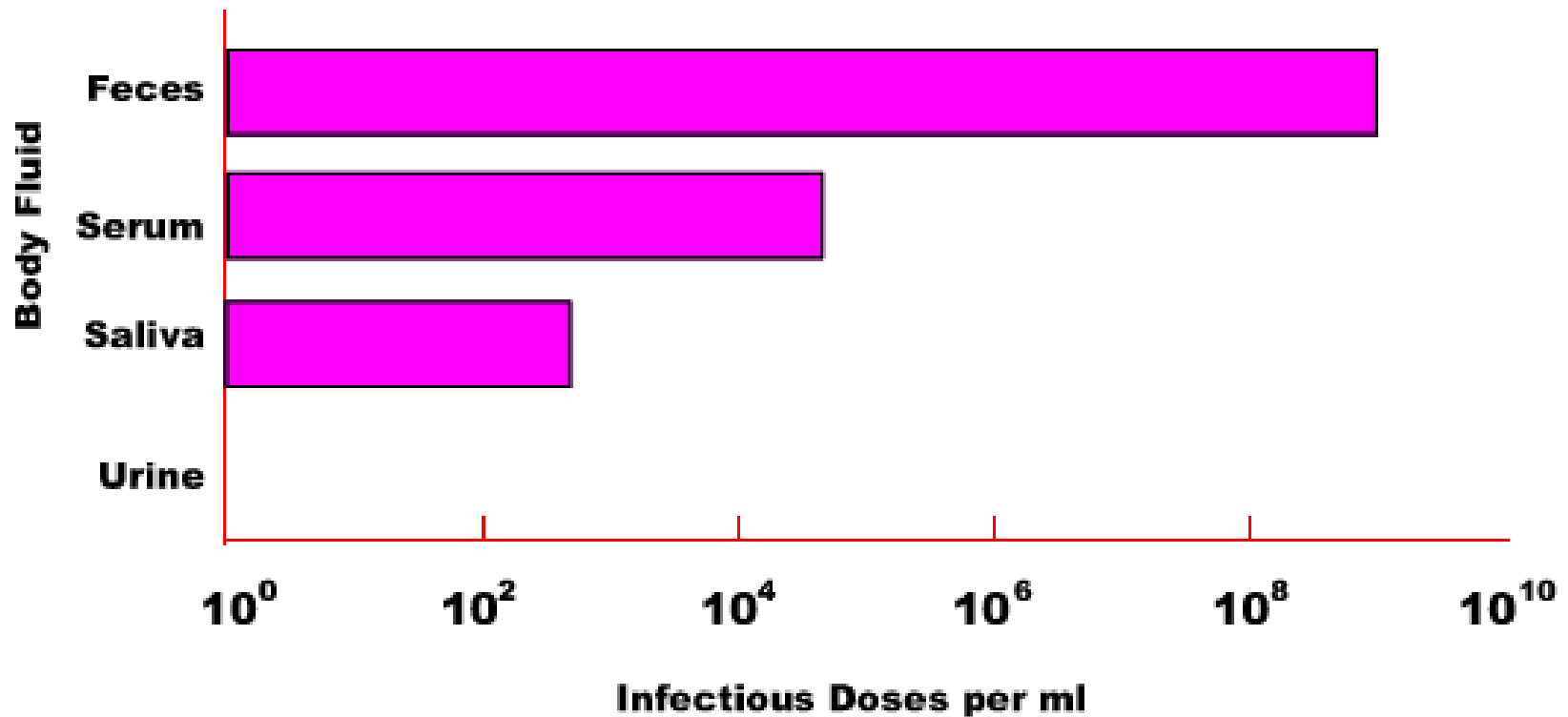




Epidemiology

- **Fecal –oral route of transmission**
 - ✓ Contaminated hands or daily used instruments
 - ✓ Contaminated drinking water
 - ✓ Contaminated food
- Vaccination available, recommended especially for travelers to countries with lower standard of hygiene

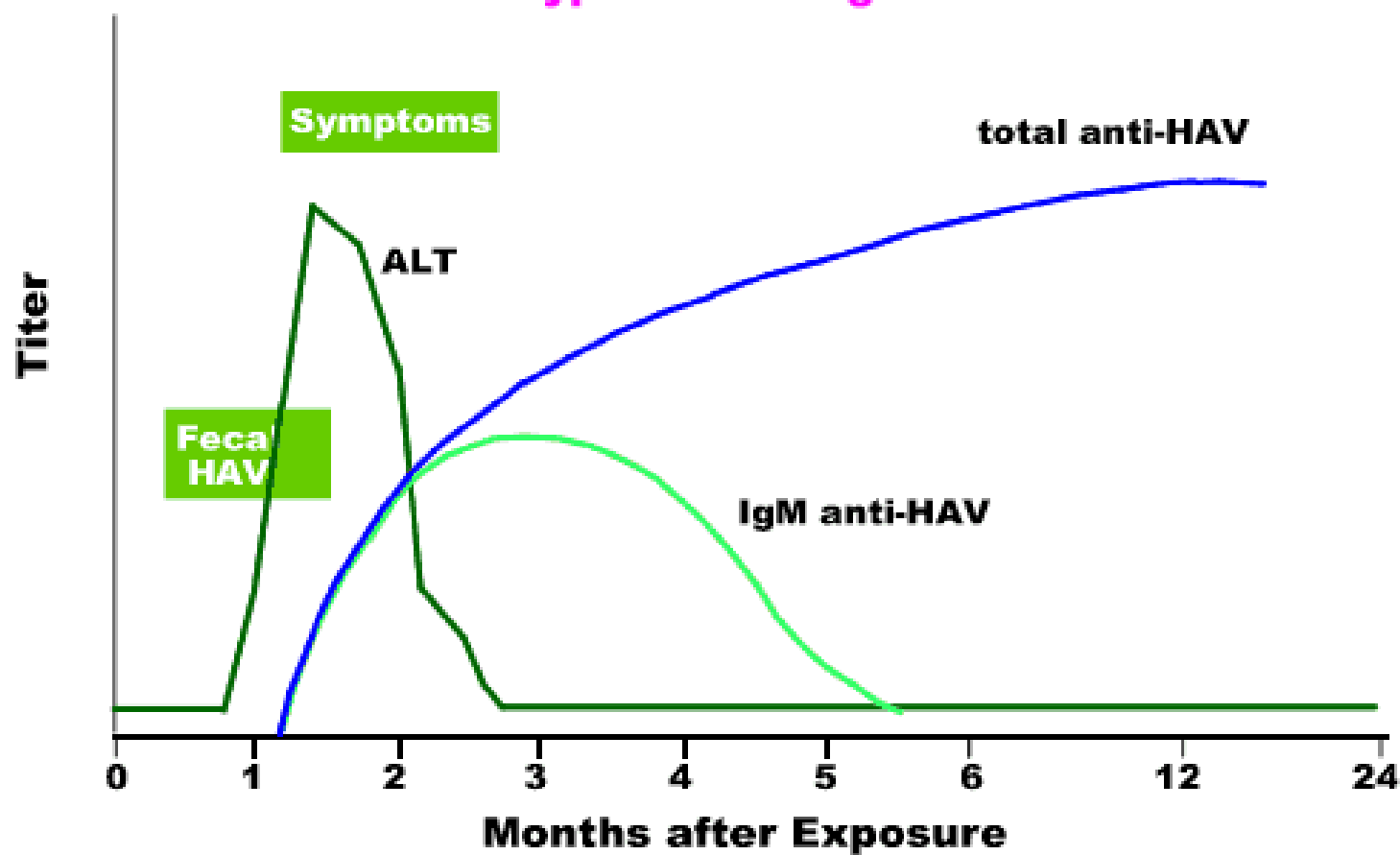
Concentration of Hepatitis A Virus in Various Body Fluids



Source: Viral Hepatitis and Liver Disease 1984;9-2
J Infect Dis 1989; 160:887-890

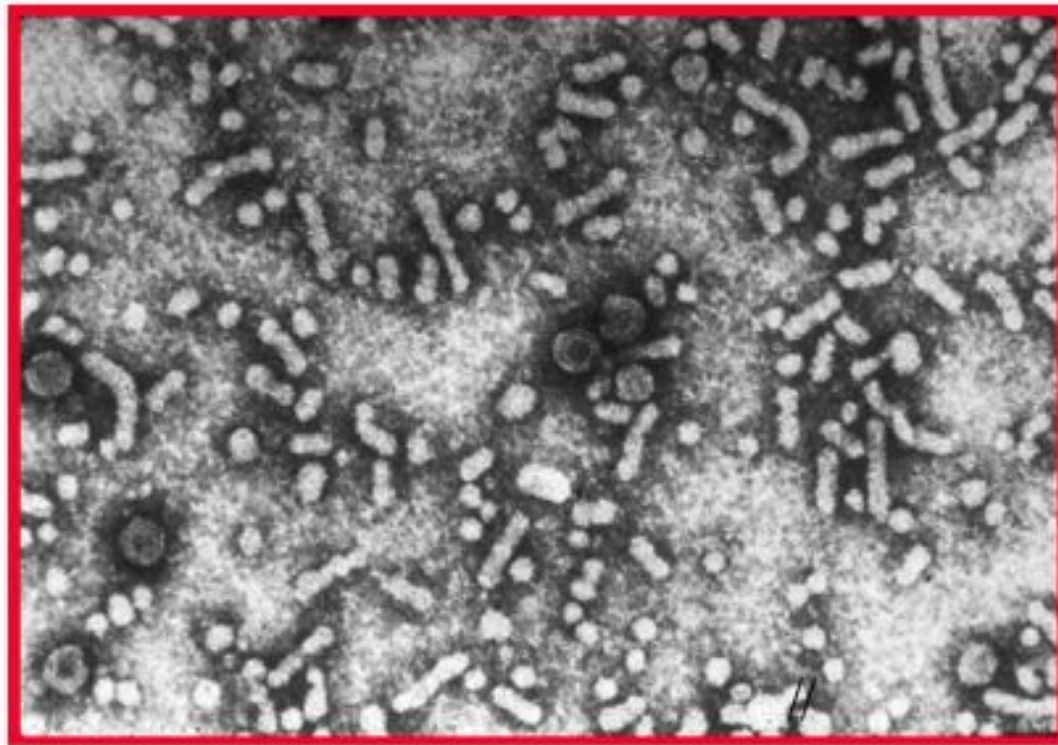
Hepatitis A Virus Infection

Typical Serologic Course



Hepatitis B

Hepatitis B Virus



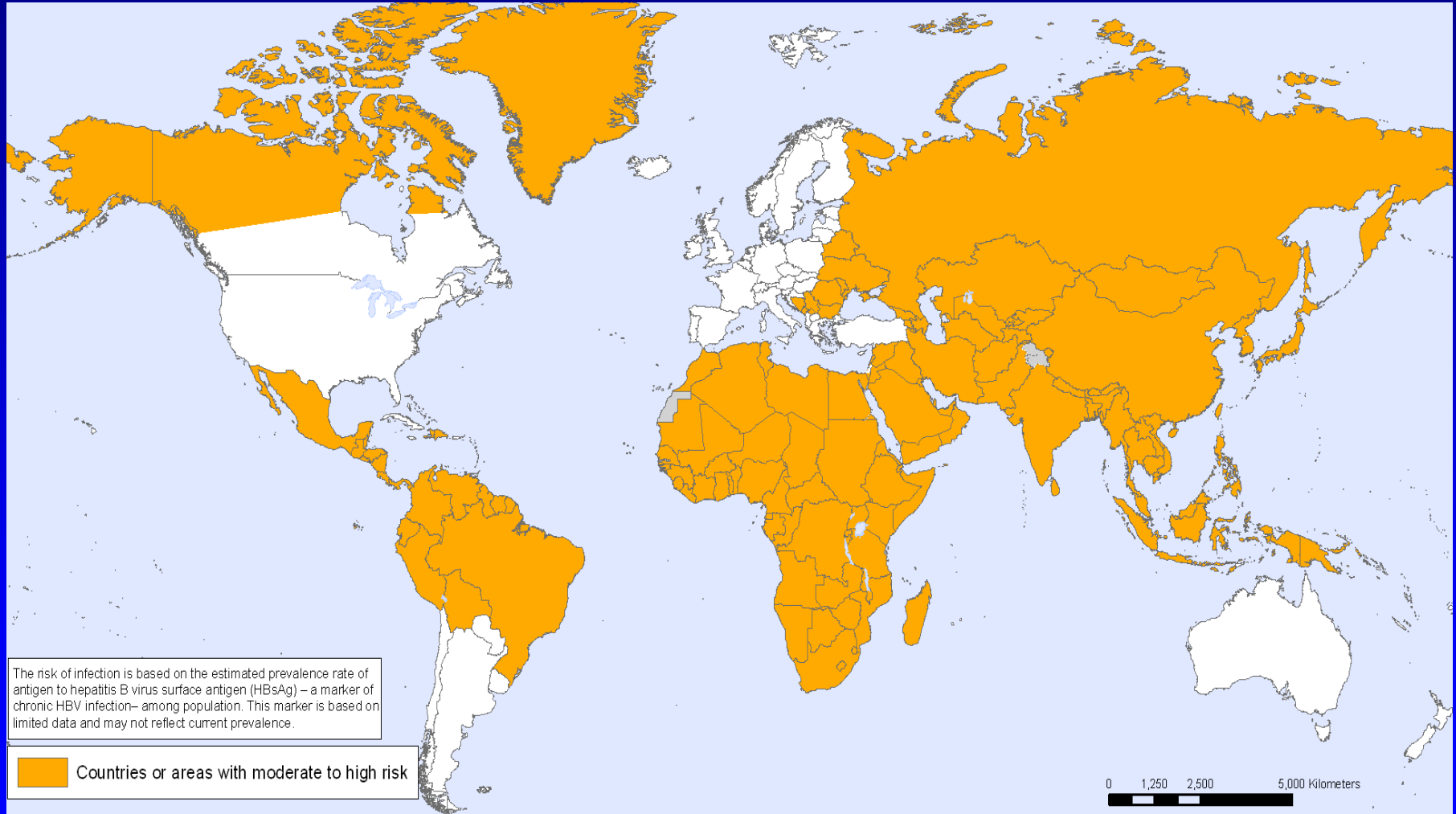
family *Hepadnaviridae*, enveloped DNA virus, 42 nm

Global significance of HEP B

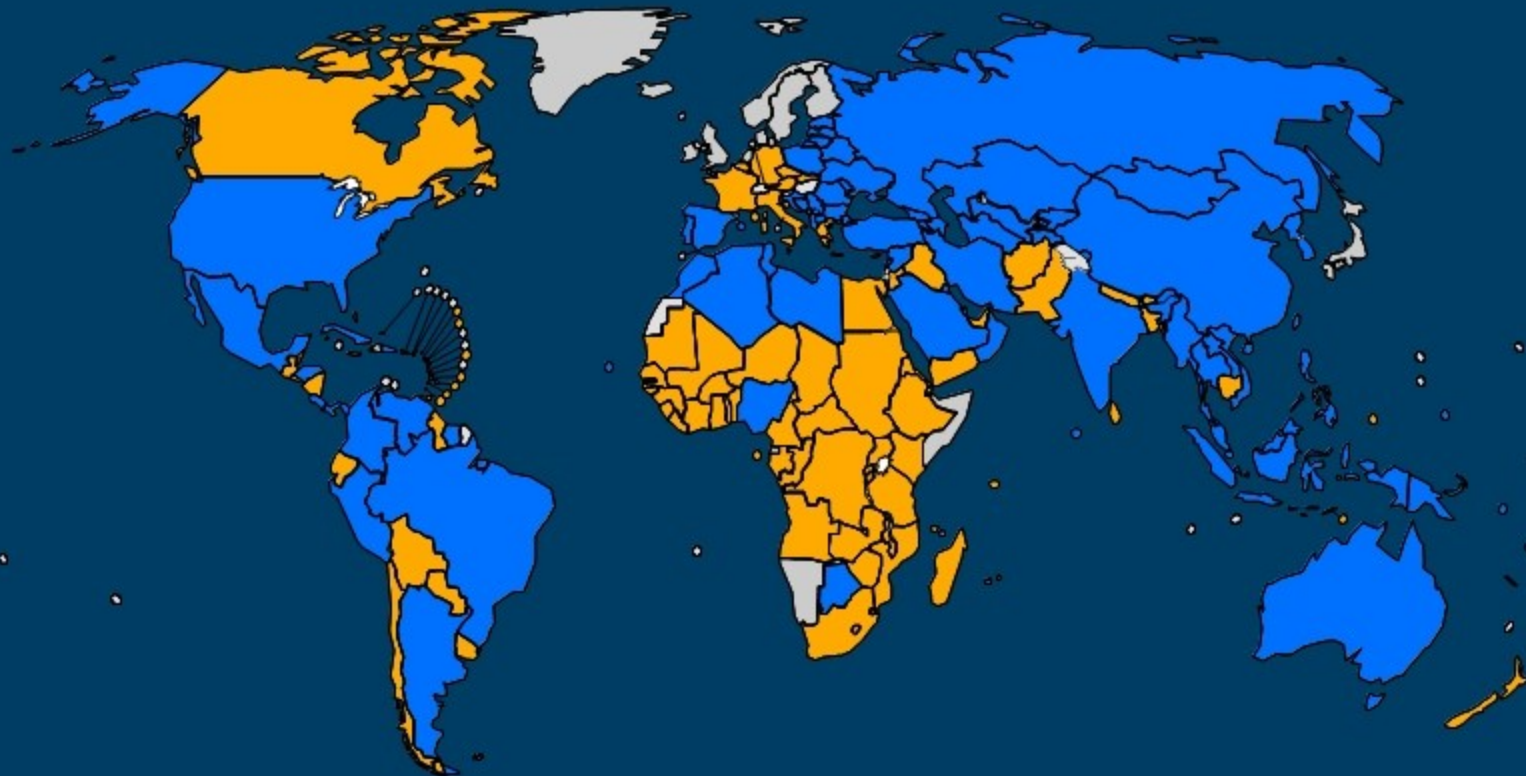
- One of the biggest global health problems
 - ✓ More than 2 billions of infections during the life
 - ✓ 350-400 million chronic carriers - China (125 million), Brazil (3,7 million), South Korea (2,6 million), Japan (1,7 million), USA (more than 1 million), Italy (900 thousand).
 - ✓ 25-40 % chronic carriers have LC or HCC, 0,5-1,0 million deaths due to decompensated LC or HCC
 - ✓ 50 thousand death annually due to fulminant hepatitis
 - ✓ Global vaccination in 177 countries (2008)






Hepatitis B



Countries using HepB in national immunization schedule, 2008



Source: WHO/IVB database, 193 WHO Member States.
Data as of August 2009
Date of slide: 24 November 2009

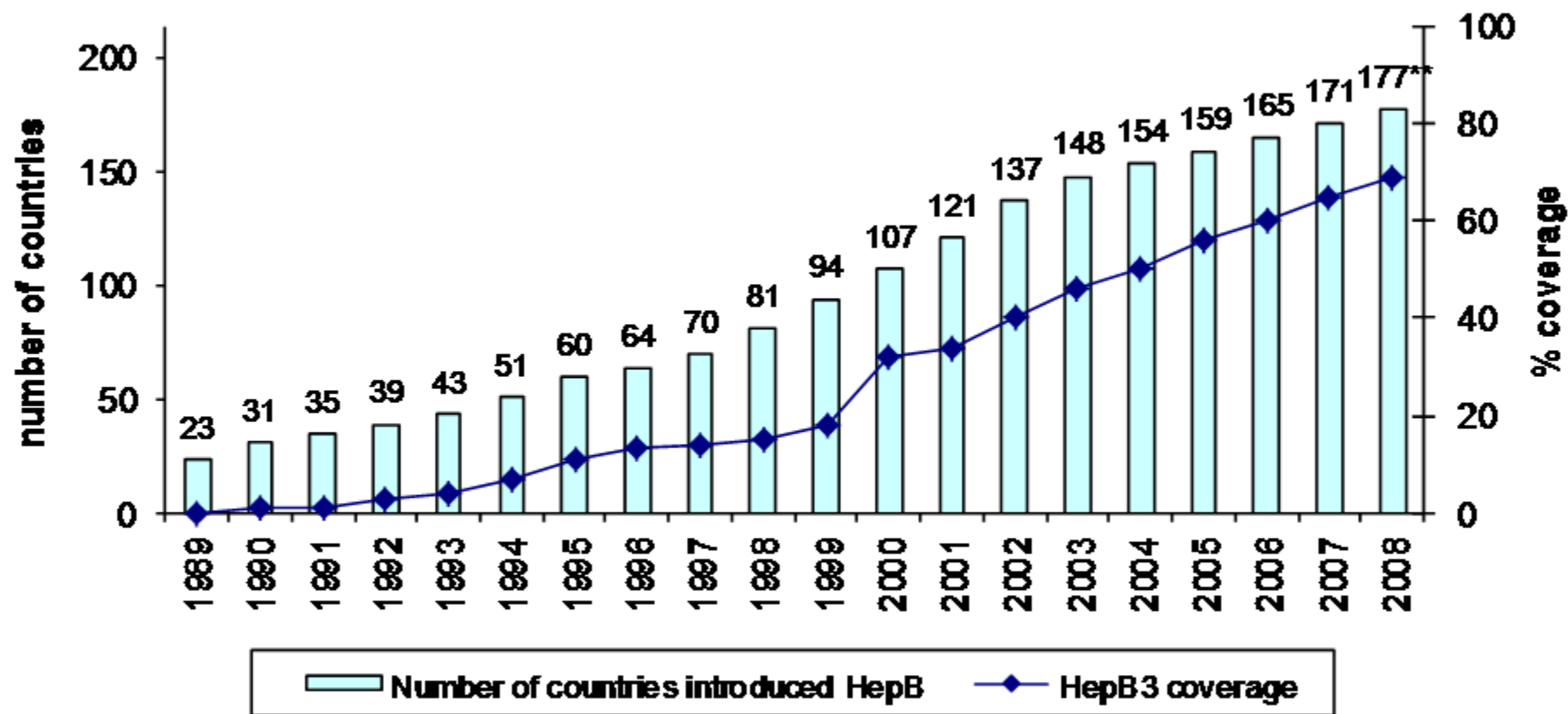
-  No HepB (16 countries¹ or 8%)
-  HepB no Birth Dose (92 countries² or 48%)
-  HepB with Birth Dose (85 countries³ or 44%)

¹Includes three countries with adolescent immunization
²Includes 21 countries with partial introduction
³Includes India with partial introduction

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its boundaries, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.
© WHO 2009. All rights reserved.



Number of countries having introduced HepB vaccine* and global infant coverage, 1989-2008



* Year of introduction can be the year of partial introduction

** Includes India and Sudan with partial introduction excluding 3 countries where HepB administered for adolescence

Source: WHO/UNICEF coverage estimates 1980-2008, August 2009, 193 WHO Member States. Date of slide: August 2009

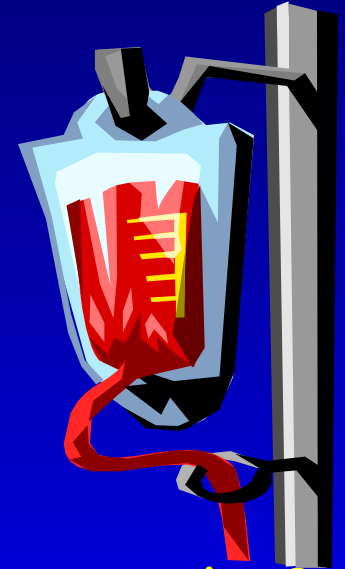


Hepatitis B in Czech Republic

- Still important infection but incidence and prevalence are gradually decreasing
 - ✓ Prevalence of chronic carriers was 0.56 % (2001)
 - ✓ Prevalence of historical antibodies anti-HBc total was 5,59% (2001)
 - ✓ Decrease of prevalence and incidence due to vaccination of high-risk persons (health care workers, newborns of HBsAg-positive mothers, before hemodialysis)
 - ✓ Global vaccination of all newborns and 12-years old children since 2001

Epidemiology of HEP B

- **Transmission**
 - ✓ blood and blood products
 - ✓ sexual intercourse
 - ✓ organ and tissue transplant recipients
 - ✓ vertically from mother to newborn
- **Who is in the highest risk in well-developed countries?**
 - ✓ intravenous drug abusers
 - ✓ persons with multiple sexual partners



Clinical pictures of acute HEP B

- **IP:** 30–180 days (mostly 2–3 months)
- **Prodromal stage** - flu-like syndrome
- **Icteric form:** < 5 years < 10 %, > 5 years (30–50 %)
- **Chronicity:** newborns > 90 %, children 30-40 %, adults 5–10 %
- **Fulminant hepatitis:** < 1 %
- **Chronic HBV infection mortality:** 15 – 25 %



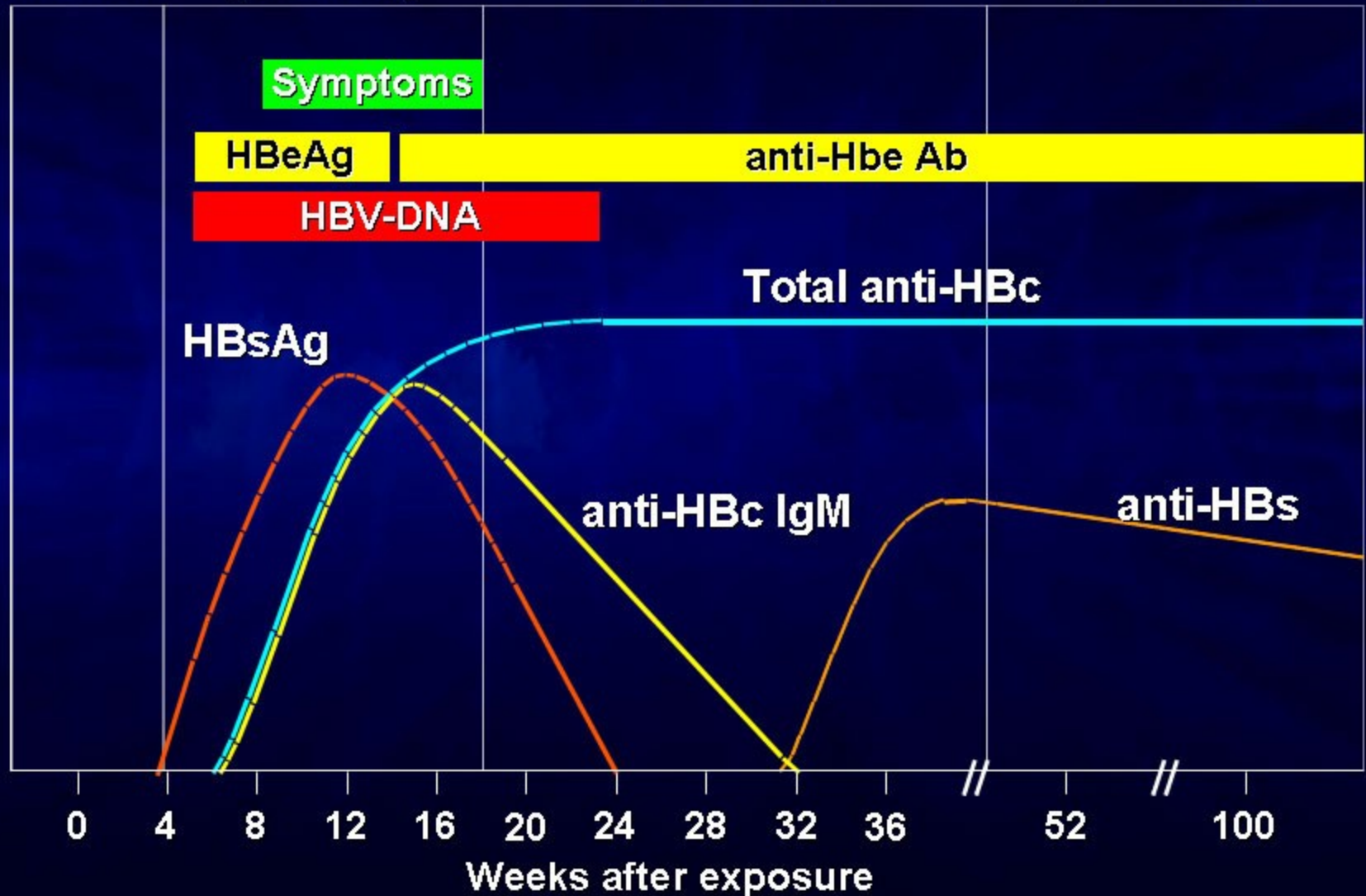
Acute Hepatitis B

Incubation
4-12 weeks

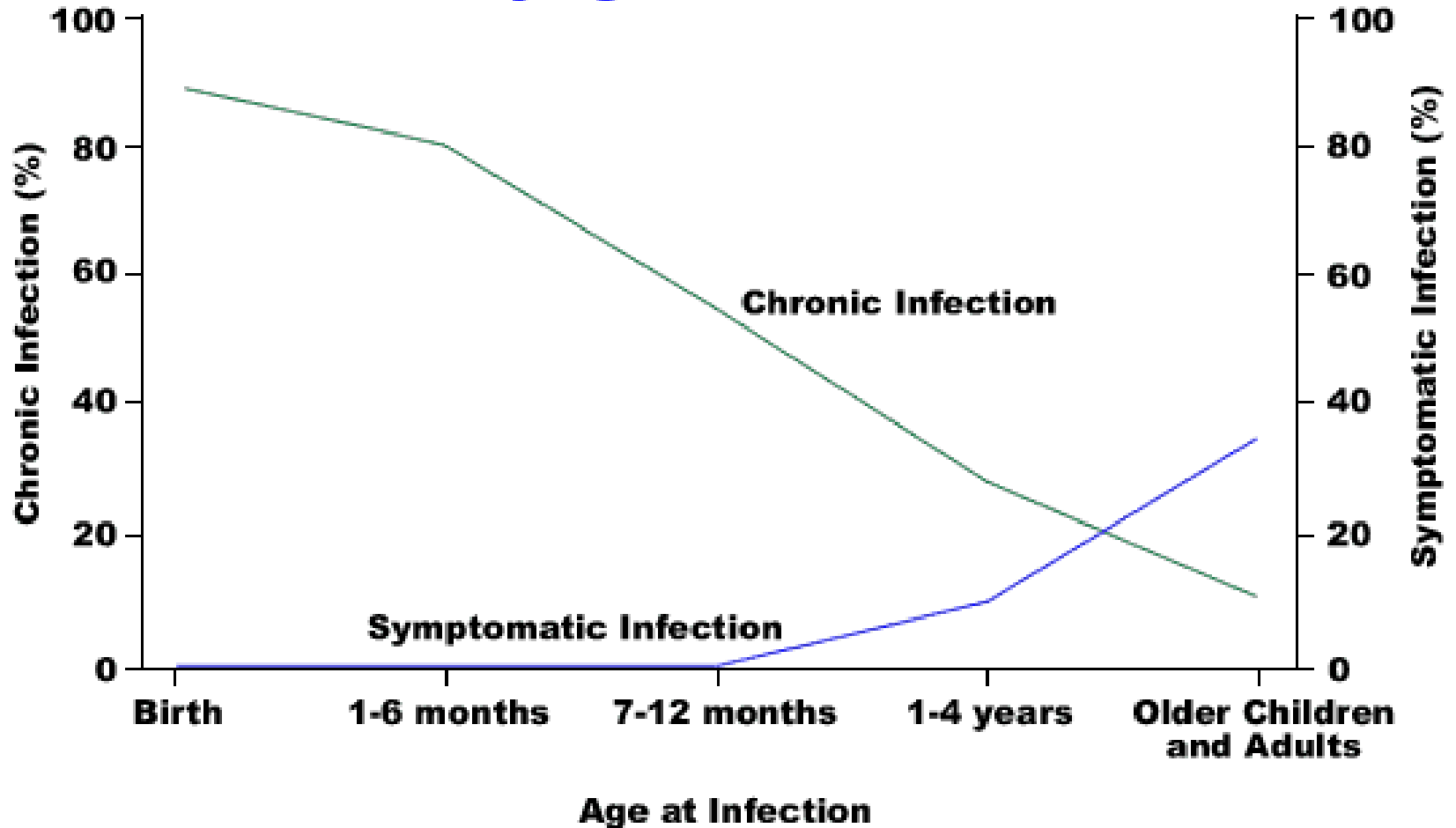
Acute infection
(2-12 weeks)

Early recovery
(12-24 weeks)

Recovery
(24-48 weeks)



Outcome of Hepatitis B Virus Infection by Age at Infection

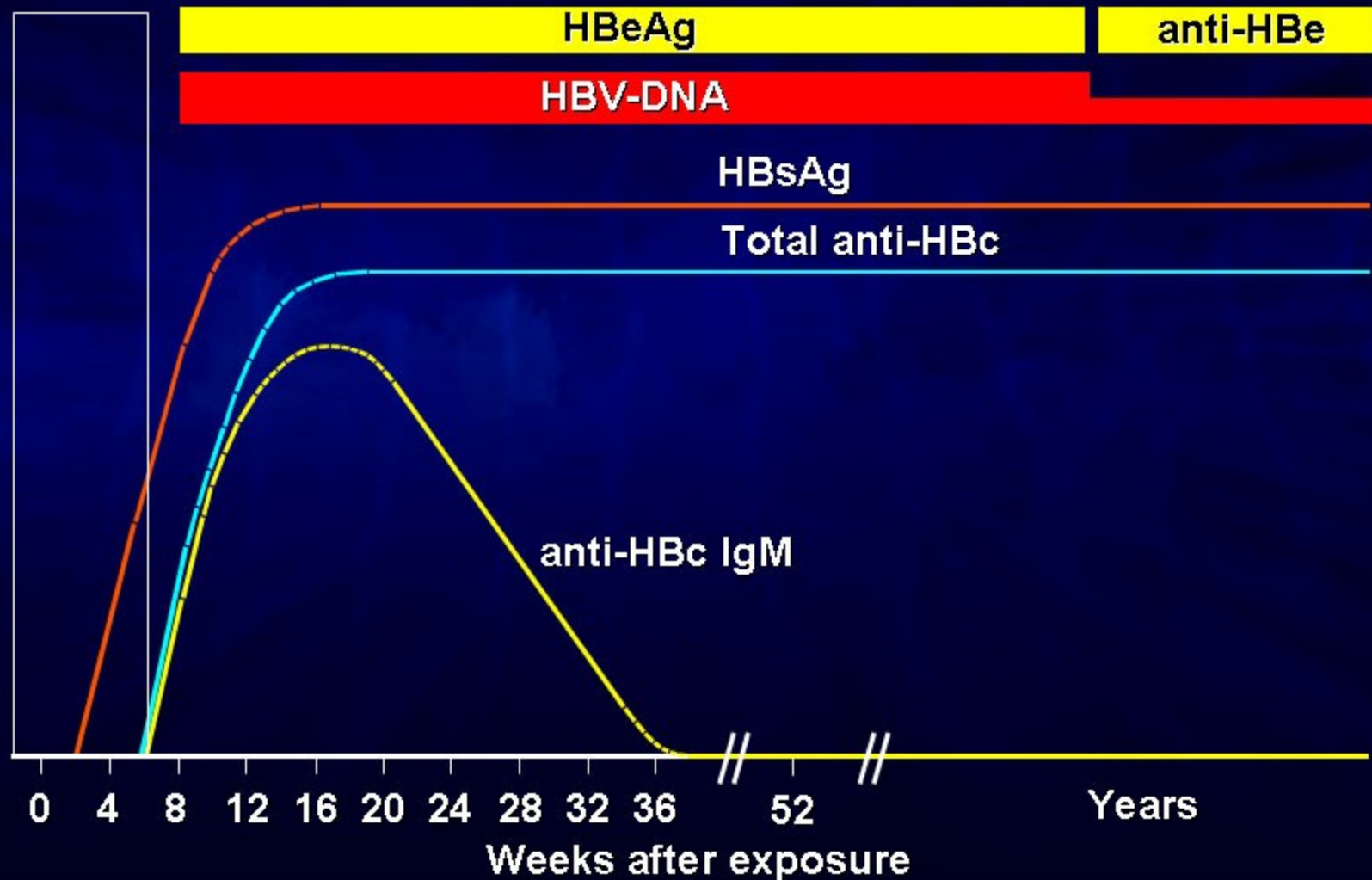


Chronic Hepatitis B (HBeAg+)

Incubation
(4-12 wk)

Acute
(6 months)

Chronic
(Years)

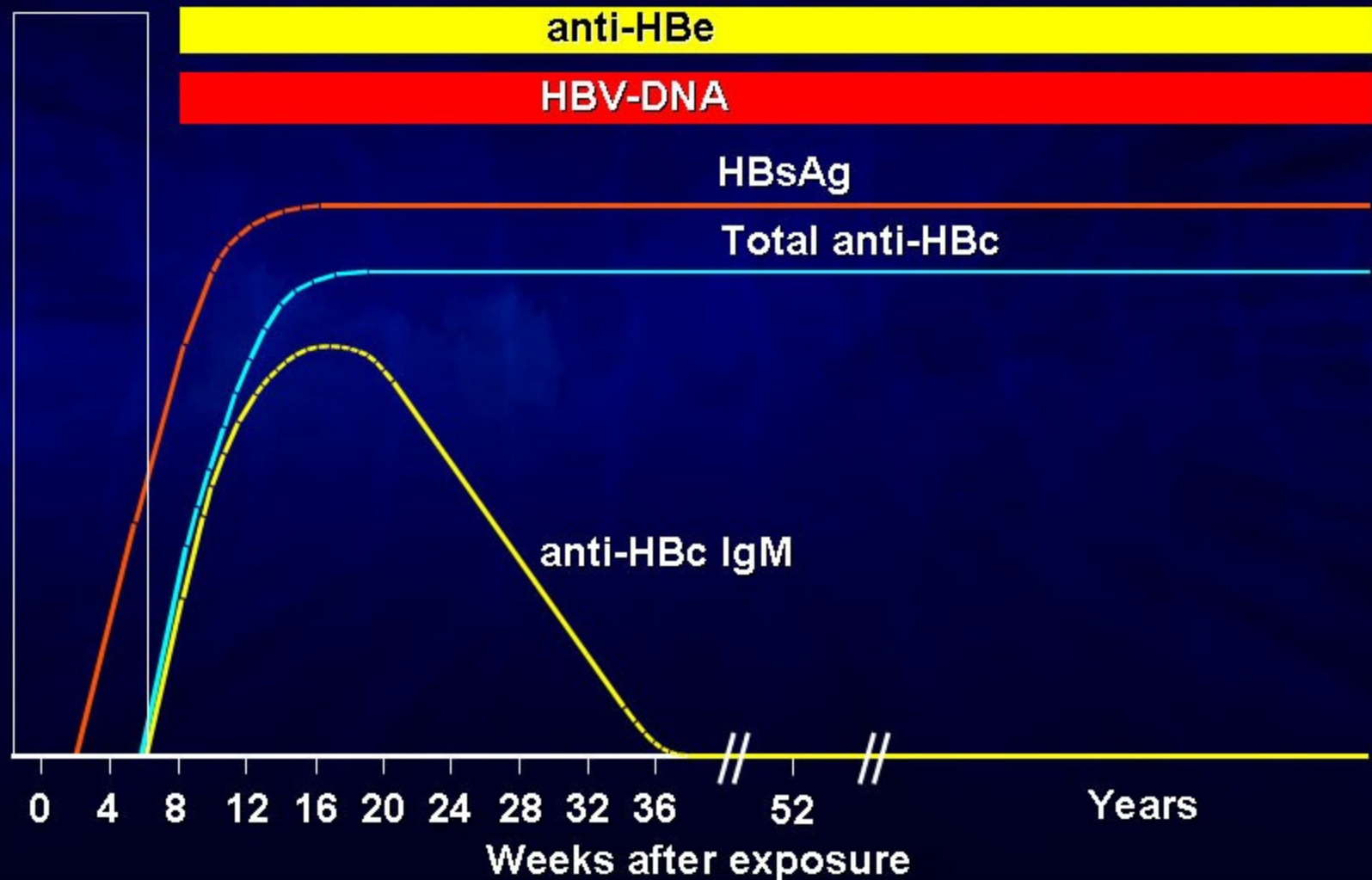


Chronic Hepatitis B (HBeAg-)

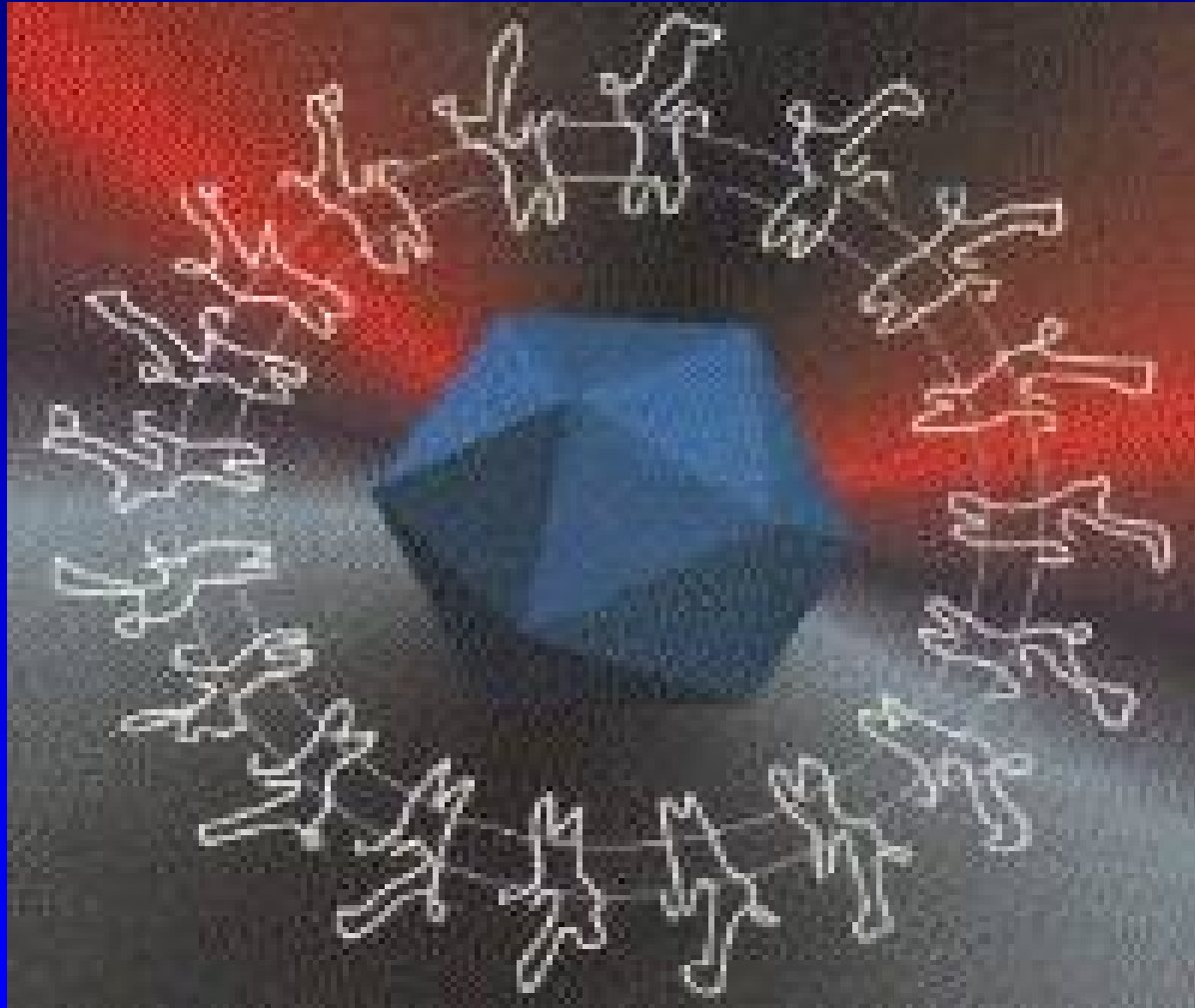
Incubation
(4-12 wk)

Acute
(6 months)

Chronic
(Years)

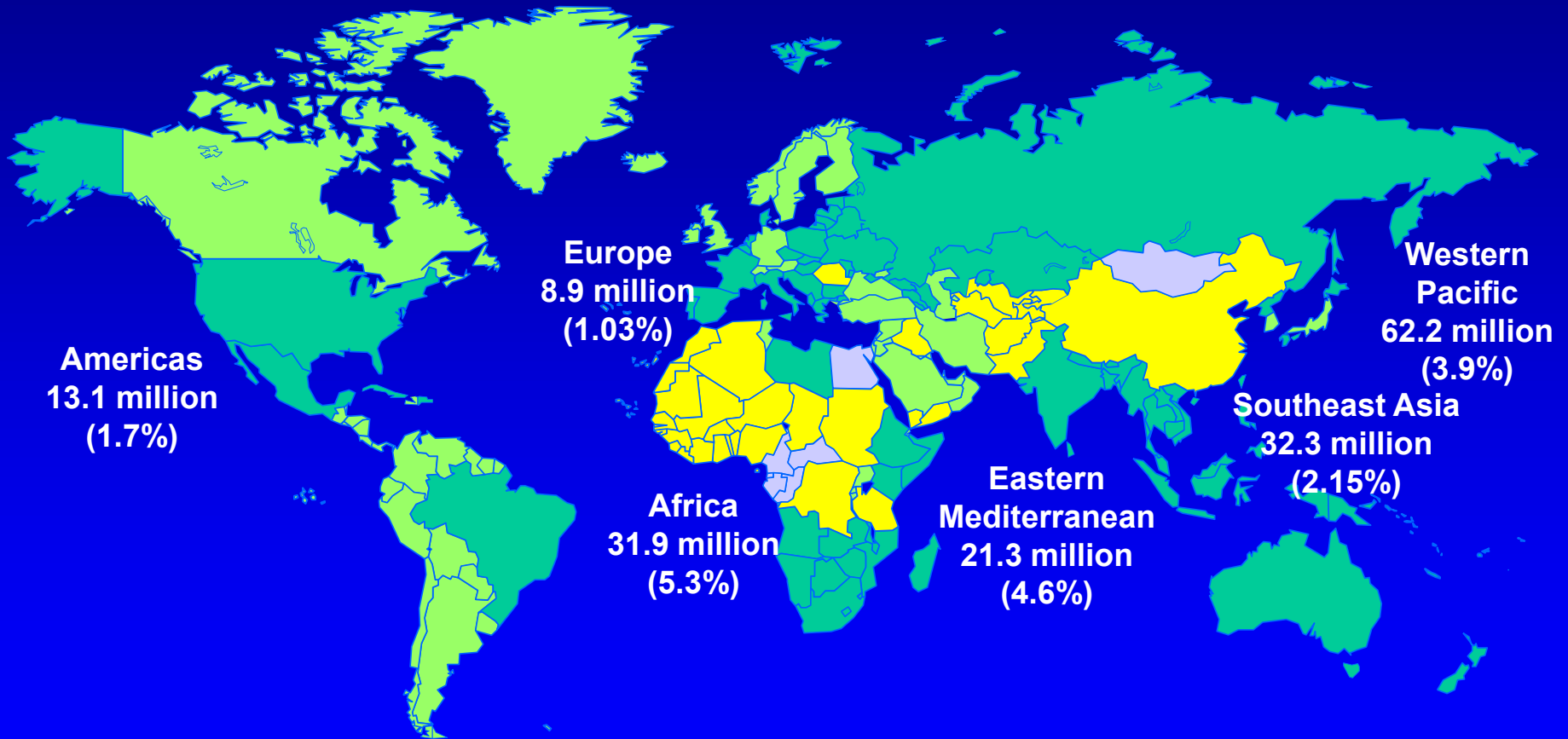


Hepatitis C



family Flaviviridae, genus Hepacivirus, enveloped RNA virus 60 nm

Hepatitis C



World Health Organization. Wkly Epid Rec .1999;74:425-427. World Health Organization. Hepatitis C: Global Prevalence: Update. 2003. Farci P, et al. Semin Liver Dis. 2000;20:103-126. Wasley A, et al. Semin Liver Dis. 2000;20:1-16.

Distribution of HCV genotypes

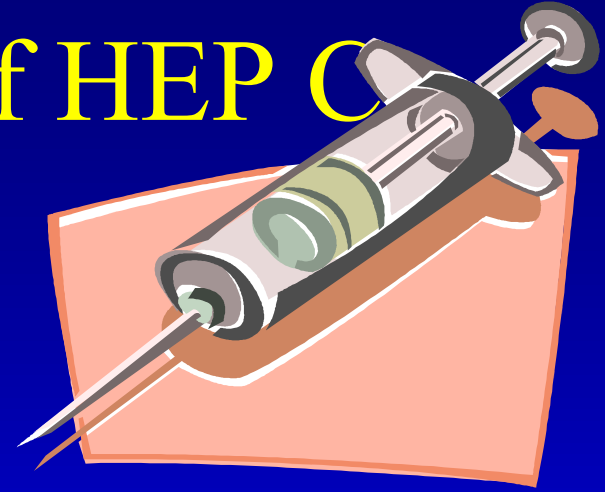




Hepatitis C

- Significant global health problem
 - ✓ about 3 % of the world population are chronically infected with HCV
 - ✓ In well-developed countries about 20 % of all acute hepatitis, 70 % chronic hepatitis, 40 % cirrhosis, 60 % HCC and indication to 30 % liver transplantations
- In Czech Republic
 - ✓ prevalence 0,2 % (2001)
- No vaccine, no hyper-immune immunoglobulin

Epidemiology of HEP C



- **Transmission:**
 - ✓ blood and blood products
 - ✓ sharing of used injection needles and syringes
 - ✓ sexually (rare)
 - ✓ vertically (rare)
- **Who is in the highest risk of HCV infection at present?**
 - ✓ intravenous drug abusers
- **Infection is frequently diagnosed in chronic stage**

Patients with higher risk of HCV infection

- ✓ Intravenous drug abusers (sharing of injection needles and syringes)
- ✓ Recipients of blood transfusions before the year 1992 (especially hemophiliacs)
- ✓ Persons with tattoo or piercing



Clinical course of HEP C

- Acute hepatitis is mostly asymptomatic
- Probability of chronicity is high (40-50% till 90-100%).

Higher probability of chronicity:

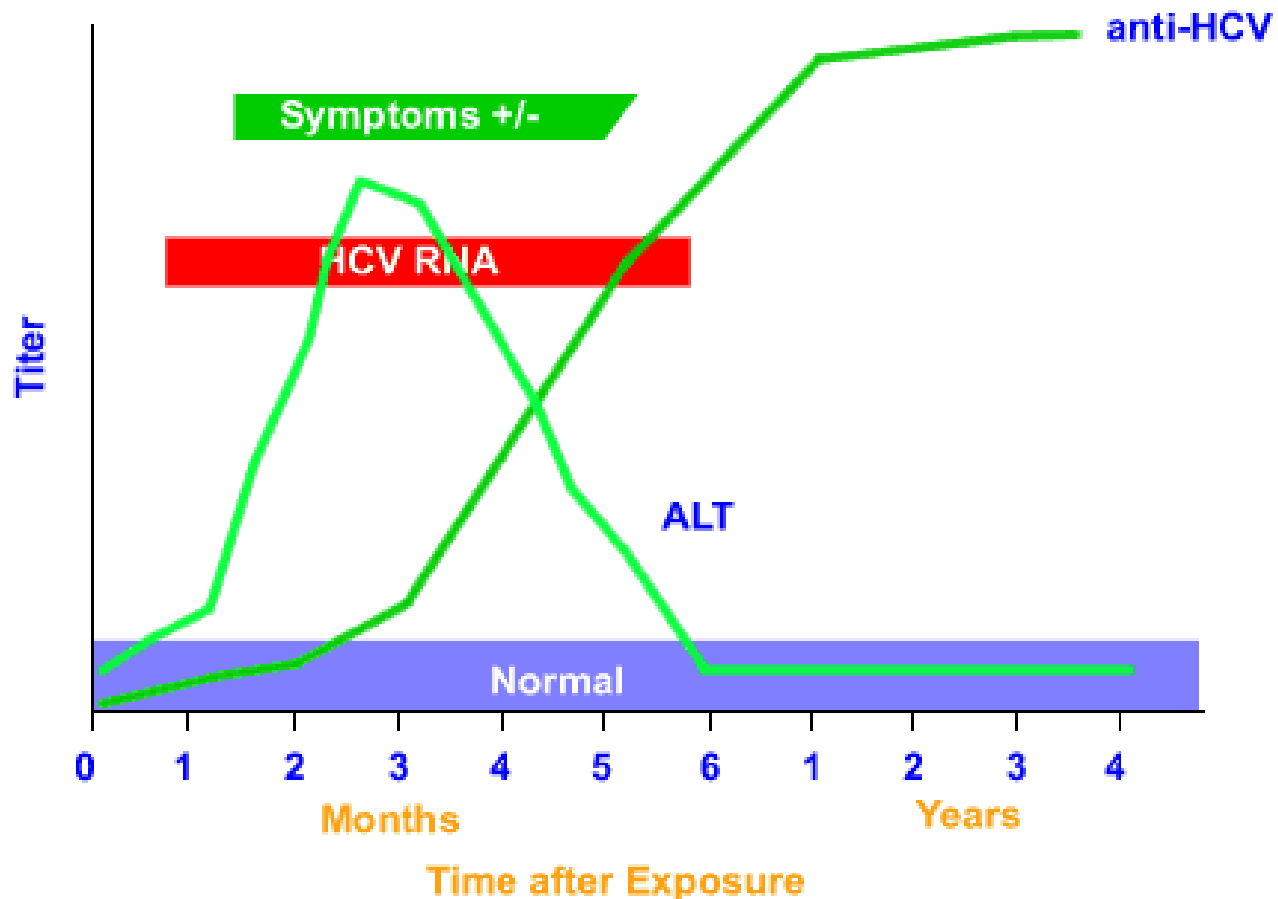
- ⇒ Older persons
- ⇒ Higher initial infection dose (transfusion versus needles)
- ⇒ HBV, HIV co-infection
- ⇒ abusus of alcohol
- ⇒ immunodeficiency

Clinical course of HEP C

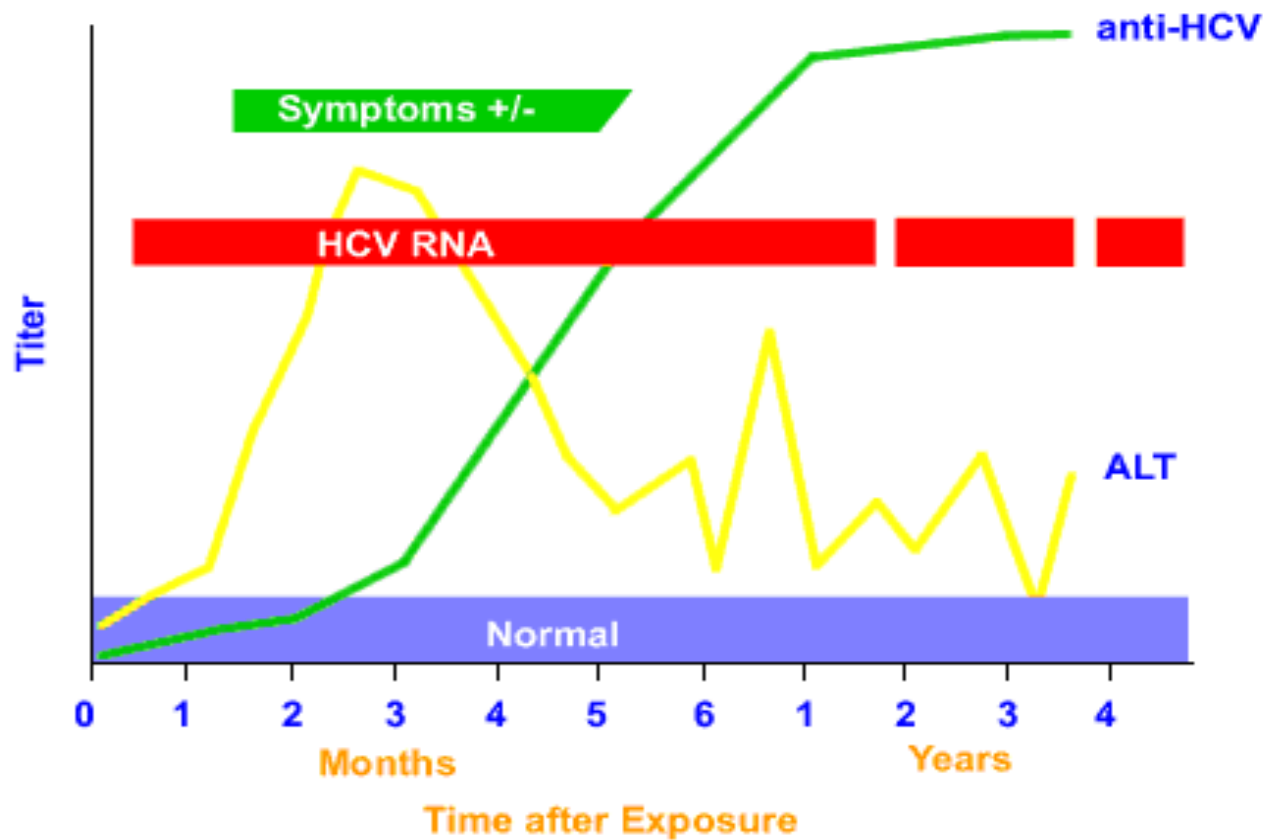
- LC in about 20 % patients with chronic HCV infection
- HCC annually in 1-4 % patients with LC
- Progression to HCC depends on:
 - ✓ age (more rapid progression in older persons)
 - ✓ alcohol abuse
 - ✓ HIV co-infection
 - ✓ HBV co-infection



Serologic Pattern of Acute HCV Infection with Recovery

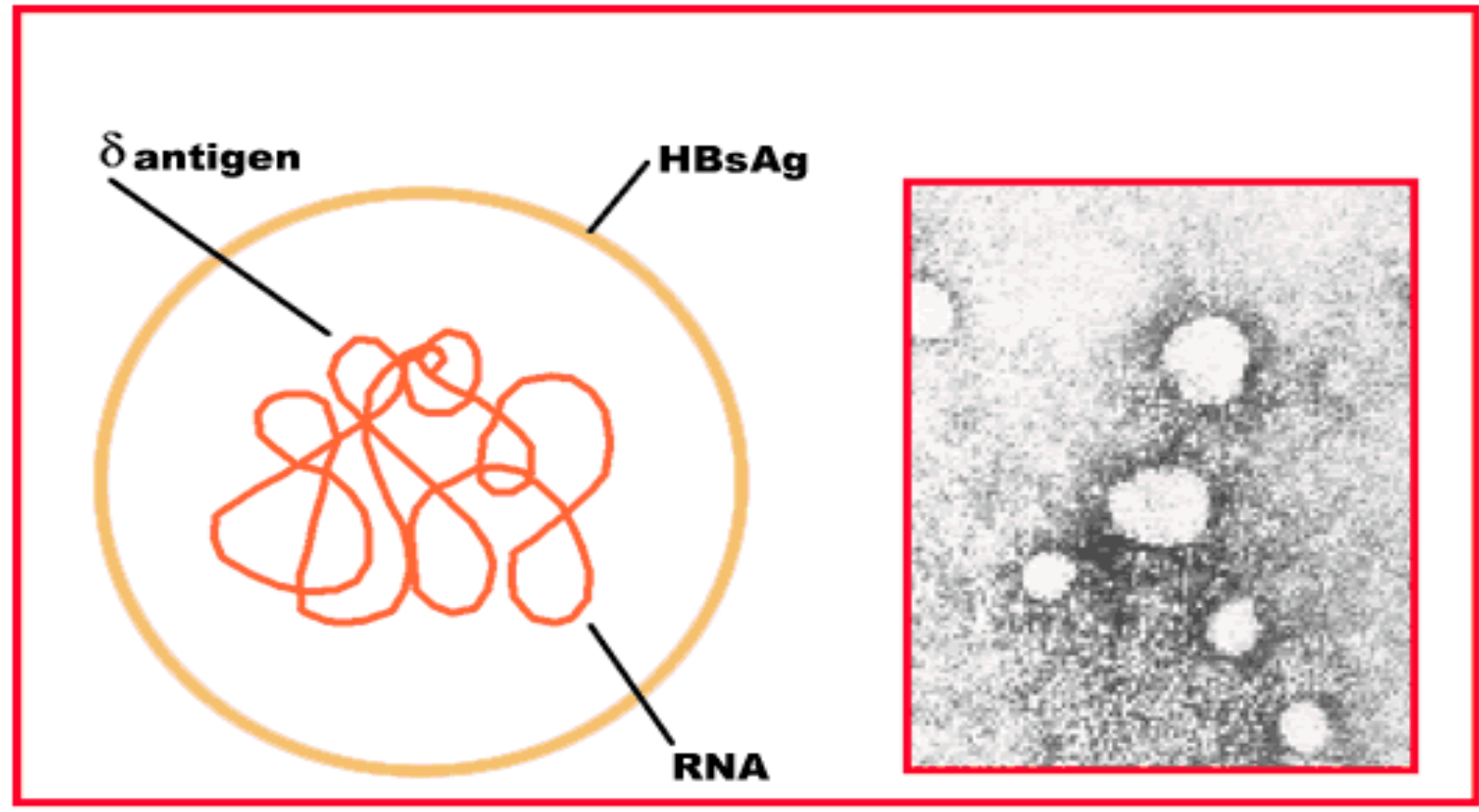


Serologic Pattern of Acute HCV Infection with Progression to Chronic Infection

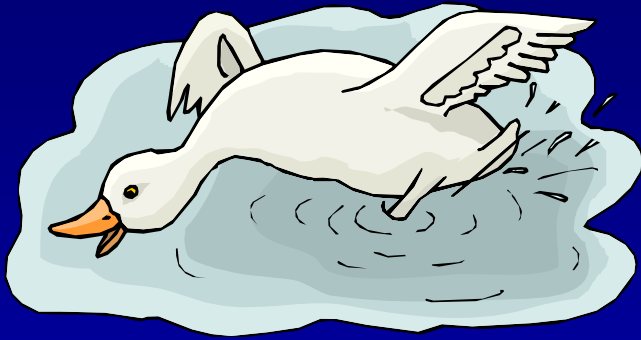


Hepatitis D

Hepatitis D (Delta) Virus



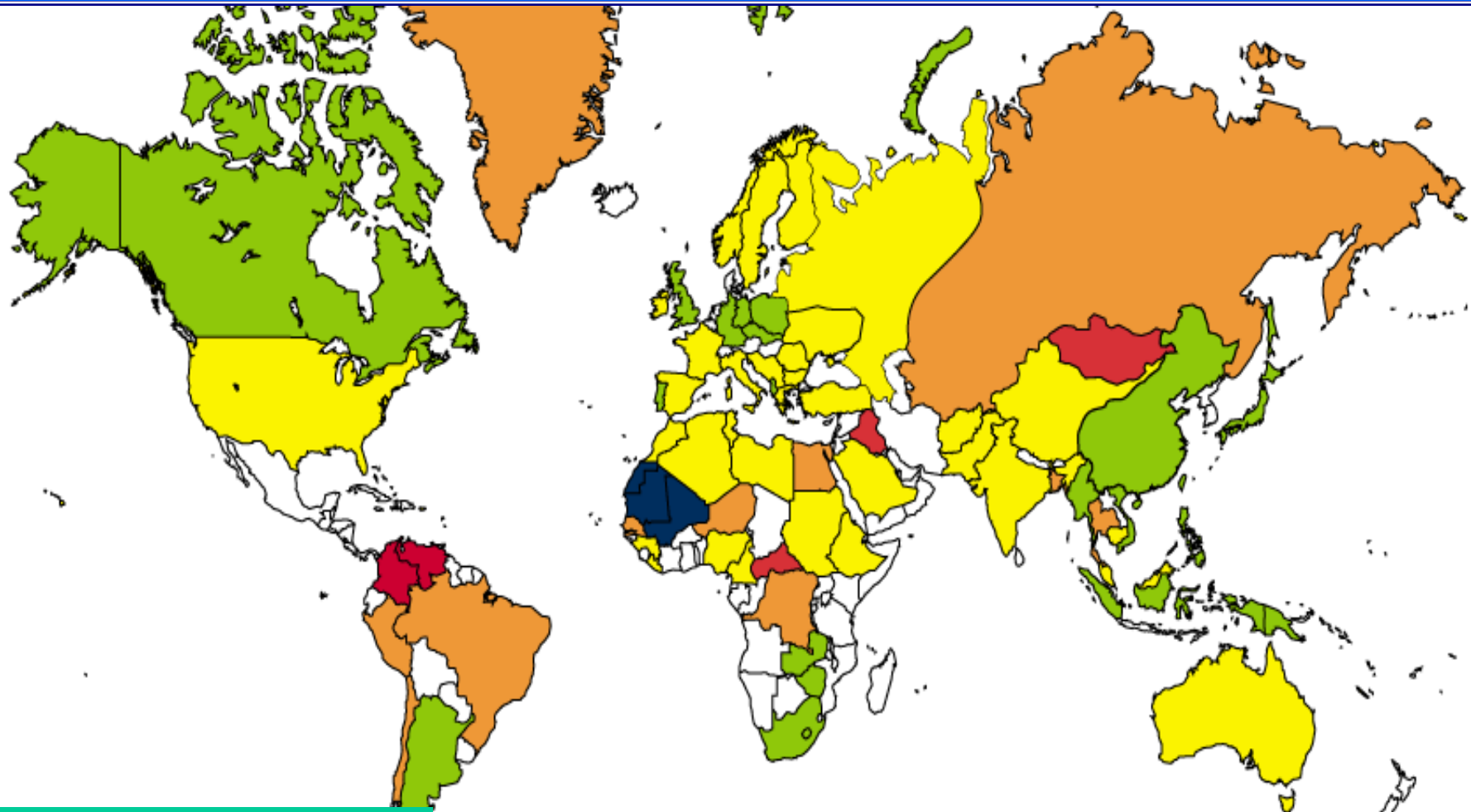
Satellite virus, family *Deltaviridae*, enveloped RNA, 40 nm



Hepatitis D

- Ability of replication only in presence of HBV infection
- ✓ Co-infection (better prognosis)
- ✓ Super-infection (worse prognosis)
- **Endemic** in South America, Mediterranean Region, Romania, Central Africa
- **Very low prevalence in CR**

Anti-HDV prevalence in HBsAg-positive (approximately 15 000 000 persons)



HDV

Anti-HD(HBsAg (+)) ? 0-5% 6-20% 21-60% >60%

Rizzetto M. *EASL 2009*

Epidemiology of HDV in Europe

1980s

-  **Endemic**
-  **In risk groups**

Drug addicts



Rizzetto M. EASL 2009

Epidemiology of HDV in Europe

2009



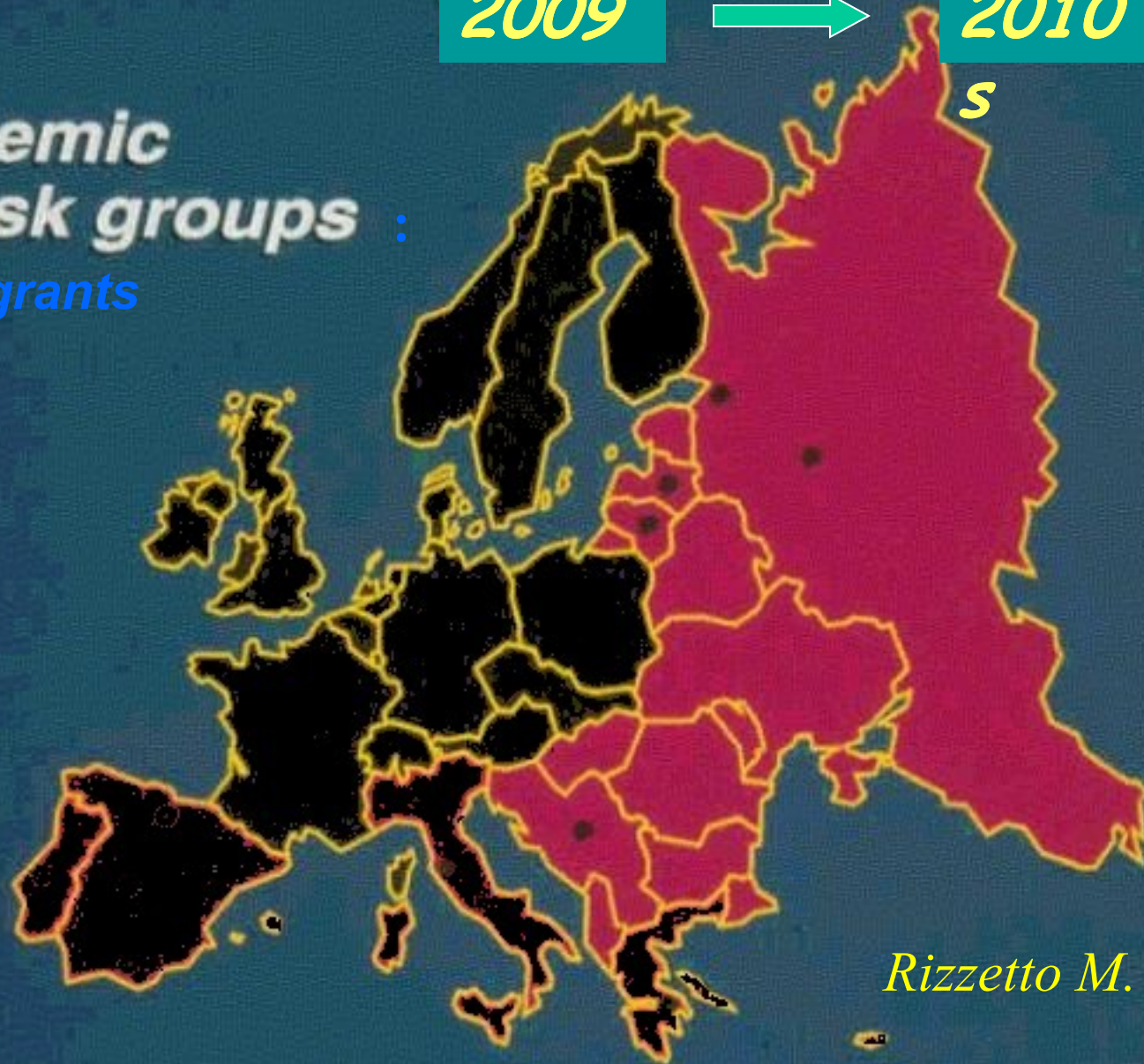
2010

5

 Endemic

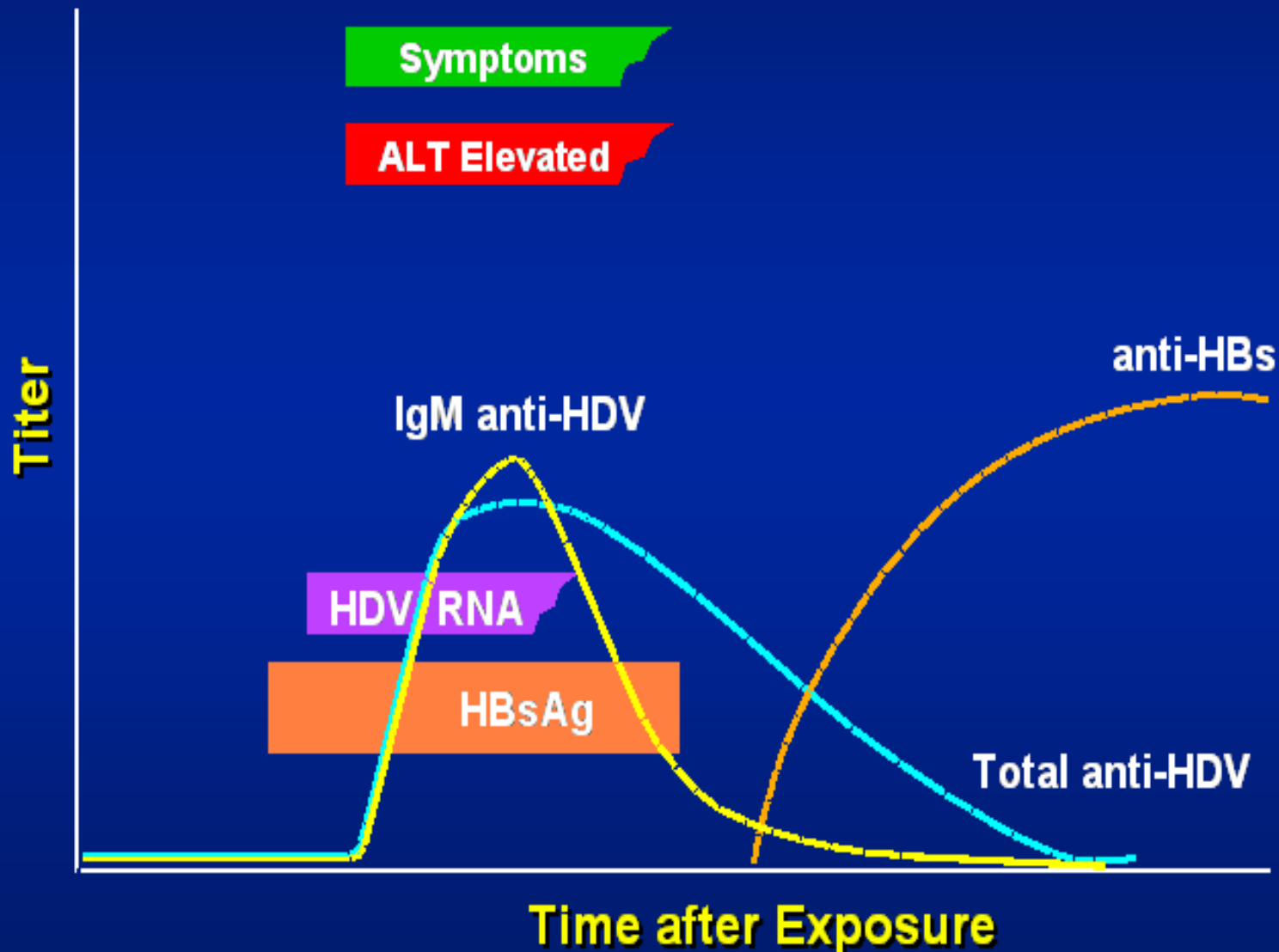
 In risk groups :

• immigrants

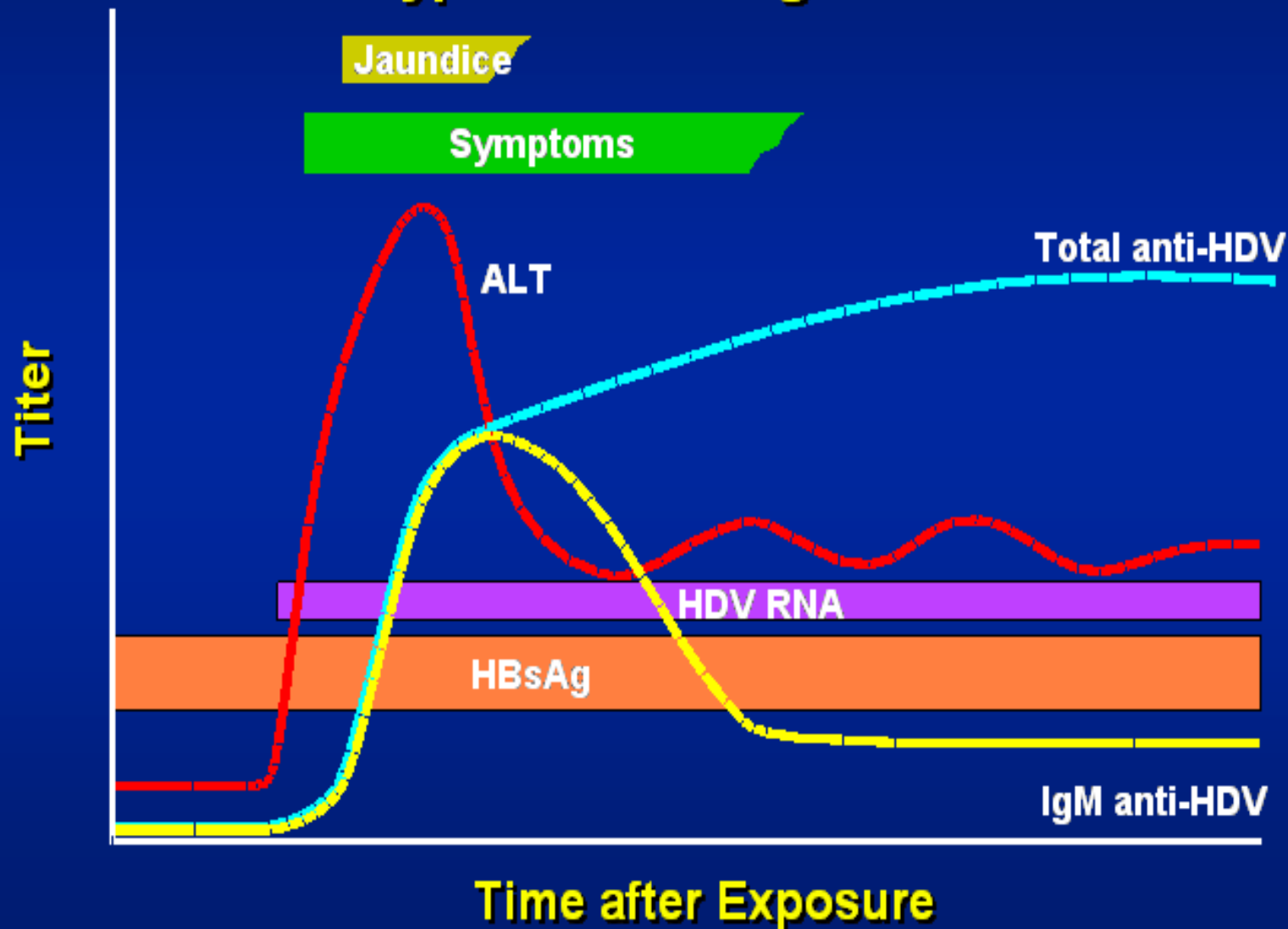


Rizzetto M. EASL 2009

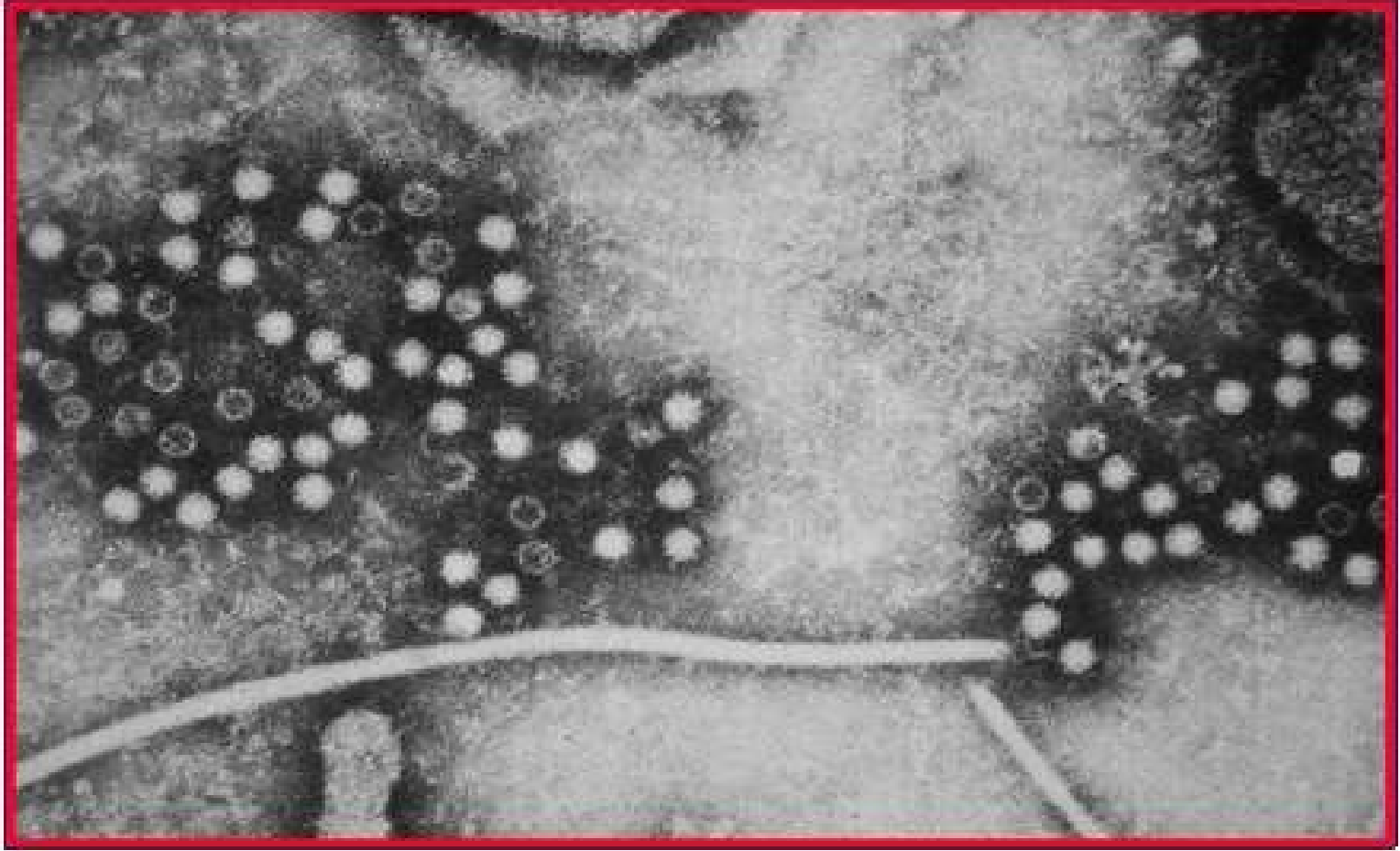
HBV - HDV Coinfection Typical Serologic Course



HBV - HDV Superinfection Typical Serologic Course

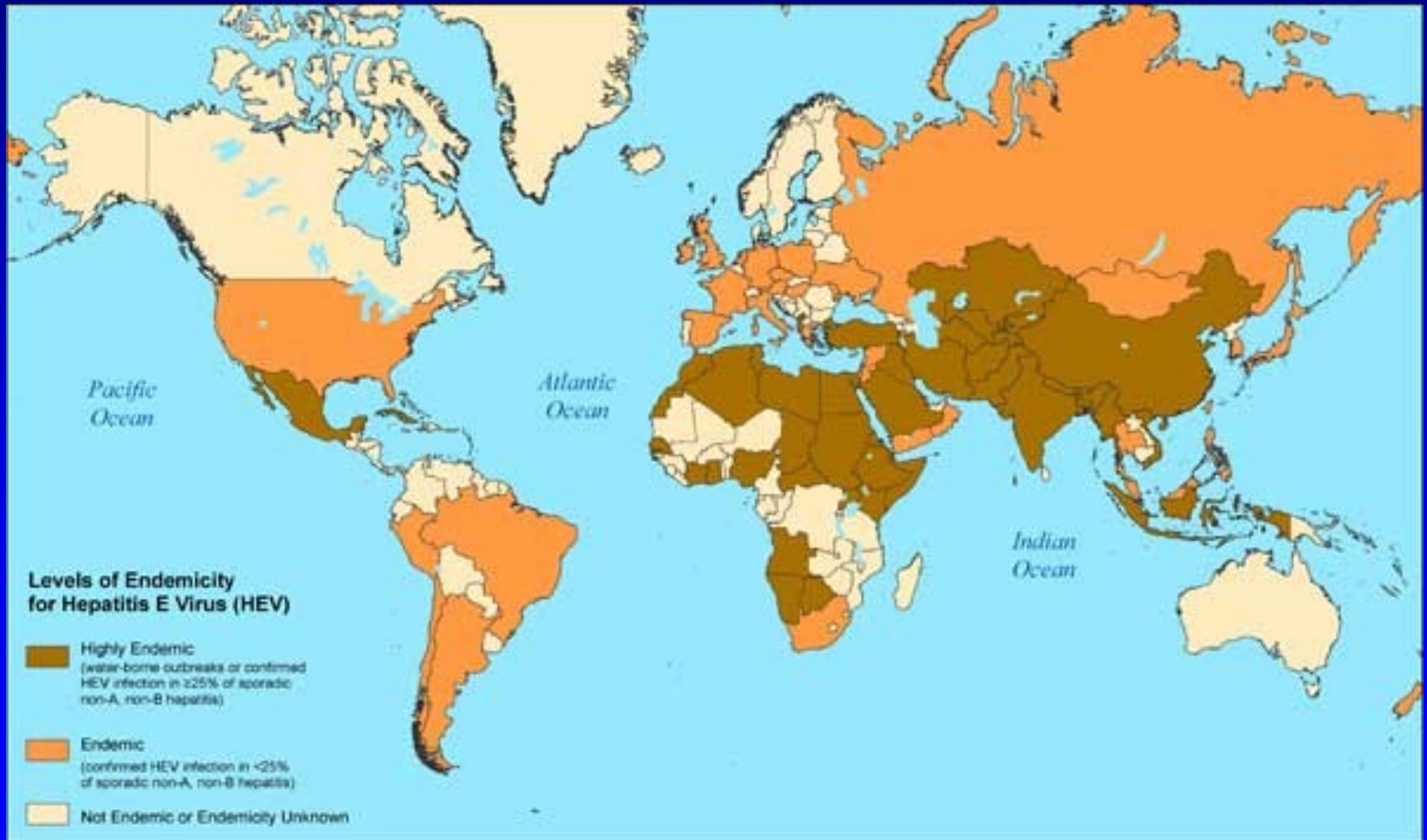


Hepatitis E Virus



Family *Hepeviridae*, genus *Hepevirus*, non-enveloped RNA virus,
27-34 nm

Hepatitis E



Source: *CDC*

HEV genotypes

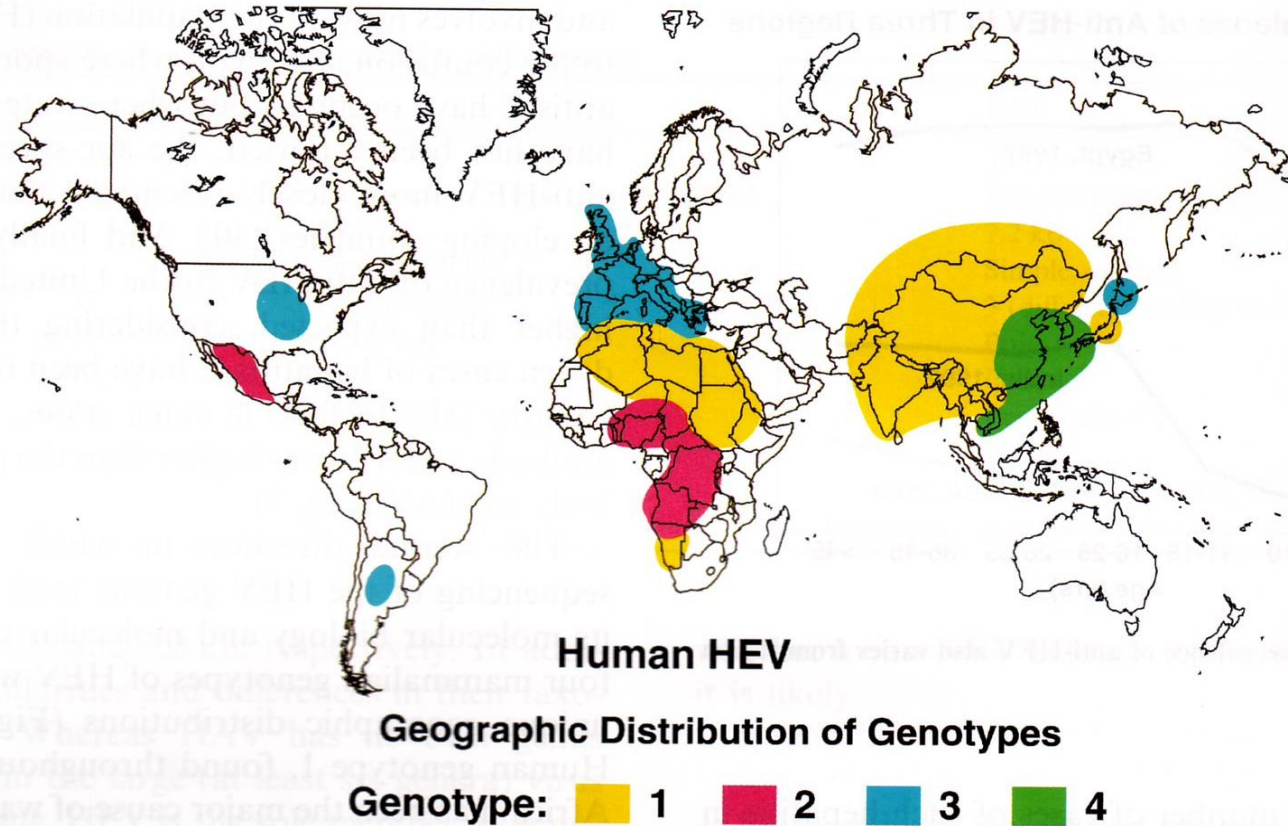


Fig. 4. Each of the four genotypes of HEV that infect humans has a distinct, and in some cases, overlapping geographic distribution.

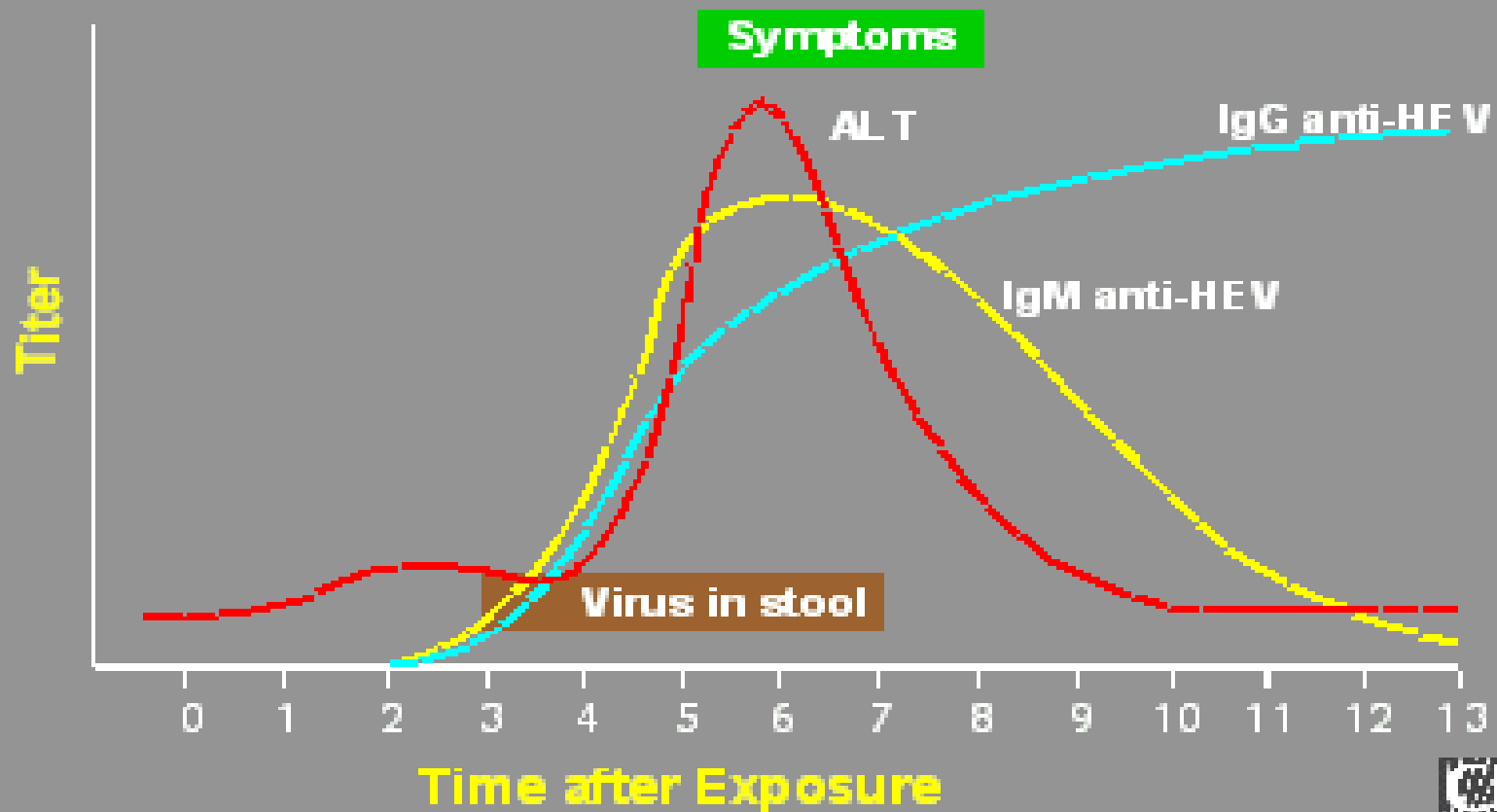


Hepatitis E

- Travel-related disease especially
- Infection is possible to acquire in CR as well (pork, sea food)
- Main route of transmission by drinking water
- Extremely serious clinical course in late pregnancy (mortality above 20 %)
- Repeated infection may be possible
- Rare cases of chronic hepatitis E in seriously immunosuppressed patients (organ recipients...)

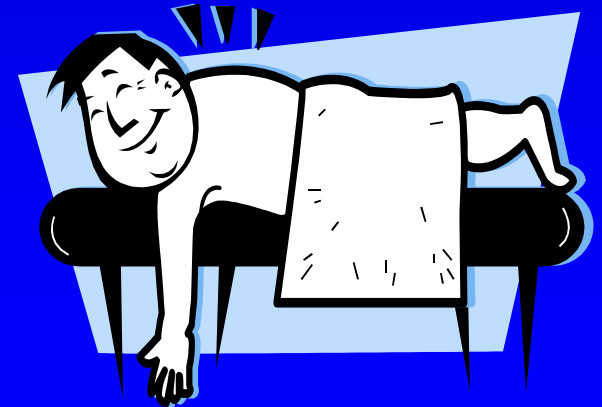
Hepatitis E Virus Infection

Typical Serological Course



Treatment of acute hepatitis

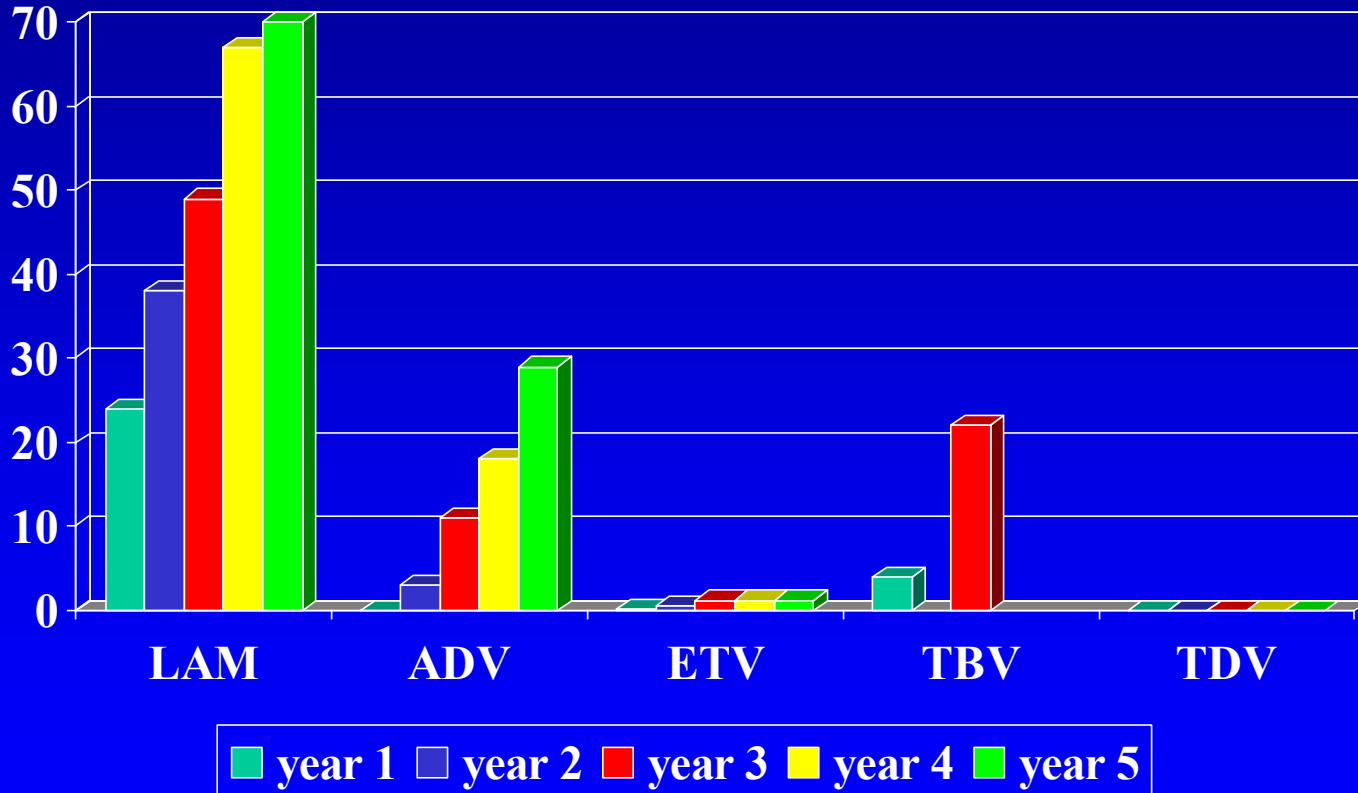
- **Symptomatic for all types**
 - ✓ physical and mental rest
 - ✓ diet
 - ✓ no alcohol, no hepatotoxic drugs
 - ✓ supportive treatment (silymarin, essential phospholipids)



Current possibilities of treatment of chronic HBV infection

- pegylated interferon alfa-2a – 48 weeks
- lamivudine - only in severe acute HEP B or protection of reactivation or recurrence
- telbivudine – for naive patients
- entecavir – for naive patients
- adefovir dipivoxil – for lamivudine-resistant mutants in combination with lamivudine
- tenofovir – both for naive and lamivudine-resistant patients

Resistance to NUCs



Standard chronic hepatitis C therapy

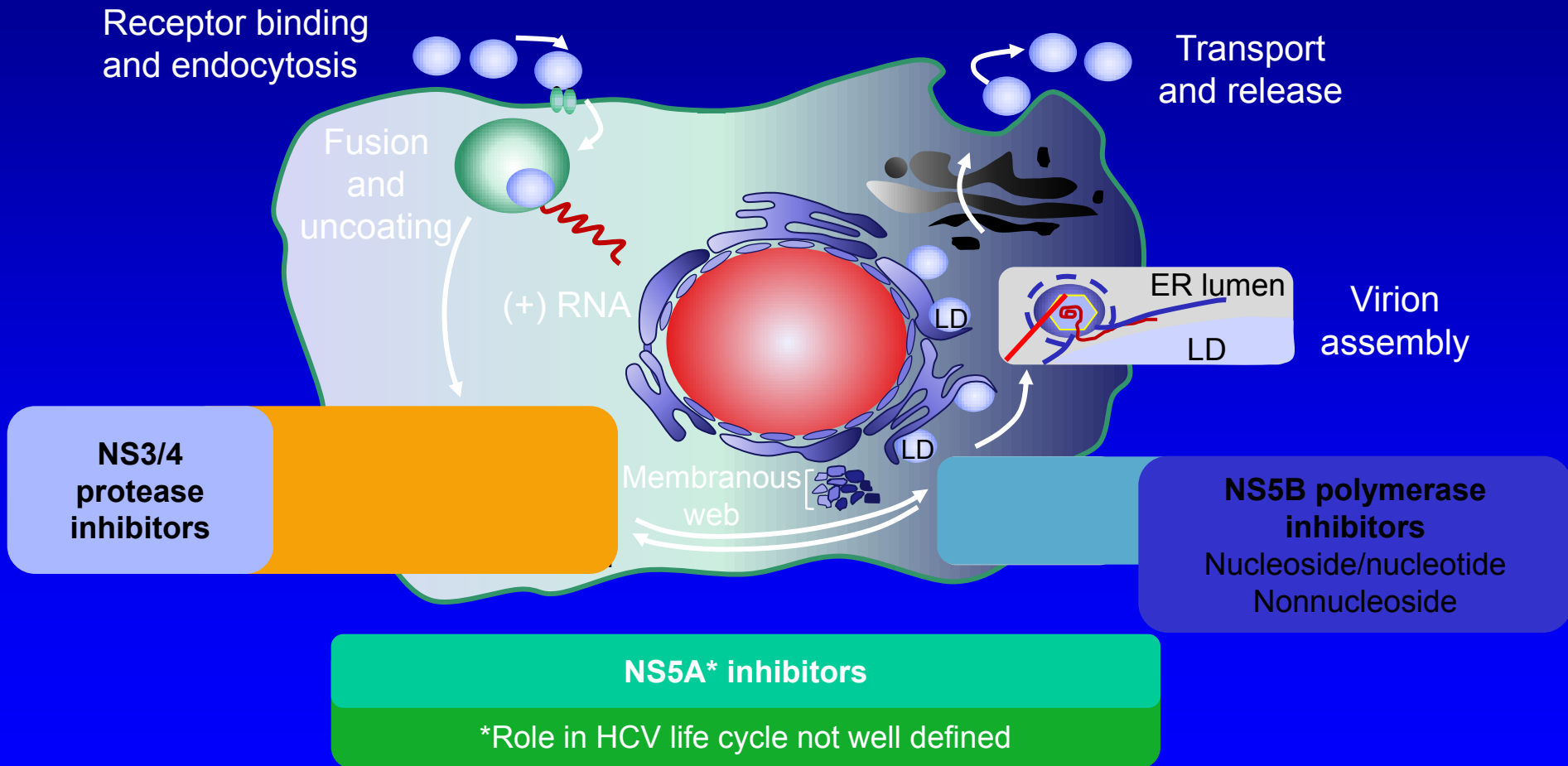
genotypes 1,4

- ✓ PEG-IFN + RBV (1000-1200mg) - 48 weeks
- ✓ PEG-IFN + RBV + DAA (boceprevir or telaprevir) – response guided therapy – 24-48 weeks

genotypes 2-3

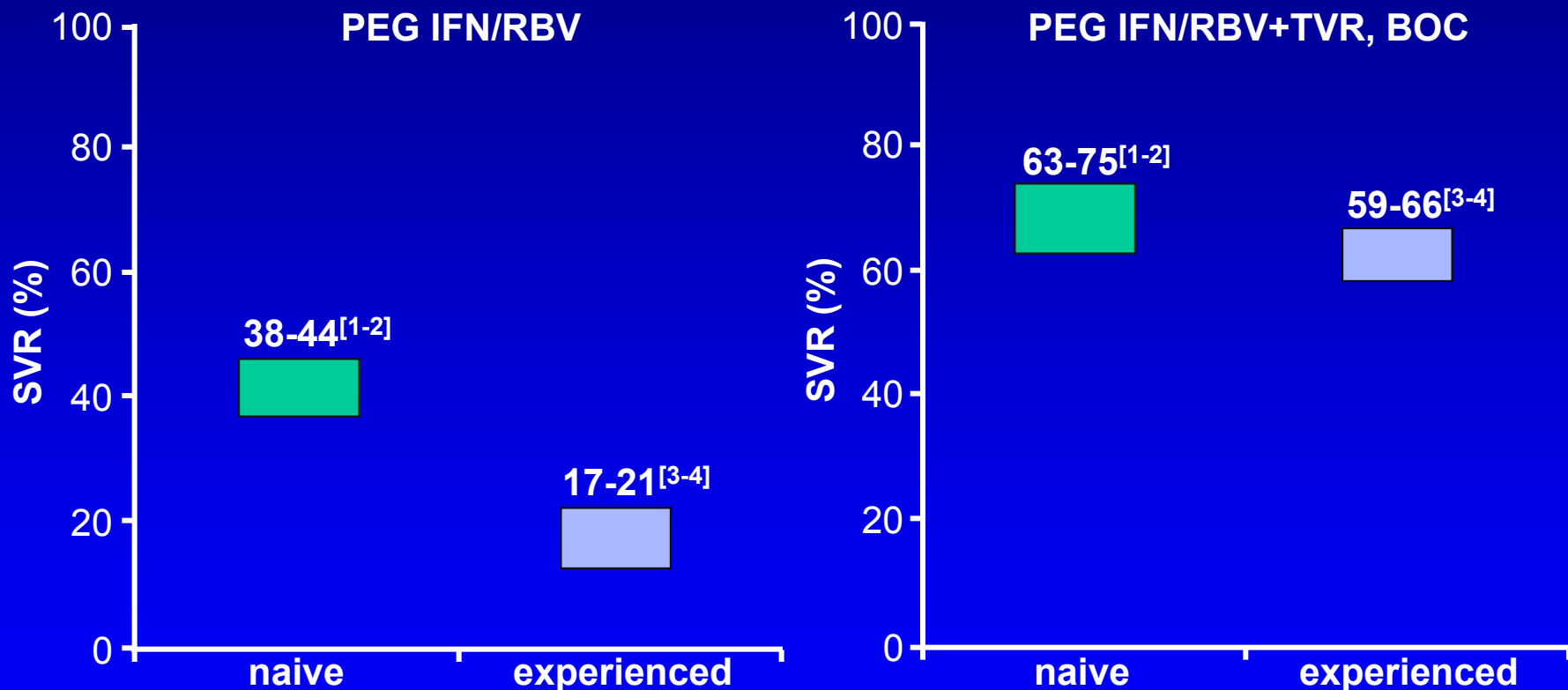
- ✓ PEG-IFN+RBV (800 mg) – 24 weeks

HCV Life Cycle and DAA Targets



Adapted from Manns MP, et al. Nat Rev Drug Discov. 2007;6:991-1000.

Efficacy of chronic hepatitis C therapy



1. Poordad F, et al. AASLD 2010. Abstract LB-4. 2. Jacobson IM, et al. AASLD 2010. Abstract 211. 3. Bacon BR, et al. AASLD 2010. Abstract 216. 4. Foster GR, et al. APASL 2011. Abstract 1529.



Thank you for your attention!

phusa@fnbrno.cz