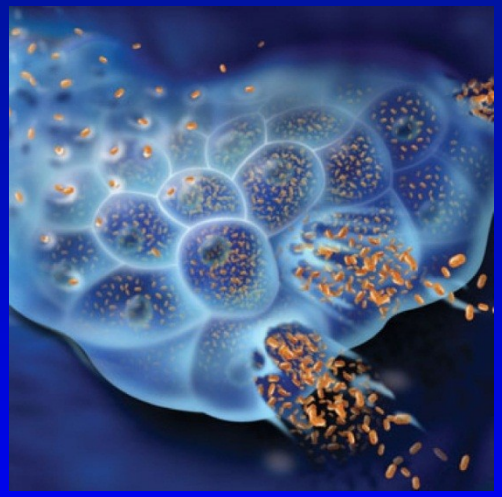
Viral Hepatitis



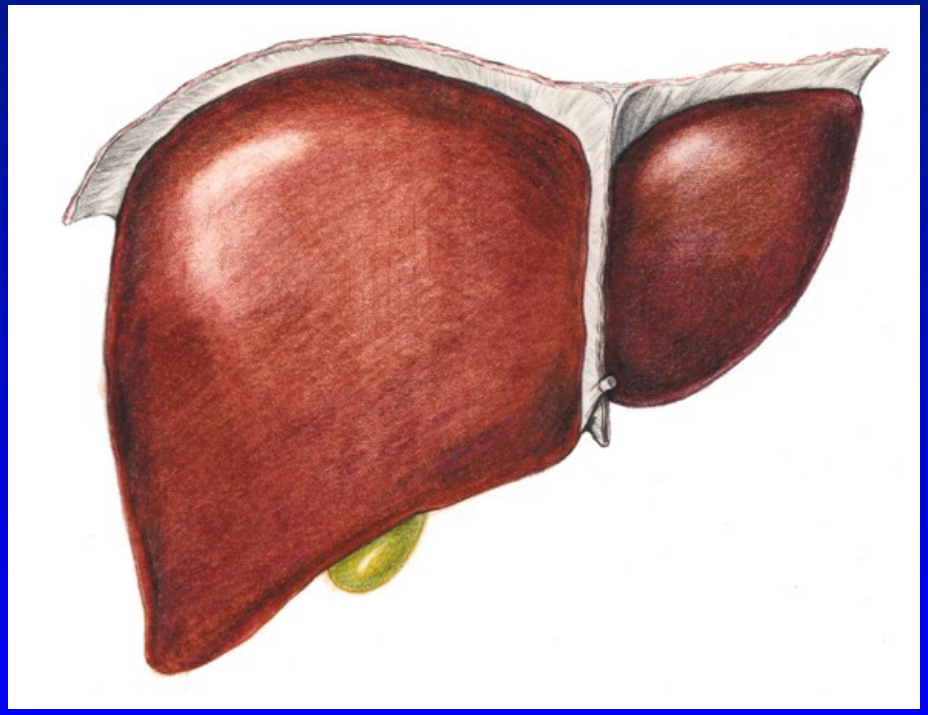
Prof. MUDr. Petr Husa, CSc.
Klinika infekčních chorob, FN Brno

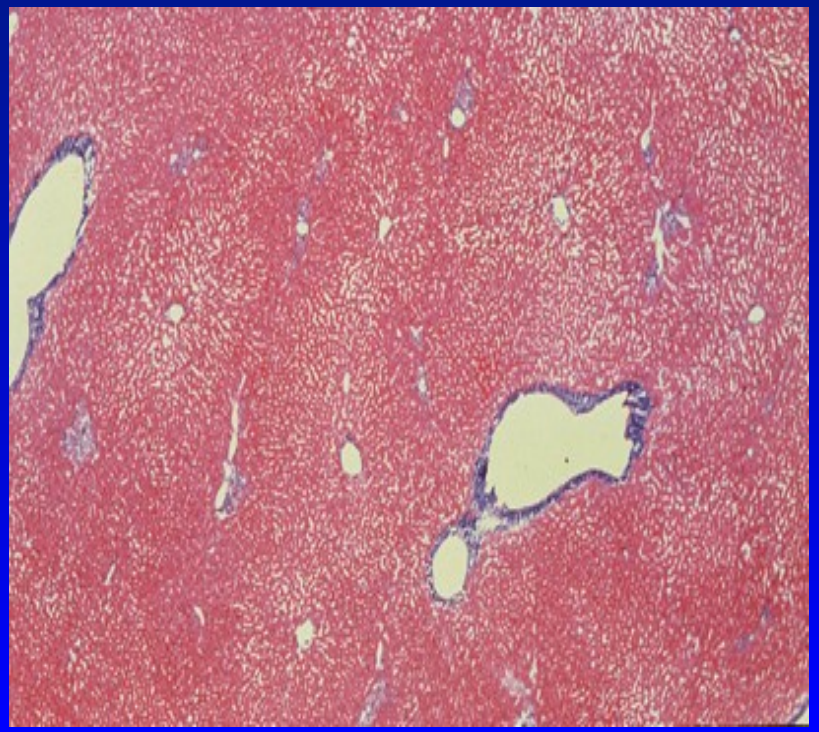
Viral Hepatitis

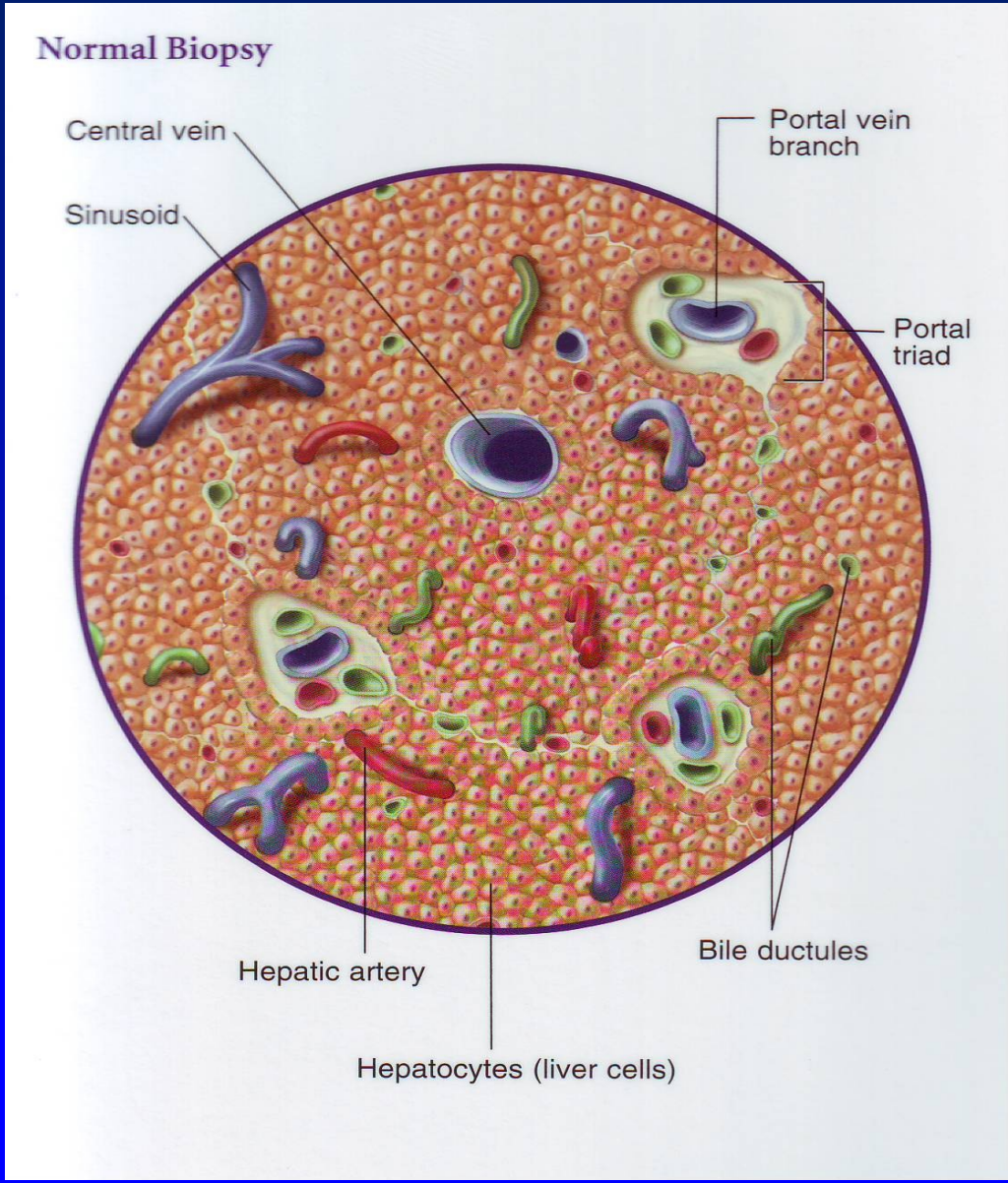
1. Enterically transmitted – no chronic stage
- VH A
- VH E –rare (immunosuppressed pts.)

2. Parenterally transmitted – possible chronic stage
- VH B
- VH C
- VH D

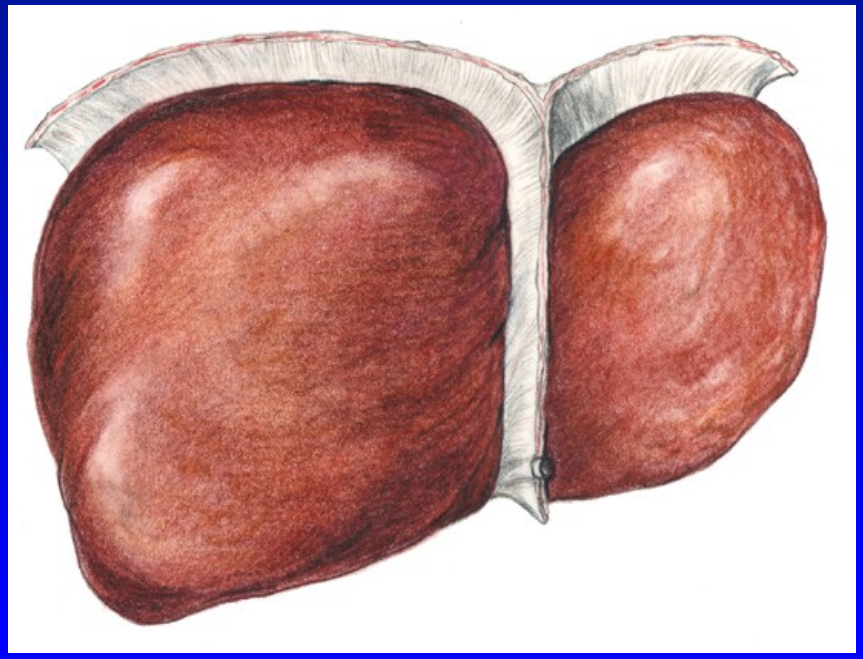
Healthy liver

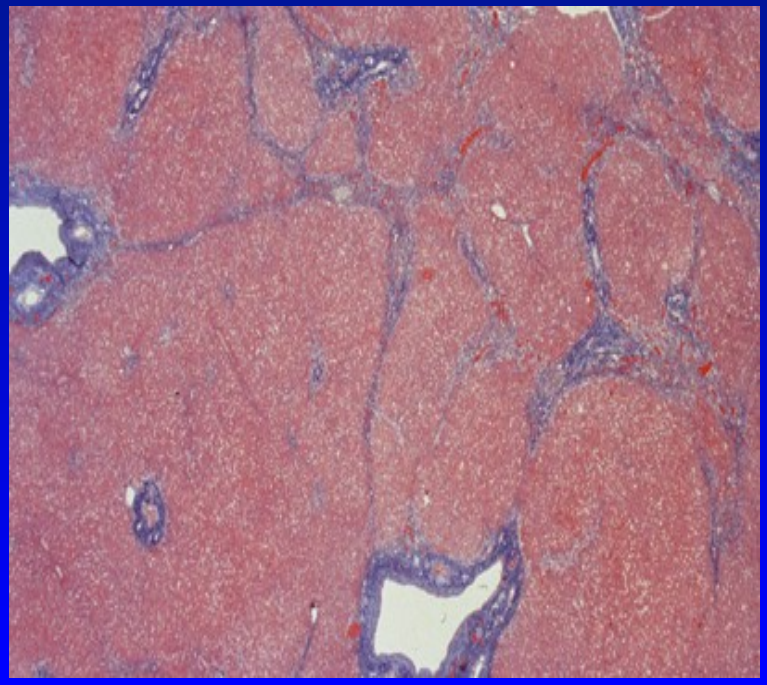




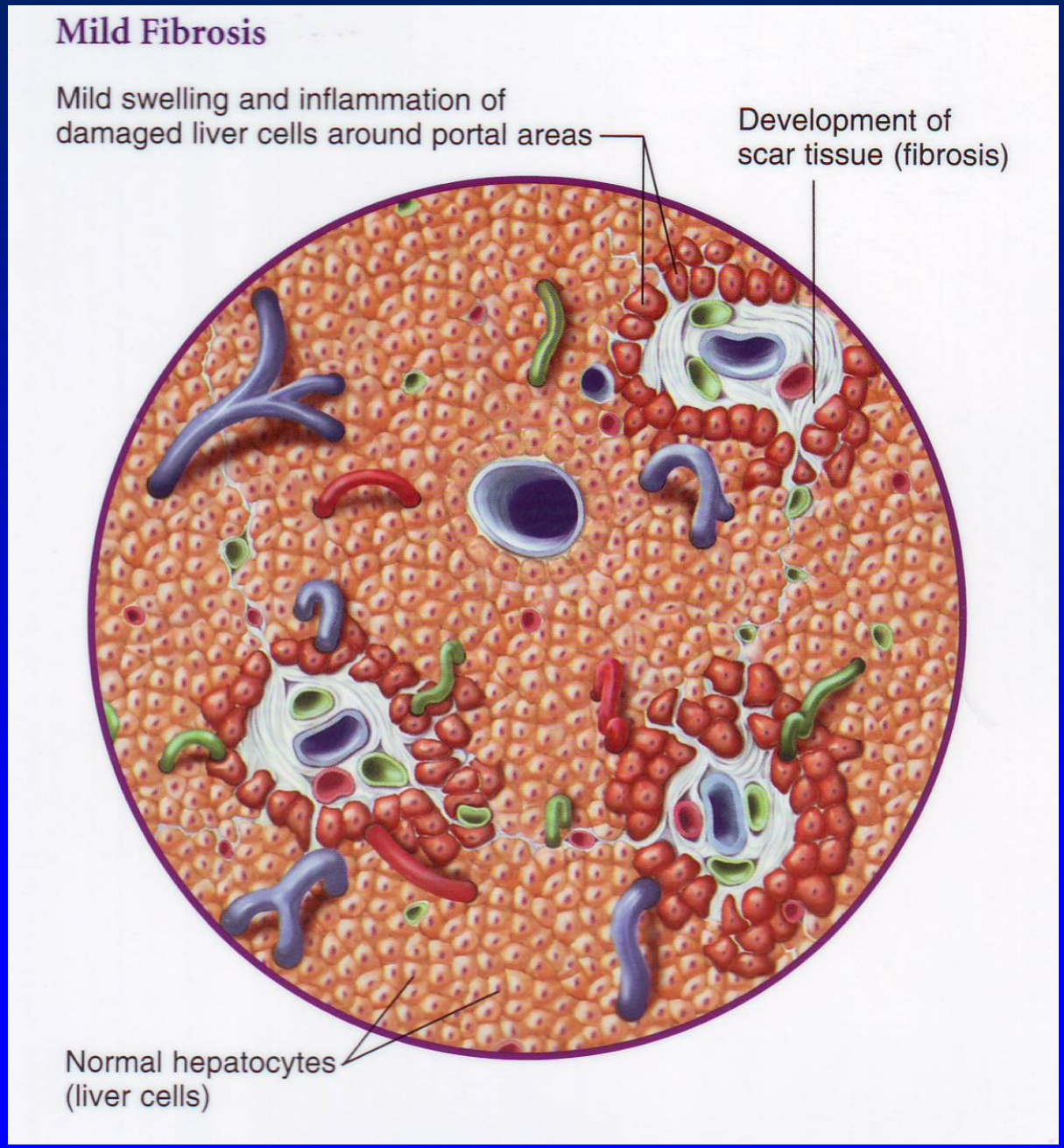

Normal Biopsy
Central vein
Portal vein branch
Sinusoid
Portal triad
Hepatic artery
Bile ductules
Hepatocytes (liver cells)

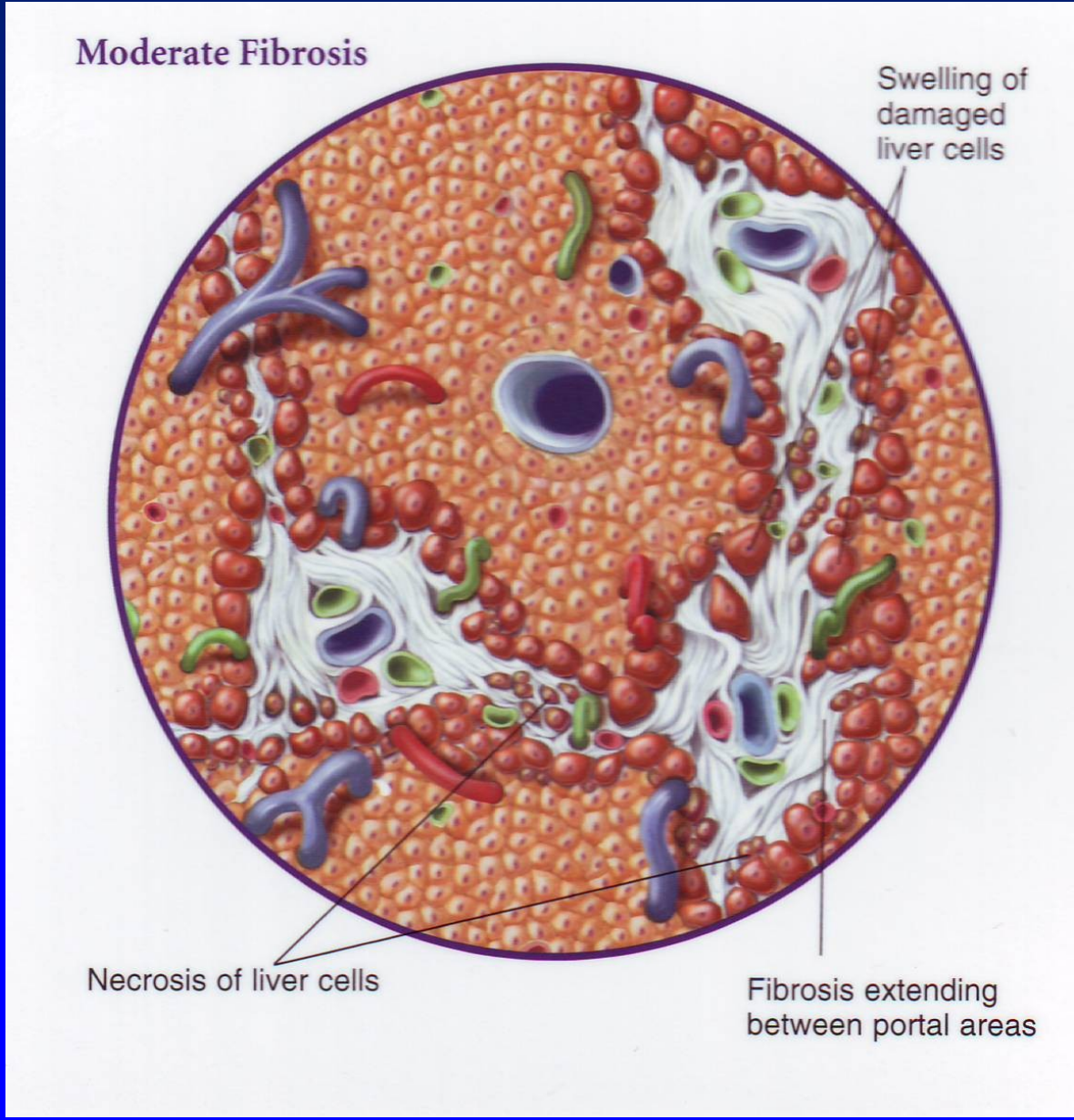
Liver fibrosis



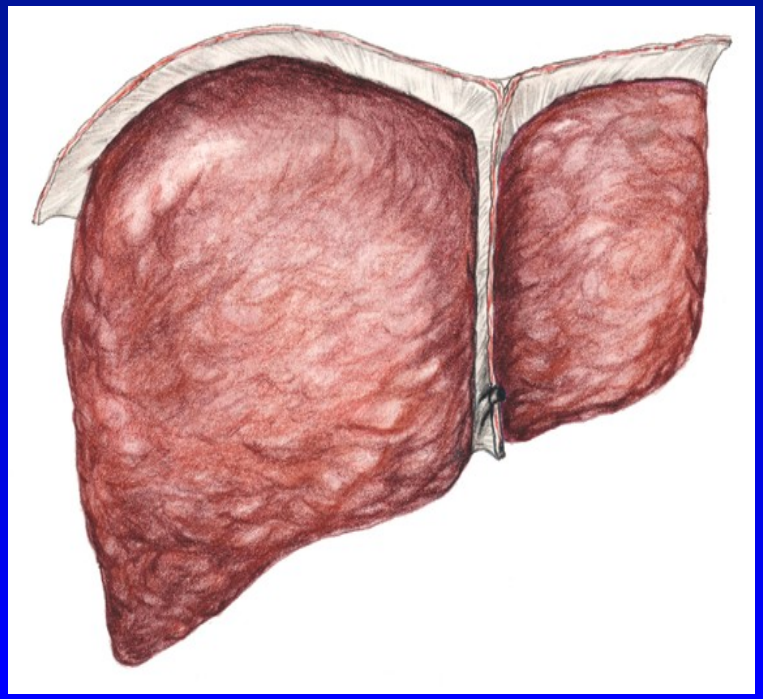


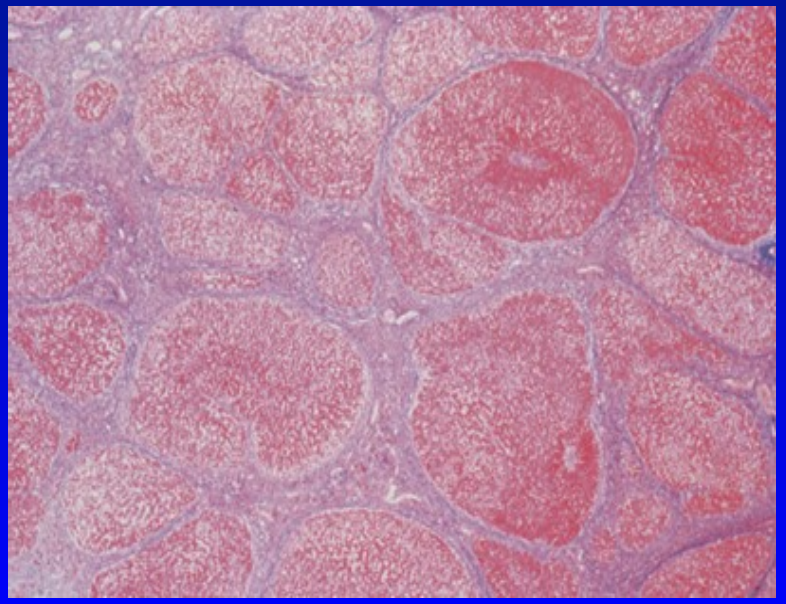
Mild Fibrosis



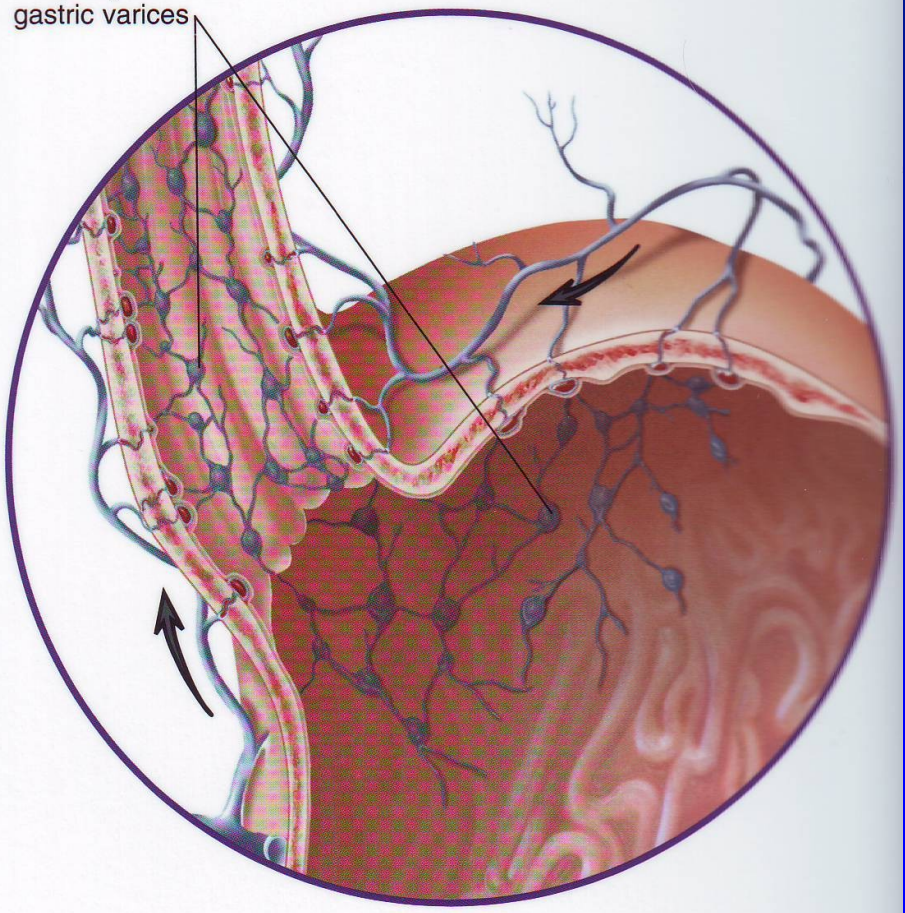

Moderate Fibrosis
Swelling of damaged liver cells
Necrosis of liver cells
Fibrosis extending between portal areas

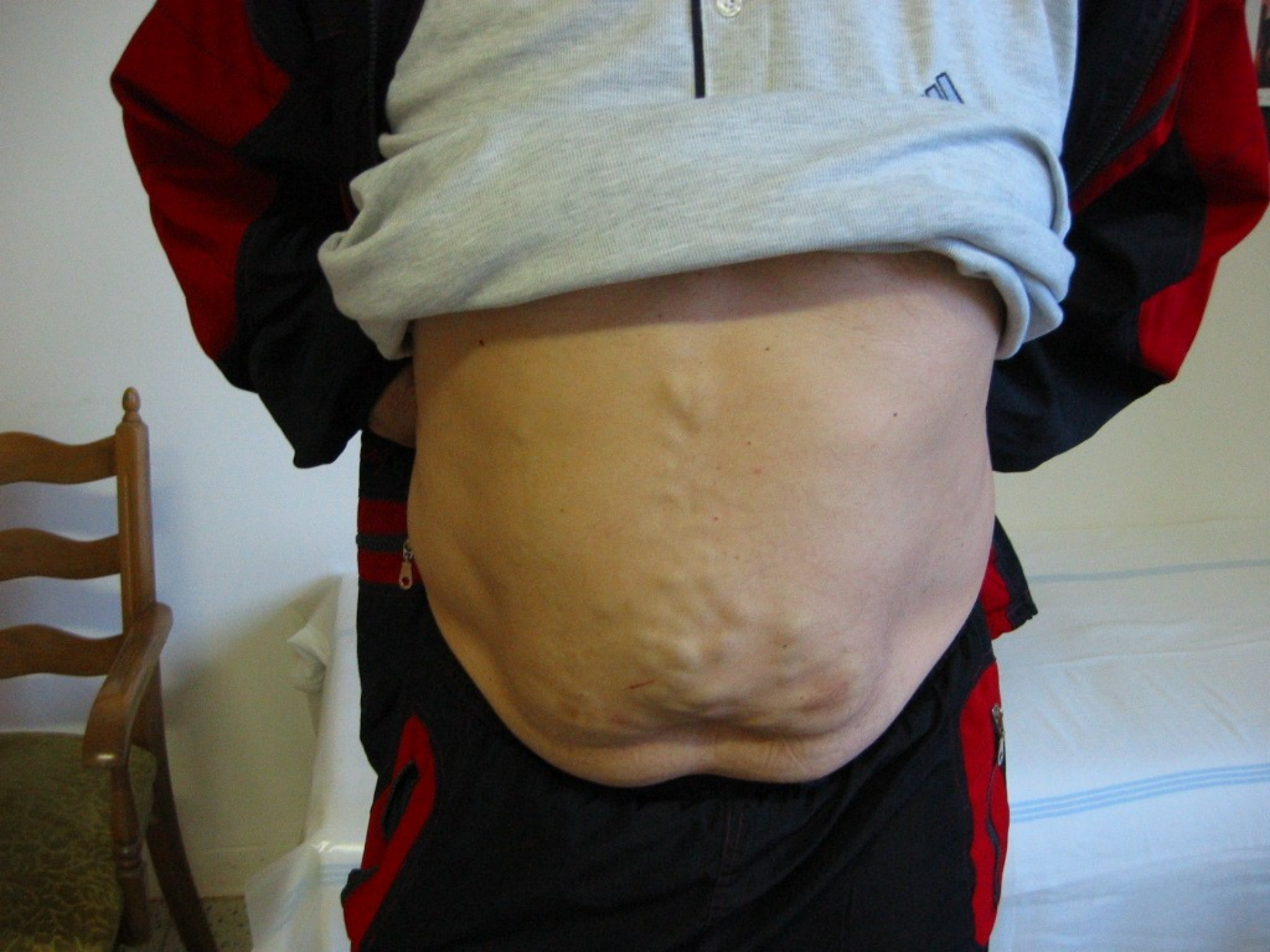
Liver cirrhosis

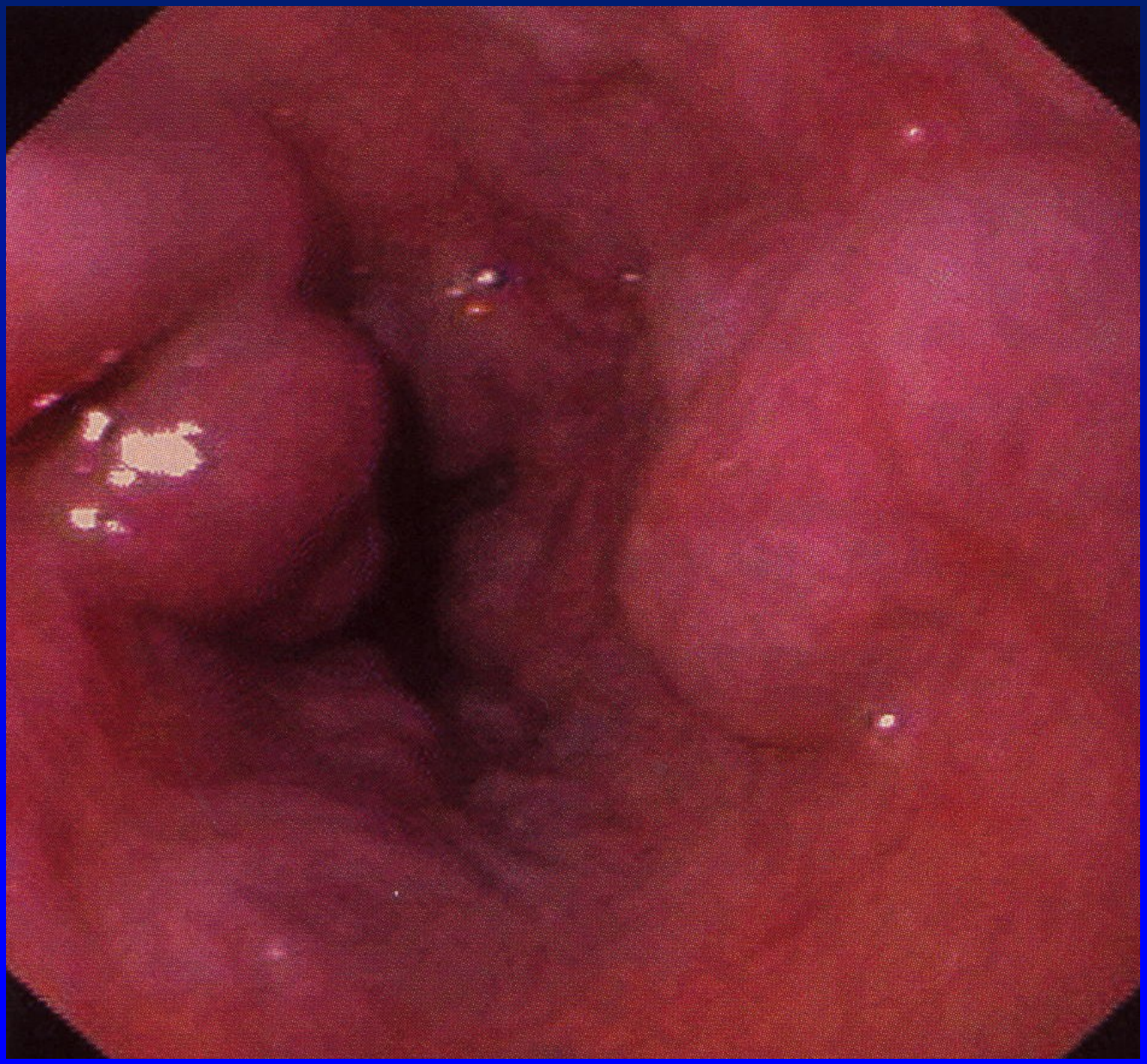


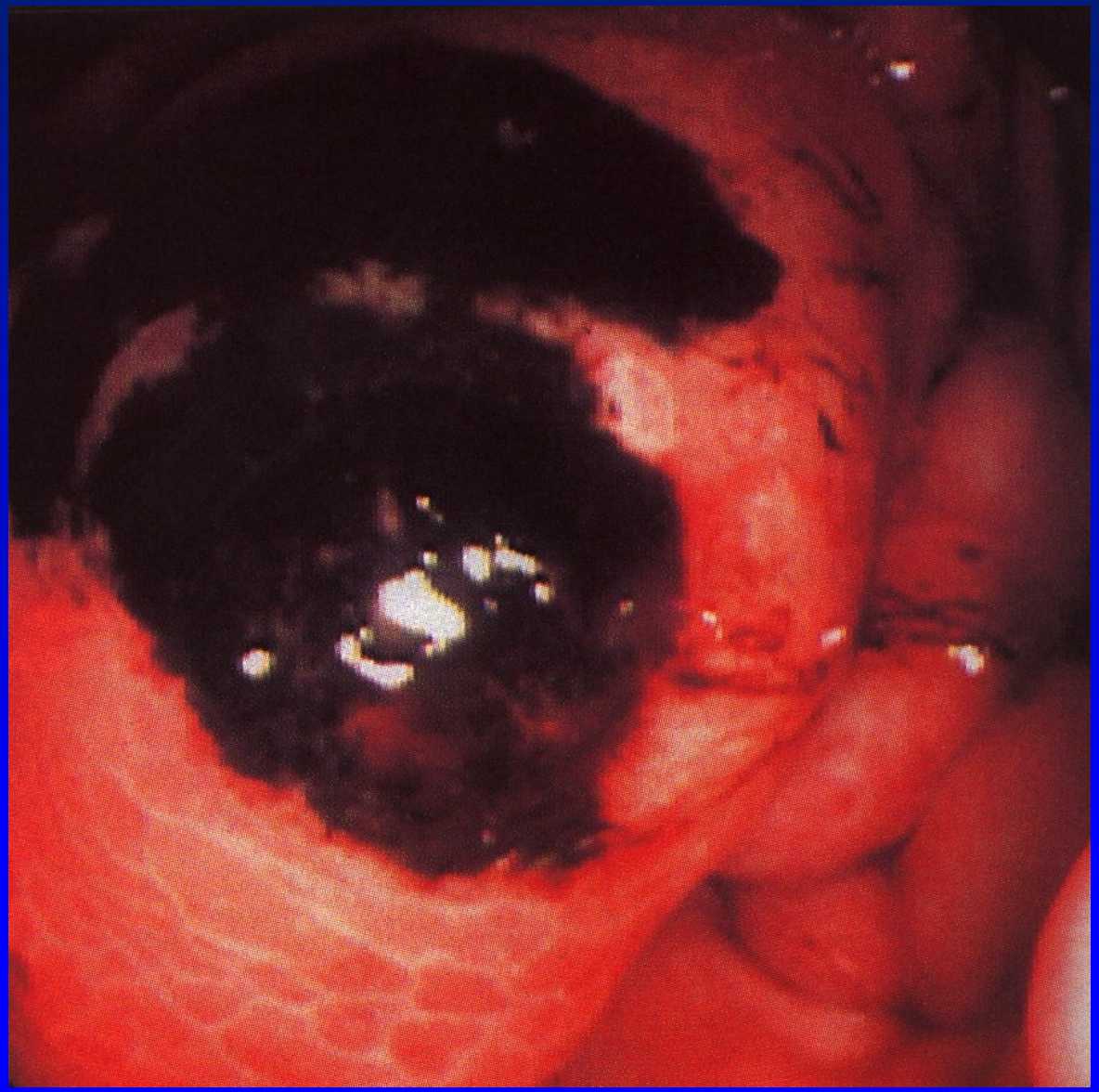


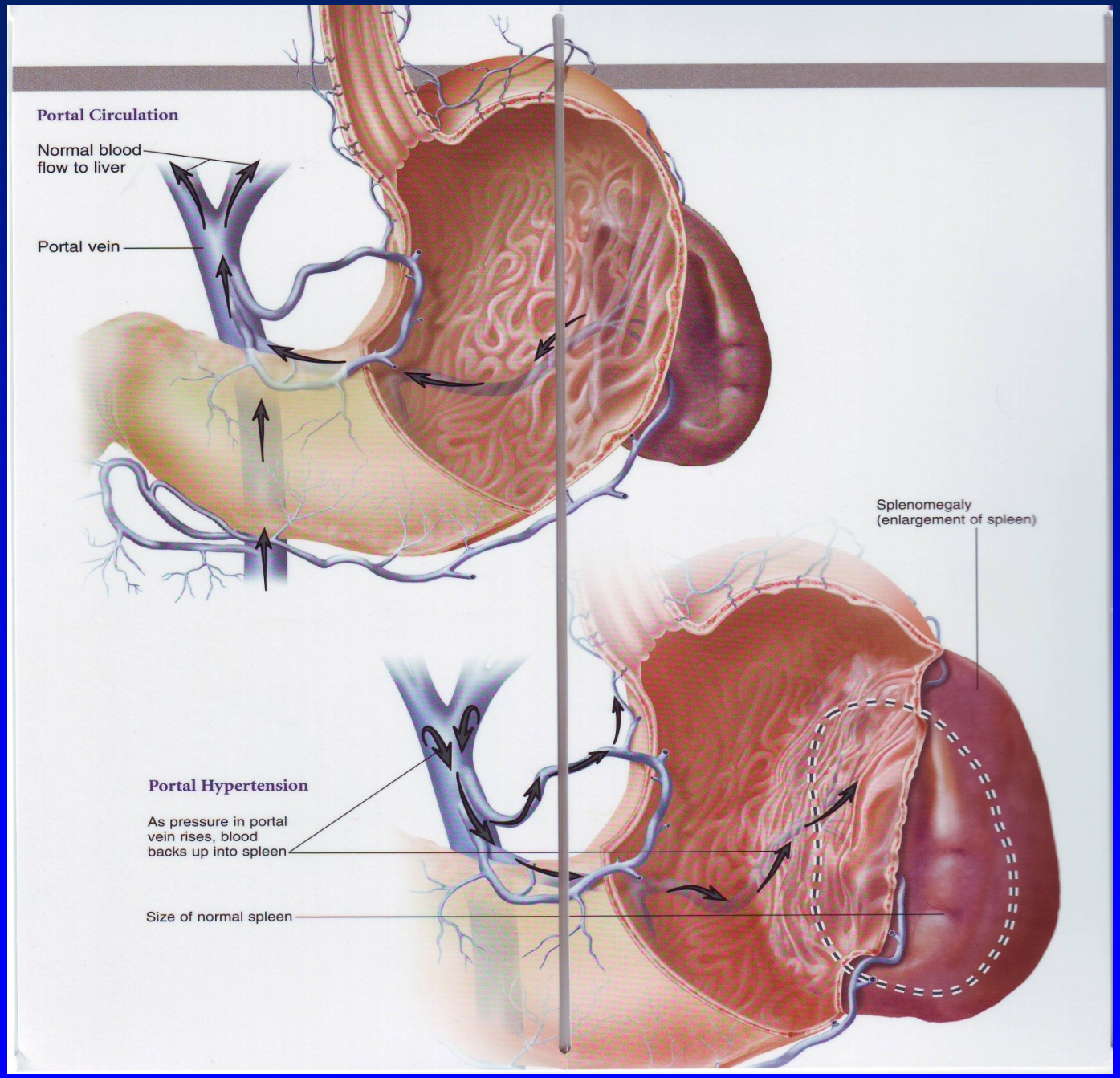
Development of Varices

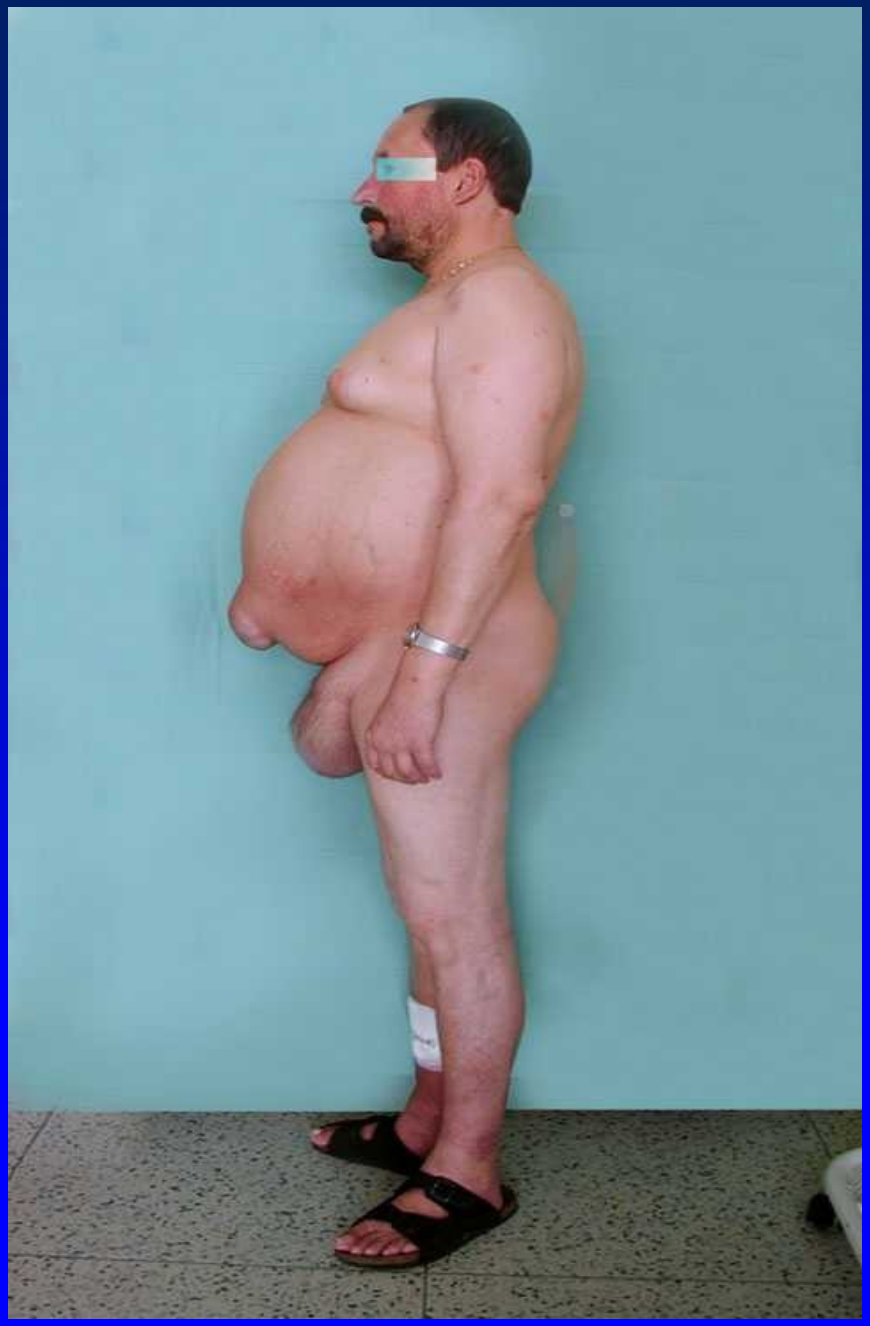


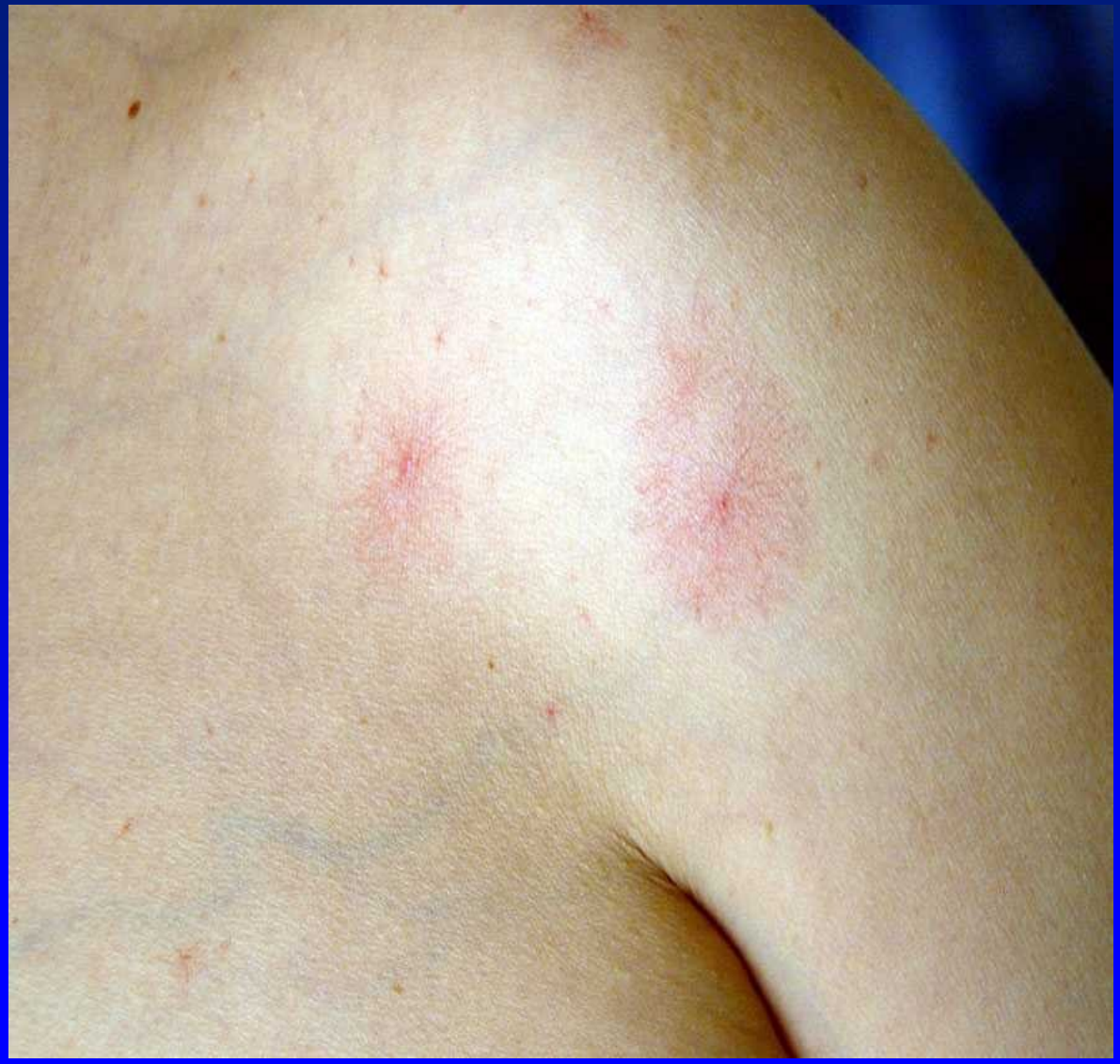




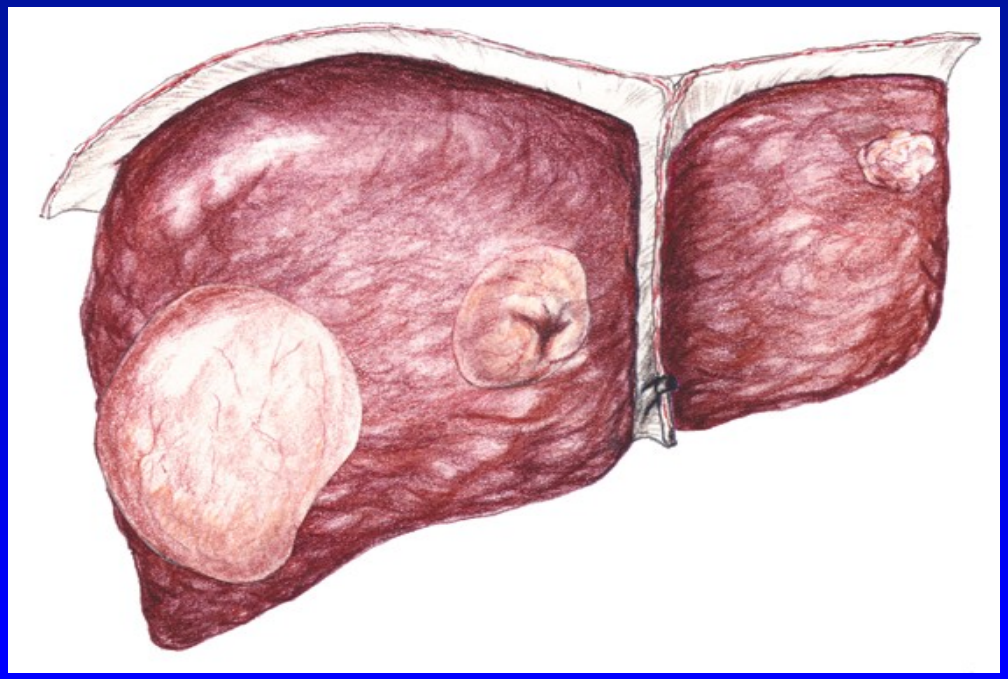


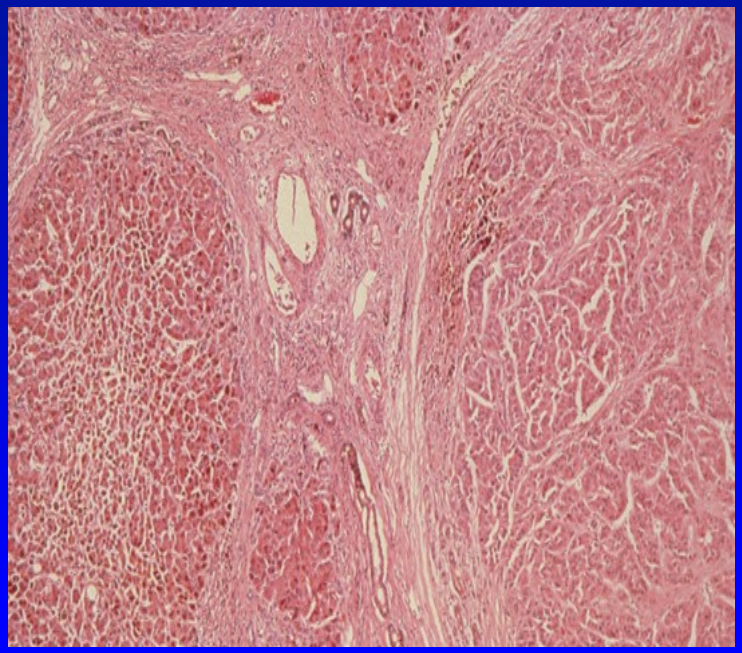

Portal Circulation
Normal blood flow to liver
Portal vein
Splenomegaly (enlargement of spleen)
Portal Hypertension
As pressure in portal vein rises, blood backs up into spleen
Size of normal spleen





Hepatocellular carcinoma

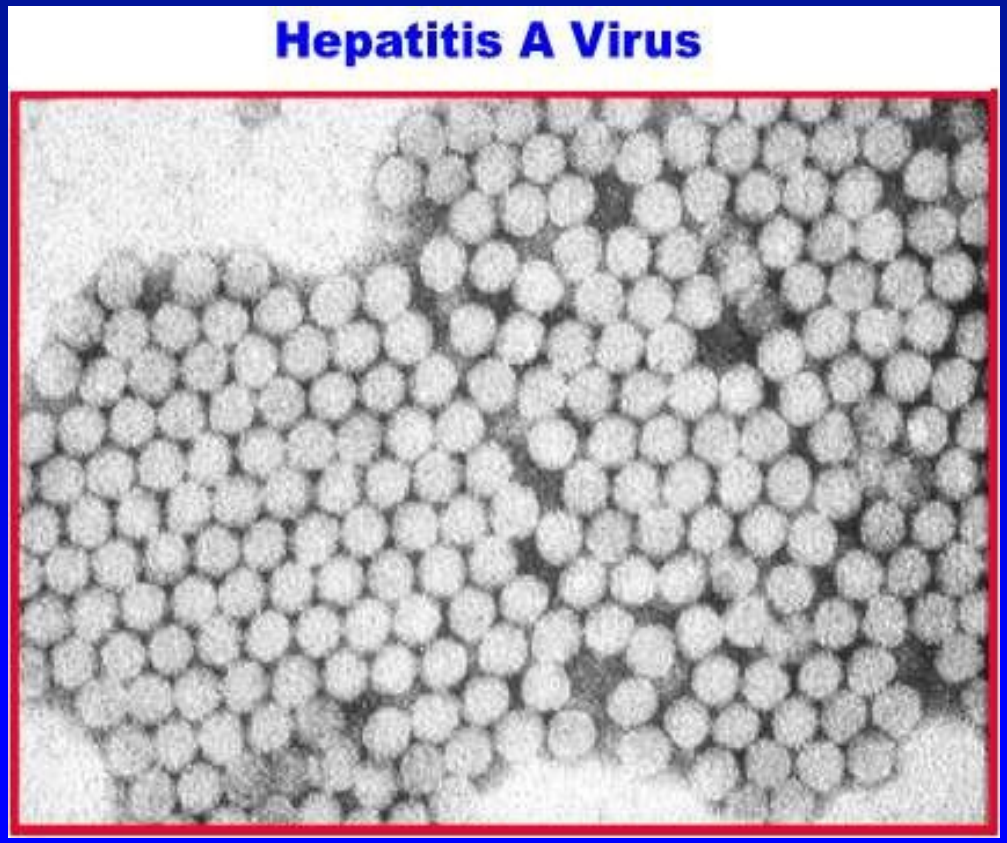




Viral Hepatitis in CR 2006-2015

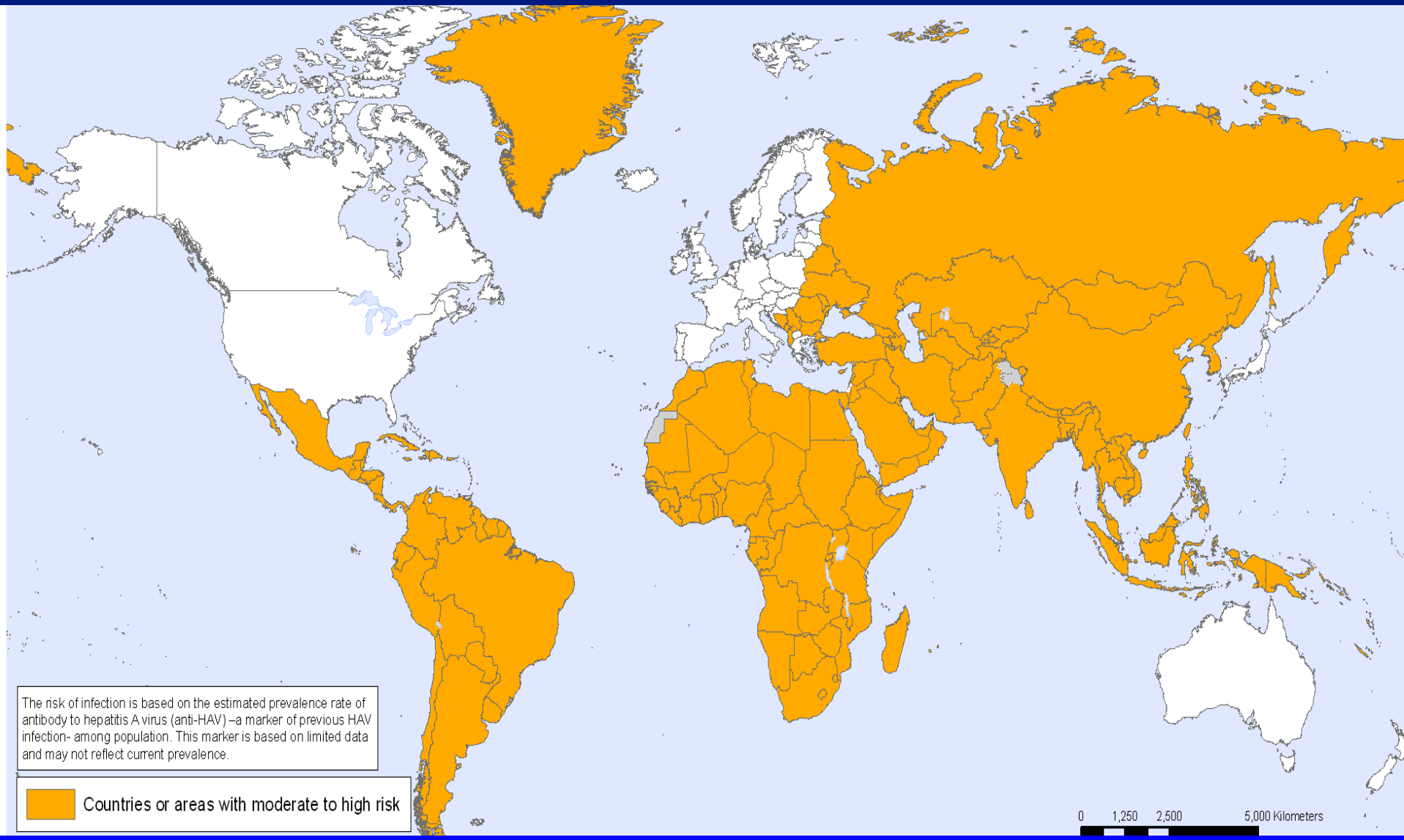
	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
VH A	132	128	1648	1104	862	264	284	348	673	723
VH B	307	307	306	247	244	192	154	133	105	90
VH C	1022	980	974	836	709	812	794	873	867	945
VH E	35	43	65	99	72	163	258	218	299	409

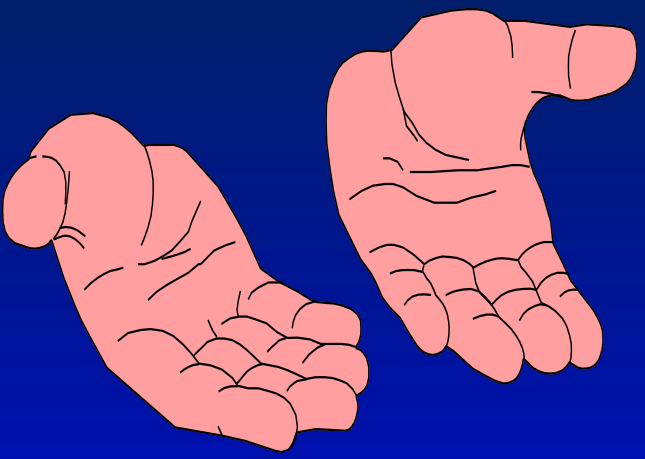
Hepatitis A virus (HAV)



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

Hepatitis A


The risk of infection is based on the estimated prevalence rate of antibody to hepatitis A virus (anti-HAV) –a marker of previous HAV infection- among population. This marker is based on limited data and may not reflect current prevalence.
Countries or areas with moderate to high risk
0 1,250 2,500 5,000 Kilometers

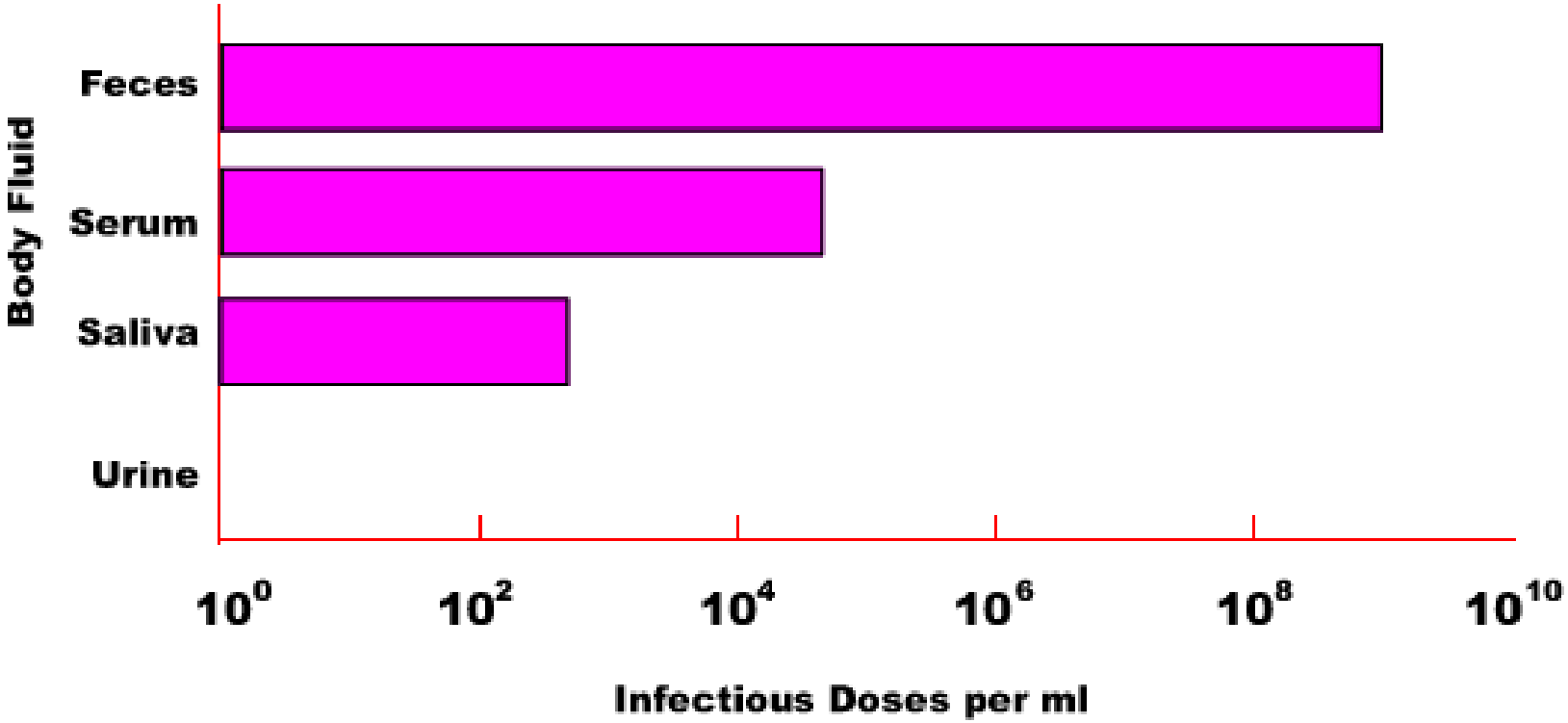


Epidemiology

- Fecal –oral route of transmission
  - ✓ Contaminated hands or daily used instruments
  - ✓ Contaminated drinking water
  - ✓ Contaminated food

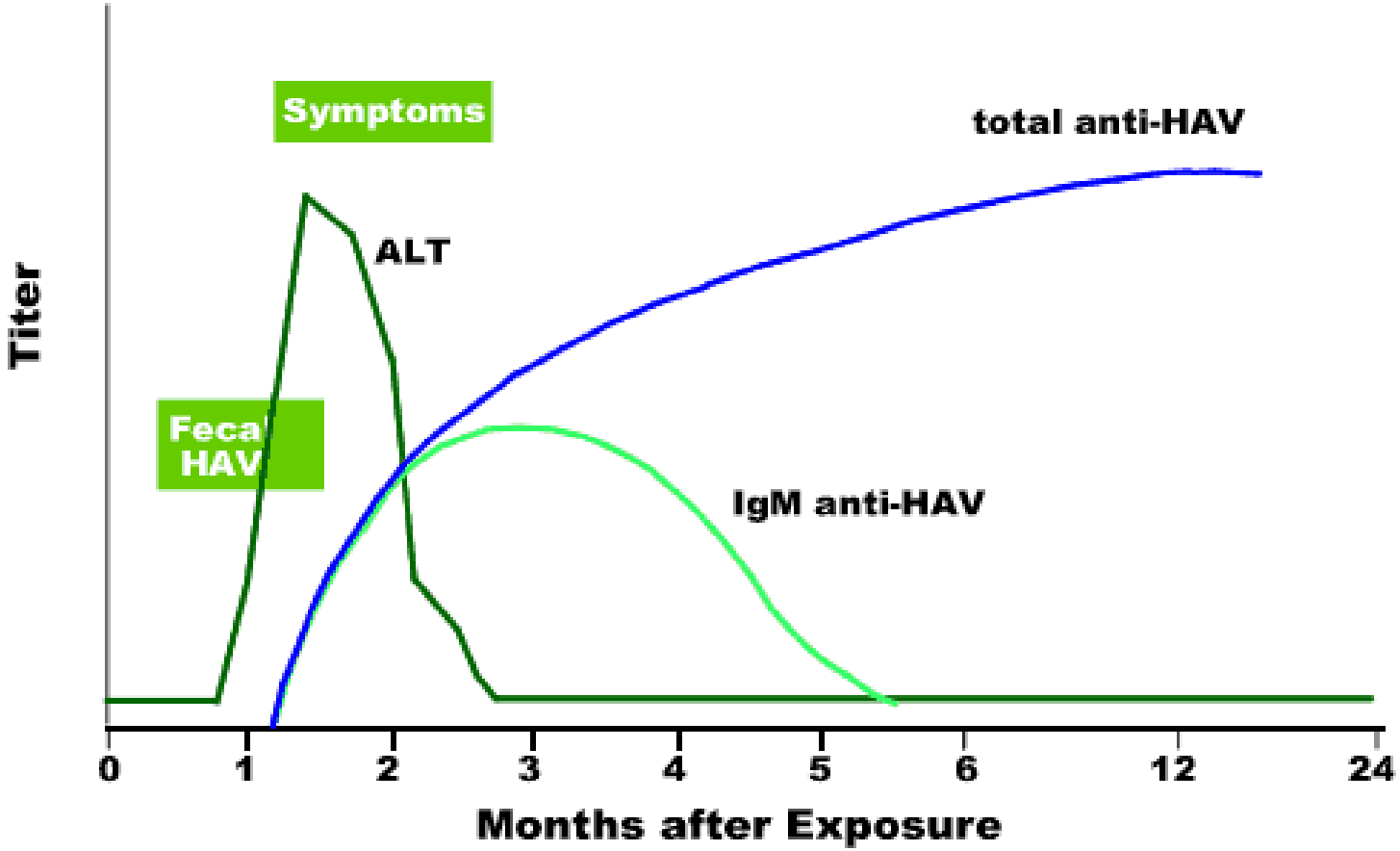
- Vaccination available, recommended especially fore travelers to countries with lower standard of hygiene

Concentration of Hepatitis A Virus in Various Body Fluids

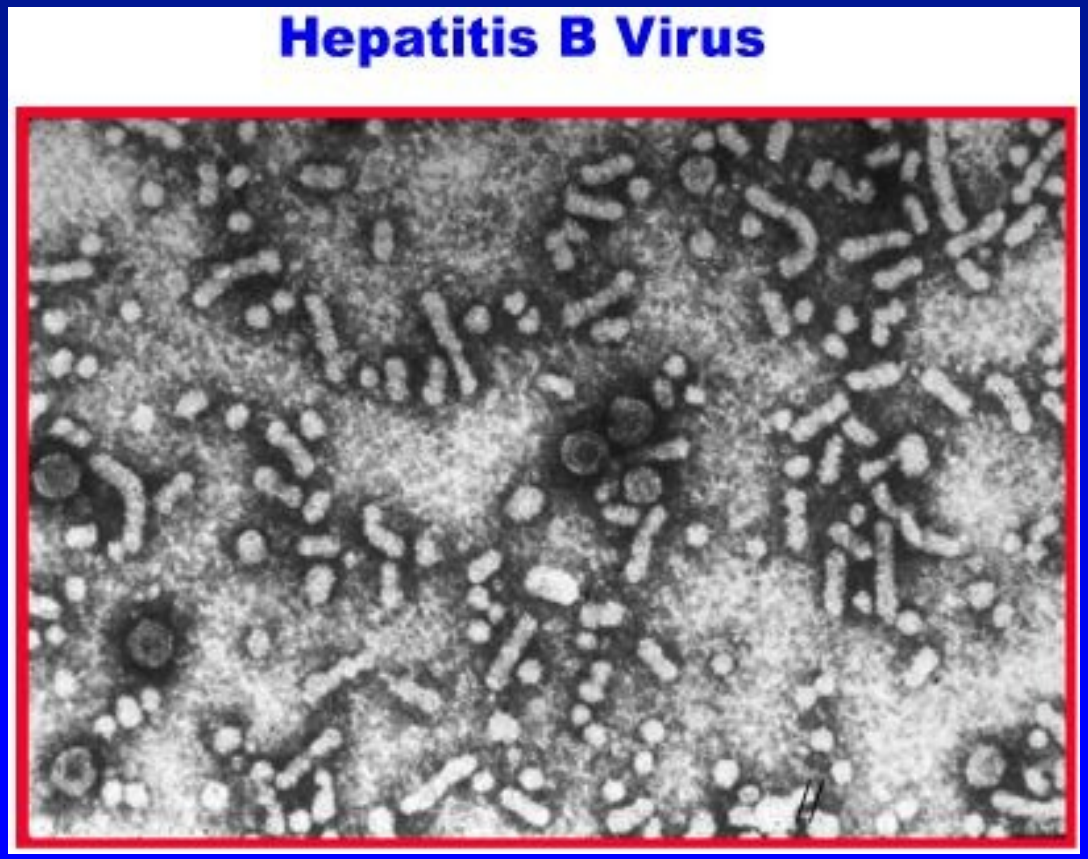


Source: Viral Hepatitis and Liver Disease 1984;9-2
J Infect Dis 1989; 160:887-890

Hepatitis A Virus Infection
Typical Serologic Course



Hepatitis B Virus (HBV)

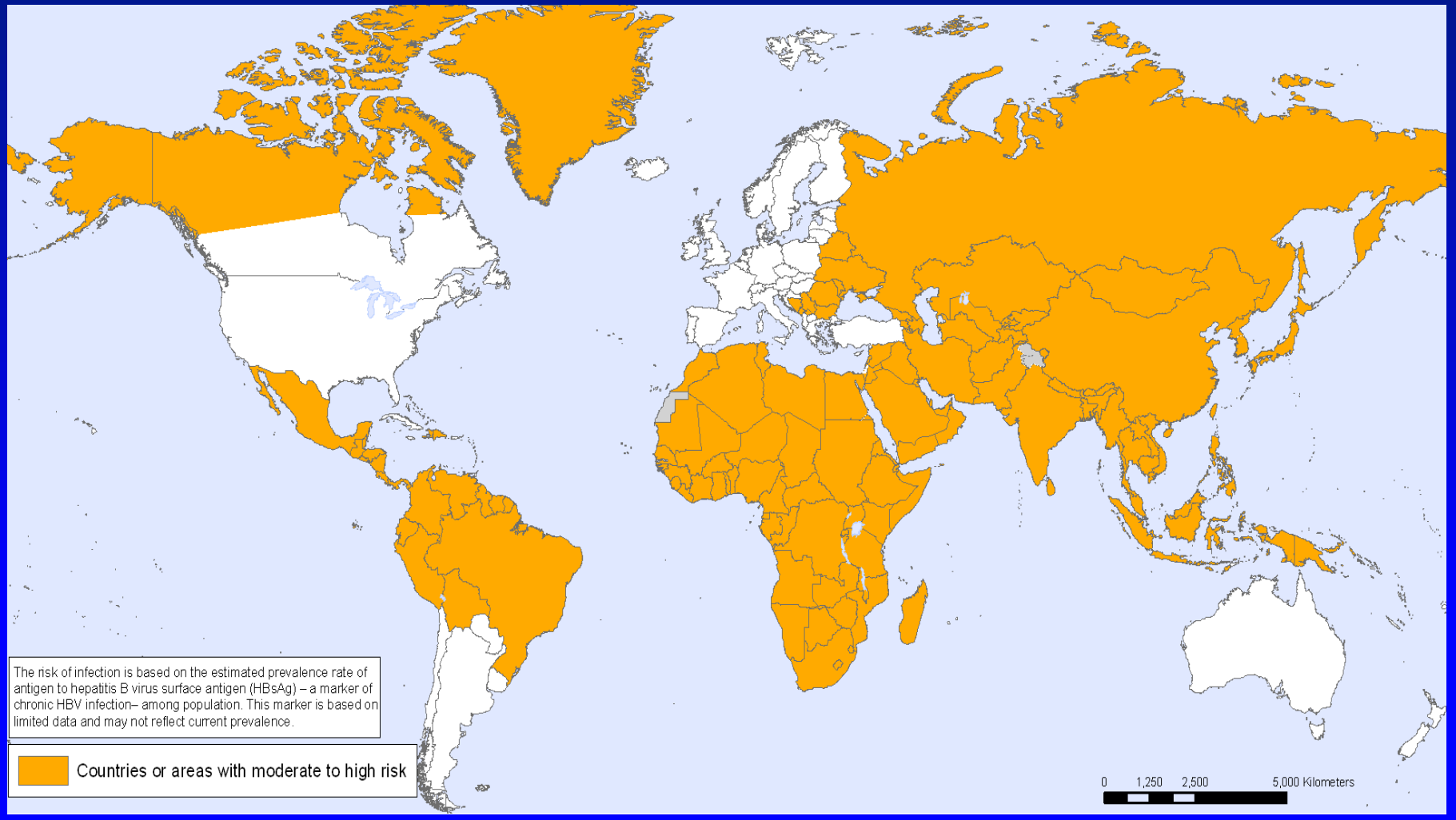


family *Hepadnaviridae*, enveloped DNA virus, 42 nm

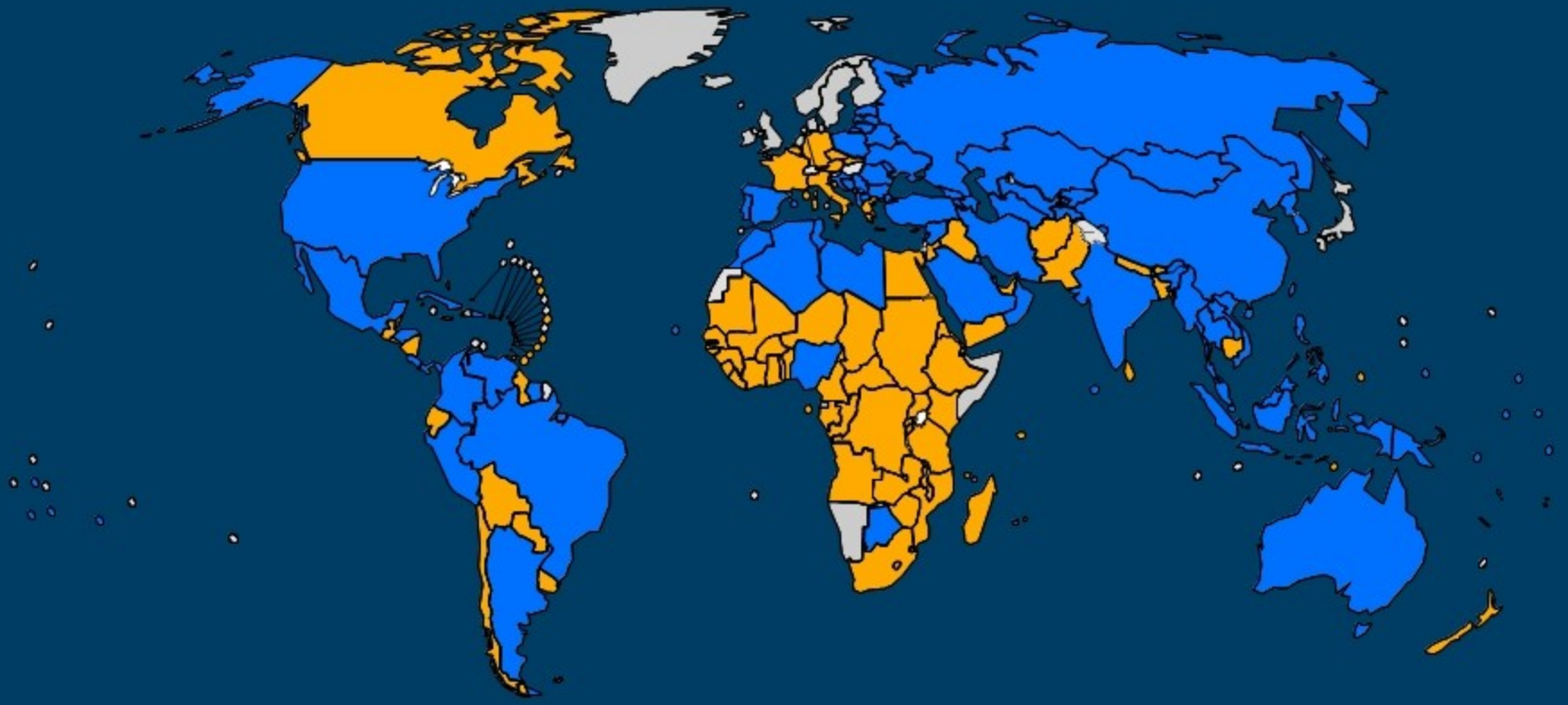
Global significance of HEP B

- 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


The risk of infection is based on the estimated prevalence rate of antigen to hepatitis B virus surface antigen (HBsAg) – a marker of chronic HBV infection– among population. This marker is based on limited data and may not reflect current prevalence.
Countries or areas with moderate to high risk
0 1,250 2,500 5,000 Kilometers

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 countries[1] or 8%)*

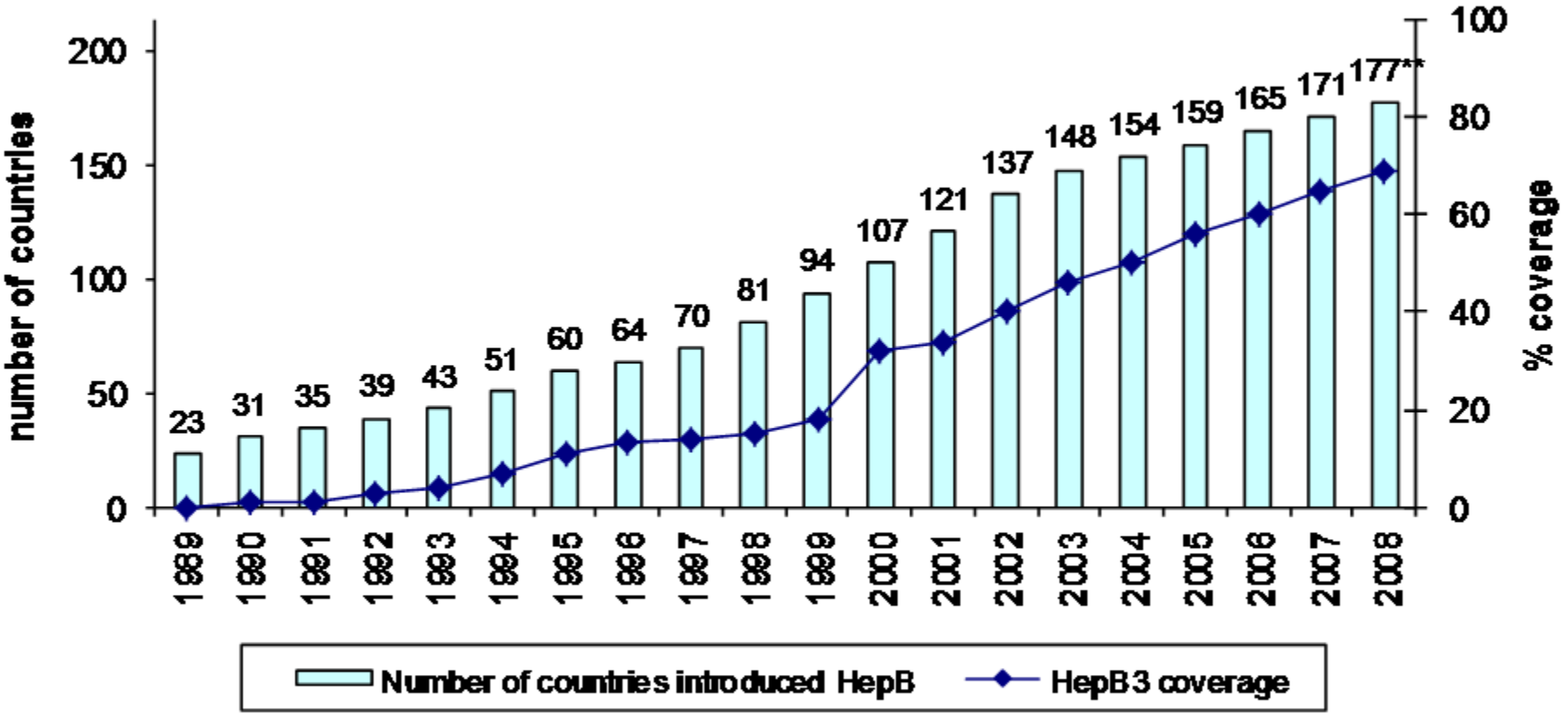
HepB no Birth Dose *(92 countries[2] or 48%)*

HepB with Birth Dose *(85 countries[3] or 44%)*

[1] Includes three countries with adolescent immunization
[2] Includes Sudan with partial introduction
[3] Includes India with partial introduction

VHPB

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

VHPB

Hepatitis B in Czech Republic

- Still important infection but incidence and prevalence are gradually decreasing

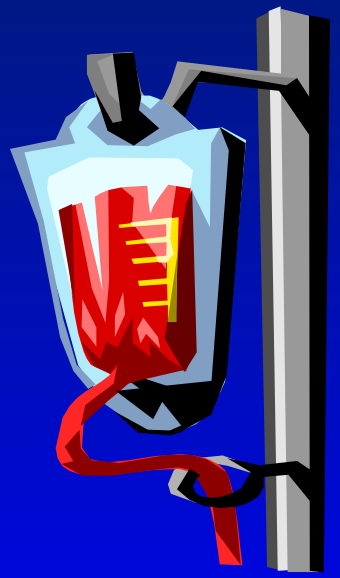
✓ Prevalence of chronic carriers was 0.56 % (2001)

✓ 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 HBV

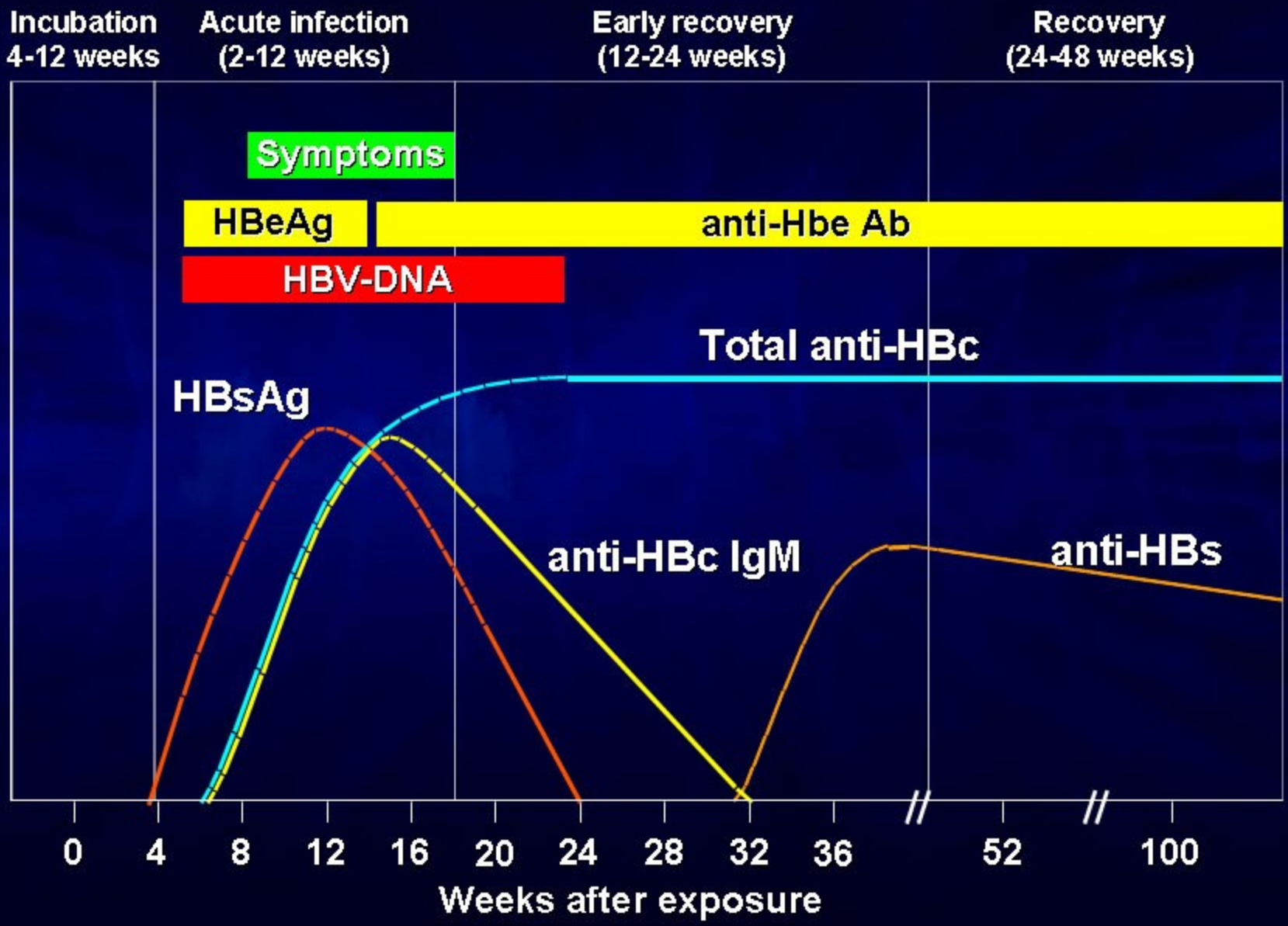


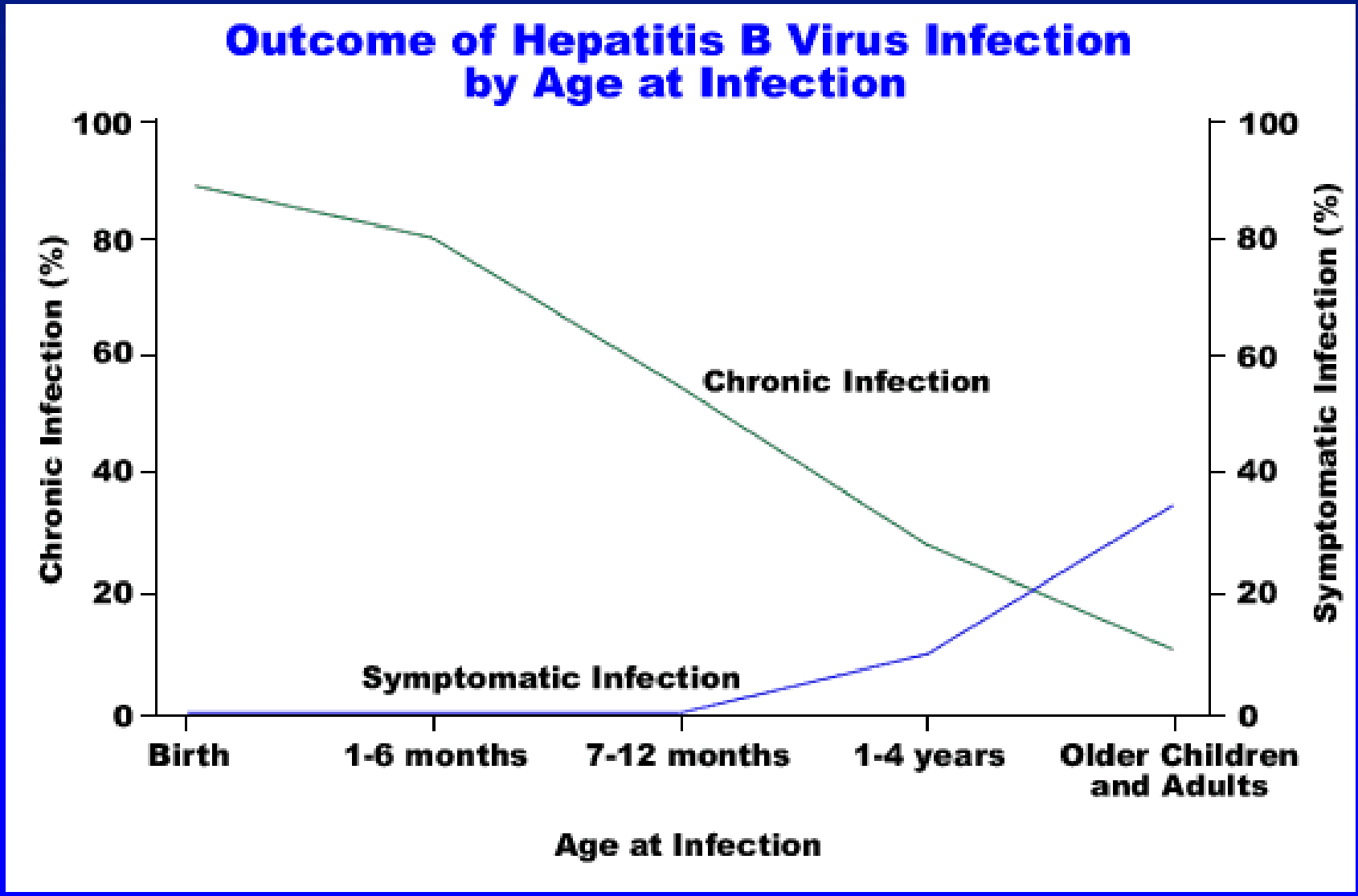
- Transmission
  - ✓ blood and blood products
  - ✓ sexual intercourse
  - ✓ organ and tissue transplant recipients
  - ✓ vertically from mother to newborn
- Who is in the highest risk in well-developed countries?
  - ✓ intravenous drug abusers
  - ✓ persons with multiple sexual partners

Clinical pictures of acute HEP B

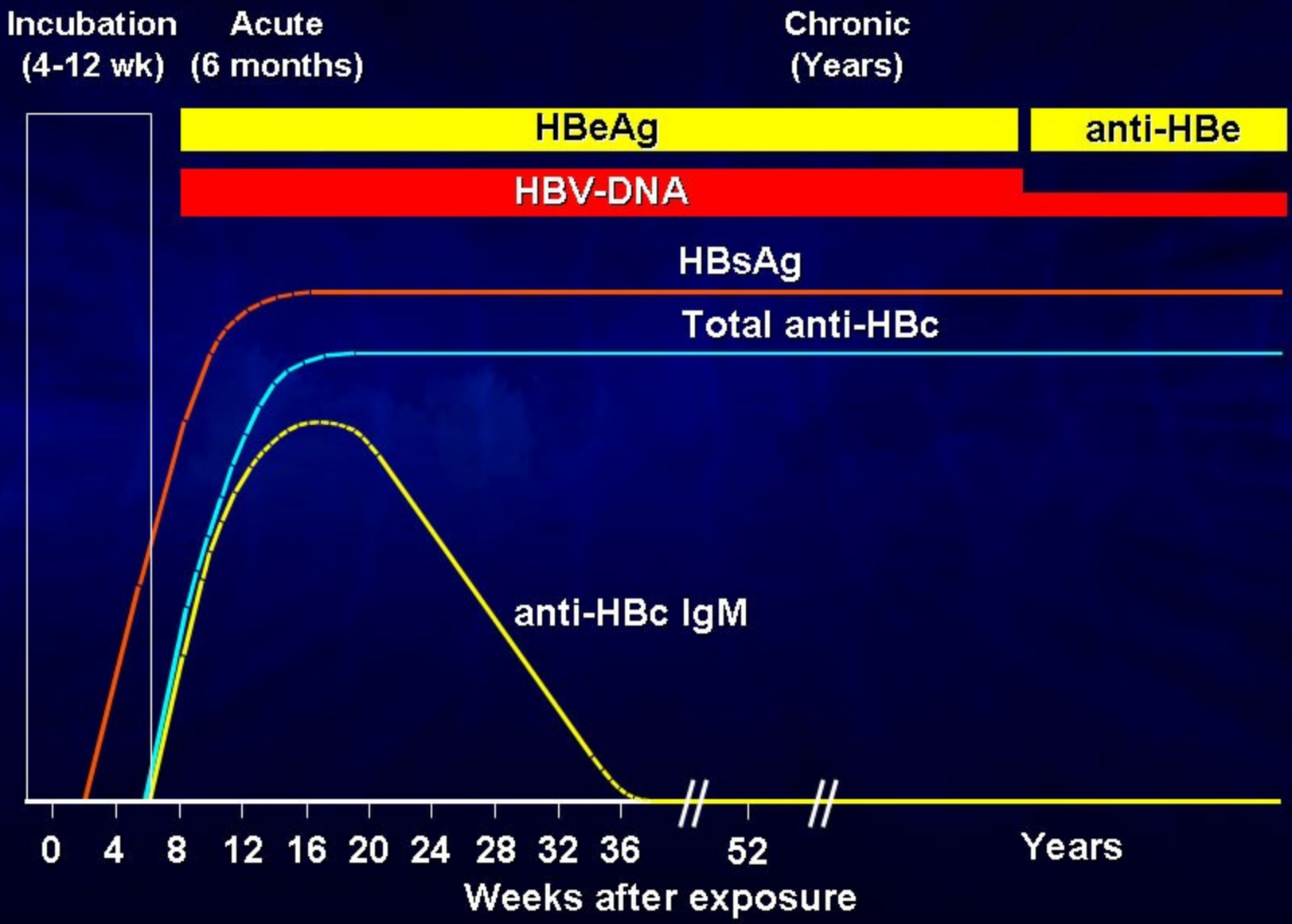
- IP: 30–180 days (mostly 2–3 months)
- Prodromal stage - flu-like syndrome
- Fulminant hepatitis: < 1 %
- Chronic HBV infection mortality: 15 – 25 %

Acute Hepatitis B

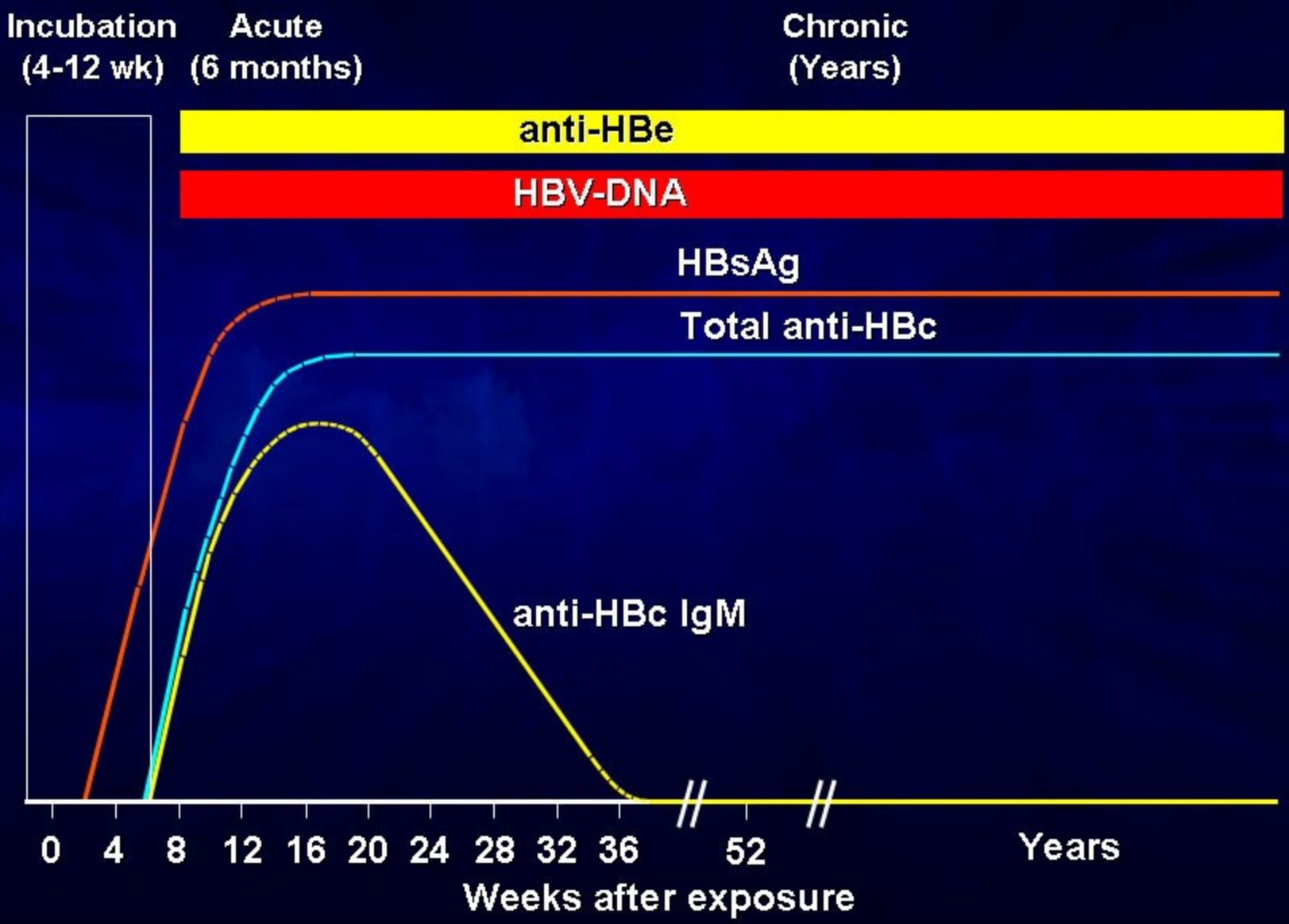



Outcome of Hepatitis B Virus Infection
by Age at Infection
Chronic Infection (%)
Symptomatic Infection (%)
100
80
60
40
20
0
Chronic Infection
Symptomatic Infection
Birth
1-6 months
7-12 months
1-4 years
Older Children and Adults
Age at Infection

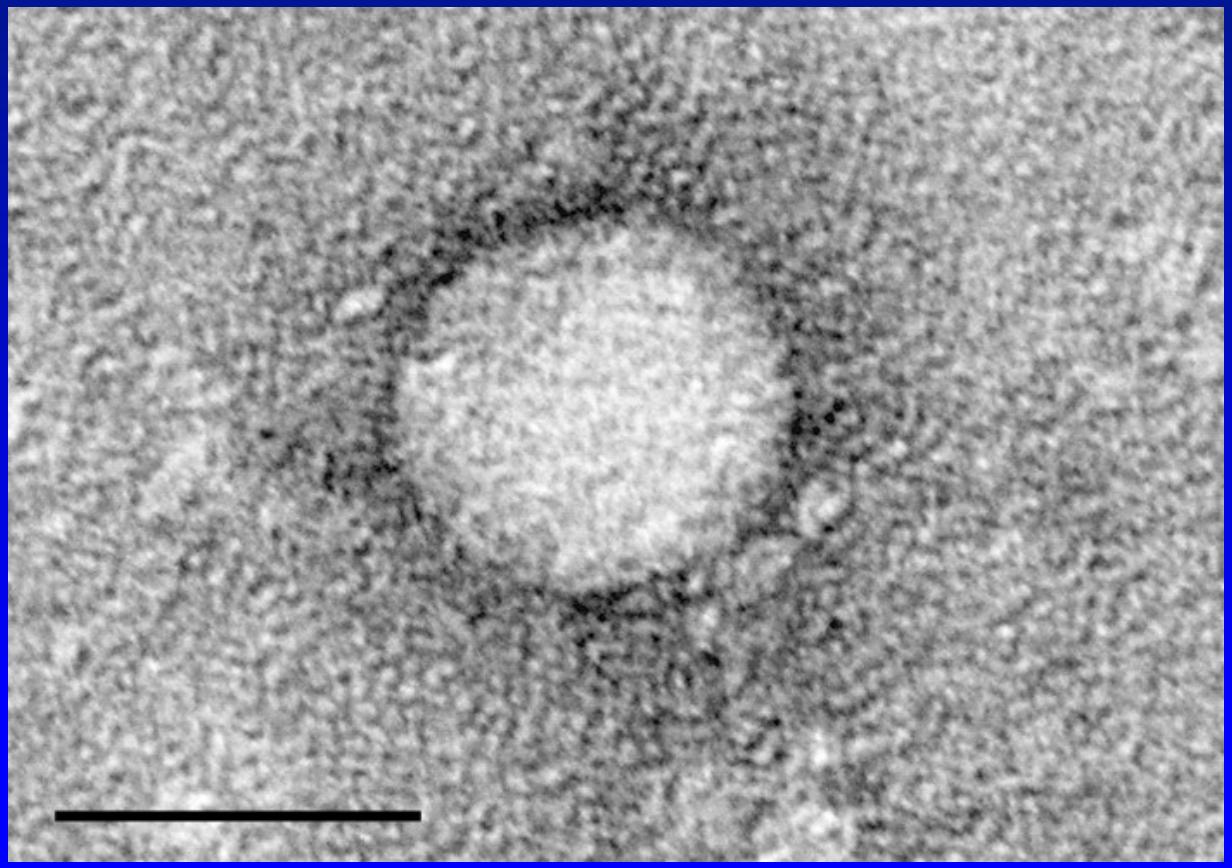
Chronic Hepatitis B (HBeAg+)



Chronic Hepatitis B (HBeAg-)

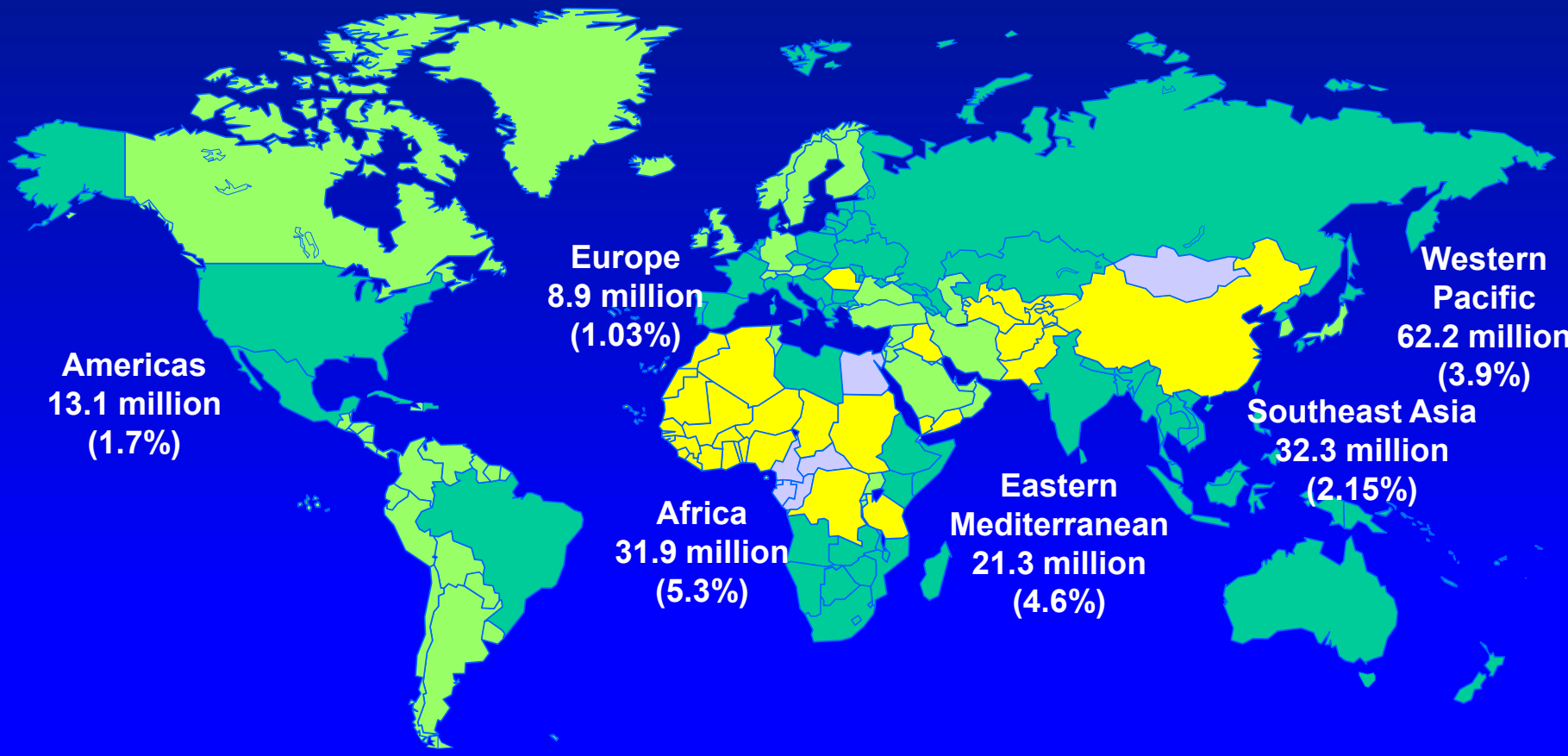


Hepatitis C virus (HCV)



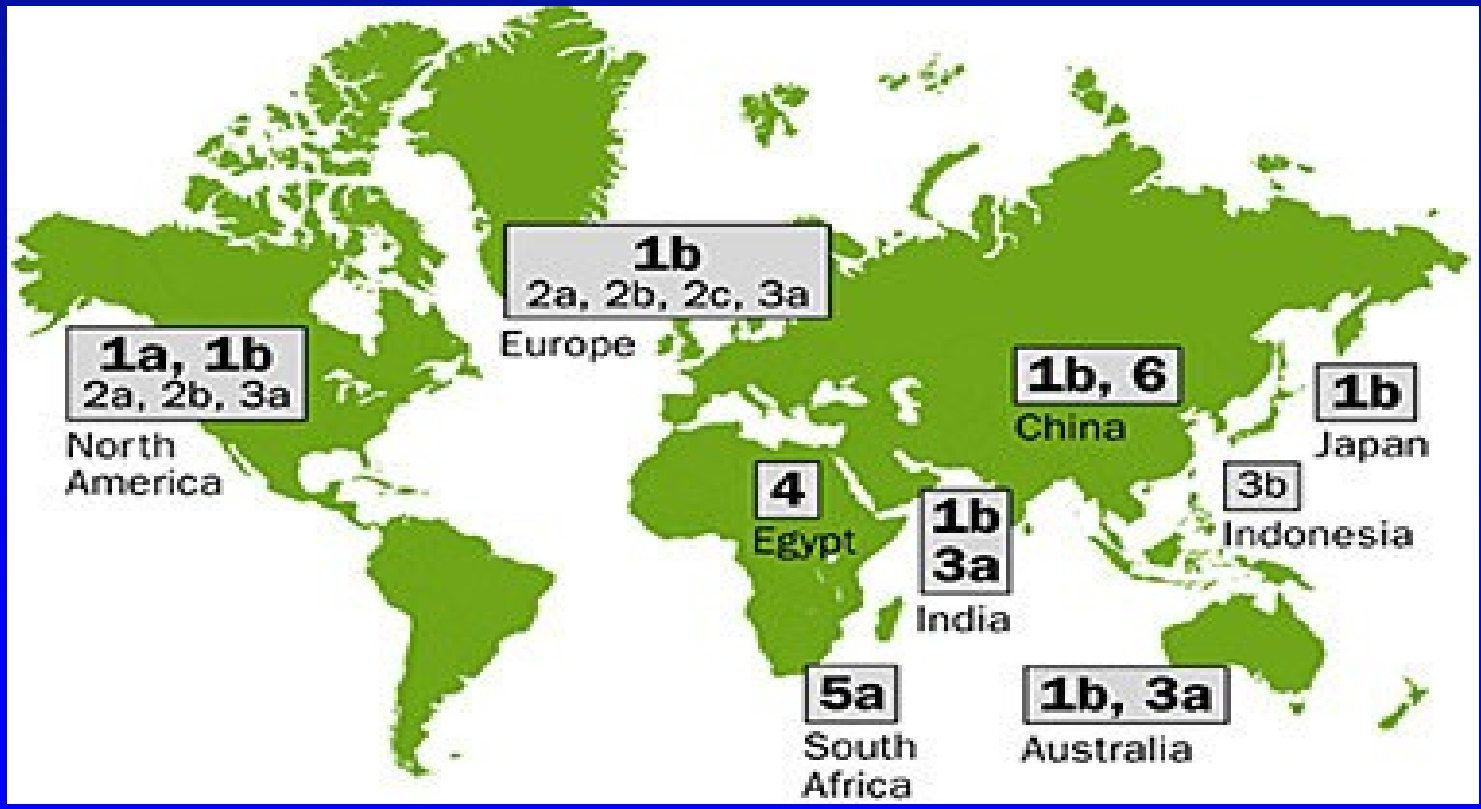
family Flaviviridae, genus Hepacivirus, enveloped RNA virus 60 nm

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.

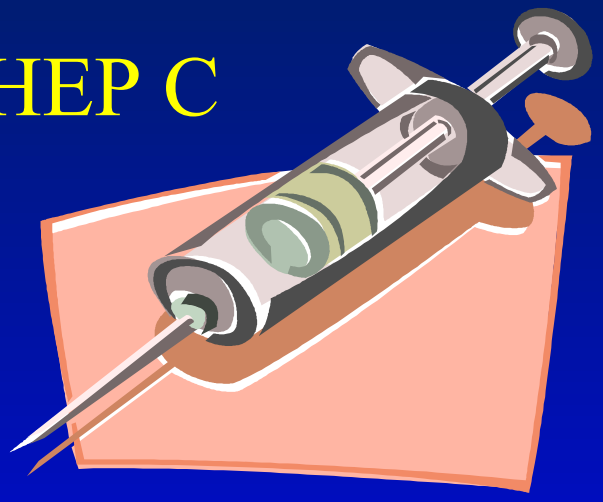
Distribution of HCV genotypes



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

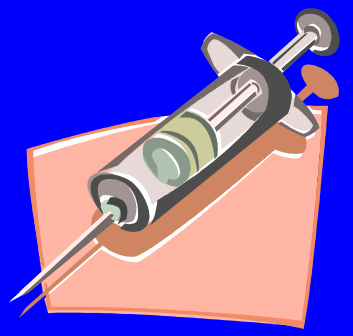
Epidemiology of HEP C



- 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

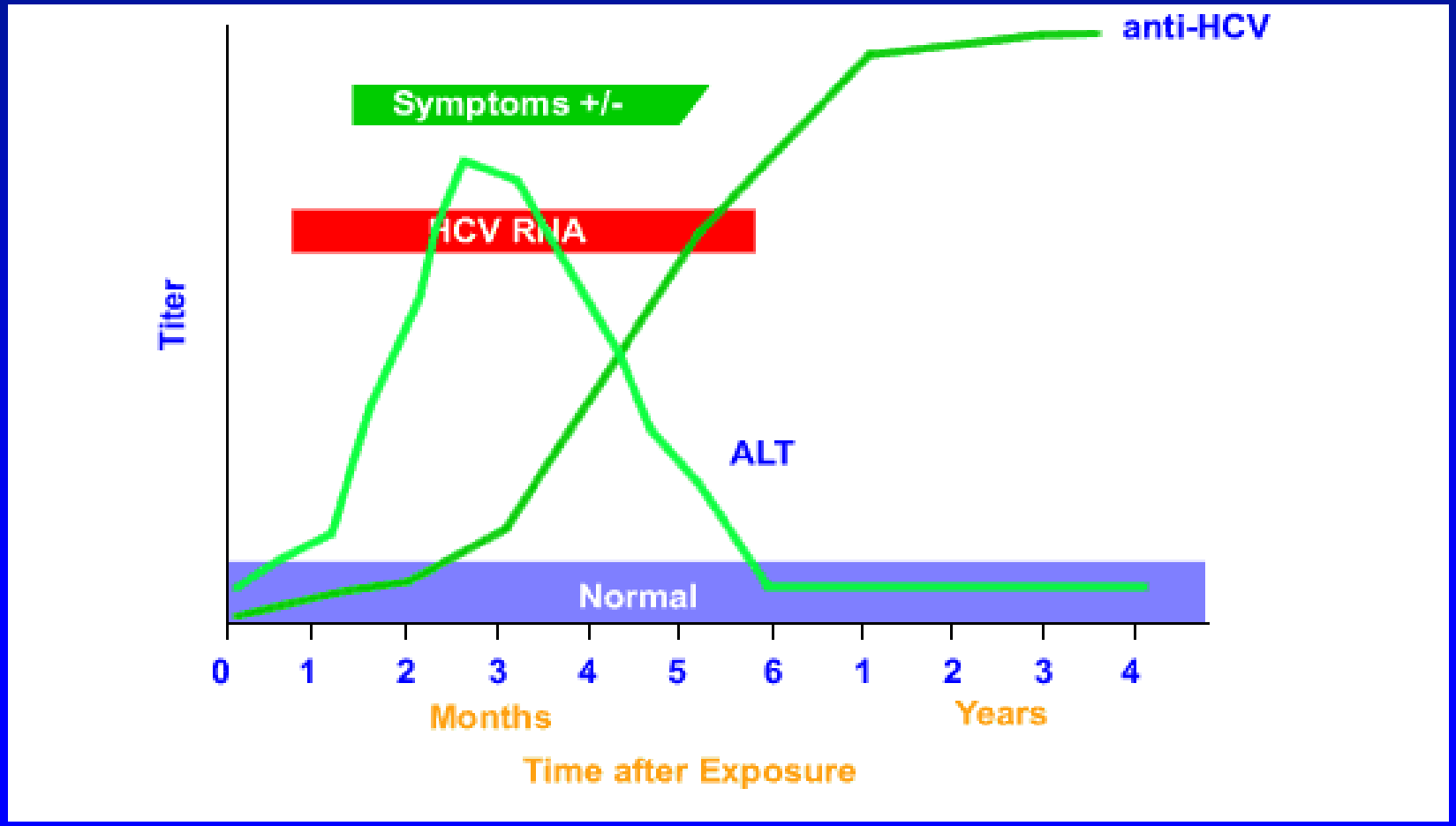
Clinical course of HEP C

- LC in about 20 % patients with chronic HCV infection
- HCC annually in 1-4 % patients with LC
- Progression to HCC depends on:

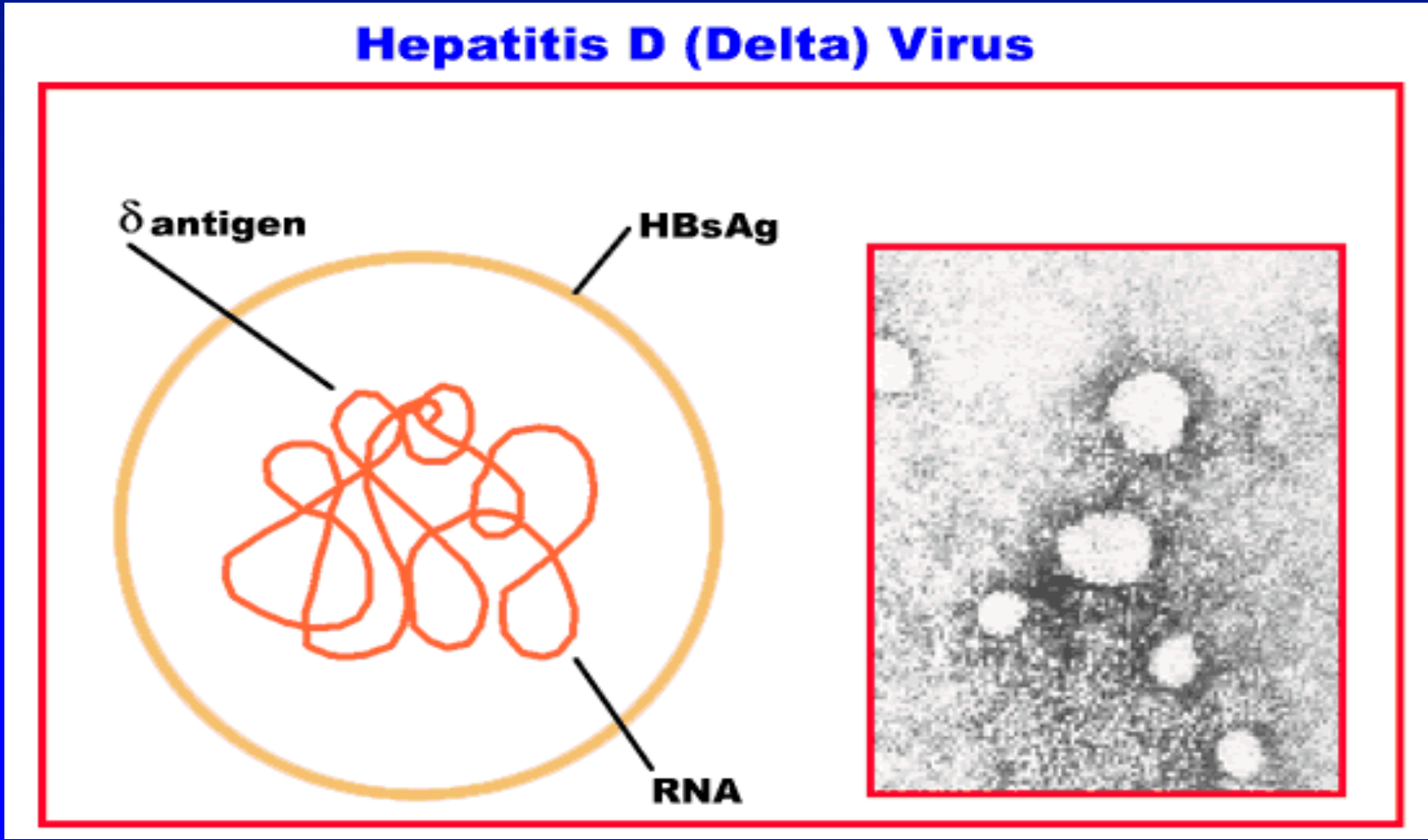
✓ age (more rapid progression in older persons)
✓ alcohol abuse
✓ HIV co-infection
✓ HBV co-infection

Diagnosis of HCV infection

Anti-HCV are total antibodies against HCV – not division into IgM and IgG class !



Hepatitis D Virus (HDV)

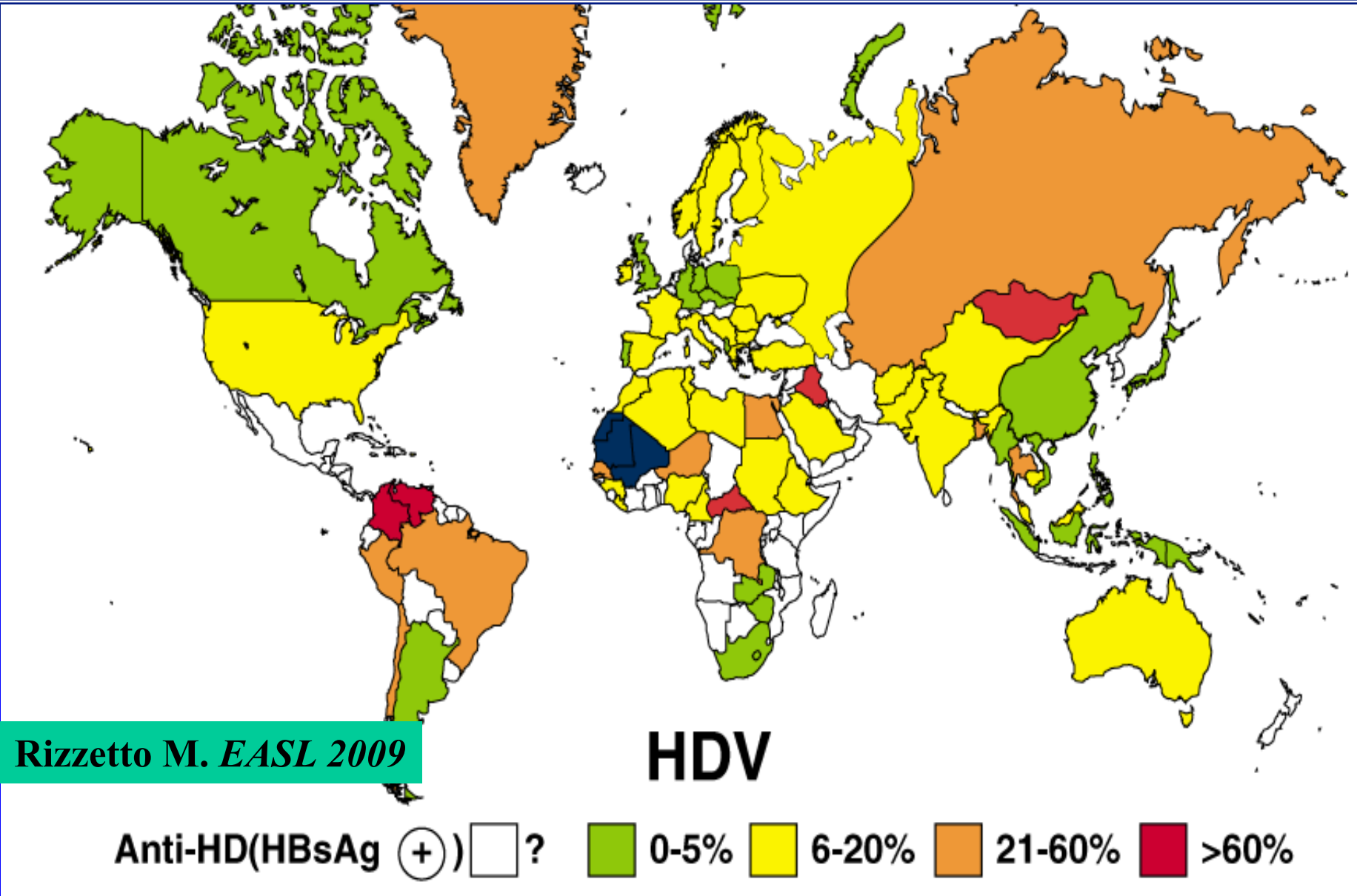


Satelite virus, family *Deltaviridae*, enveloped RNA, 40 nm

Hepatitis D

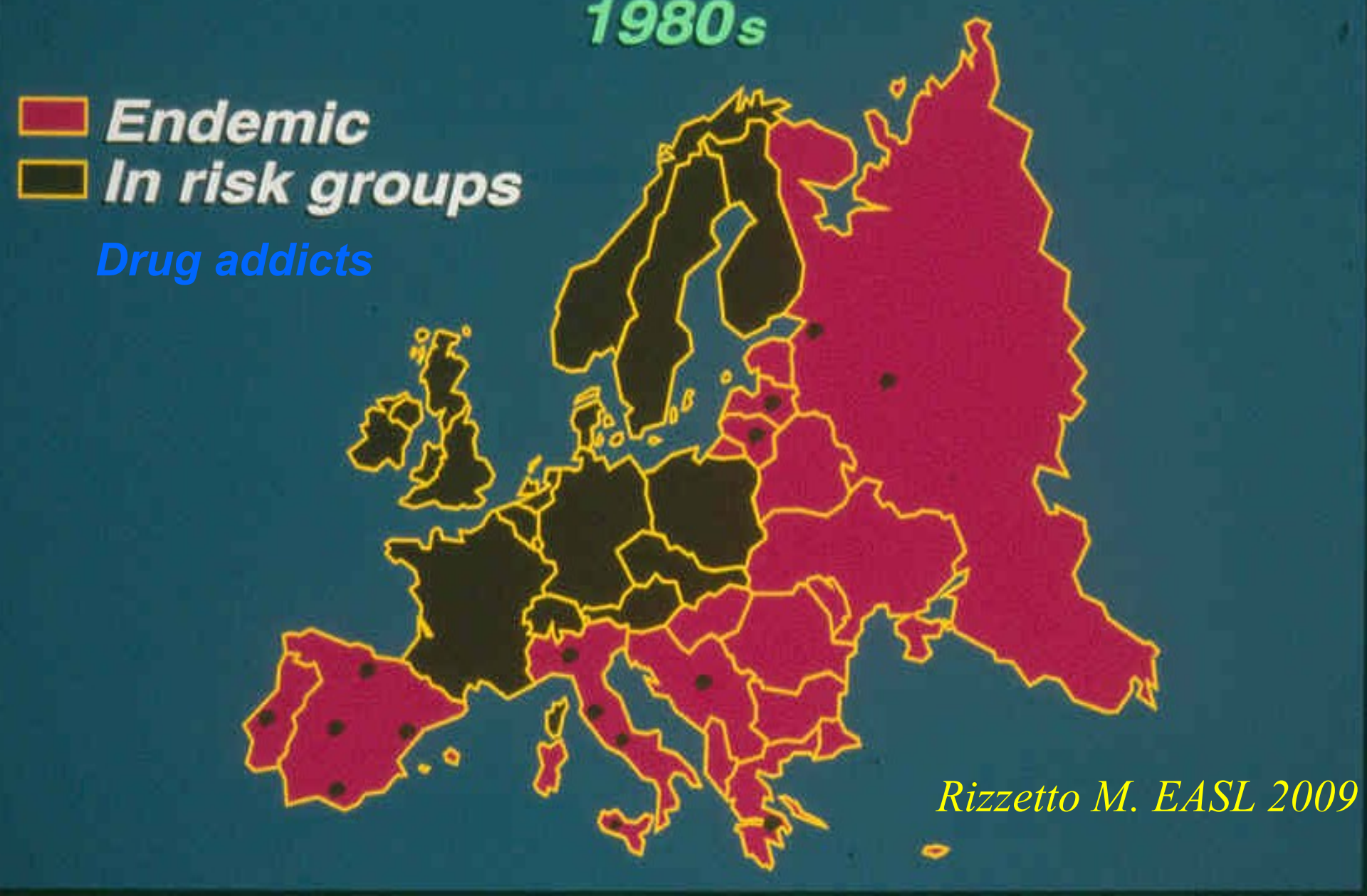
- Ability of replication only in presence of HBV infection
- ✓ Co-infection (better prognosis)
- ✓ Super-infection (worse prognosis)
- Endemic in South America, Mediterranean Region, Romania, Central Africa
- Very low prevalence in CR

Anti-HDV prevalence in HBsAg-positive (approximately 5%)



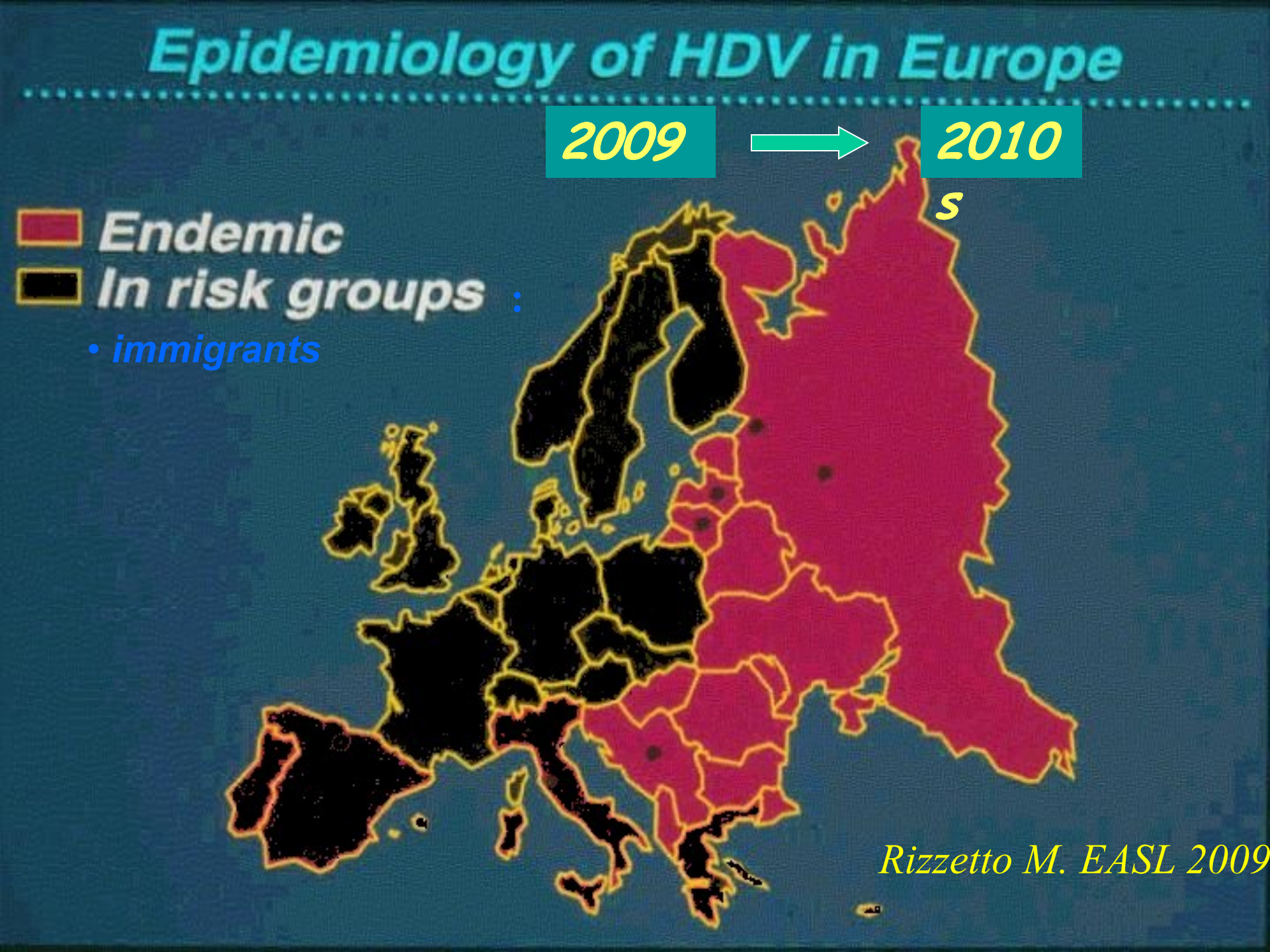
Rizzetto M. *EASL 2009*

Epidemiology of HDV in Europe

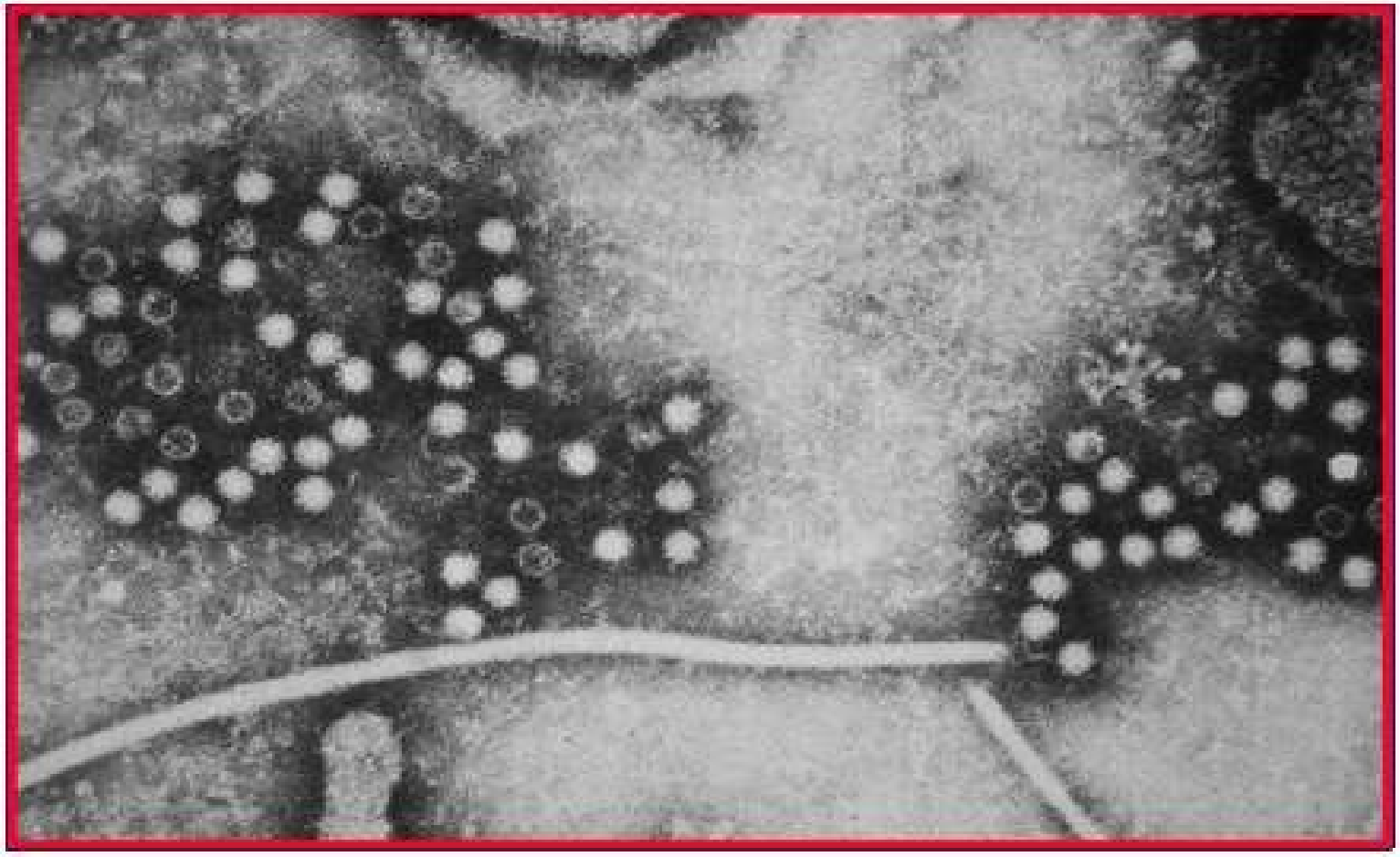


Rizzetto M. EASL 2009

Epidemiology of HDV in Europe



Hepatitis E Virus



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

HEV genotypes

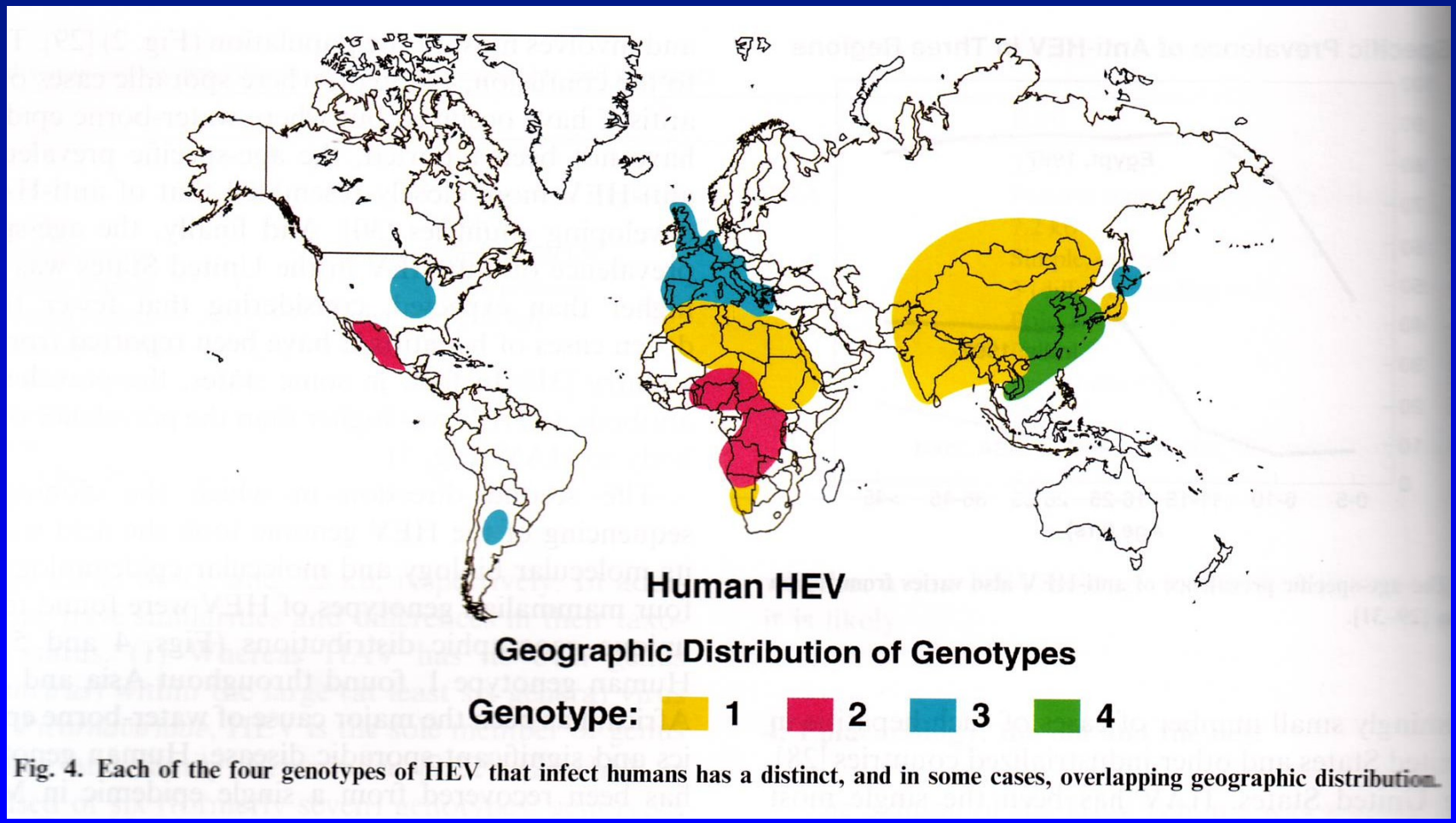
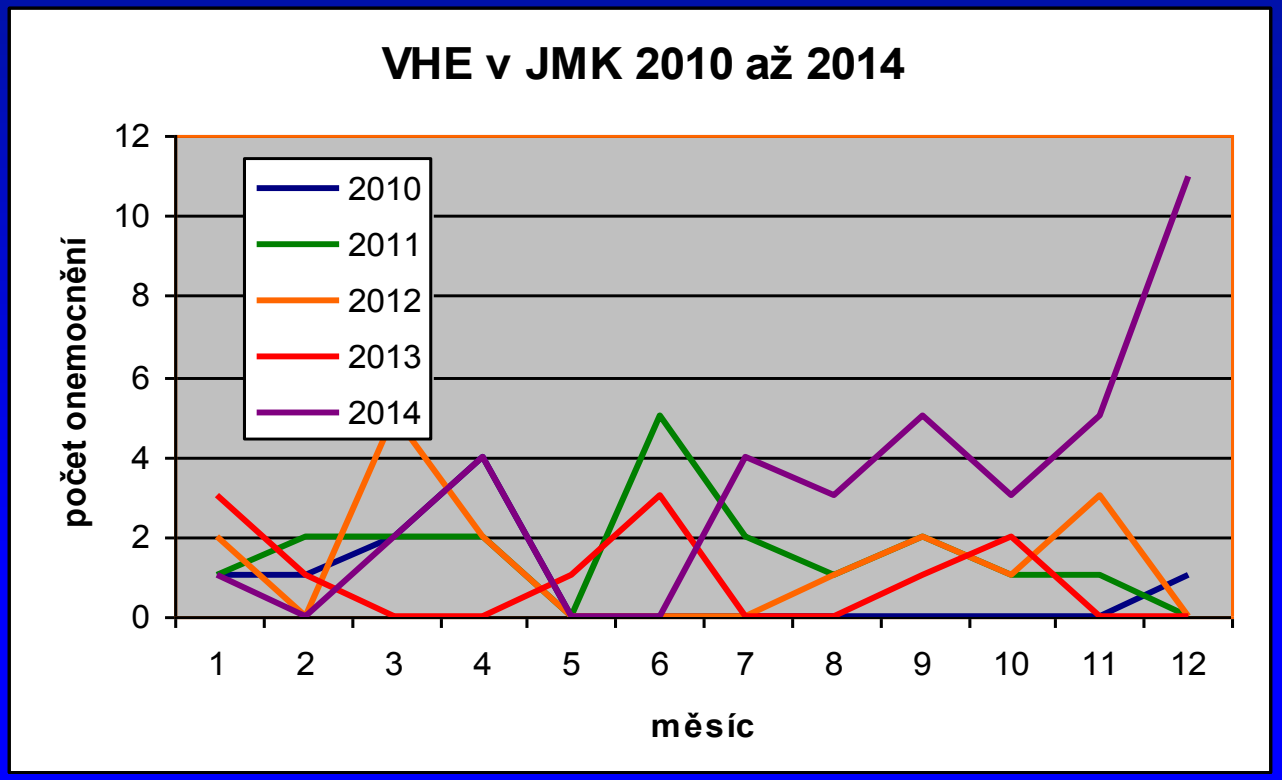


Fig. 4. Each of the four genotypes of HEV that infect humans has a distinct, and in some cases, overlapping geographic distribution.

Purcell RH, Emerson SU. *J Hepatol* 48 (2008) 494-503

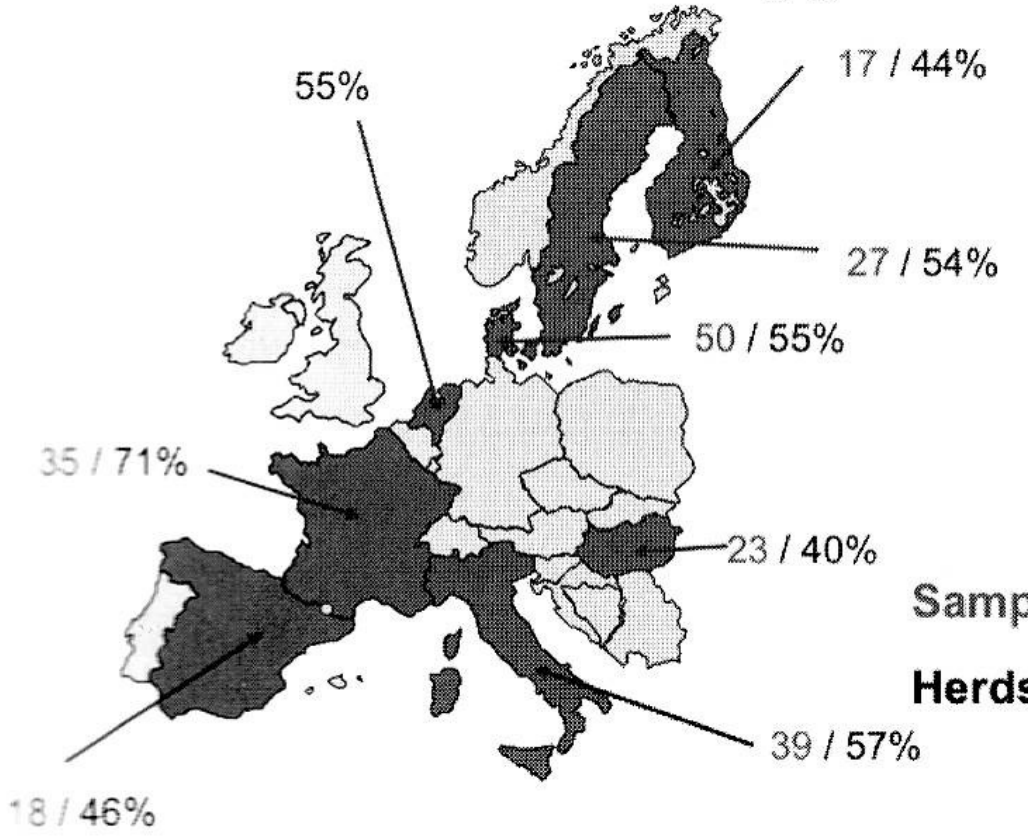
Hepatitis E in Southern Moravia



Hepatitis E

- Travel-related disease (G-1+2 – faecely contaminated water)
- Infection is currently more frequently acquired in CR (G-3 - pork, game meat)
- Extremely serious clinical course in late pregnancy (mortality above 20 %) and in patients with alcoholic liver cirrhosis (mortality 60-70%)
- Repeated infection may be possible
- Rare cases of chronic hepatitis E in seriously immunosuppressed patients (organ recipients…)

Prevalence of HEV in swine herds (pigs 1 to 5 months of age)



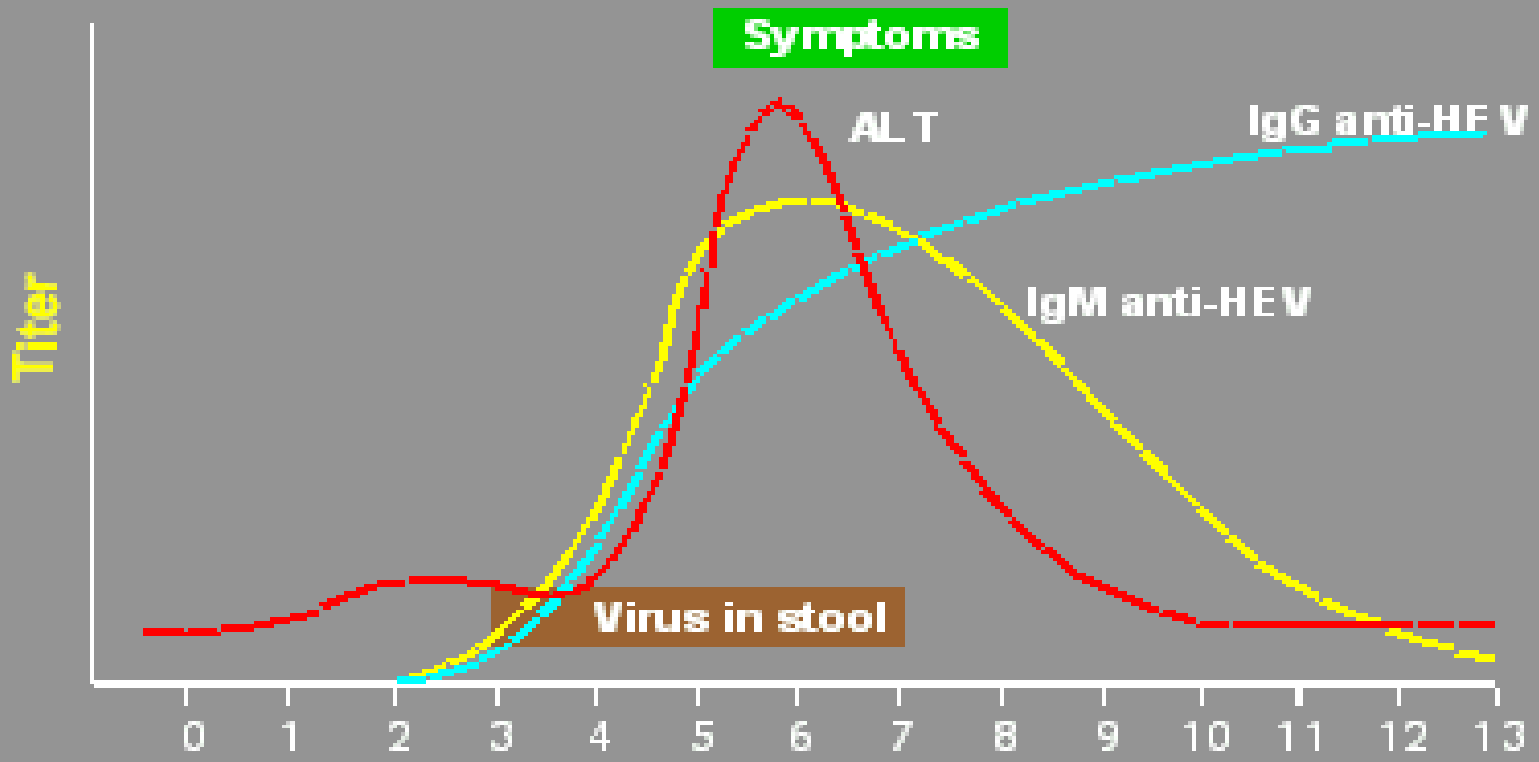
Samples: Avg = 32%

Herds: Avg = 52%

Figatellu – sausage with raw pork liver

Hepatitis E Virus Infection

Typical Serological Course



Rapid progression of chronic hepatitis E

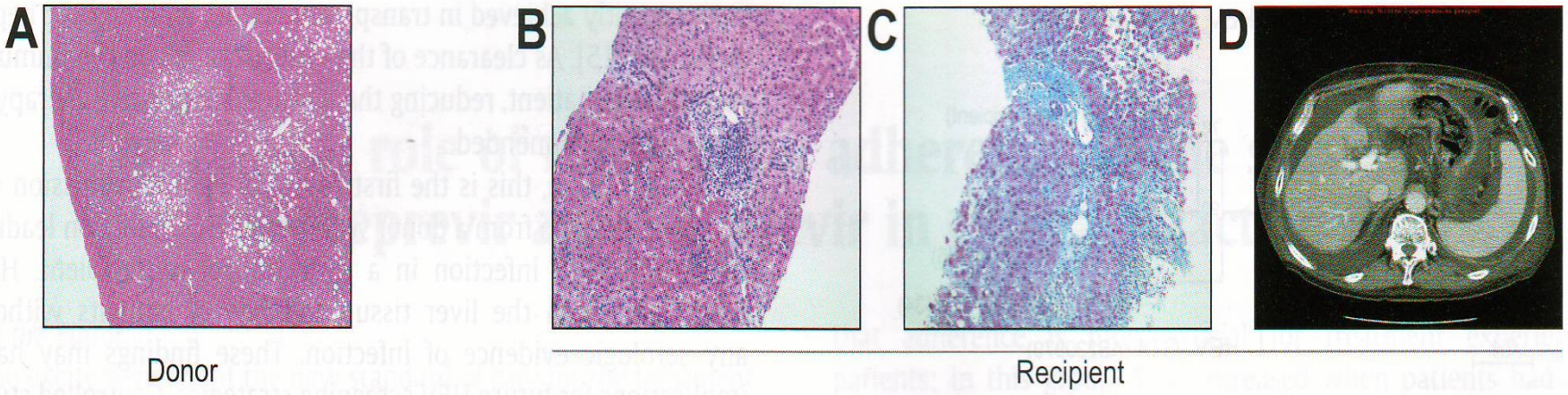
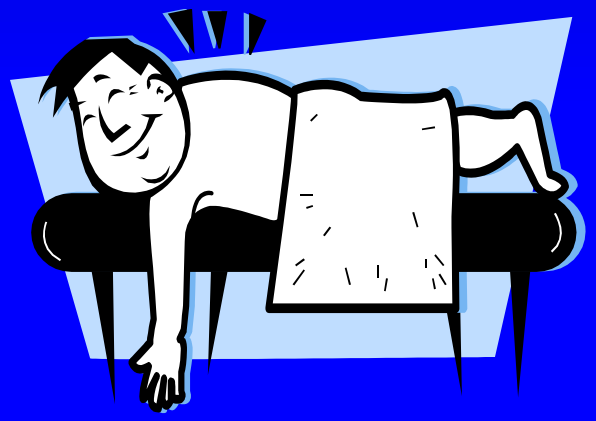


Fig. 1. Histologic assessment of the liver tissue before and after OLT and CT scan after OLT. (A) The liver tissue of the donor revealed absence of significant signs of chronic hepatitis but vesicular fatty liver disease was diagnosed. (B) Second biopsy. One hundred and fifty days after OLT, chronic inflammation with portal and interface hepatitis was described which was interpreted as an acute rejection. (C) Third biopsy. Three hundred and forty seven days after OLT, persistence of chronic hepatitis was associated with portal and septal bridging signs of fibrosis. (D) CT scan performed 1 year after liver transplantation revealed signs of portal hypertension including ascites, splenomegaly and gastric varices compatible with decompensated liver cirrhosis.

Treatment of acute hepatitis (all types)

- Symptomatic for all types

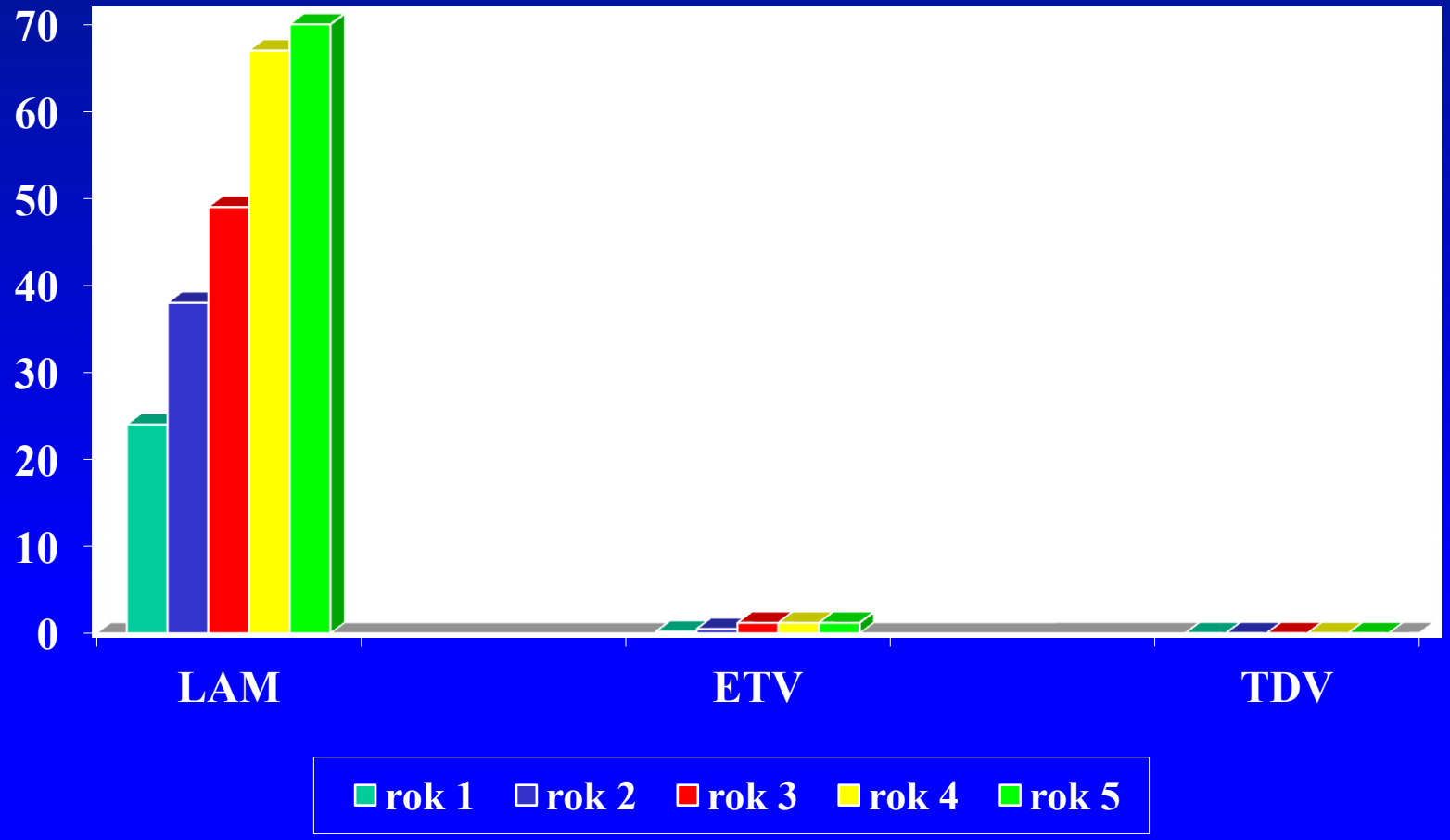
✓ physical and mental rest
✓ diet
✓ no alcohol, no hepatoxic drugs
✓ supportive treatment (silymarin, essential phosholipids)



Current possibilities of treatment of HBV infection

- pegylated interferon alfa-2a – 48 weeks
- lamivudine - only in severe acute HEP B or protection of reactivation or recurence
- entecavir – for naive patients
- tenofovir – both for naive and lamivudine-resistant patients

HBV resistance during therapy



Drugs for hepatitis C therapy

- ✓ PEG-IFN alfa-2a, -2b
- ✓ Ribavirin
- ✓ Boceprevir (BOC) – protease inhibitor of the 1st generation
- ✓ Telaprevir (TVR) – protease inhibitor of the 1st generation

- ✓ Sofosbuvir (SOF) – since January 2014 – nucleotide inhibitor of NS5B polymerase
- ✓ Simeprevir (SMV) – since May 2014 – new wave of protease inhibitor of the 1st generation
- ✓ Daclatasvir (DCV) – since August 2014 – NS5A inhibitor
- ✓ Ledipasvir (LDV) – since November 2014 – NS5A inhibitor – only fixed combination with SOF
- ✓ 3D kombinace – since January 2015 - paritaprevir/ritonavir – PI, ombitasvir - NS5A, dasabuvir – non-nucleoside polymerase inhibitor

IFN-free regimens for HCV infection

- Very probably the future of HCV therapy
- Combination of oral drugs
- High efficacy
- Almost no adverse events
- Short duration of therapy – 12-24 weeks

Hepatitis D therapy

- very problematic – low efficacy
- PEG-IFN long-term (more than 1 year)
- TDV, TDV – not effective

Chronic hepatitis E therapy

- Still unknown
- Only case reports with ribavirin in various therapeutic regimens

Thank you for your attention!

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