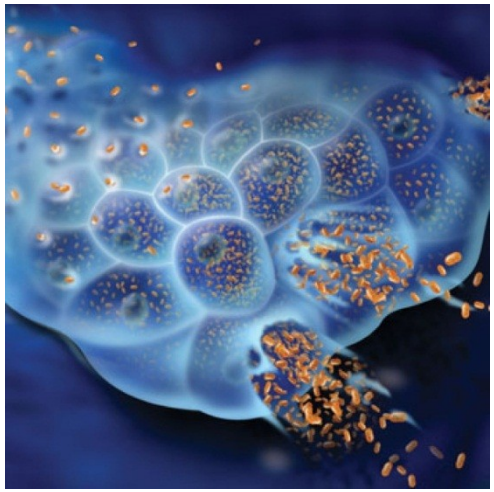
# Viral Hepatitis



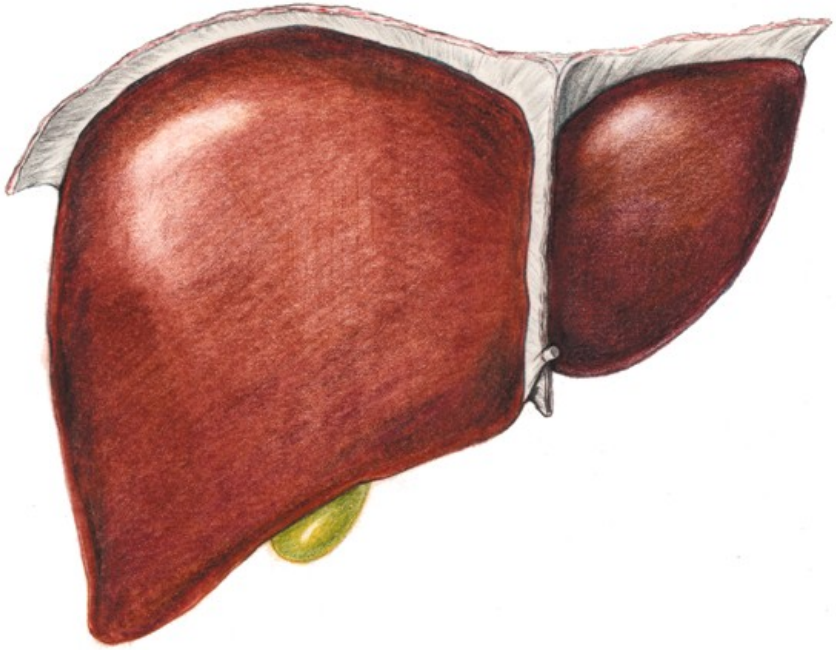
prof. MUDr. Petr Husa, CSc.
Klinika infekčních chorob, FN Brno

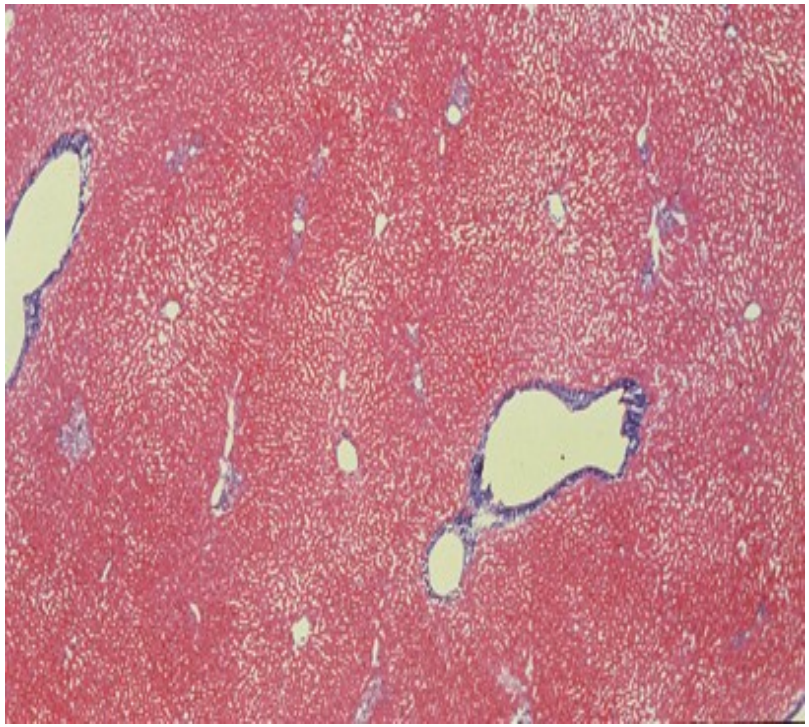
# Viral Hepatitis

- Diffuse necro-inflammatory liver process
- On the opposite bacterial infections lead to formation of liver abscesses
- Division of viral hepatitis

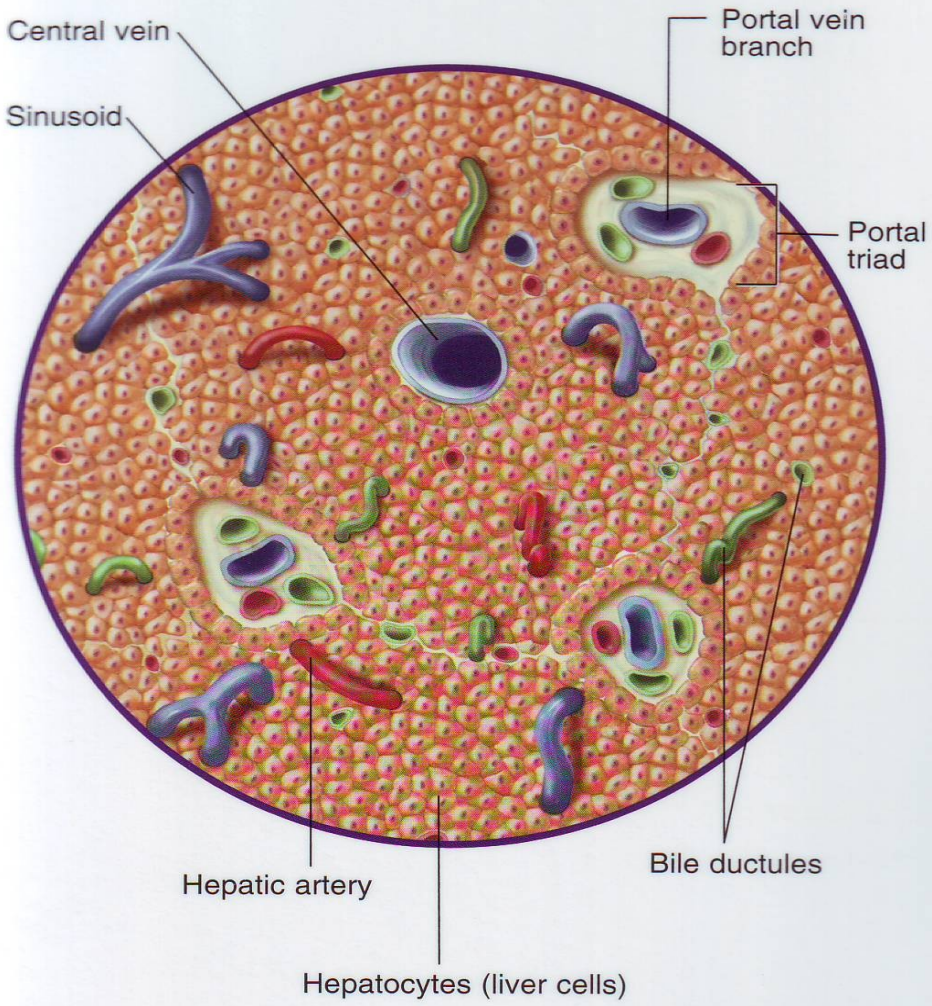
1. Enterically transmissible
   - VH A – only acute
   - VH E – chronic in immunosuppressed pts.
2. Parenterally transmissible – possible chronic stage
   - VH B
   - VH C
   - VH D

# Healthy liver

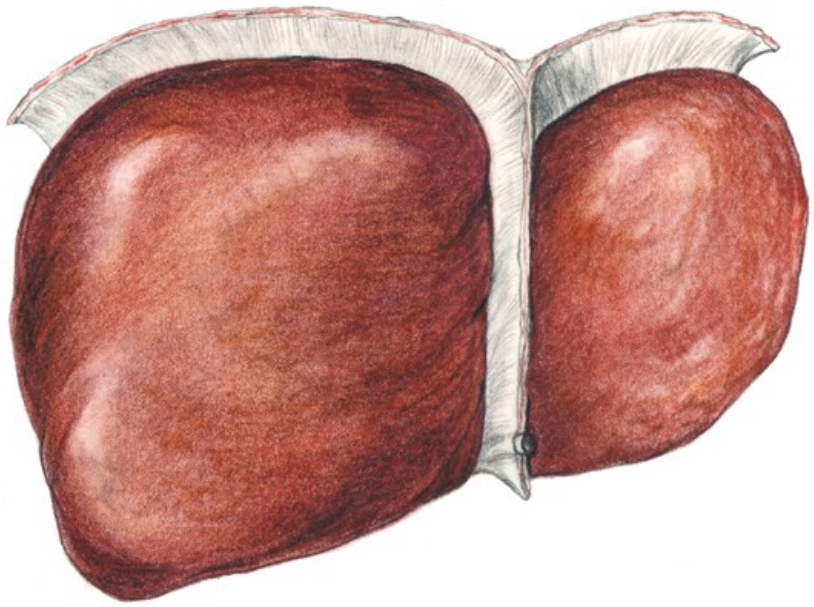


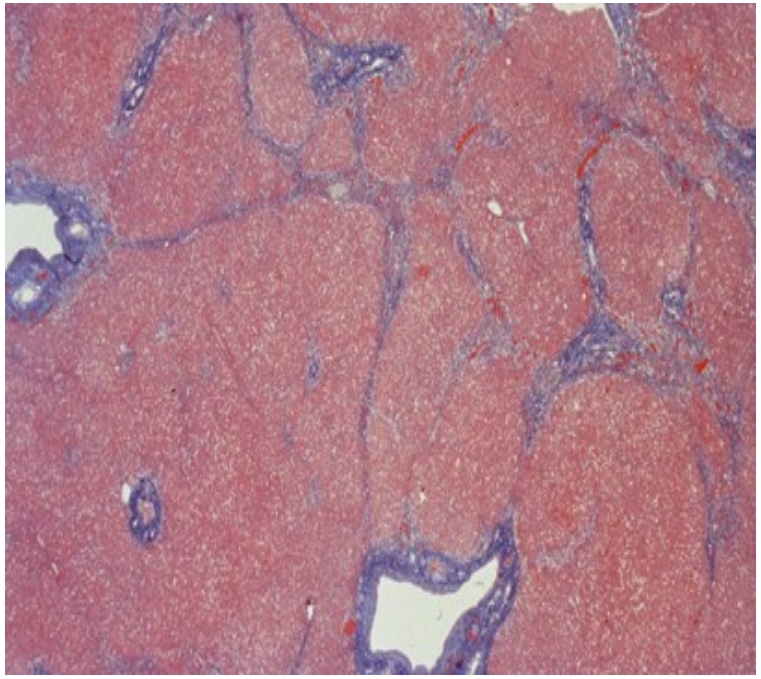


## Normal Biopsy

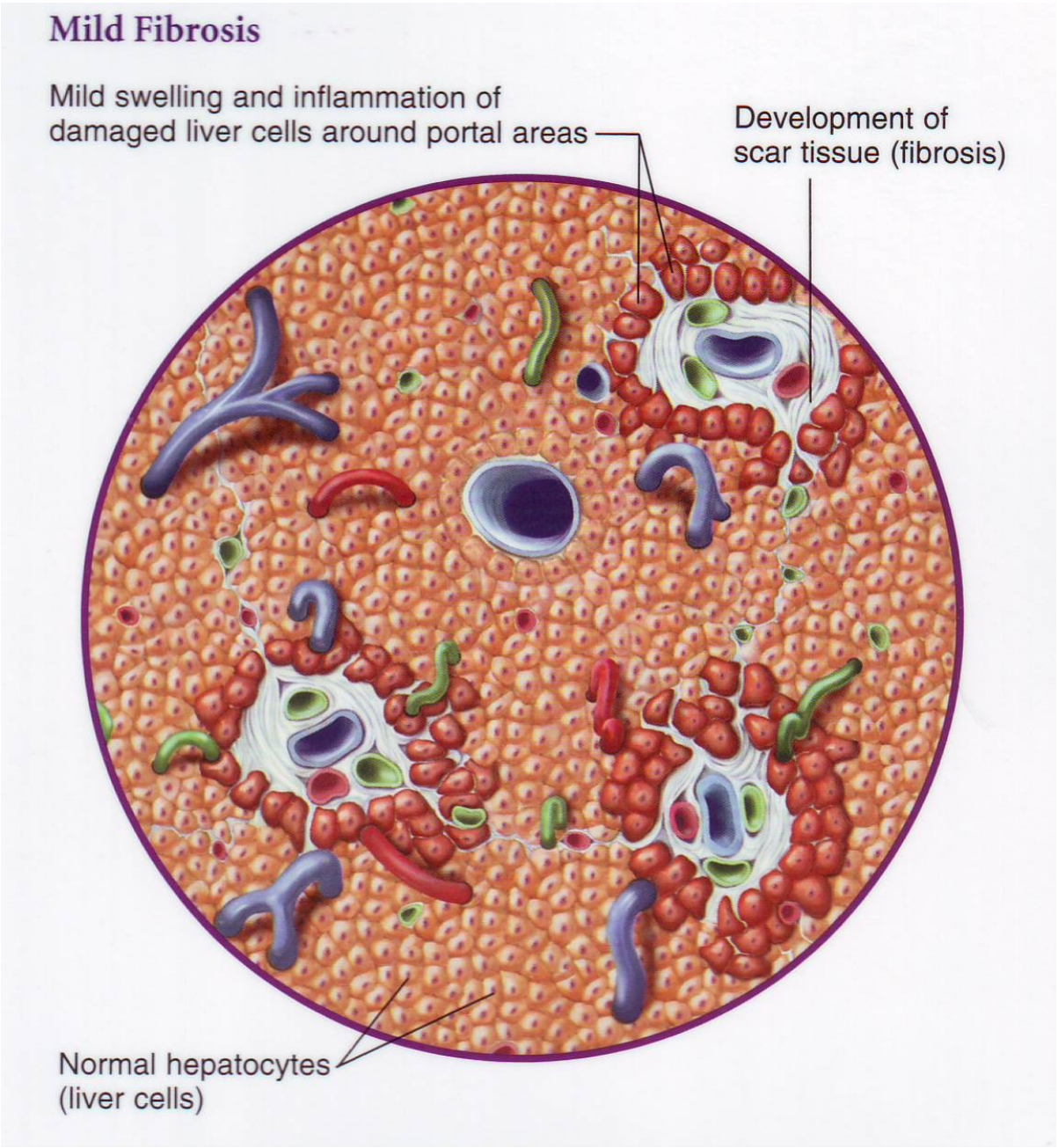


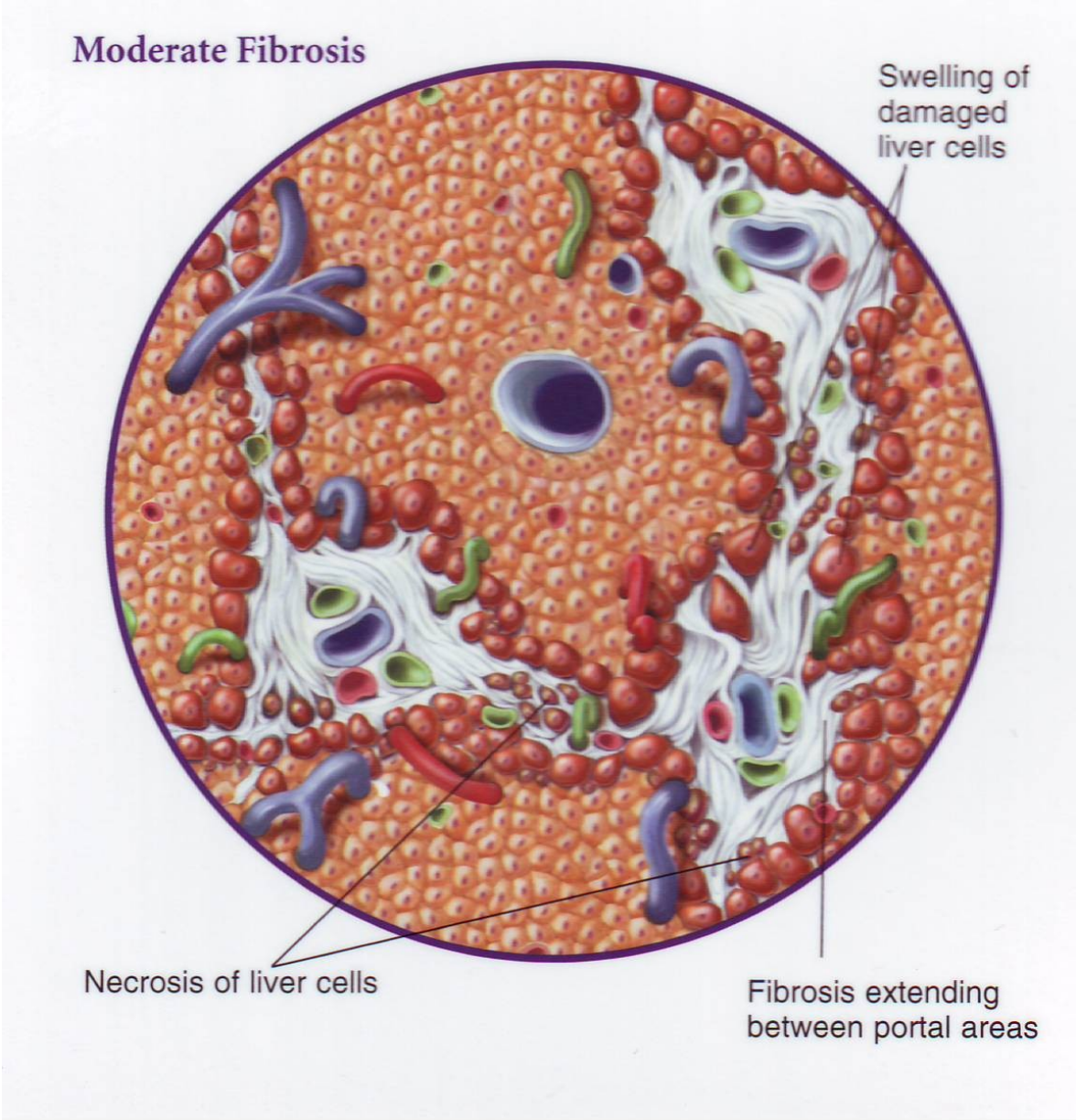
# Liver fibrosis



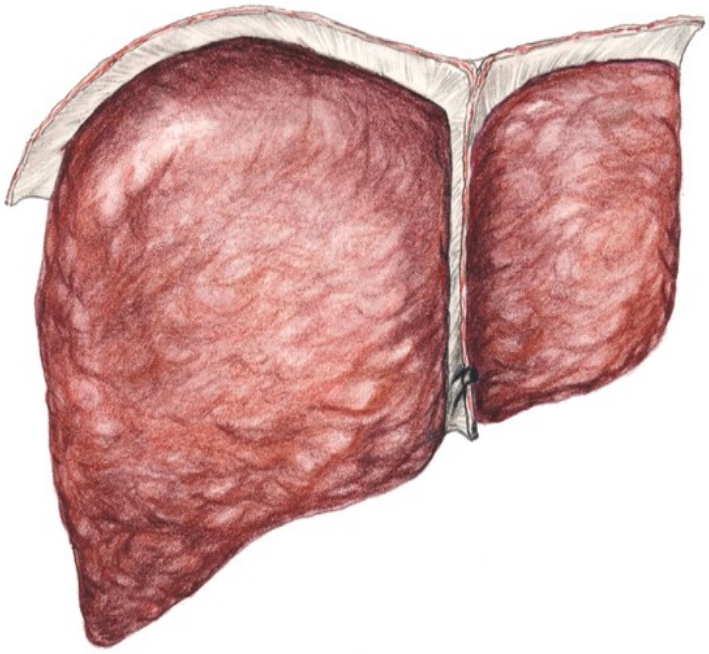


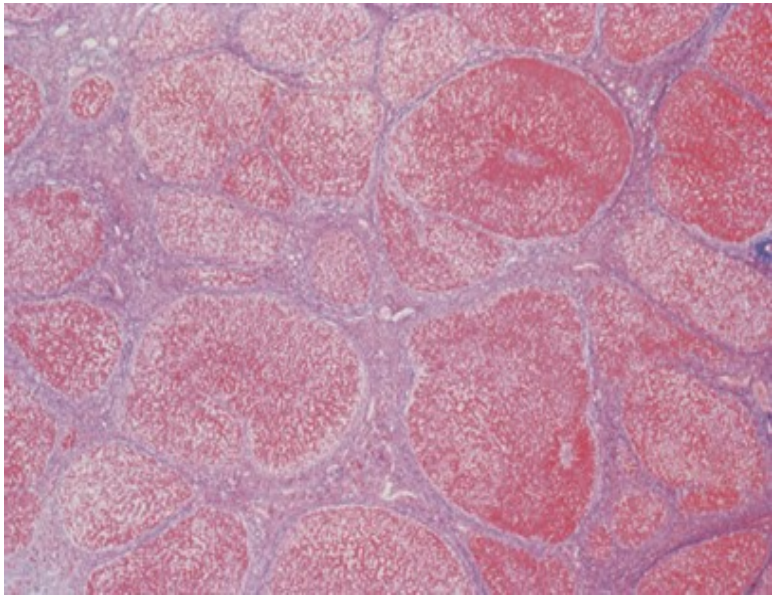
## Mild Fibrosis



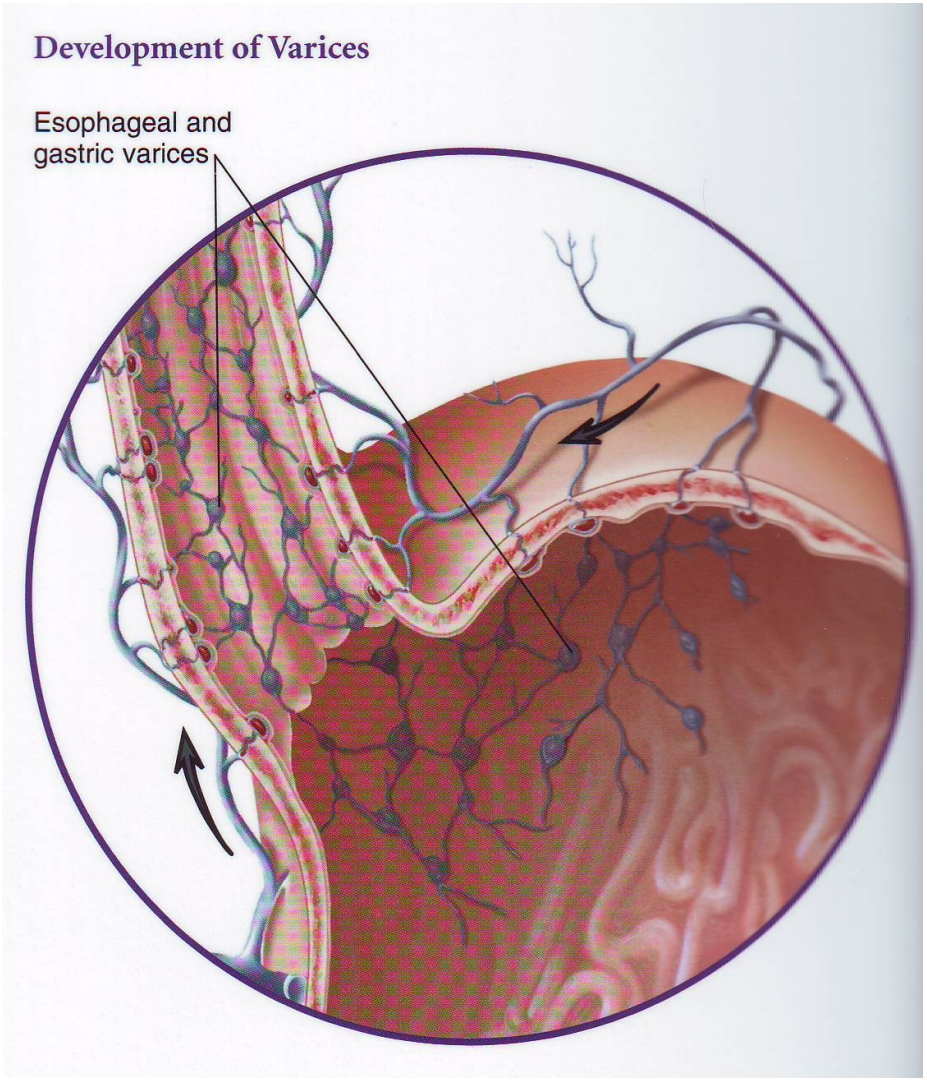

Moderate Fibrosis
Swelling of damaged liver cells
Necrosis of liver cells
Fibrosis extending between portal areas

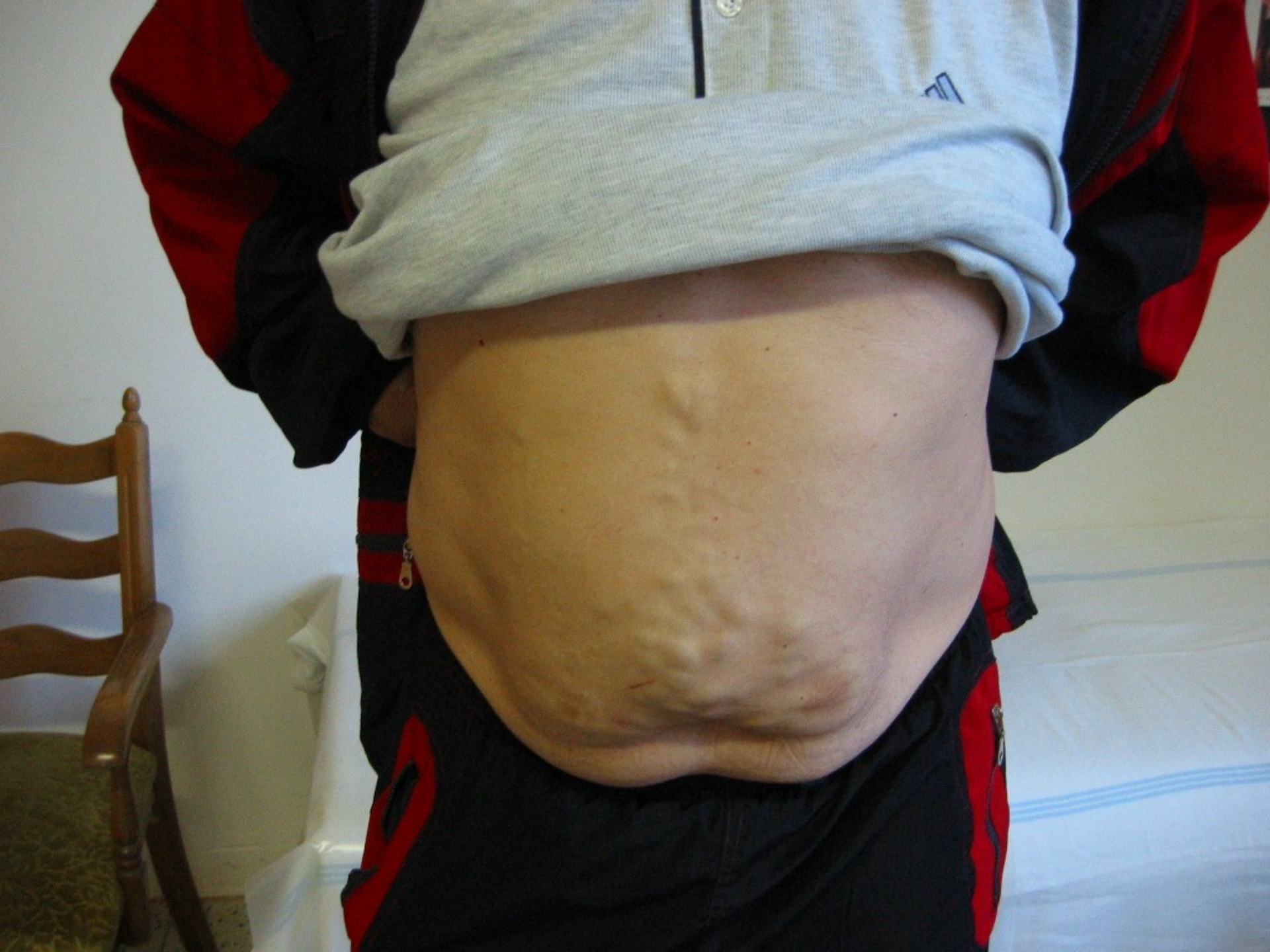
# Liver cirrhosis

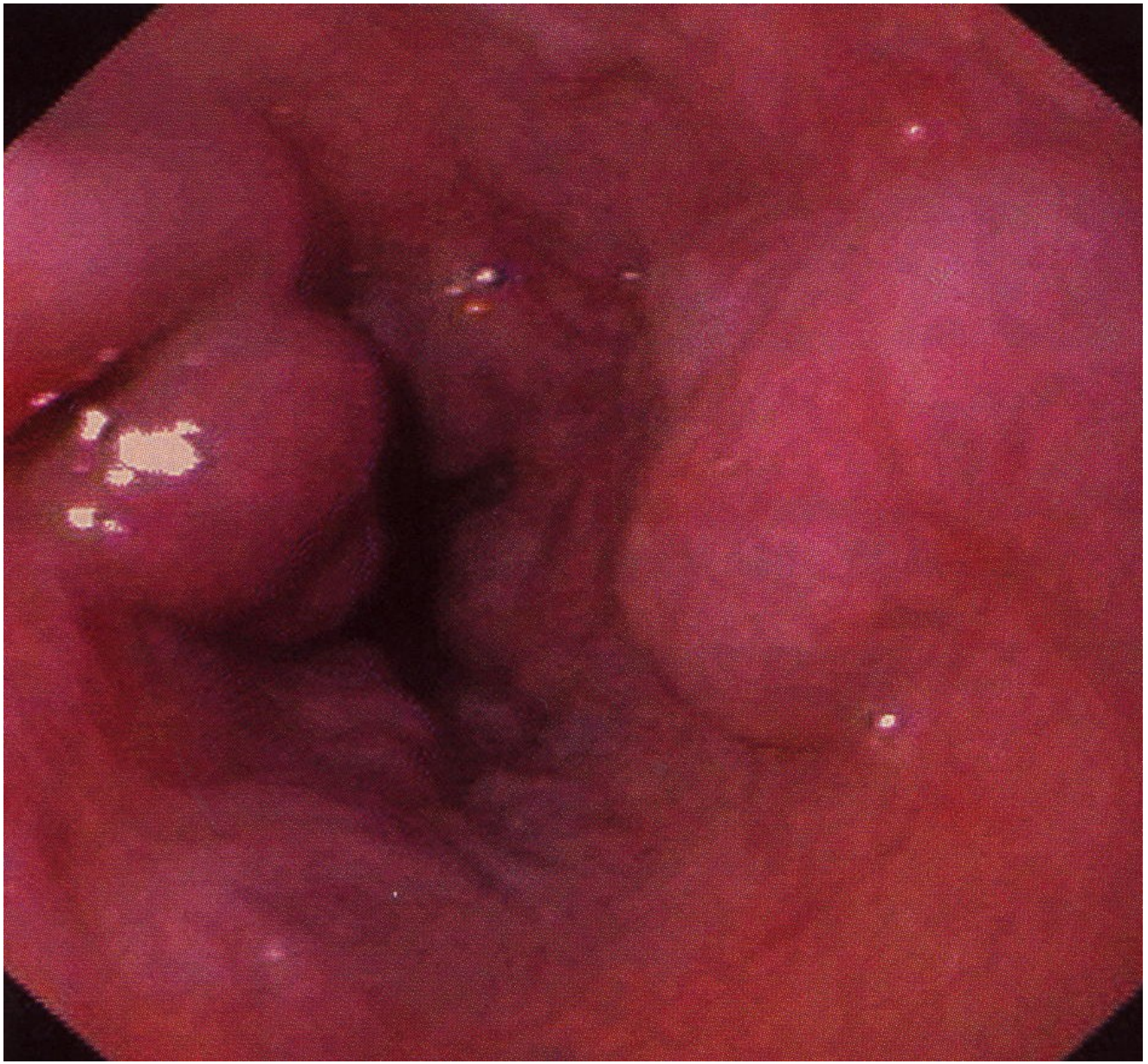


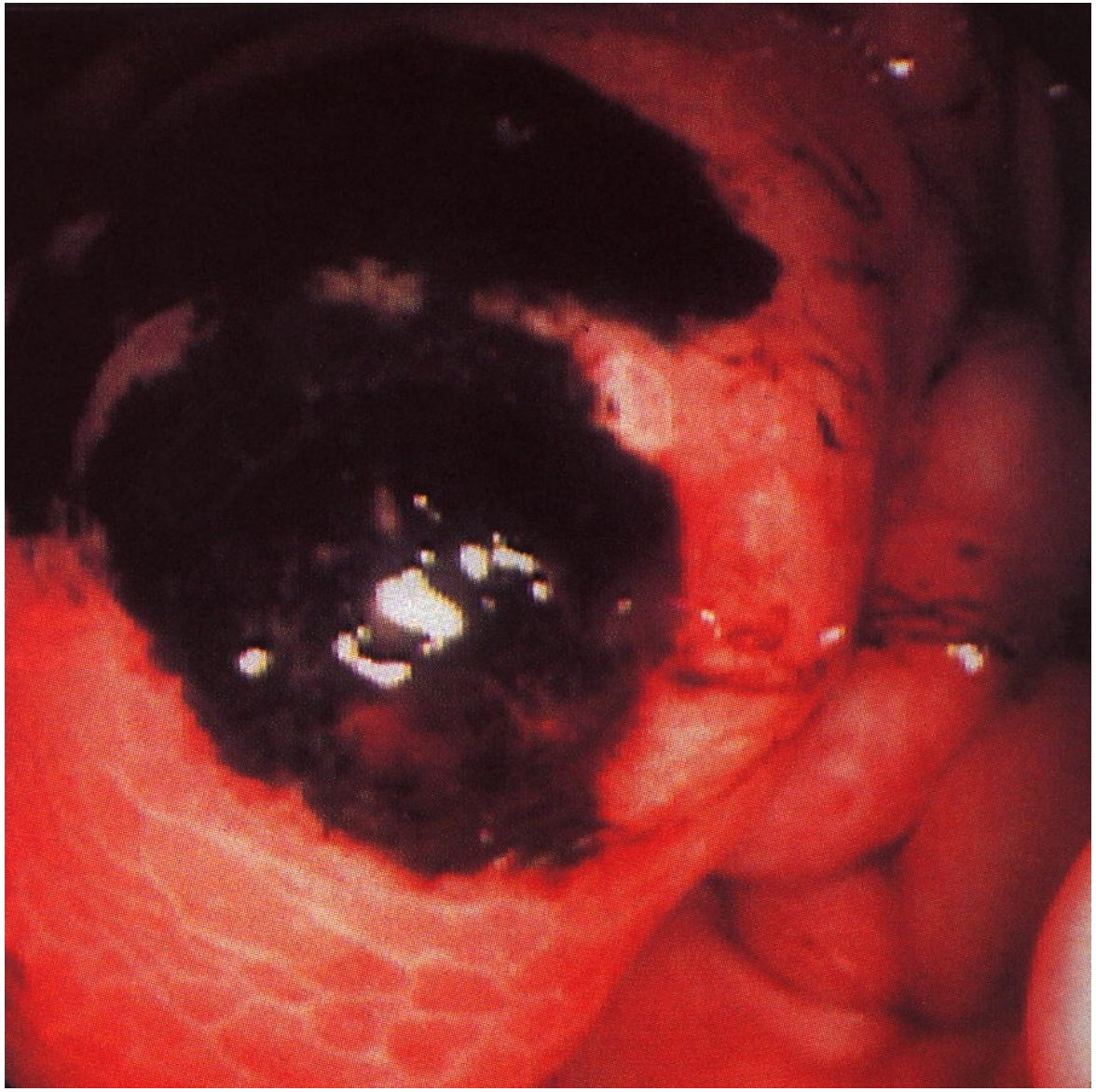


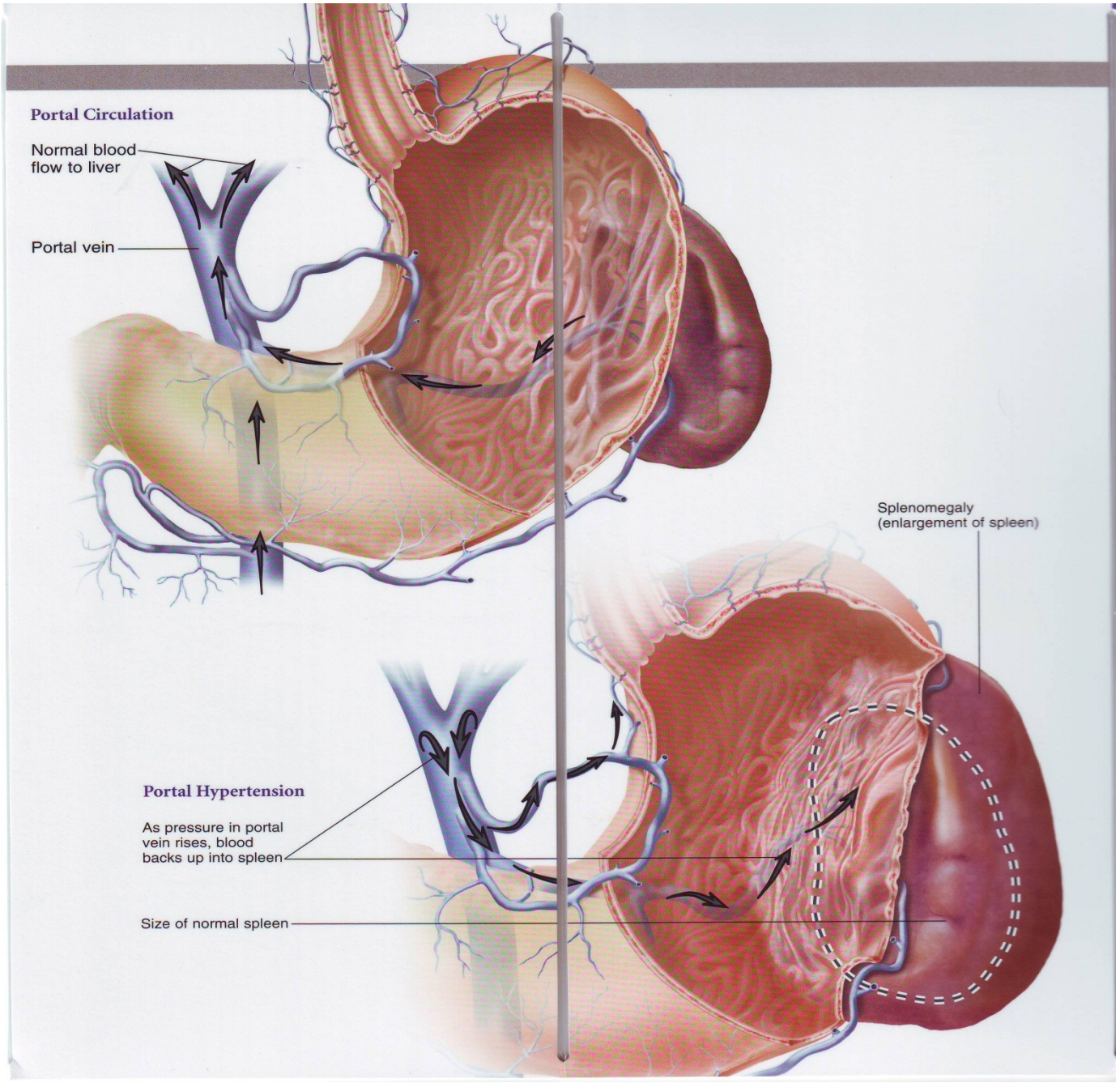
## Development of Varices

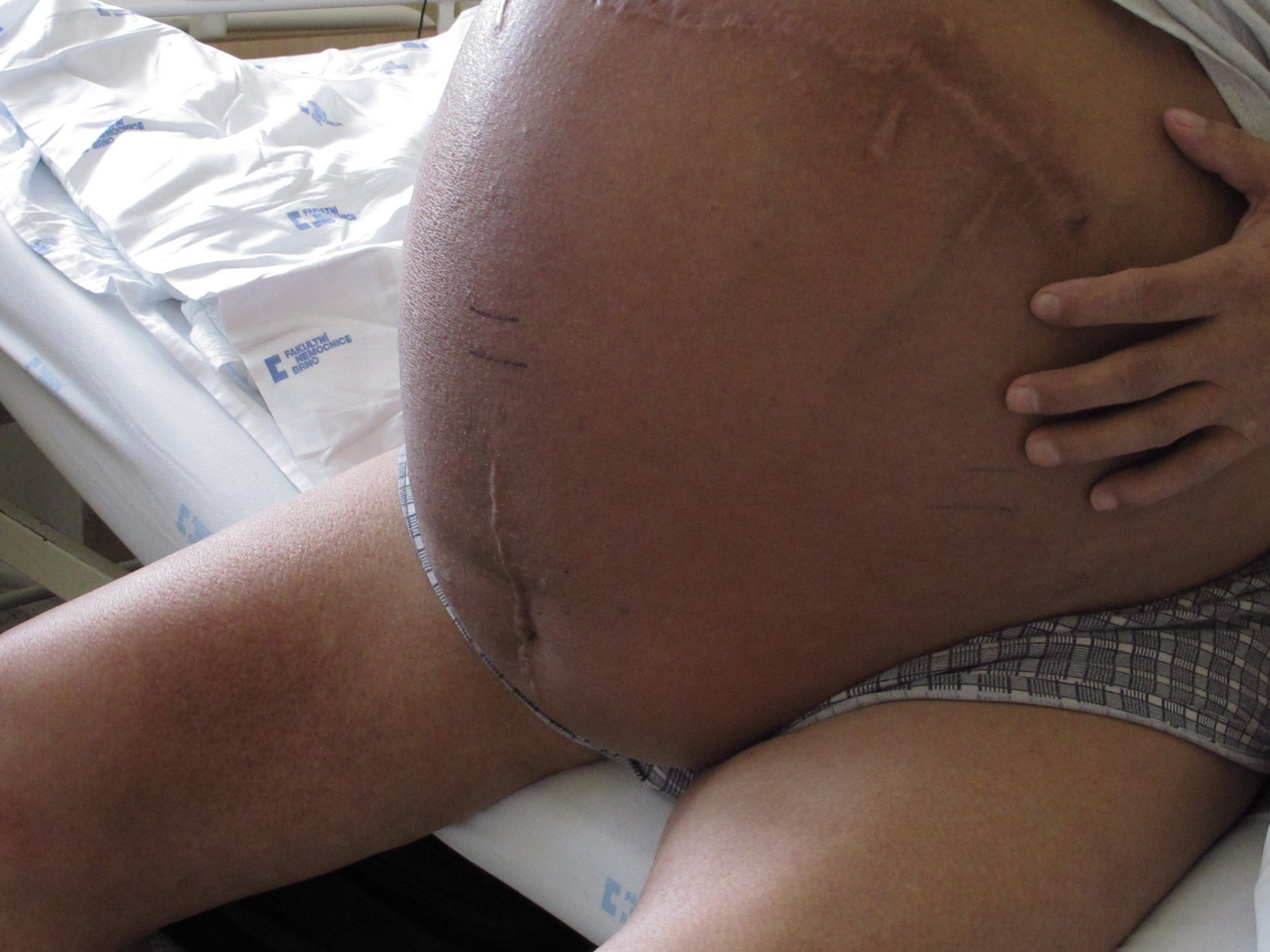


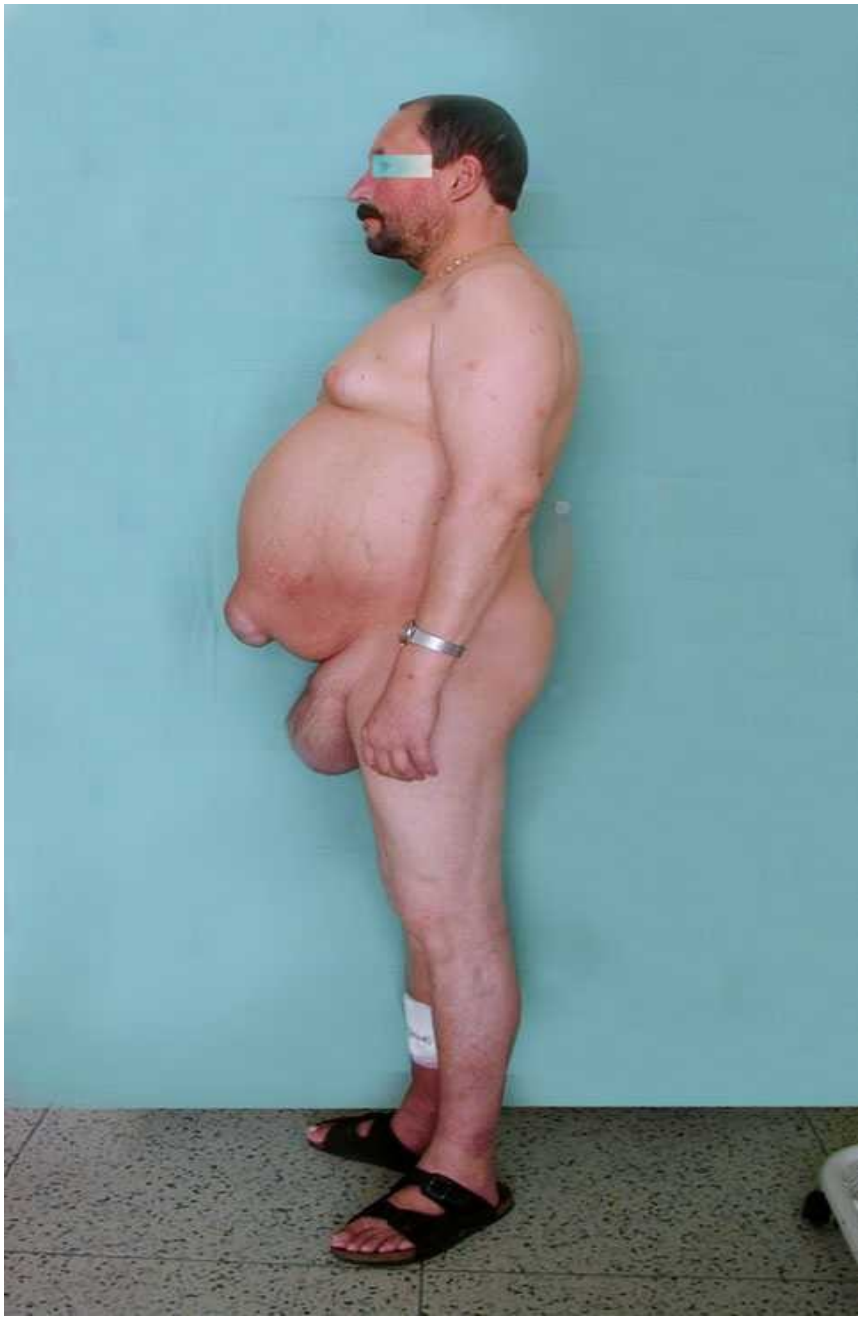


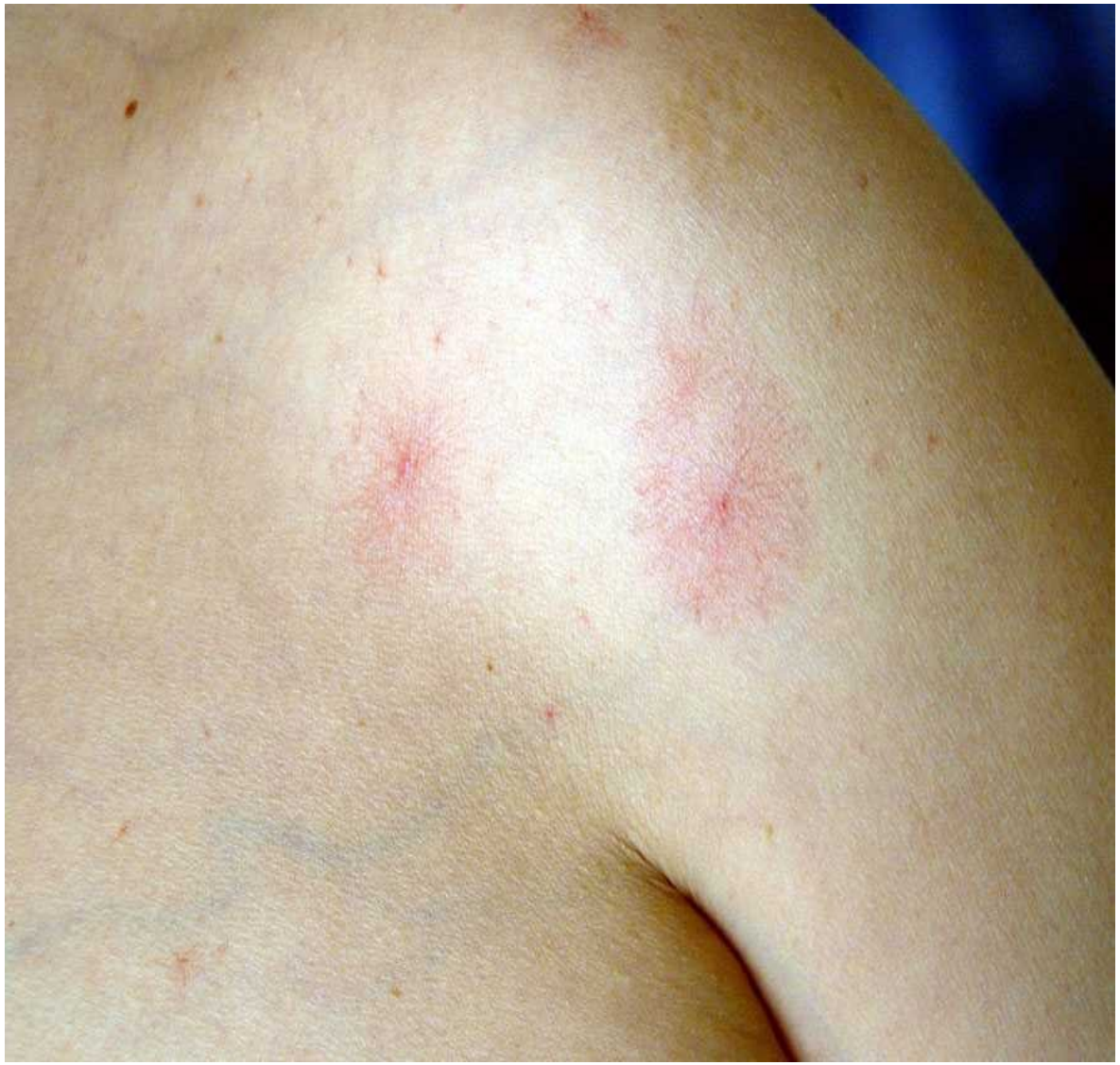




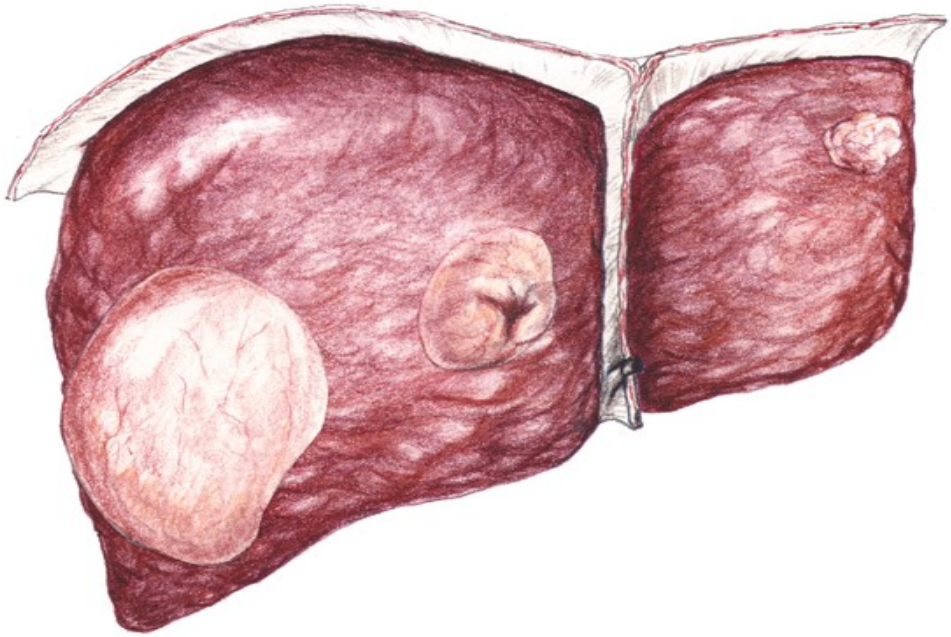

Portal Circulation
Normal blood flow to liver
Portal vein
Splenomegaly (enlargement of spleen)
Portal Hypertension
As pressure in portal vein rises, blood backs up into spleen
Size of normal spleen

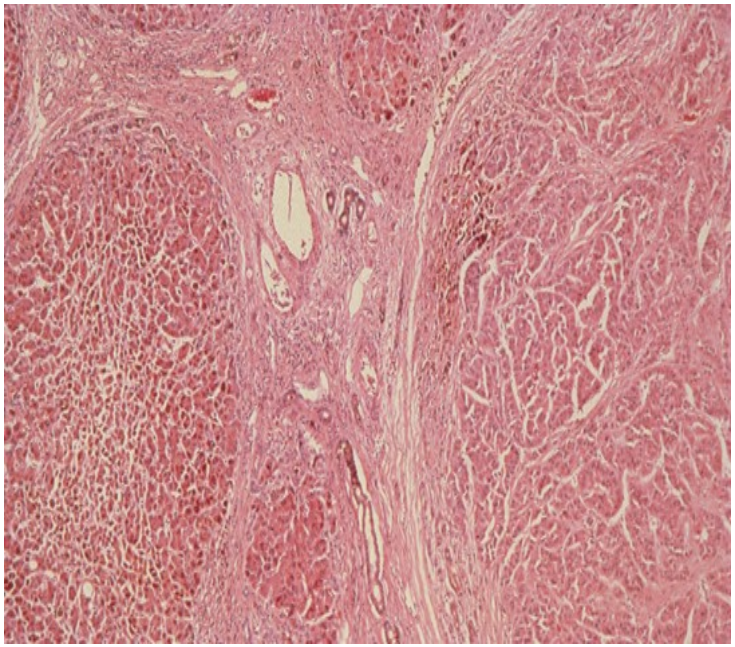

FAKULTNÍ NEMOCNICE BRNO





# Hepatocellular carcinoma

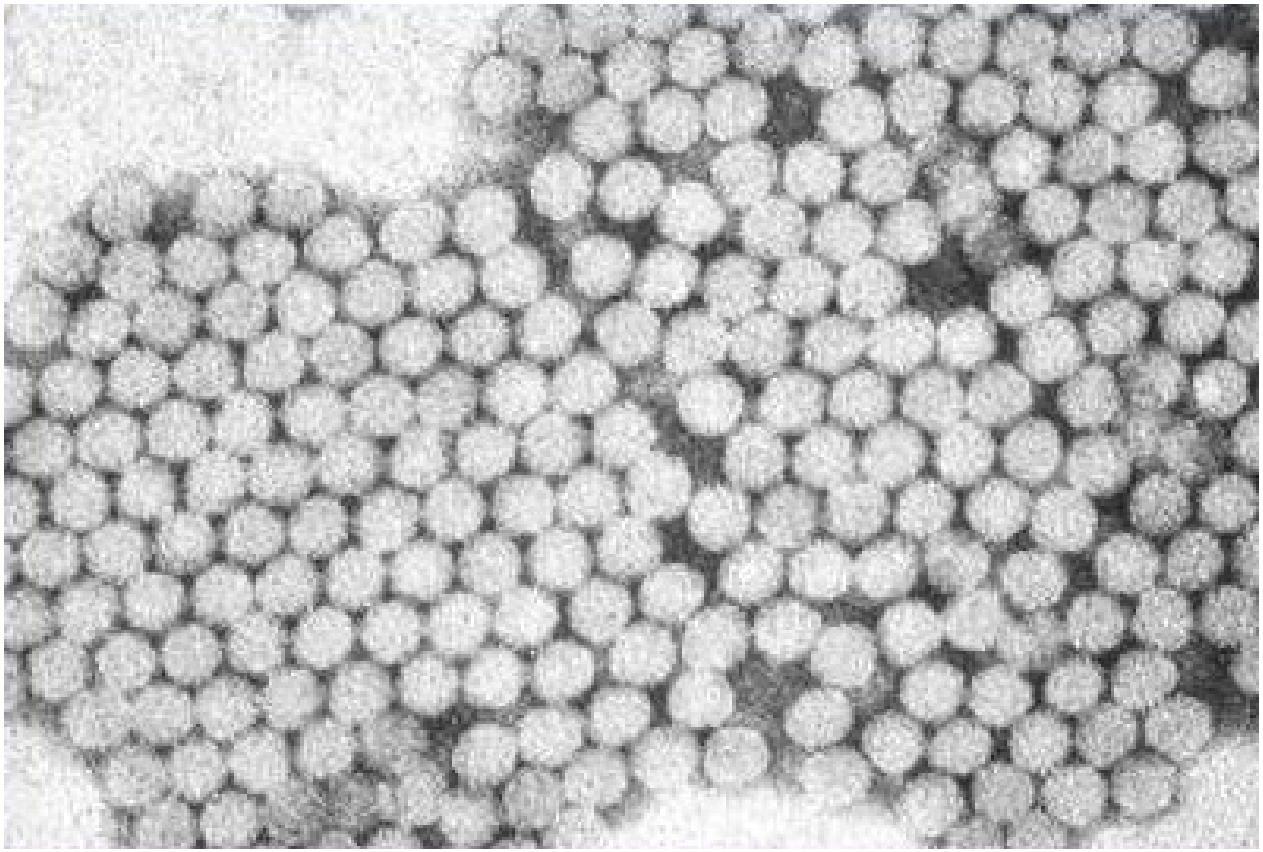




# Viral hepatitis in CR 2008-2017

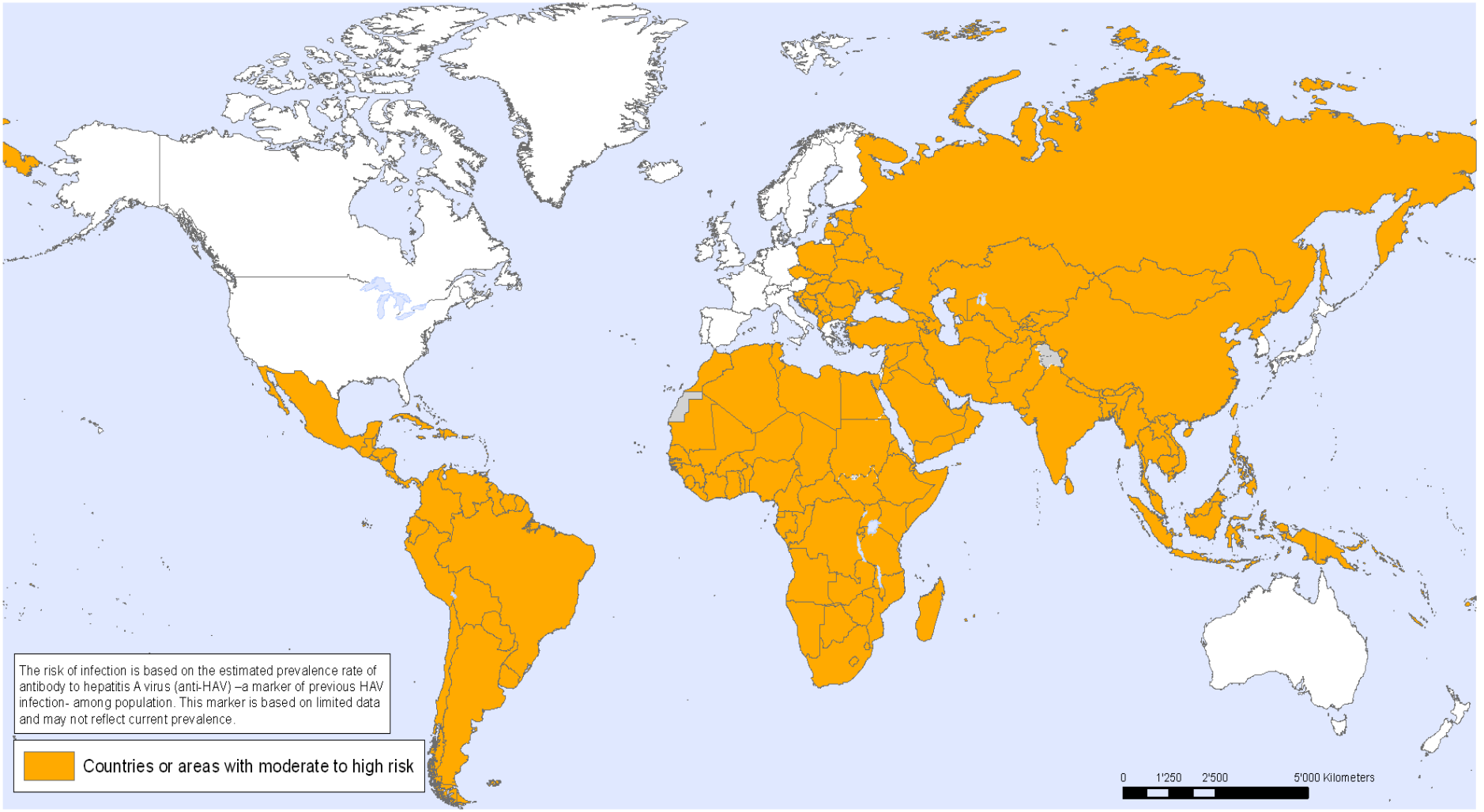
| | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 |
|---|---|---|---|---|---|---|---|---|---|---|
| **VH A** | 1648 | 1104 | 862 | 264 | 284 | 348 | 673 | 723 | 930 | 772 |
| **VH B** | 306 | 247 | 244 | 192 | 154 | 133 | 105 | 90 | 73 | 85 |
| **VH C** | 974 | 836 | 709 | 812 | 794 | 873 | 867 | 945 | 1103 | 992 |
| **VH E** | 65 | 99 | 72 | 163 | 258 | 218 | 299 | 409 | 339 | 344 |

# Hepatitis A virus (HAV)



Family Picornaviridae, genus *Hepatovirus* – non-enveloped RNA, 27 nm
3 human genotypes (I-III), worldwide G-I dominates, subtypes A a B, 3 exclusively simian genotypes(IV-VI)

# Hepatitis A, countries or areas at risk

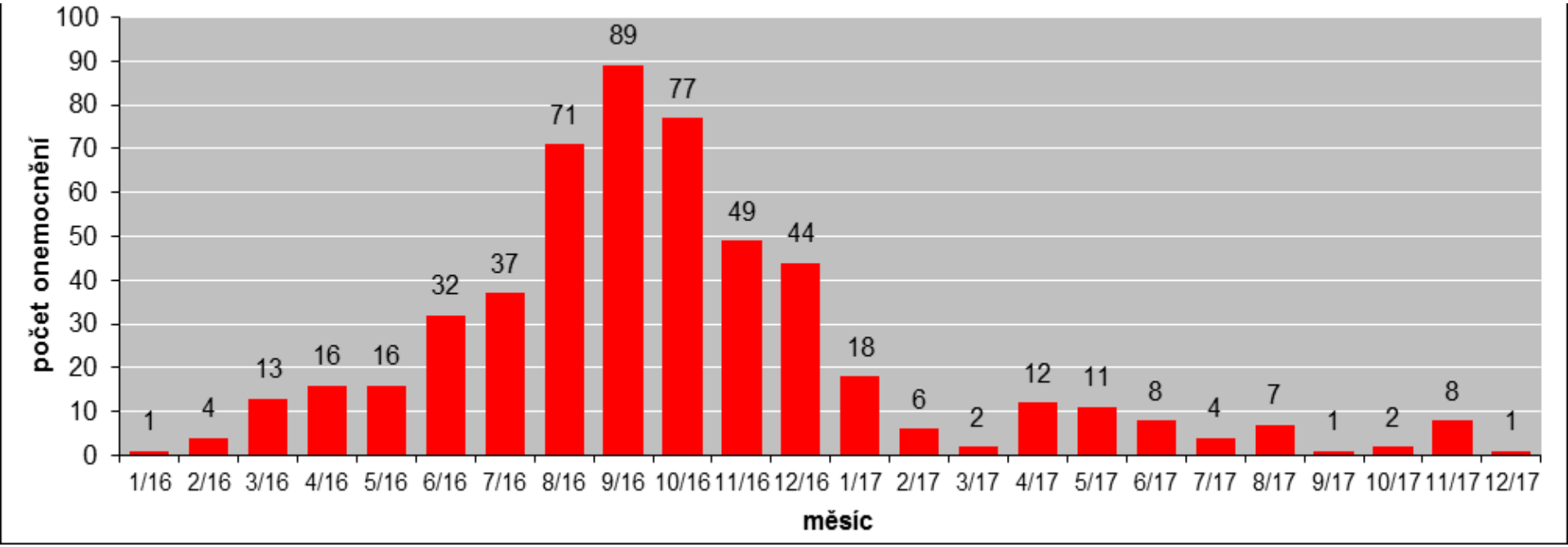


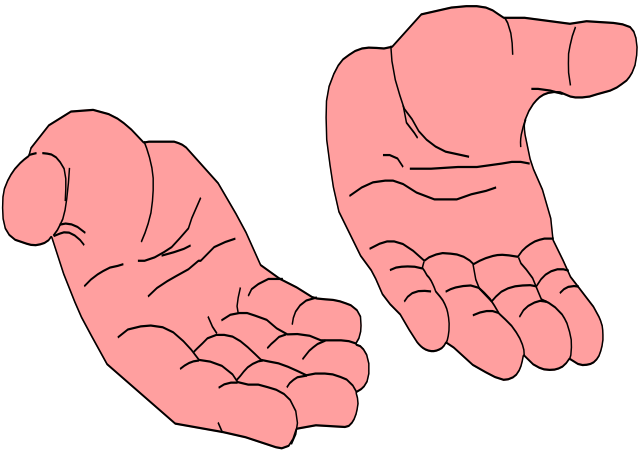

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers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

Data Source: World Health Organization.
Jacobsen KH, Wiersma ST. Hepatitis A virus seroprevalence by age and world region, 1990 and 2005. Vaccine 2010 Sep;28(41):6653-7
Map Production: Public Health Information and Geographic Information Systems (GIS)
World Health Organization

World Health Organization

# HAV epidemic in the South Moravia 2016-2017



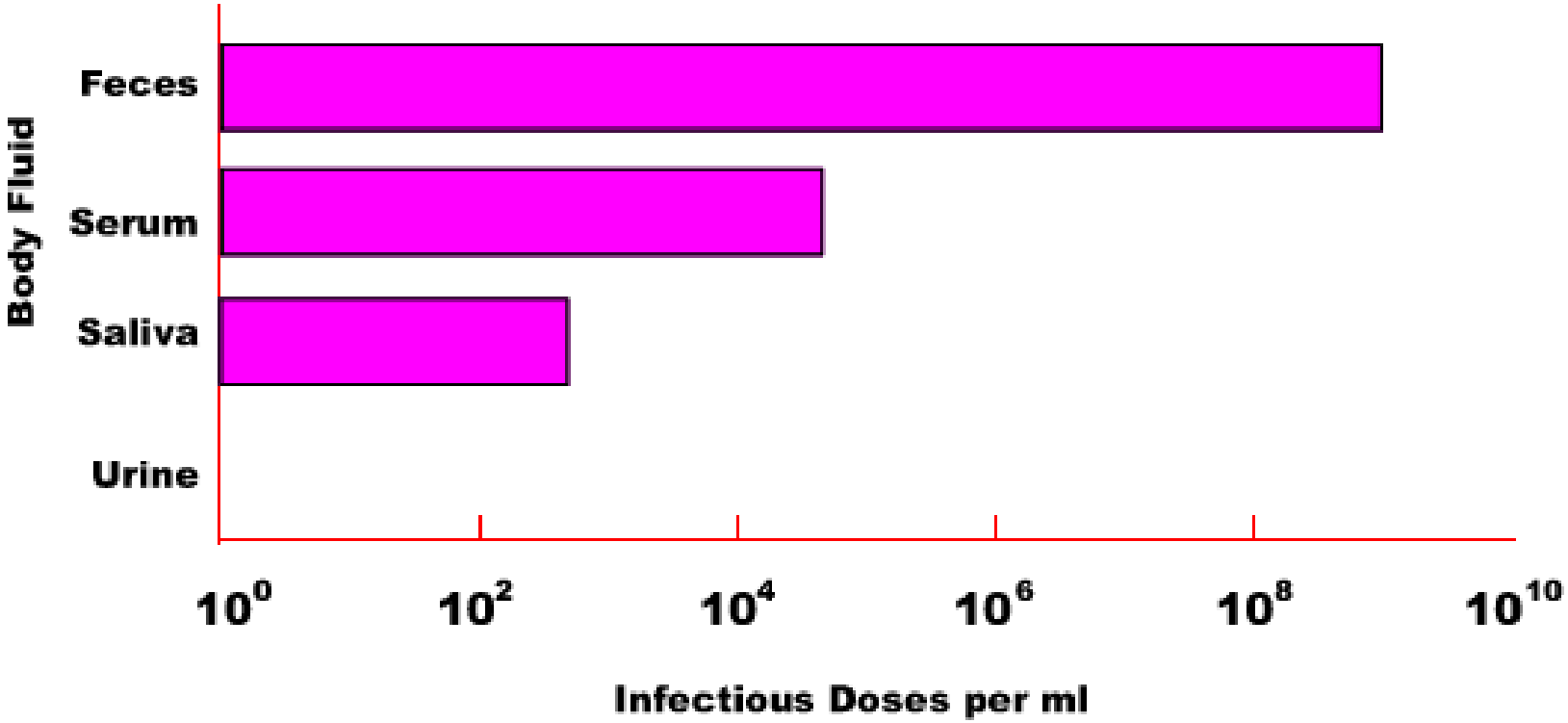


# Epidemiology

- 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

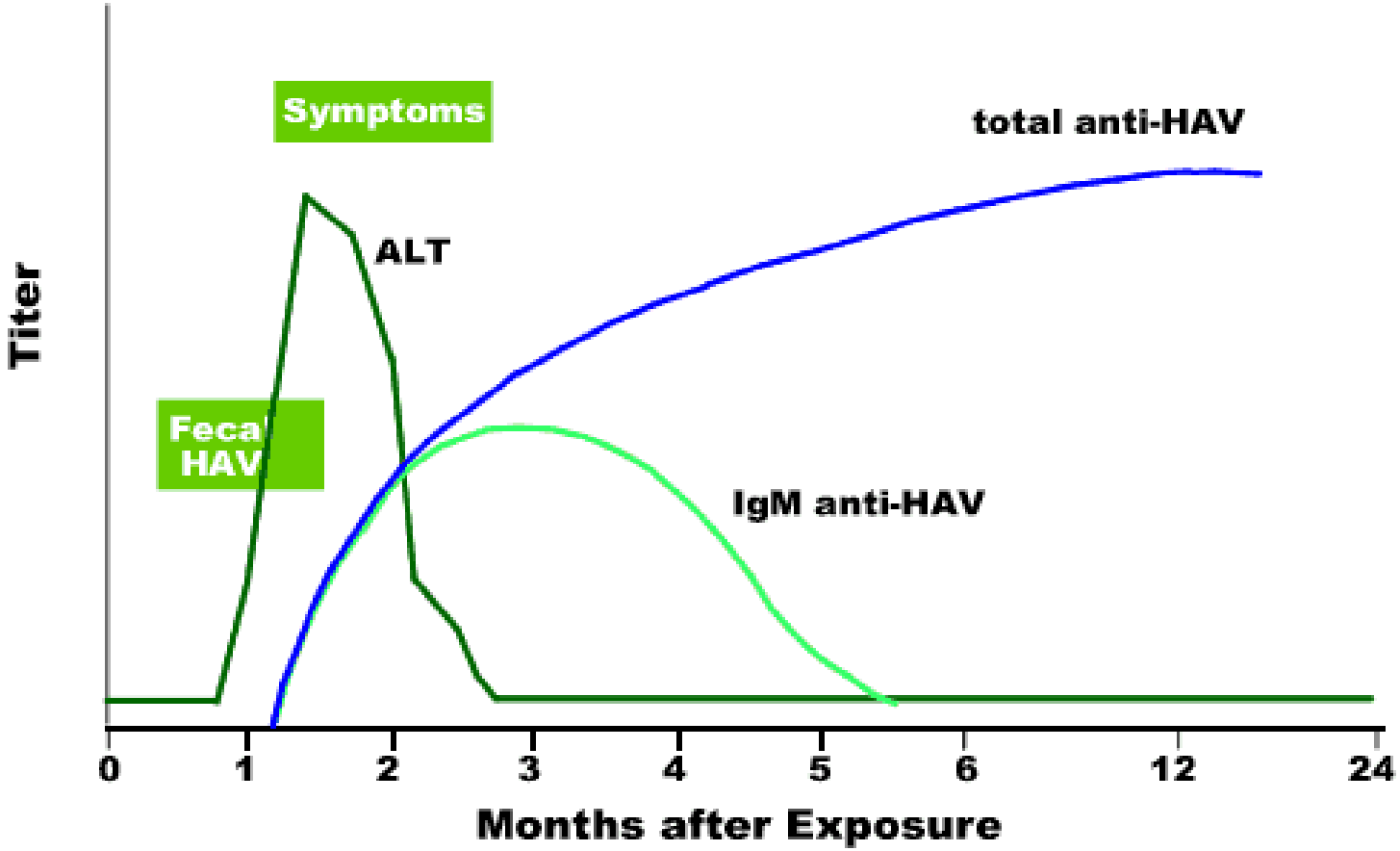
# Concentration of Hepatitis A Virus in Various Body Fluids



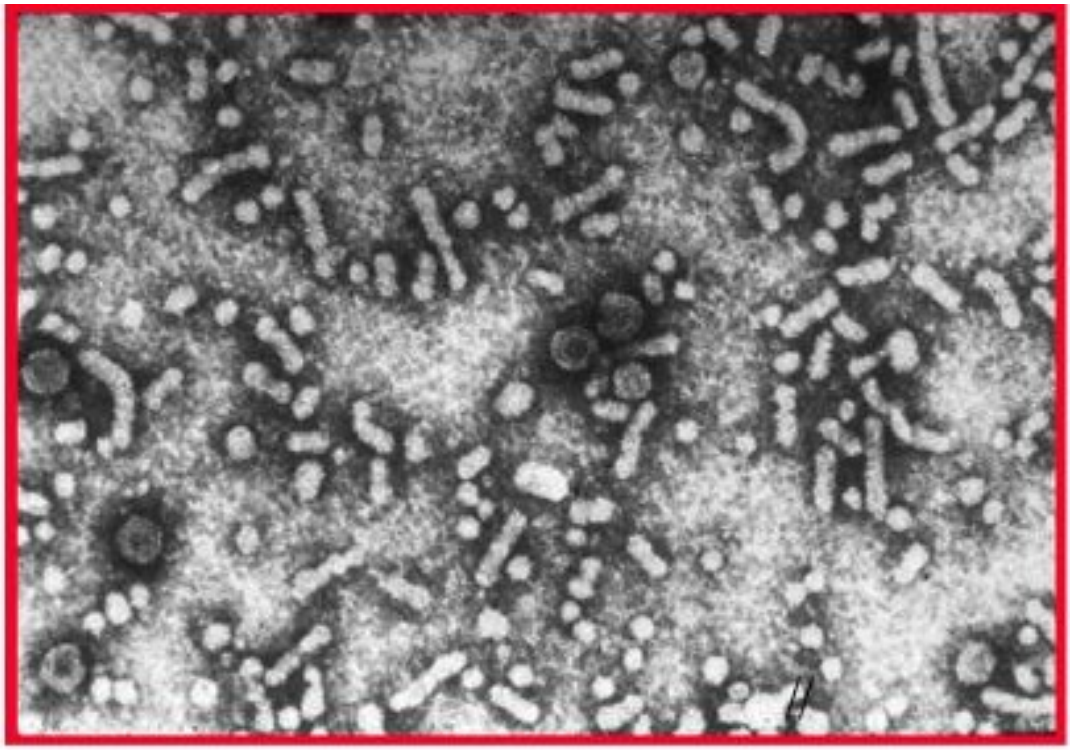

Source: Viral Hepatitis and Liver Disease 1984;9-2
J Infect Dis 1989; 160:887-890

# Hepatitis A Virus Infection

## Typical Serologic Course



# Hepatitis B Virus (HBV)



Family Hepadnaviridae, genus *Orthohepadnavirus*, enveloped DNA, 42 nm,
9 genotypes (A-I), Europe A,D, Asie B,C, several subtypes

# Global significance of HEP B

- One of the biggest global health problems

✓ More than 2 billions of infections during the life

✓ 240 million chronic carriers

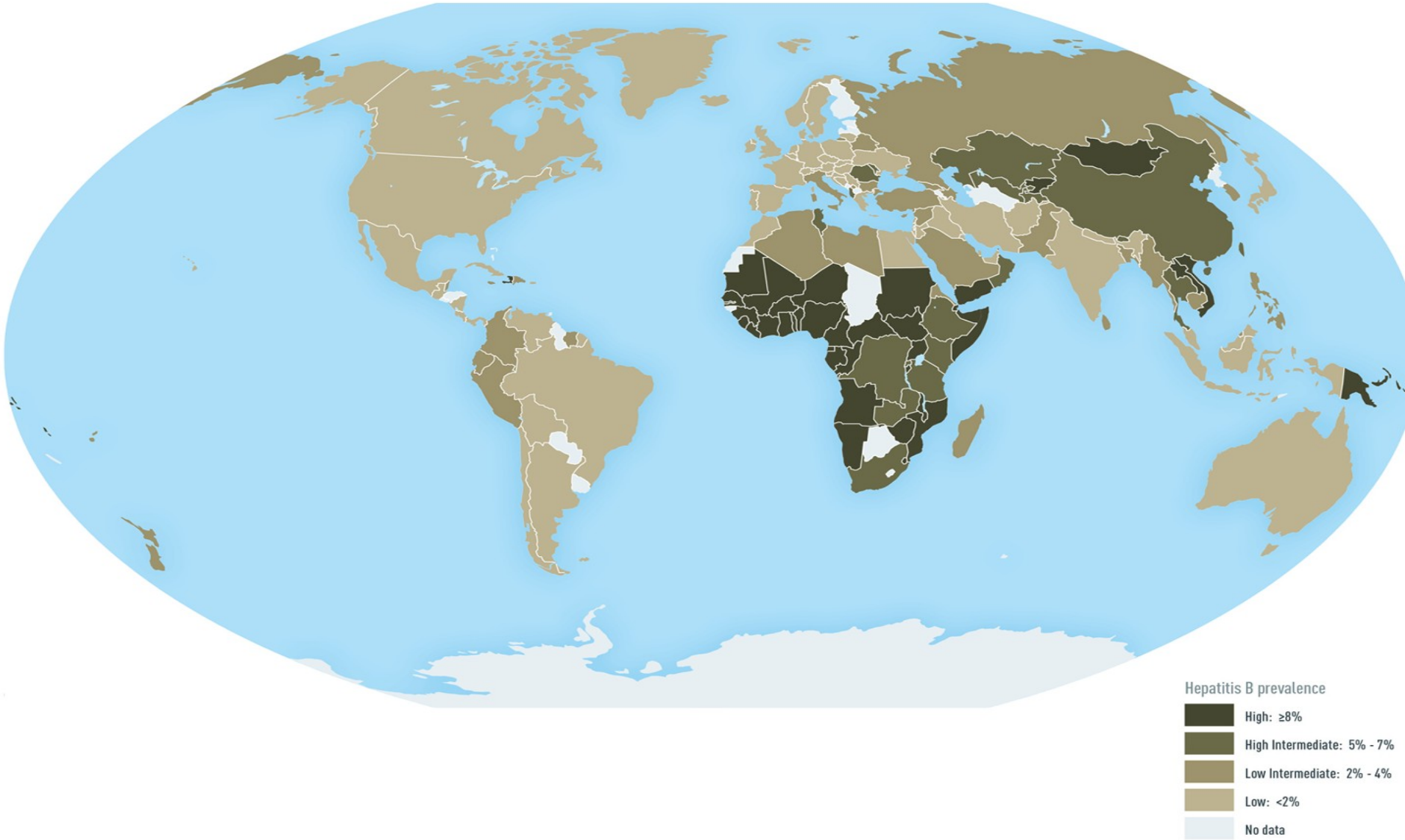
✓ 686 000 deaths anually due to LC or HCC (2013, increase about one third since 1990)

✓ Indication for 5-10 % liver transplantations globally

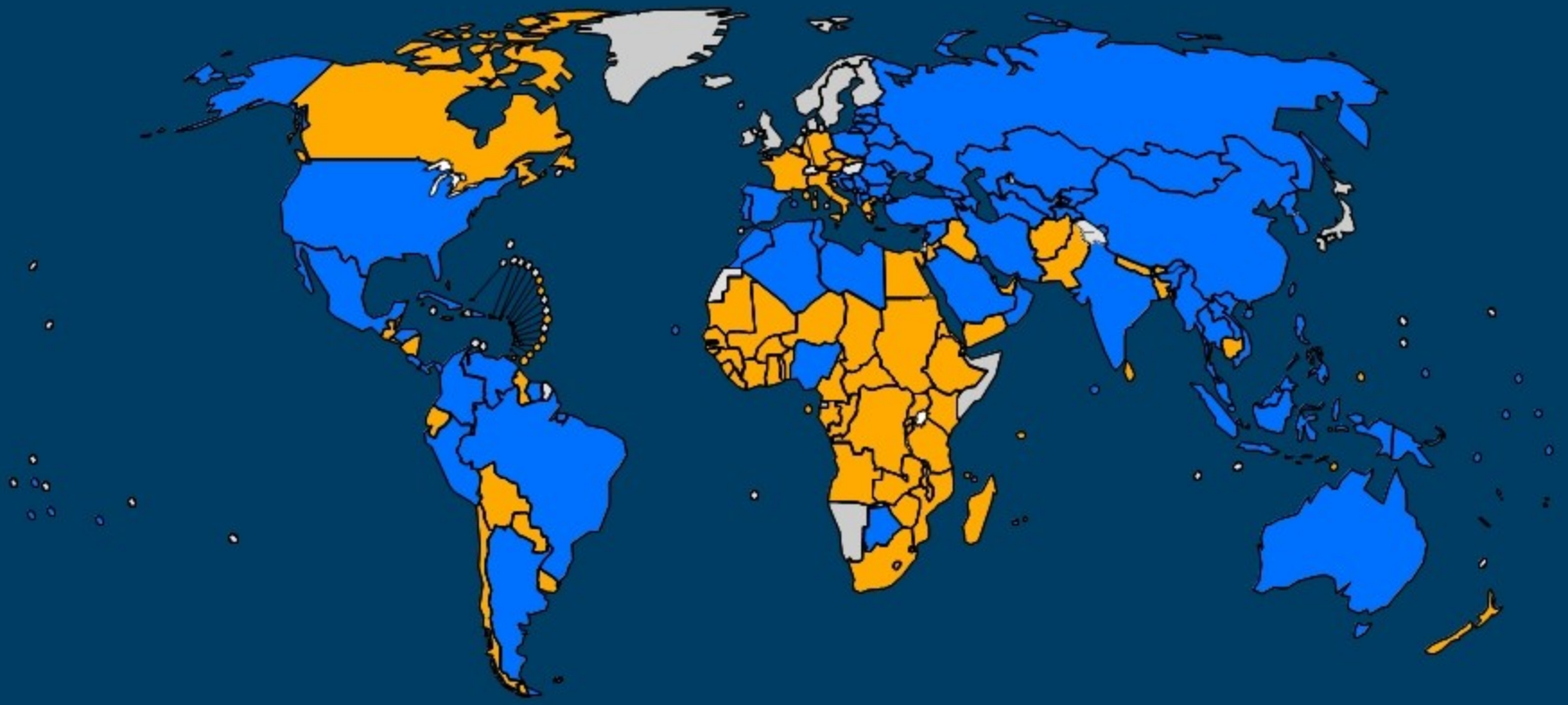
✓ 50 thousand death annually due to fulminant hepatitis

✓ Global vaccination in 177 countries

# Chronic HBV infection (CDC 2017)



# 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%)*

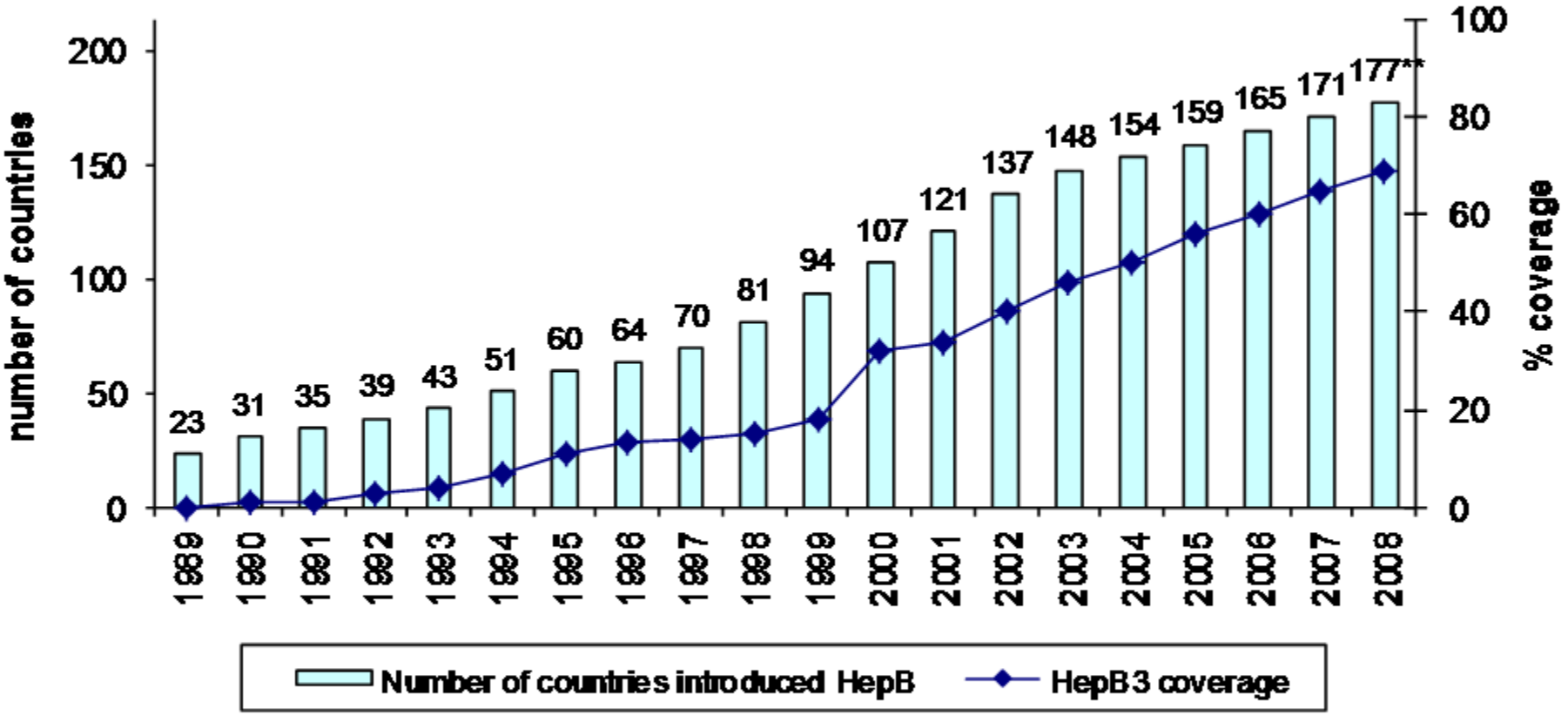
HepB with Birth Dose *(85 countries[3] or 44%)*

[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) …0,064 %(2013)
- ✓ 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 2001-2013, now only newborns (hexavaccine)

# Epidemiology of HBV

- HBV transmission

✓ sexual intercourse

✓ vertically from mother to newborn during delivery or in the last trimester

✓ sharing of instruments among IUDs

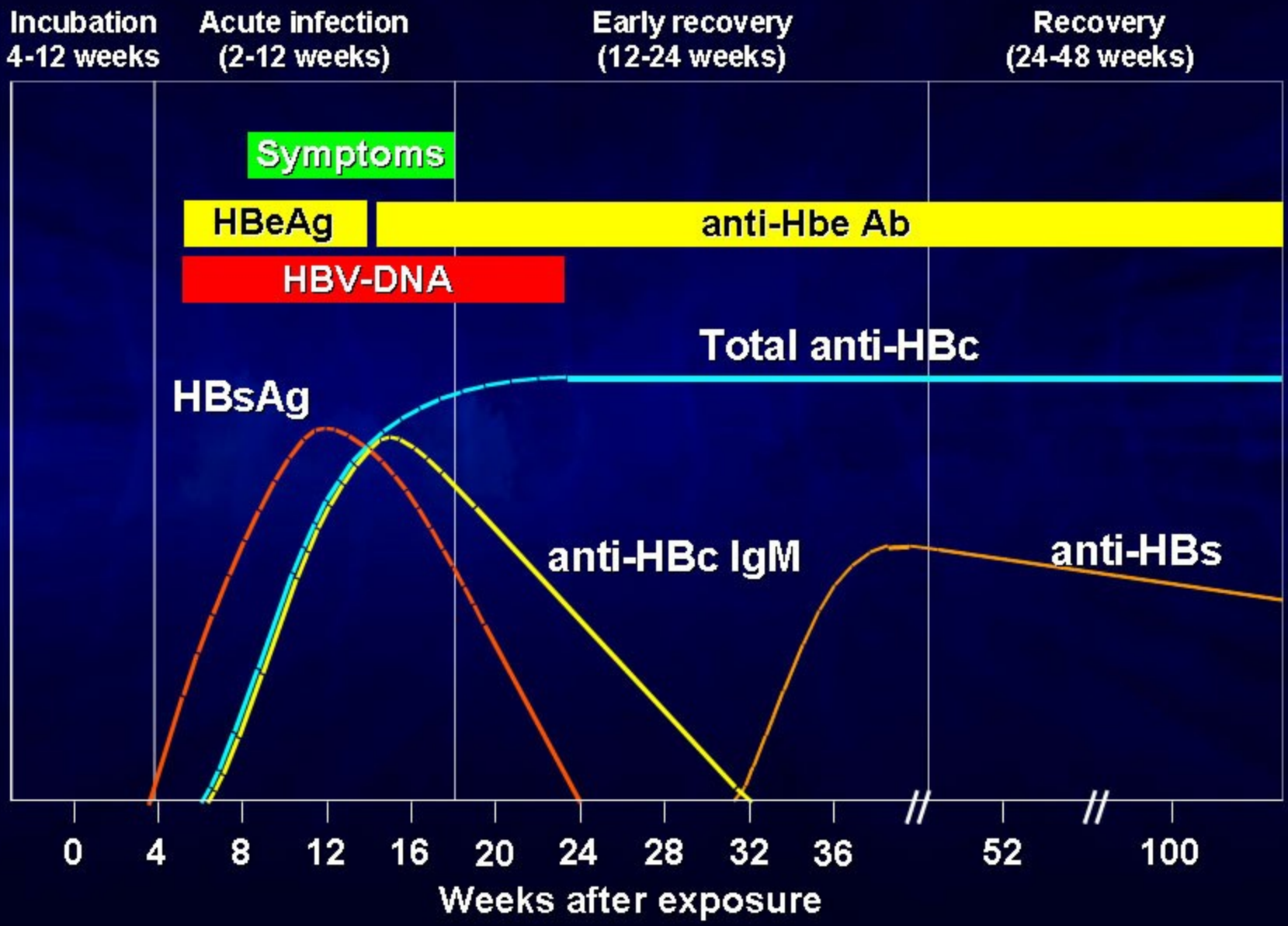
✓ blood and blood products

✓ organ and tissue transplant recipients

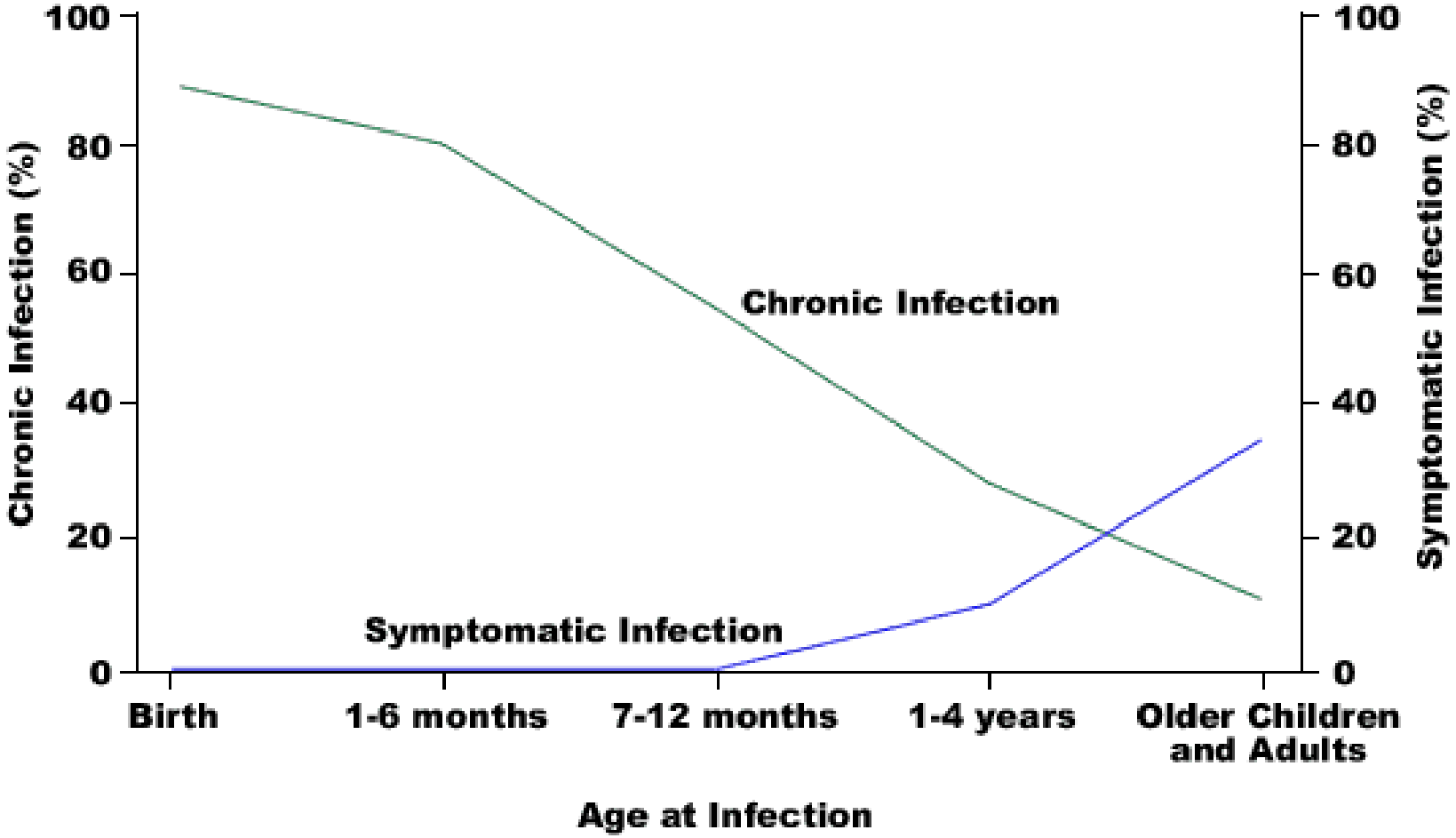
# Clinical findings in acute HEP B

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

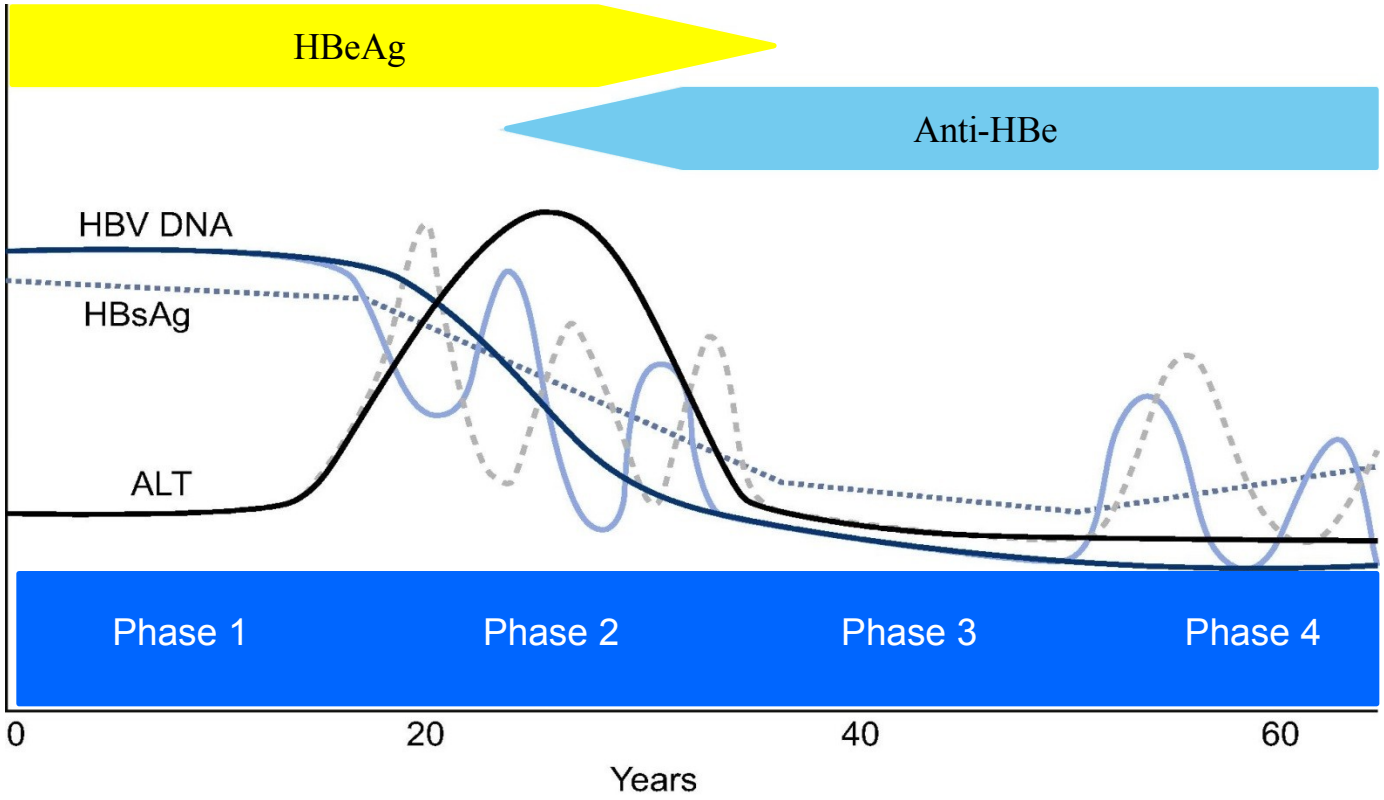
# Acute Hepatitis B



# Outcome of Hepatitis B Virus Infection by Age at Infection



# Phases of chronic HBV infection

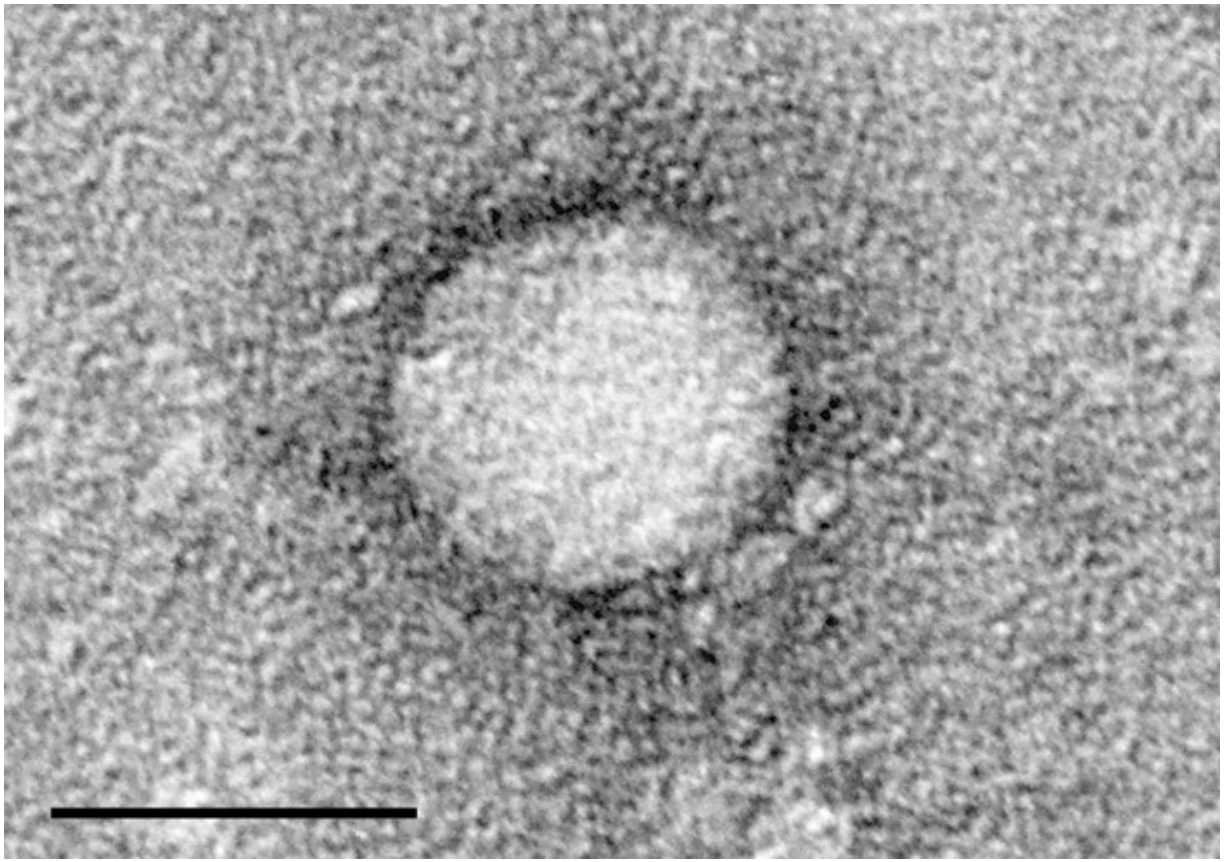



| **Nomenclature** | HBeAg-positive chronic HBV infection | HBeAg-positive chronic hepatitis | HBeAg-negative chronic HBV infection | HBeAg-negative chronic hepatitis |
|---|---|---|---|---|

treatment

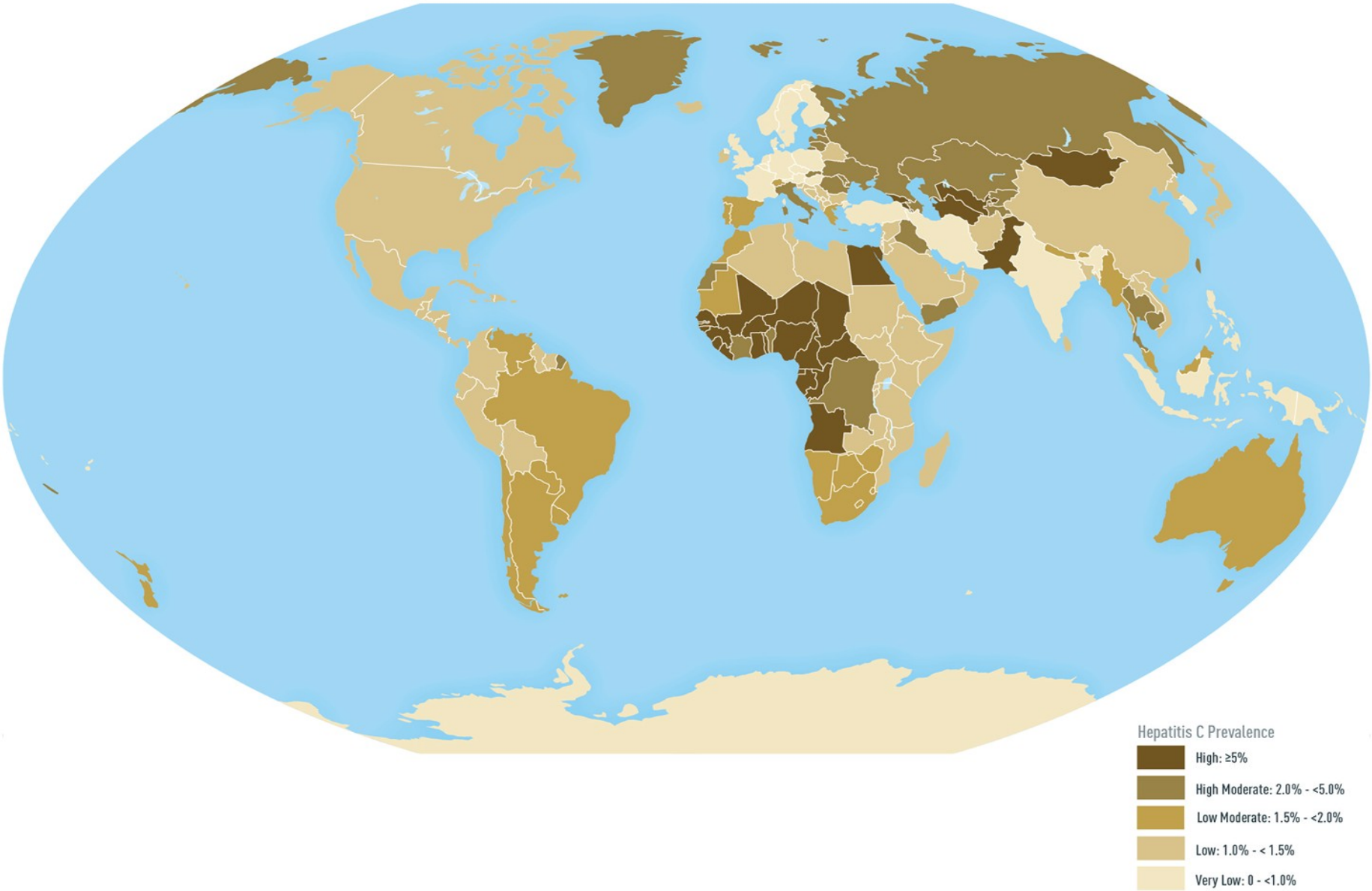
treatment

# Hepatitis C virus (HCV)



Family Flaviviridae, genus *Hepacivirus*, enveloped RNA virus 60 nm,
6 (7) genotypů (1-6), minimally 67 subtypes (a…)

# Chronic HCV infection (CDC 2017)



# Distribution of HCV genotypes

# Hepatitis C

- Significant global health problem

✓ 70-80 million persons worldwide 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), current estimations 0.4-0.5 %

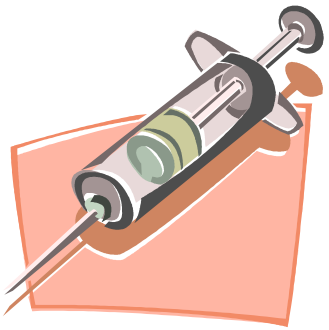
- No vaccine, no hyper-immune immunoglobulin

# Epidemiology of HEP C

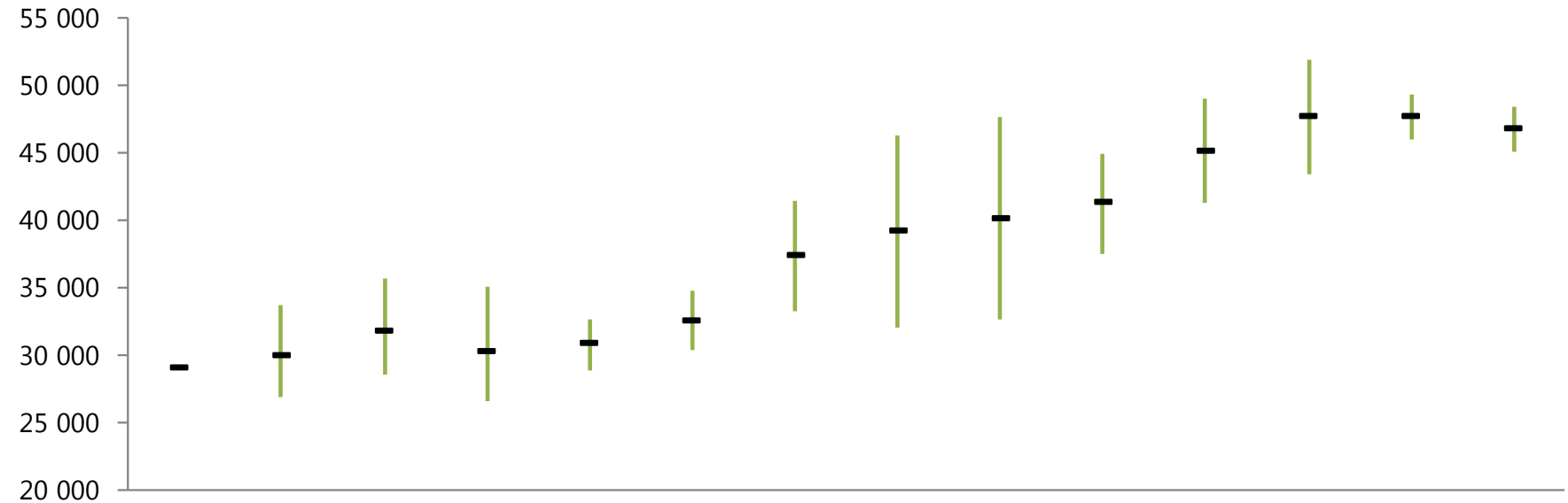
- Transmission:
  - ✓ blood and blood products
  - ✓ sharing of used injection needles and syringes
  - ✓ sexually (rare)
  - ✓ vertically (rare)
- Who is in the highest risk of HCV infection at present?
  - ✓ intravenous drug abusers
- Infection is frequently diagnosed in chronic stage

# 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



# Problematic IUDs (pervitin and opioids)

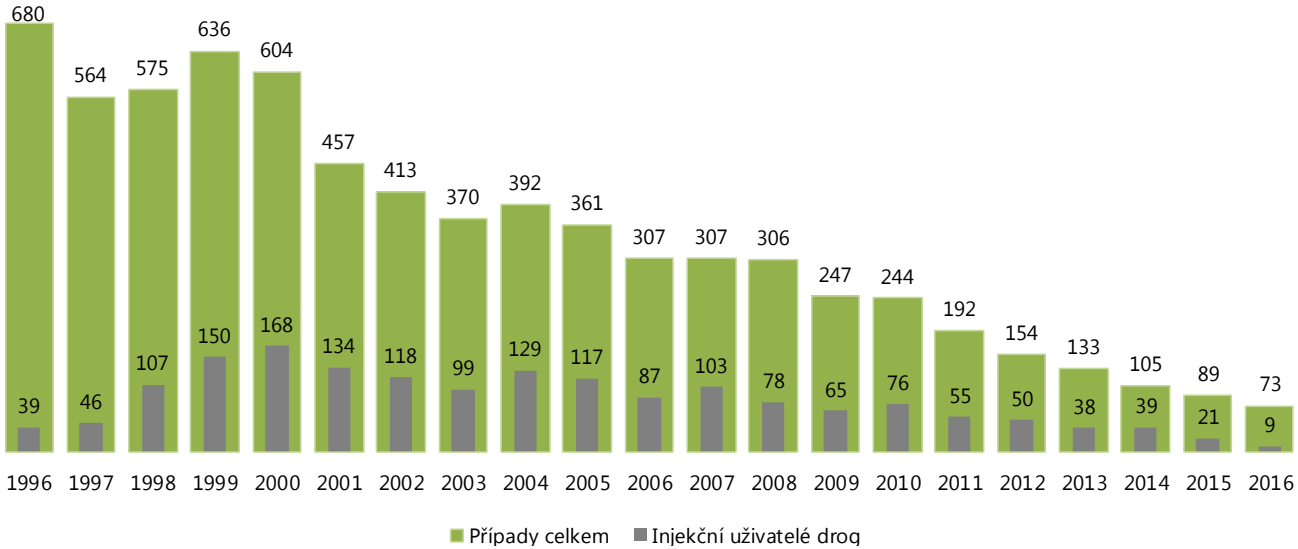



| | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015* | 2016 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 95% CI dolní | | 26 900 | 28 600 | 26 500 | 28 900 | 30 400 | 33 300 | 32 000 | 32 700 | 37 500 | 41 300 | 43 400 | 46 000 | 45 100 |
| 95% CI horní | | 33 700 | 35 700 | 35 100 | 32 700 | 34 700 | 41 500 | 46 300 | 47 700 | 45 000 | 49 100 | 51 900 | 49 400 | 48 400 |
| Střední odhad | 29 000 | 30 000 | 31 800 | 30 200 | 30 900 | 32 500 | 37 400 | 39 200 | 40 200 | 41 300 | 45 200 | 47 700 | 47 700 | 46 800 |

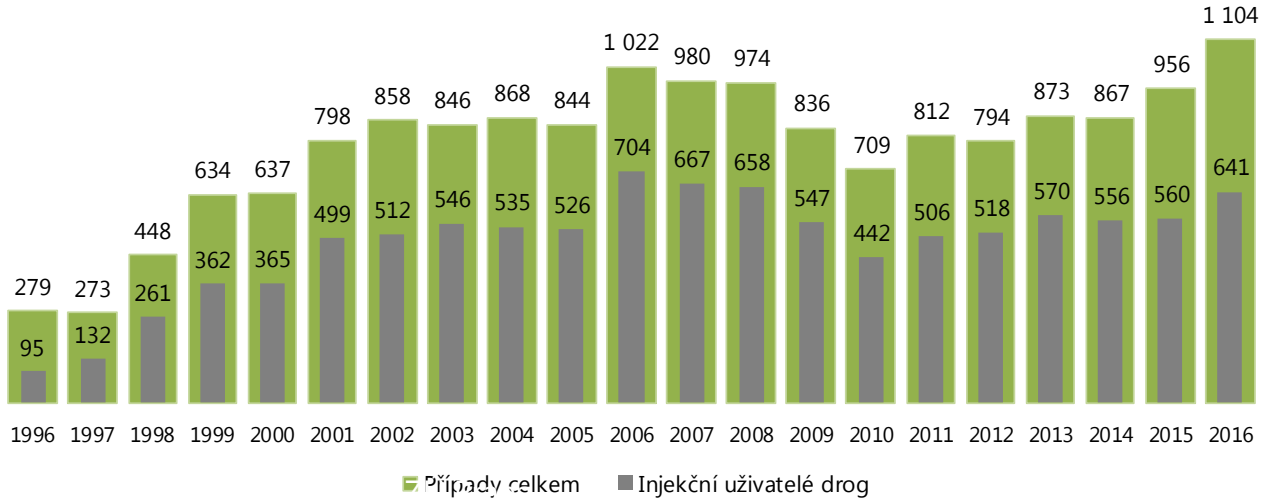
# Problematic IUDs (pervitin and opioids) - 2016

# Infectious diseases in IUDs – new cases 1996-2016

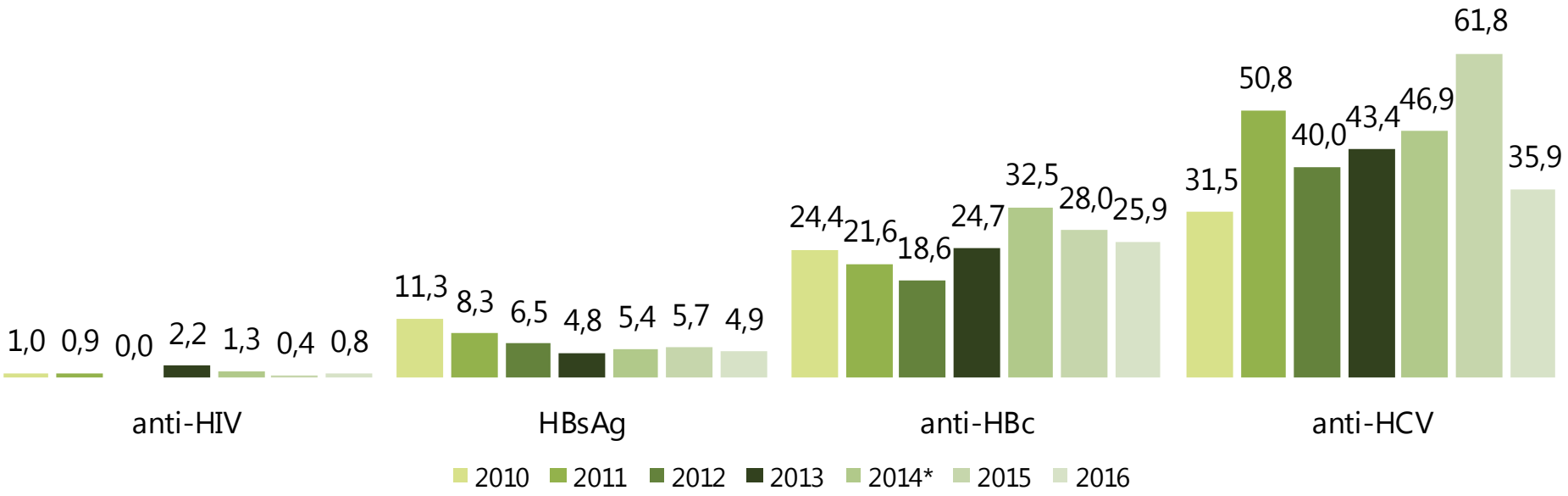
*Acute HBV*




*Acute and chronic HCV*



# Infectious diseases in IUD in prison (%)



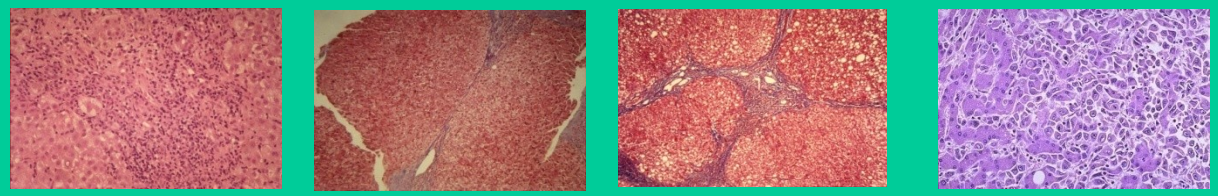
# Clinical course of HCV infection

Slow

> 30 years

80% 80% 20% 1-5%/year

Acute infection → Chronic infection → Chronic hepatitis → Cirrhosis → HCC



0.....1.....2.....3.....4

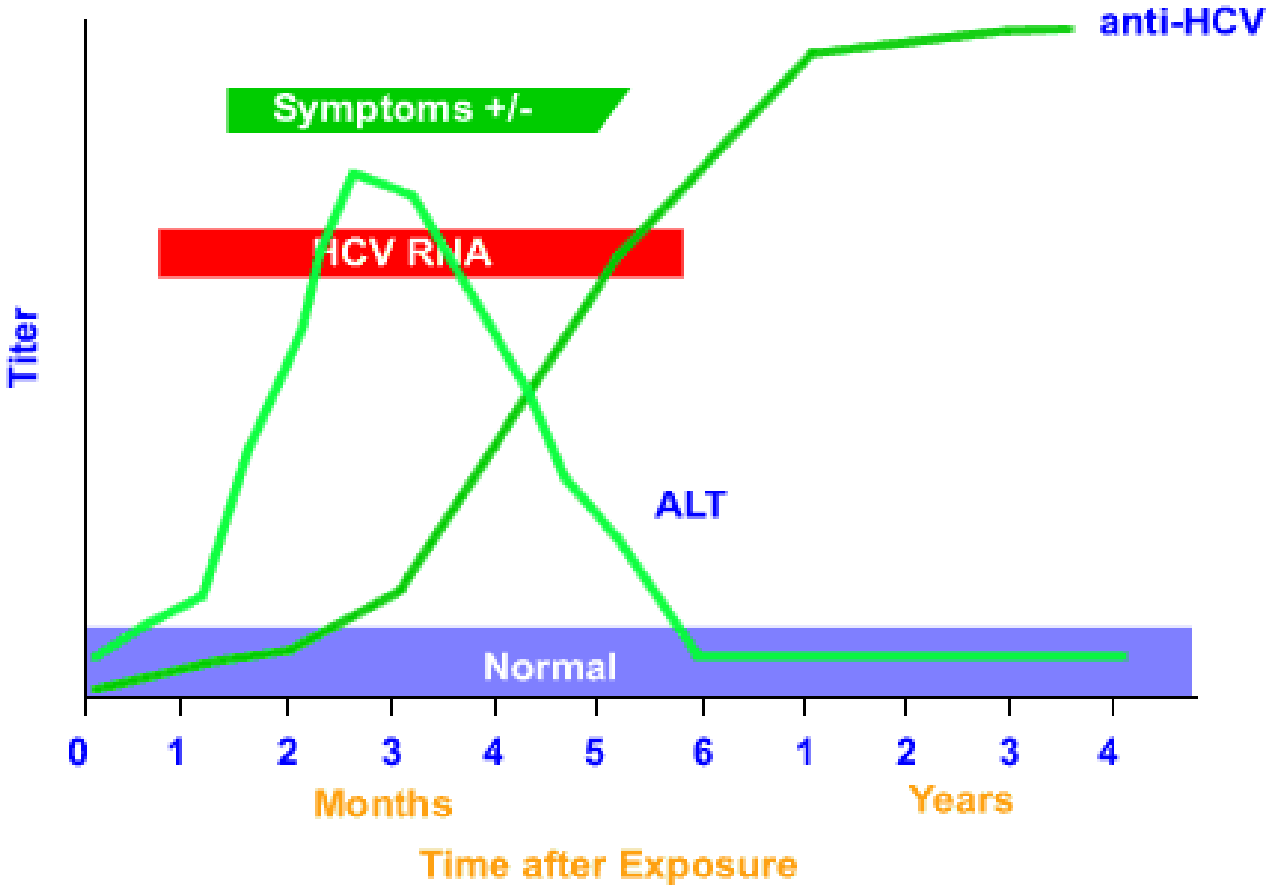
Fibrosis

Rapid

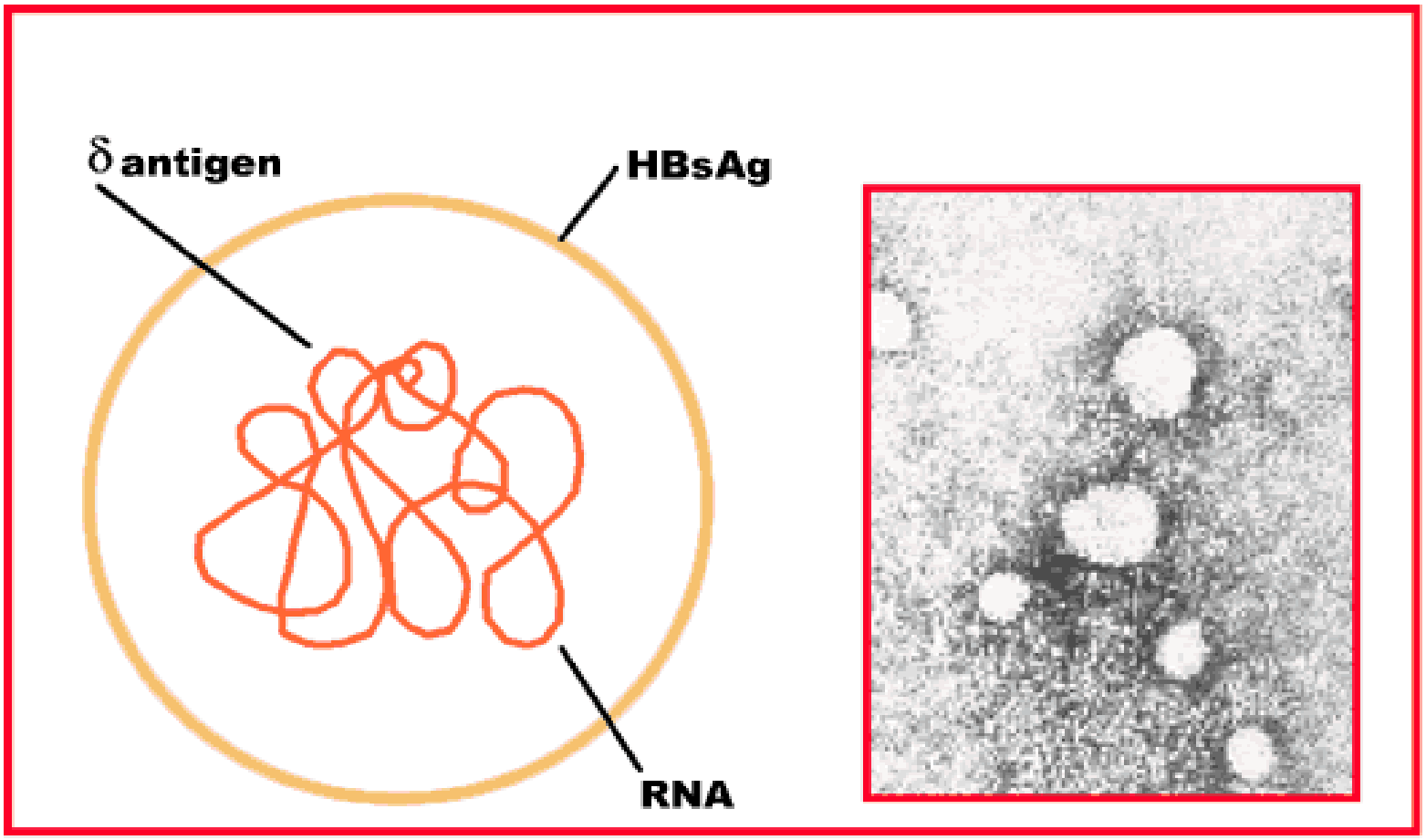
< 20 years

*Alcohol, co-infection (HBV,HIV),*

# Diagnosis of HCV infection



# Hepatitis D Virus (HDV)

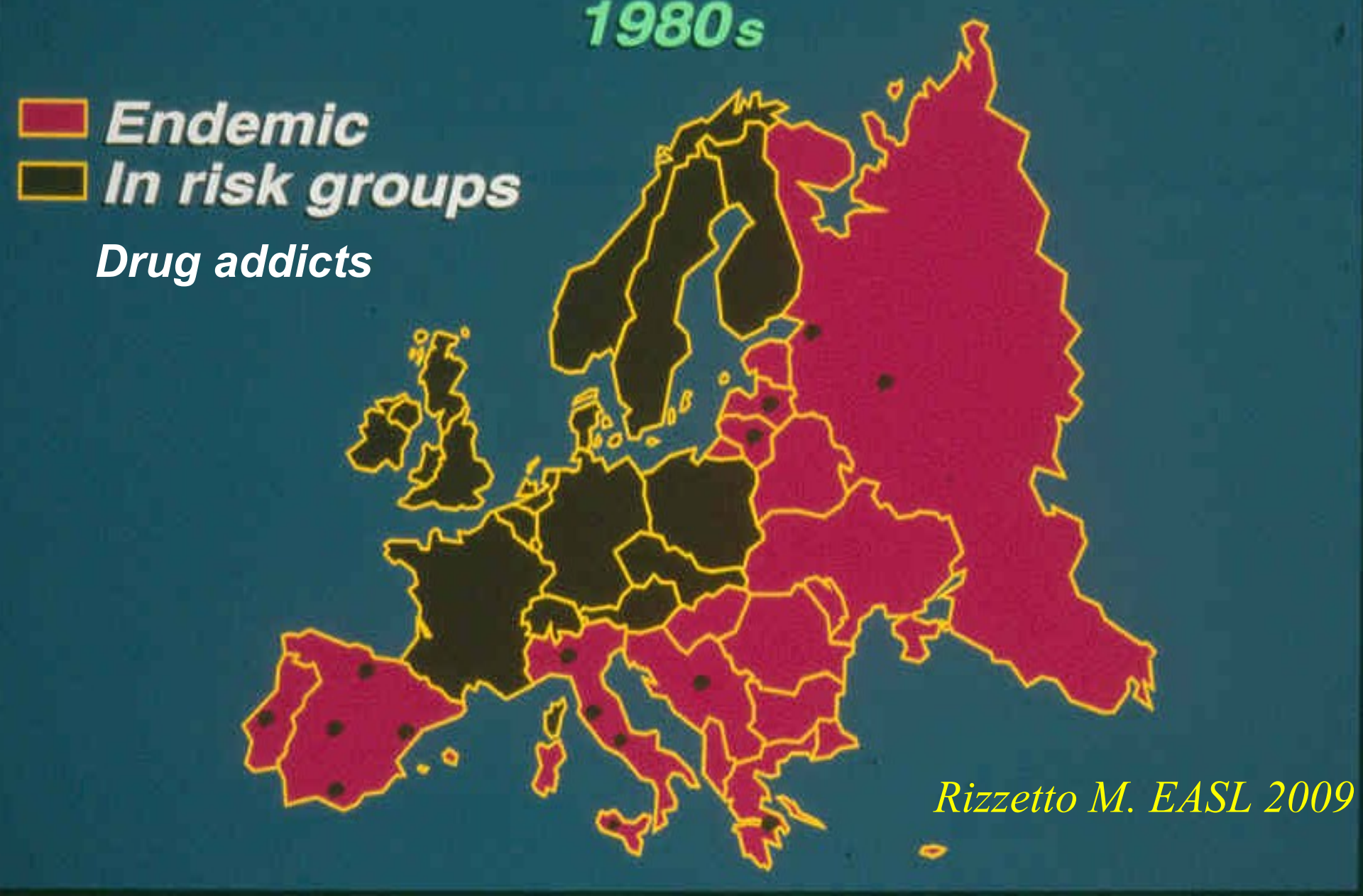



Satelite virus, family Deltaviridae, genus *Deltavirus*, enveloped RNA, 36 nm, 8 genotypes (I-VIII), genotype 1 the most common worldvide

# Hepatitis D

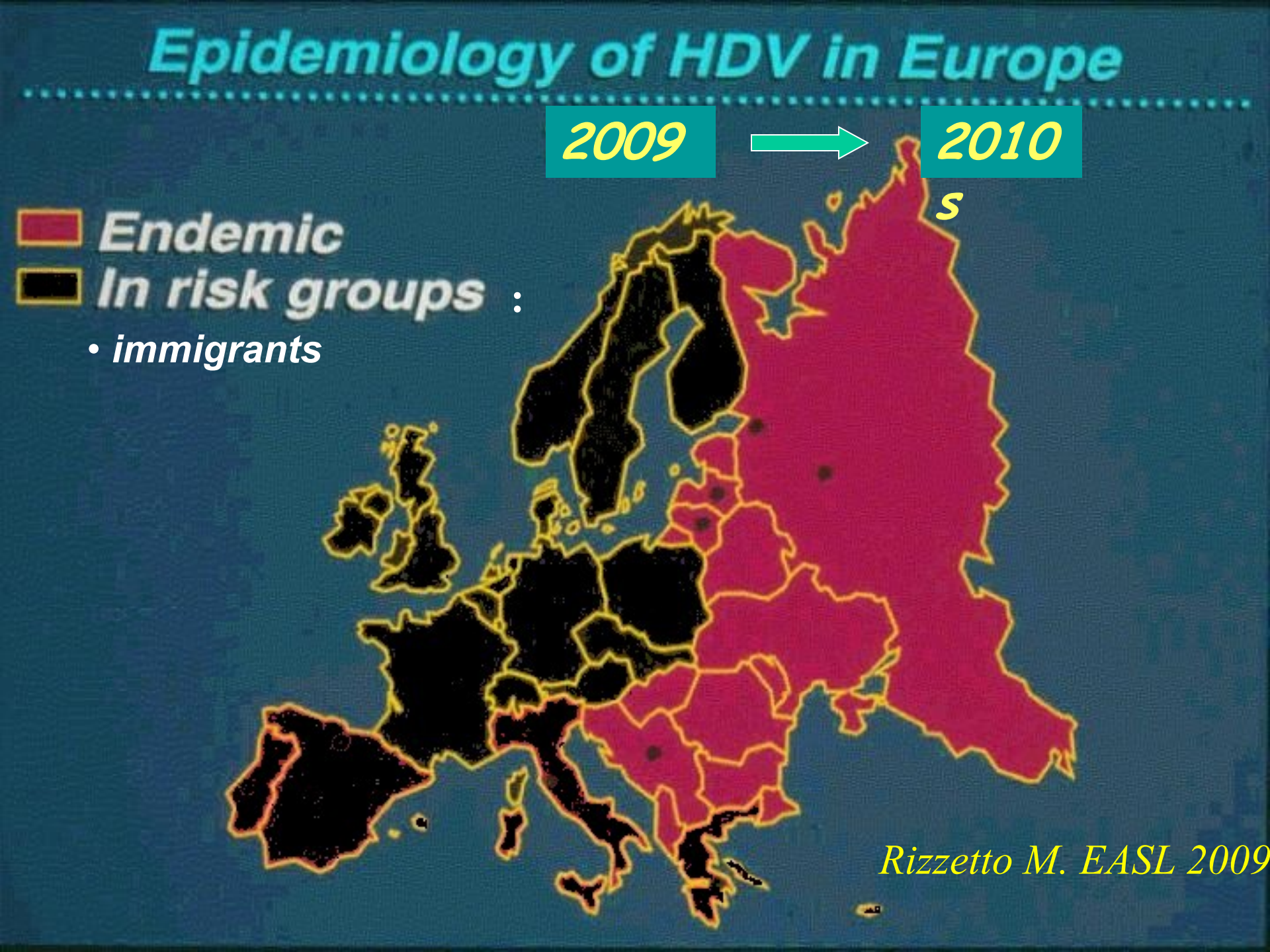
- Ability of replication only in presence of HBV infection (vaccination against HBV is potent against HDV as well)
- ✓ Co-infection (better prognosis)
- ✓ Super-infection (worse prognosis)
- Globally gradually decreasing HDV prevalence due to massive vaccination against HBV
- Very low prevalence in CR

# Epidemiology of HDV in Europe




*Rizzetto M. EASL 2009*

# Epidemiology of HDV in Europe



# Significant incidence and prevalence (since 2006)

PAKISTANI[1]

INDIA[2]

MONGOLIA[3]

IRAN[4]

VIETNAM[5]

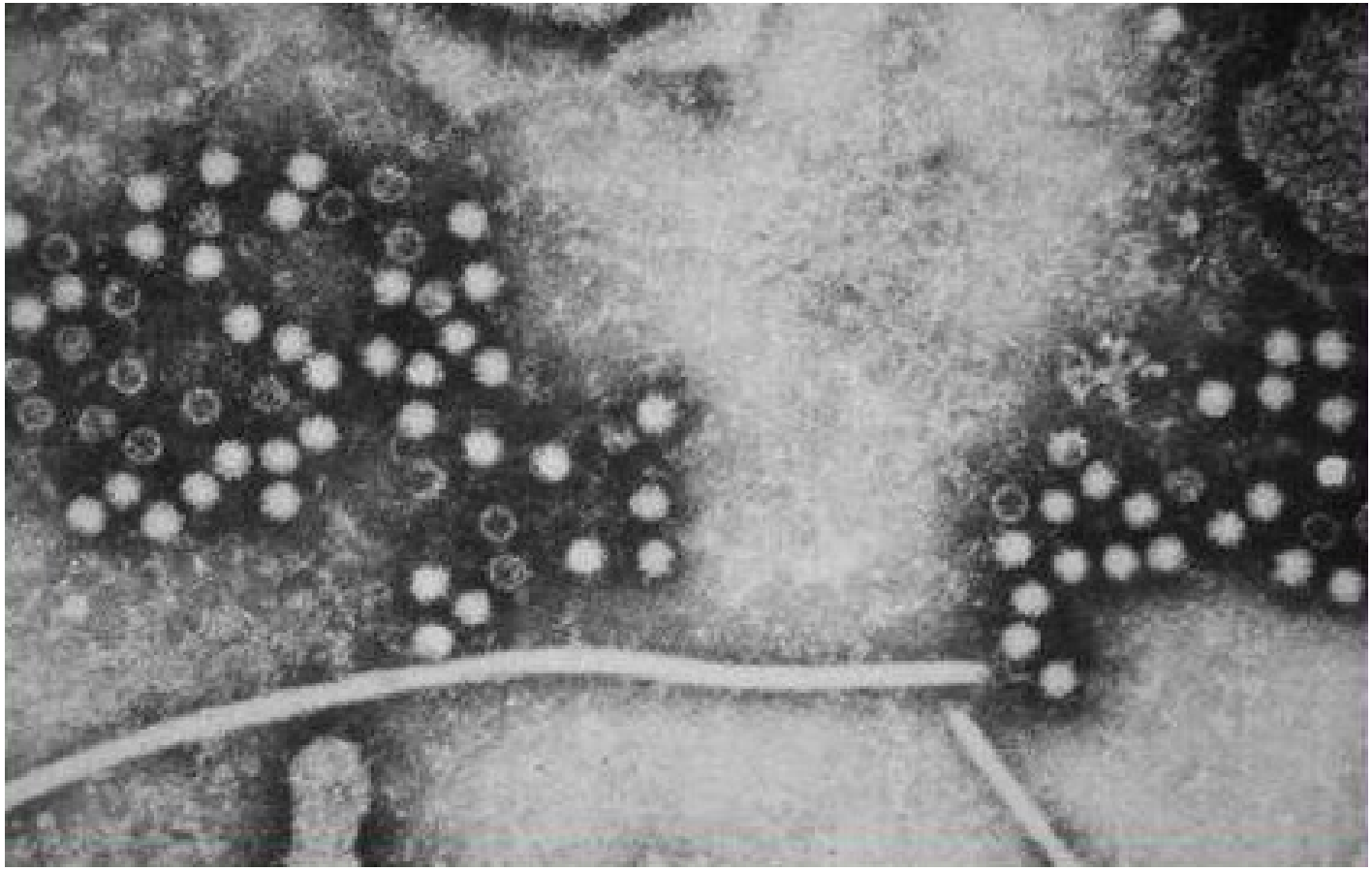
TAJIKISTAN[6]

TUNISIA[7]

MAURETANIA[8]

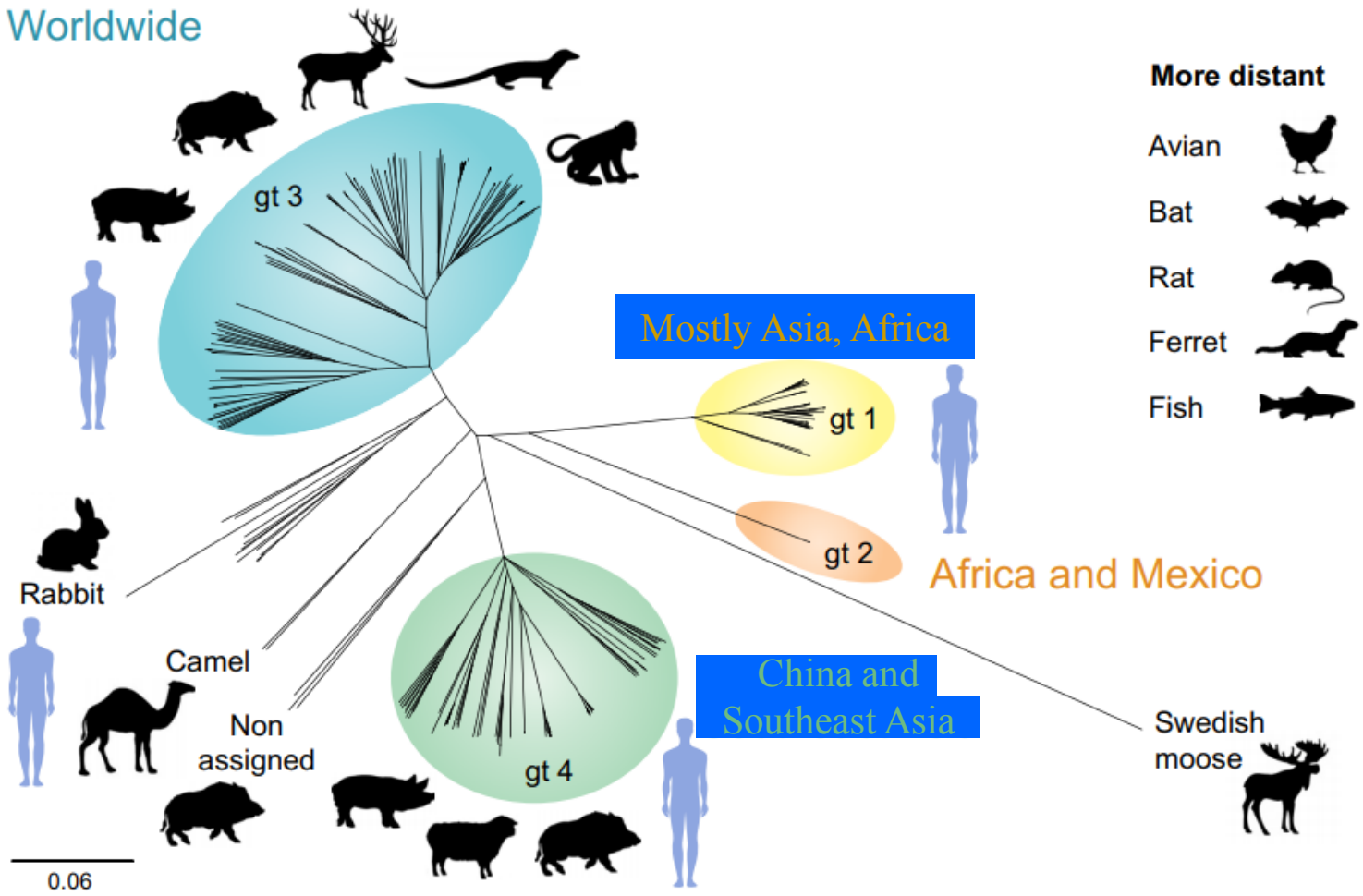
*1. Zuberi BF, 2006; 2. Acharya SK, 2006; 3.Tsatsralt-Od B, 2006; 4. Roshandel G, 2007; 5. Nguyen VT, 2007; 6. Khan A, 2008; 7. Djebbi A, 2009; 8. Lunel F, personal communication*

# Hepatitis E virus



Non-enveloped RNA virus, family Hepeviridae, *genus Orthohepevirus,* 27-34 nm, 8 genotypes (1-8), human infections by G1-4

# Phylogenetic relationship of hepeviruses identified in various hosts




Debing Y, et al. J Hepatol 2016;65:200–12

# HEV genotypes

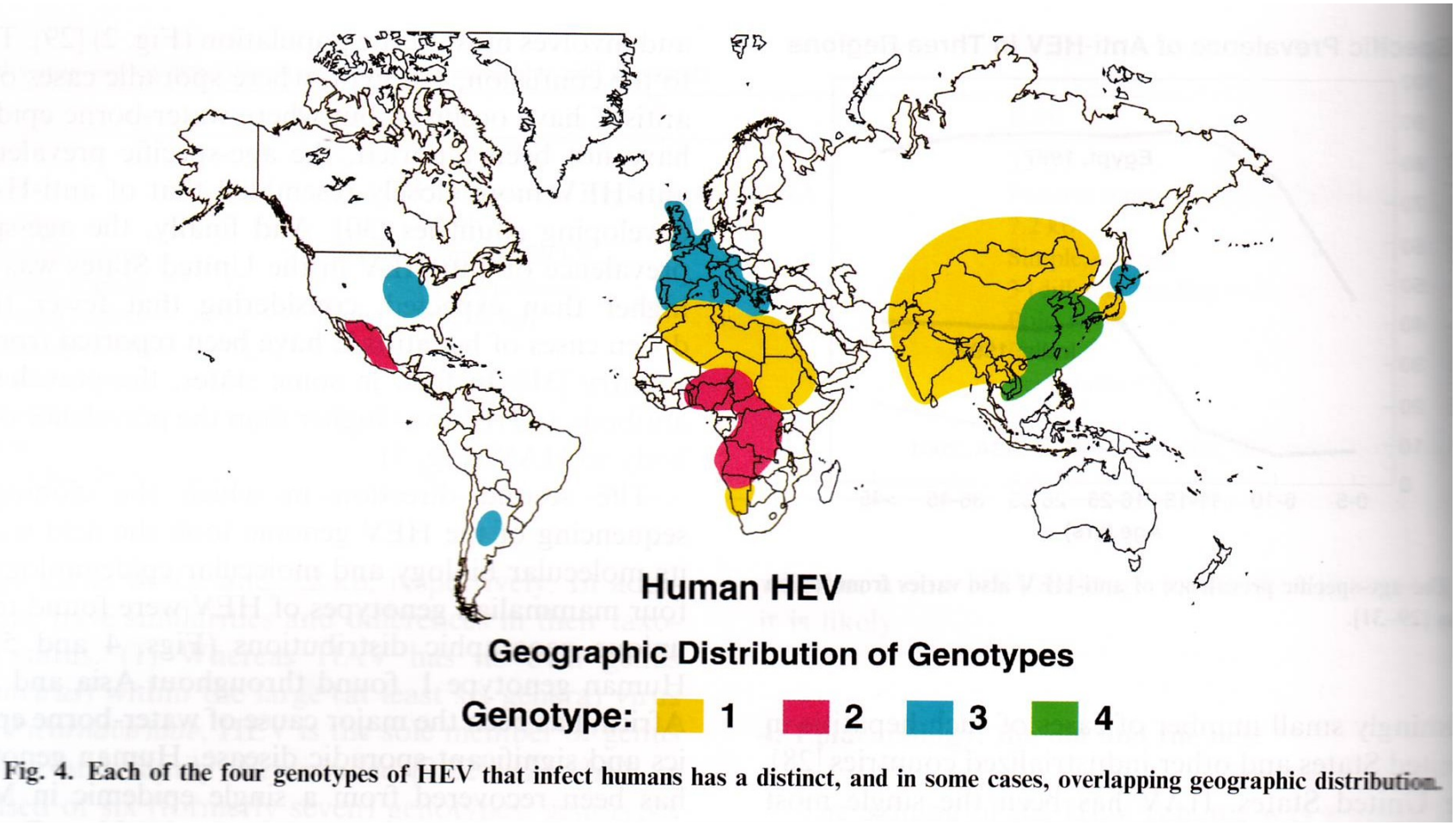



Fig. 4. Each of the four genotypes of HEV that infect humans has a distinct, and in some cases, overlapping geographic distribution.

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

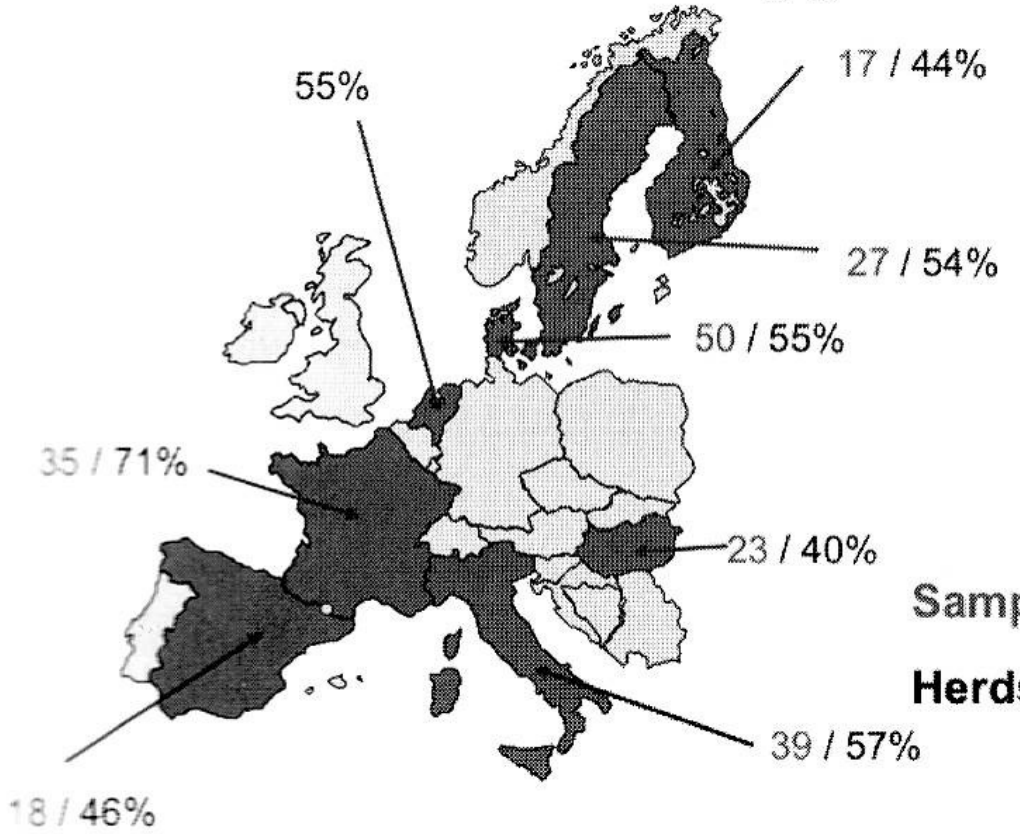
# Infection with G-1,2 HEV

- Only human infection
- Mostly Asia, Africa
- Extremely serious clinical course in late pregnancy (mortality about 25 %)
- No chronicity
- Possibility of acute-on-chronic liver failure

# Infection with G-3,4 HEV

- Both human and zoonotic infection
- Pigs are the main reservoir
- G-3 – worldwide distribution, G-4 – China a southeast Asia
- ≥ 2 million locally acquired HEV infections/year in Europe (G-3), mostly asymptomatic (minimally 95 %), tend to affect older males
- Possibility od chronic infection in persons with immunosuppression (after solid organ transplantation 50-66% probability of chronicity, patients with haematological disorders, individuals living with HIV, patients with rheumatic disorders receiving heavy immunosuppression)
- High mortality in patients with liver cirrhosis (60-70 %) - acute-on-chronic liver failure

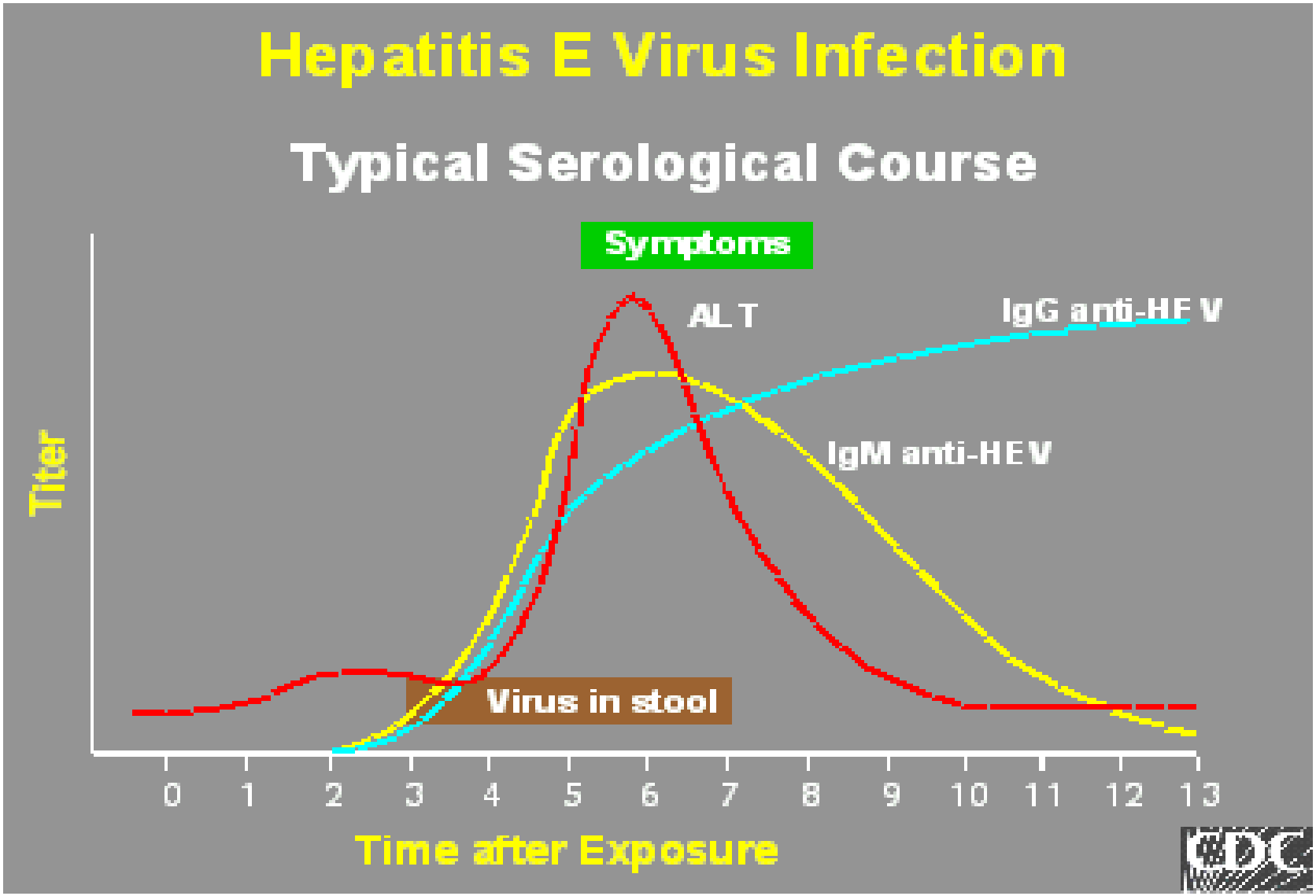
Prevalence of HEV in swine herds (pigs 1 to 5 months of age)




**Samples: Avg = 32%**

**Herds: Avg = 52%**

# Figatellu – sausage with raw pork liver


Hepatitis E Virus Infection
Typical Serological Course
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
Time after Exposure

# Rapid progression of chronic hepatitis E

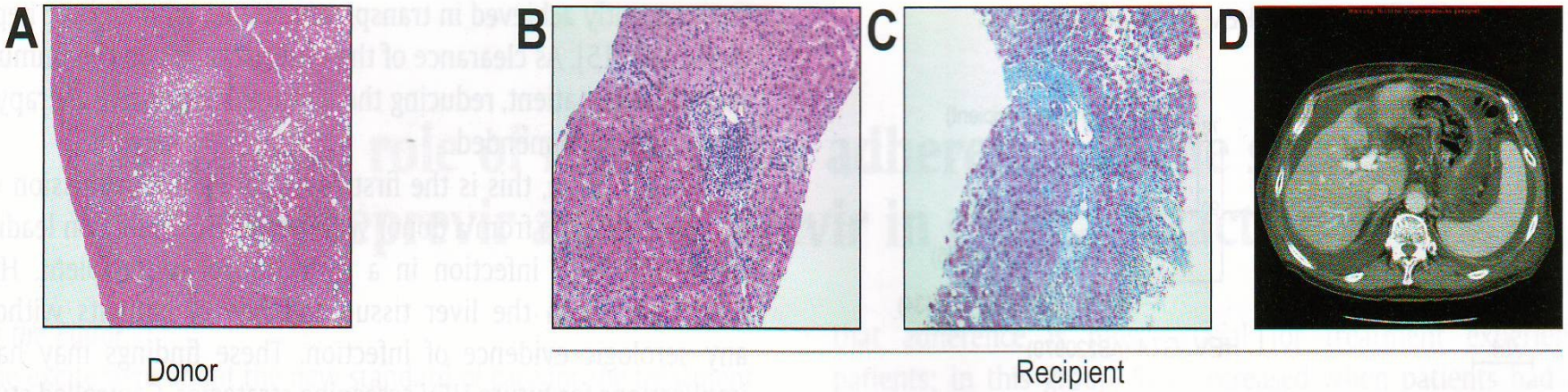



**Fig. 1. Histologic assessment of the liver tissue before and after OLT and CT scan after OLT.** (A) The liver tissue of the donor revealed absence of significant signs of chronic hepatitis but vesicular fatty liver disease was diagnosed. (B) Second biopsy. One hundred and fifty days after OLT, chronic 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 hepatitis types

✓ physical and mental rest

✓ no alcohol, no hepatoxic drugs

✓ diet (?)

✓ supportive treatment (silymarin, essential phosholipids) (?)

# Therapy of acute HEP B

- Antiviral therapy is indicated only in serious (INR > 1,5) or prolongated (pronounced icterus > 4 weeks) clinical course od acute hepatitis B
- Therapy only with oral virostatics (NA)

✓ tenofovir disoproxil
✓ entecavir
✓ tenofovir alafenamid (?)
✓ lamivudin

- Interferon alfa (standard or pegylated) is absolutely contra-indicated – danger of acute liver failure!

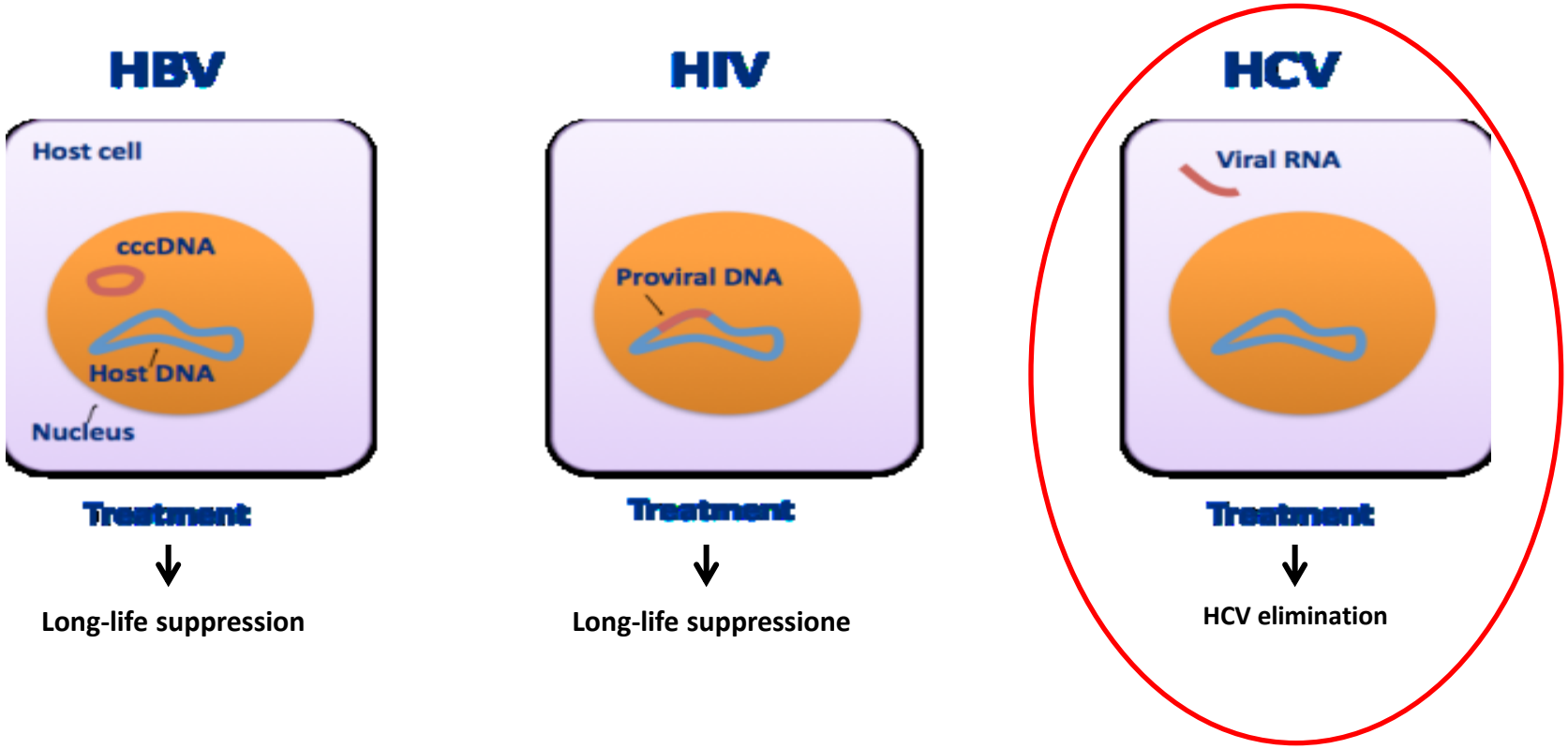
# Current possibilities of treatment of chronic HEP B

- tenofovir disoproxil or alafenamide – both for naive and lamivudine-resistant patients
- entecavir – for naive patients
- pegylated interferon alfa-2a – 48 weeks

# IFN-free regimens for HCV infection

- Current standard of HCV therapy
- Combination of oral drugs – DAA – direct-acting antivirals
- High efficacy – minimally 95 %
- Almost no adverse events
- Short duration of therapy – 8-12 weeks

# HCV infection is curable in majority of patients




- SVR – sustained virological response = the definite eradication of HCV infection

1. Pawlotsky JM. J Hepatol 2006;44:S10–3; 2. Siliciano JD, et al. J Antimicrob Chemother 2004;54:6–9; 3. Lucas GM. J Antimicrob Chemother 2005;55:413–6; 4. van der Meer AJ, et al. JAMA 2014;312:1927–8; 5. Burki T. Lancet Infect Dis 2014;14:452–3

# Direct Acting Antivirals against HCV

| Lék | zkratka | třída |
|---|---|---|
| Glecaprevir | GLE | NS3/4A protease inhibitor |
| Pibrentasvir | PIP | NS5A inhibitor |
| Voxilaprevir | VOX | NS3/4A protease inhibitor |
| Daclatasvir | DCV | NS5A inhibitor |
| Dasabuvir | DSV | Non-nucleoside NS5B polymerase inhibitorázy |
| Elbasvir | EBR | NS5A inhibitor |
| Grazoprevir | GZR | NS3/4A protease inhibitor |
| Ledipasvir | LDV | NS5A inhibitor |
| Ombitasvir | OBV | NS5A inhibitor |
| Paritaprevir | PTV | NS3/4A protease inhibitor |
| Sofosbuvir | SOF | Nucleotide NS5B polymerase inhibitor |
| Velpatasvir | VEL | NS5A inhibitor |

# Hepatitis D therapy

- very problematic – low efficacy
- PEG-IFN long-term (more than 1 year)
- ETV, TDF, TAF – not  effective (absence of target enzyme – reverse transcriptase)

# Chronic hepatitis E therapy

- Acute hepatitis E

✓ Spontaneous infection elimination without therapy

✓ fulminant course – ribavirin – mortality lowering

- Chronic hepatitis E

✓ Reduction of immunosupression – infection elimination in about 30 % patients

✓ ribavirin for 3-6 months

✓ PEG-IFN for 3 months – only after liver transplantation

# Thank you for your attention!

phusa@fnbrno.cz