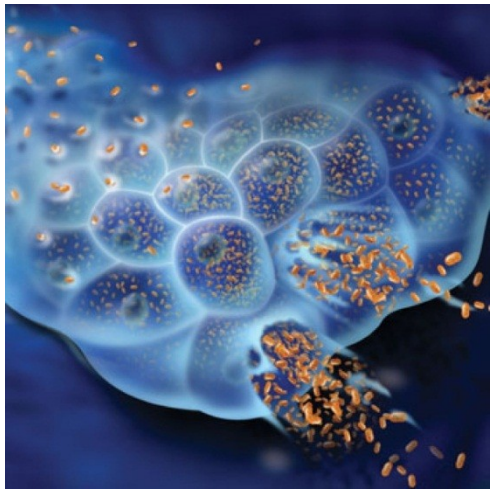
Viral Hepatitis



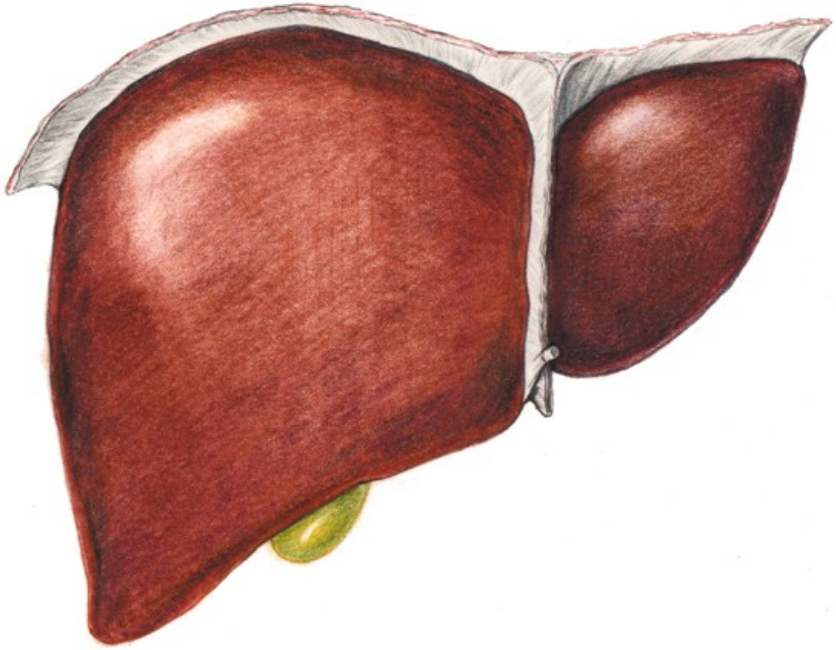
prof. MUDr. Petr Husa, CSc.
Klinika infekčních chorob, FN Brno

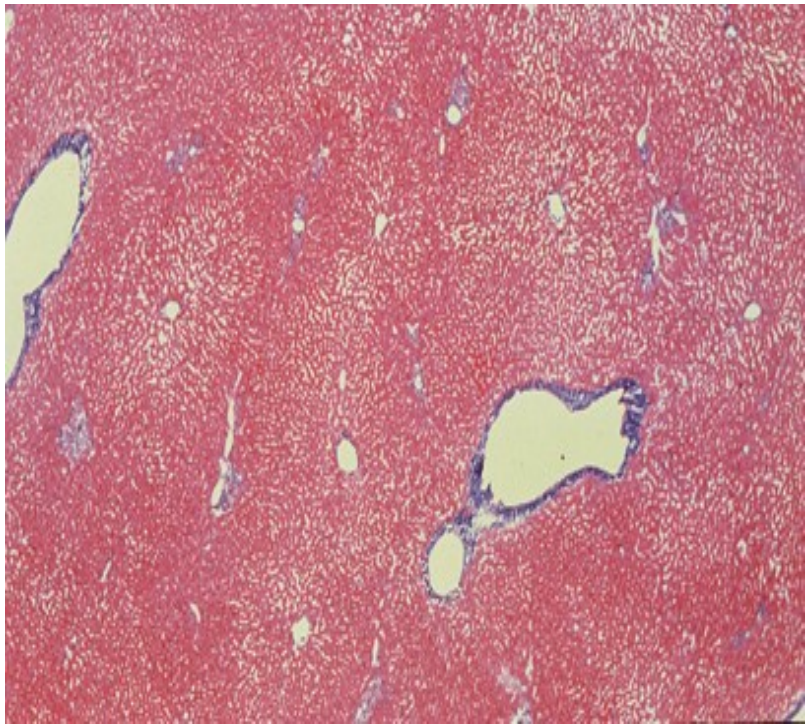
Viral Hepatitis

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

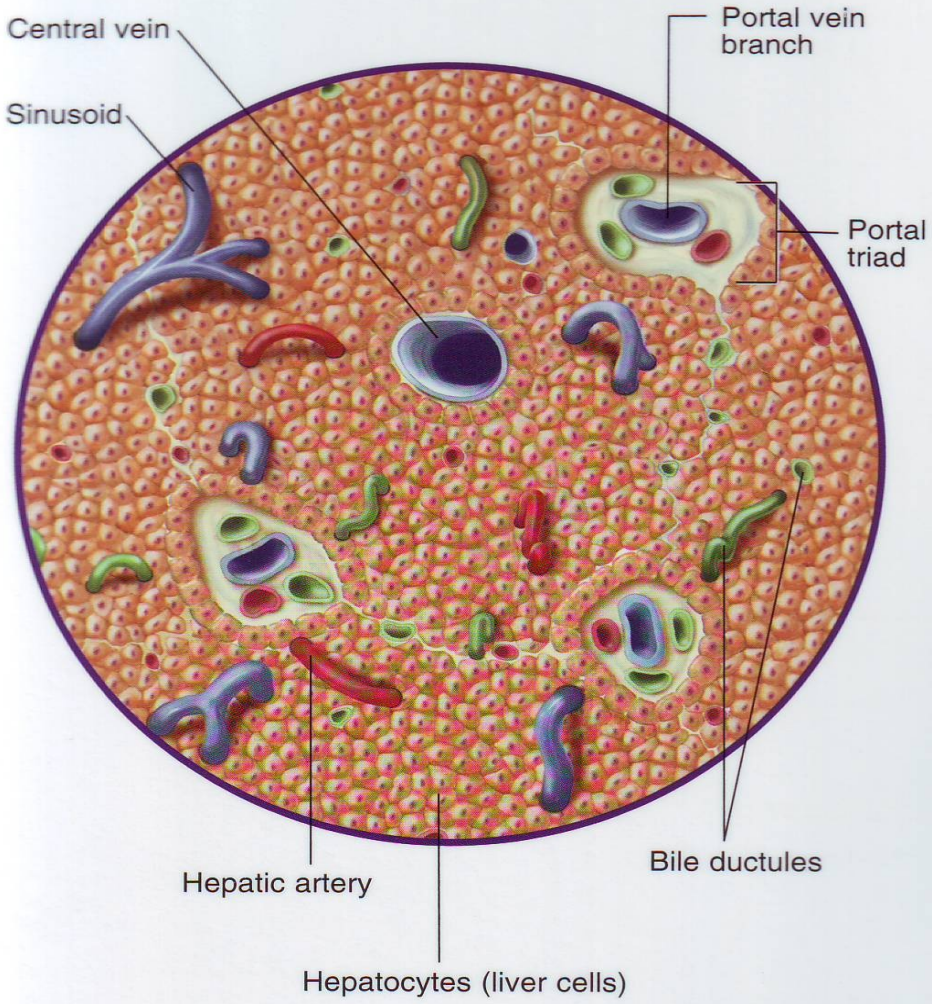
1. Enterically transmissible
   - HEP A – only acute
   - HEP E – chronic in immunosuppressed pts.
2. Parenterally transmissible – possible chronic stage
   - HEP B
   - HEP C
   - HEP D

Healthy liver

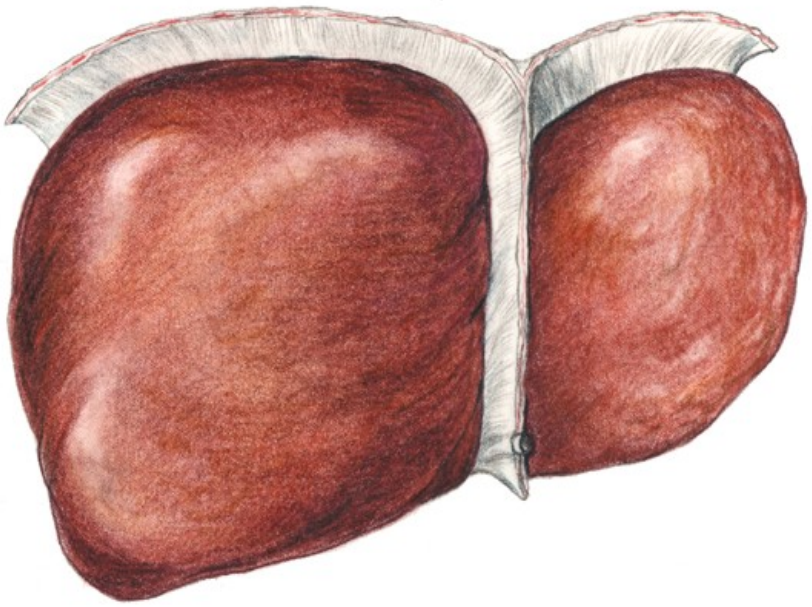


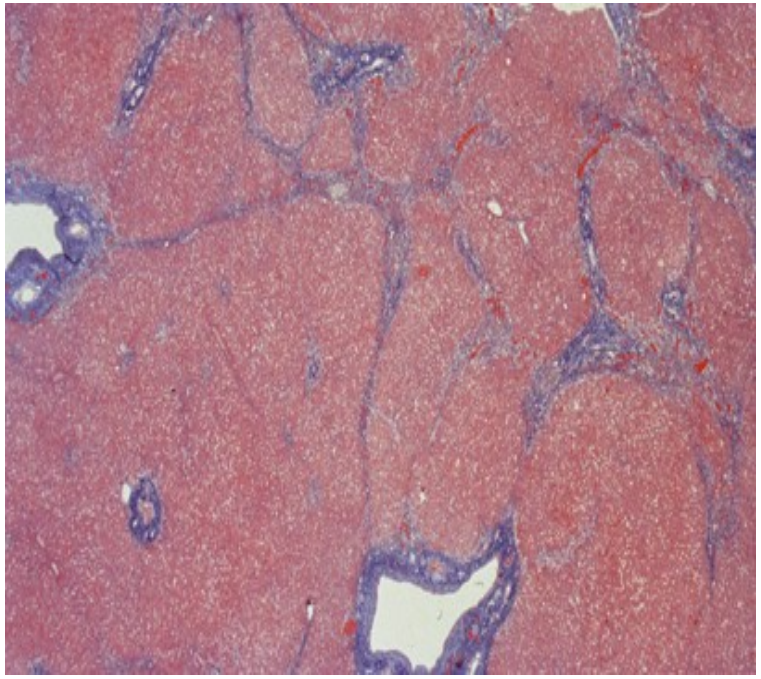


Normal Biopsy

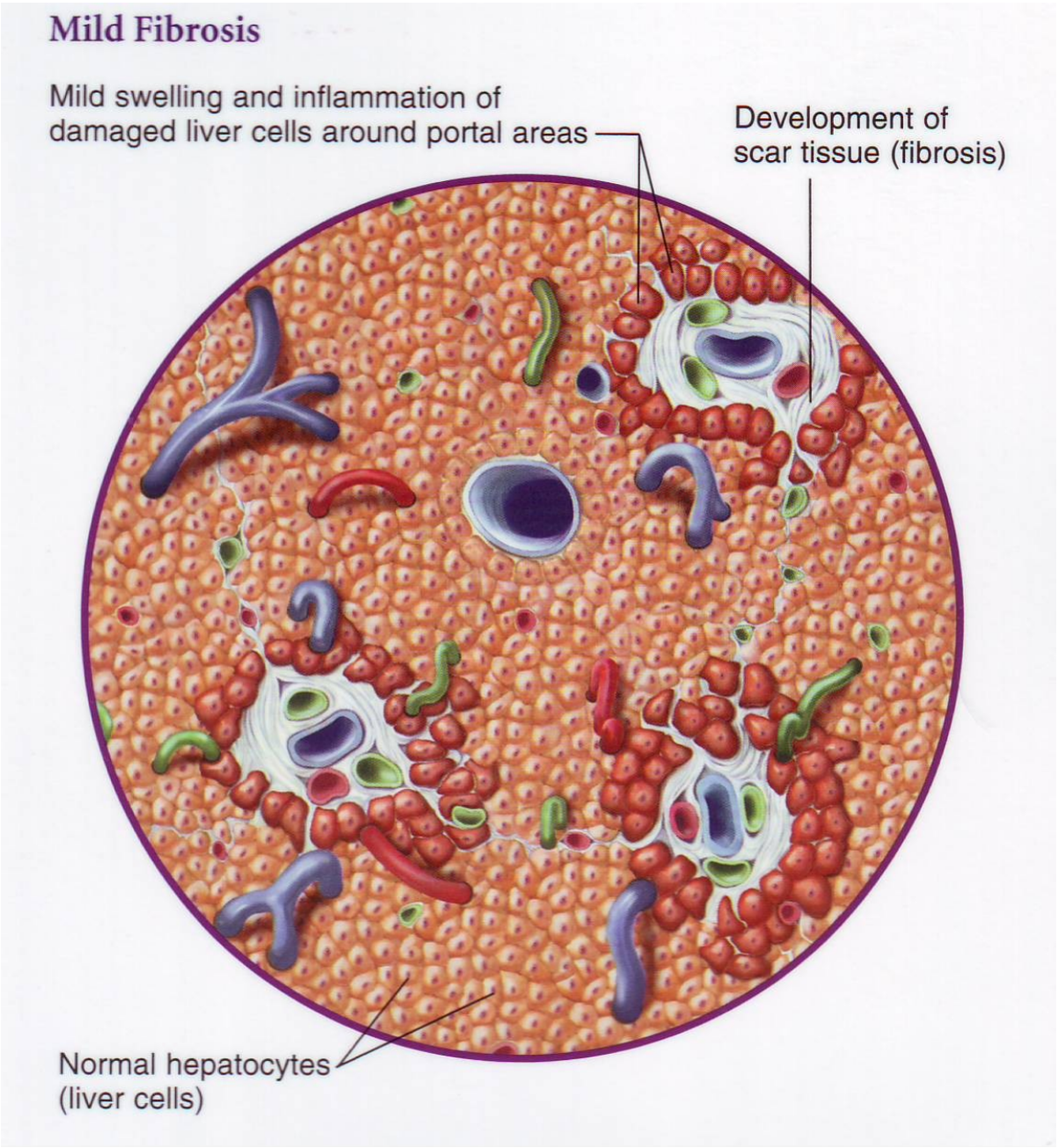


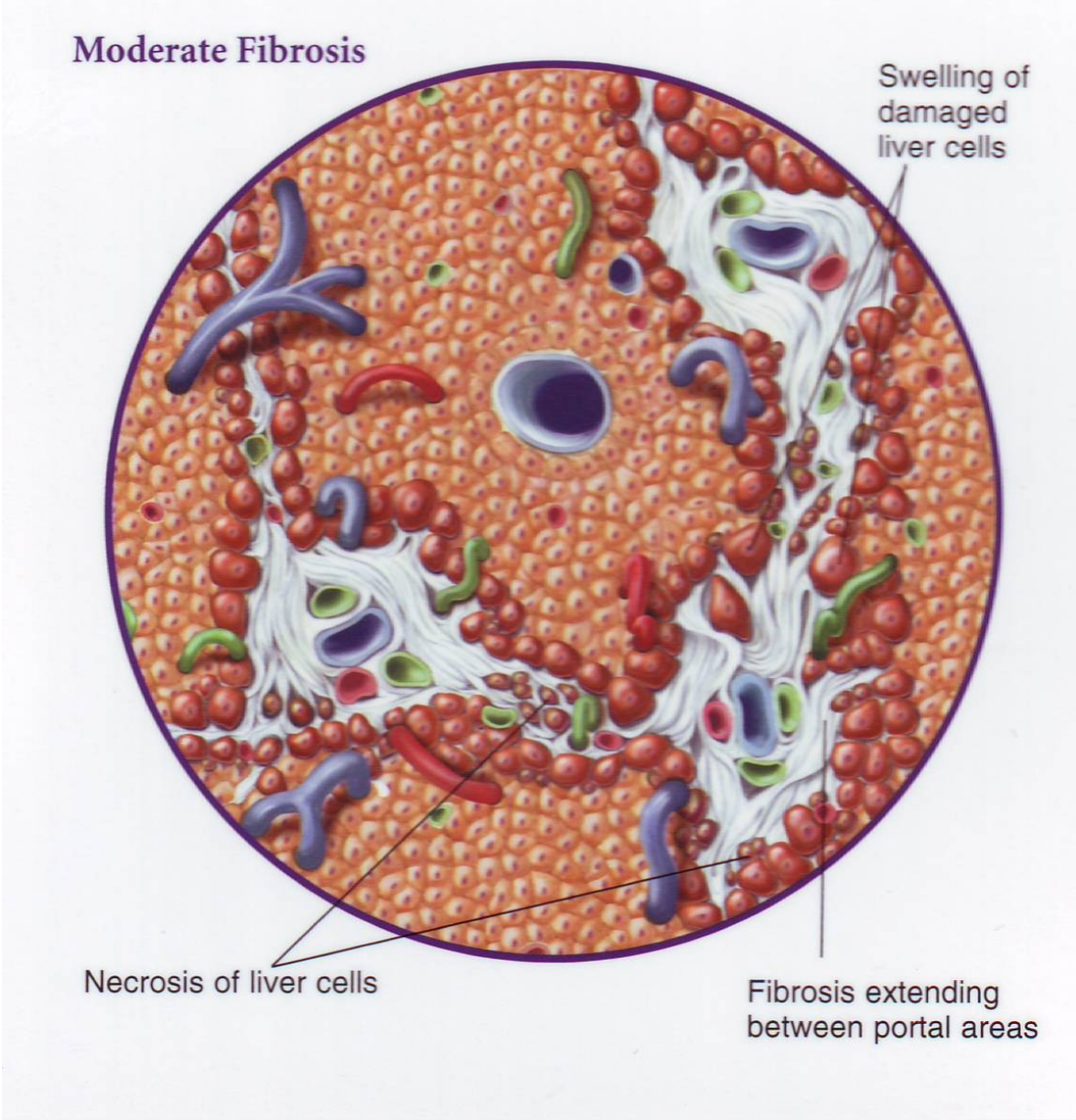
Liver fibrosis



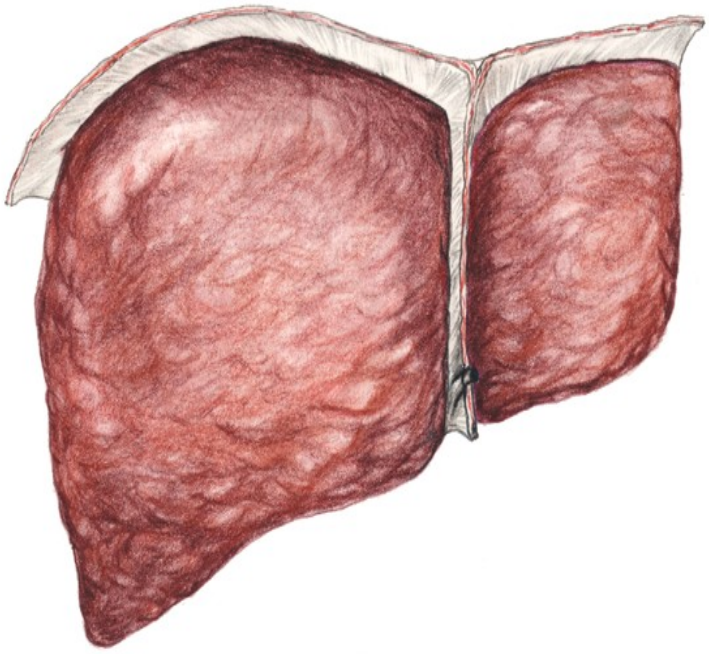


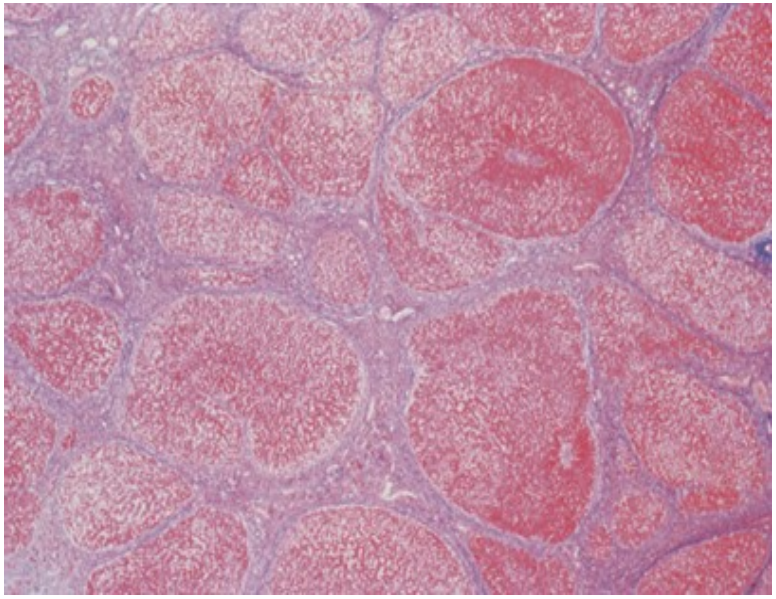
Mild Fibrosis



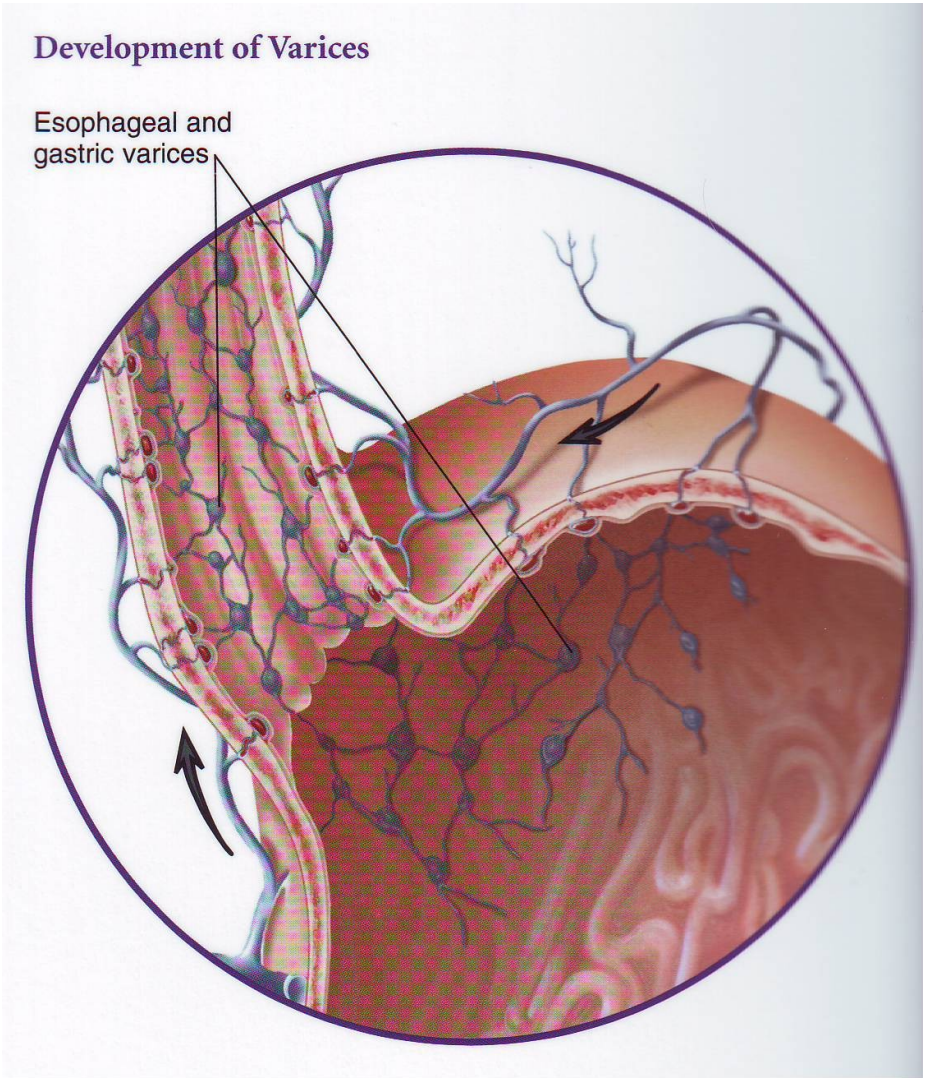

Moderate Fibrosis
Swelling of damaged liver cells
Necrosis of liver cells
Fibrosis extending between portal areas

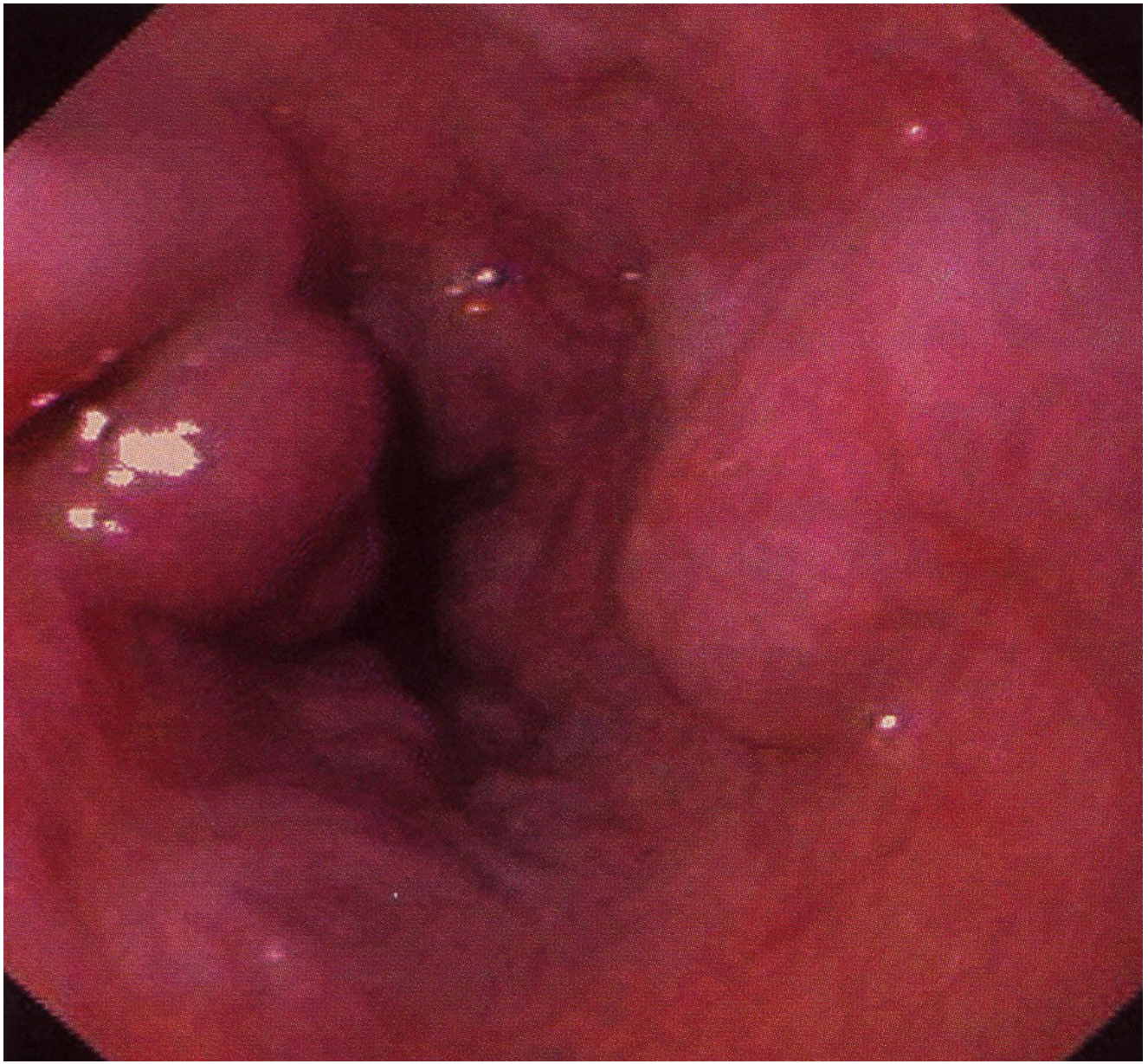
Liver cirrhosis

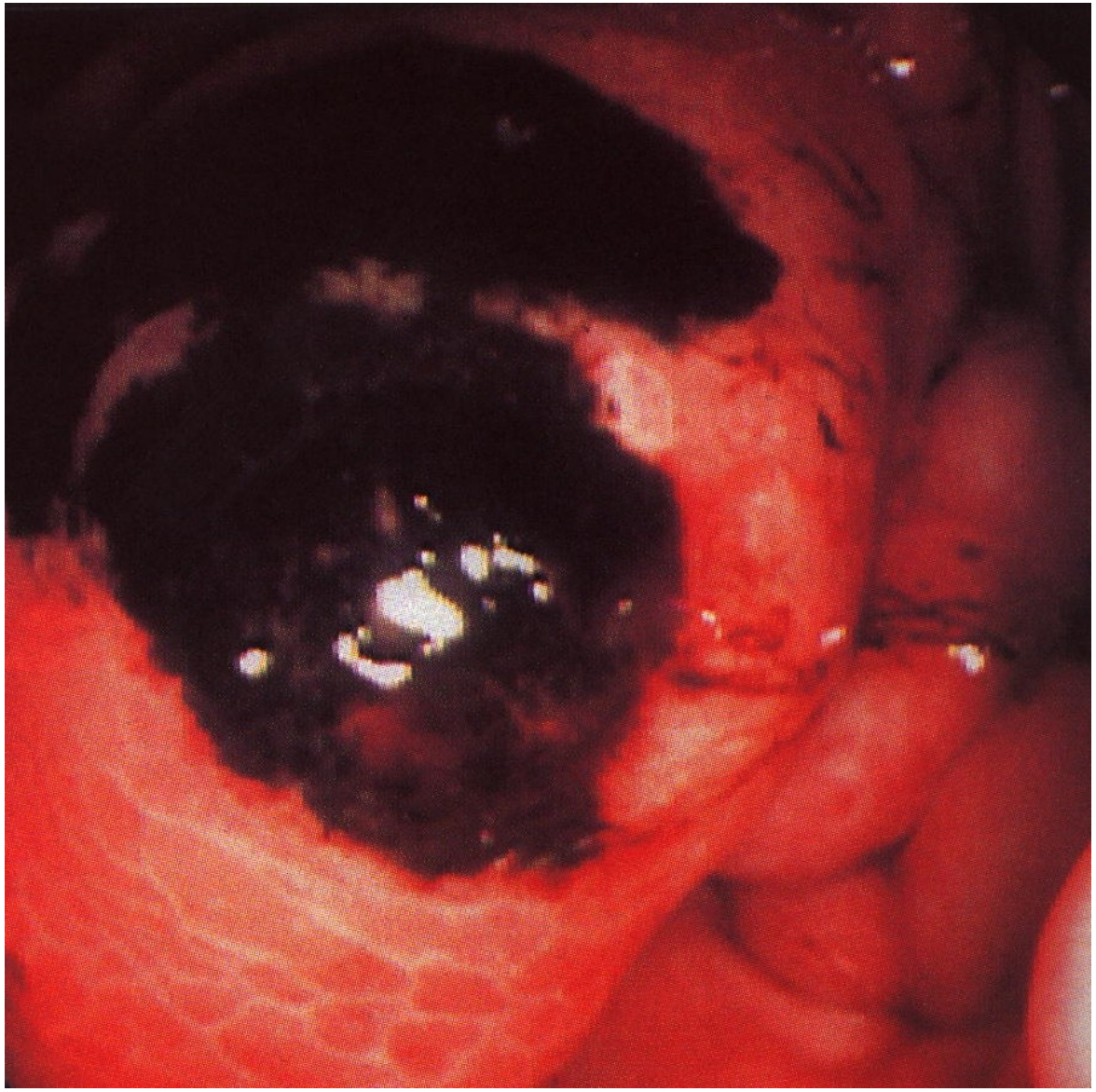


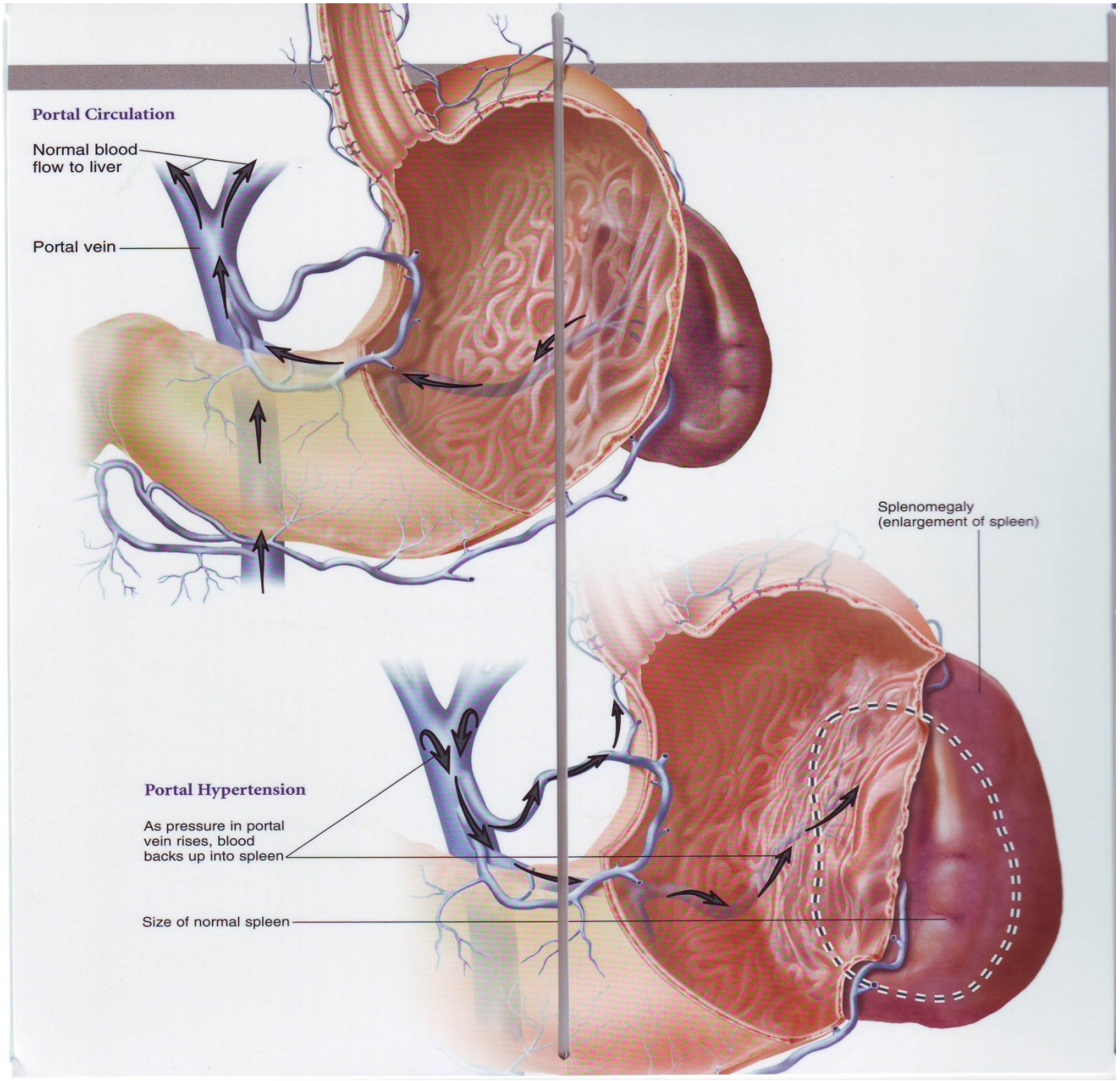


Development of Varices



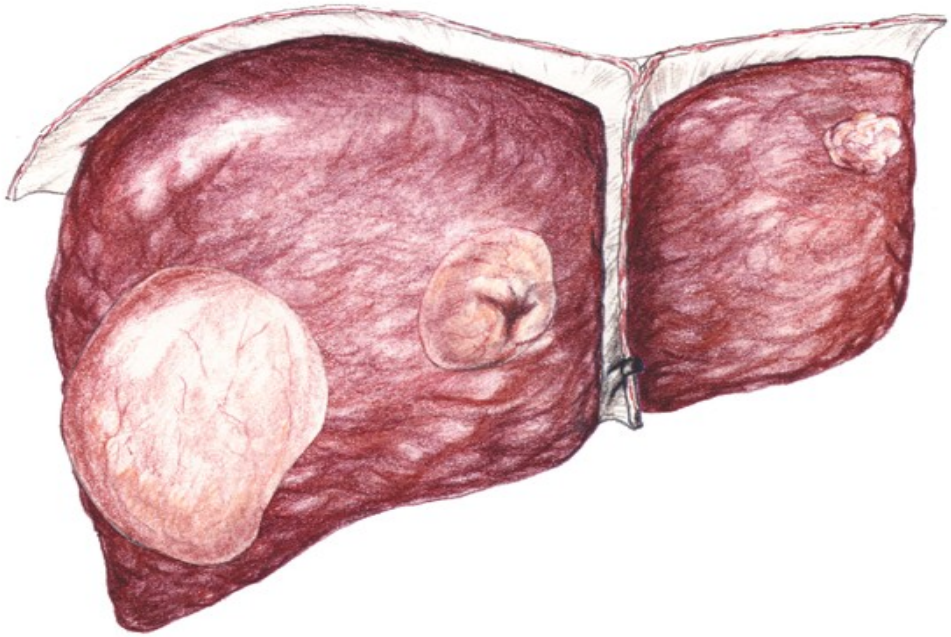


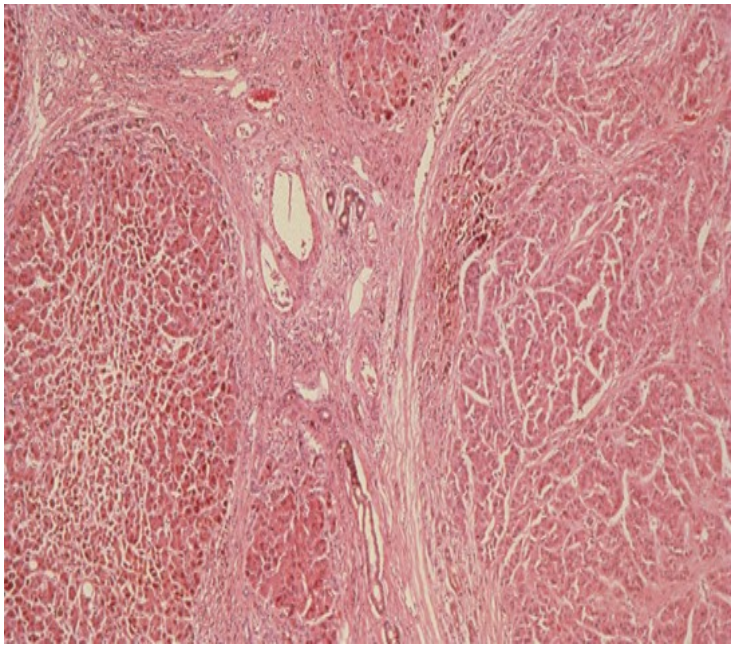



Portal Circulation
Normal blood flow to liver
Portal vein
Splenomegaly (enlargement of spleen)
Portal Hypertension
As pressure in portal vein rises, blood backs up into spleen
Size of normal spleen


FAKULTNÍ NEMOCNICE BRNO

Hepatocellular carcinoma



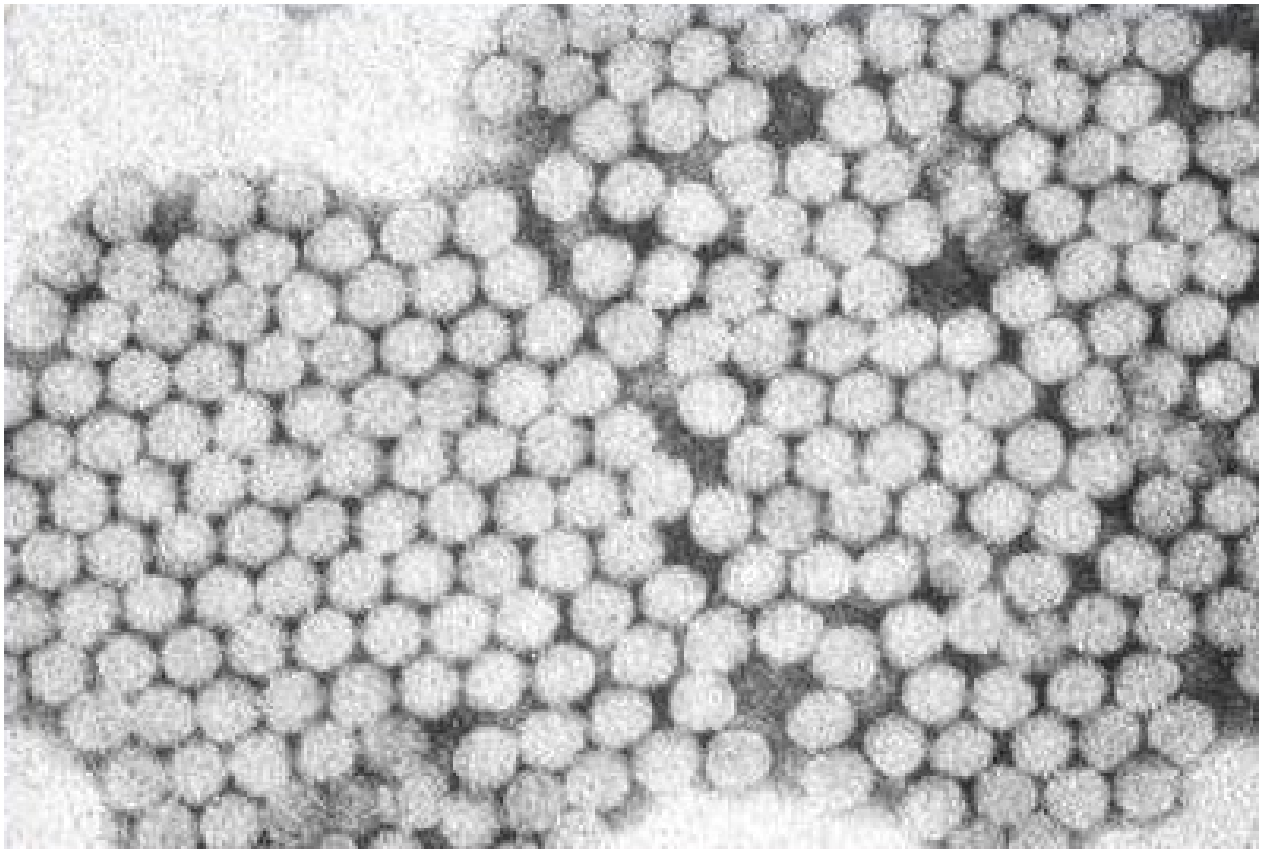


Viral hepatitis in CR 2011-2020

	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
VH A	264	284	348	673	723	930	772	211	240	183
acute VH B	192	154	133	105	90	73	85	54	41	27
chronic VH B	162	147	147	193	193	208	248	269	276	142
VH C	812	794	873	867	945	1103	992	1050	1138	771
VH E	163	258	218	299	409	339	344	272	268	223

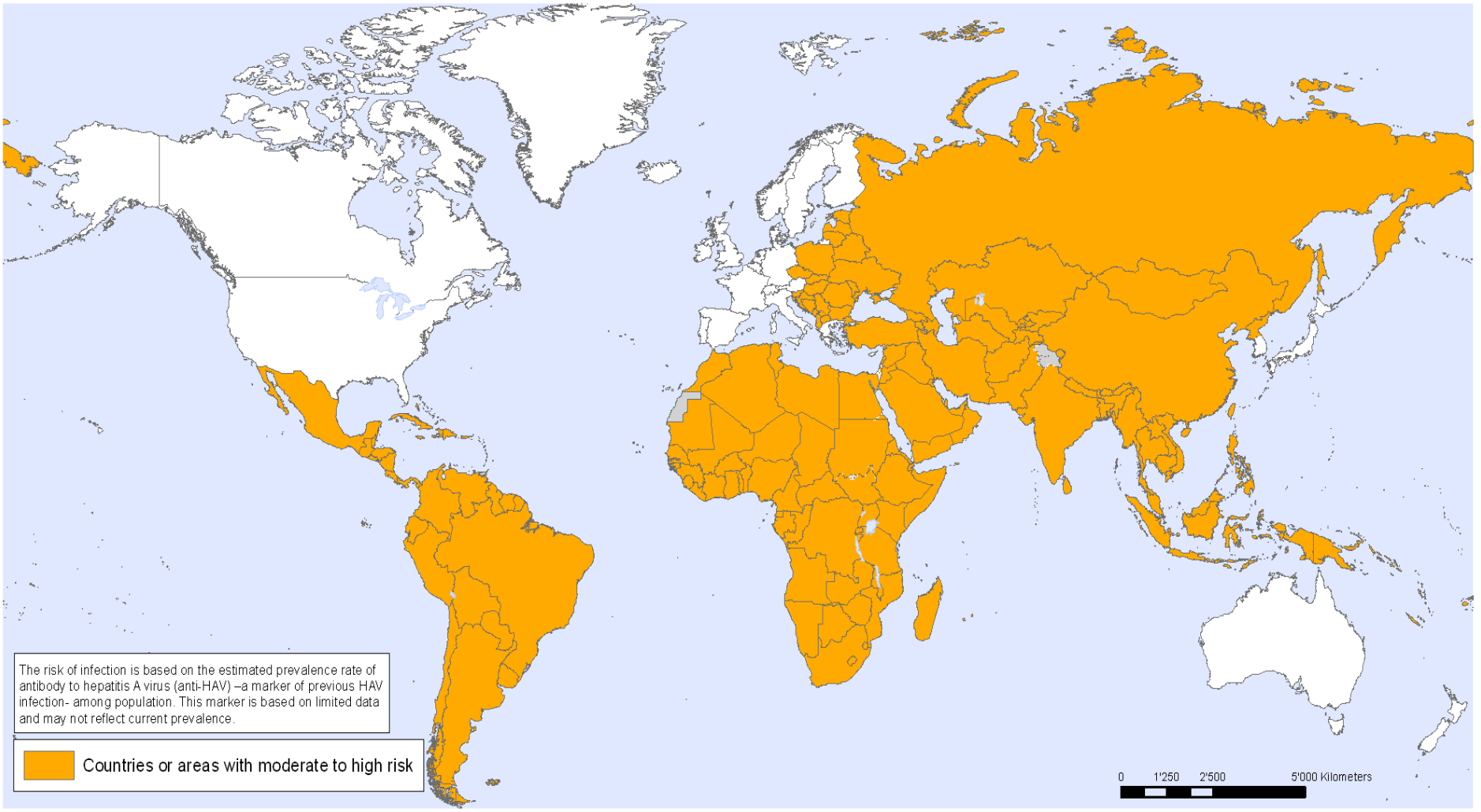
Source: ISIN

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), 1 serotype

Hepatitis A, countries or areas at risk

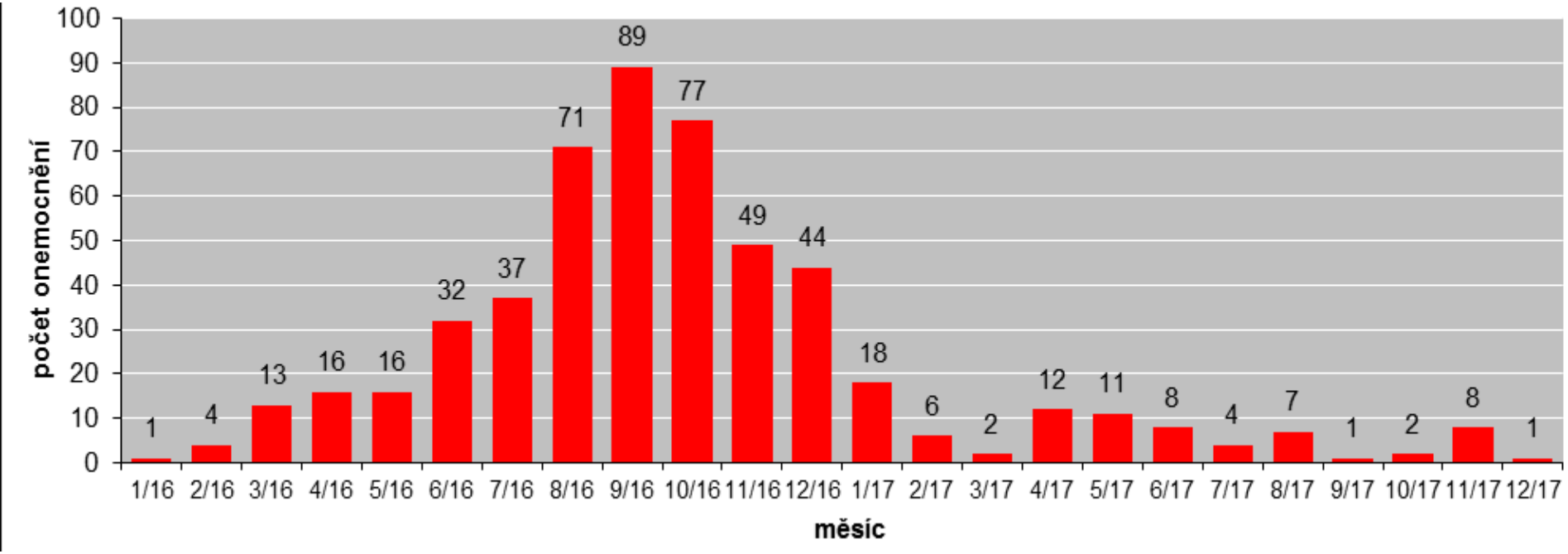


The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers 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

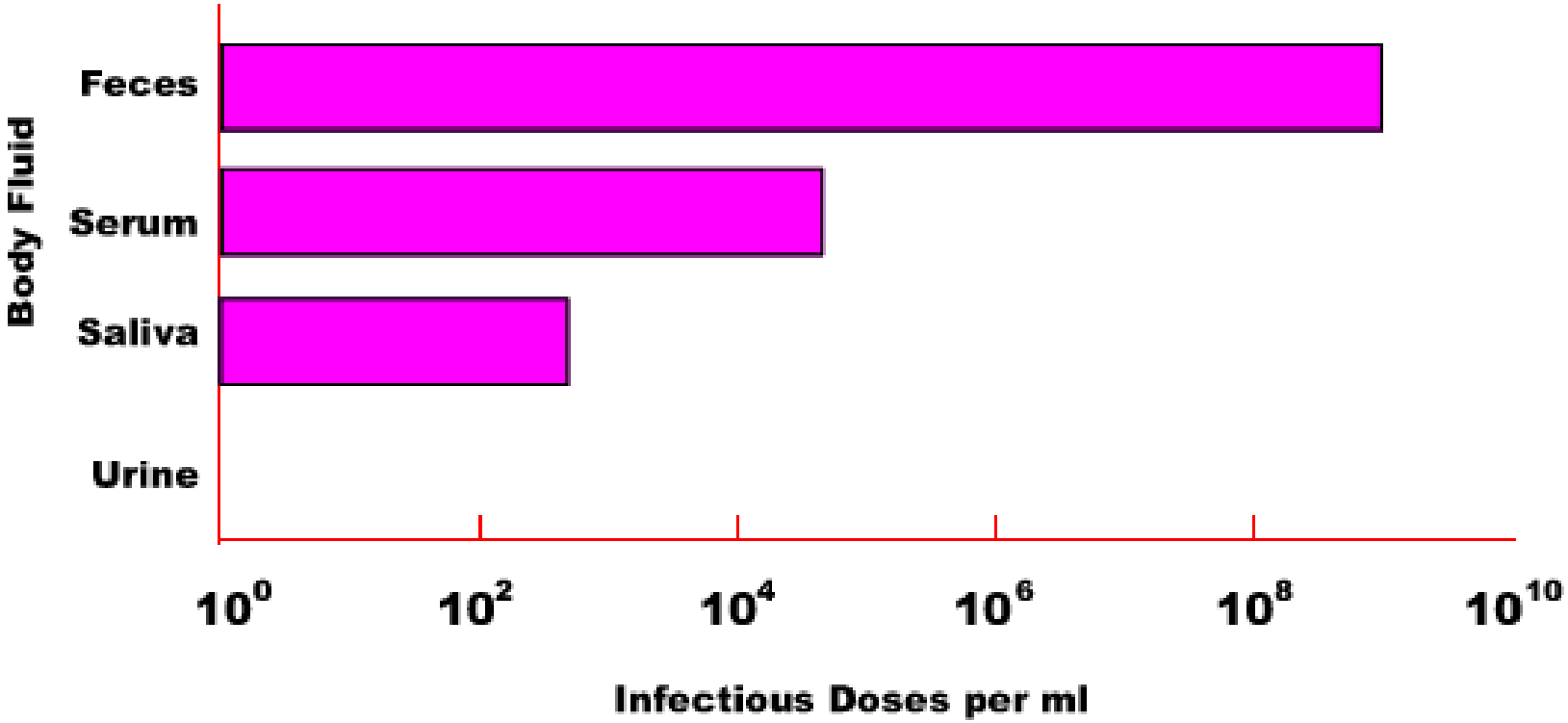


Epidemiology

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

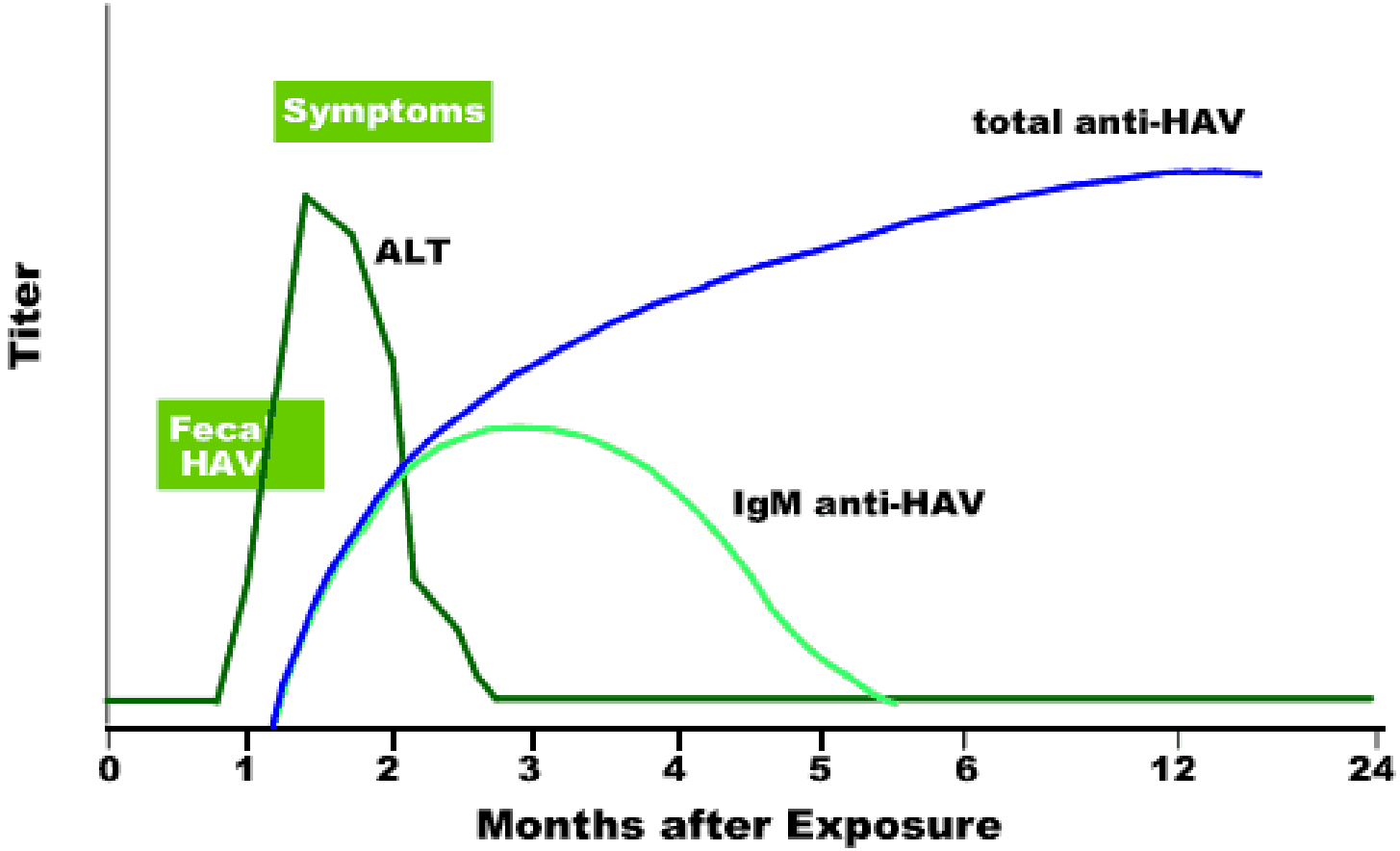
- Vaccination available, recommended especially fore travelers to countries with lower standard of hygiene

Concentration of Hepatitis A Virus in Various Body Fluids

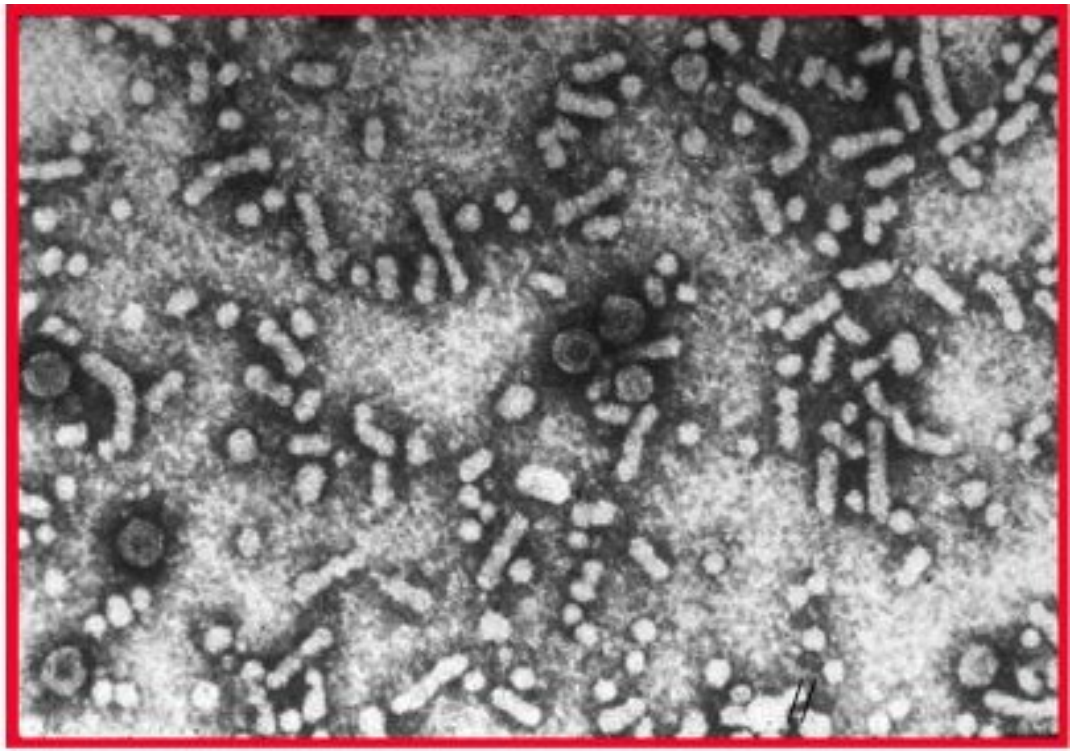


Source: Viral Hepatitis and Liver Disease 1984;9-2
J Infect Dis 1989; 160:887-890

Hepatitis A Virus Infection
Typical Serologic Course



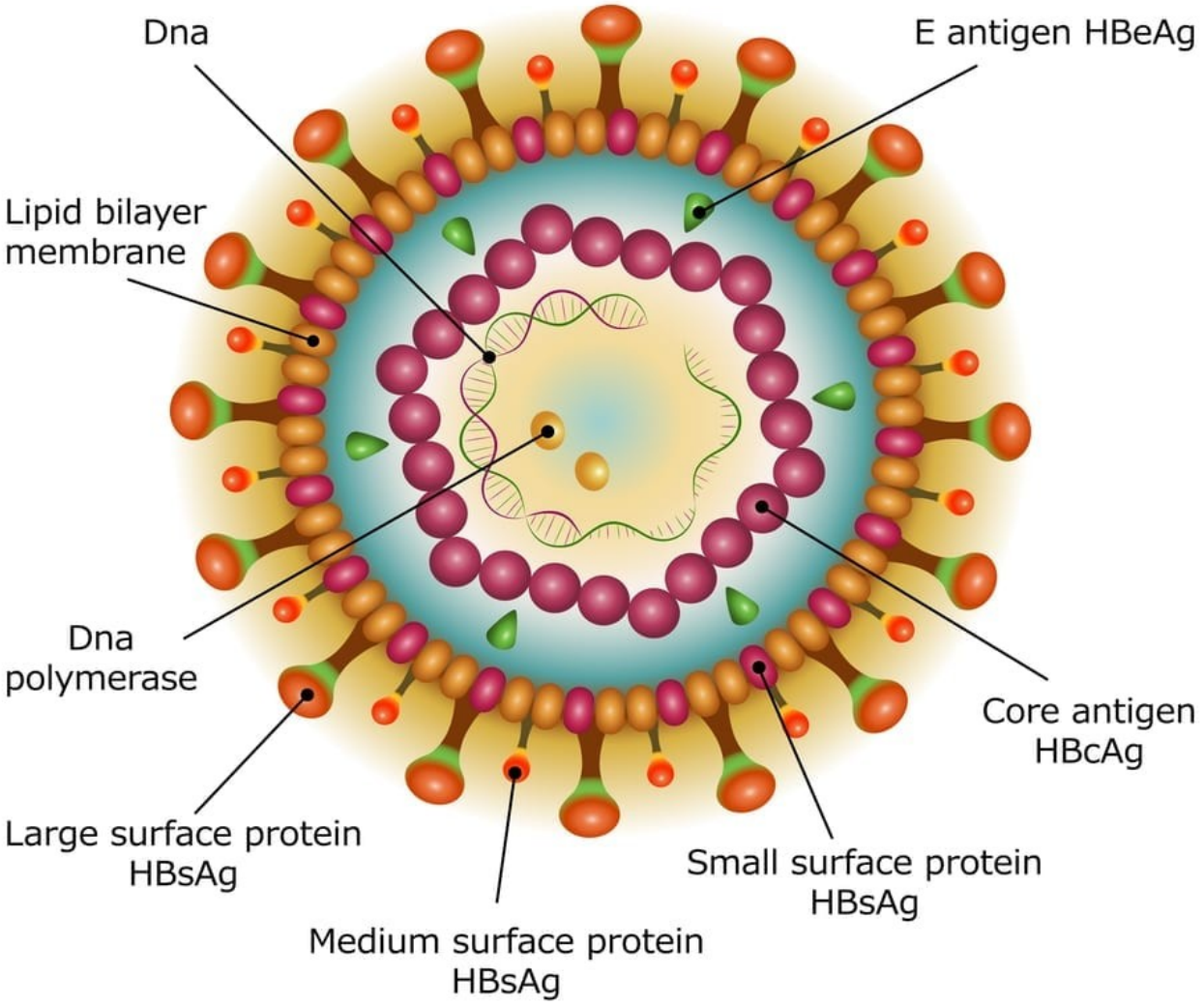
Hepatitis B Virus (HBV)



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

Hepatitis B Virus

Baltimore Group VII (dsDNA-RT)



Global significance of HEP B

- One of the biggest global health problems

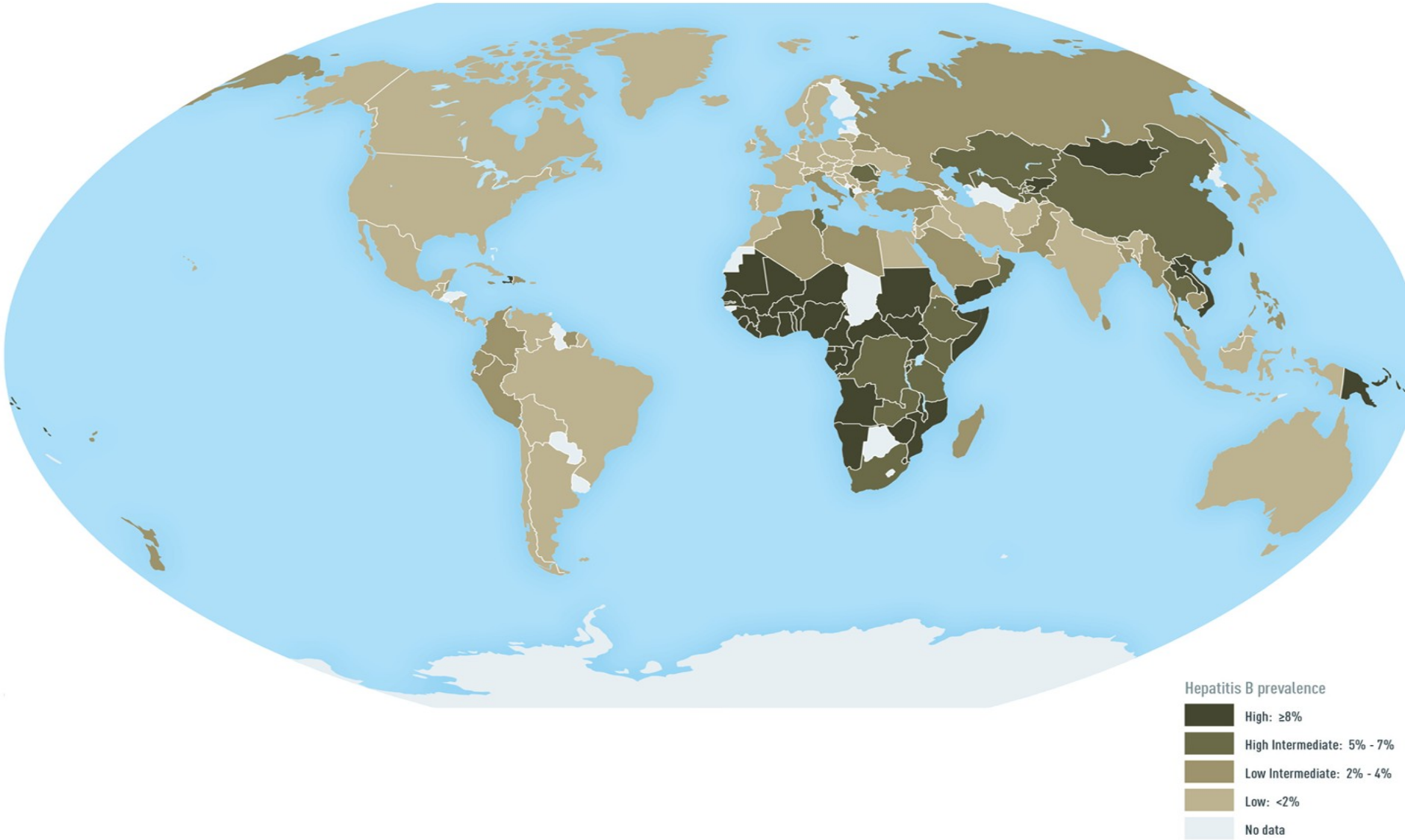
✓ More than 2 billions of infections during the life

✓ 240 million chronic carriers

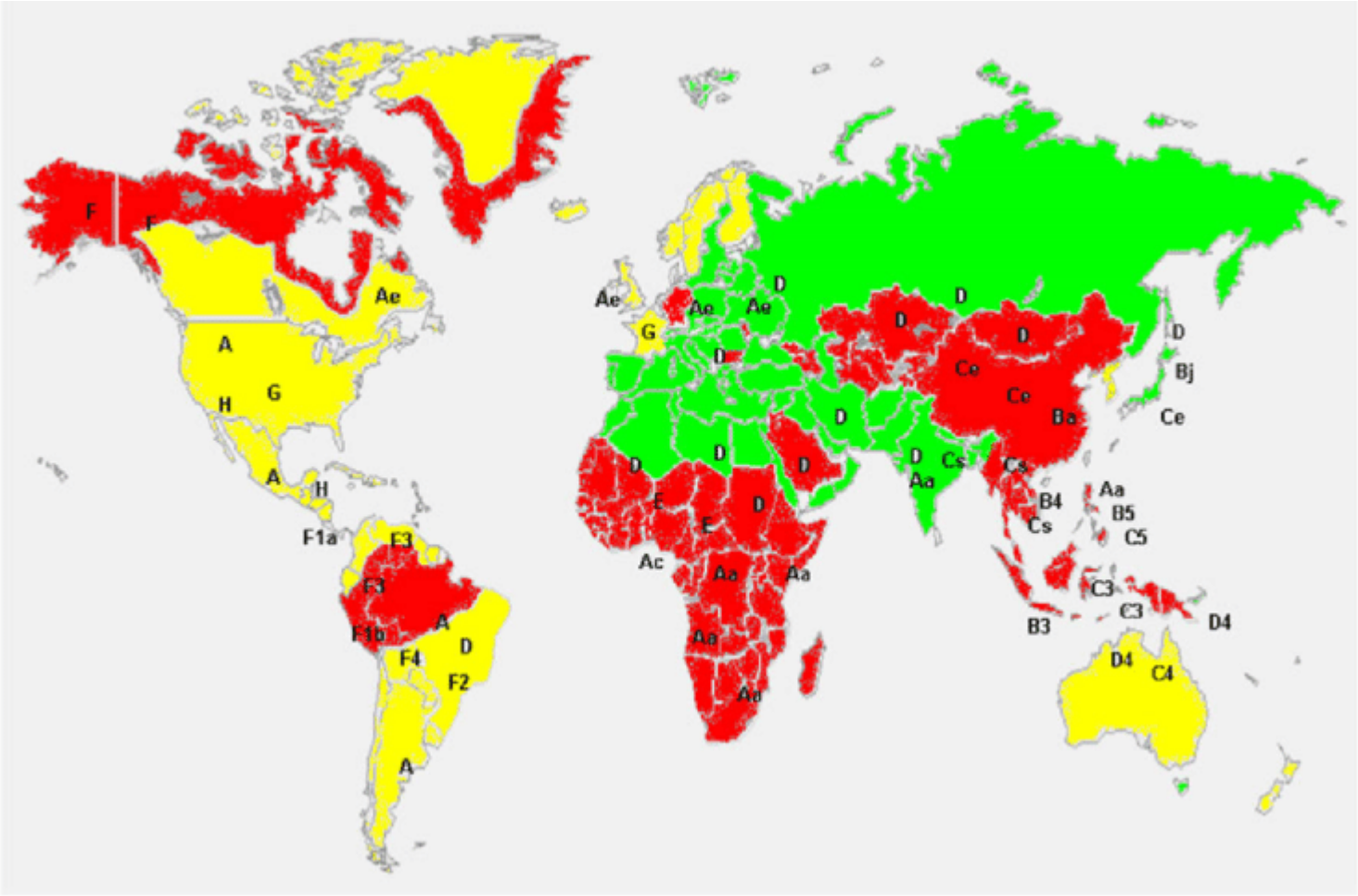
✓ Indication for 5-10 % liver transplantations globally

✓ Global vaccination in 184 countries

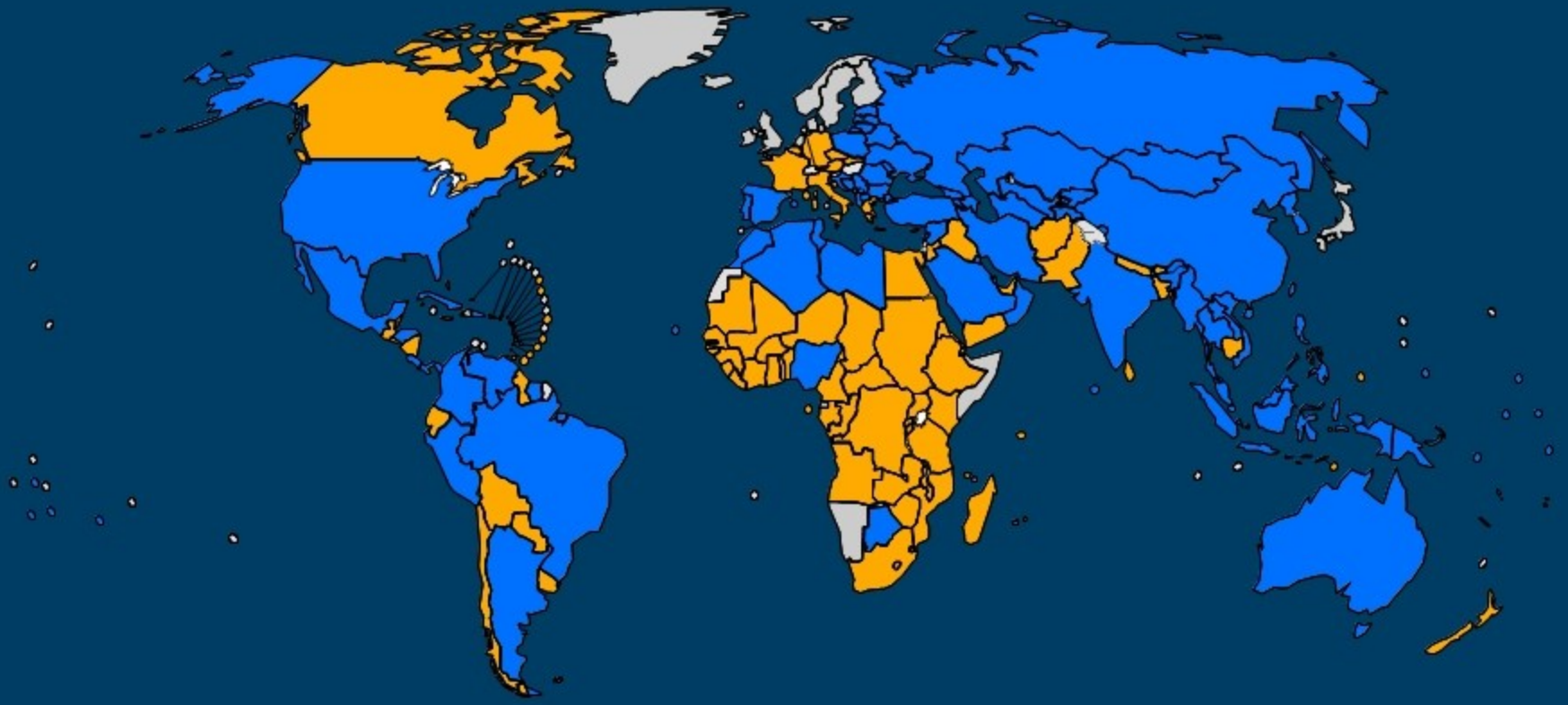
Chronic HBV infection (CDC 2020)



HBV genotypes (A-I)



Countries using HepB in national immunization schedule, 2008



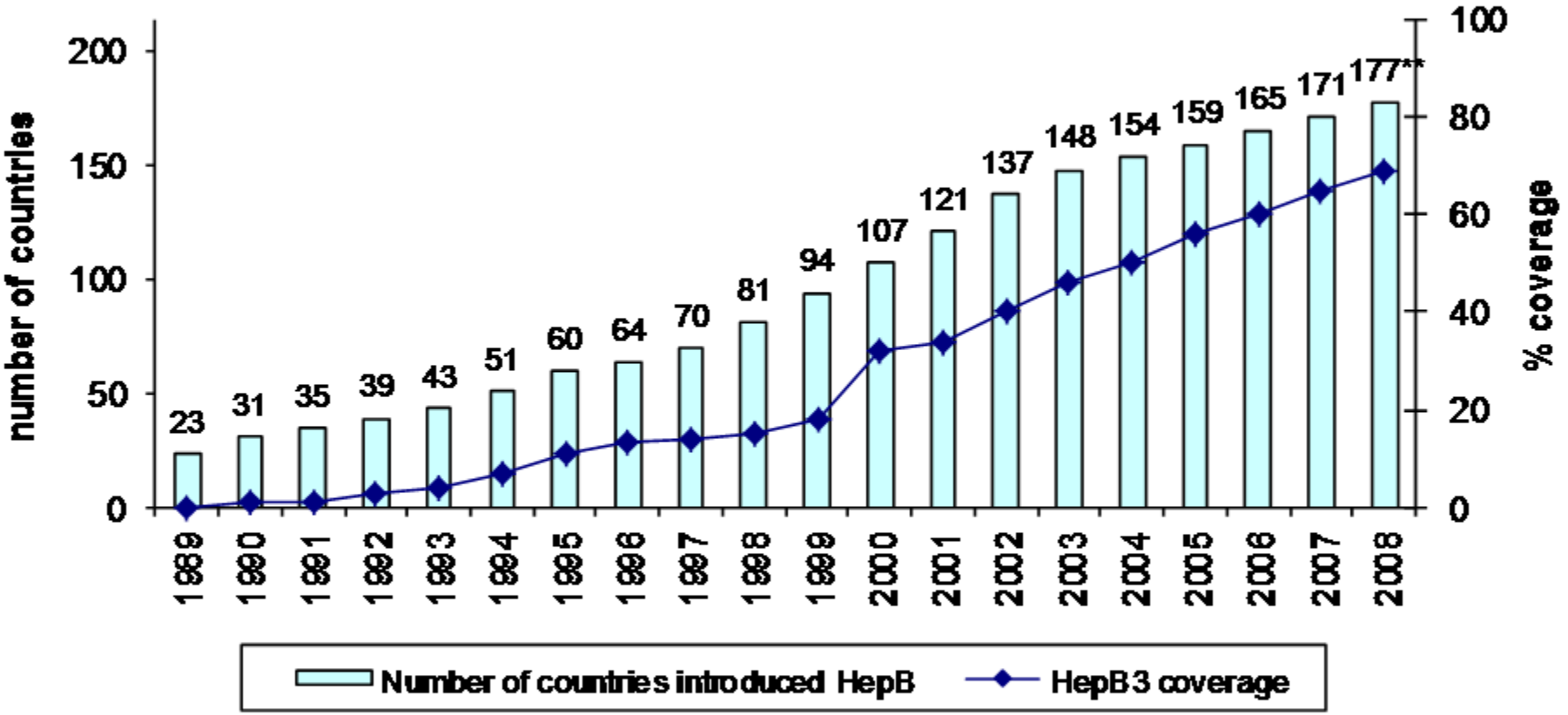
Source: WHO/IVB database, 193 WHO Member States.
Data as of August 2009
Date of slide: 24 November 2009

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

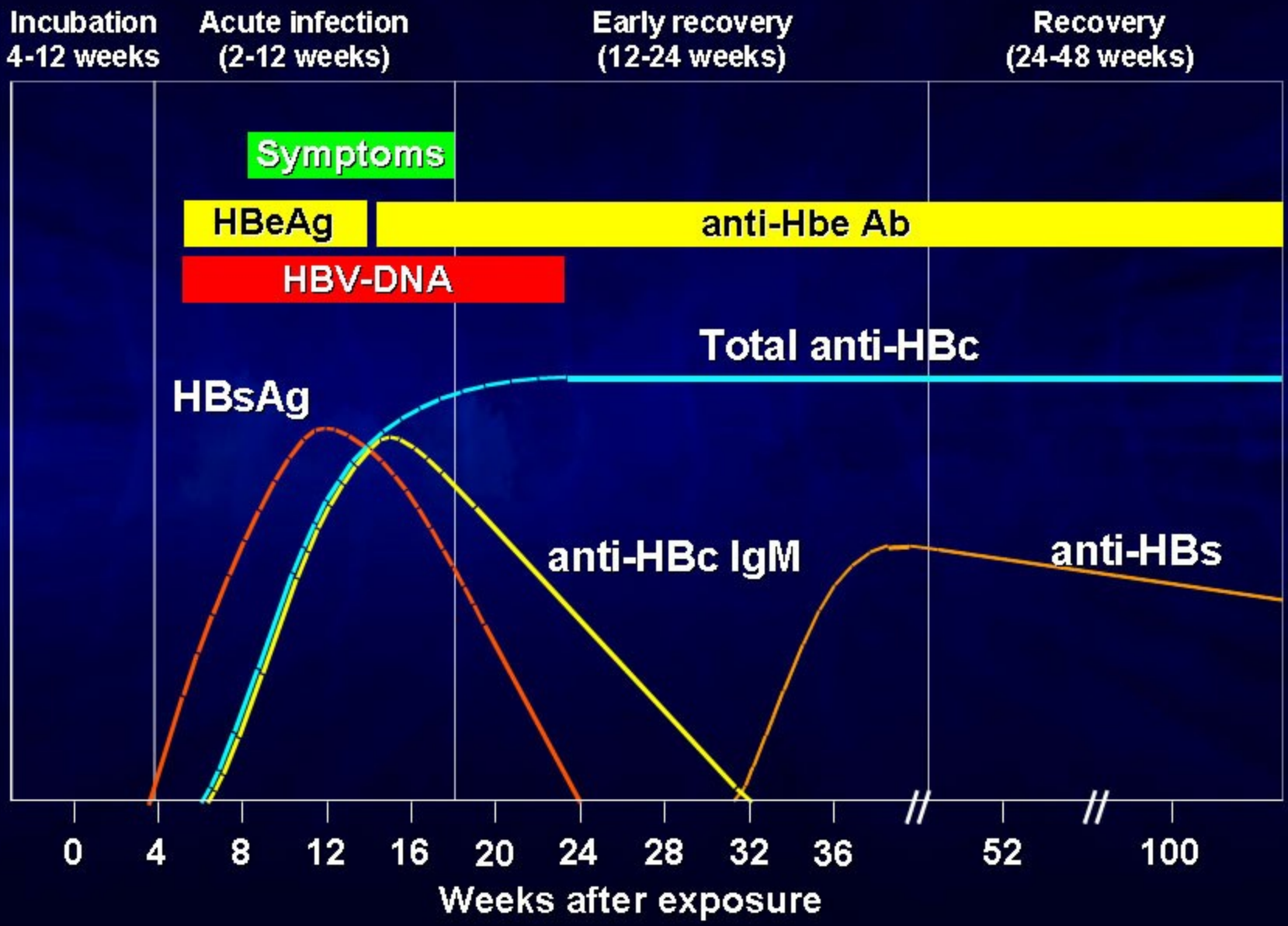
✓ blood and blood products

✓ organ and tissue transplant recipients

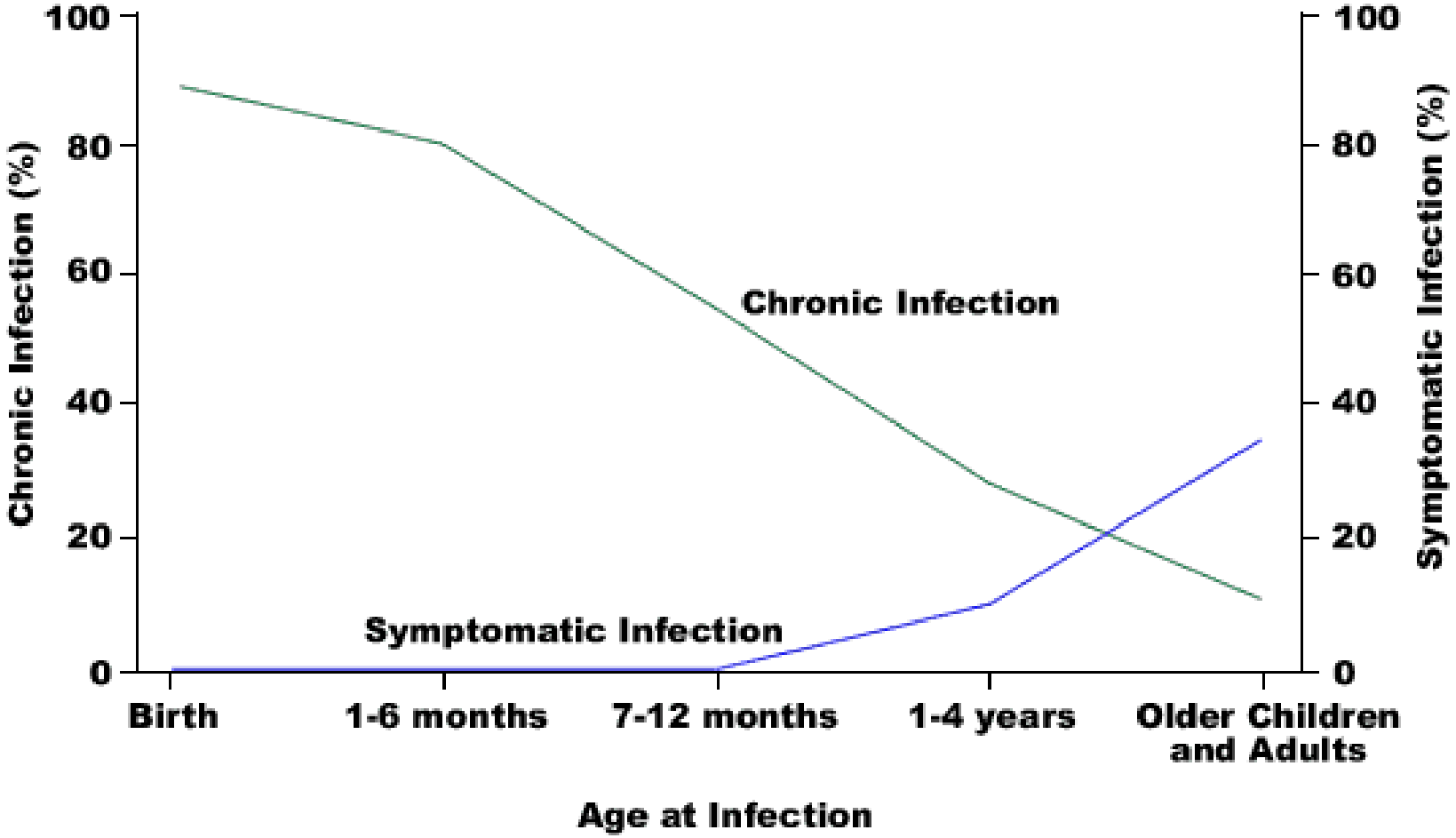
Clinical findings in acute HEP B

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

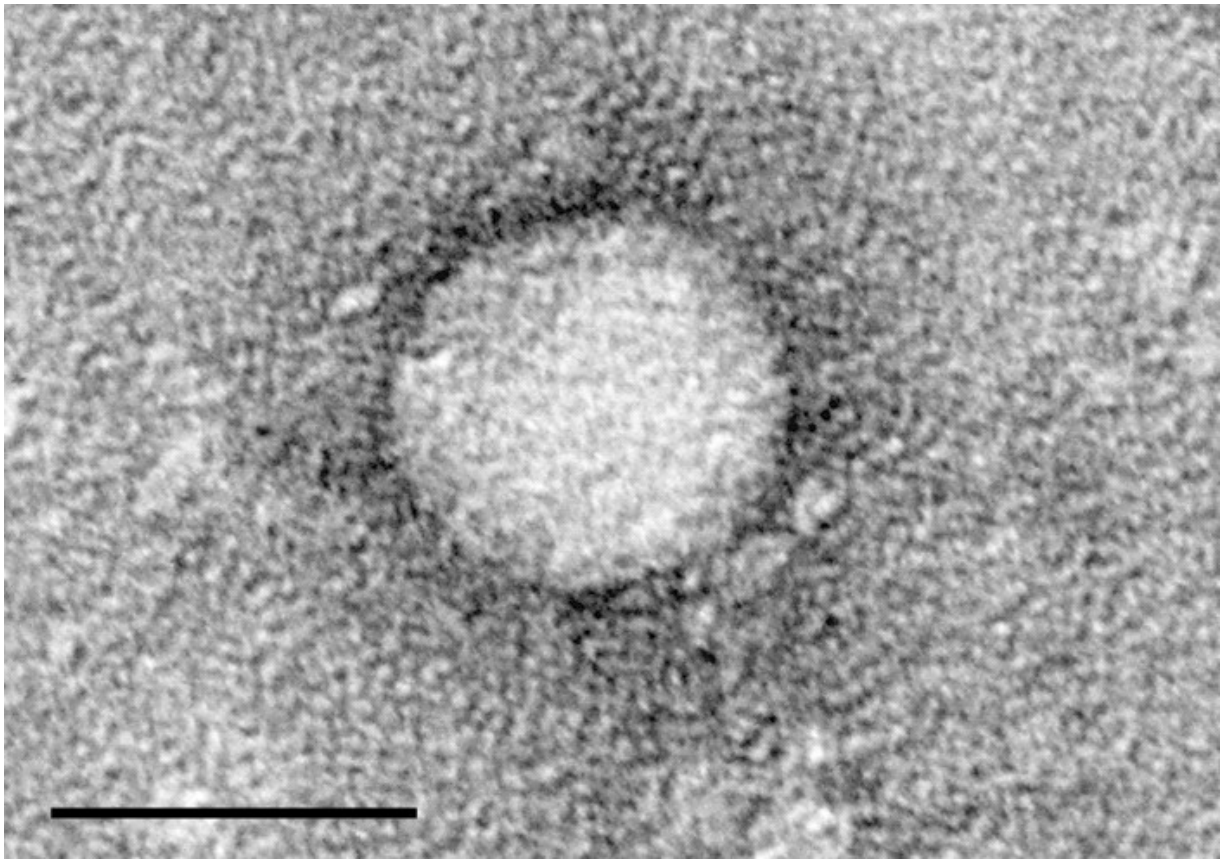
Acute Hepatitis B



Outcome of Hepatitis B Virus Infection by Age at Infection

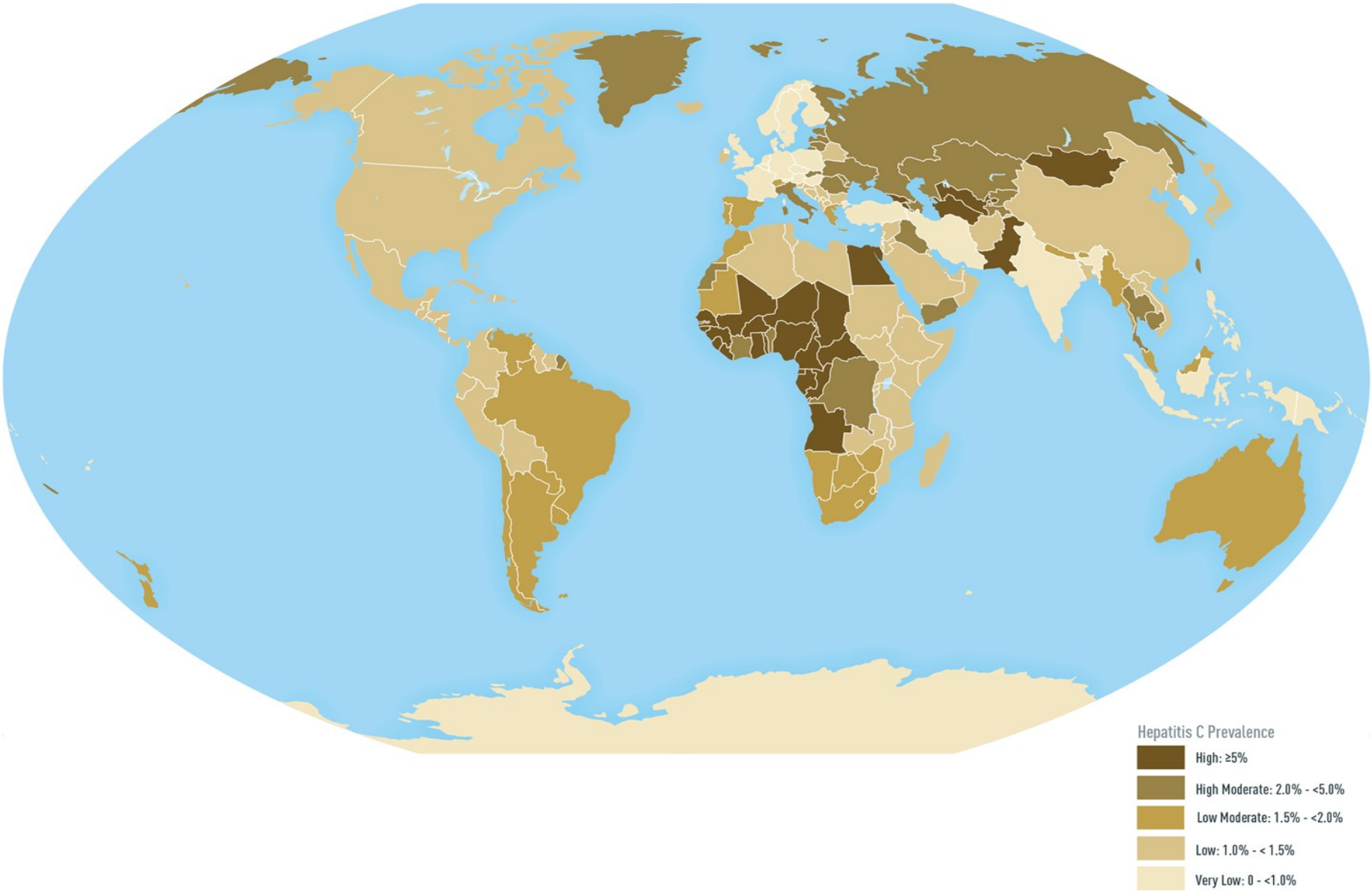


Hepatitis C Virus (HCV)

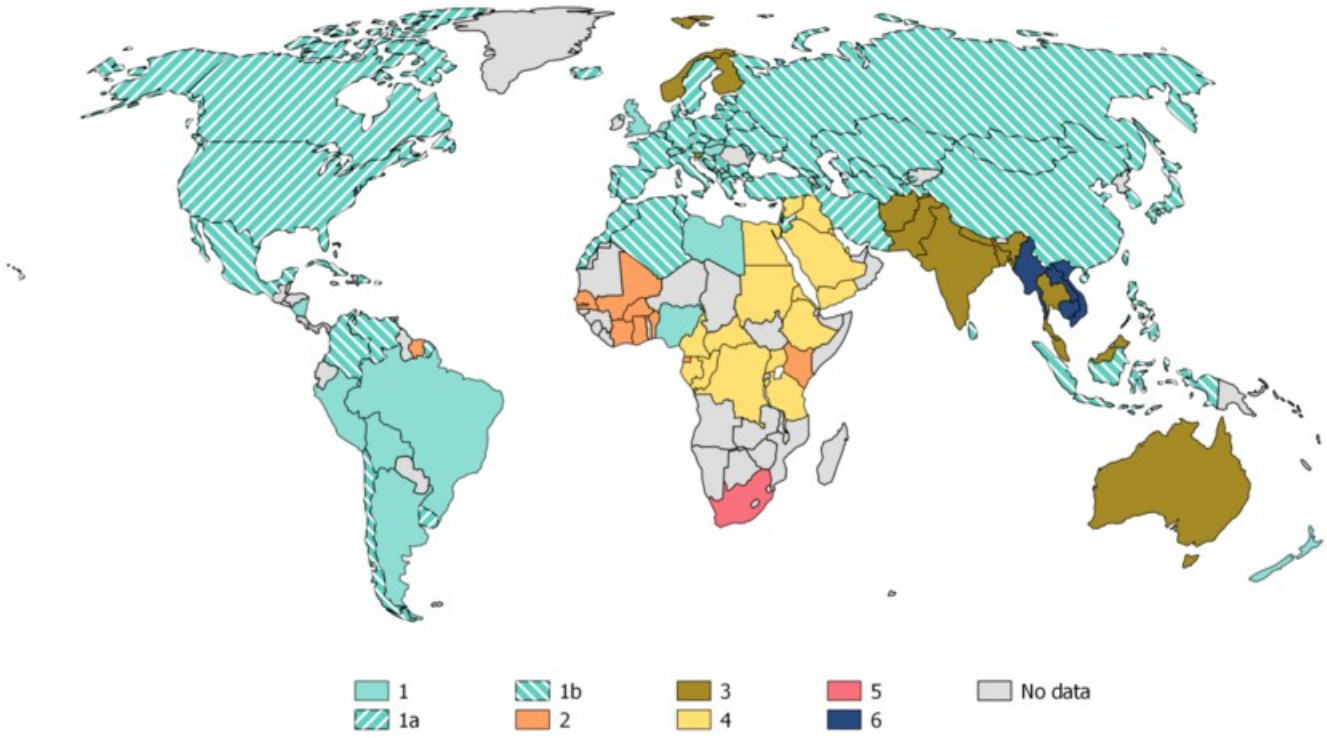


Family Flaviviridae, genus *Hepacivirus*, enveloped RNA virus 60 nm,
8 genotypes (1-8), many subtypes (a…)

Chronic HCV infection (CDC 2020)



HCV genotypes distribution



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

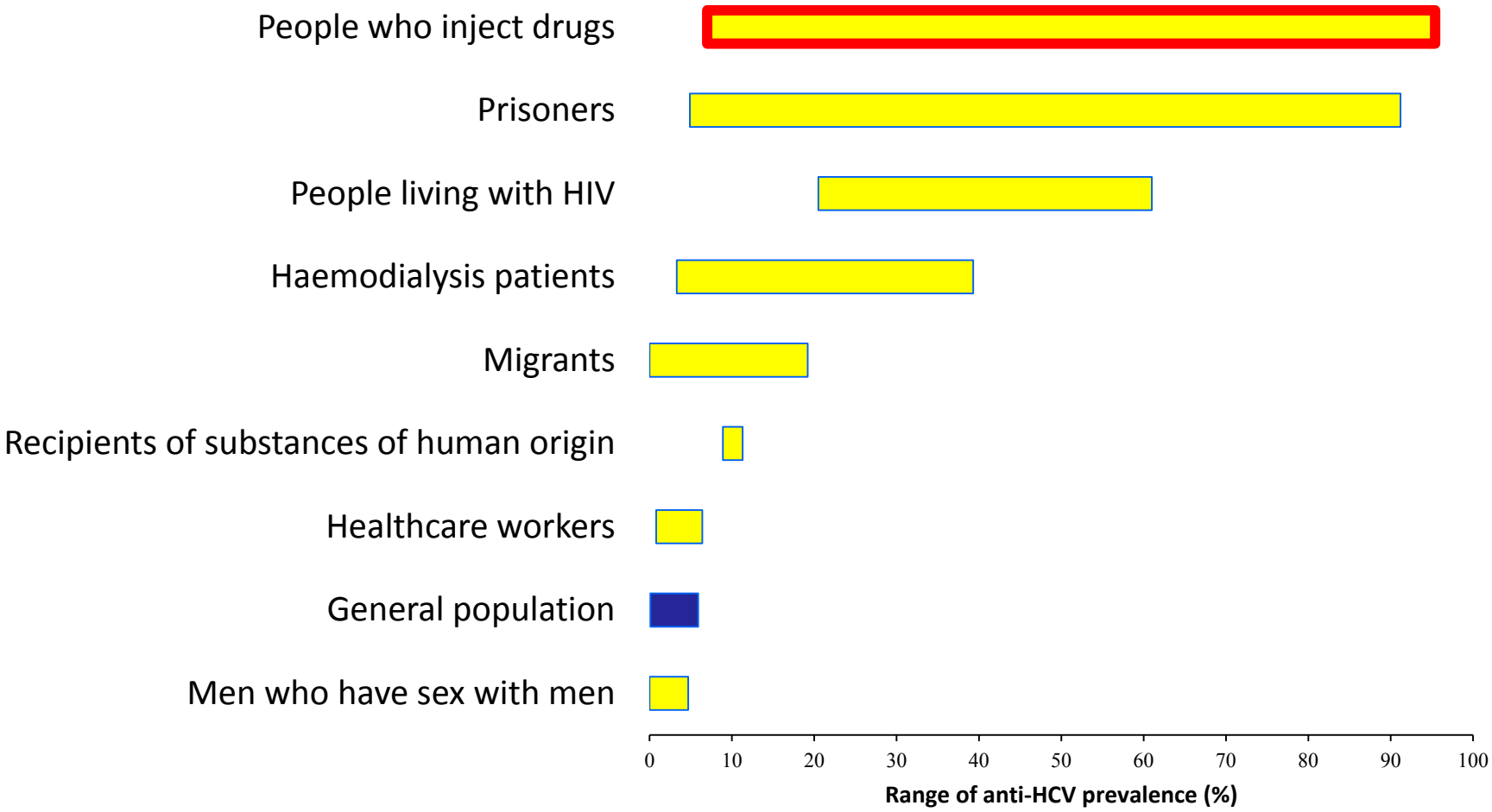
✓ prevalence 0.2 % (2001), current estimations 0.4-0.5 %

- 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

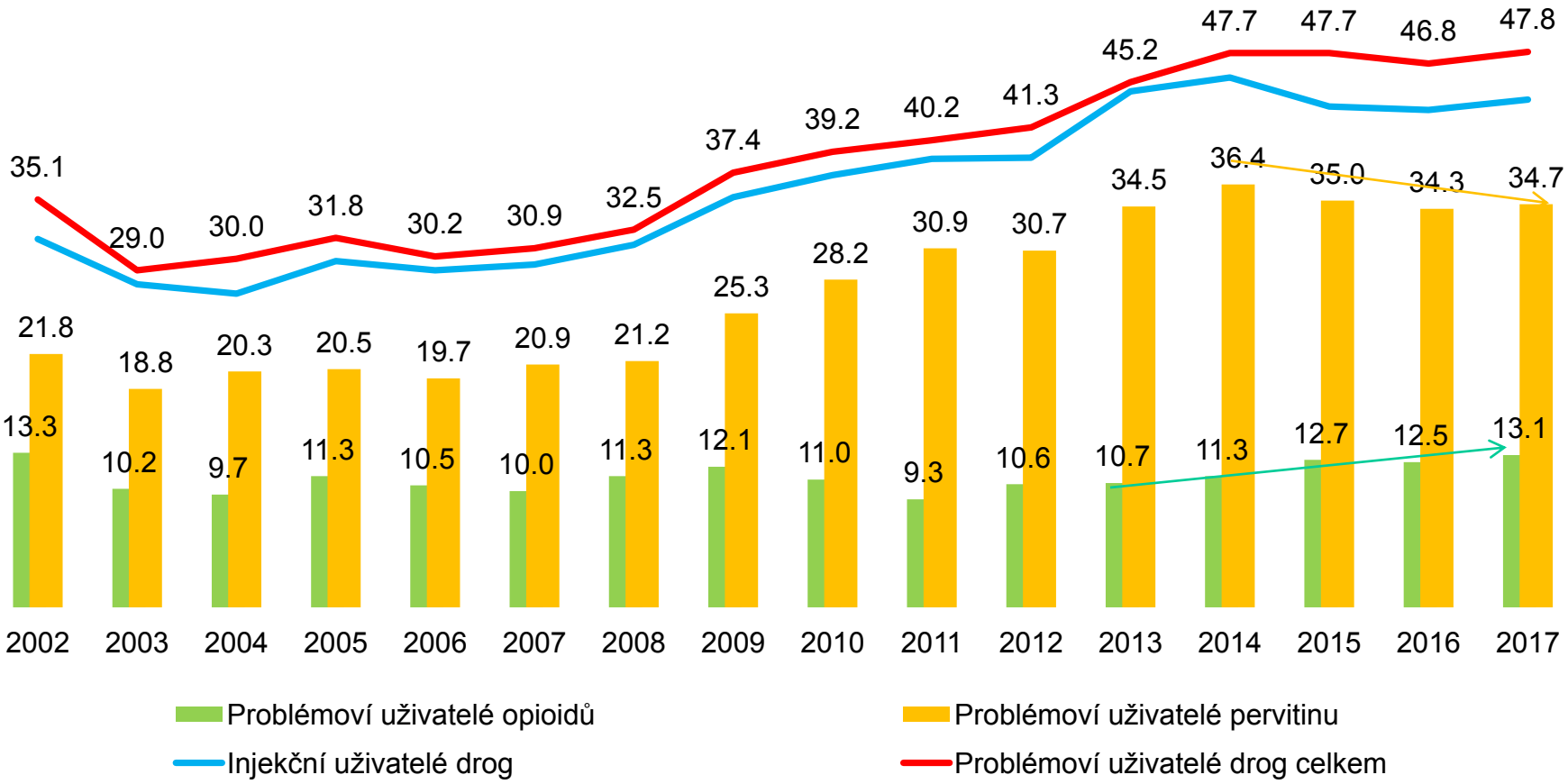
HCV prevalence in risk groups of inhabitants in EU/EEA countries



Source: ECDC reports - Hepatitis B and C epidemiology in Selected Populations and Systematic review on Hepatitis B and C prevalence in the EU/EEA https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/systematic-review-hepatitis-B-C-prevalence.pdf

Problematic drug abusers in the CR (2017)

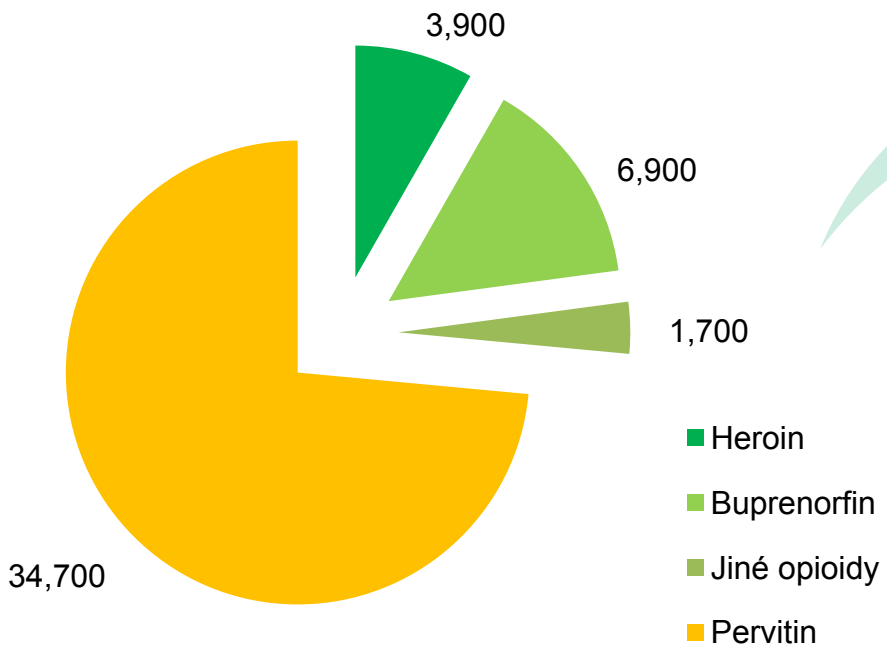
About 44 000 intravenous drug abusers (cca 90 % of all)



Zdroj: Národní monitorovací středisko pro drogy a závislosti (2018)

Problematic drug abusers in the CR (2017)

2017 - Estimation in the CR - 47 800 problematic drug abusers, about 90 % intravenous

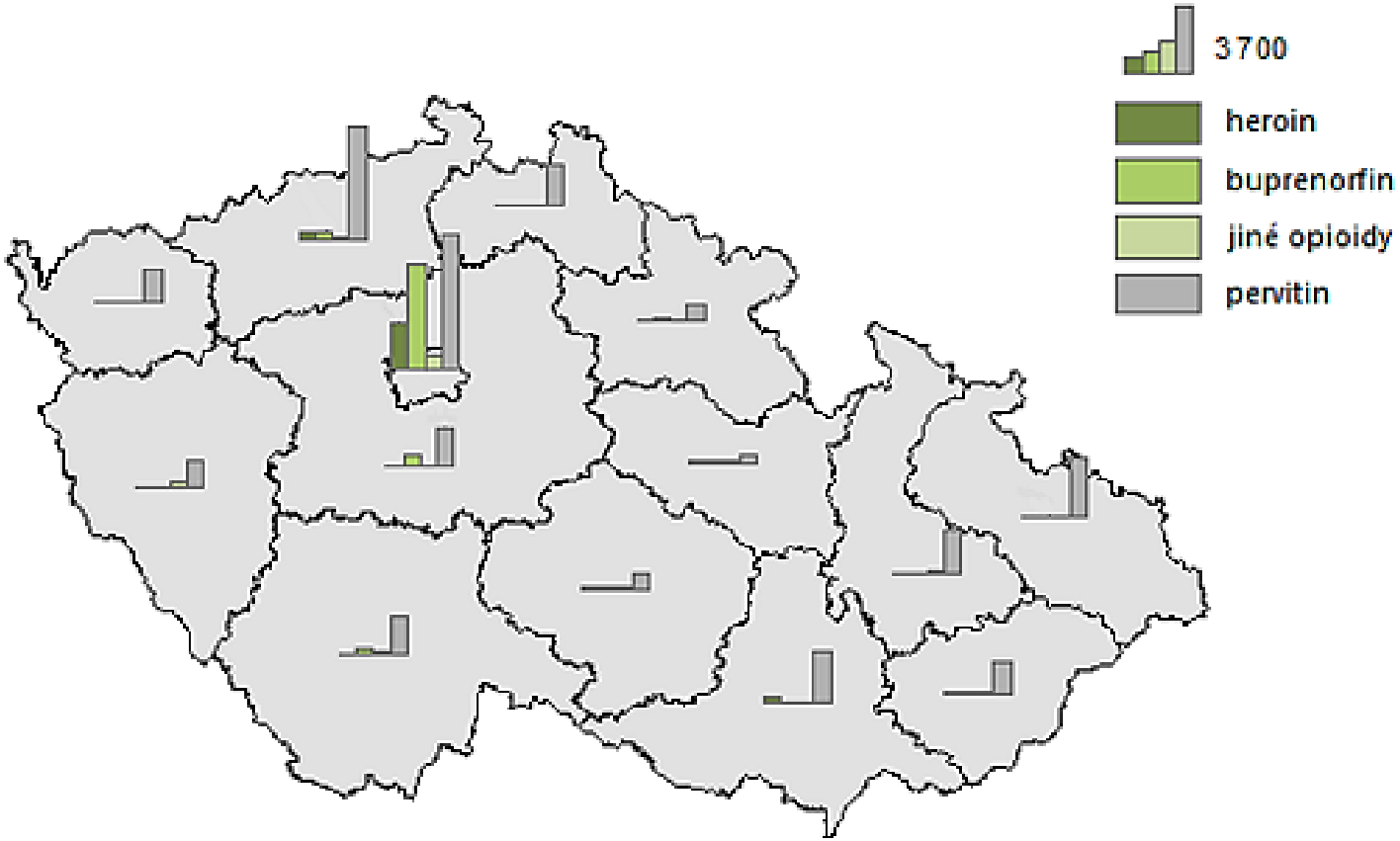


opiates

- fentanyl
- Vendal® Retard (morfin)
- Palladone® (hydromorfon)
- oxycodon

Zdroj: Národní monitorovací středisko pro drogy a závislosti (2018)

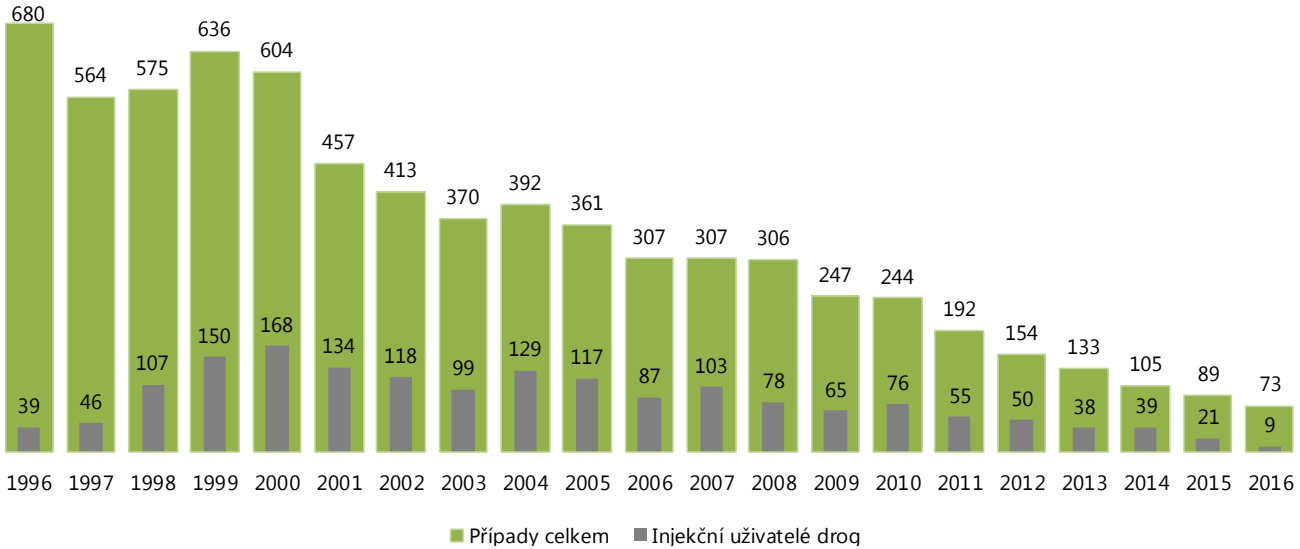
Opiates and pervitin abusus



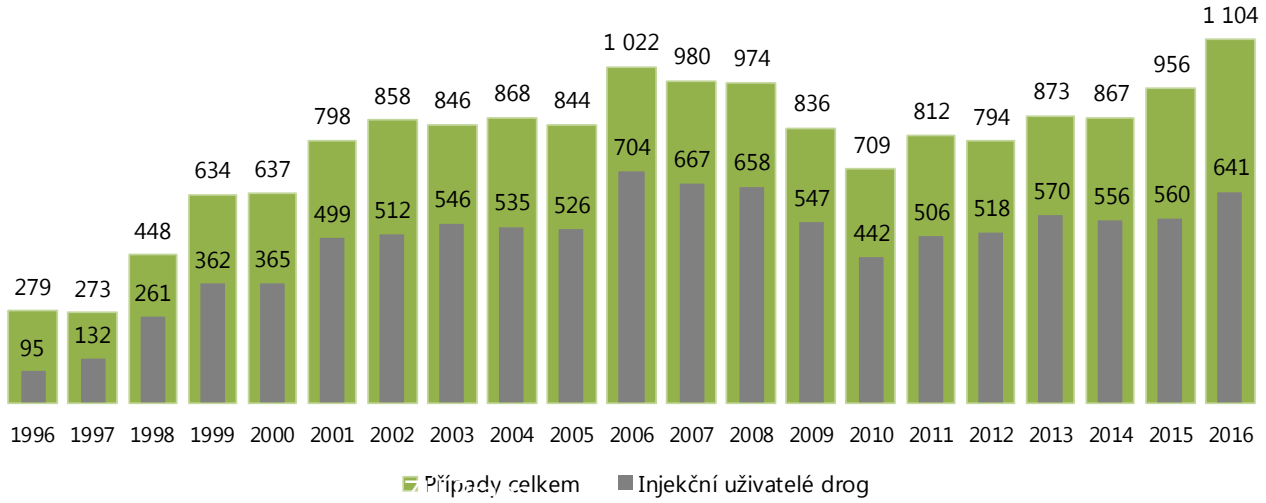
Zdroj: Národní monitorovací středisko pro drogy a závislosti (2018)

Infectious diseases in IUDs – new cases 1996-2016

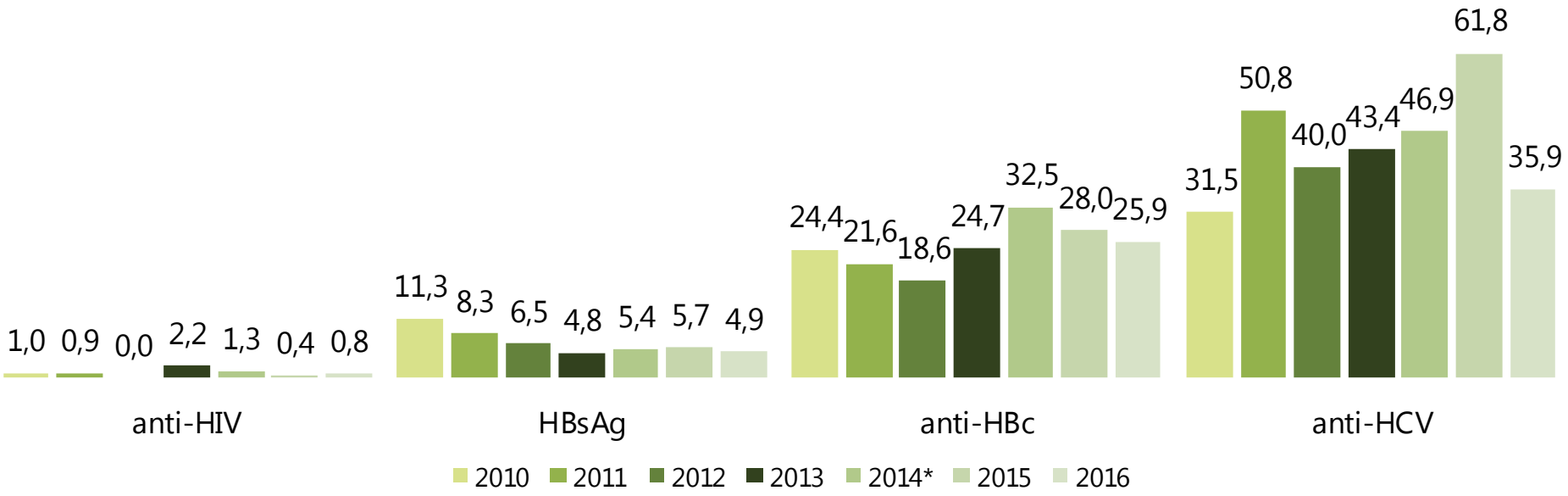
Acute HBV



Acute and chronic HCV



Infectious diseases in IUD in prison (%)



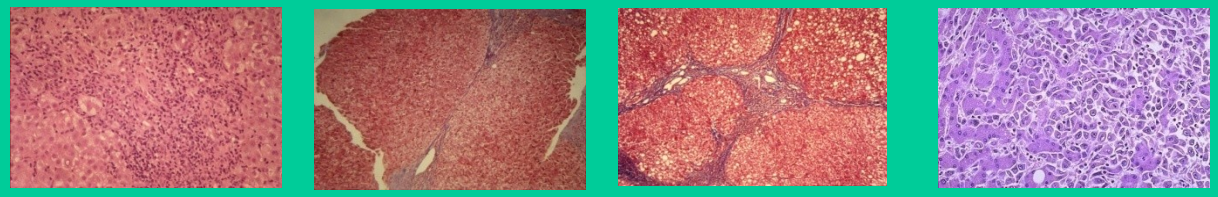
Clinical course of HCV infection

Slow

> 30 years

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

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



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

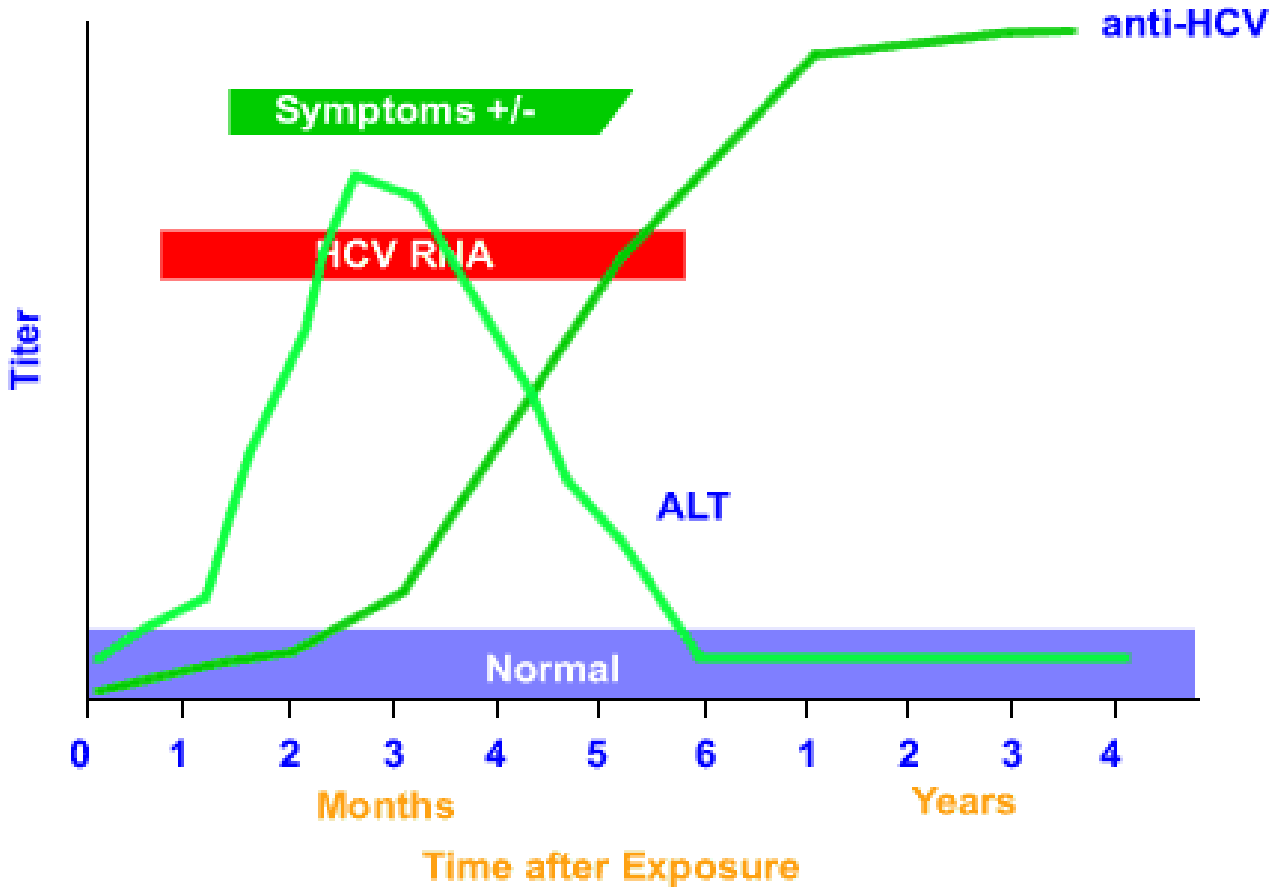
Fibrosis

Rapid

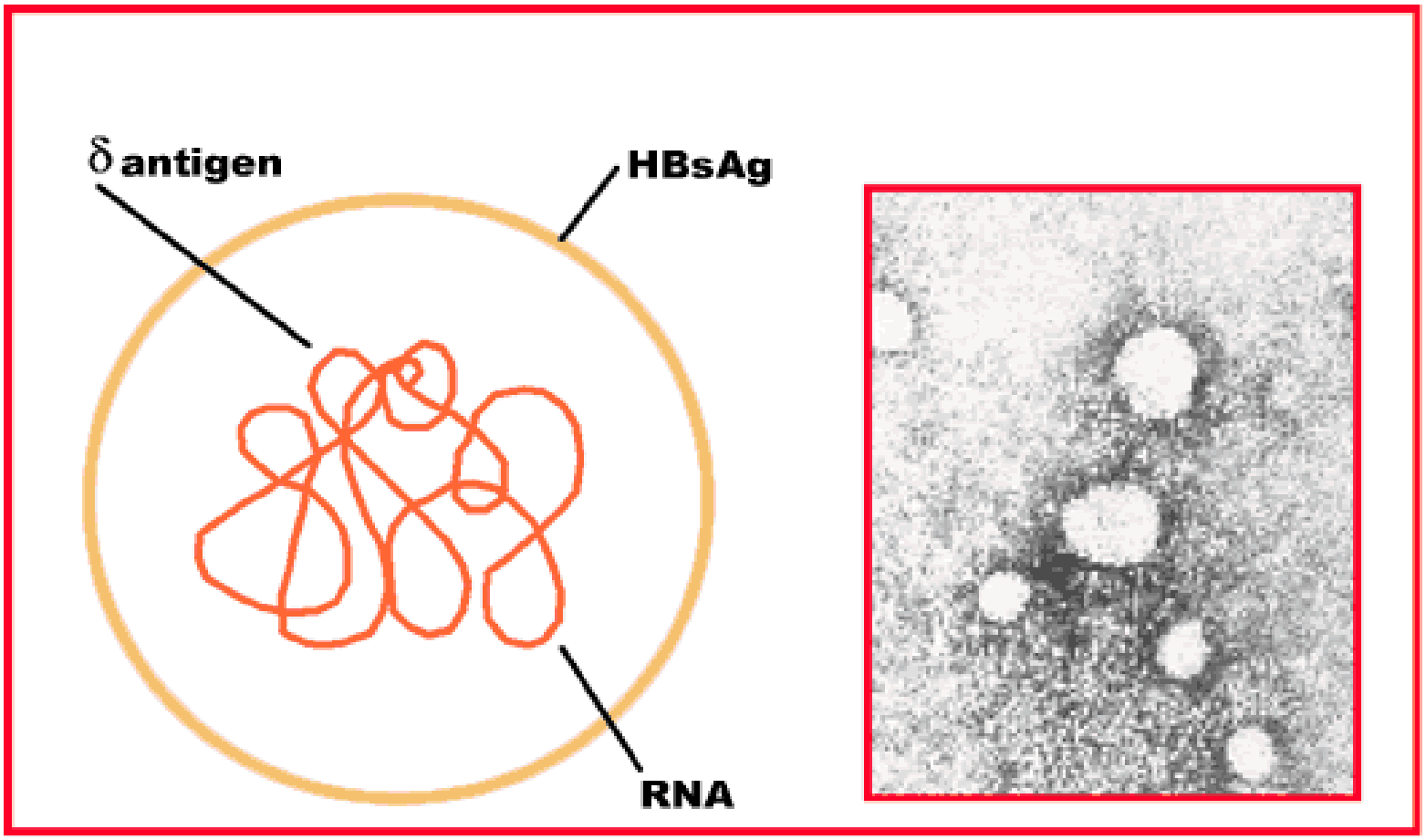
< 20 years

Alcohol, co-infection (HBV,HIV),

Diagnosis of HCV infection



Hepatitis D (Delta) Virus (HDV)



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

Hepatitis D: fast facts

9-60 million people infected with HDV globally

Defective RNA virus, requiring HBV for infection

4.5-13% of HBV carriers co-infected with HDV

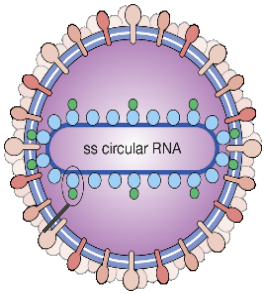
Most severe form of viral hepatitis

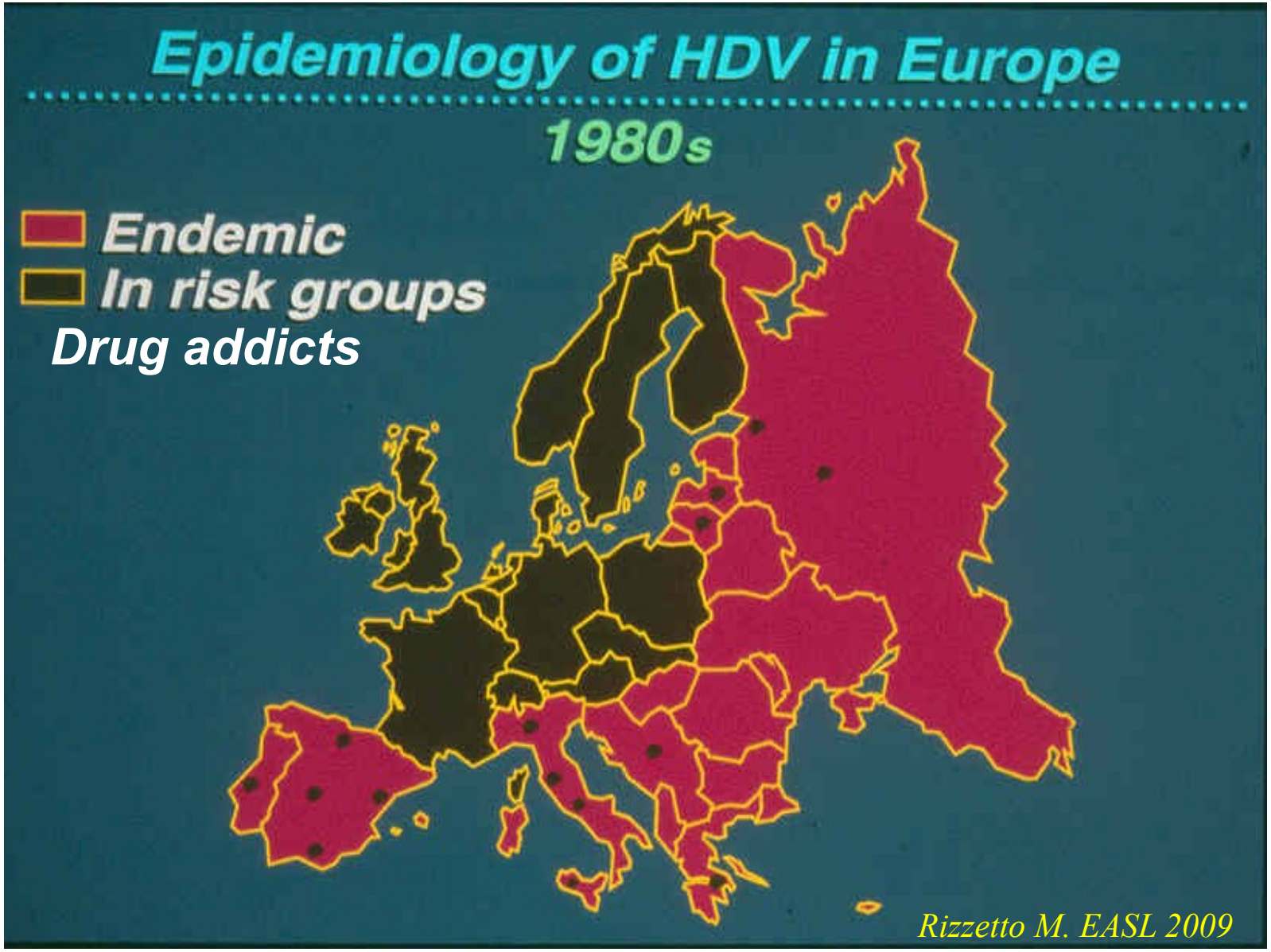
Increased risk of cirrhosis/HCC and higher mortality vs HBV

Progression to cirrhosis within 5 years and to HCC within 10 years

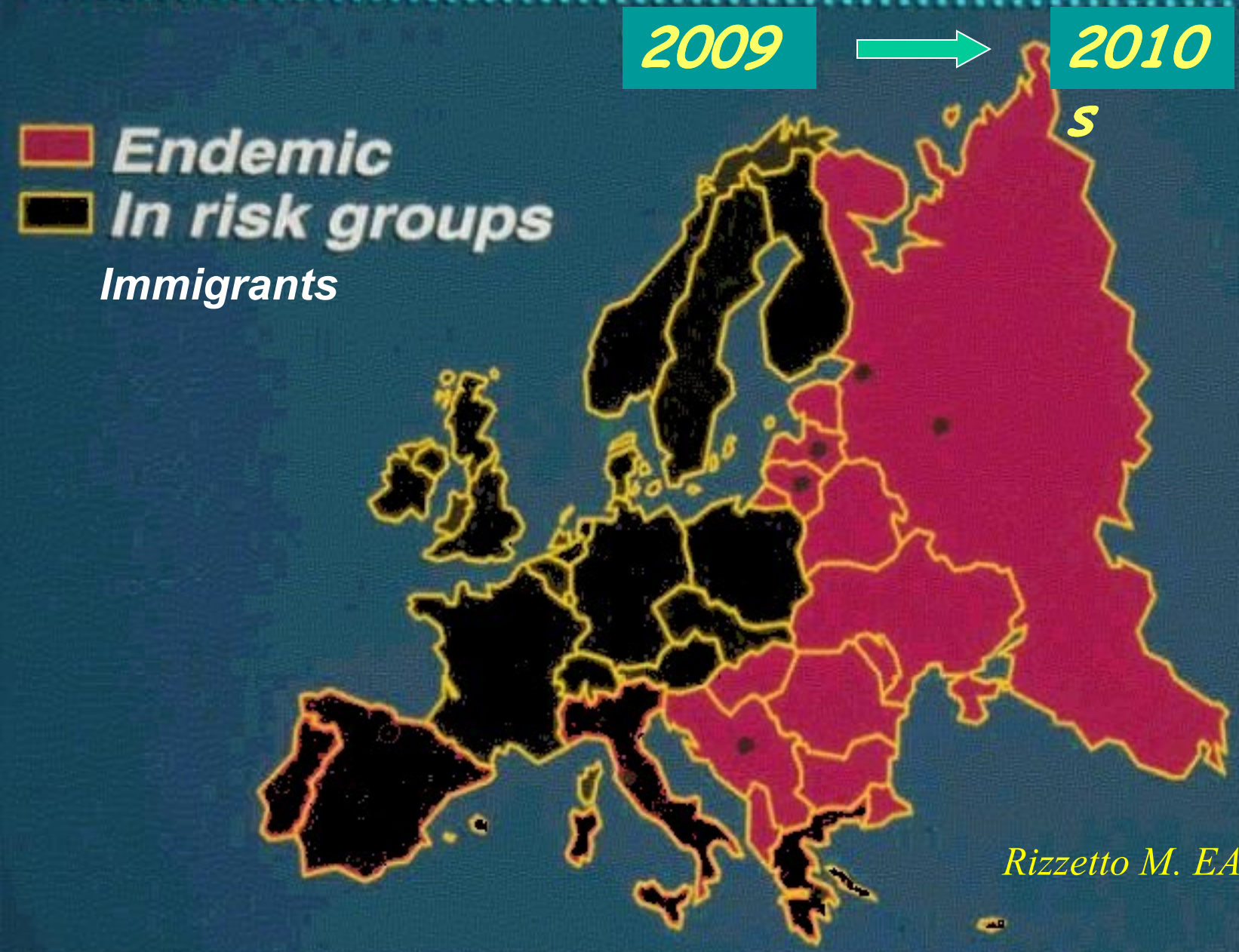
Eight HDV genotypes

Until recently, no approved therapeutic options

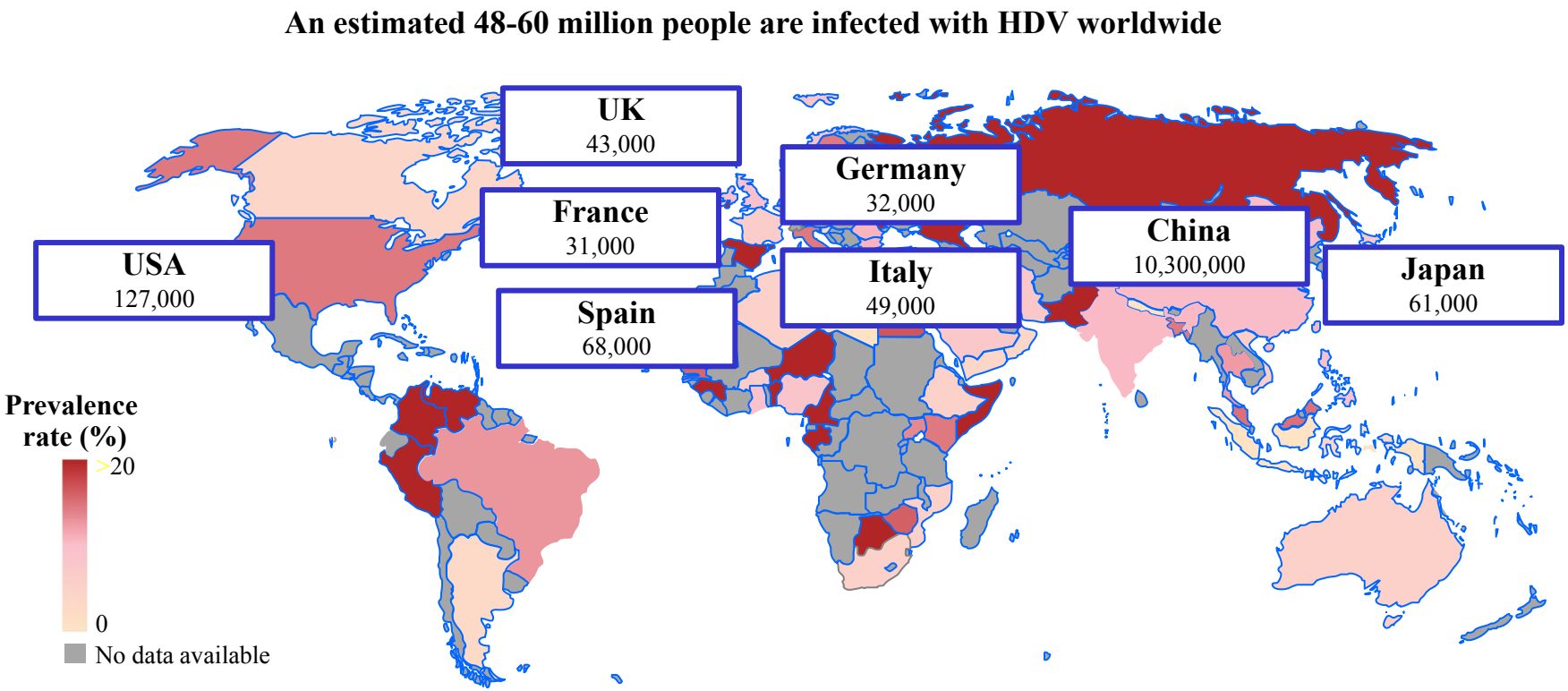



Epidemiology of HDV in Europe
1980s
Endemic
In risk groups
Drug addicts
Rizzetto M. EASL 2009

Epidemiology of HDV in Europe

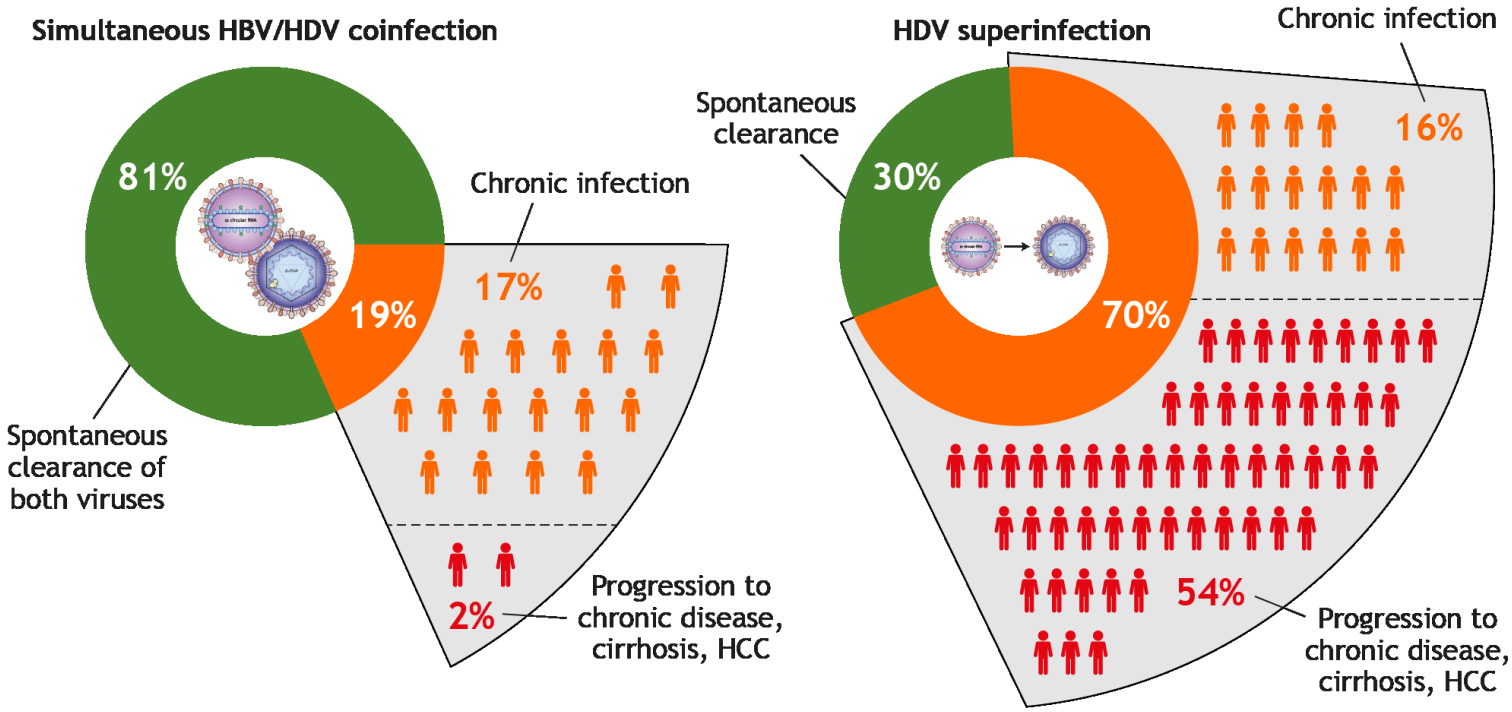


Estimated number of individuals with HDV in selected countries



Numbers shown are patient numbers, ie prevalence of HDV in HBsAg-positive patients.
HBsAg: hepatitis B surface antigen; HDV: hepatitis delta virus.

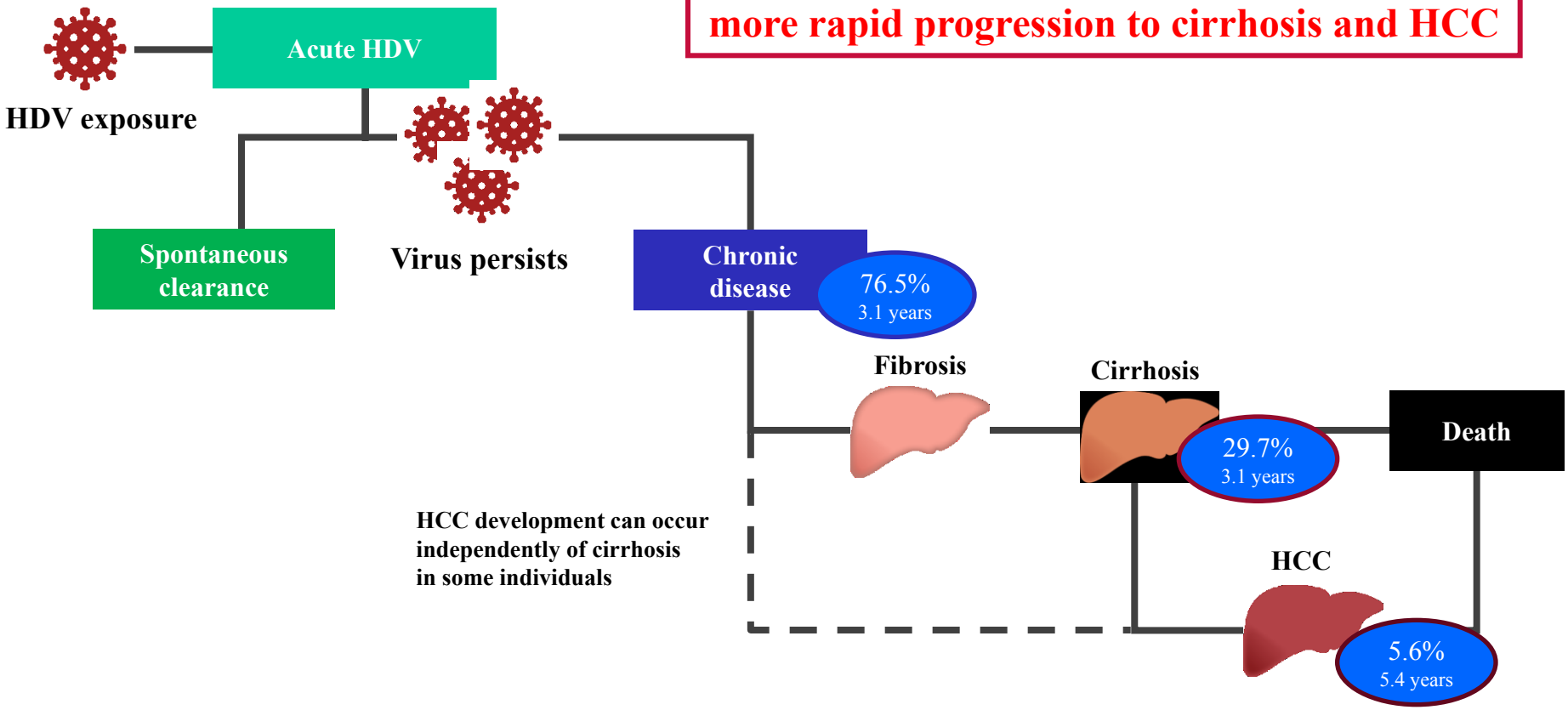
Clinical course of HBV/HDV infection depends on timing of HDV infection



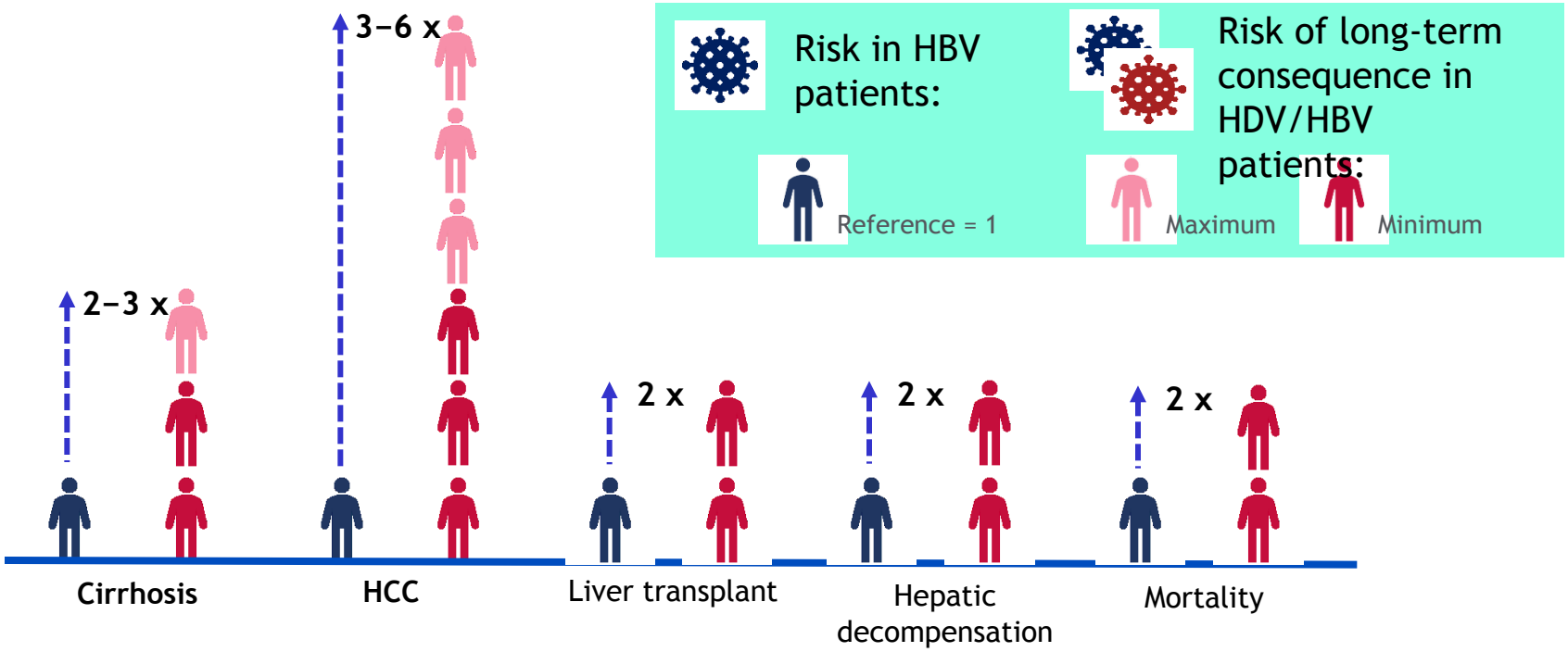
Data presented are based on estimates of HDV prevalence and disease progression rates determined in a large global epidemiology analysis.
HBV: hepatitis B virus; HCC: hepatocellular carcinoma; HDV: hepatitis delta virus.

Clinical course of hepatitis delta

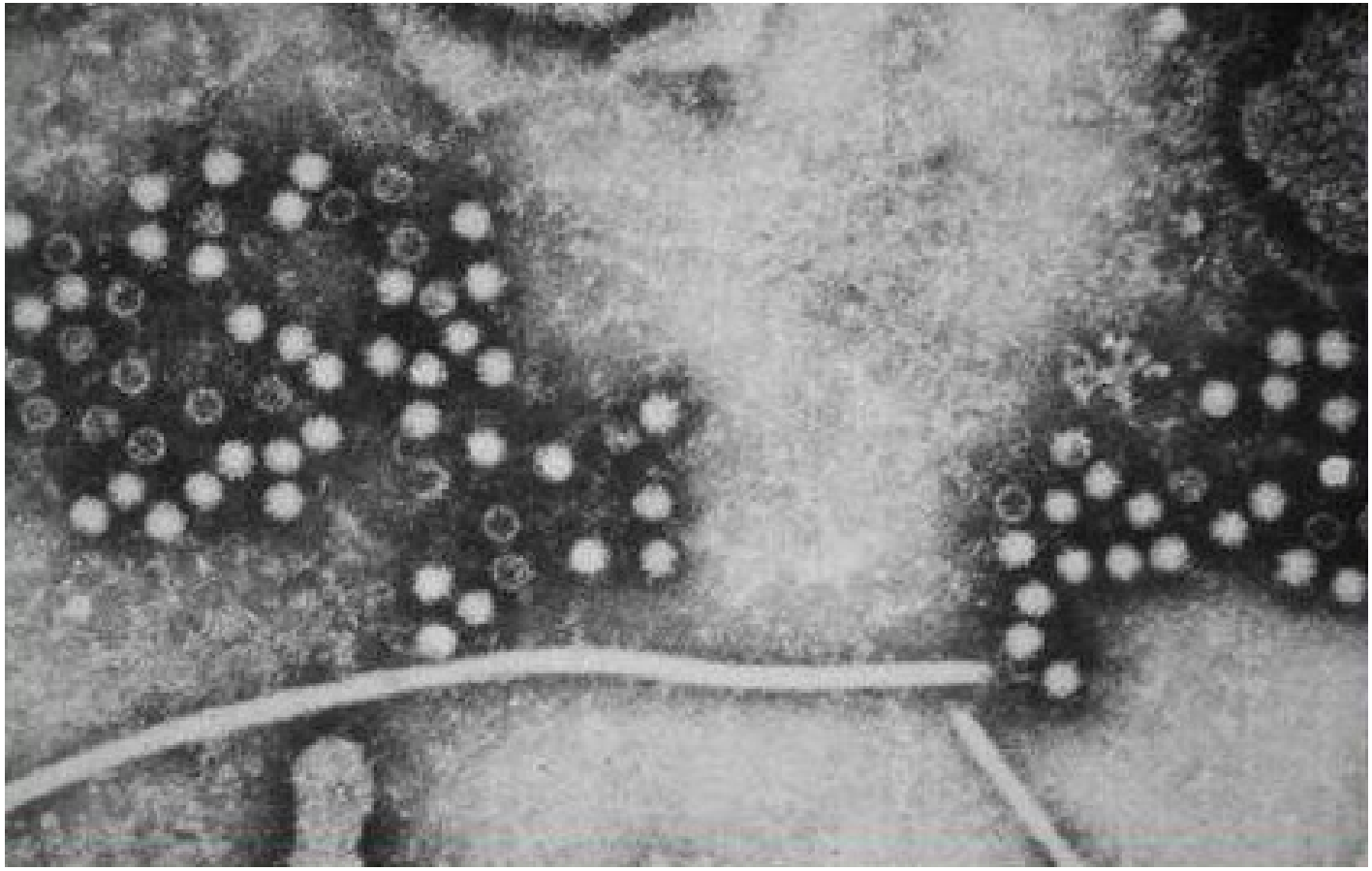
HDV/HBV vs HBV monoinfection:
more rapid progression to cirrhosis and HCC



Increased risk of long-term consequences of viral hepatitis in HBV/HDV patients versus HBV monoinfection

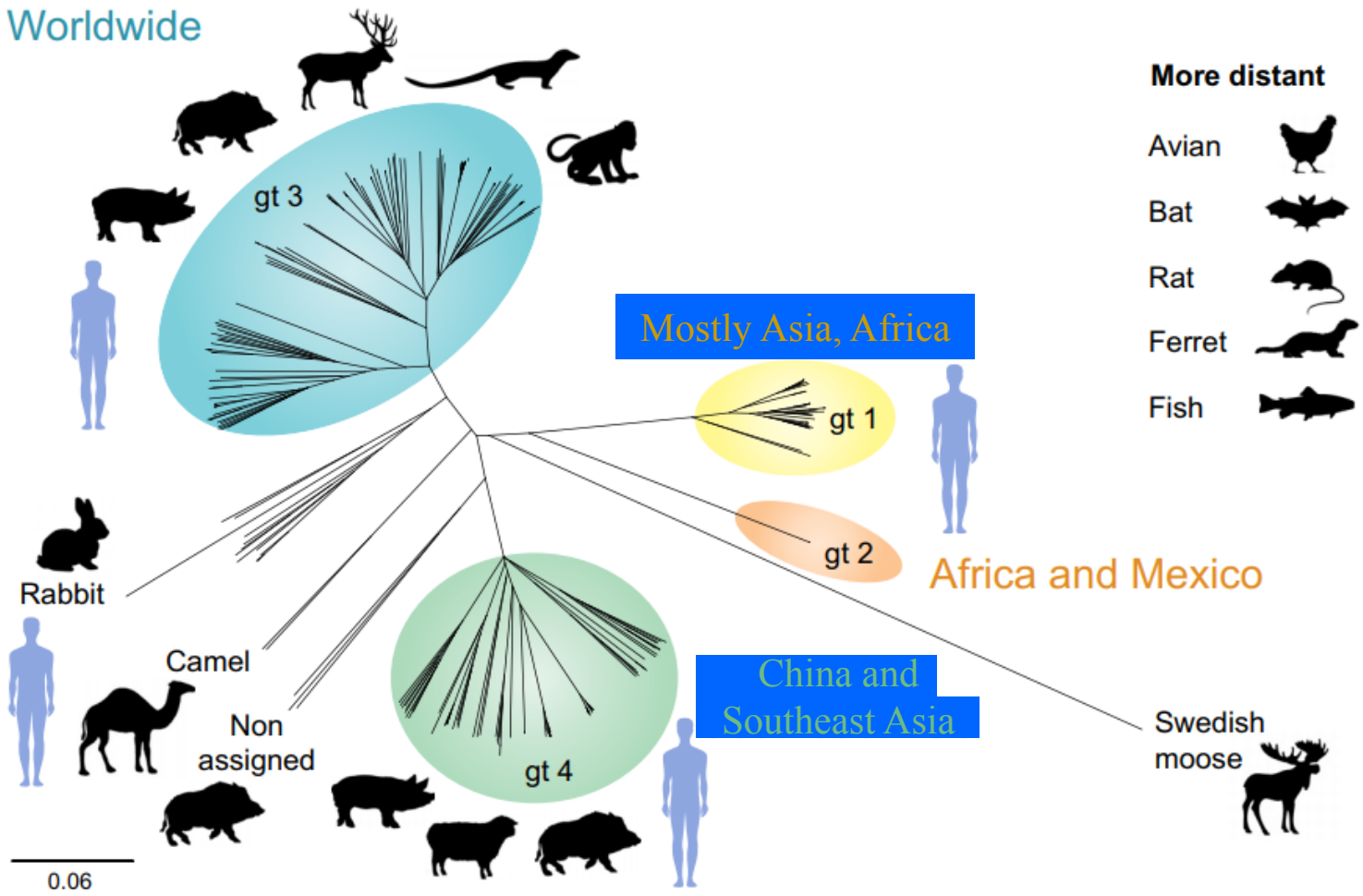


Hepatitis E virus



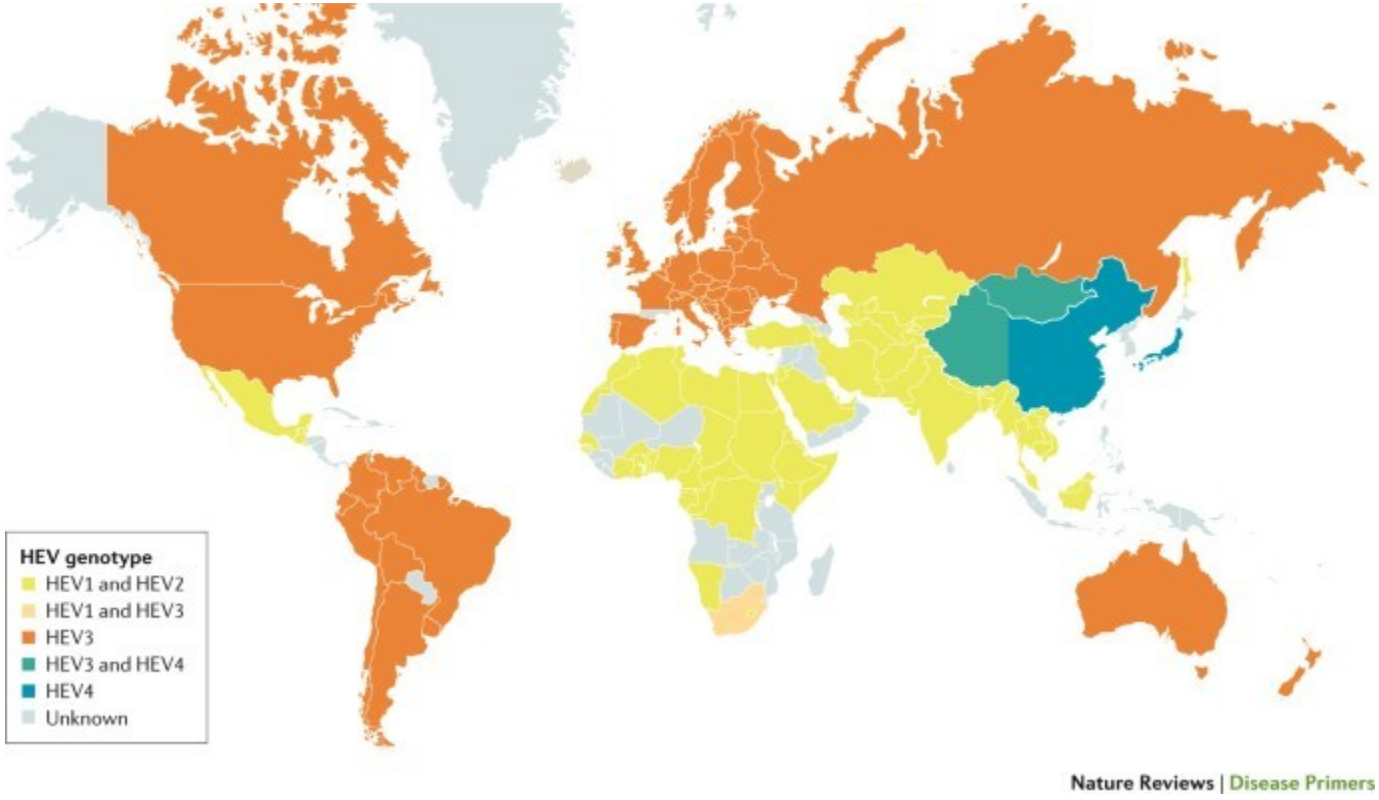
Non-enveloped RNA virus, family Hepeviridae, *genus Orthohepevirus,* 27-34 nm, 8 genotypes (1-8), human infections by G1-4

Phylogenetic relationship of hepeviruses identified in various hosts

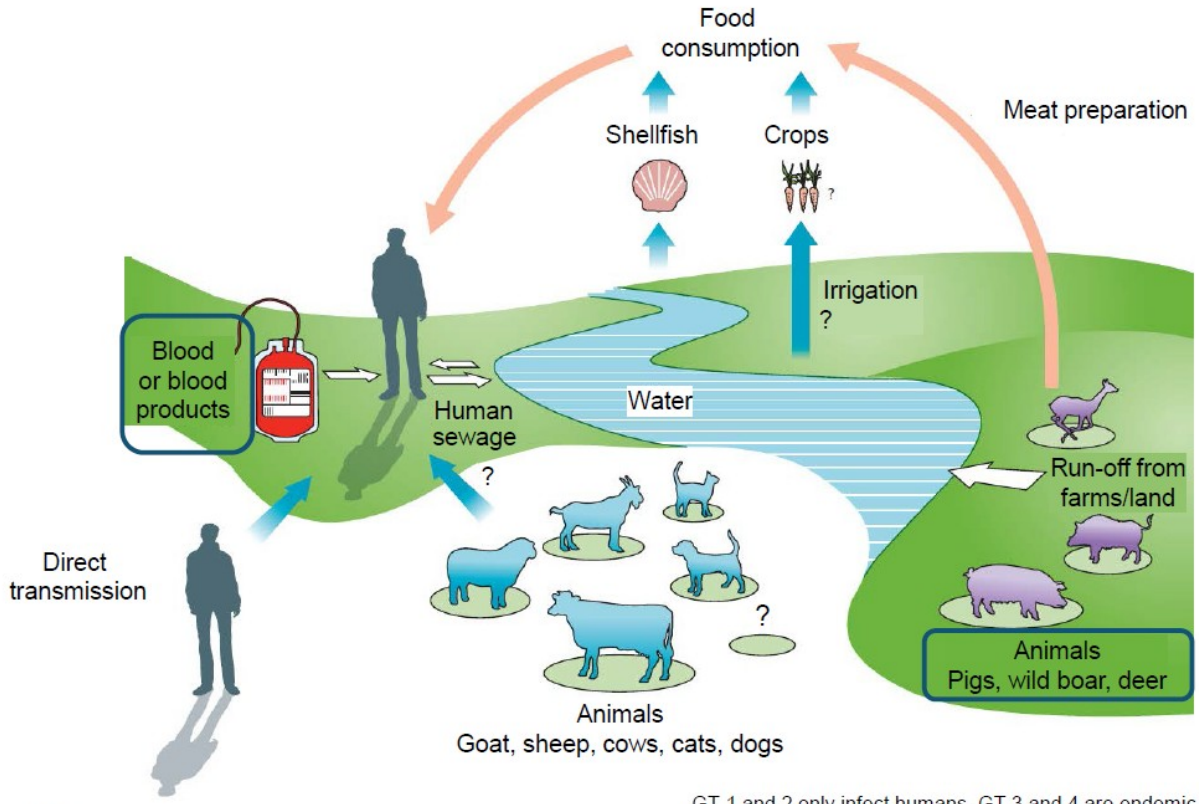


Debing Y, et al. J Hepatol 2016;65:200–12

HEV genotypes (1-4)



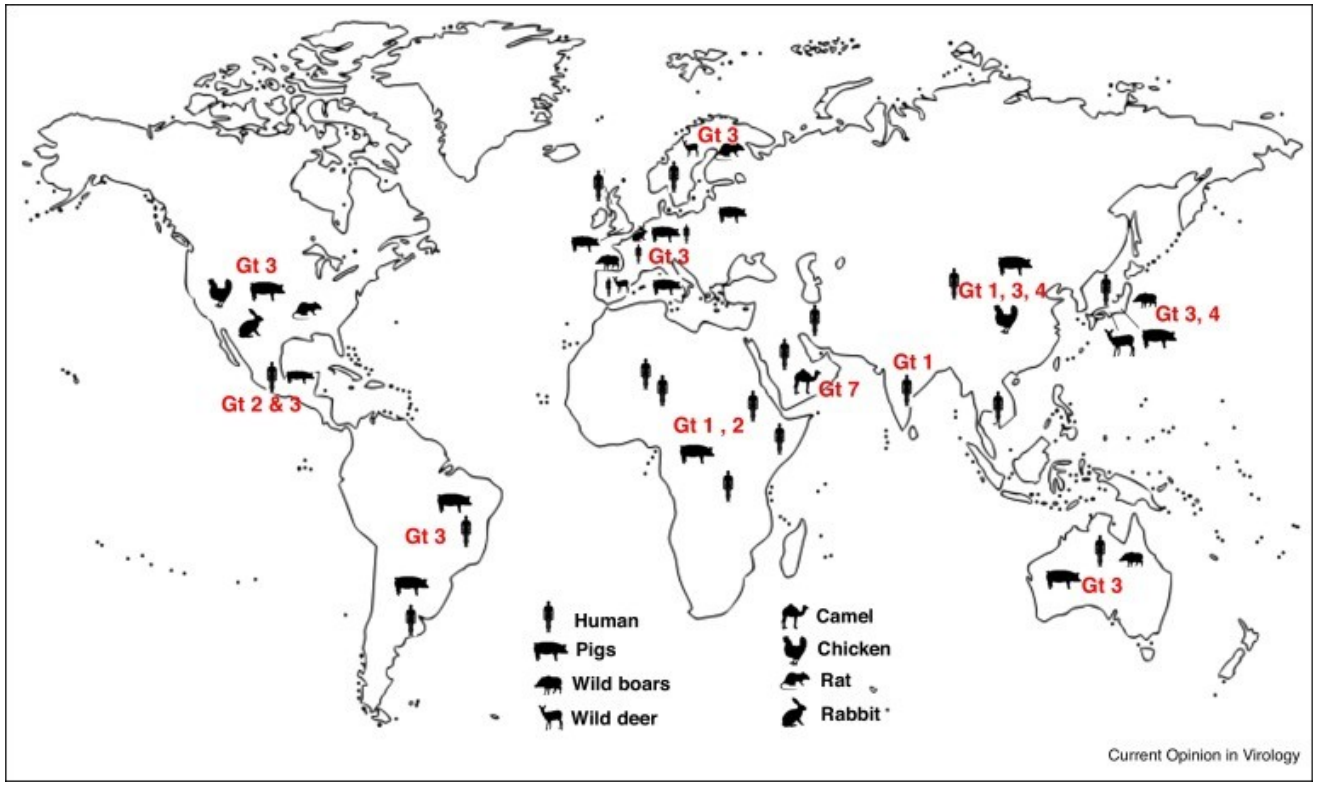
Transmission of HEV



Kamar N, et al. Lancet 2012; 379:2477–88

GT 1 and 2 only infect humans. GT 3 and 4 are endemic in animal species such as pigs and wild boar, causing zoonotic infections in humans via consumption of contaminated meat, direct contact or other probable routes.

Sources of HEV infection



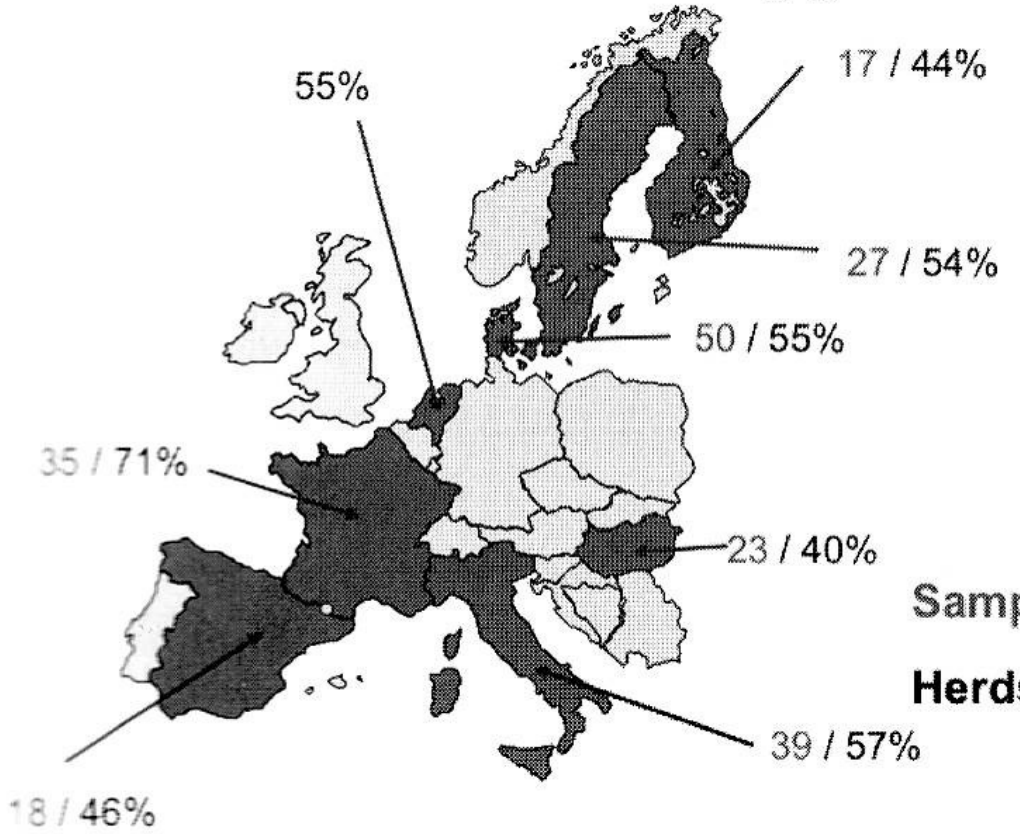
Infection with G-1,2 HEV

- 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 (venison as well)
- 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)



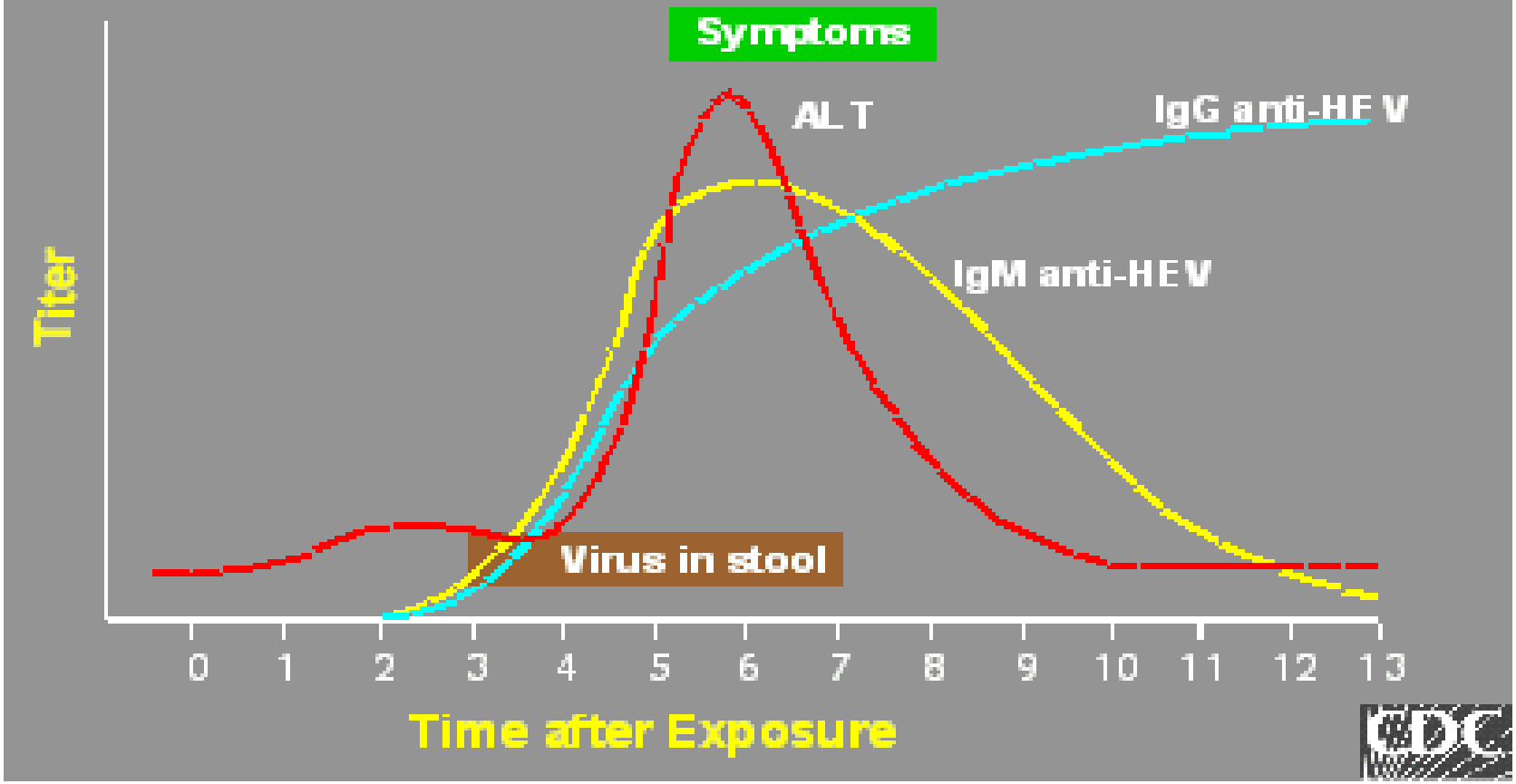
Samples: Avg = 32%

Herds: Avg = 52%

Figatellu – sausage with raw pork liver

Hepatitis E Virus Infection

Typical Serological Course



Rapid progression of chronic hepatitis E

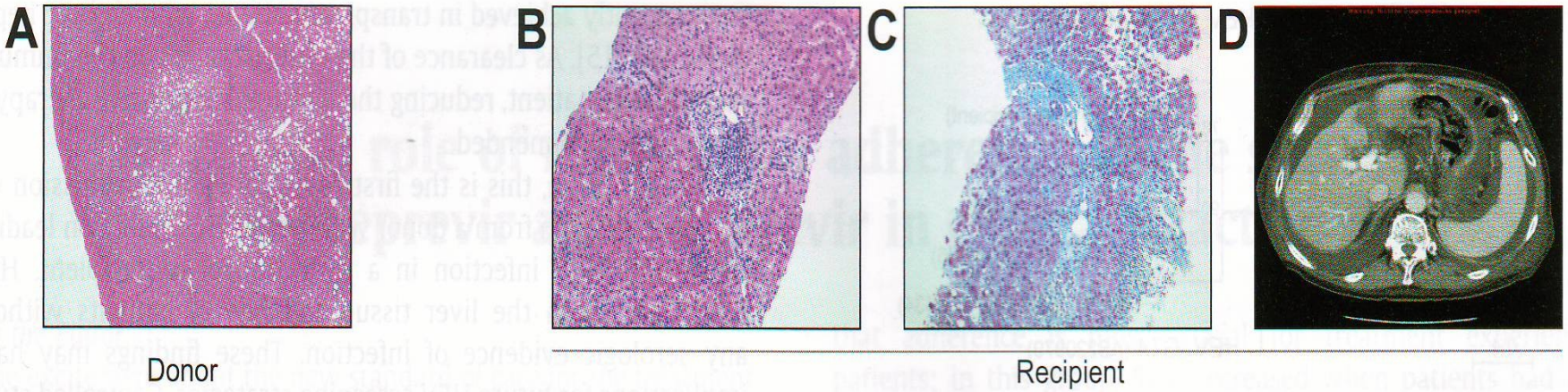


Fig. 1. Histologic assessment of the liver tissue before and after OLT and CT scan after OLT. (A) The liver tissue of the donor revealed absence of significant signs of chronic hepatitis but vesicular fatty liver disease was diagnosed. (B) Second biopsy. One hundred and fifty days after OLT, chronic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

✓ antivirals for complicated acute HEP B and E

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

✓ entecavir

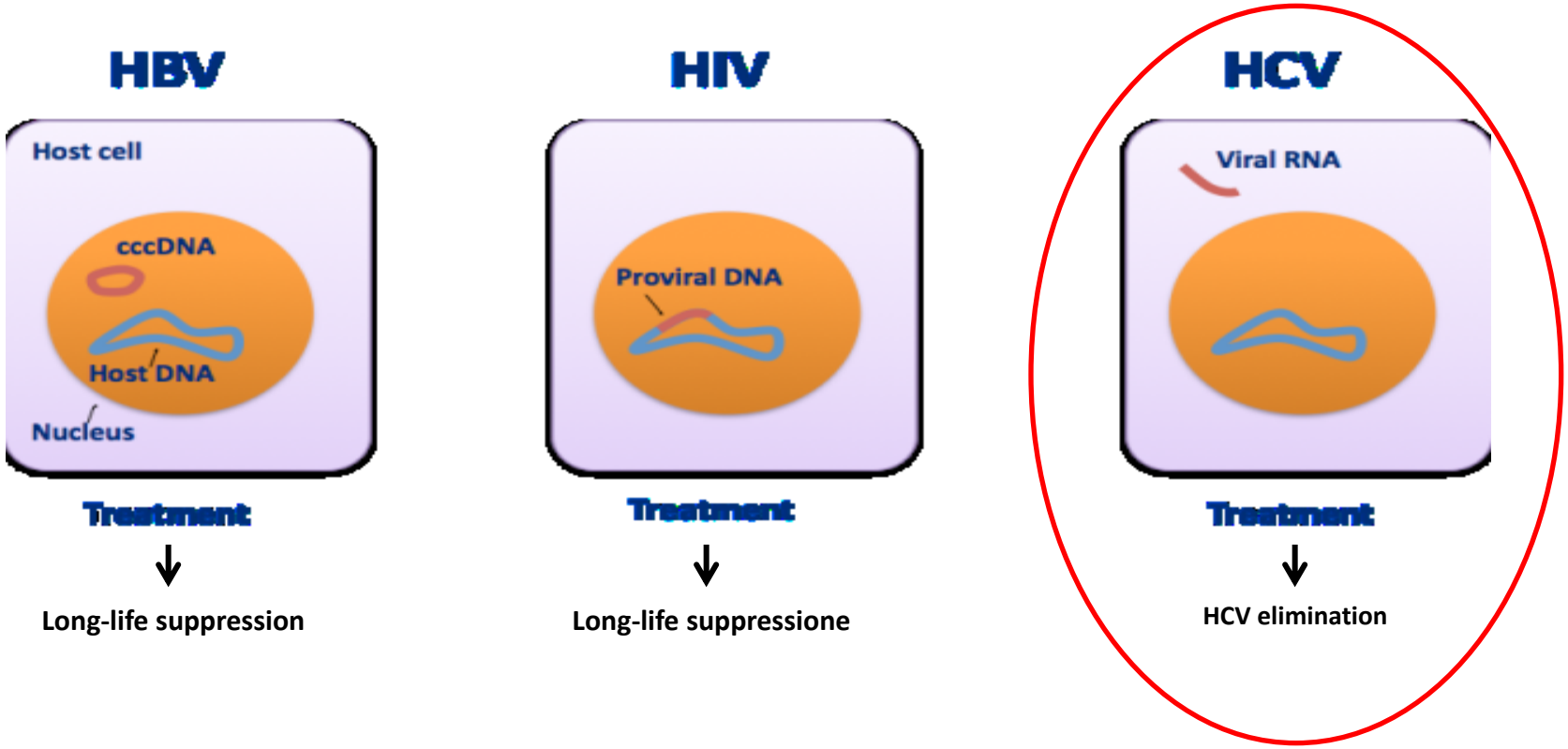
Current possibilities of treatment of chronic HEP B

- tenofovir
- entecavir

IFN-free regimens for HCV infection

- Current standard of HCV therapy
- Combination of oral drugs – DAA – direct-acting antivirals
- High efficacy – minimally 99 %
- Almost no adverse events
- Short duration of therapy – 8 or 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

Hepatitis D treatment

- PEG-IFN – 1 × weekly s.c.

✓ duration of therapy minimally 1 year

✓ In most cases only temporary effect – frequent relapses after treatment discontinuation

- LAM, ETV, TDF, TAF – non-effective – HDV has no target enzyme – reverse transcriptase
- Bulevirtid (entry inhibitor) s.c. 1× daily, duration of therapy was not definitely established

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!

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