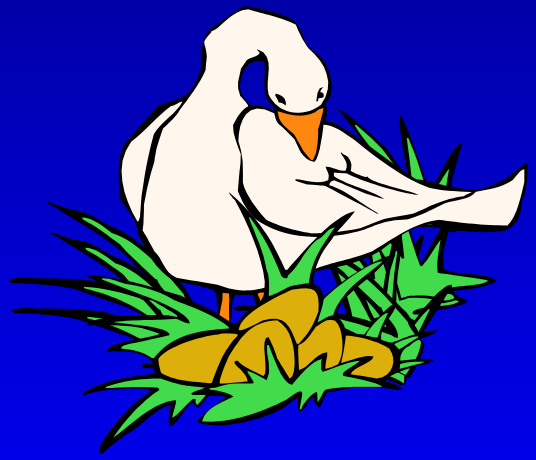
Viral Hepatitis

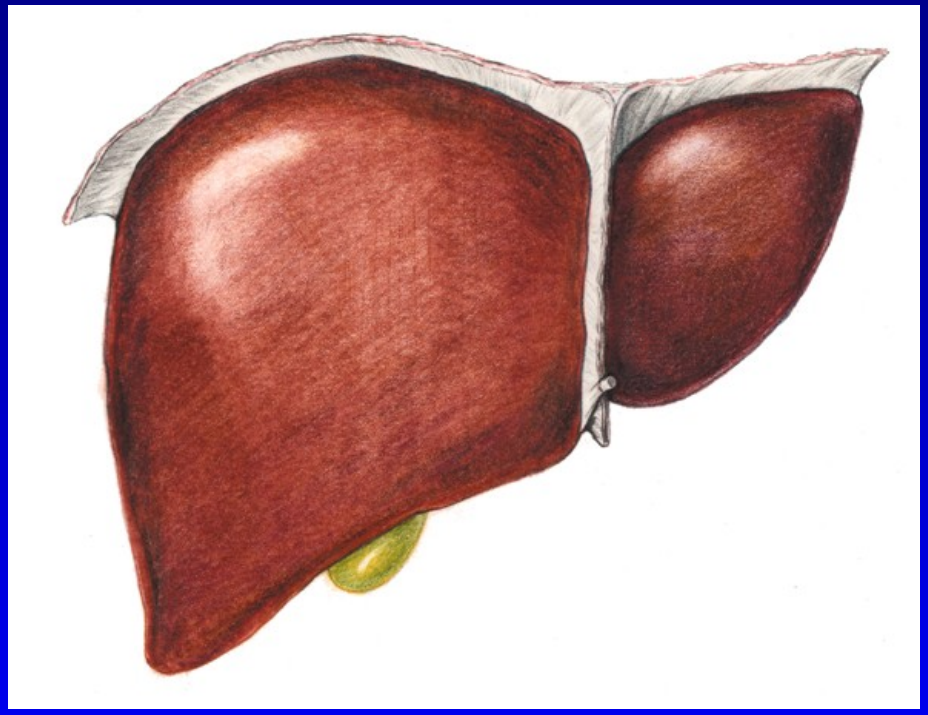


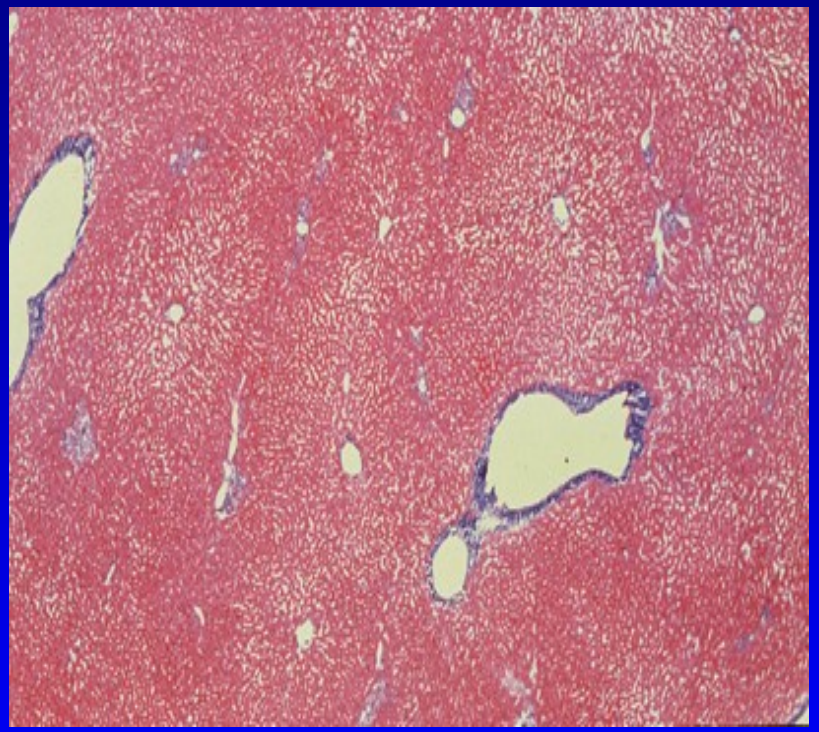
Prof. MUDr. Petr Husa, CSc.
Klinika infekčních chorob, FN Brno

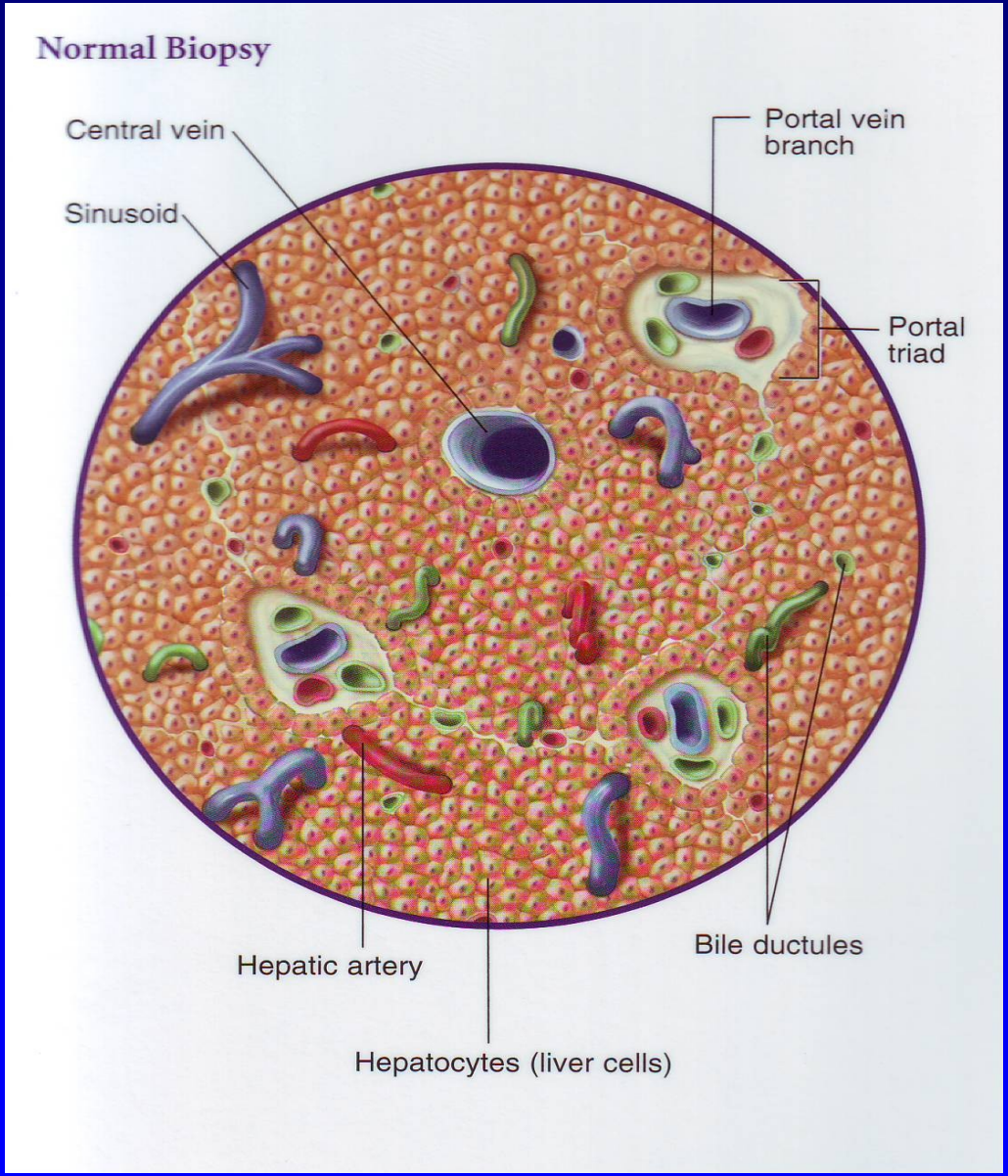
Viral Hepatitis

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

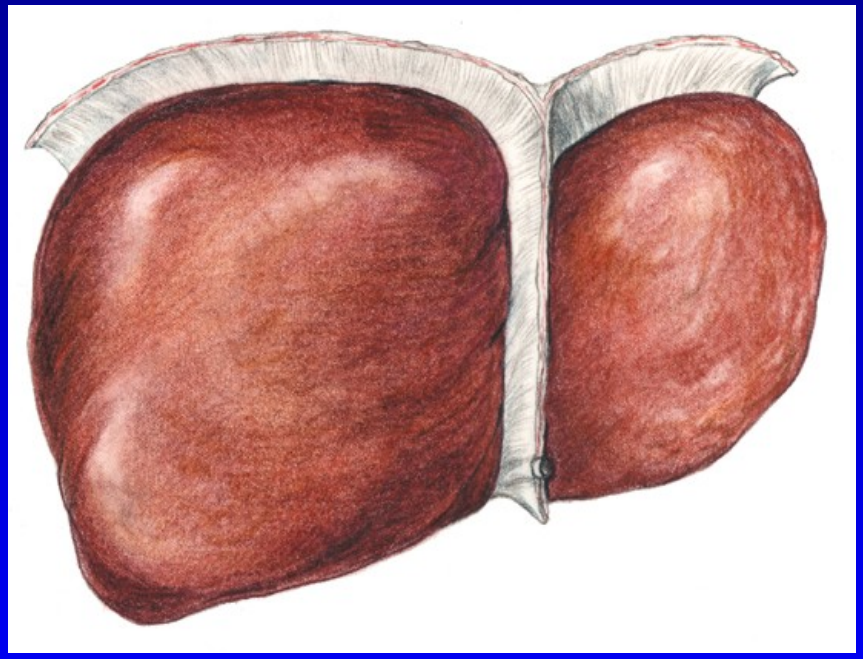
Healthy liver

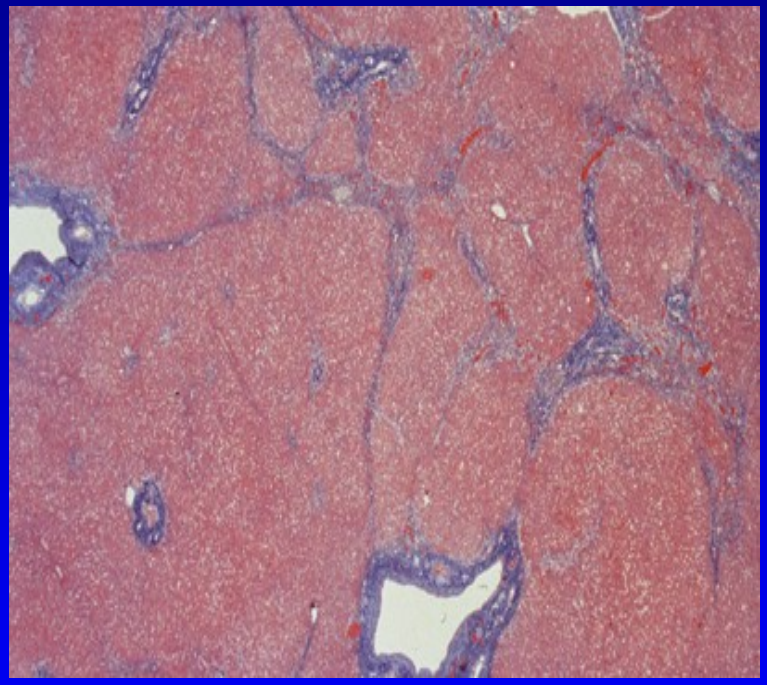




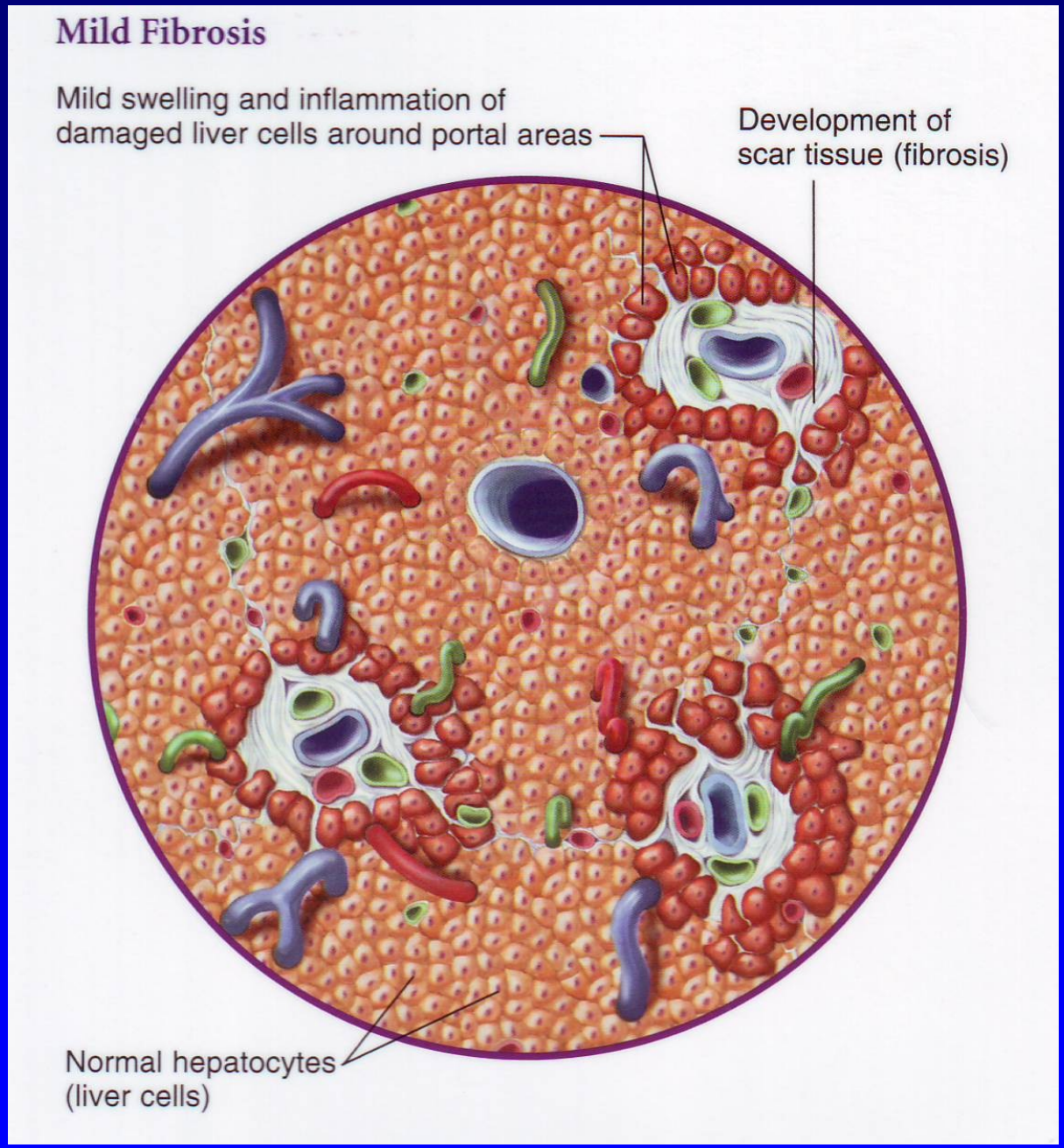

Normal Biopsy
Central vein
Portal vein branch
Sinusoid
Portal triad
Hepatic artery
Bile ductules
Hepatocytes (liver cells)

Liver fibrosis

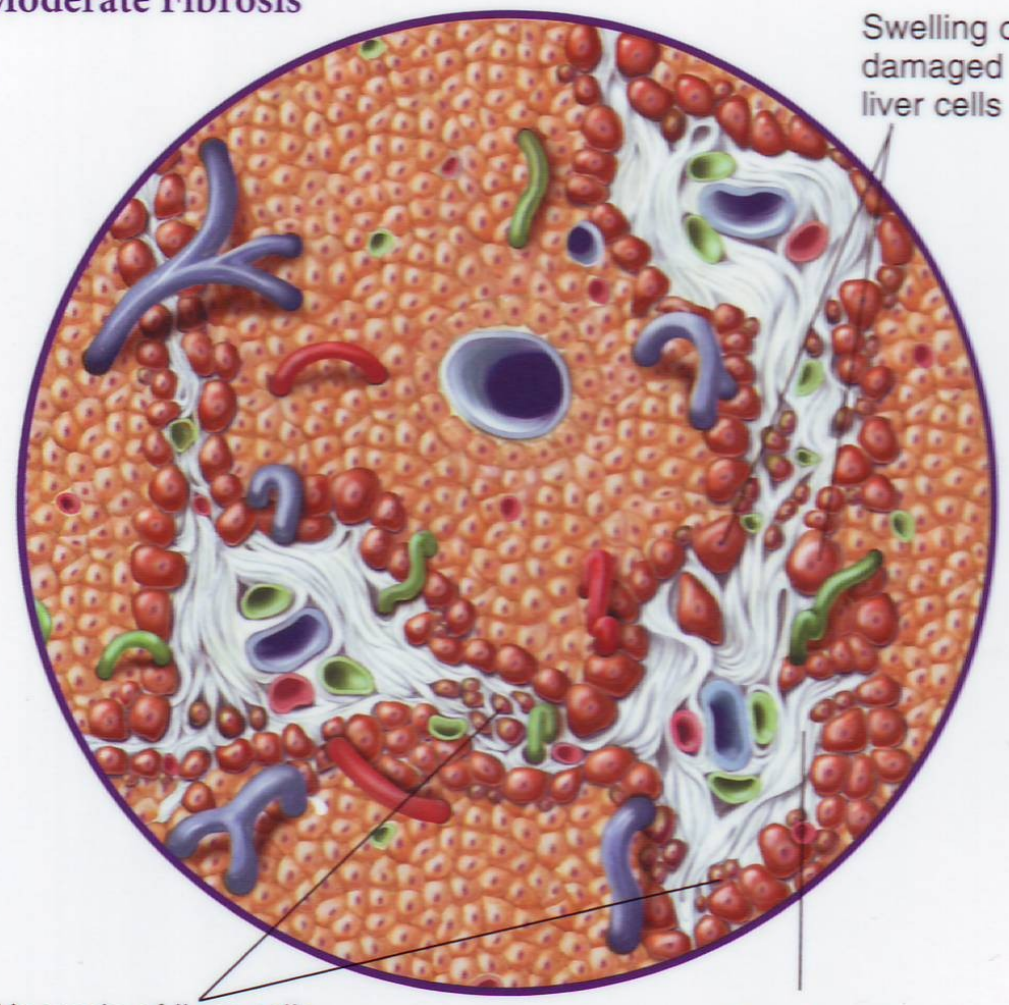




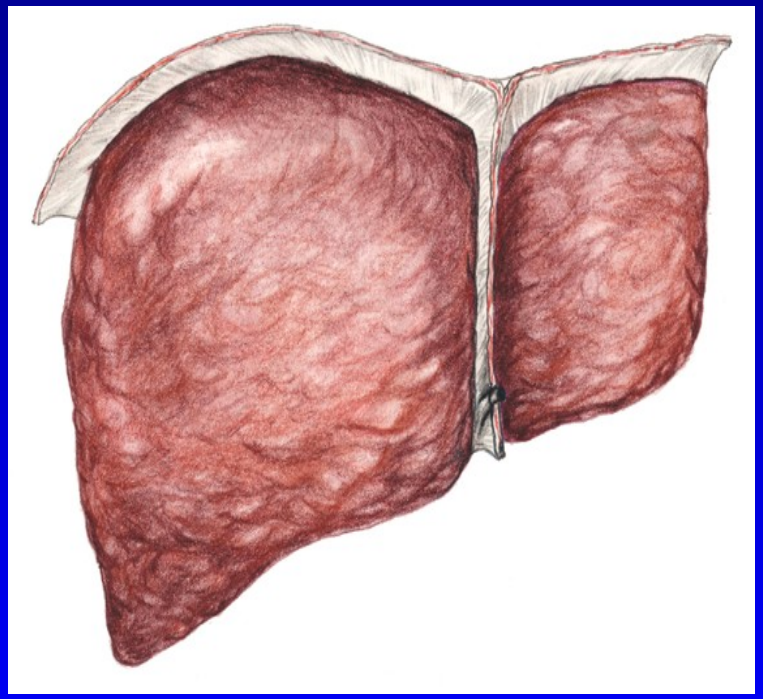
Mild Fibrosis

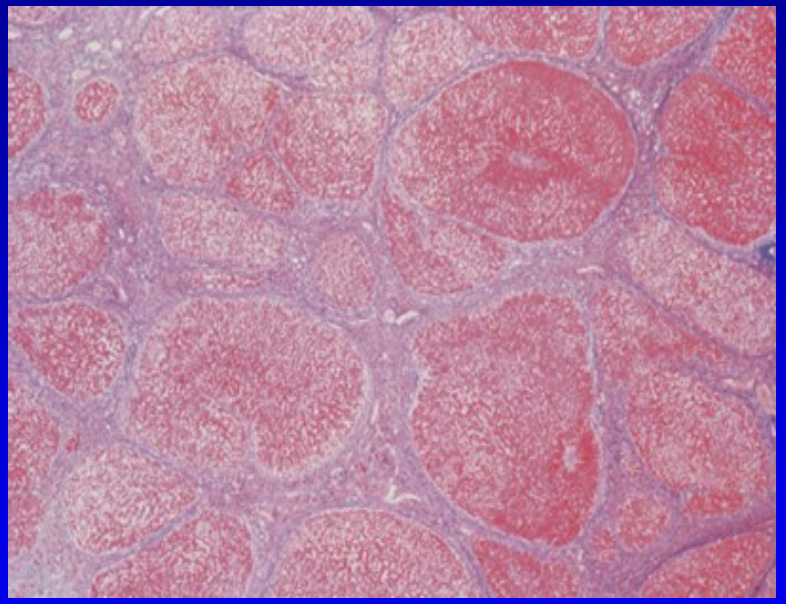


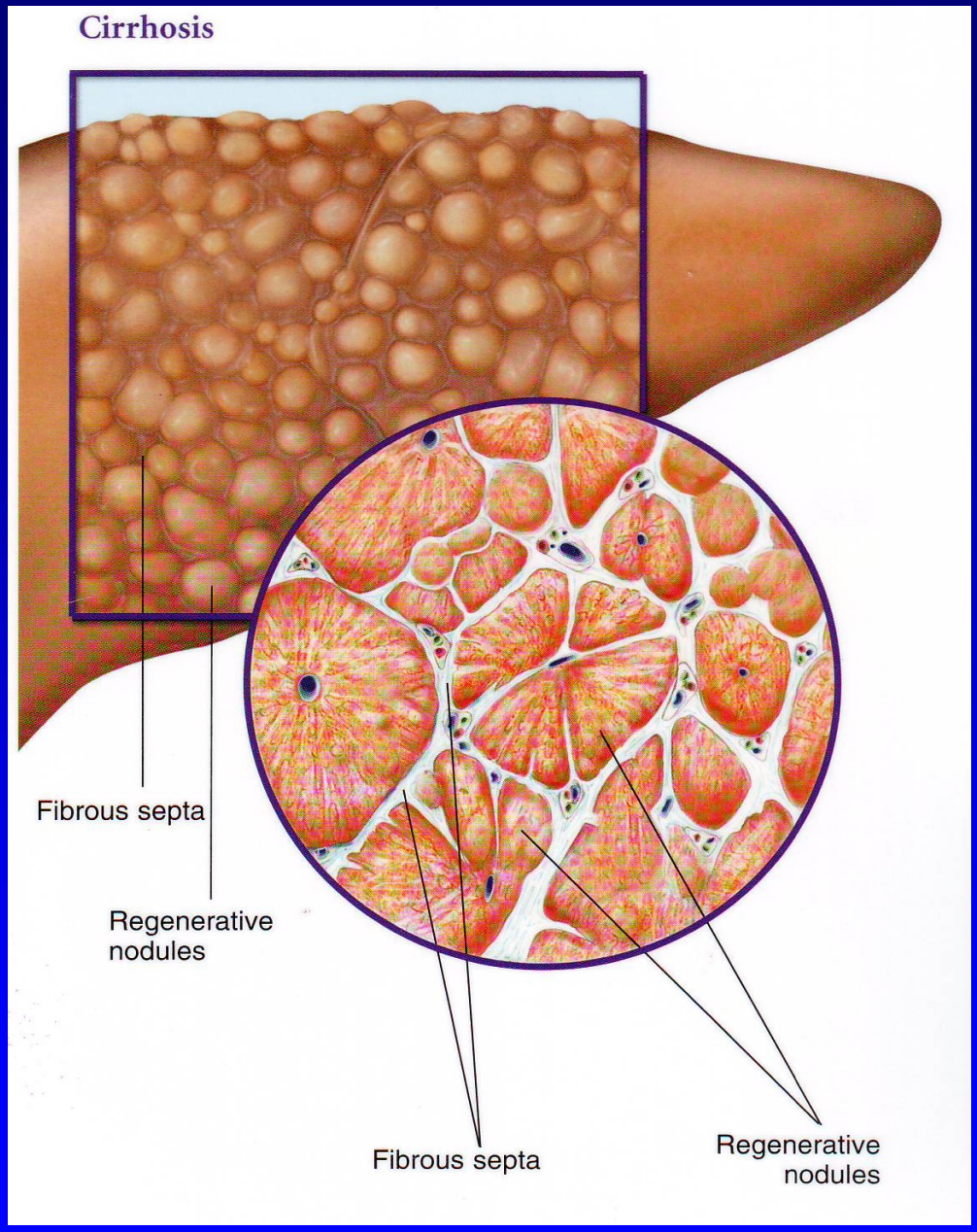
Moderate Fibrosis



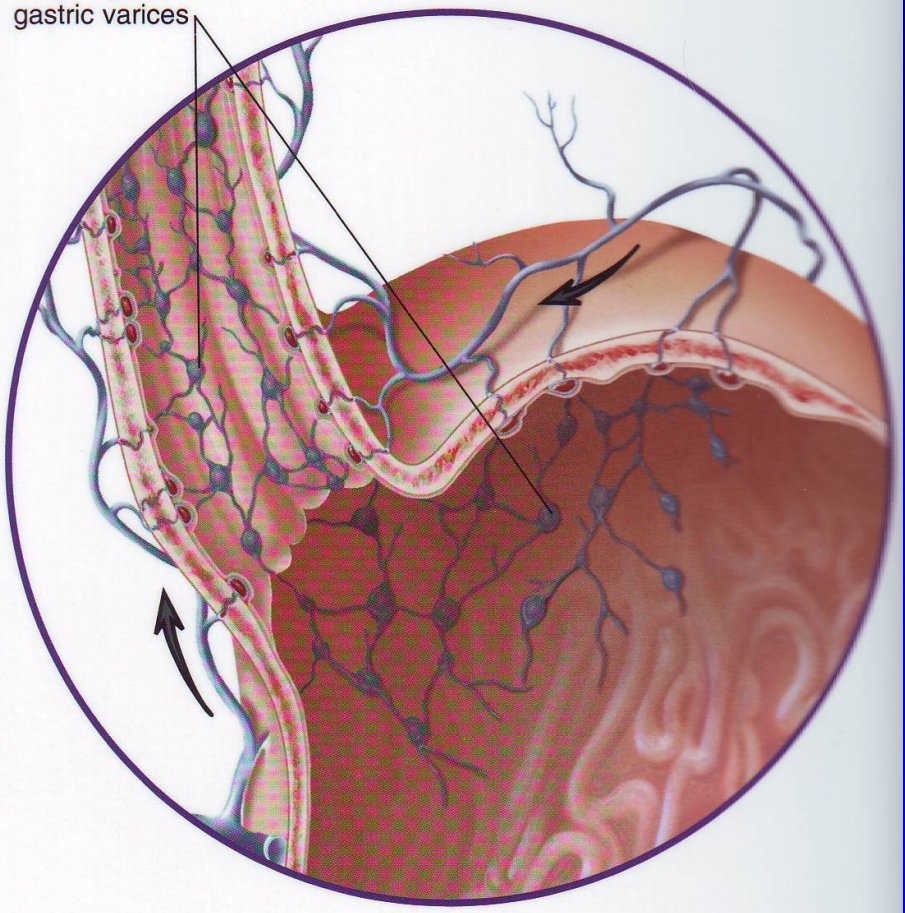
Liver cirrhosis

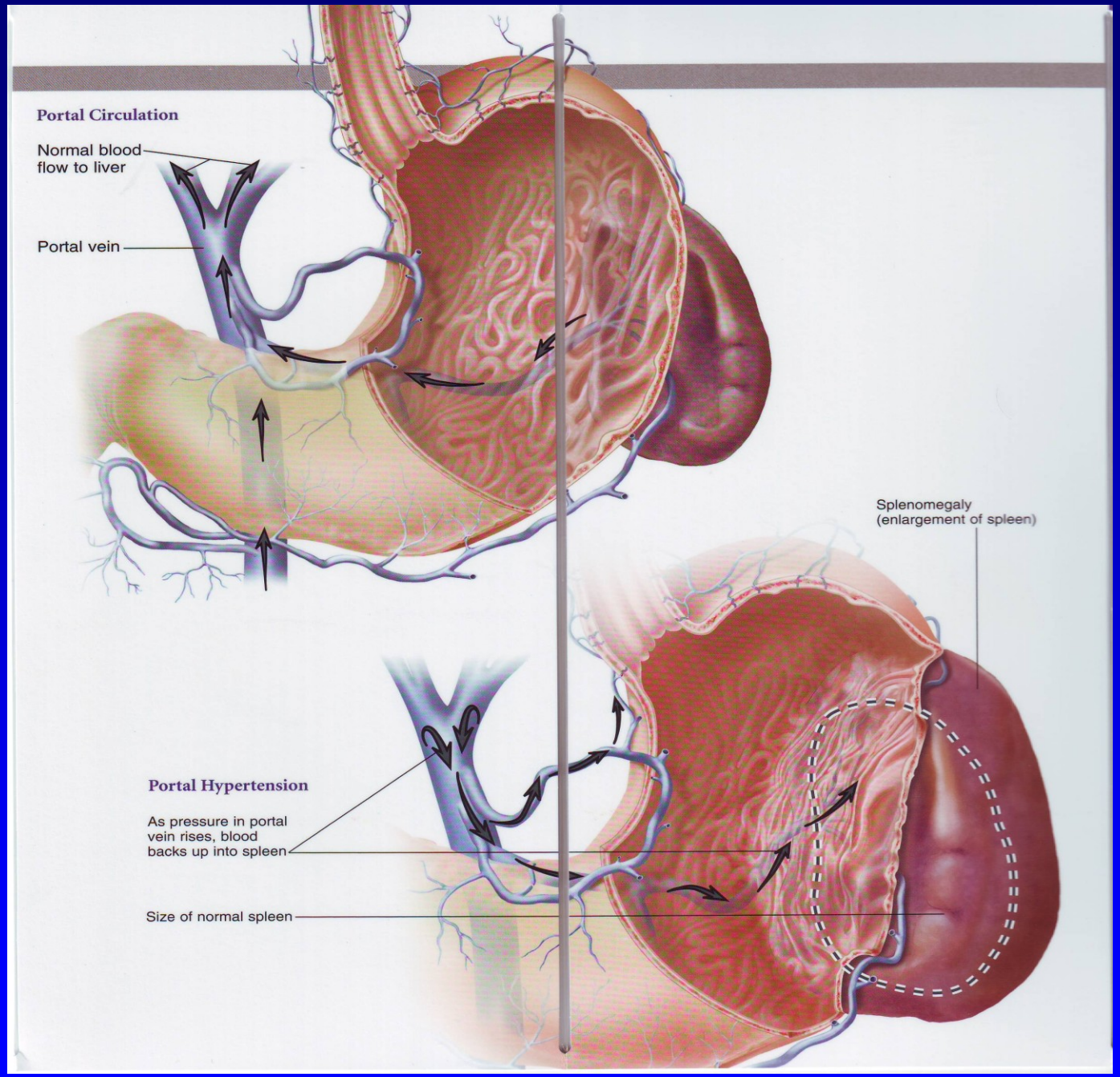


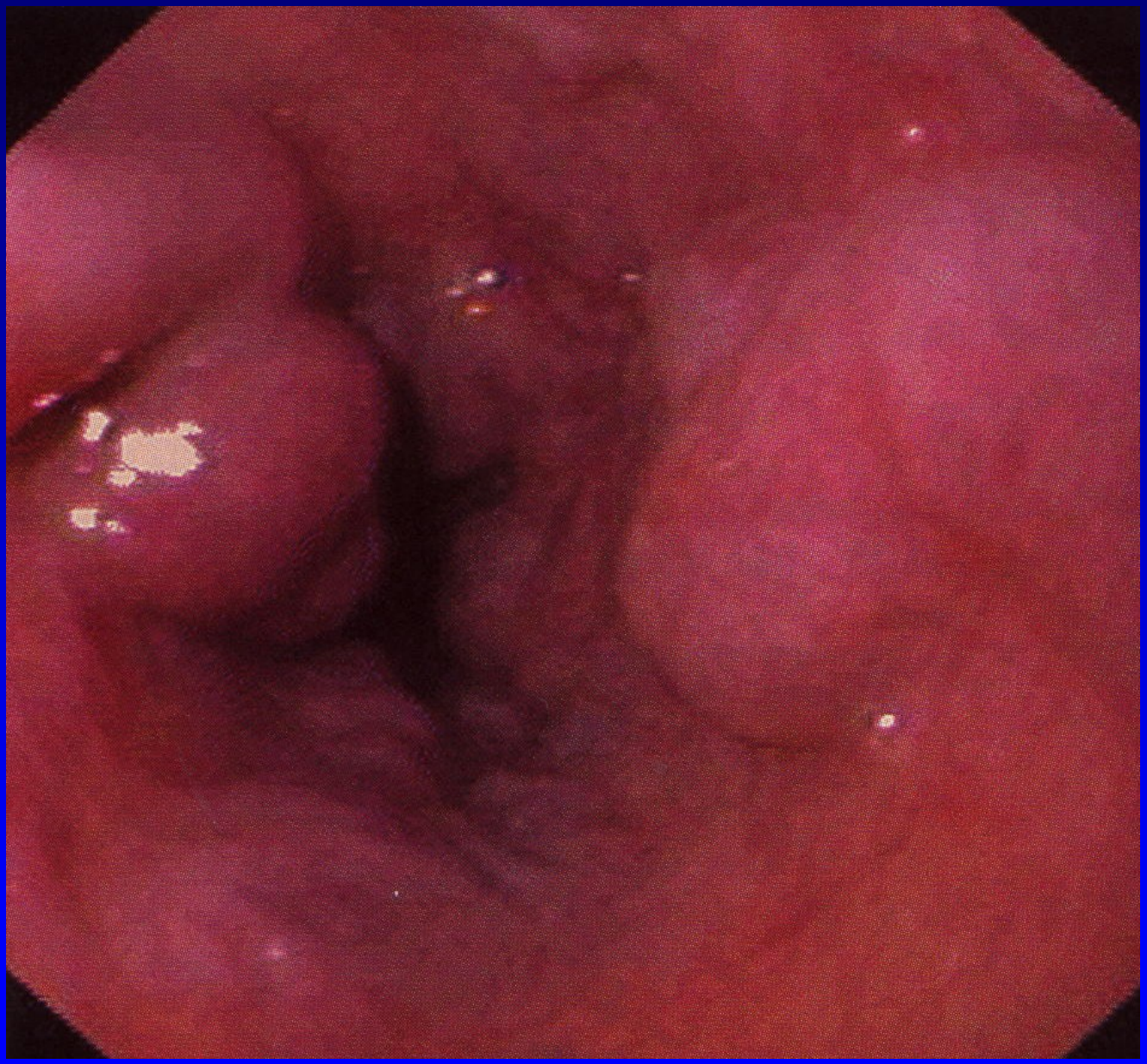


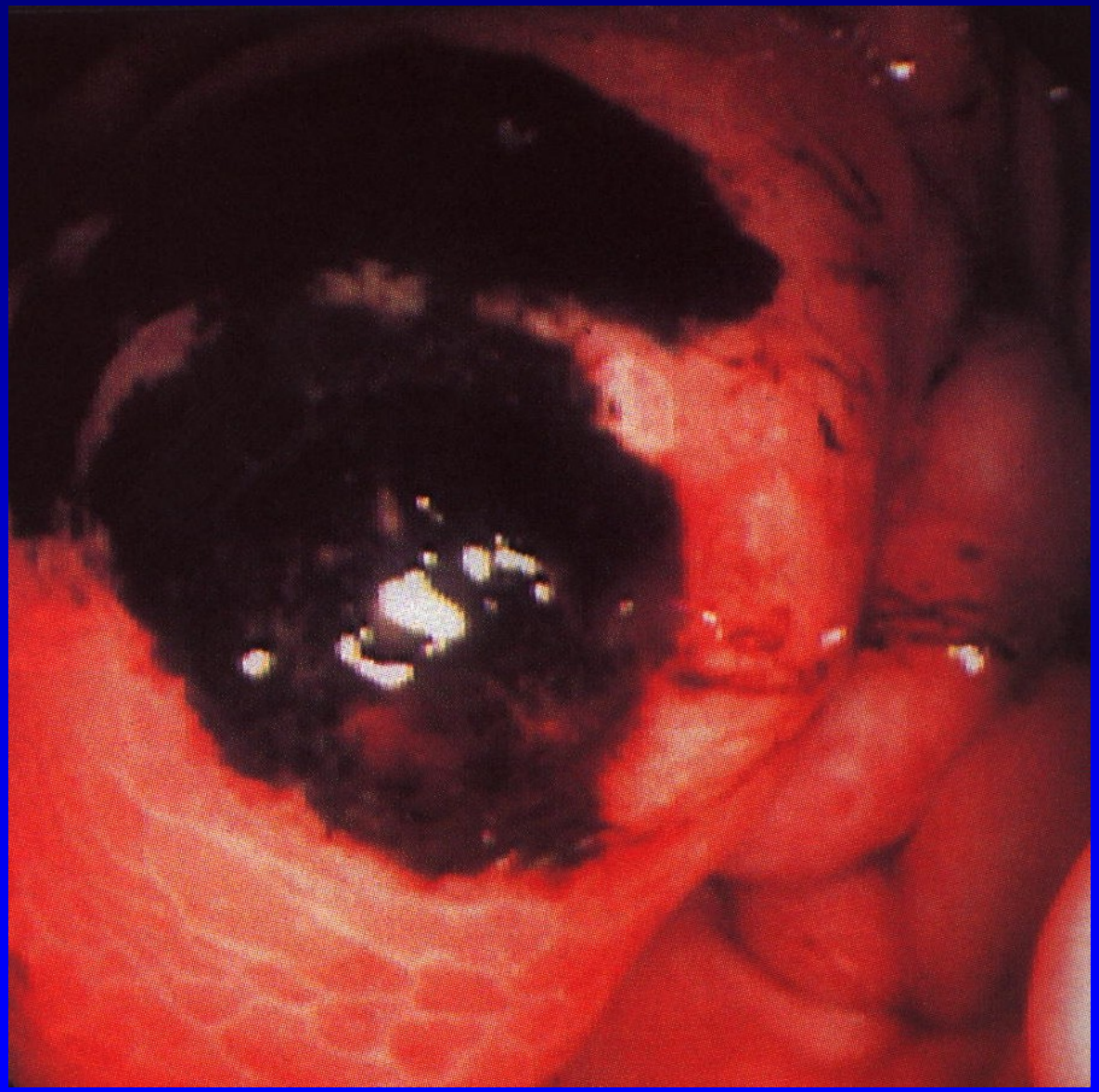

Cirrhosis
Fibrous septa
Regenerative nodules
Fibrous septa
Regenerative nodules

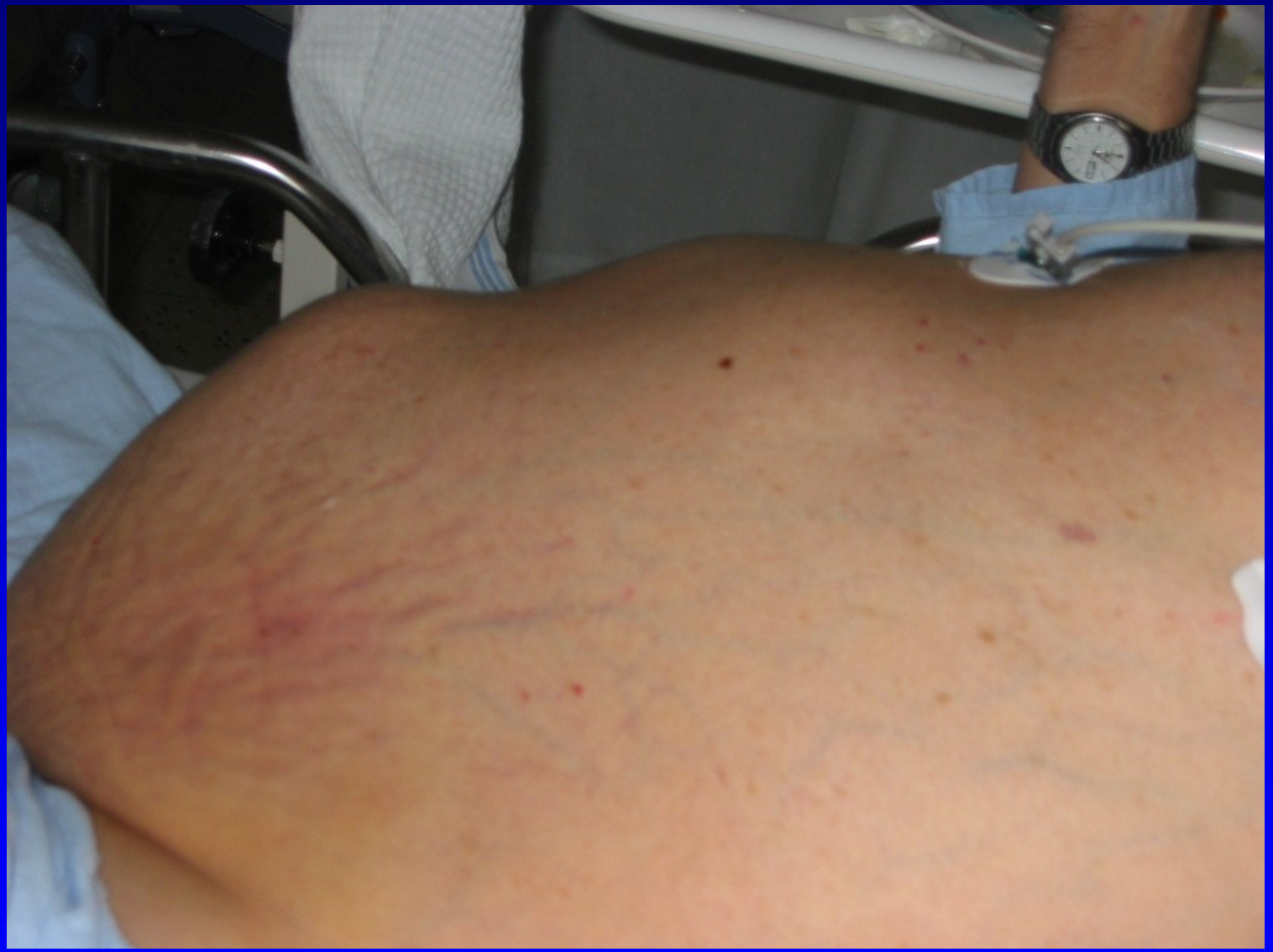
Development of Varices



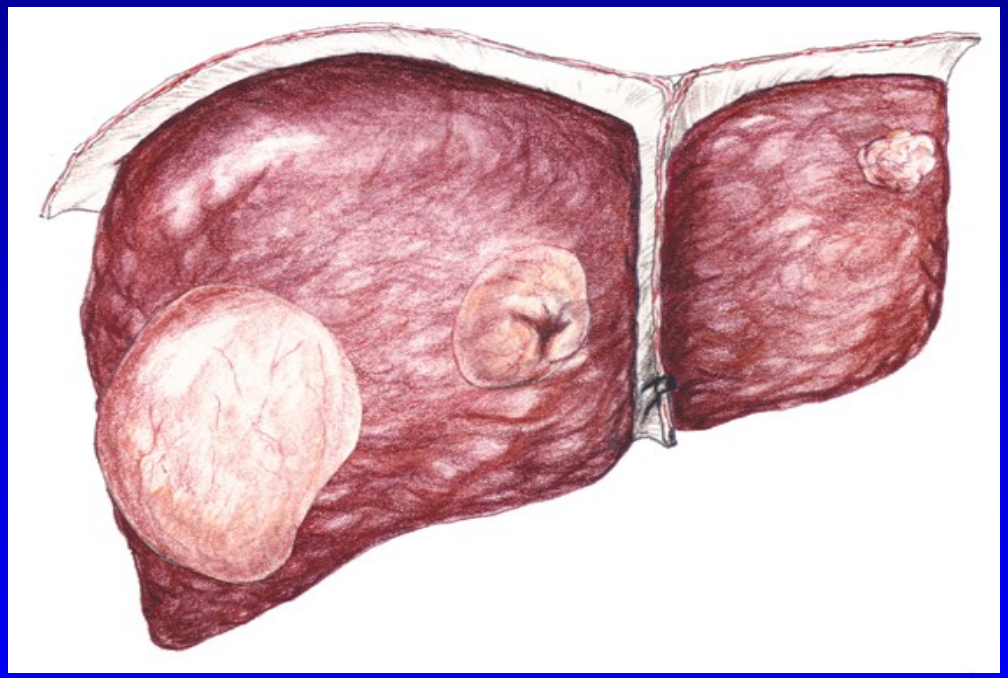

Portal Circulation
Normal blood flow to liver
Portal vein
Splenomegaly (enlargement of spleen)
Portal Hypertension
As pressure in portal vein rises, blood backs up into spleen
Size of normal spleen

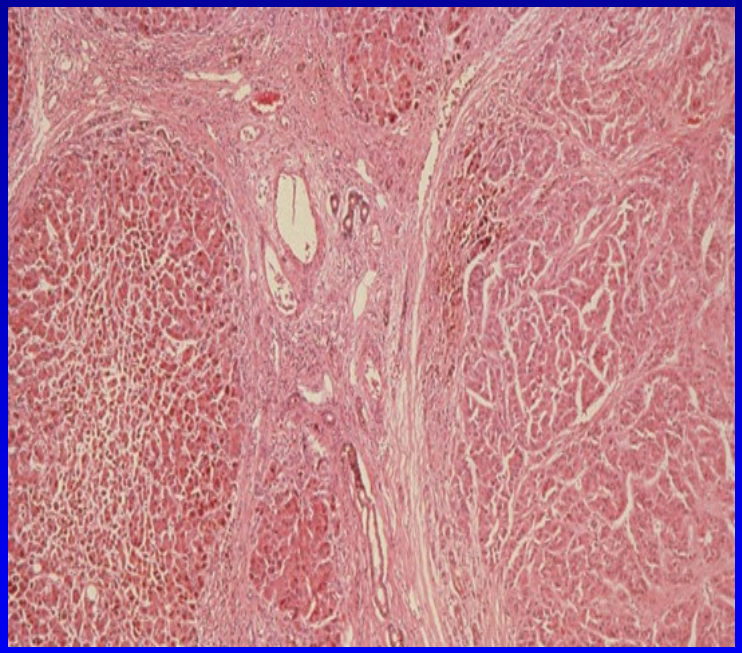






Hepatocellular carcinoma



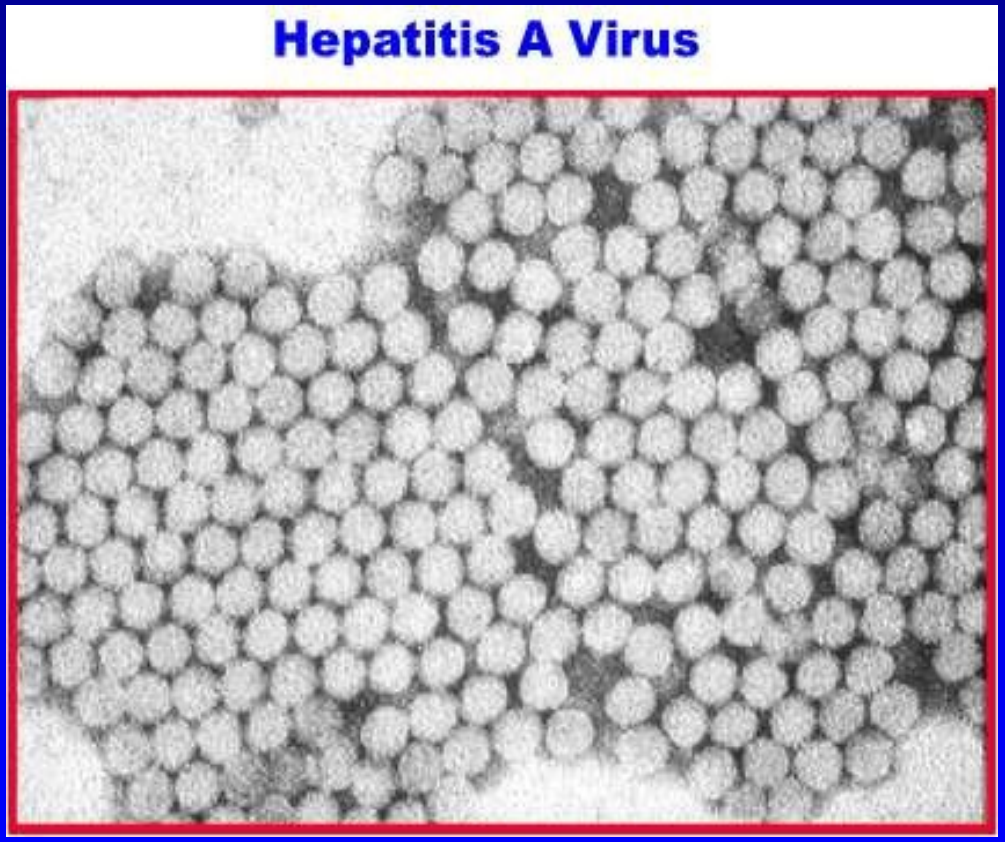


Viral Hepatitis in CR 2002-2011

	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
VH A	127	114	70	322	132	128	1648	1104	862	264
VH B	413	370	392	361	307	307	306	247	244	192
VH C	858	846	868	844	1022	980	974	836	709	812
VH E	12	21	36	37	35	43	65	99	72	163

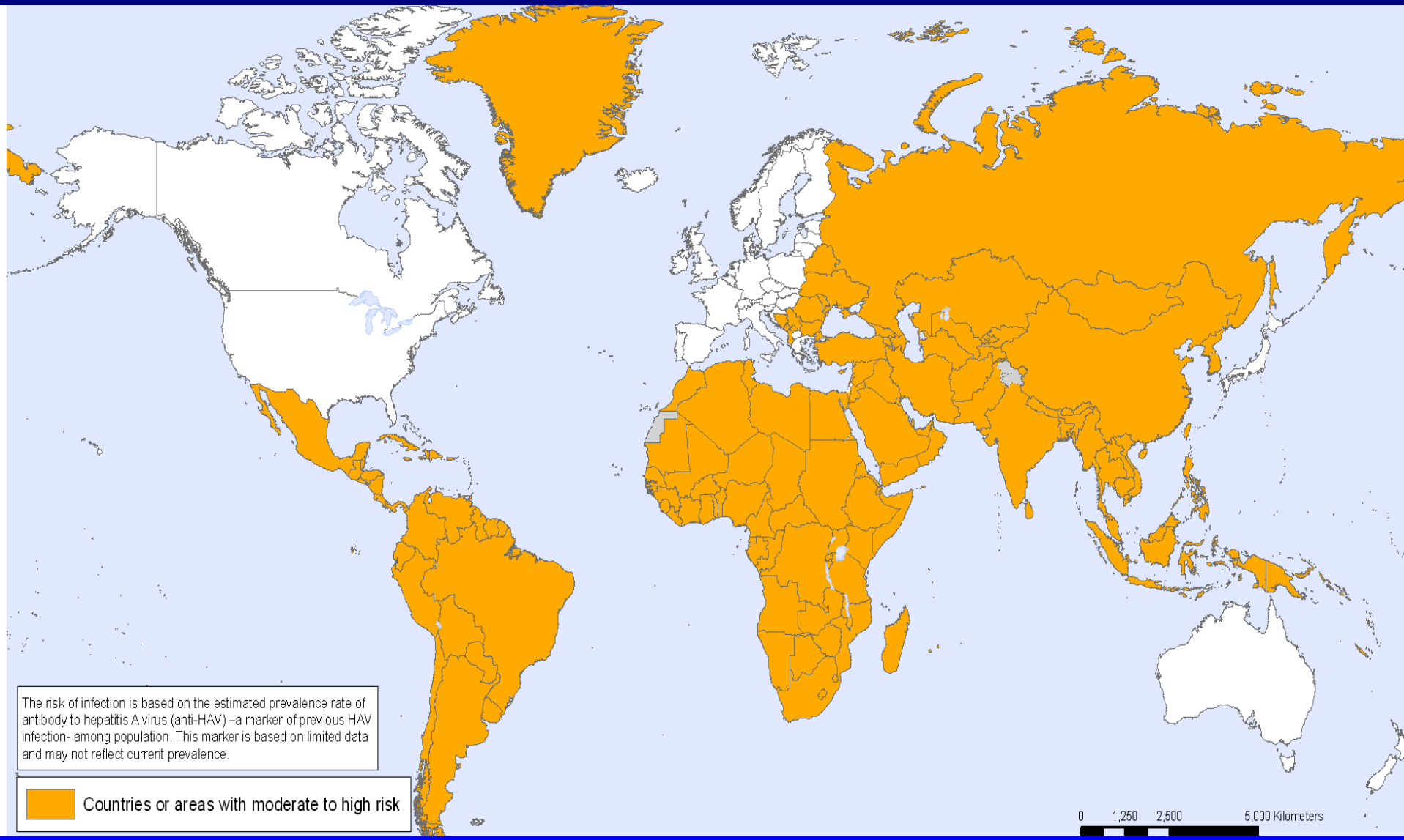
	A	B	C	D	E
Genom	RNA	DNA	RNA	RNA	RNA
Incubation	15-50	30-180	15-180	30-180	15-60
Enteral	Yes	No	No	No	Yes
Parenteral	Rare	Yes	Yes	Yes	No
Sexual	Rare	Yes	Rare	Yes	Rare
Vertical	No	Yes	Rare	Yes	Yes
Chronicity	No	Yes	Yes	Yes	Very rare
Vaccination	Yes	Yes	No	VH B	No
Imunoglob.	Yes	Yes	No	VH B	No

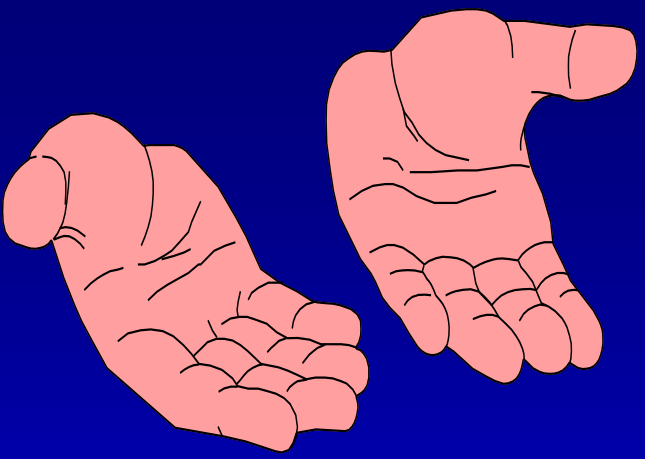
Hepatitis A



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

Hepatitis A


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

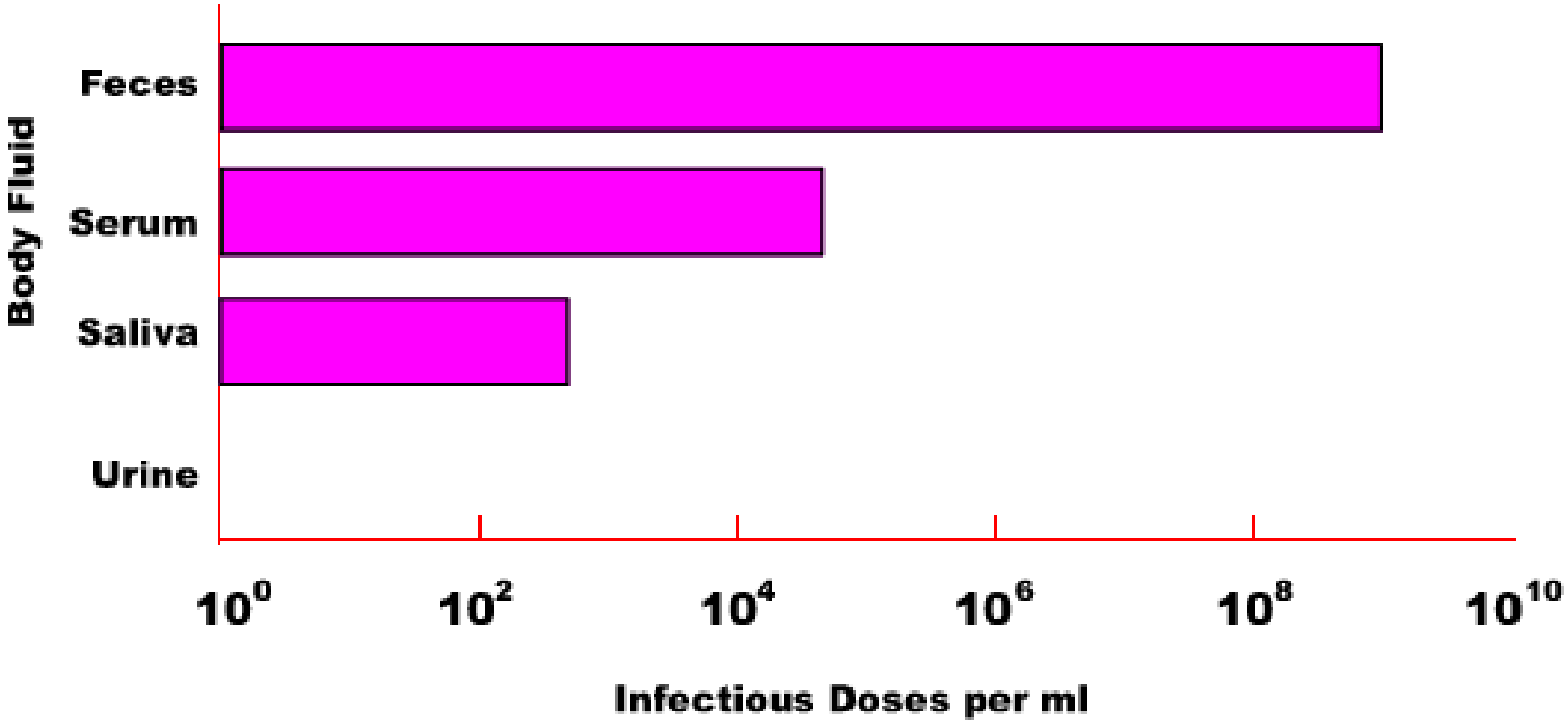
✓ Contaminated hands or daily used instruments

✓ Contaminated drinking water

✓ Contaminated food

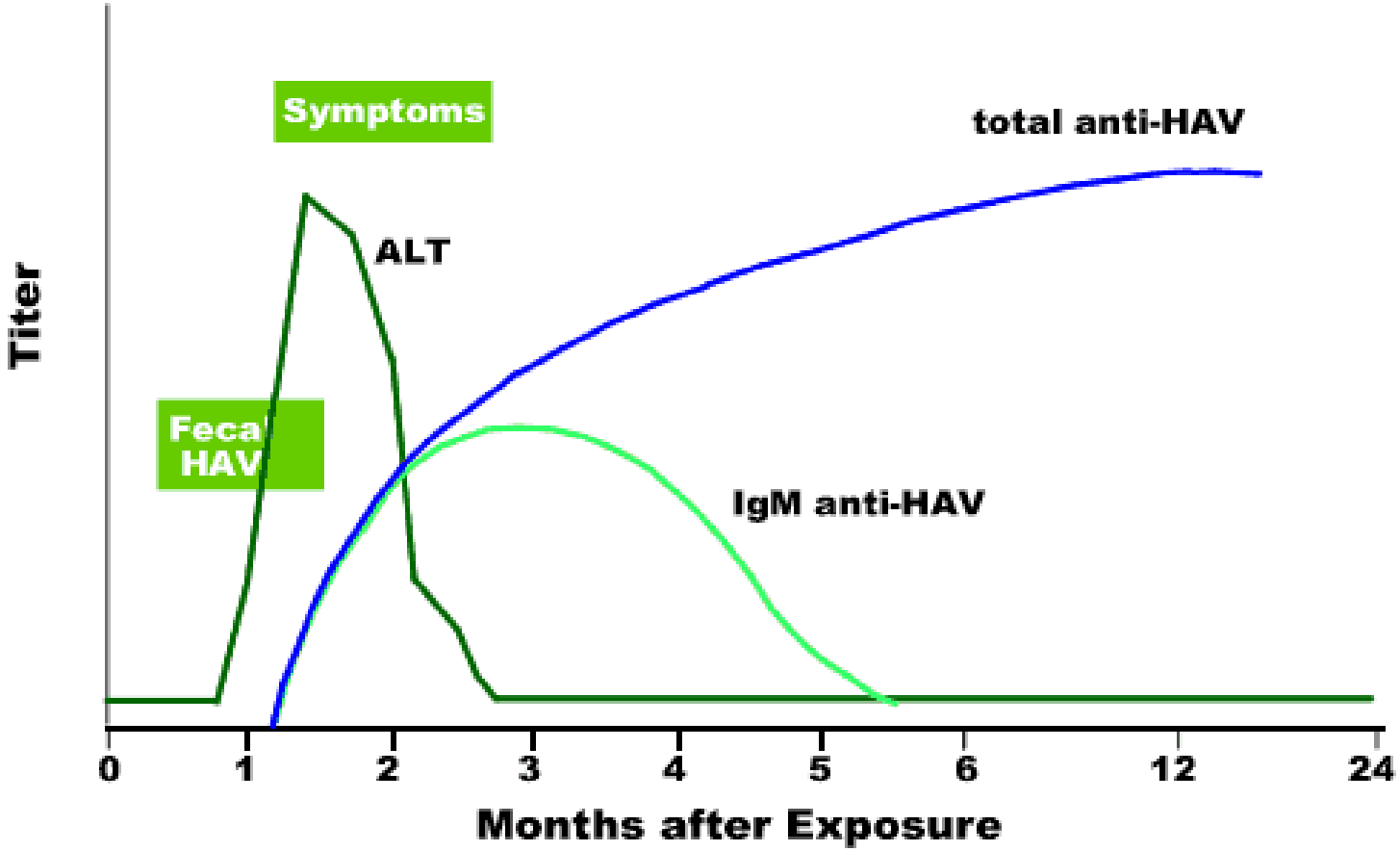
- Vaccination available, recommended especially fore travelers to countries with lower standard of hygiene

Concentration of Hepatitis A Virus in Various Body Fluids

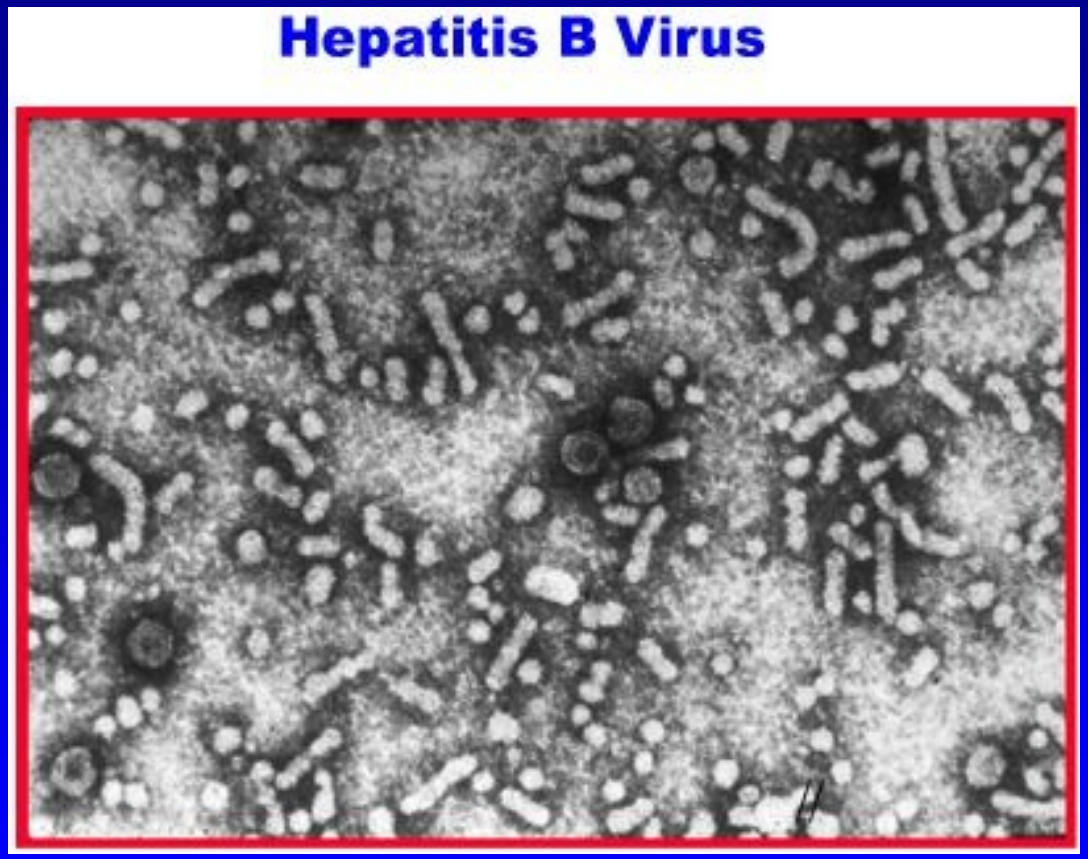


Source: Viral Hepatitis and Liver Disease 1984;9-2
J Infect Dis 1989; 160:887-890

Hepatitis A Virus Infection
Typical Serologic Course



Hepatitis B



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

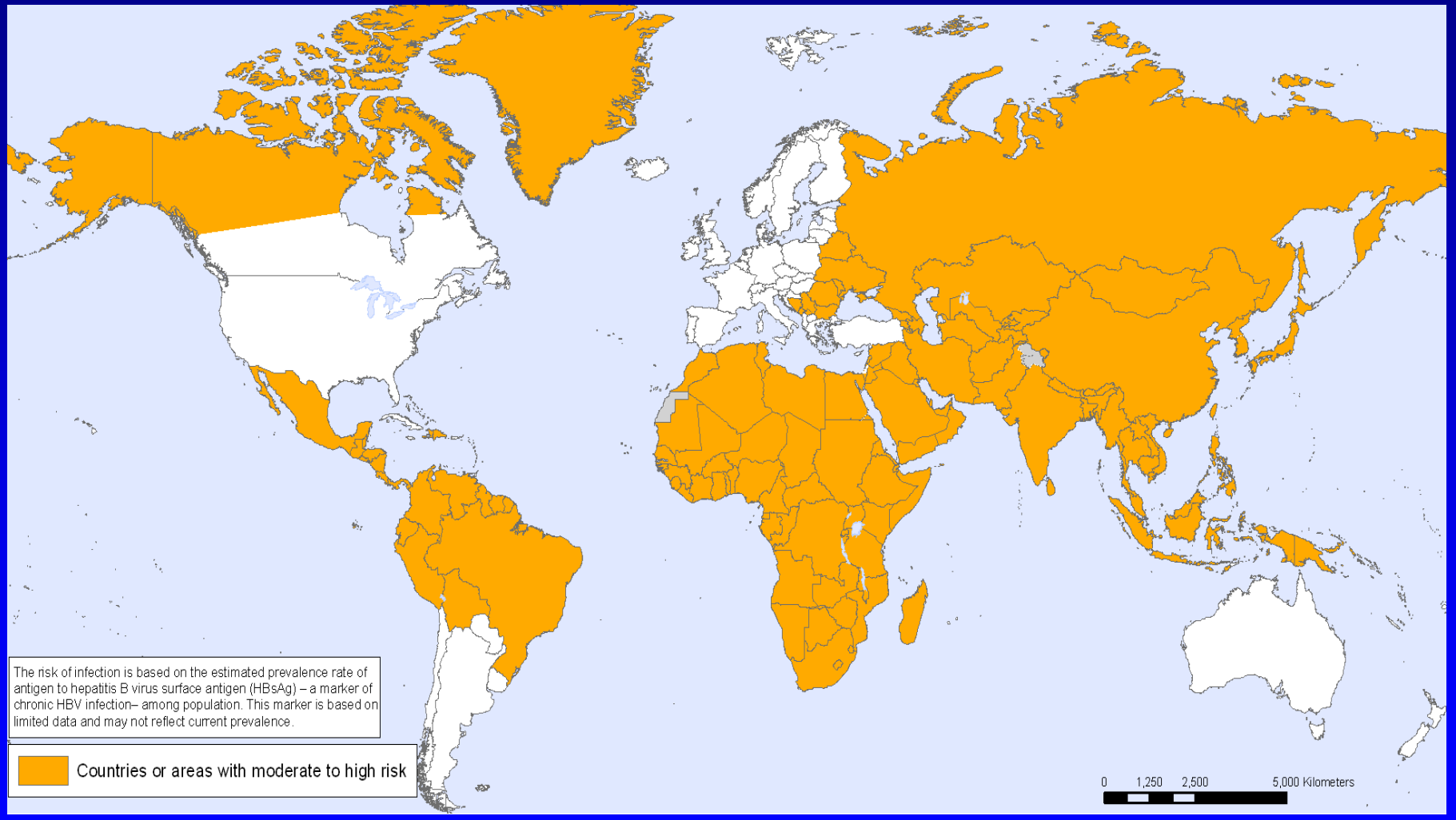
✓ 350-400 million chronic carriers - China (125 million), Brazil (3,7 million), South Korea (2,6 million), Japan (1,7 million), USA (more than 1 million), Italy (900 thousand).

✓ 25-40 % chronic carriers have LC or HCC, 0,5-1,0 million death due to decompensated LC or HCC

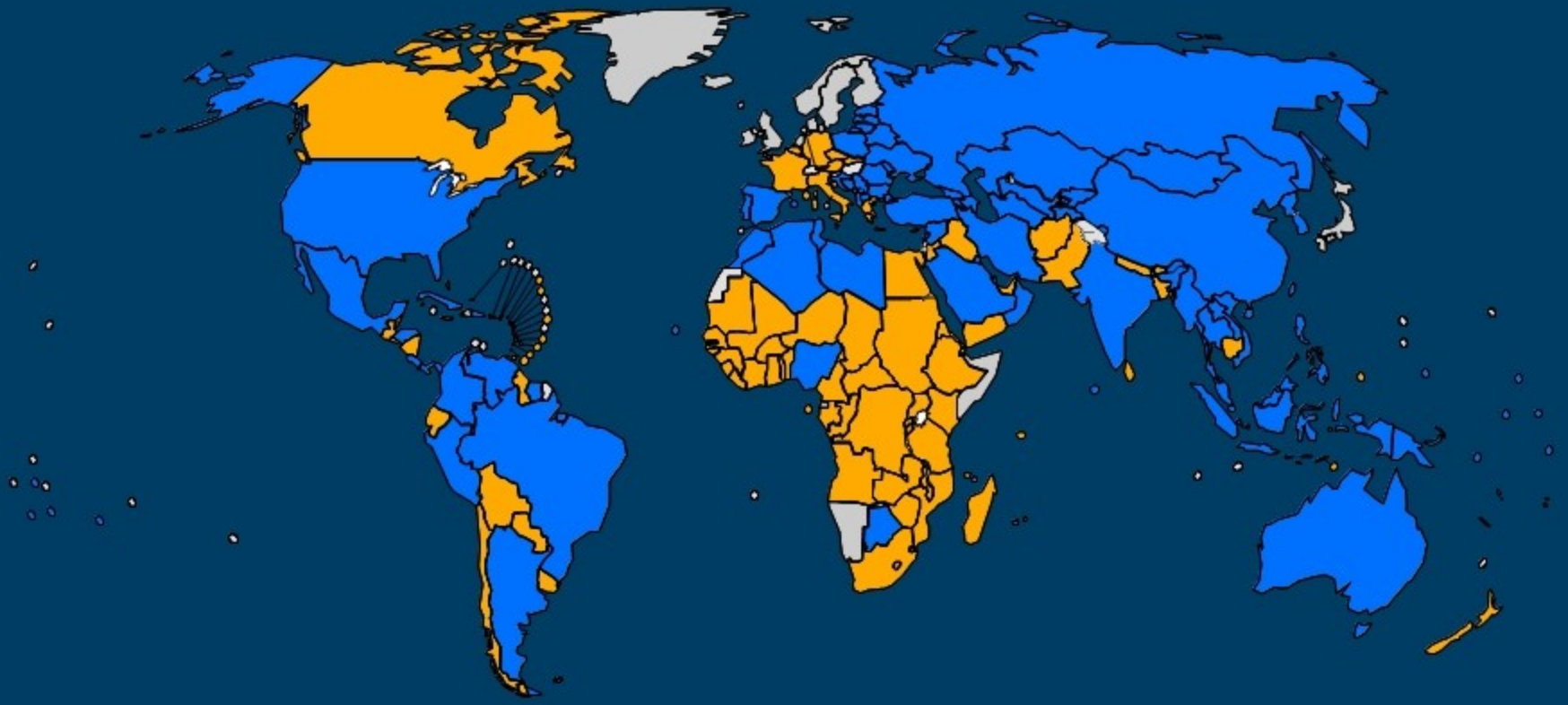
✓ 50 thousand death annually due to fulminant hepatitis

✓ 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%)*

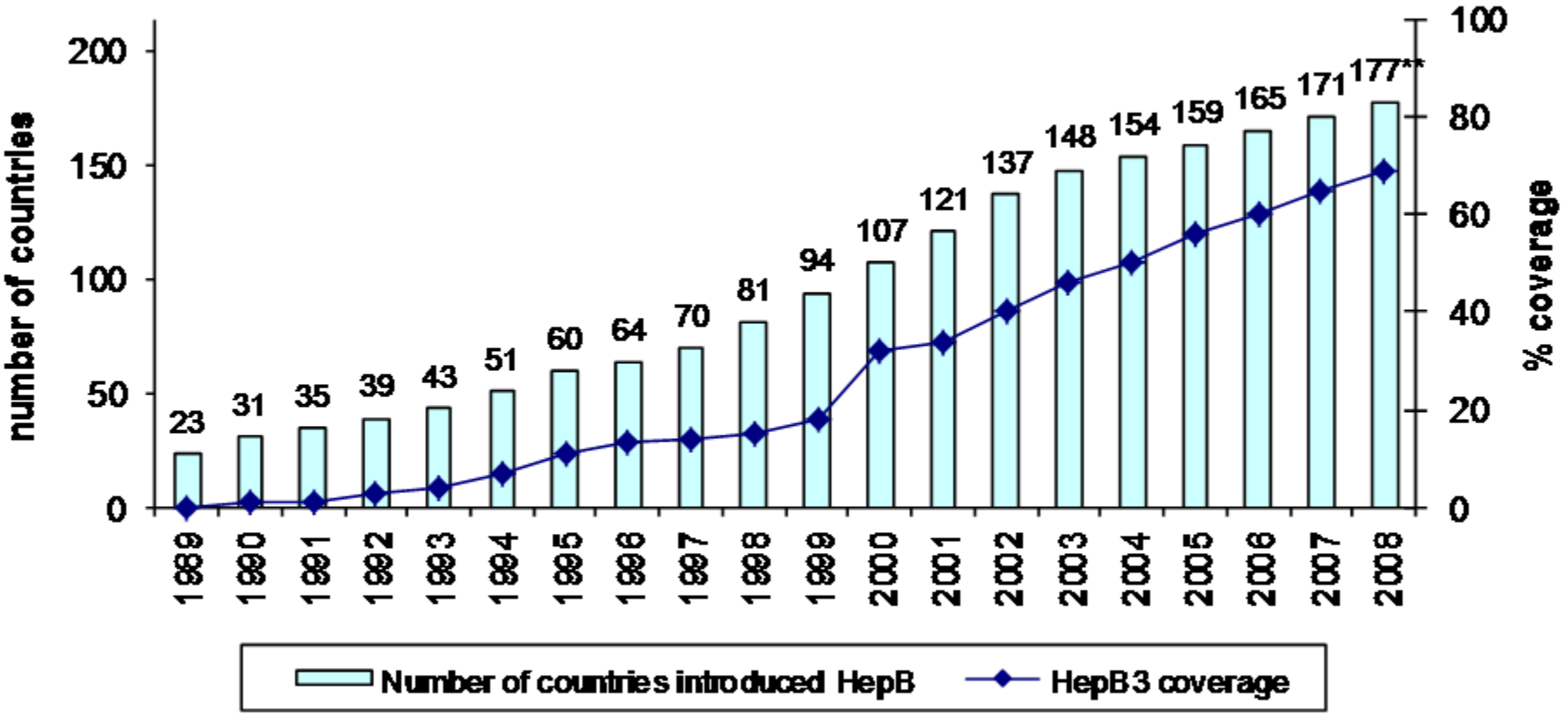
HepB no Birth Dose *(92 countries[2] or 48%)*

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



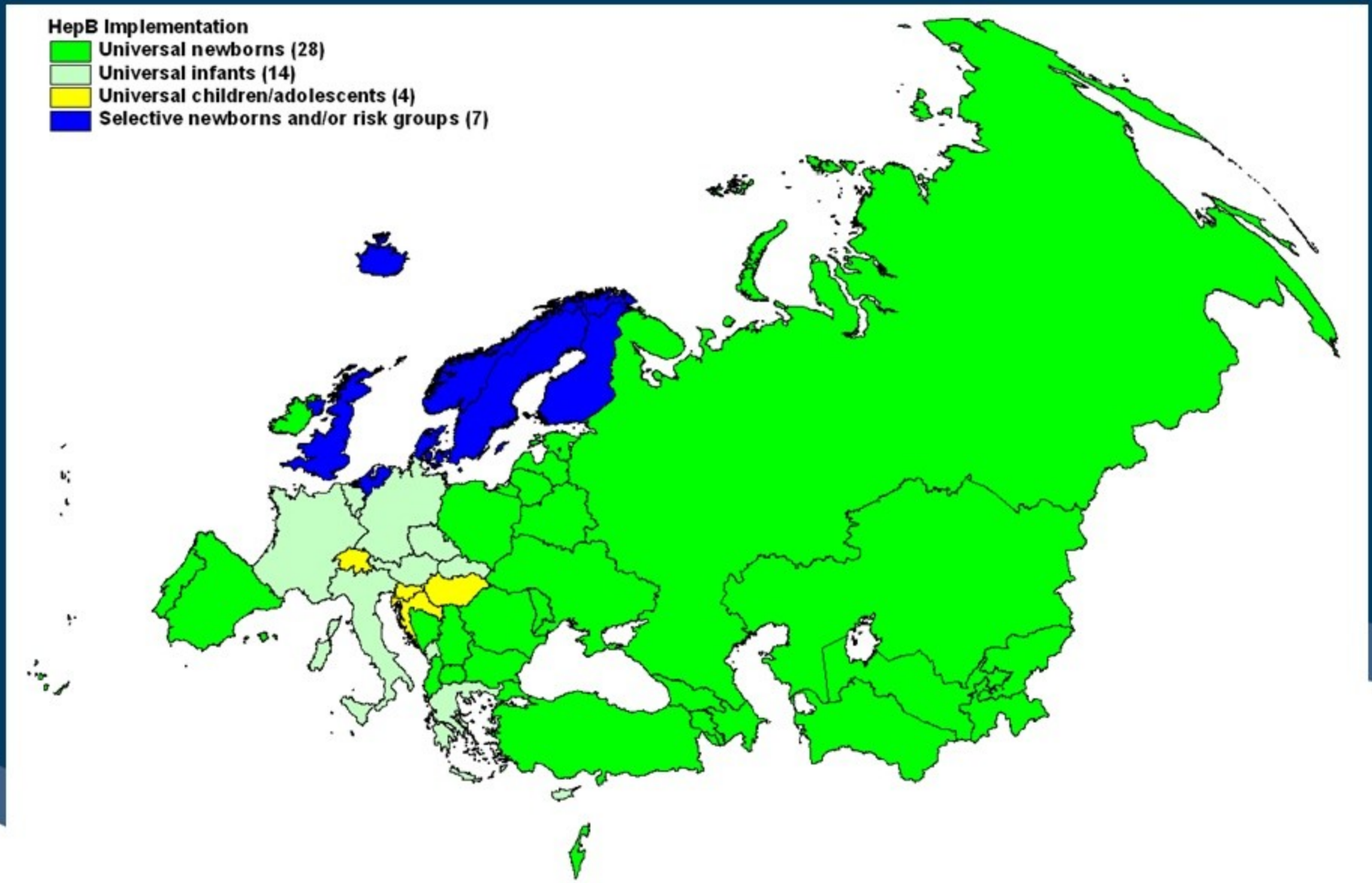
* Year of introduction can be the year of partial introduction

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

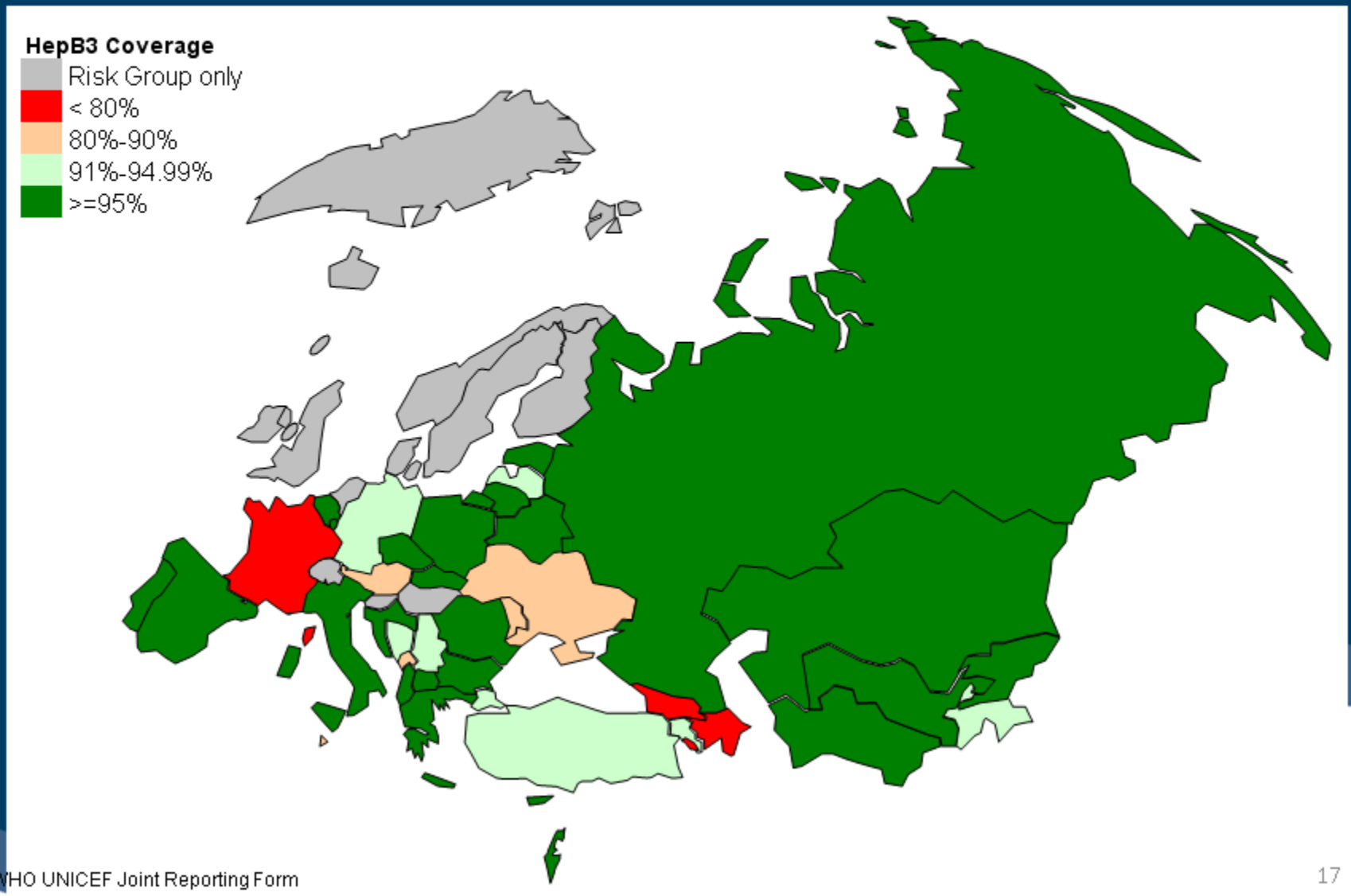
Source: WHO/UNICEF coverage estimates 1980-2008, August 2009, 193 WHO Member States. Date of slide August 2009

VHPB

Hep B vaccine immunization policy WHO European Region, 2009



HepB 3 Coverage, WHO European Region, 2009



Source: WHO UNICEF Joint Reporting Form

Hepatitis B in Czech Republic

- Still important infection but incidence and prevalence are gradually decreasing

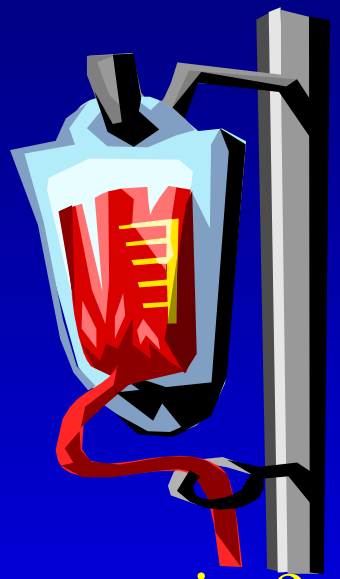
✓ Prevalence of chronic carriers was 0.56 % (2001)

✓ 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

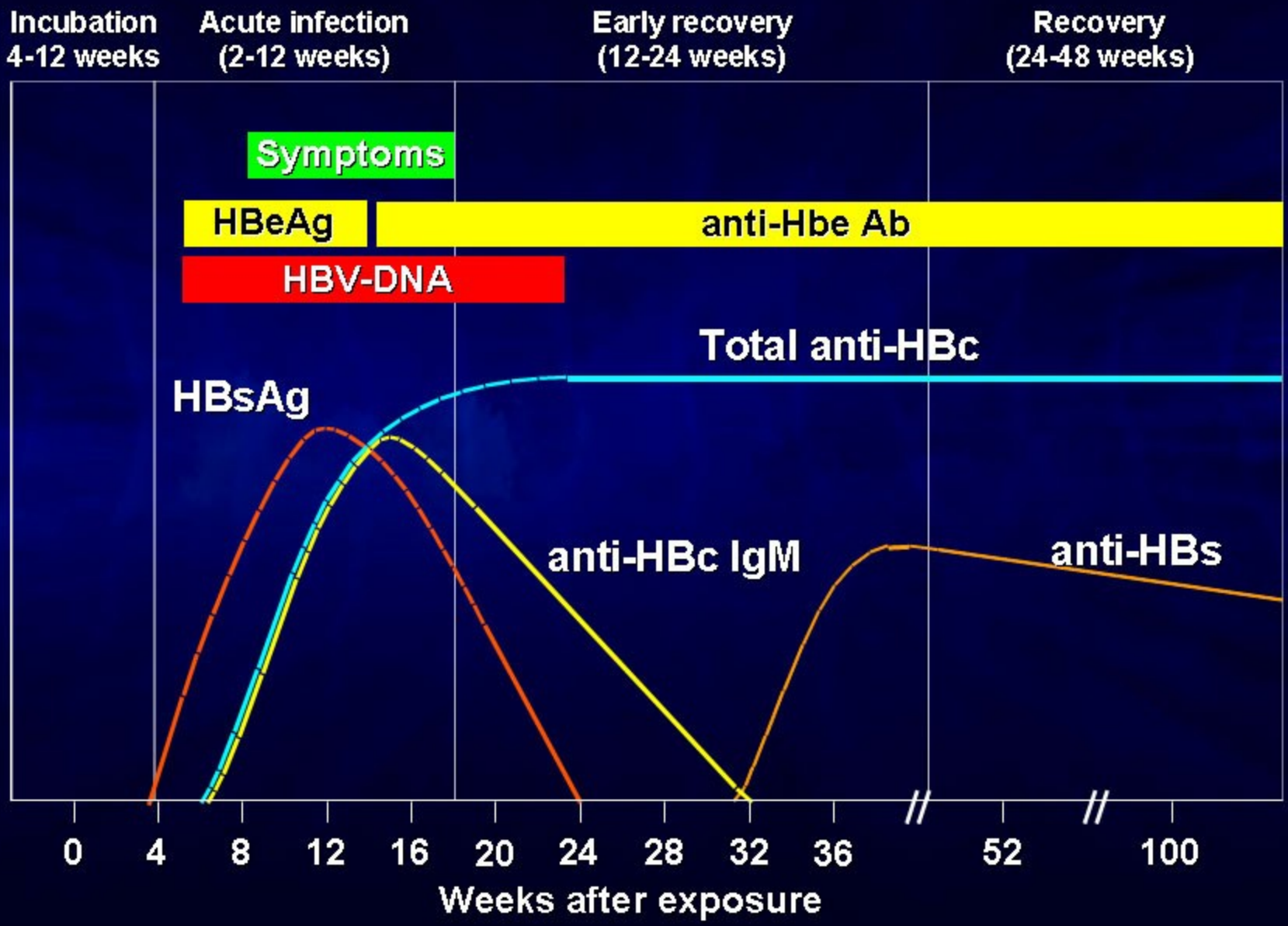


- Transmission
  - ✓ blood and blood products
  - ✓ sexual intercourse
  - ✓ organ and tissue transplant recipients
  - ✓ vertically from mother to newborn
- Who is in the highest risk in well-developed countries?
  - ✓ intravenous drug abusers
  - ✓ persons with multiple sexual partners

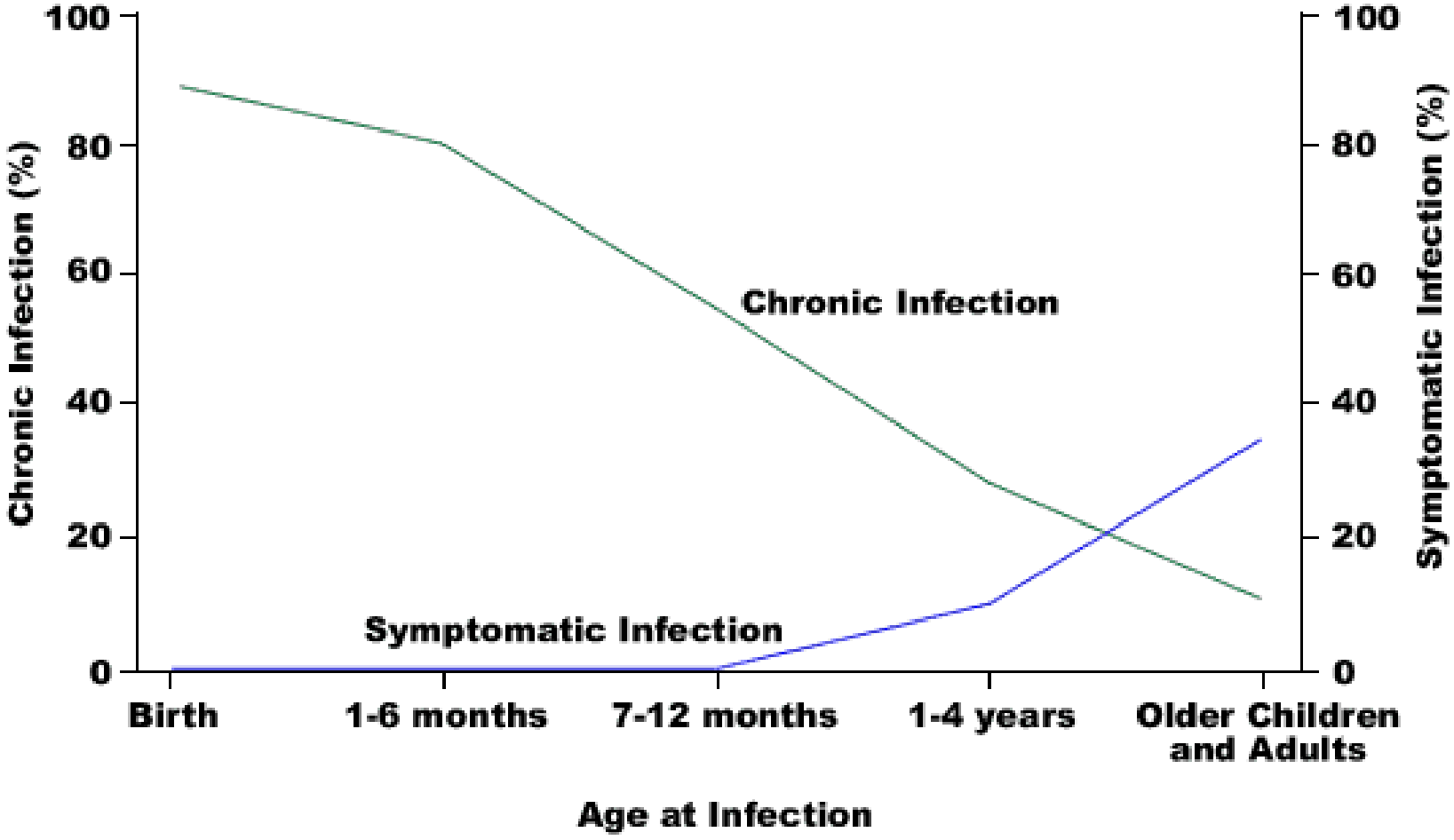
Clinical pictures of acute HEP B

- 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 %

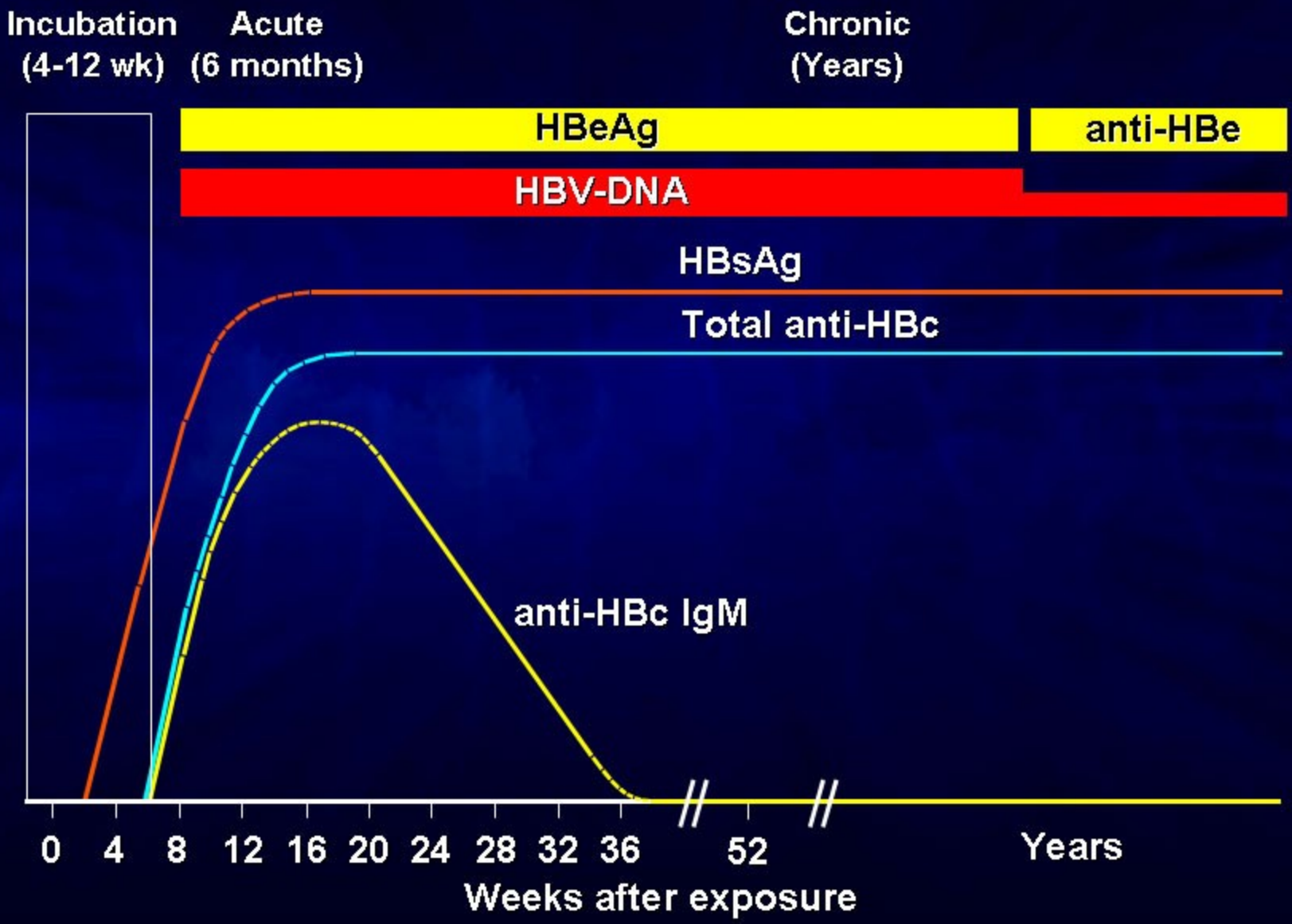
Acute Hepatitis B



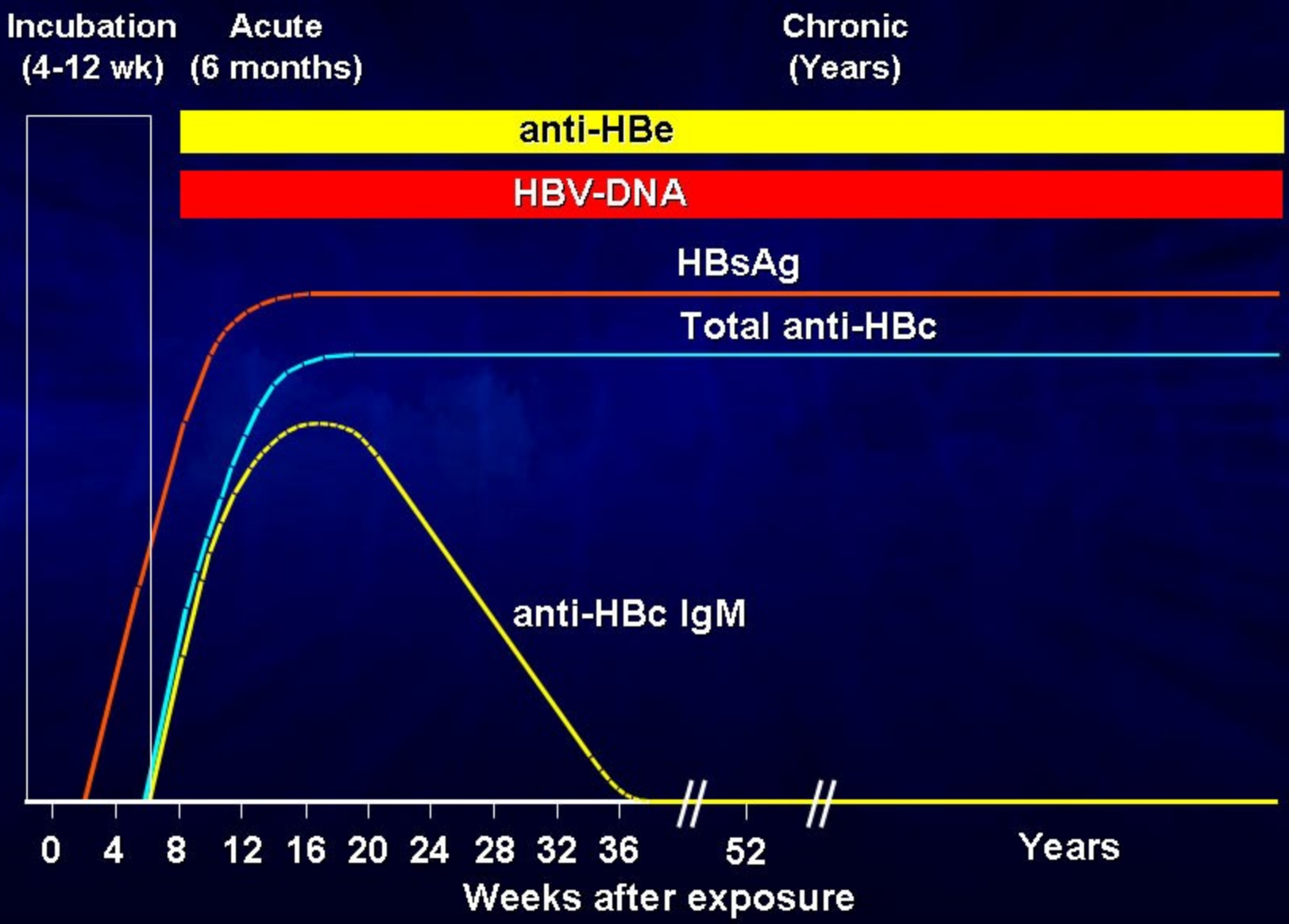
Outcome of Hepatitis B Virus Infection by Age at Infection



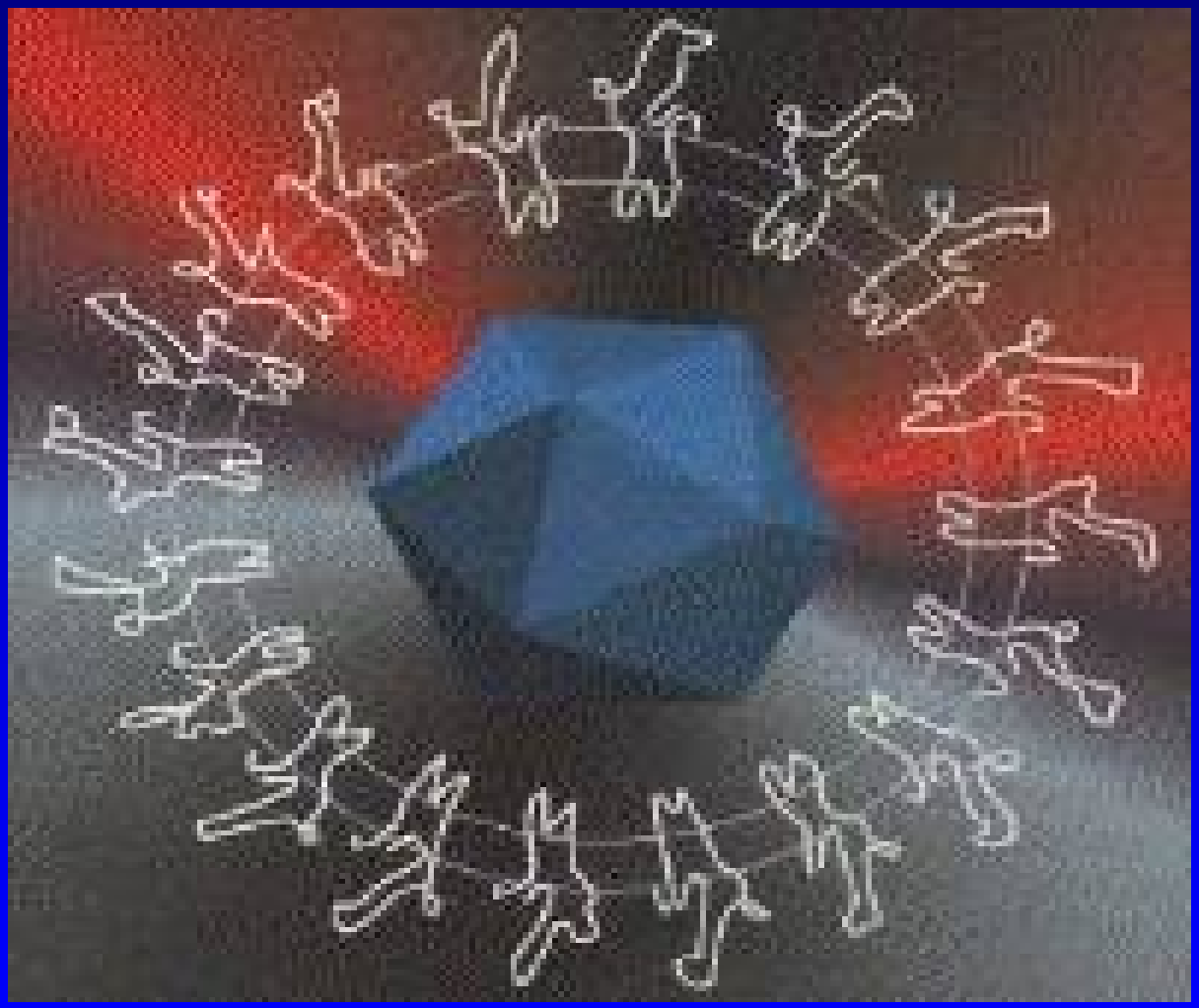
Chronic Hepatitis B (HBeAg+)



Chronic Hepatitis B (HBeAg-)

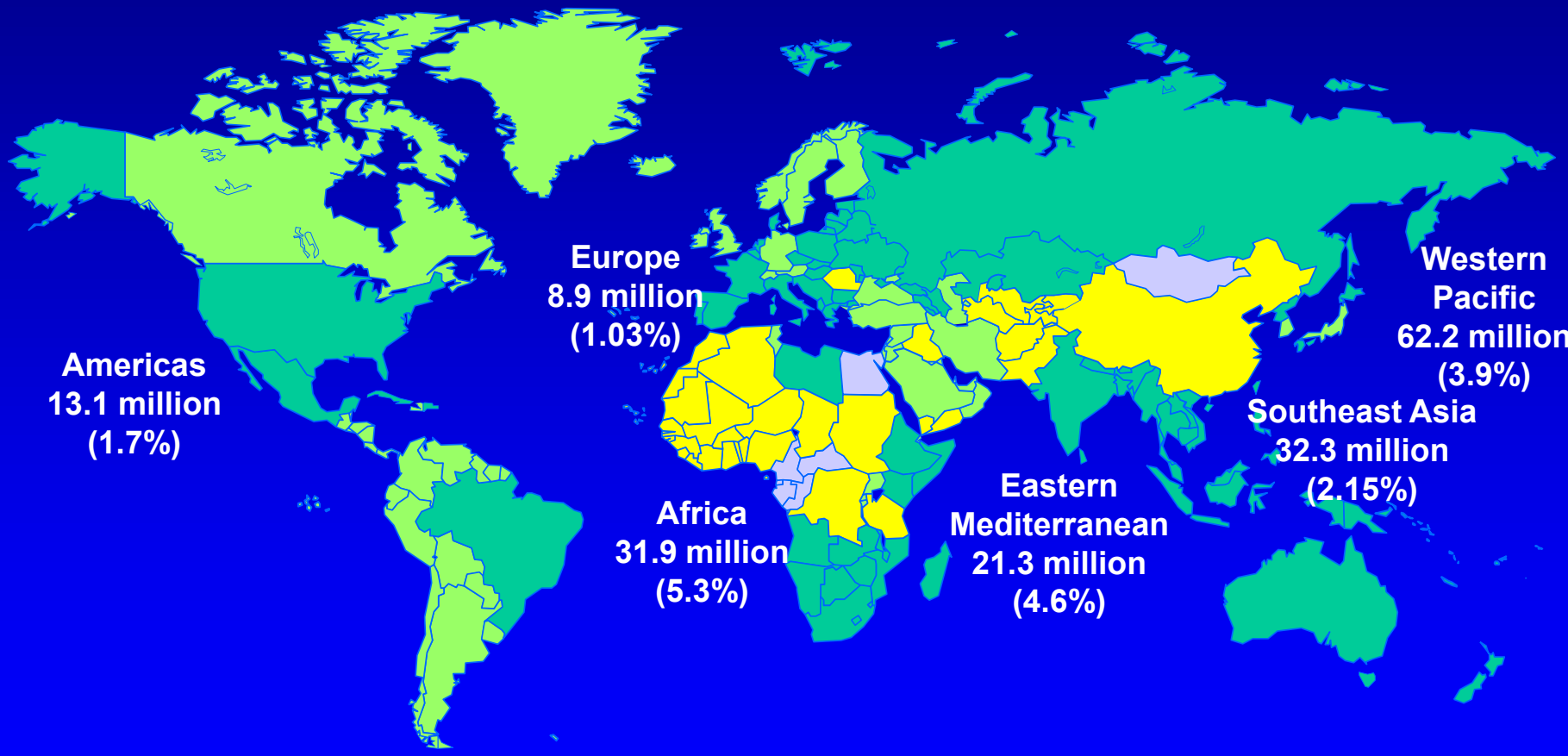


Hepatitis C



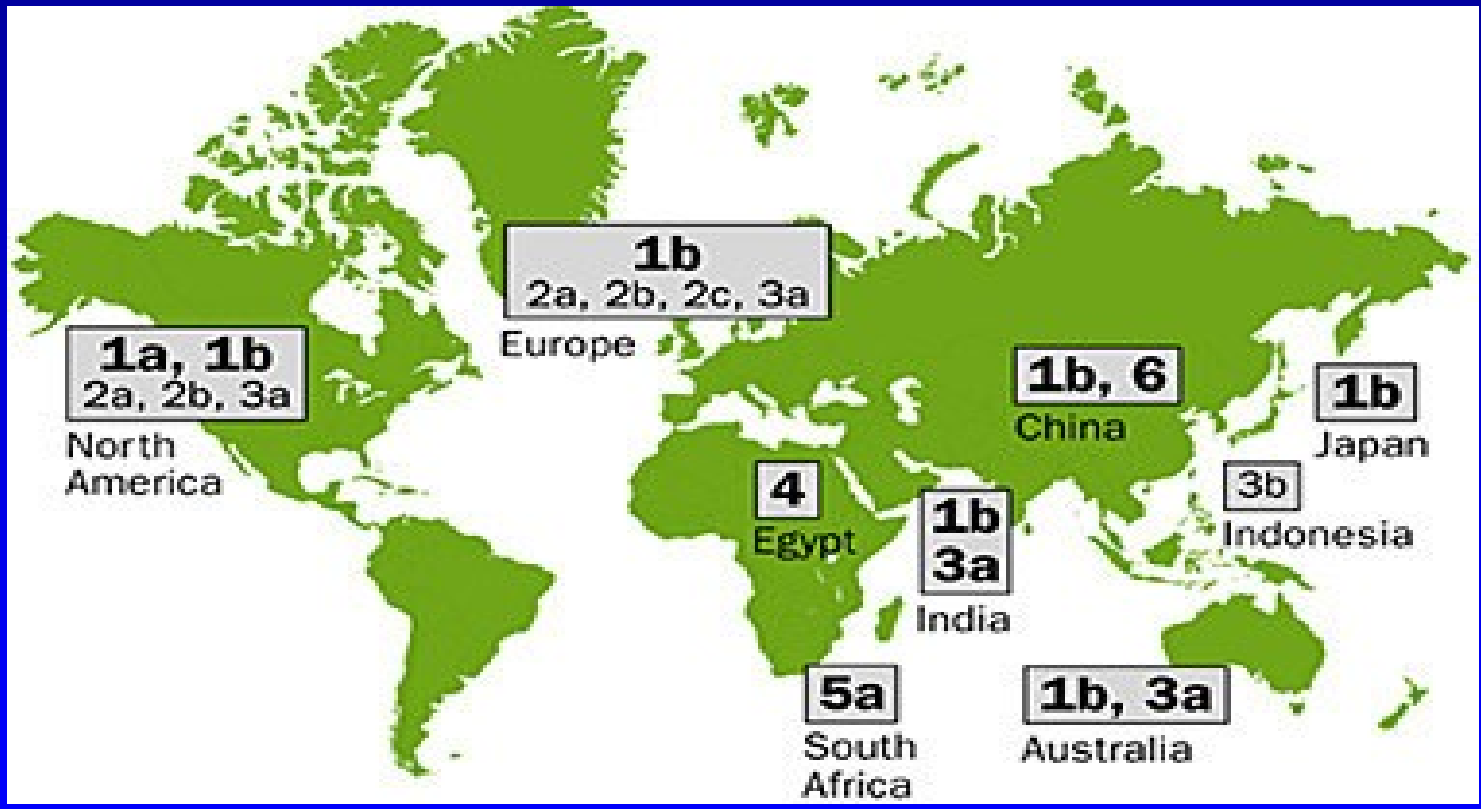
family Flaviviridae, genus Hepacivirus, enveloped RNA virus 60 nm

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

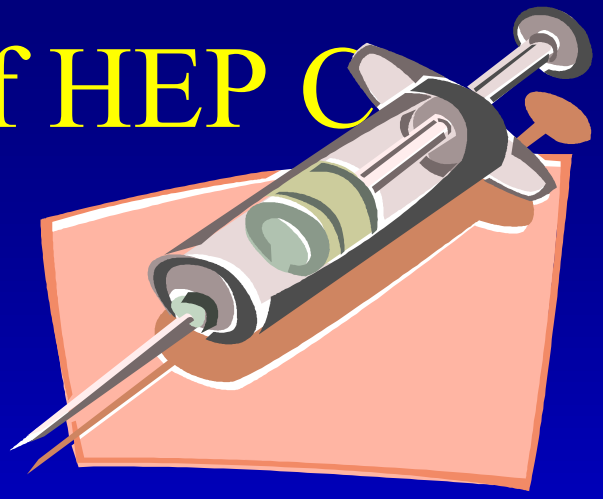
✓ In well-developed countries about 20 % of all acute hepatitis, 70 % chronic hepatitis, 40 % cirrhosis, 60 % HCC and indication to 30 % liver transplantations

- In Czech Republic

✓ prevalence 0,2 % (2001)

- No vaccine, no hyper-immune immunoglobulin

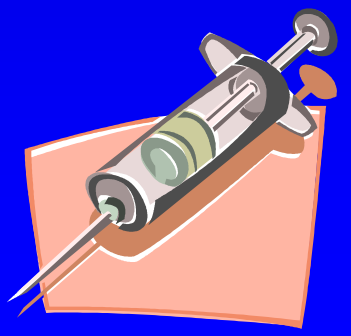
Epidemiology of HEP C



- 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

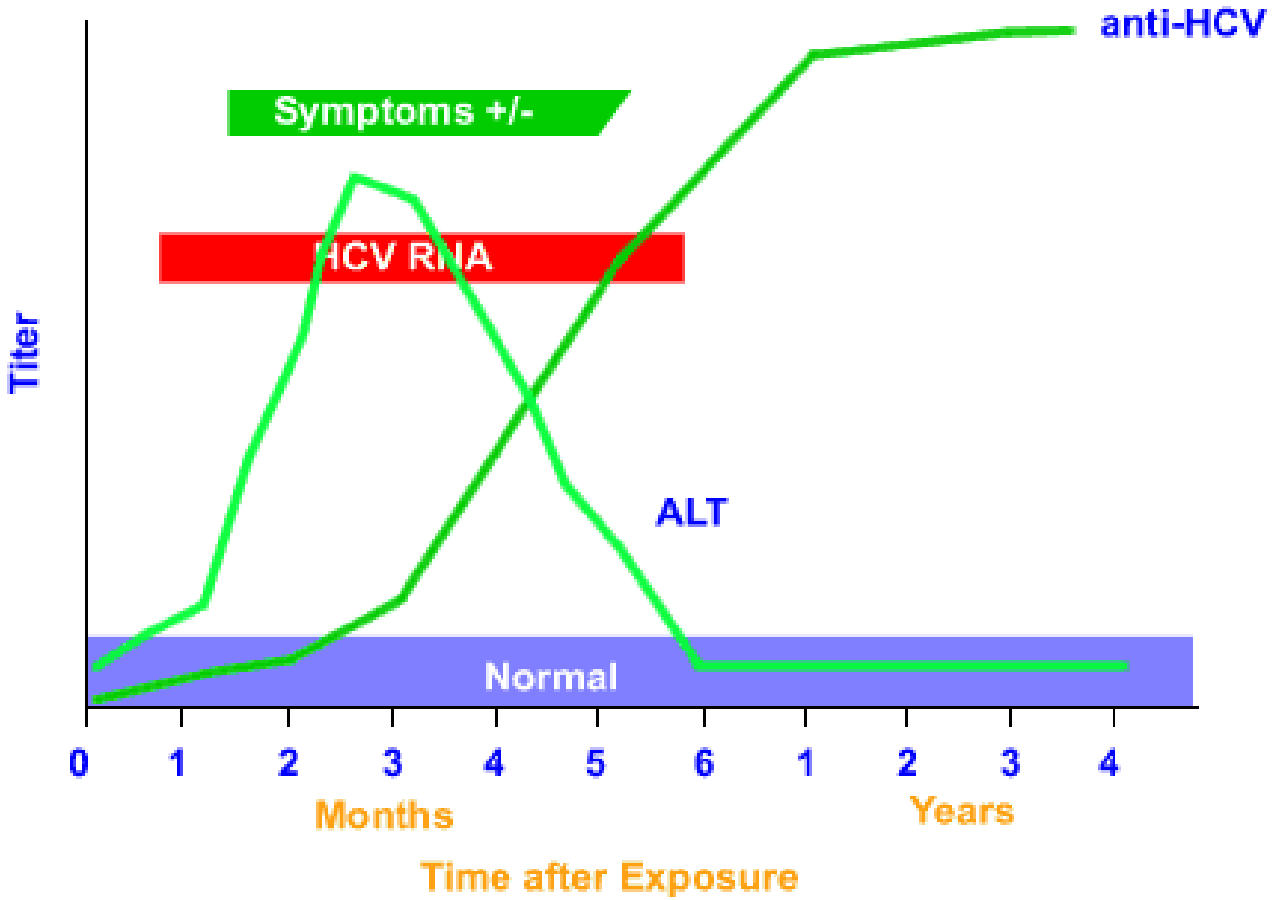
⇨ immunodeficiency

Clinical course of HEP C

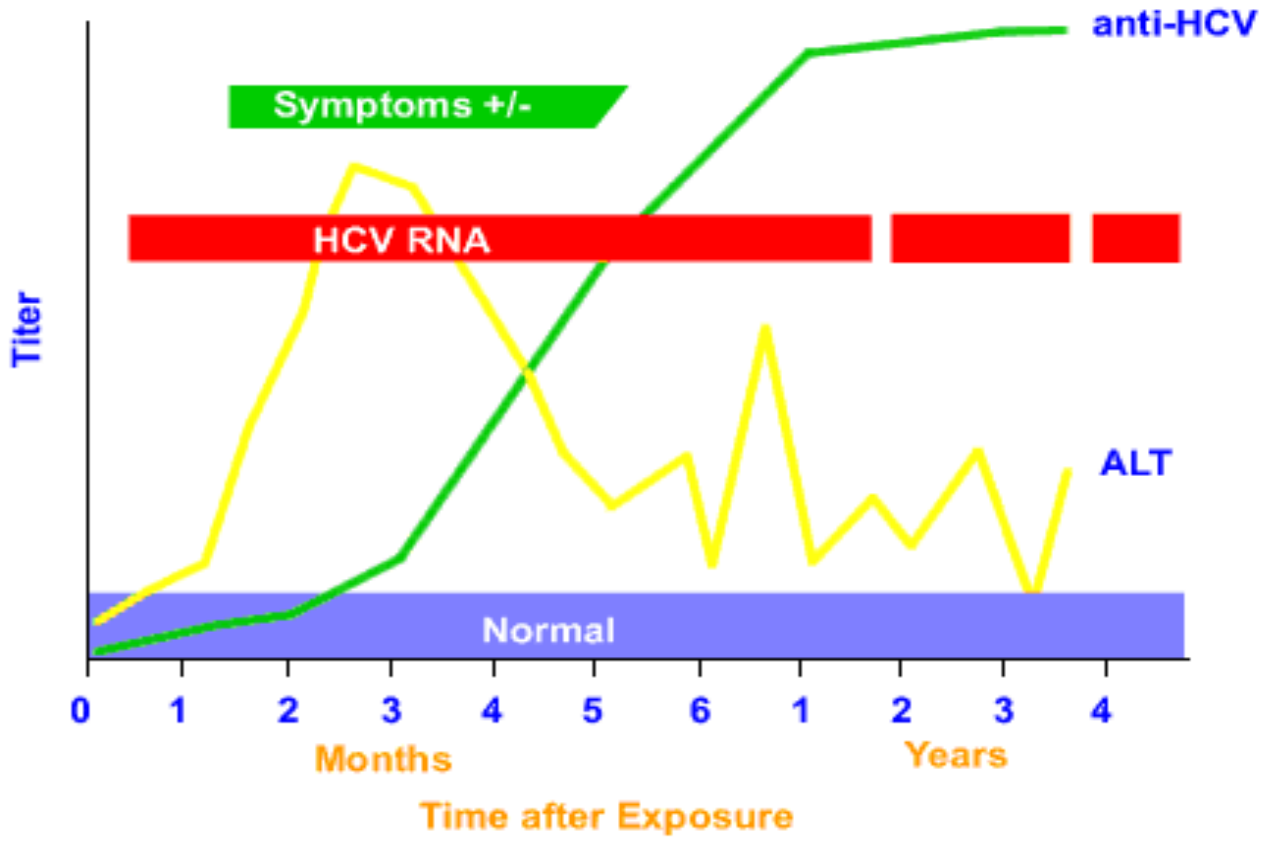
- LC in about 20 % patients with chronic HCV infection
- HCC annually in 1-4 % patients with LC
- Progression to HCC depends on:

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

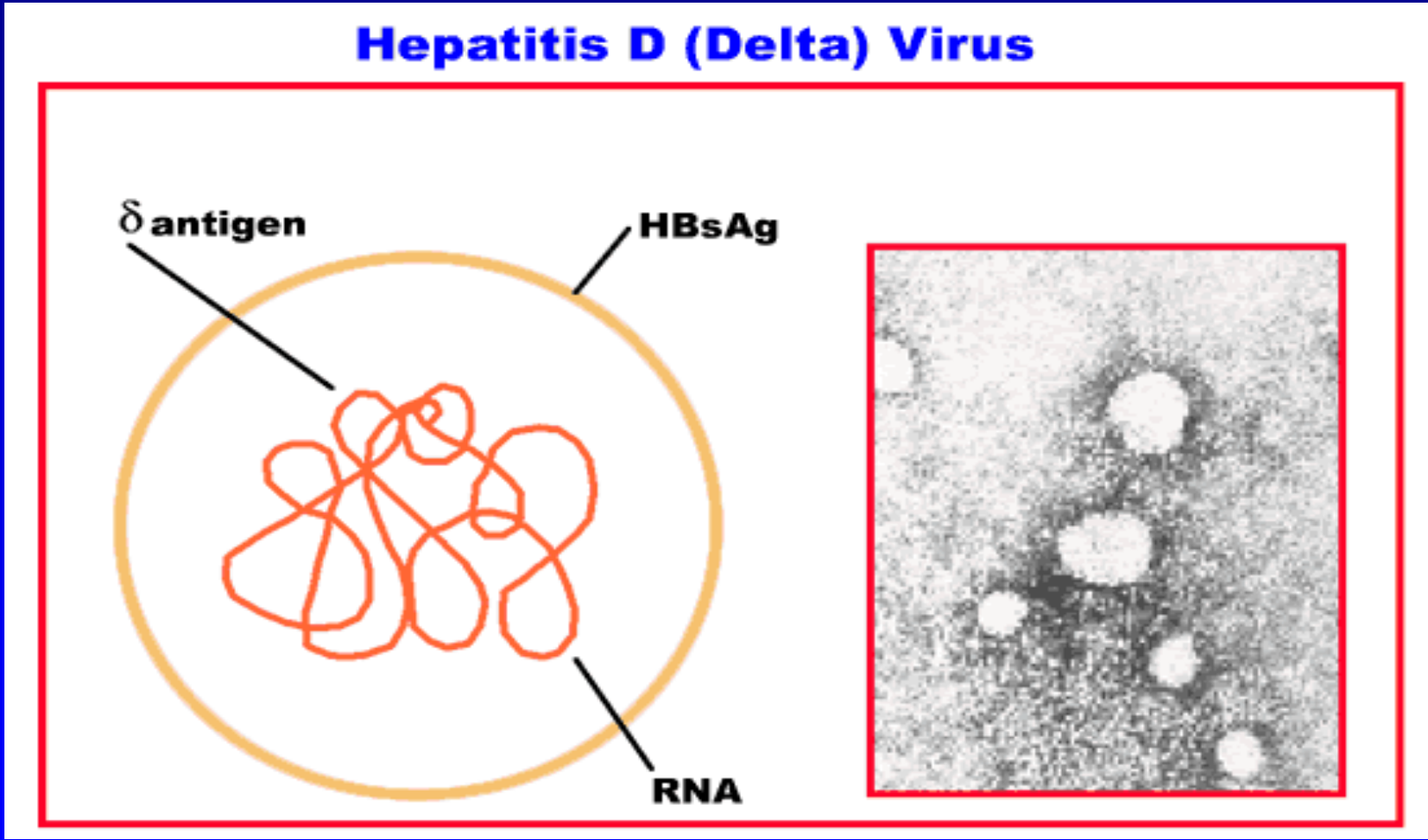
Serologic Pattern of Acute HCV Infection with Recovery



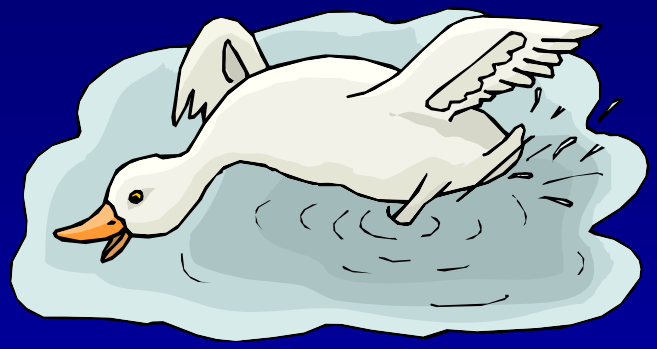
Serologic Pattern of Acute HCV Infection with Progression to Chronic Infection



Hepatitis D



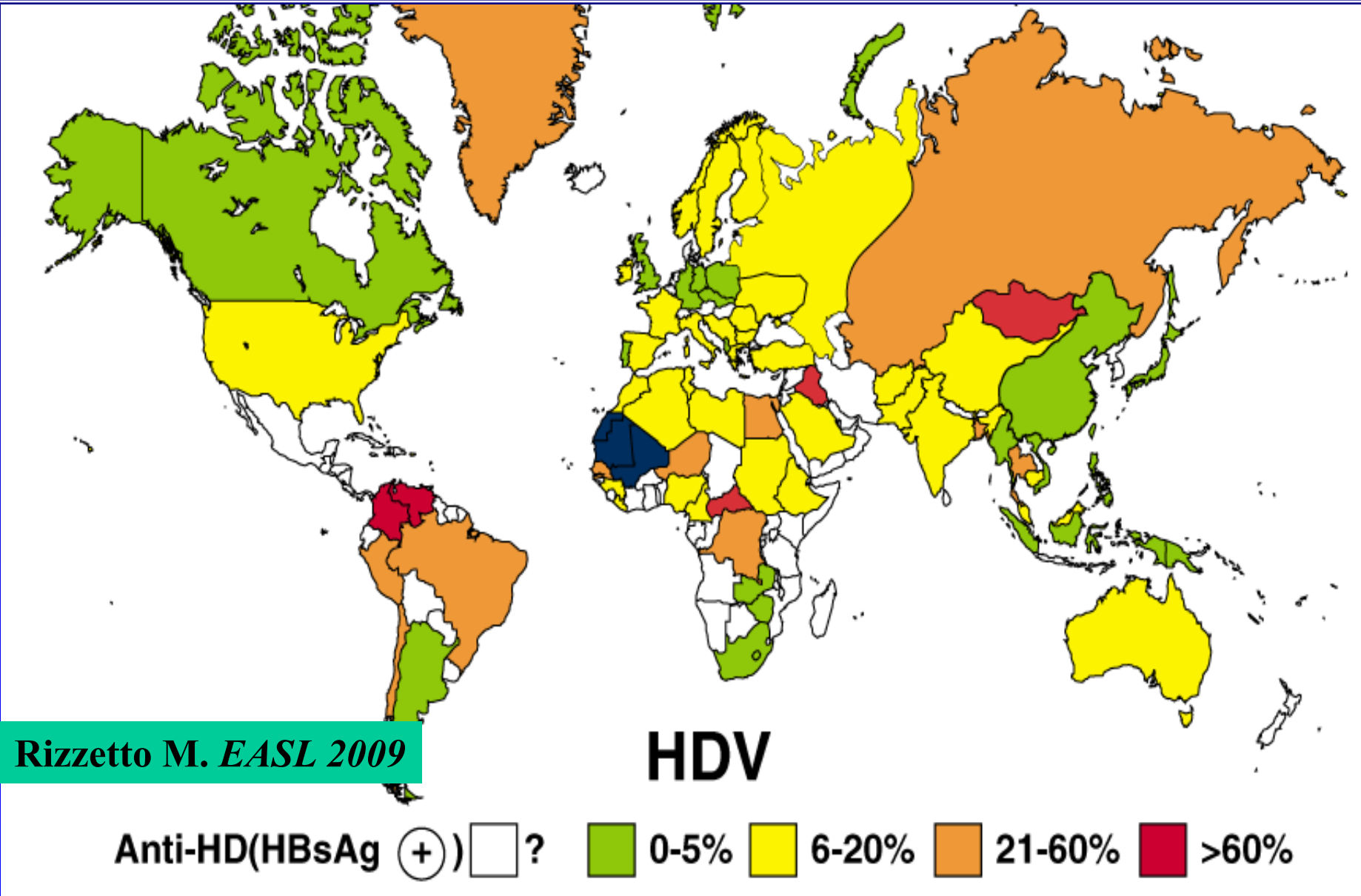
Satelite virus, family *Deltaviridae*, enveloped RNA, 40 nm



Hepatitis D

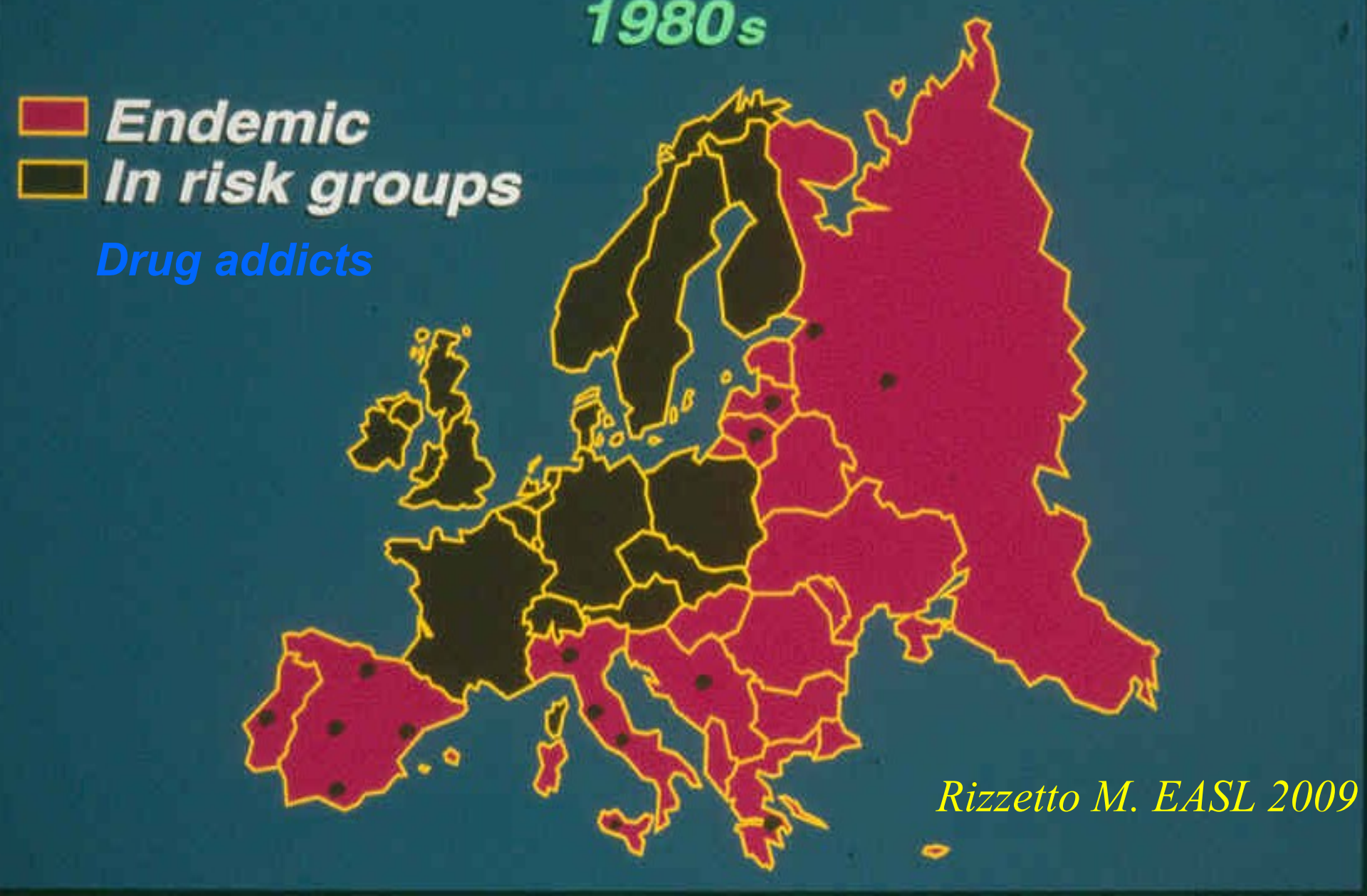
- Ability of replication only in presence of HBV infection
- ✓ Co-infection (better prognosis)
- ✓ Super-infection (worse prognosis)
- Endemic in South America, Mediterranean Region, Romania, Central Africa
- Very low prevalence in CR

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



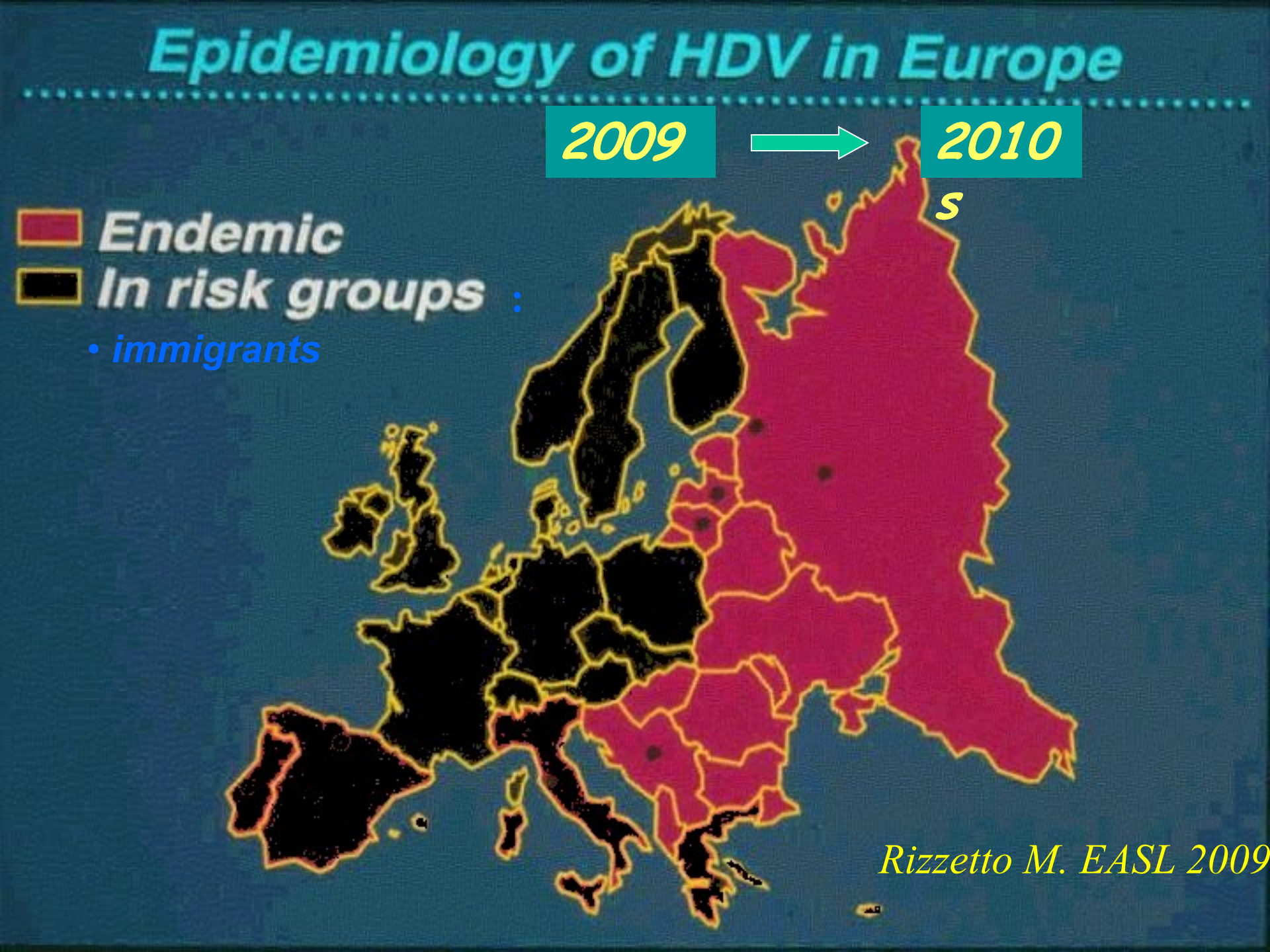
Rizzetto M. *EASL 2009*

Epidemiology of HDV in Europe



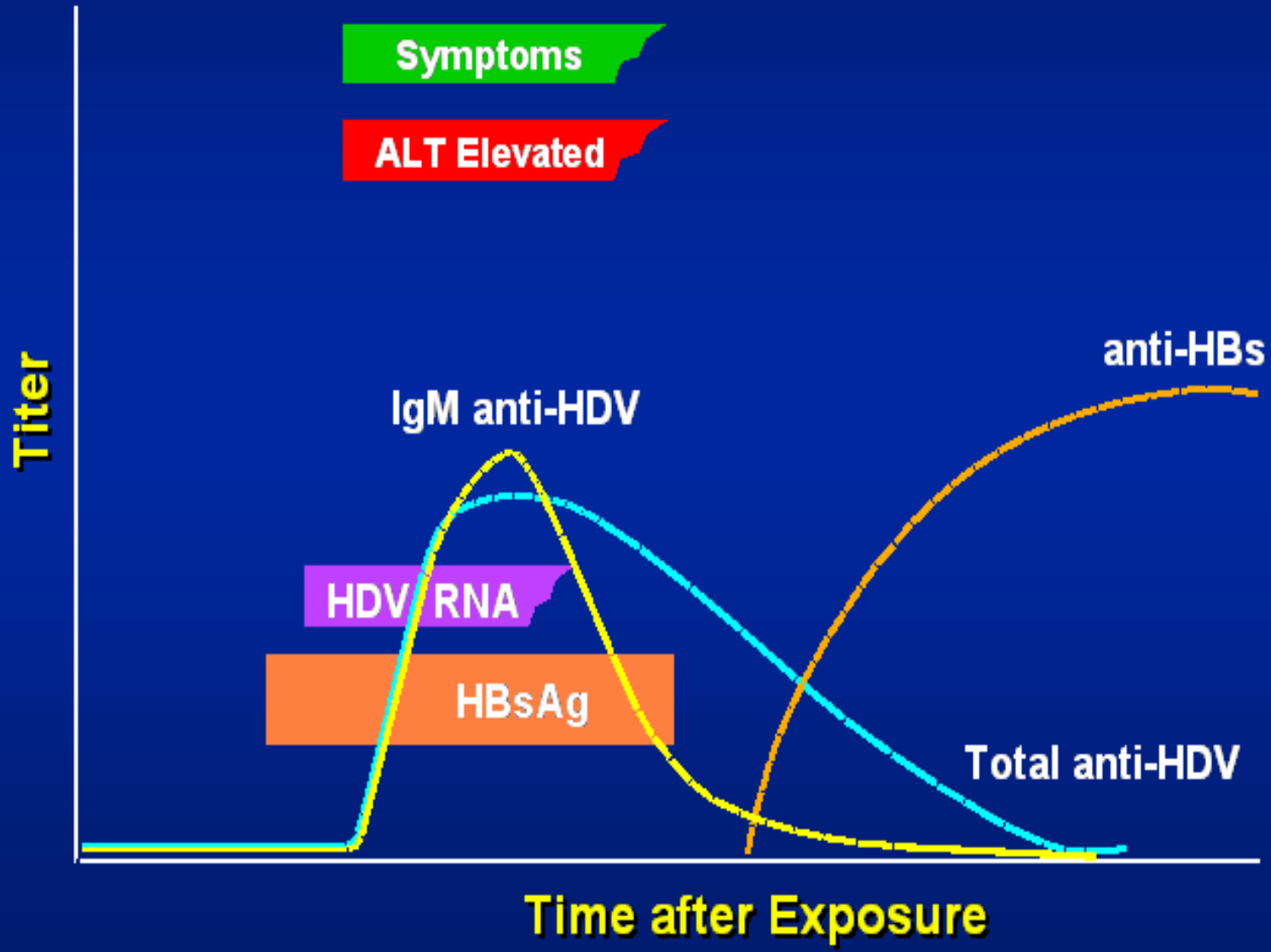
Rizzetto M. EASL 2009

Epidemiology of HDV in Europe



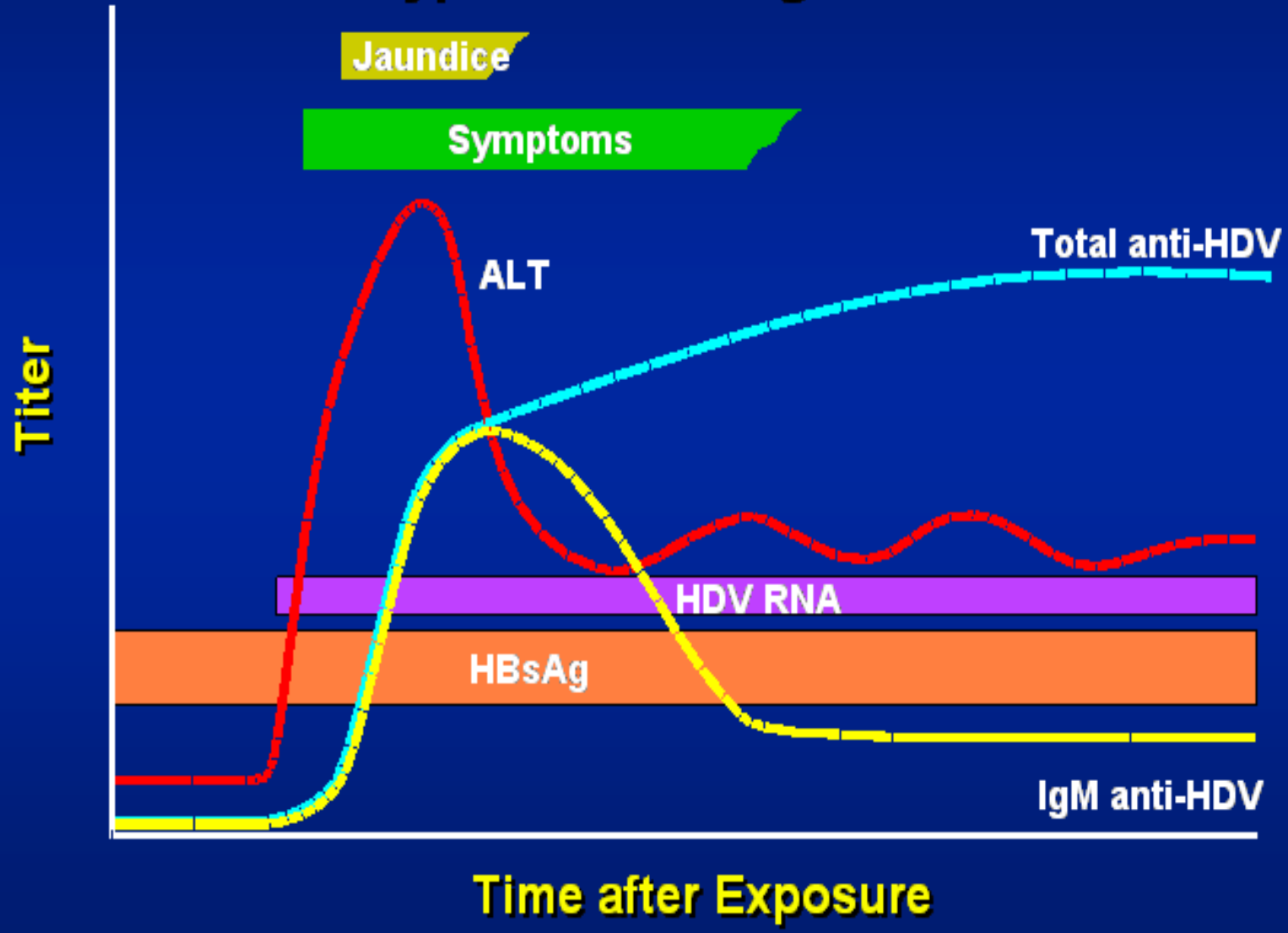
HBV - HDV Coinfection

Typical Serologic Course



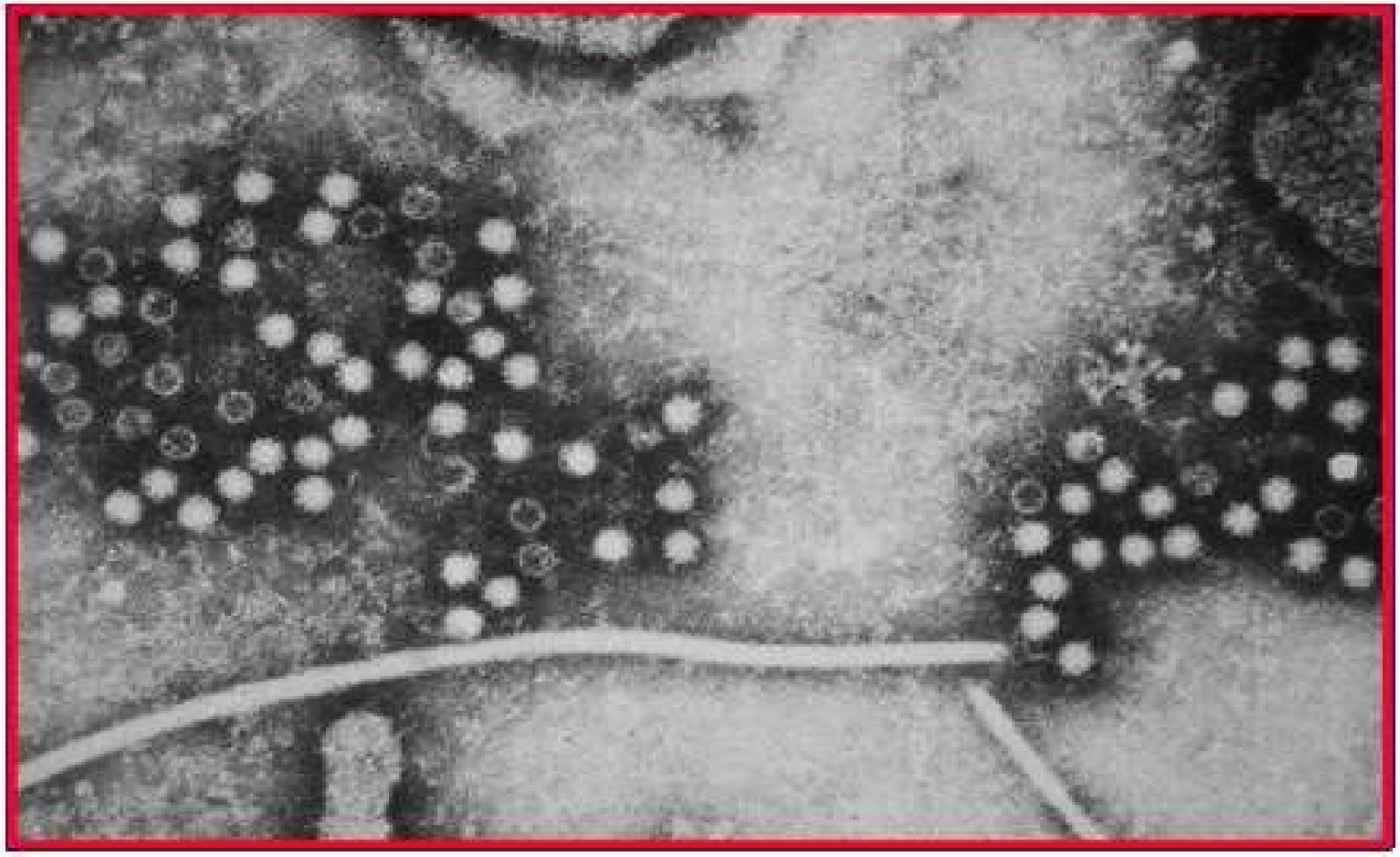
HBV - HDV Superinfection

Typical Serologic Course



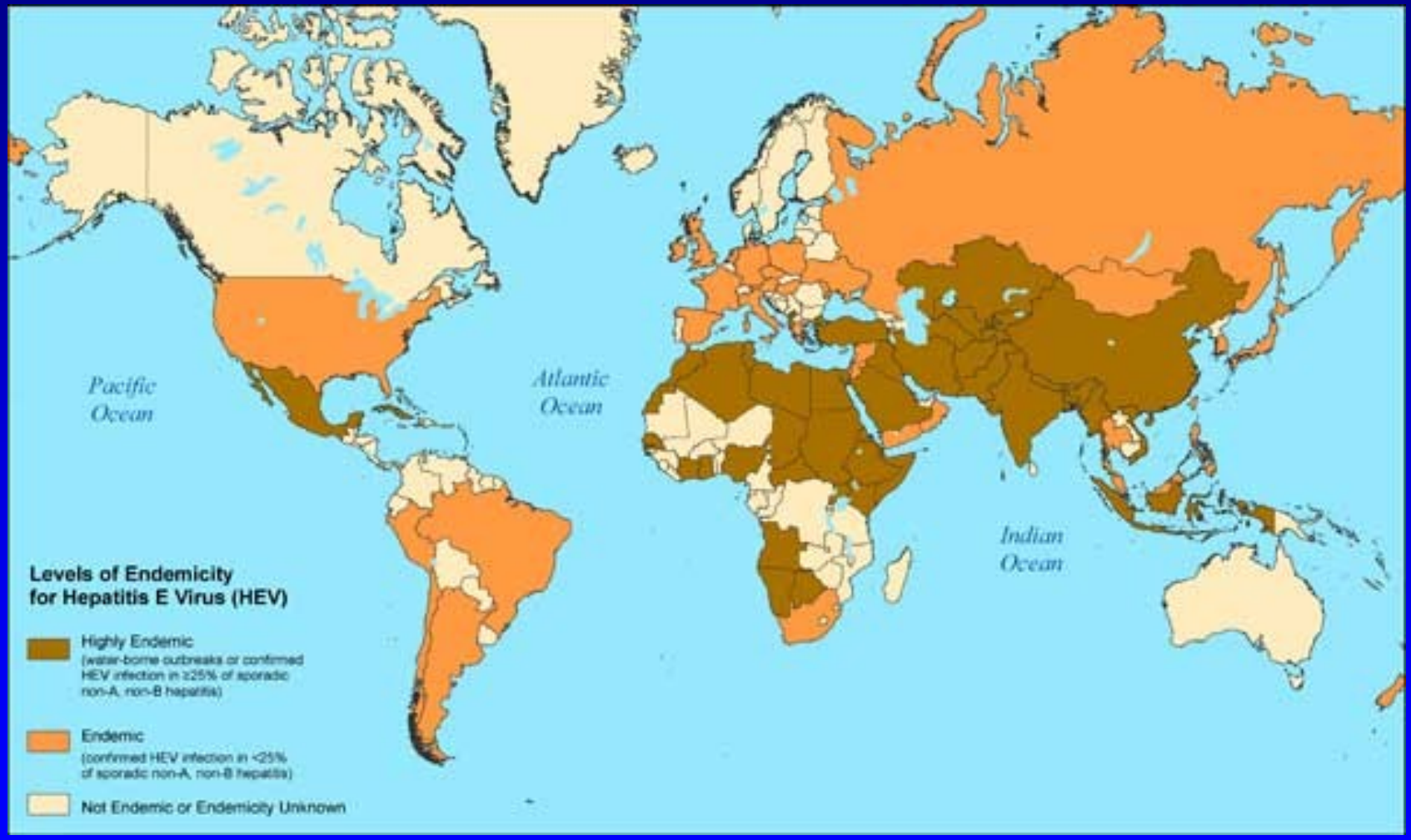
CDC

Hepatitis E Virus



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

Hepatitis E



Source: *CDC*

HEV genotypes

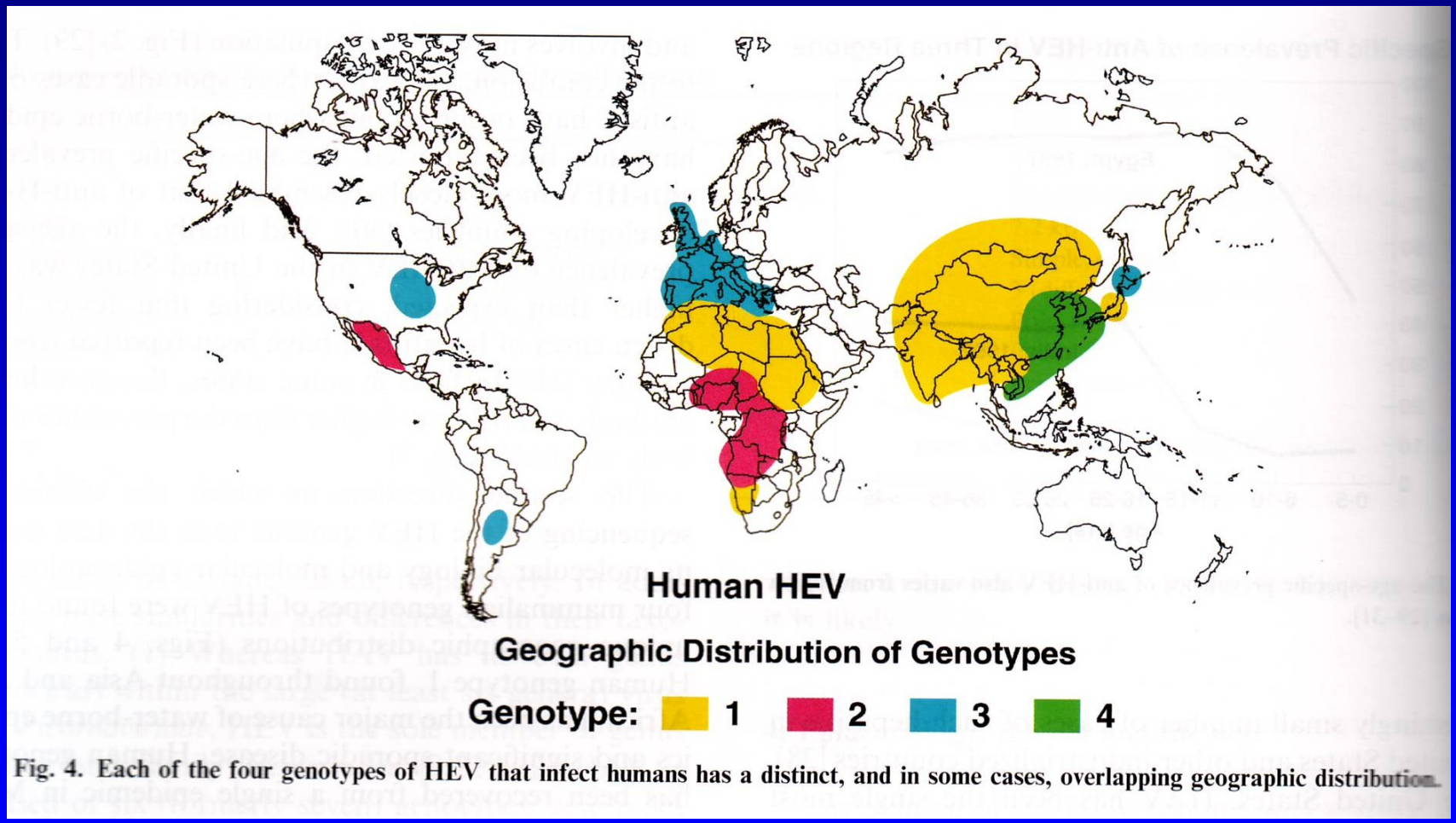


Fig. 4. Each of the four genotypes of HEV that infect humans has a distinct, and in some cases, overlapping geographic distribution.

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

Genotypes of swine HEV

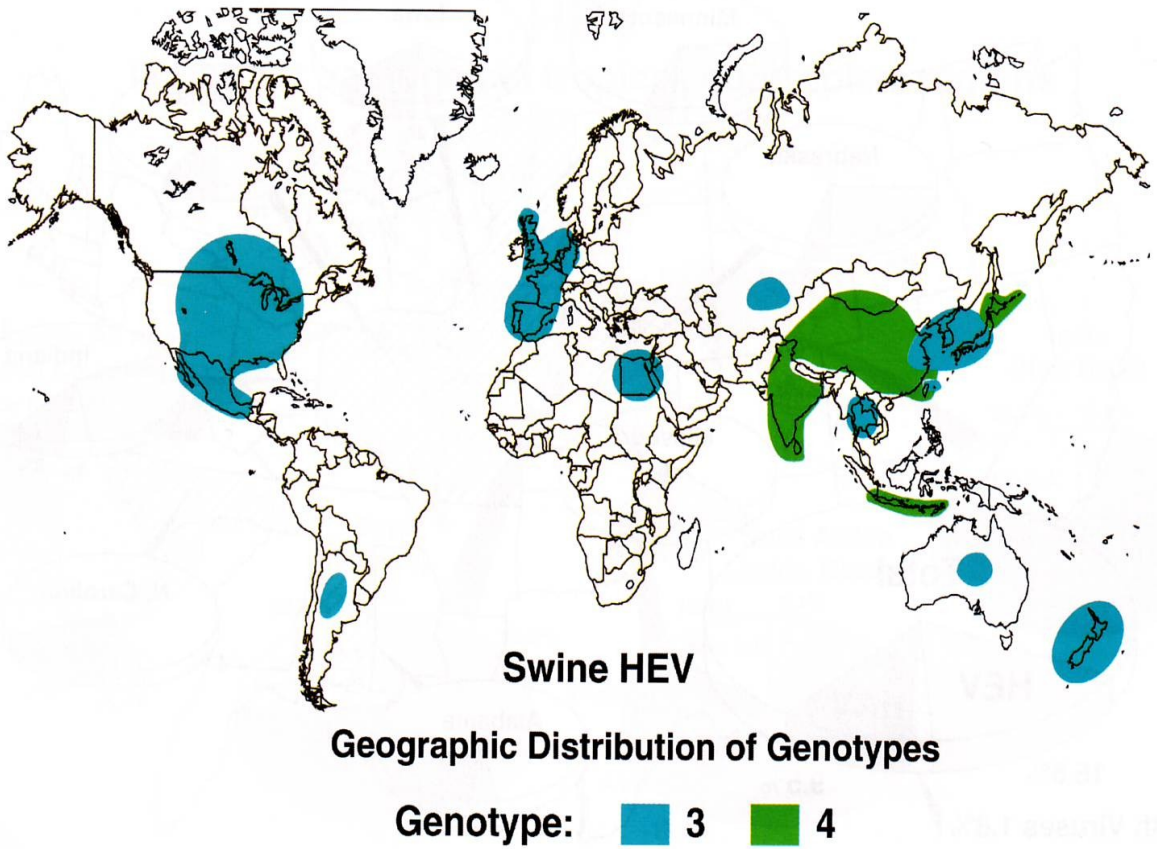


Fig. 5. HEV genotypes 3 and 4, which infect both humans and swine, have been recovered from pigs in regions that roughly parallel the distribution of these viruses in human infections. However, there are exceptions.

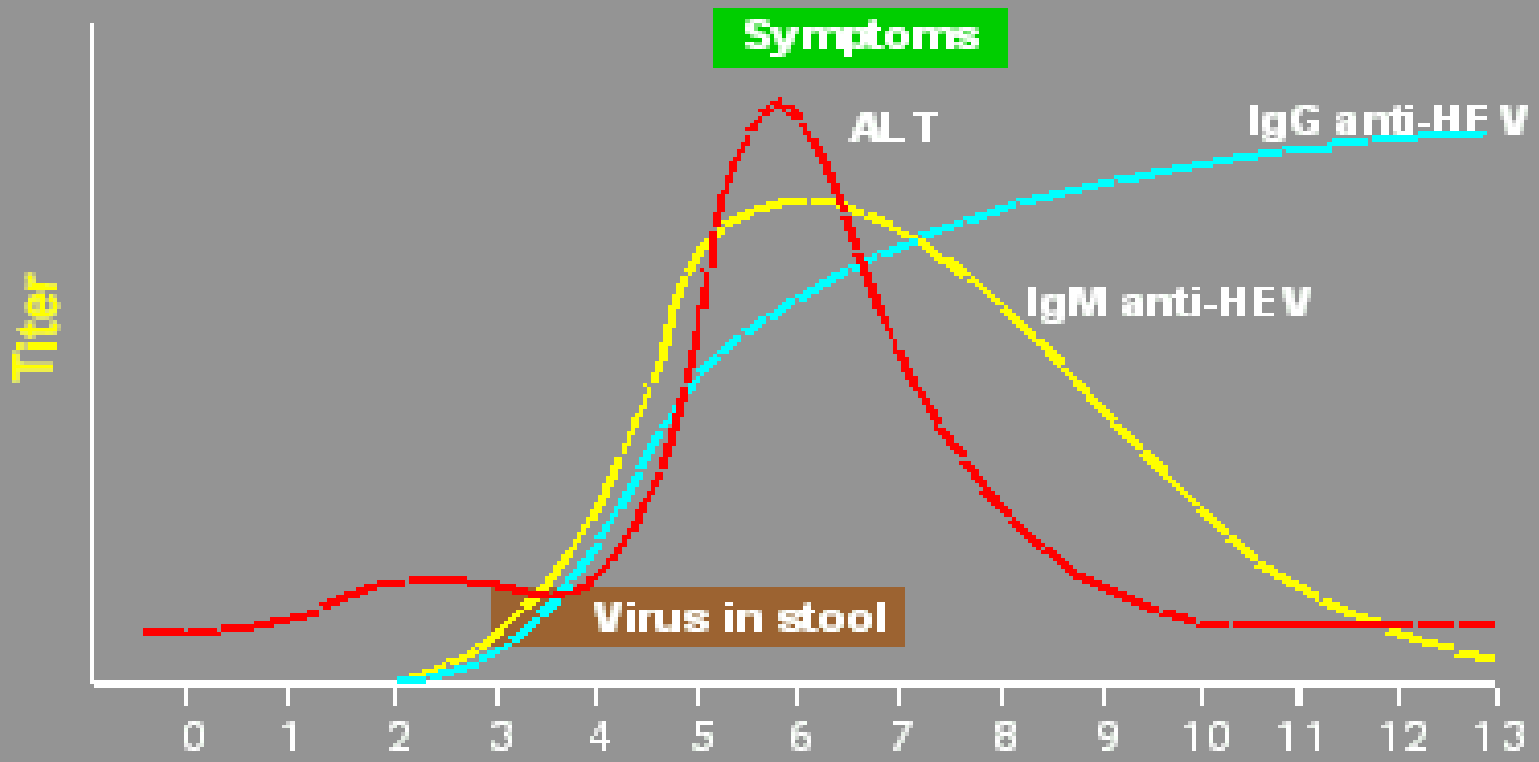
Purcell RH, Emerson SU. *J Hepatol* 48 (2008) 494-503

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

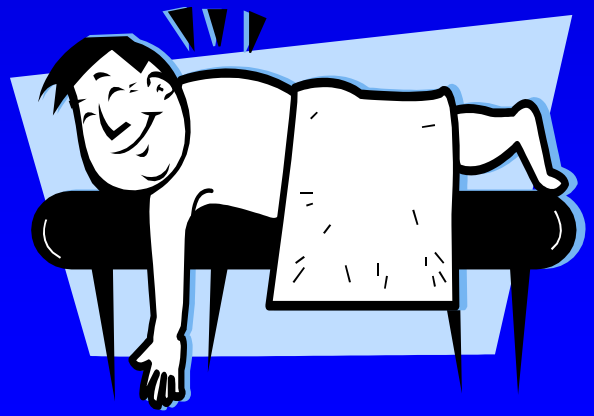
- Symptomatic for all types

✓ physical and mental rest

✓ diet

✓ no alcohol, no hepatoxic drugs

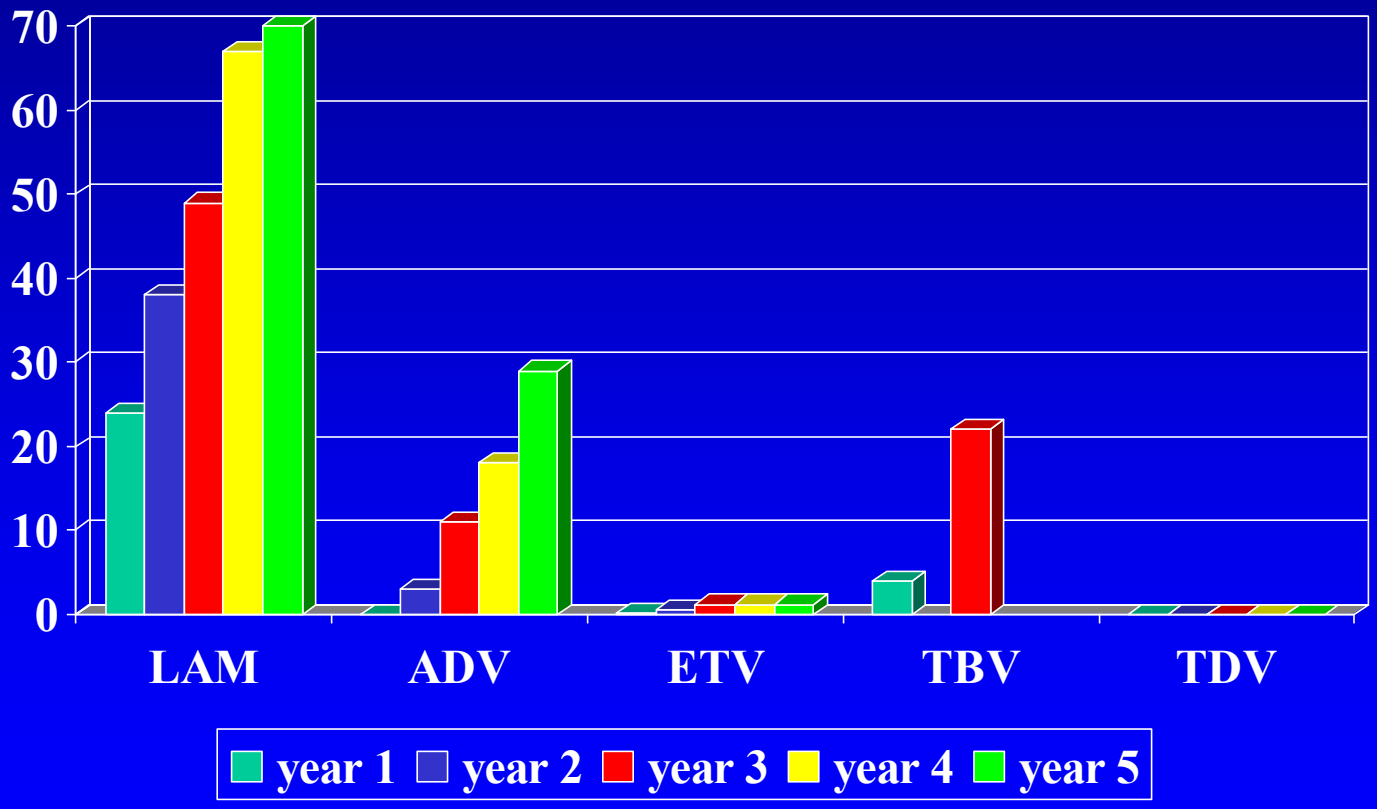
✓ supportive treatment (silymarin, essential phosholipids)



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 recurence
- 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



Current possibilities of treatment of chronic HCV infection

- Pegylated interferon alfa-2a or alfa-2b + ribavirin

✓ Genotype 1 or 4 – 48 weeks, SVR about 60 %

✓ Genotype 2 or 3 – 24 weeks, SVR about 85 %

Standard chronic hepatitis C therapy

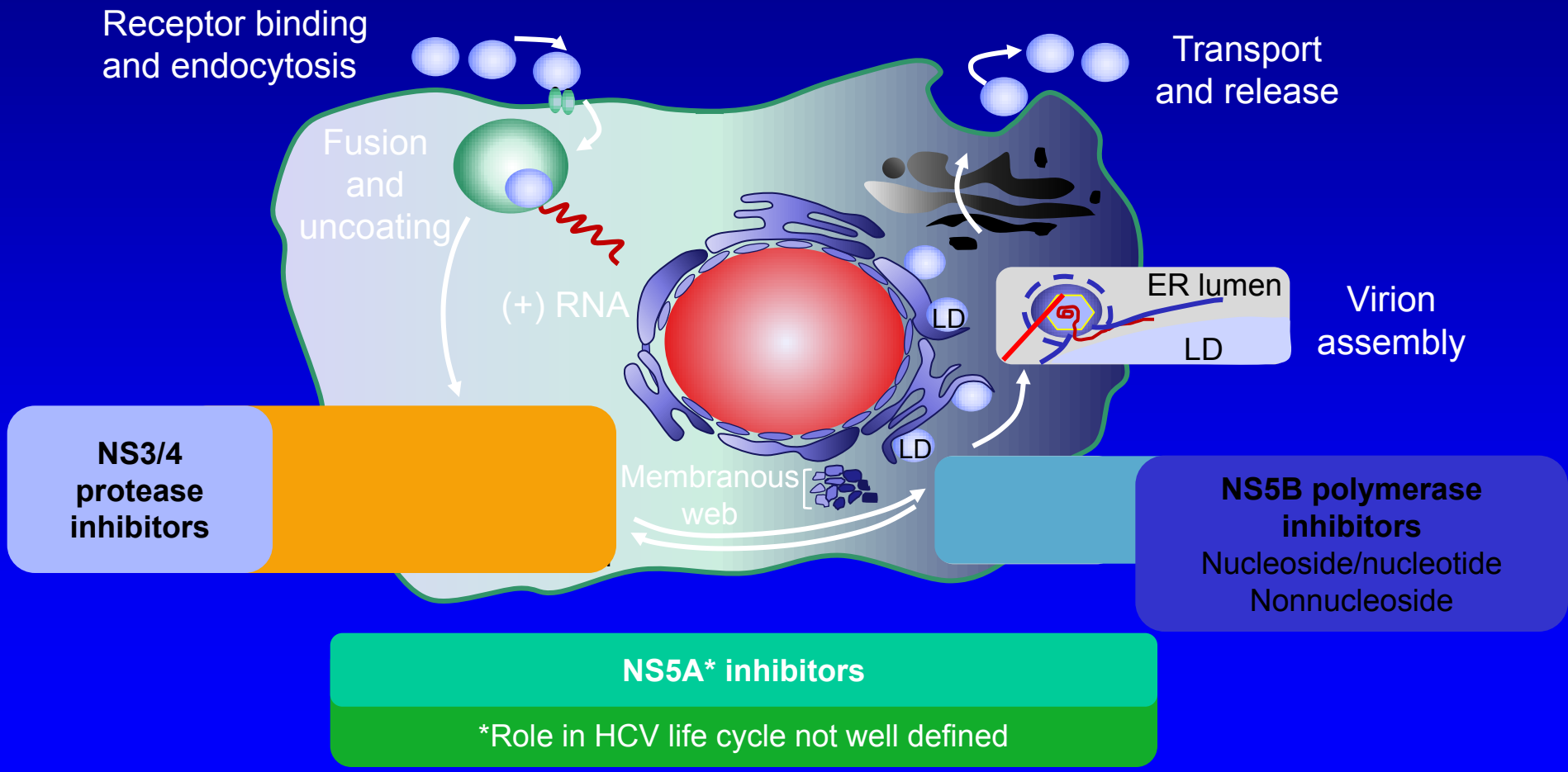
genotypes 1,4

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

genotypes 2-3

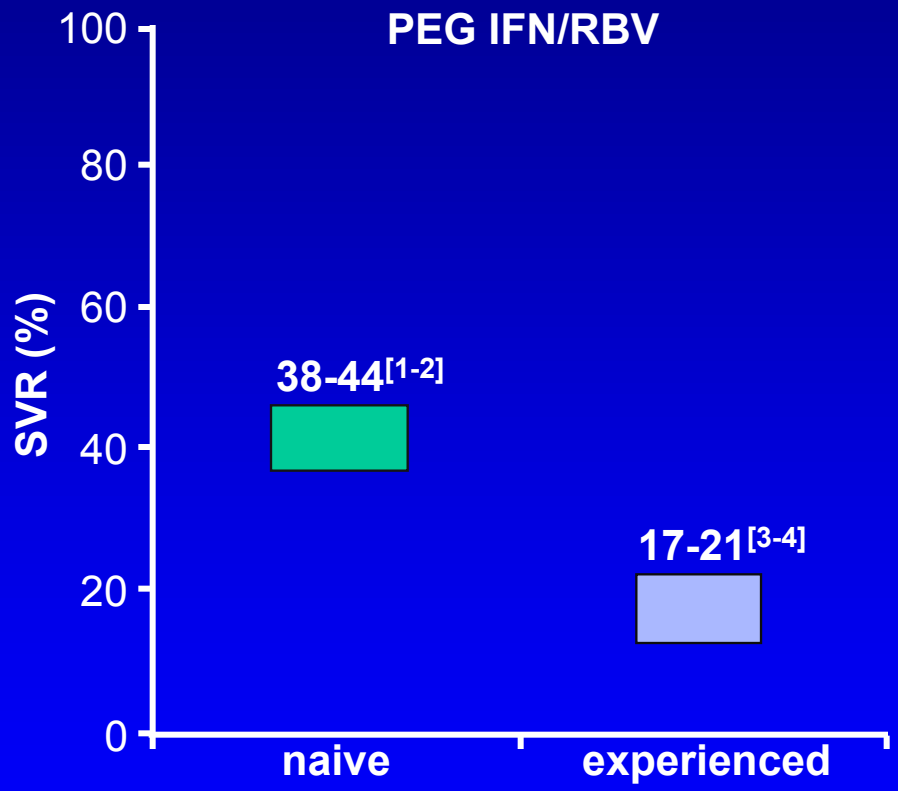
- ✓ PEG-IFN+RBV (800 mg) – 24 weeks

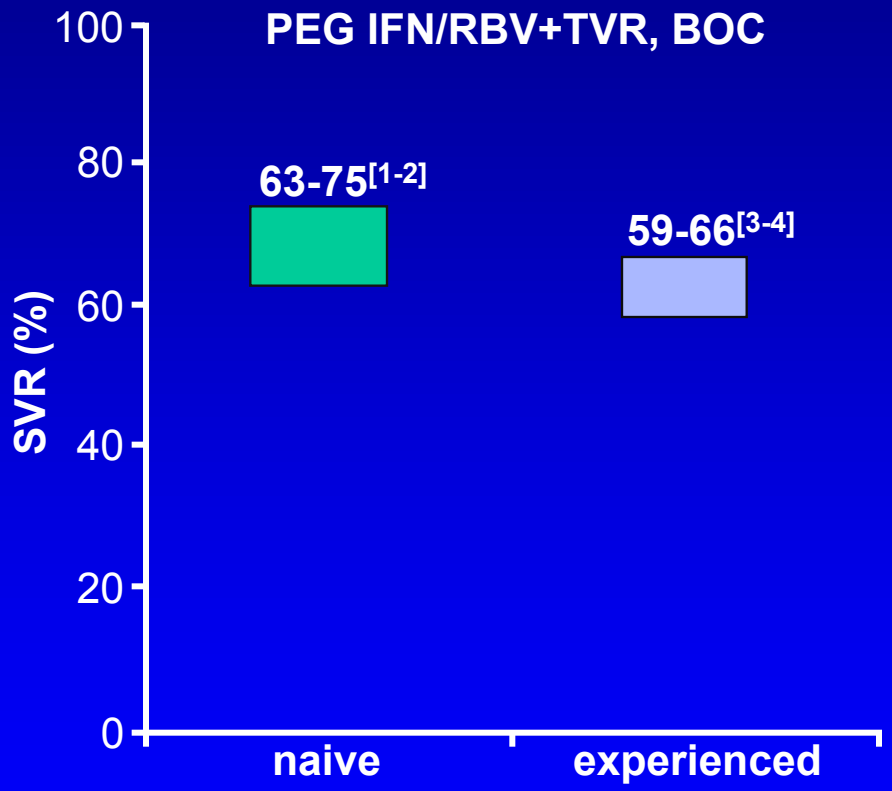
HCV Life Cycle and DAA Targets



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!

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