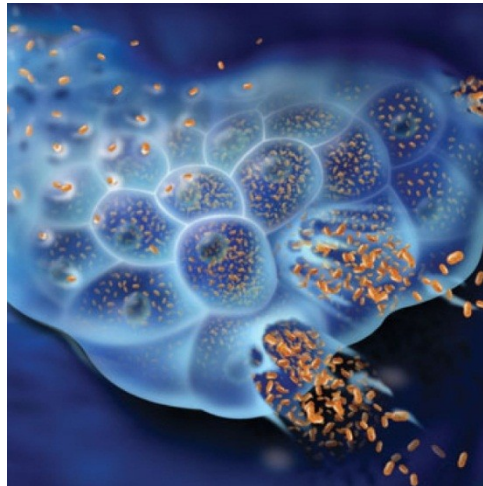


Viral Hepatitis

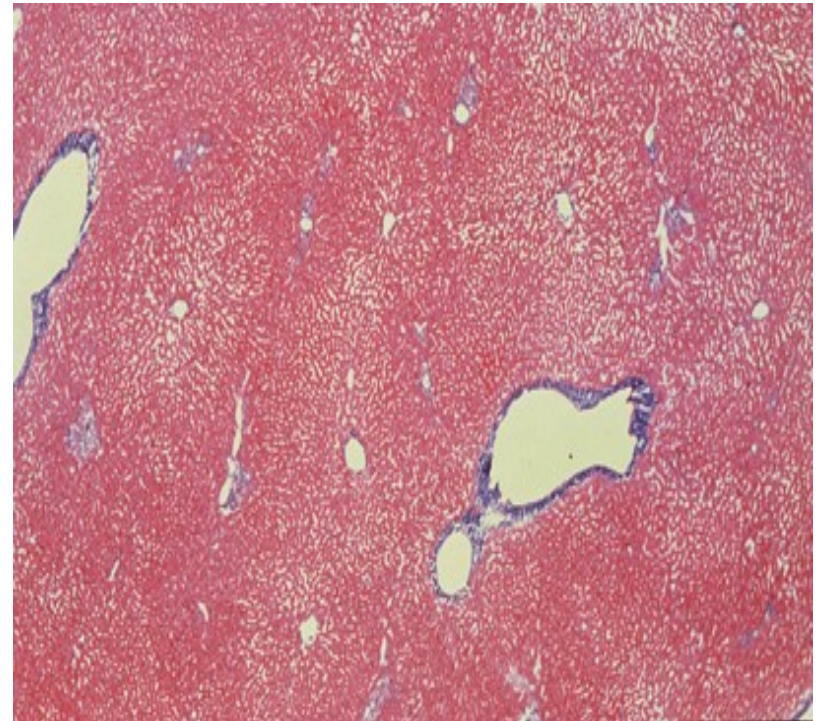
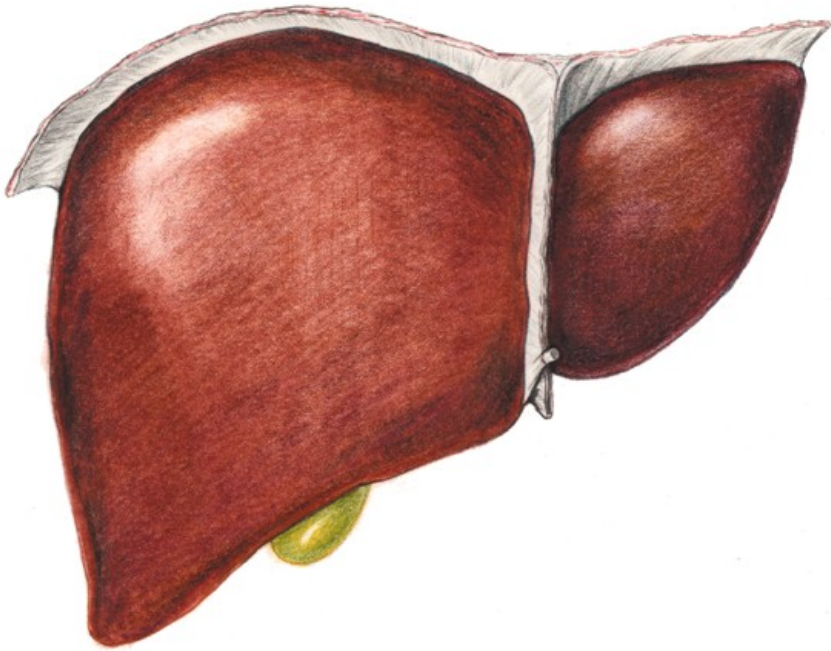


prof. MUDr. Petr Husa, CSc.
Klinika infekčních chorob, FN Brno

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

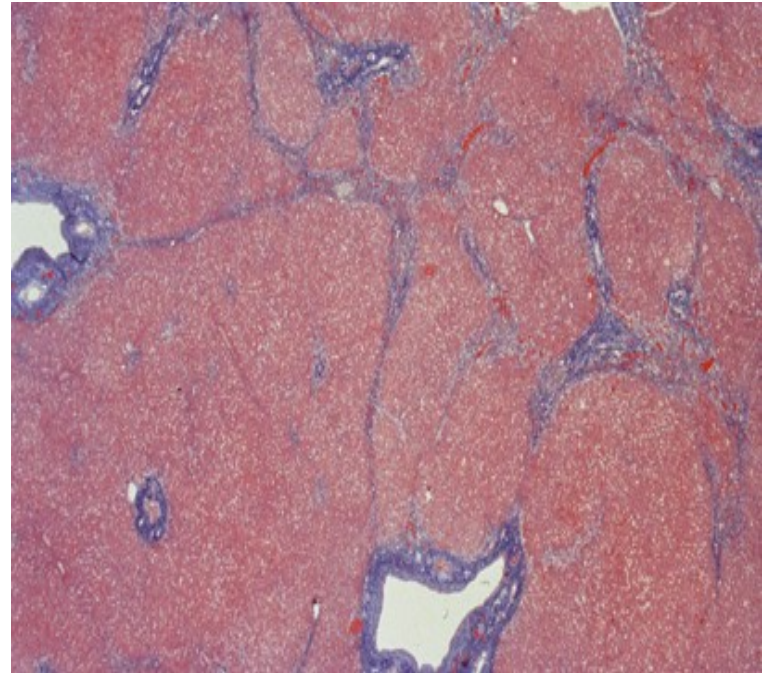
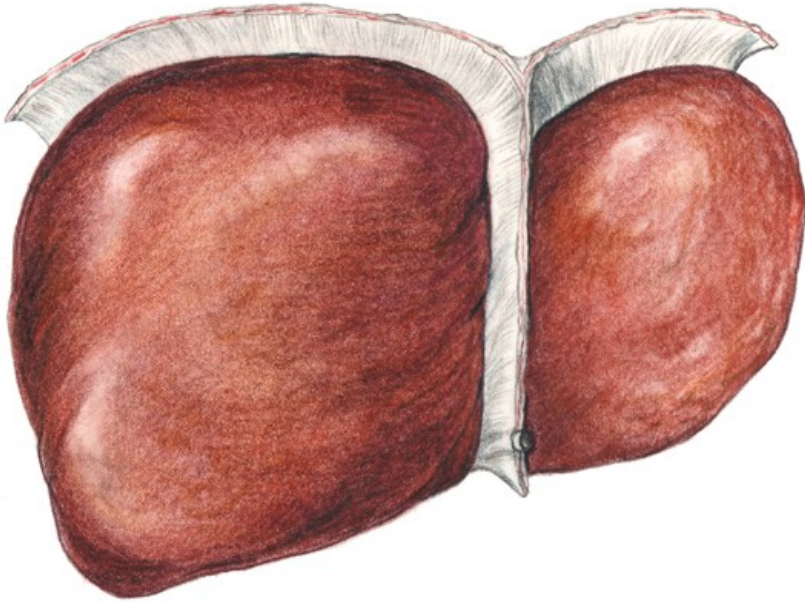
Healthy liver



Normal Biopsy



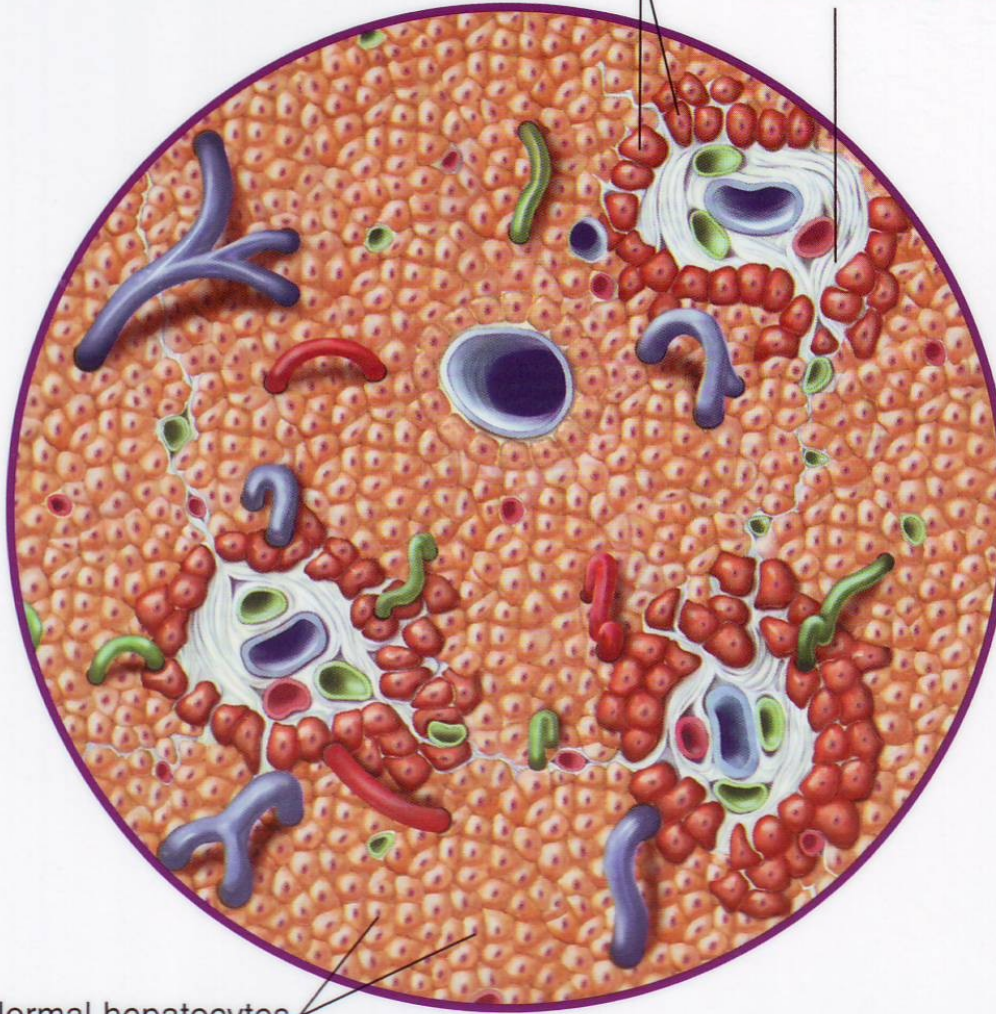
Liver fibrosis



Mild Fibrosis

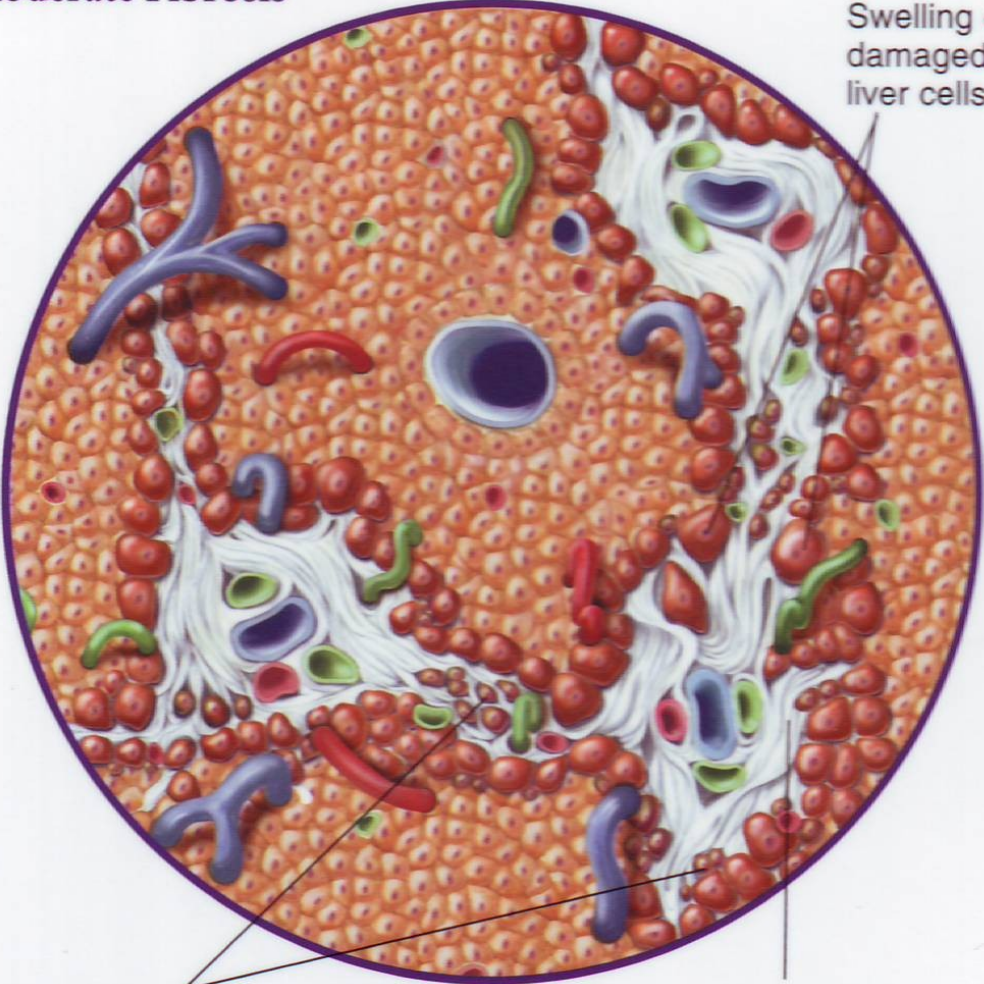
Mild swelling and inflammation of
damaged liver cells around portal areas

Development of
scar tissue (fibrosis)



Normal hepatocytes
(liver cells)

Moderate Fibrosis

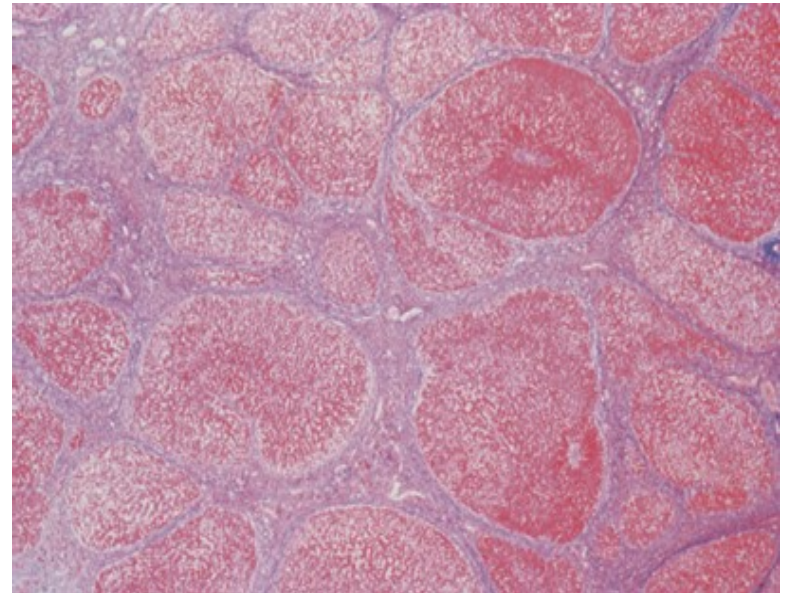
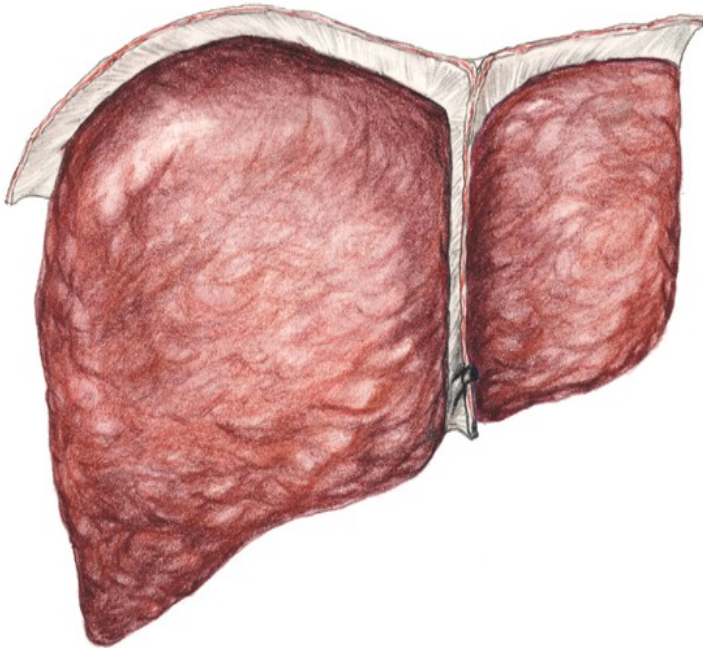


Swelling of
damaged
liver cells

Necrosis of liver cells

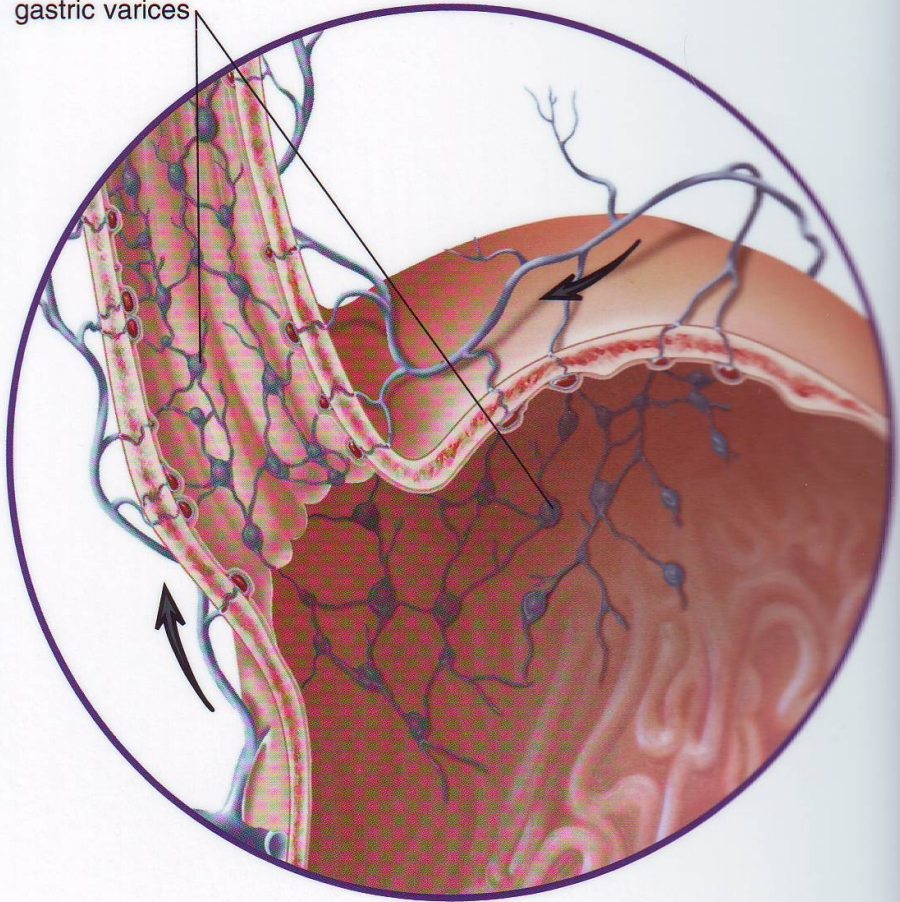
Fibrosis extending
between portal areas

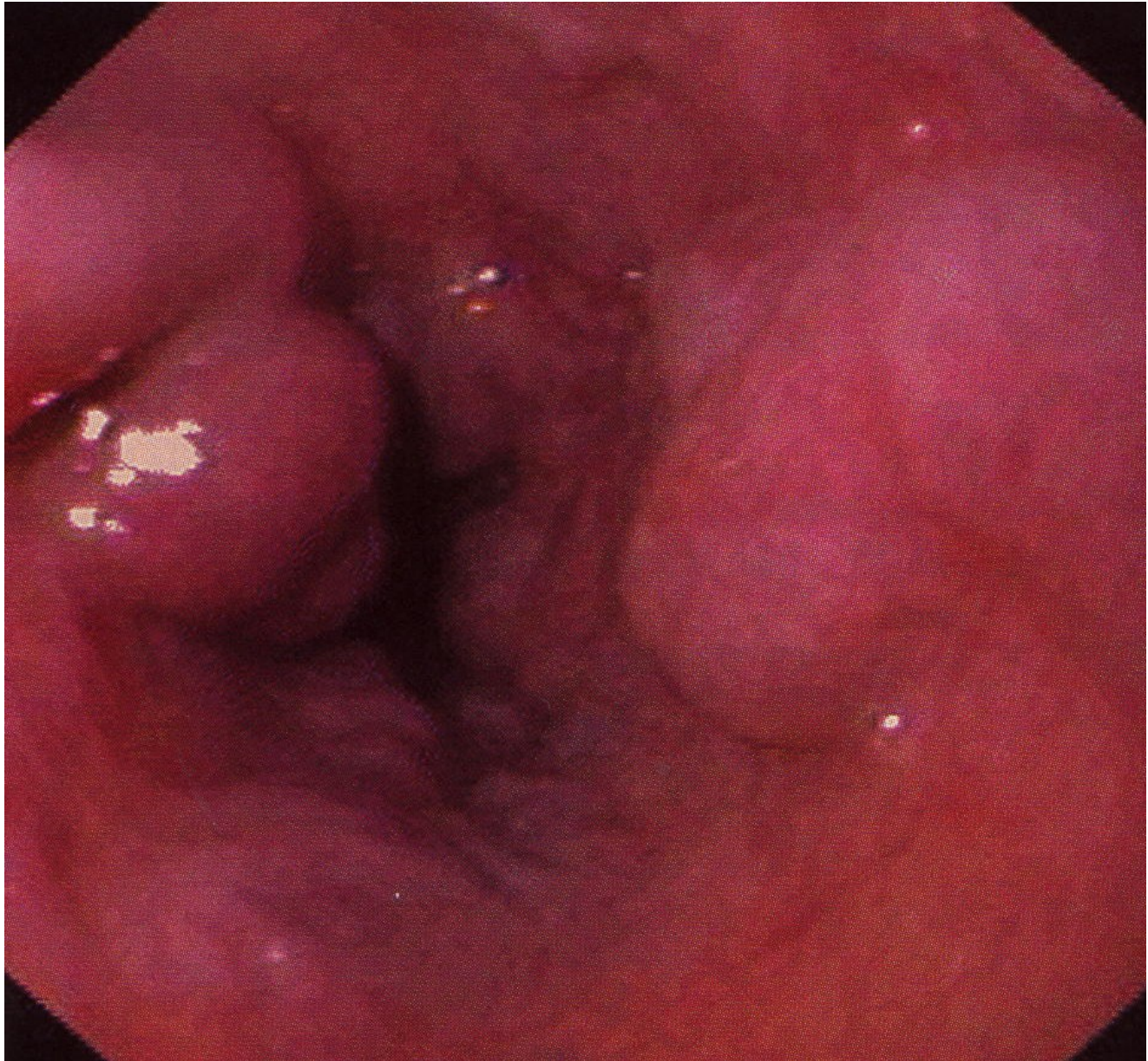
Liver cirrhosis

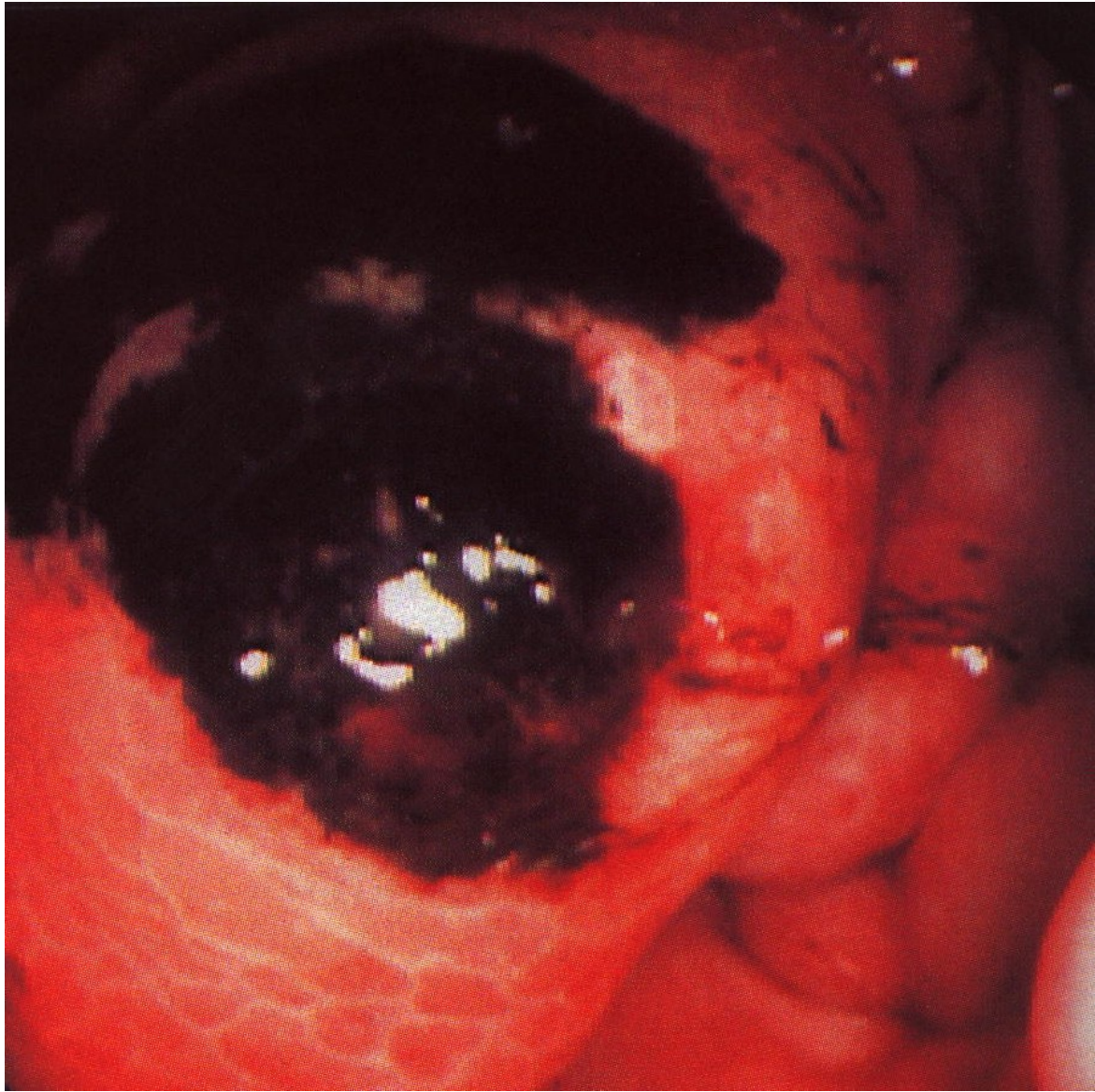


Development of Varices

Esophageal and gastric varices



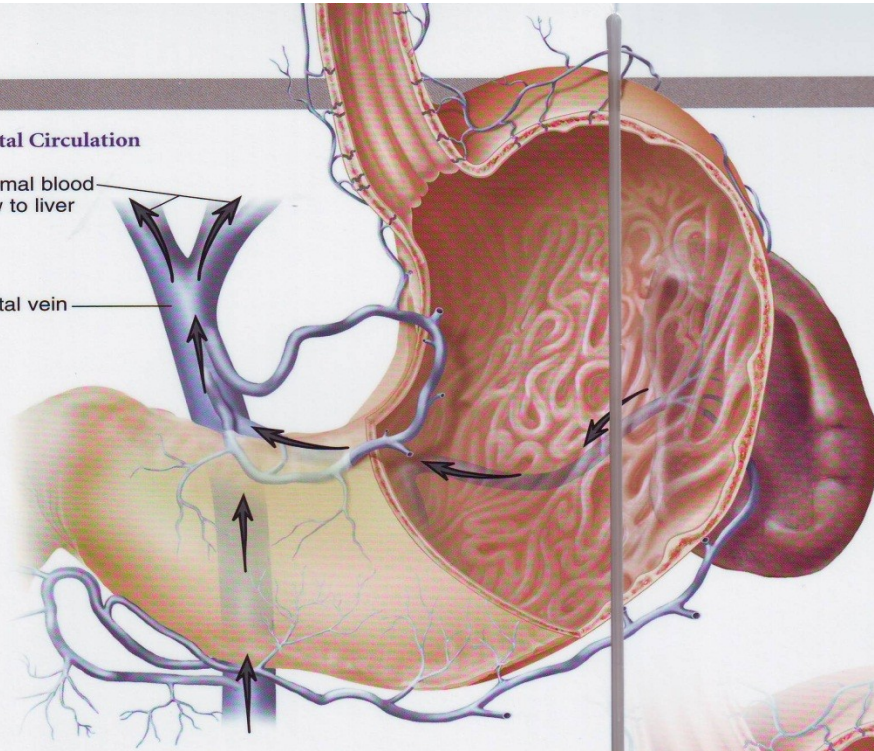




Portal Circulation

Normal blood flow to liver

Portal vein

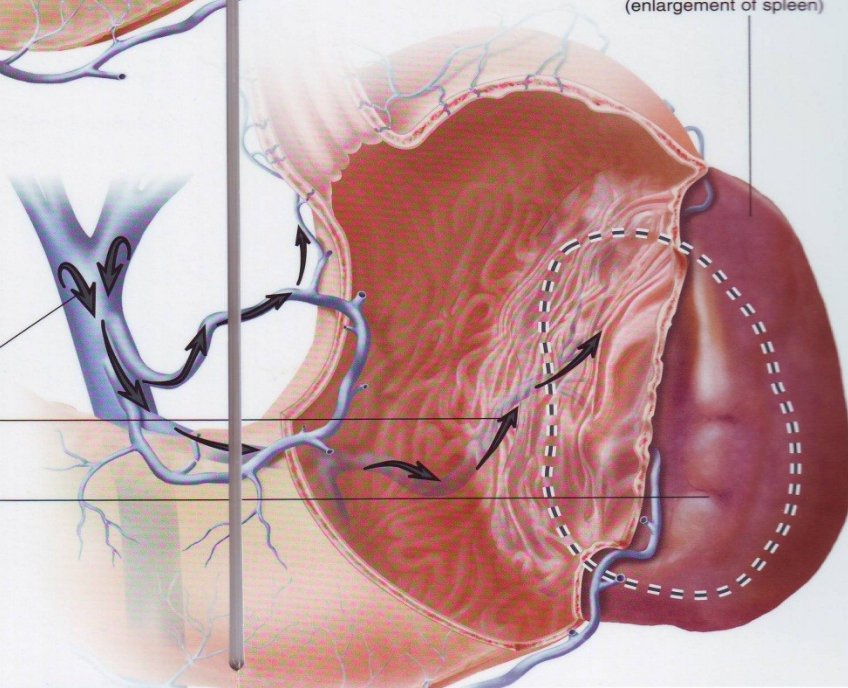


Splenomegaly
(enlargement of spleen)

Portal Hypertension

As pressure in portal vein rises, blood backs up into spleen

Size of normal spleen

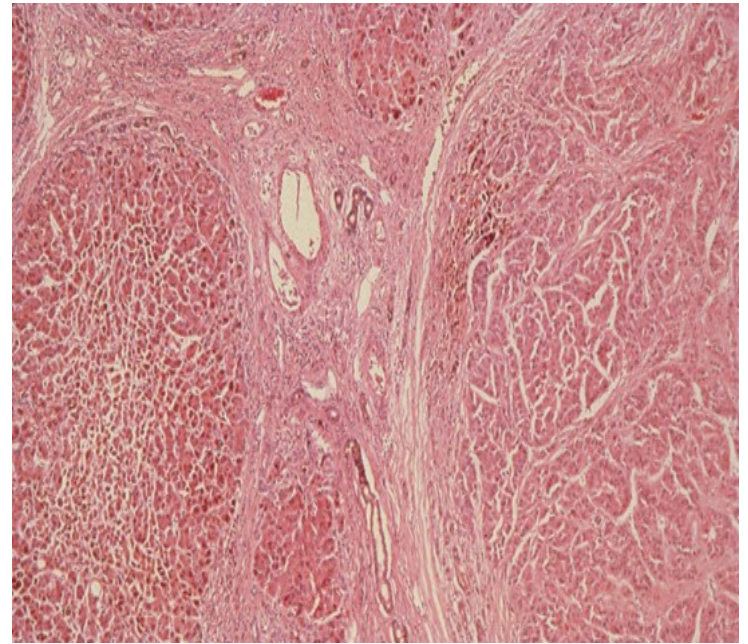
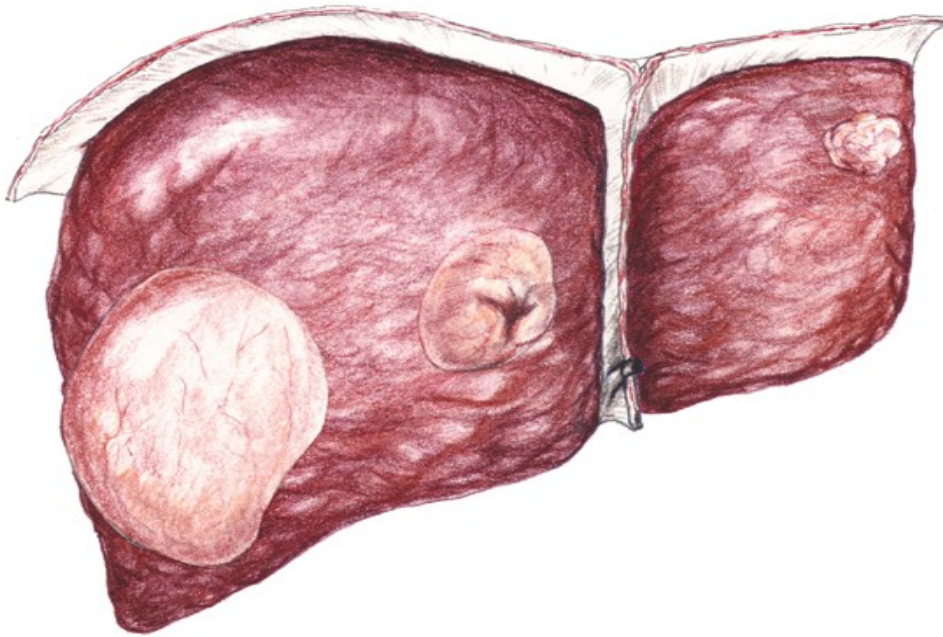








Hepatocellular carcinoma

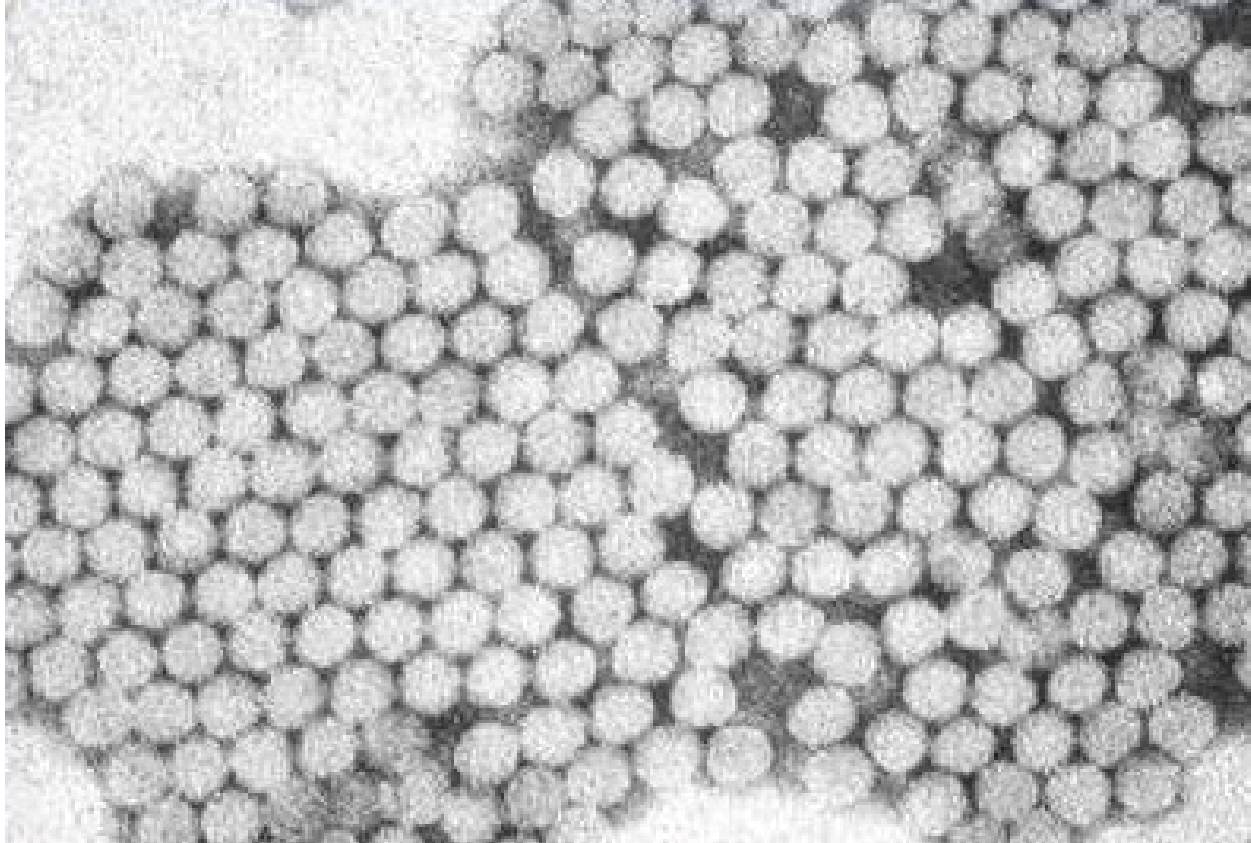




Viral hepatitis in CR 2014-2023

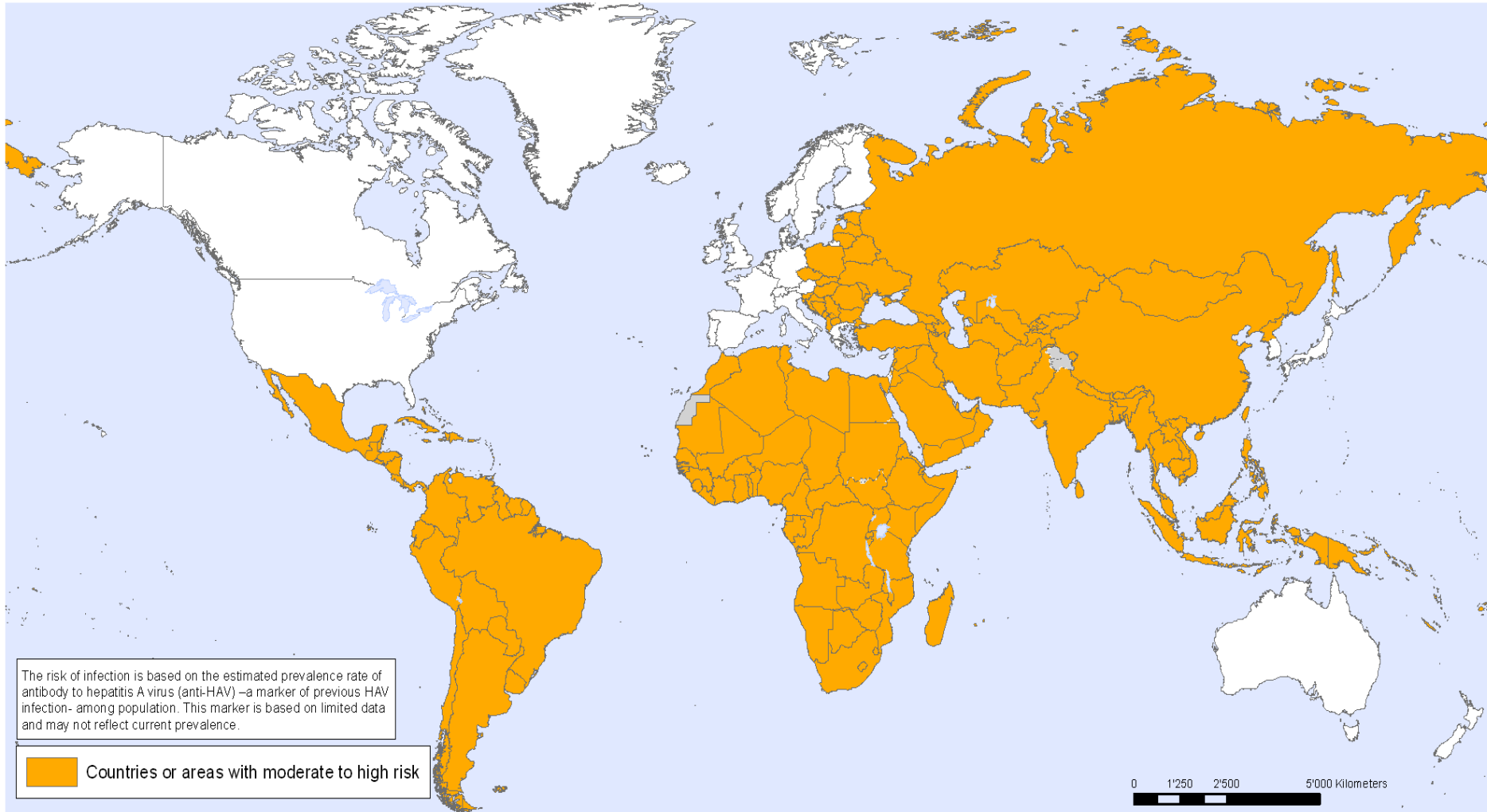
	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
VH A	673	723	930	772	211	240	183	210	70	66
acute VH B	105	90	73	85	54	41	27	17	48	37
chronic VH B	193	193	208	248	269	276	142	127	244	378
VH C	867	945	1103	992	1050	1138	770	665	921	1301
VH E	299	409	339	344	272	268	223	201	319	684

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



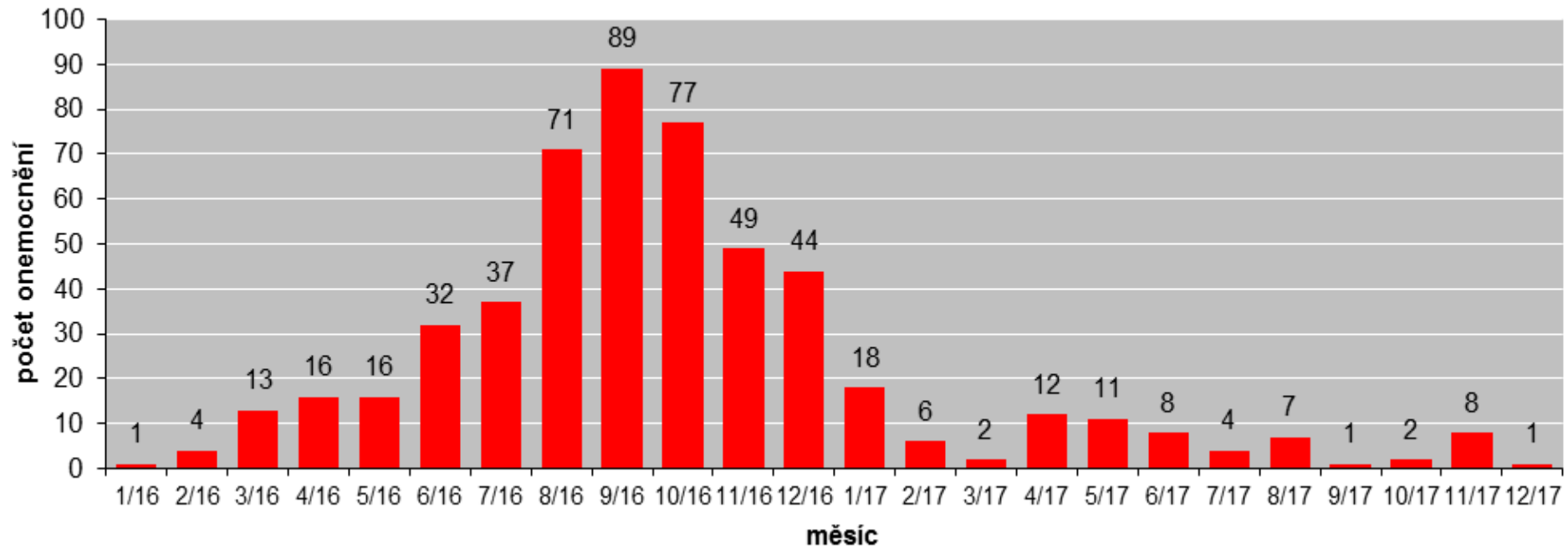
The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers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



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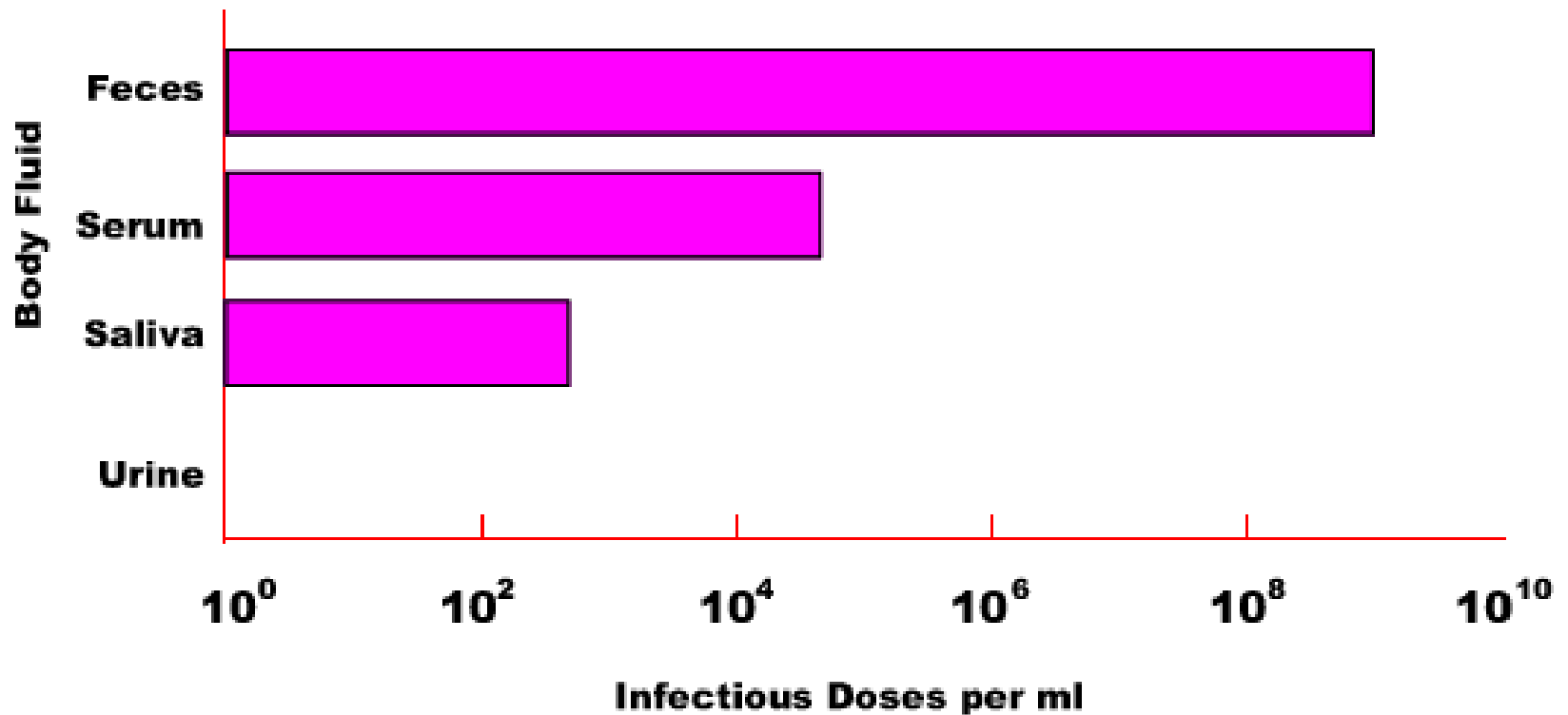
HAV epidemic in the South Moravia 2016-2017



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

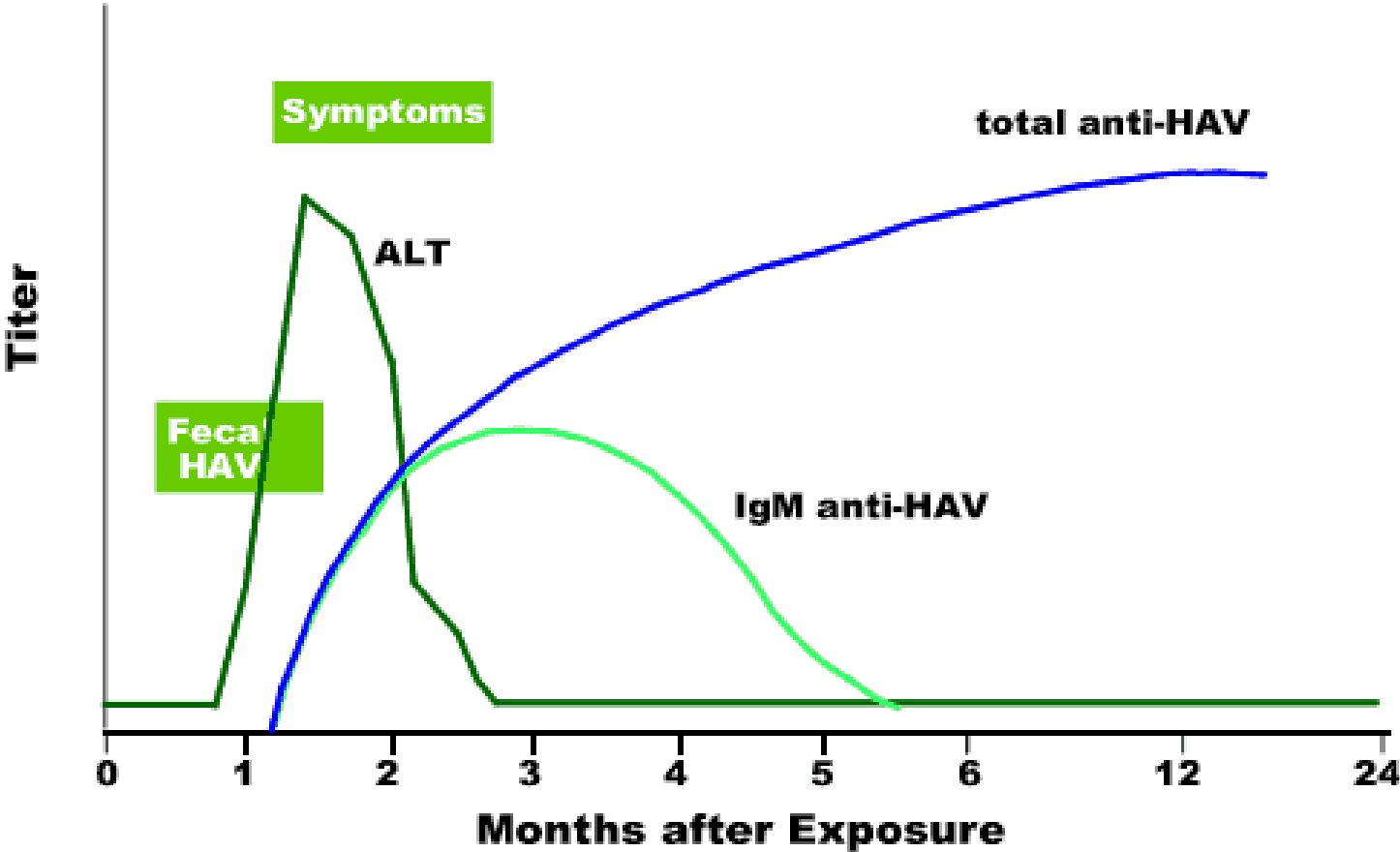
Concentration of Hepatitis A Virus in Various Body Fluids



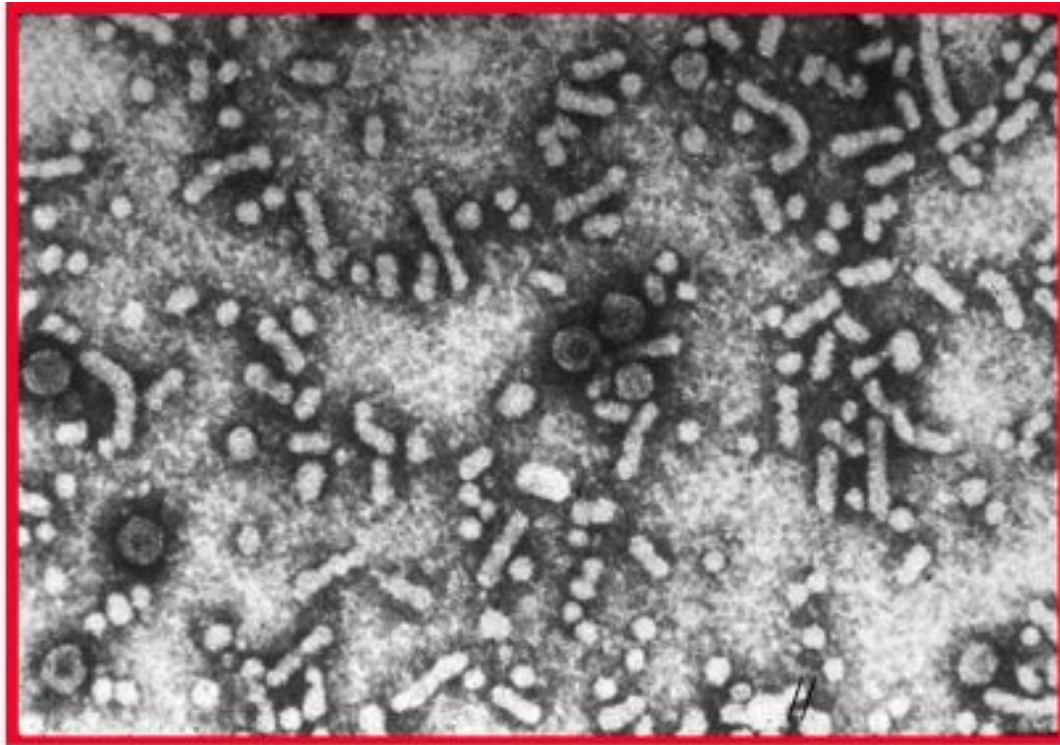
Source: Viral Hepatitis and Liver Disease 1984;9-2
J Infect Dis 1989; 160:887-890

Hepatitis A Virus Infection

Typical Serologic Course



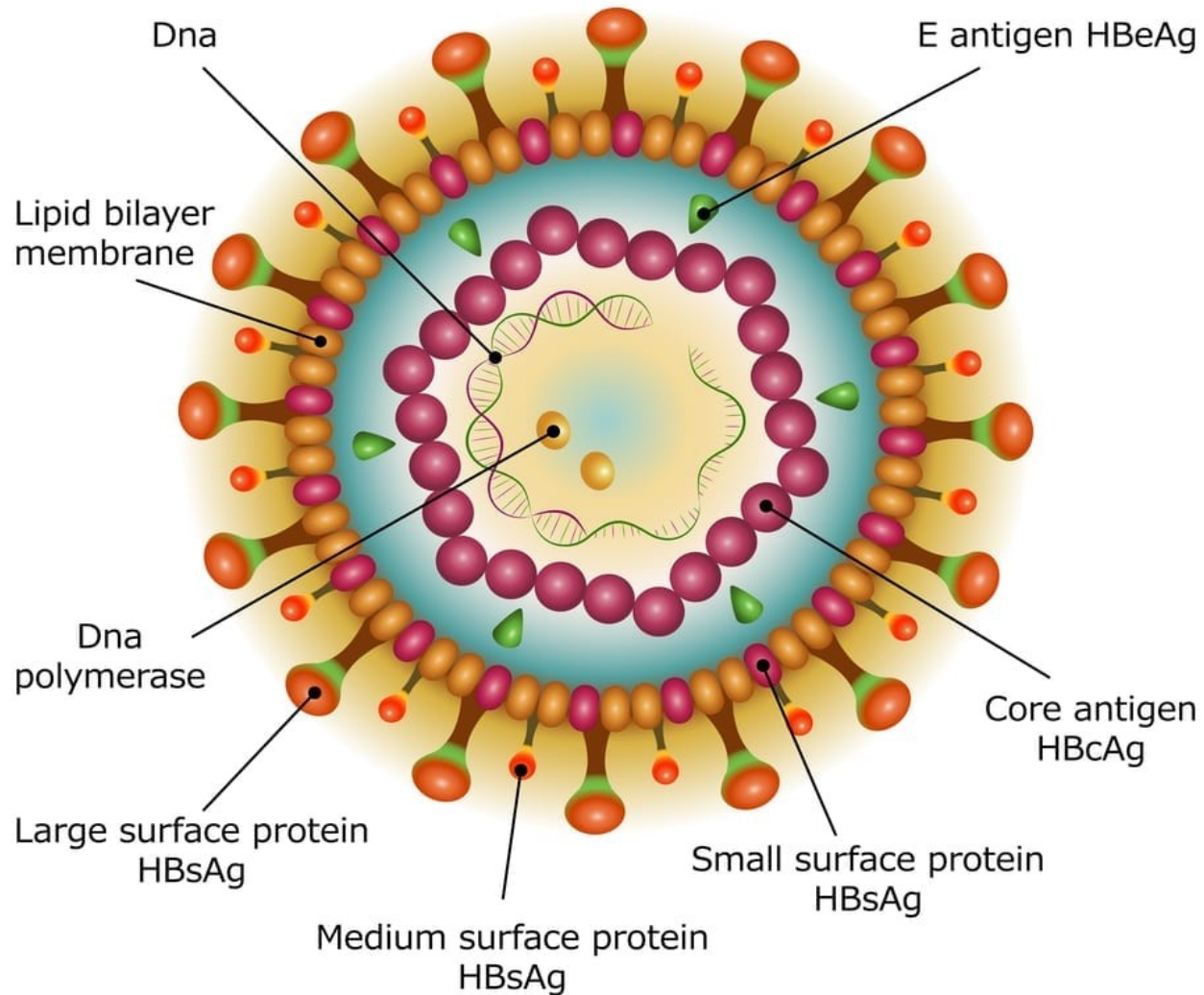
Hepatitis B Virus (HBV)



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

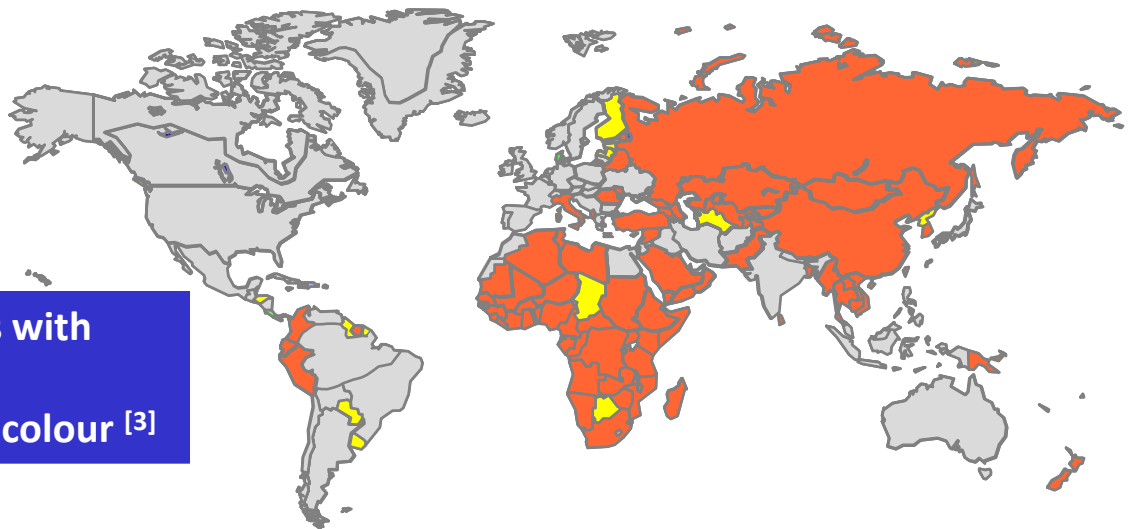
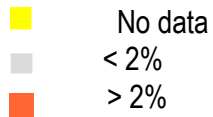
Hepatitis B Virus

Baltimore Group VII (dsDNA-RT)



Estimated chronic HBV infection prevalence

- Worldwide: 240-350 million^[1] USA: 1.5-2.2 million^[2]



Need of HBV screening in countries with prevalence $\geq 2\%$

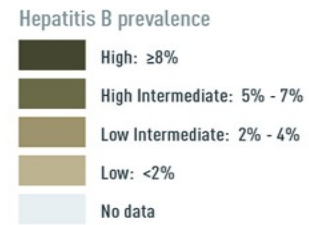
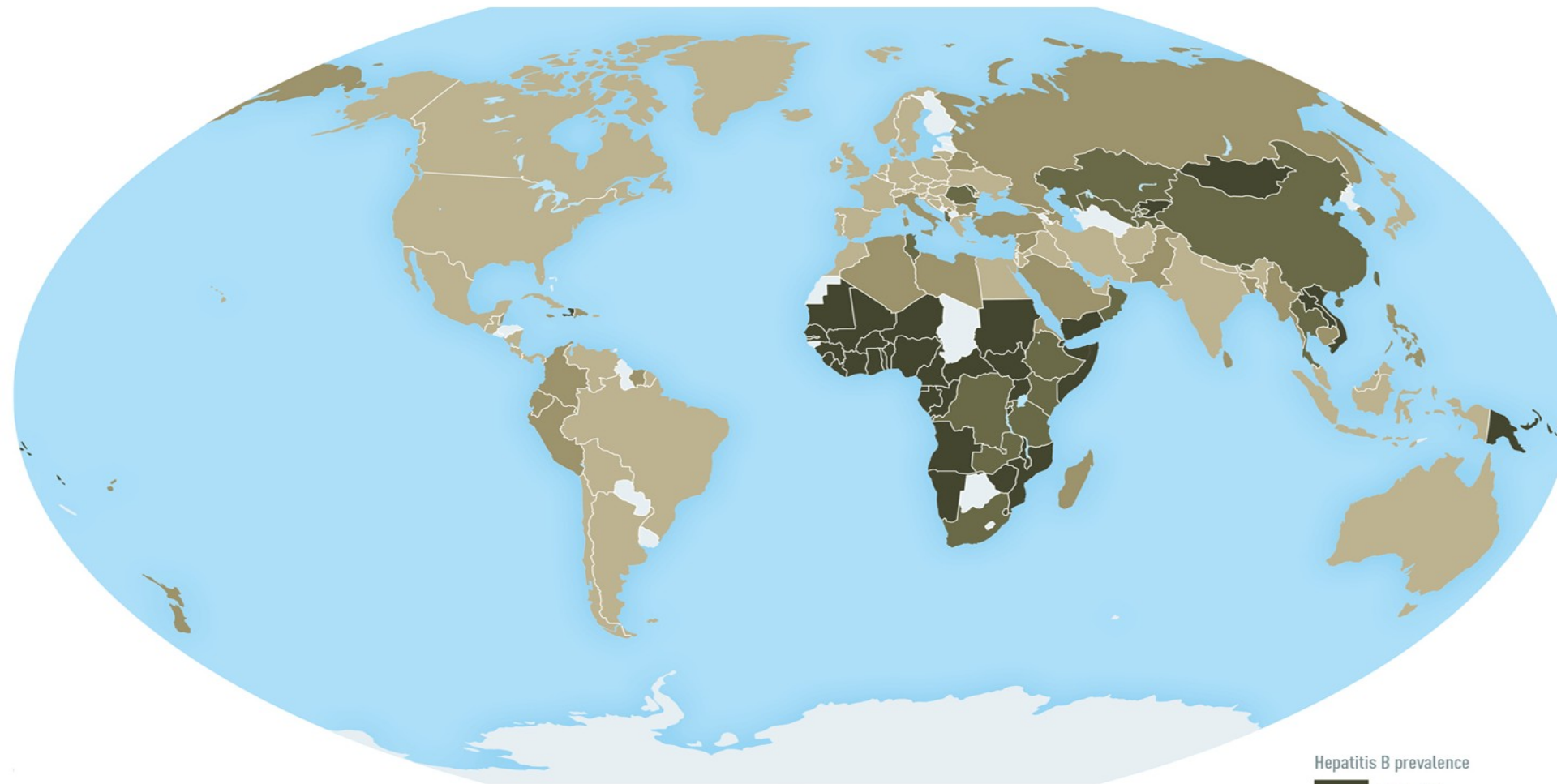
→ It means in all countries out of grey colour ^[3]

1. MacLachlan. Cold Spring Harb Perspect Med. 2015;5:a021410. 2. Kim. Hepatology. 2009;49:S28. 3. Nguyen. Clin Microbiol Rev. 2020;33:e00046.

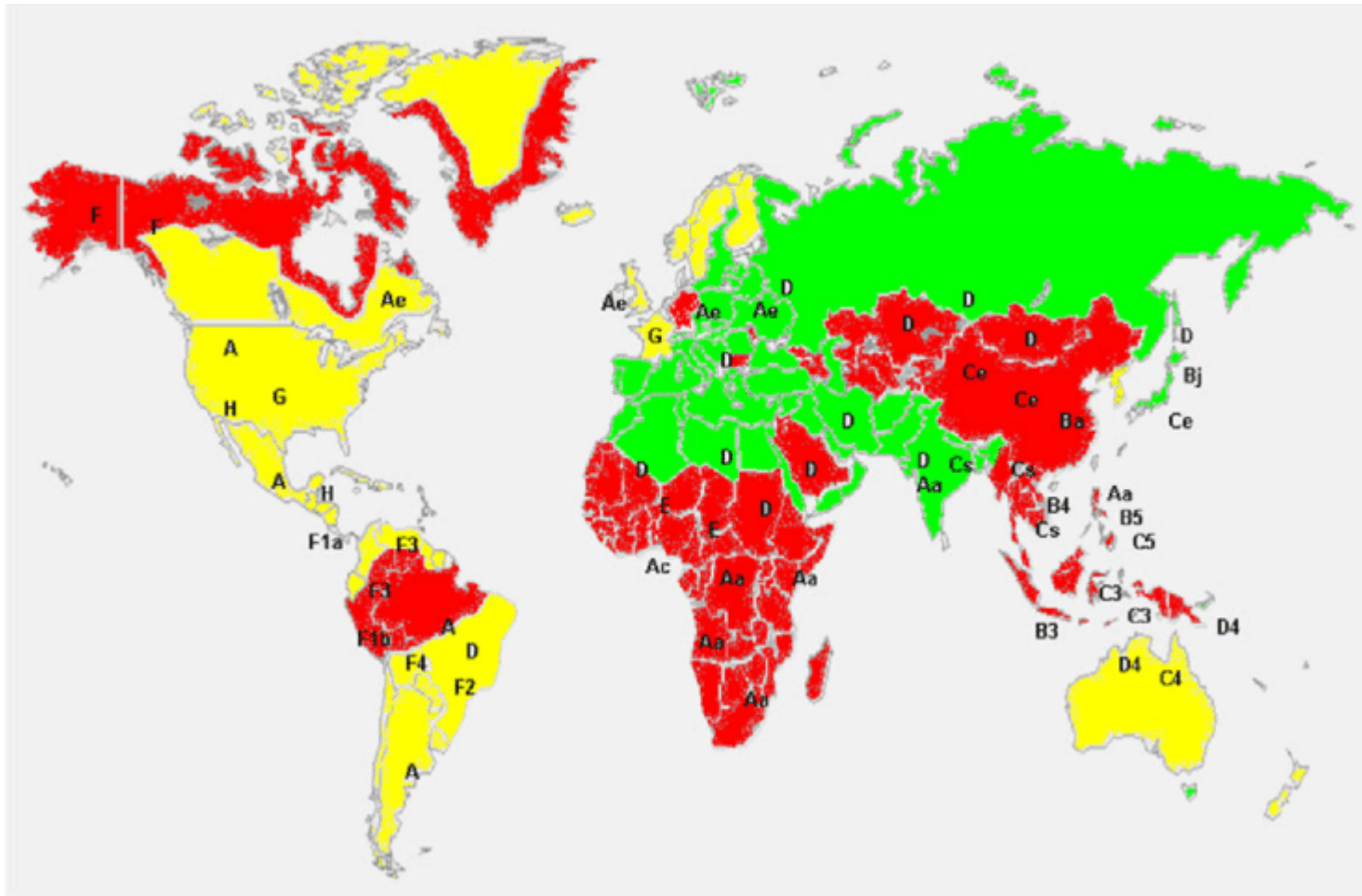
Global significance of HEP B

- One of the biggest global health problems
- ✓ More than 2 billions of infections during the life
- ✓ 240-350 million chronic HBsAg carriers
- ✓ Indication for 5-10 % liver transplantations globally
- ✓ Global vaccination in almost all countries

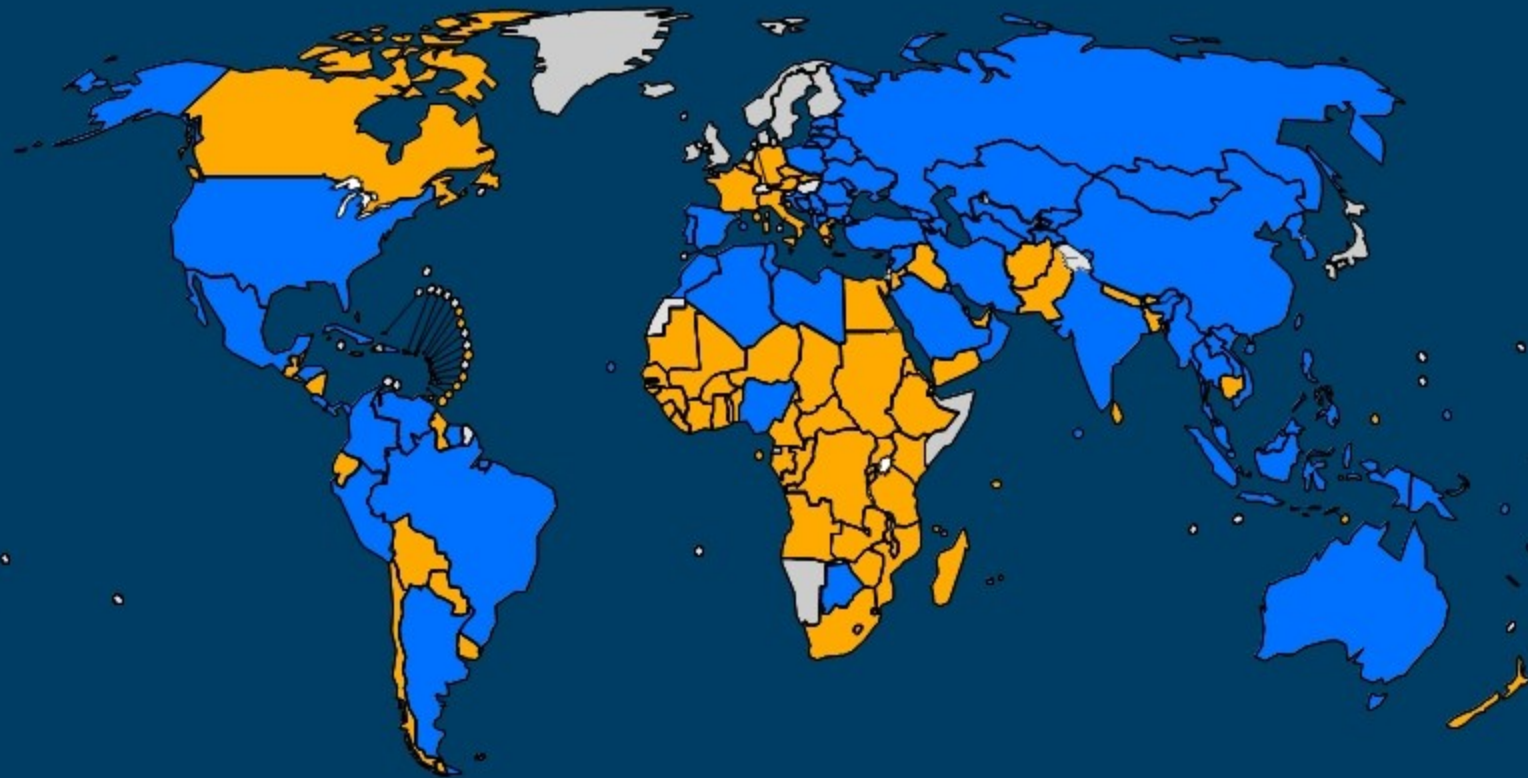
Chronic HBV infection (CDC 2020)






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

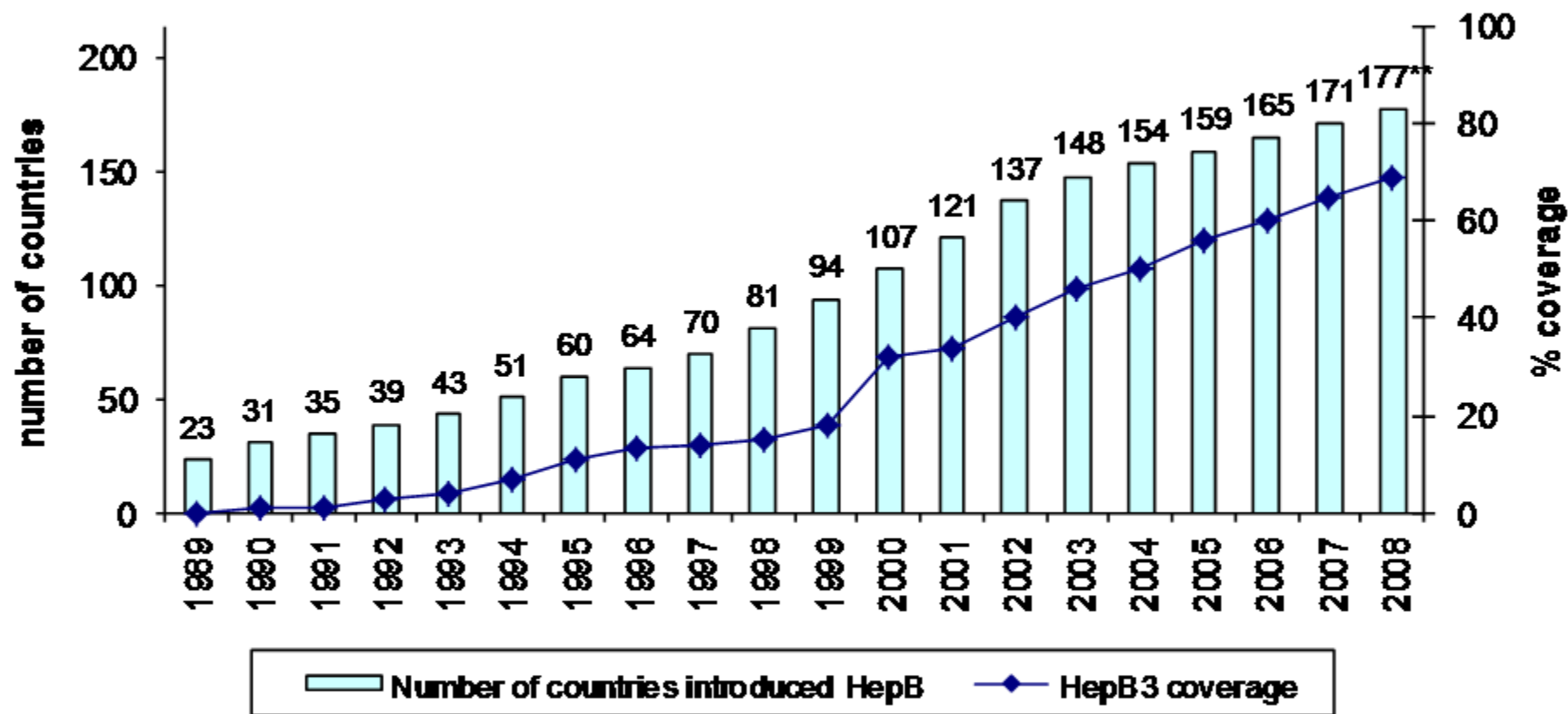
-  No HepB (16 countries¹ or 8%)
-  HepB no Birth Dose (92 countries² or 48%)
-  HepB with Birth Dose (85 countries³ or 44%)

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

The boundaries and names shown and the designations used on this map do not imply the endorsement of any specific view or views 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 lines on maps represent approximate border lines for which there may not be full agreement.
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Number of countries having introduced HepB vaccine* and global infant coverage, 1989-2008



* Year of introduction can be the year of partial introduction

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

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



Hepatitis B in Czech Republic

- Still important infection but incidence and prevalence are gradually decreasing
- ✓ Prevalence of chronic carriers was 0.56 % (2001) ...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 %

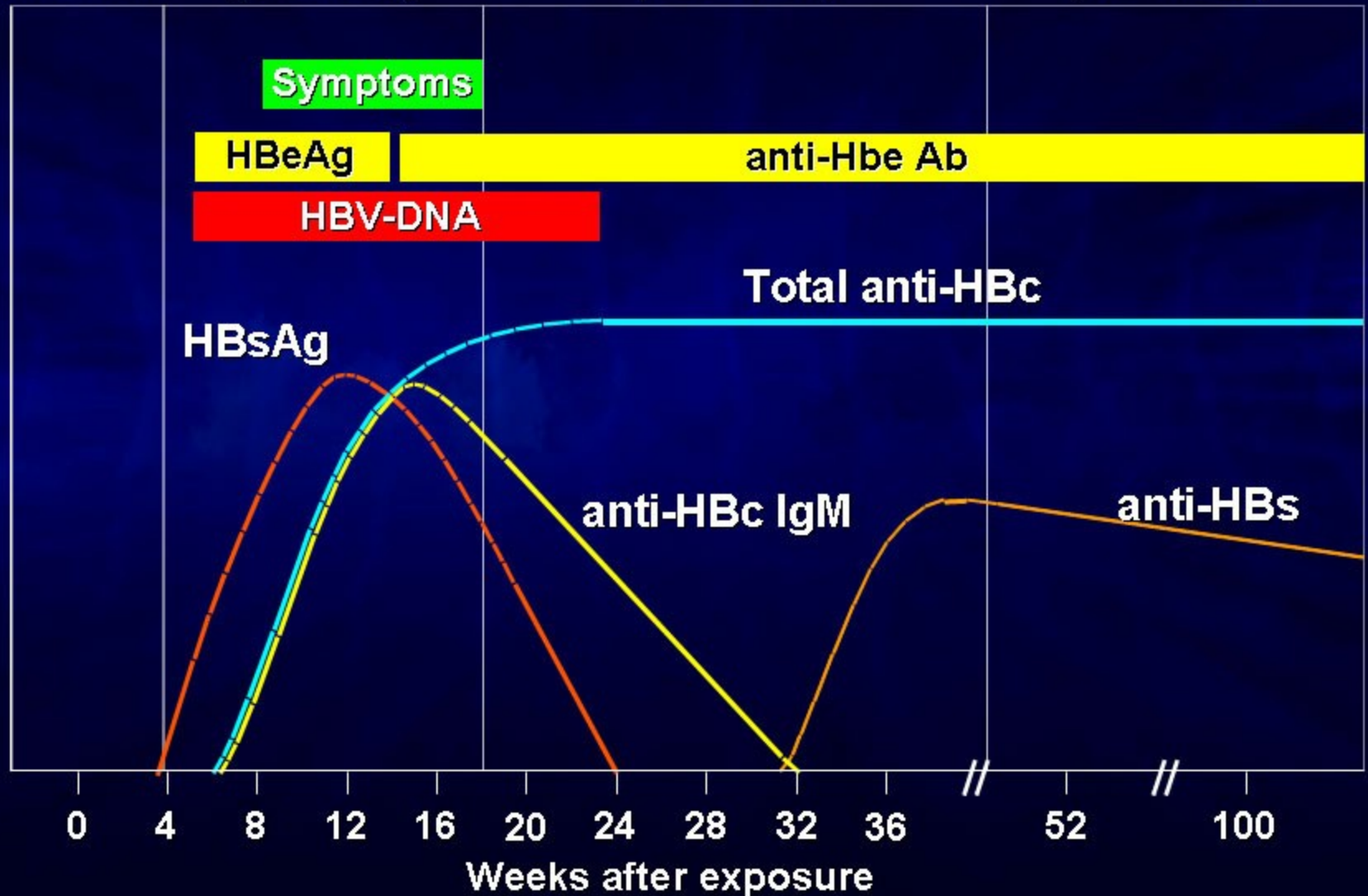
Acute Hepatitis B

Incubation
4-12 weeks

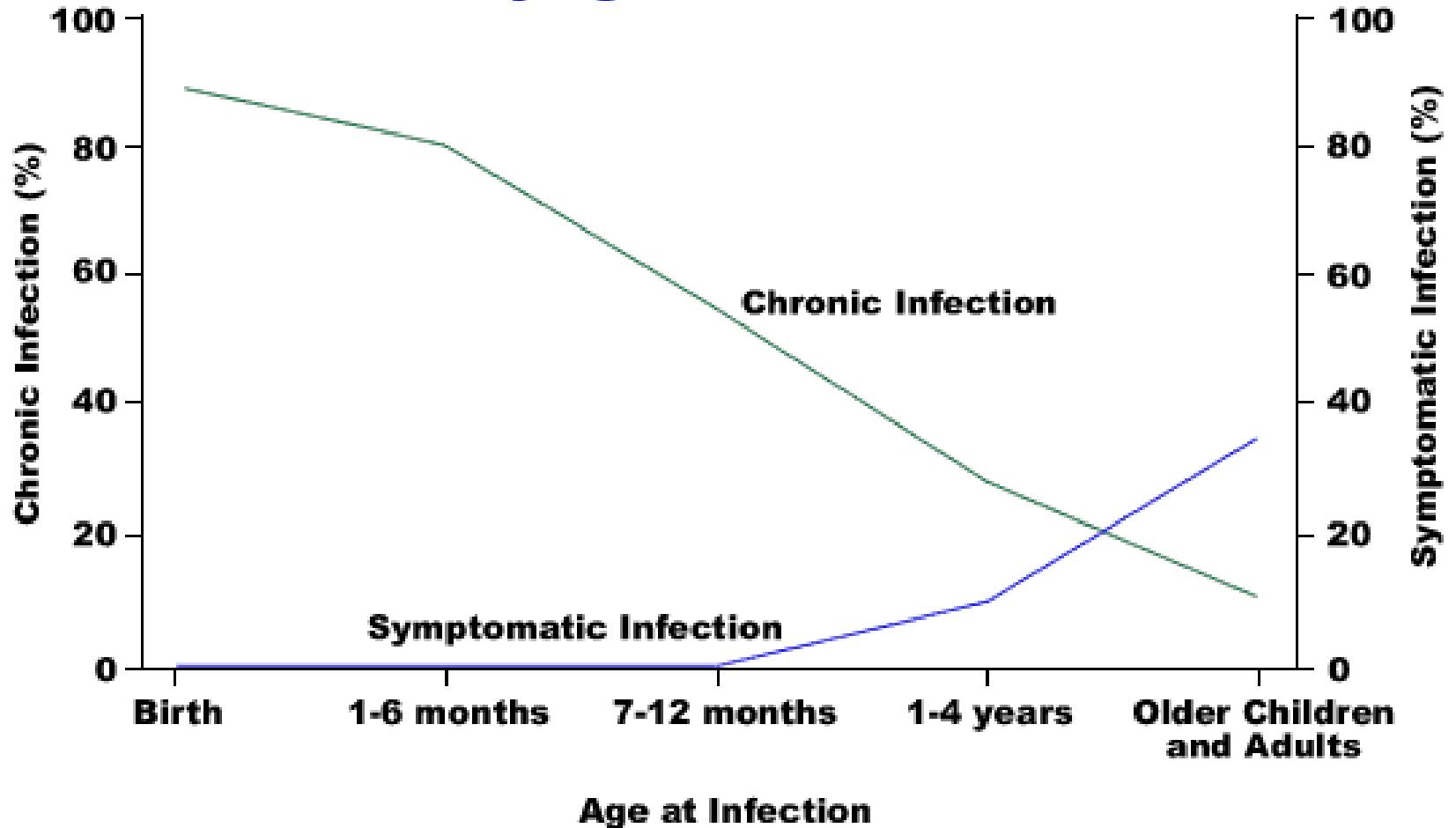
Acute infection
(2-12 weeks)

Early recovery
(12-24 weeks)

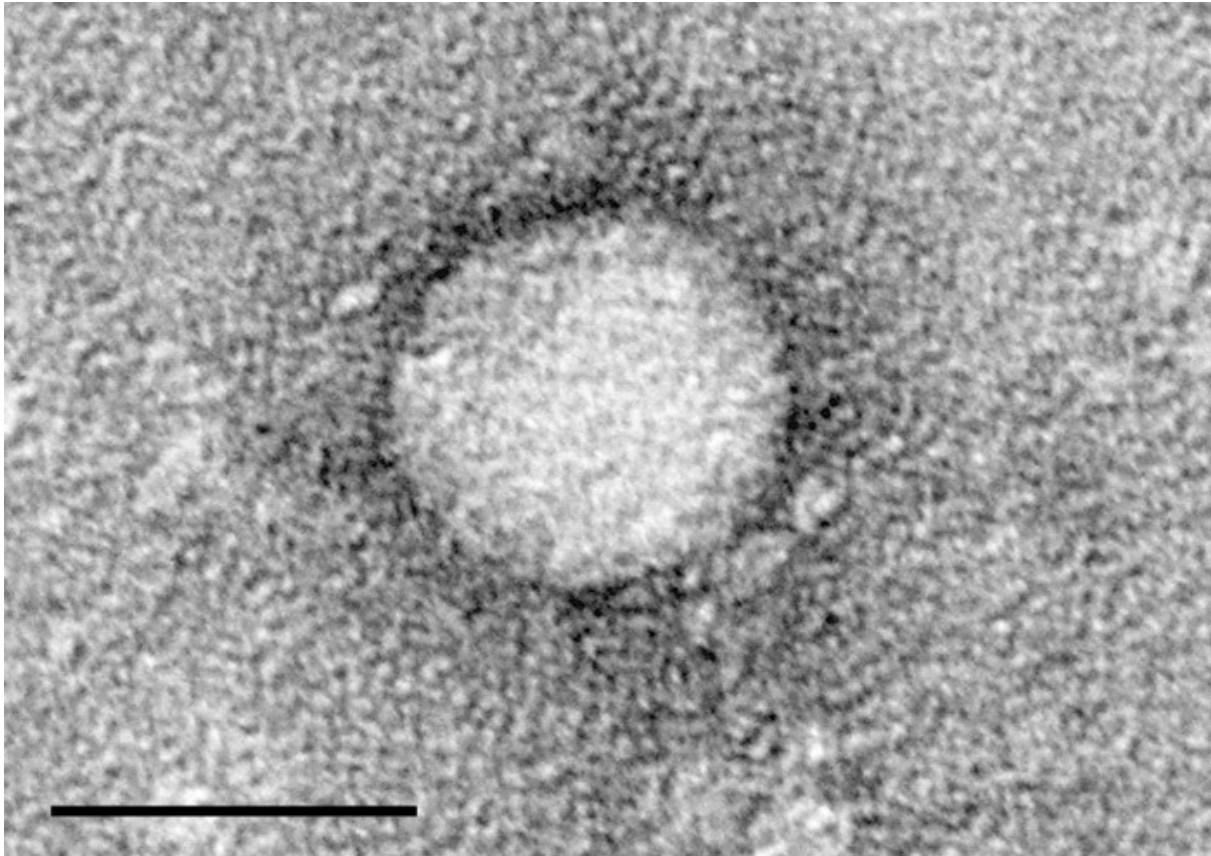
Recovery
(24-48 weeks)



Outcome of Hepatitis B Virus Infection by Age at Infection

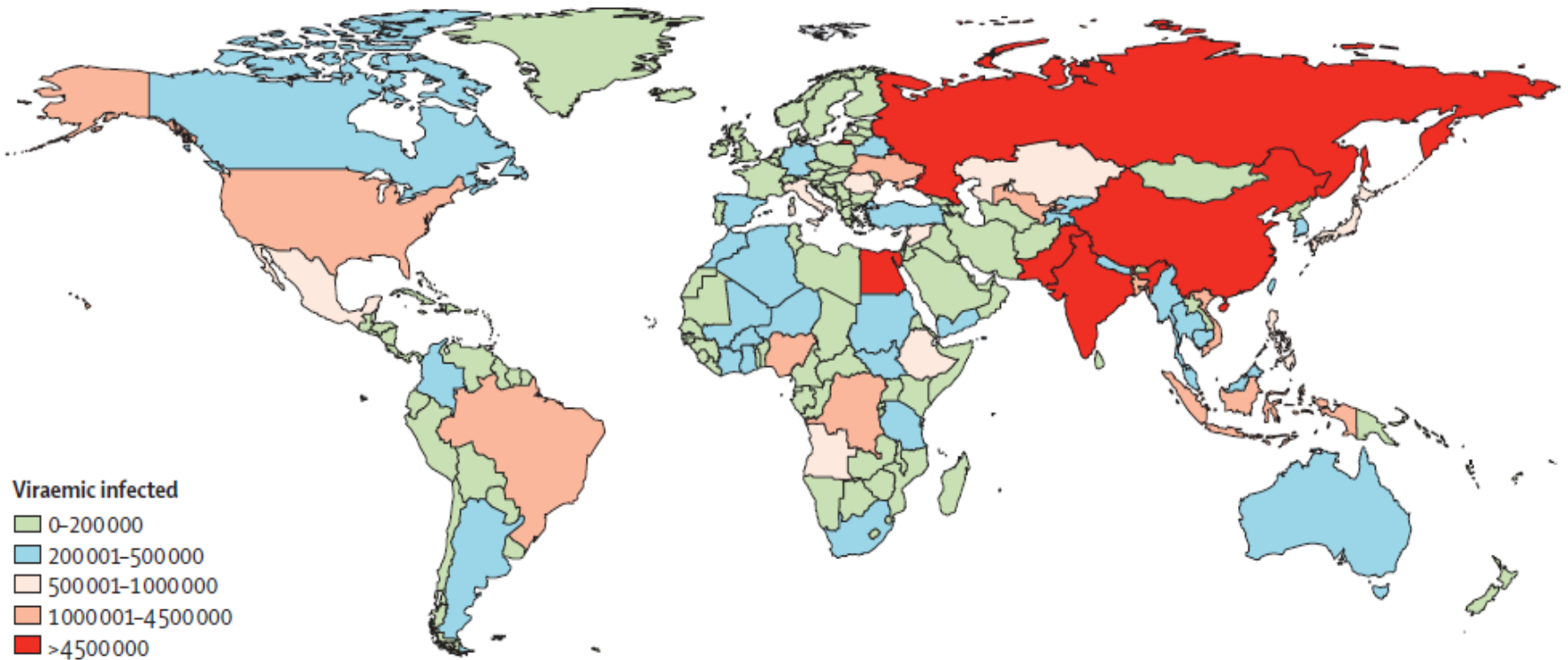


Hepatitis C Virus (HCV)



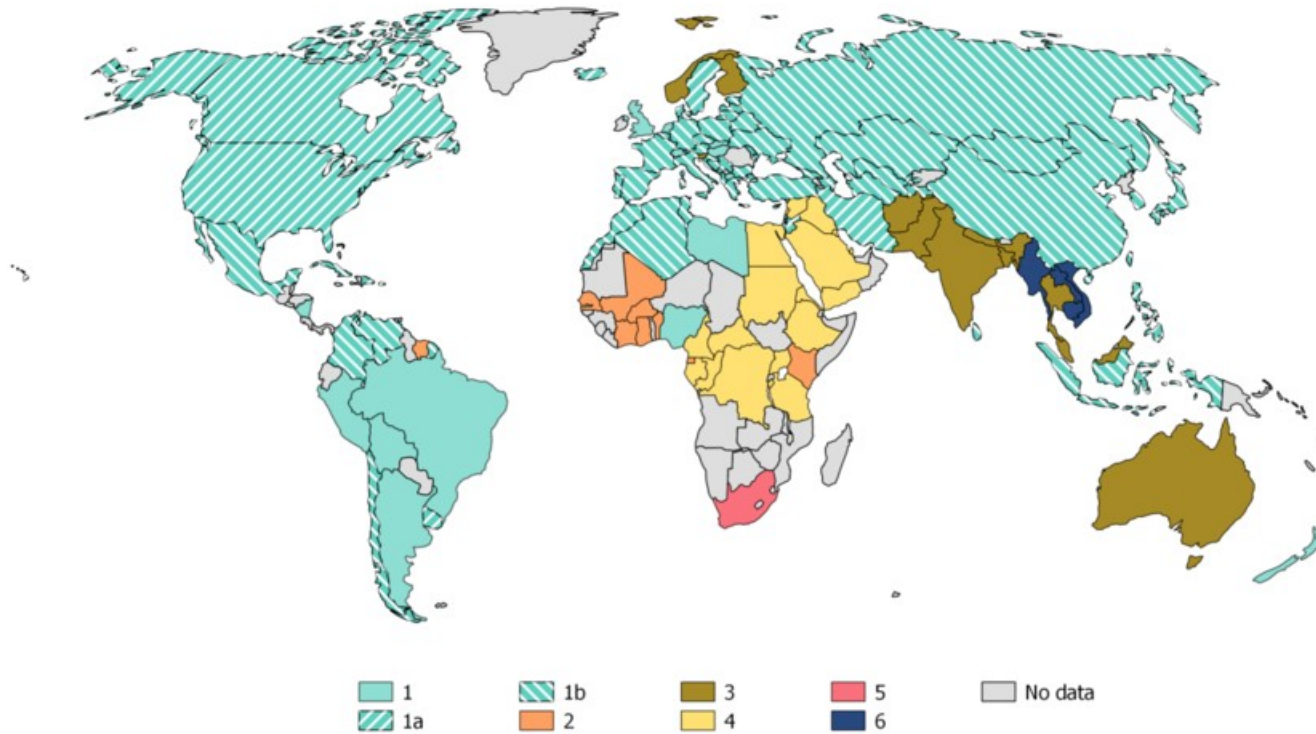
Family Flaviviridae, genus *Hepacivirus*, enveloped RNA virus 60 nm,
8 genotypes (1-8), many subtypes (a...)

Global estimations: 70-80 million persons with chronic HCV infection

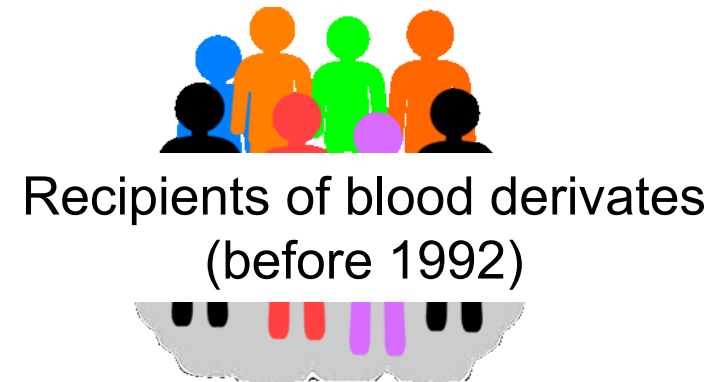


Approximately 700 000 persons died annually due to complications related to HCV infection: liver cirrhosis, HCC, and liver failure

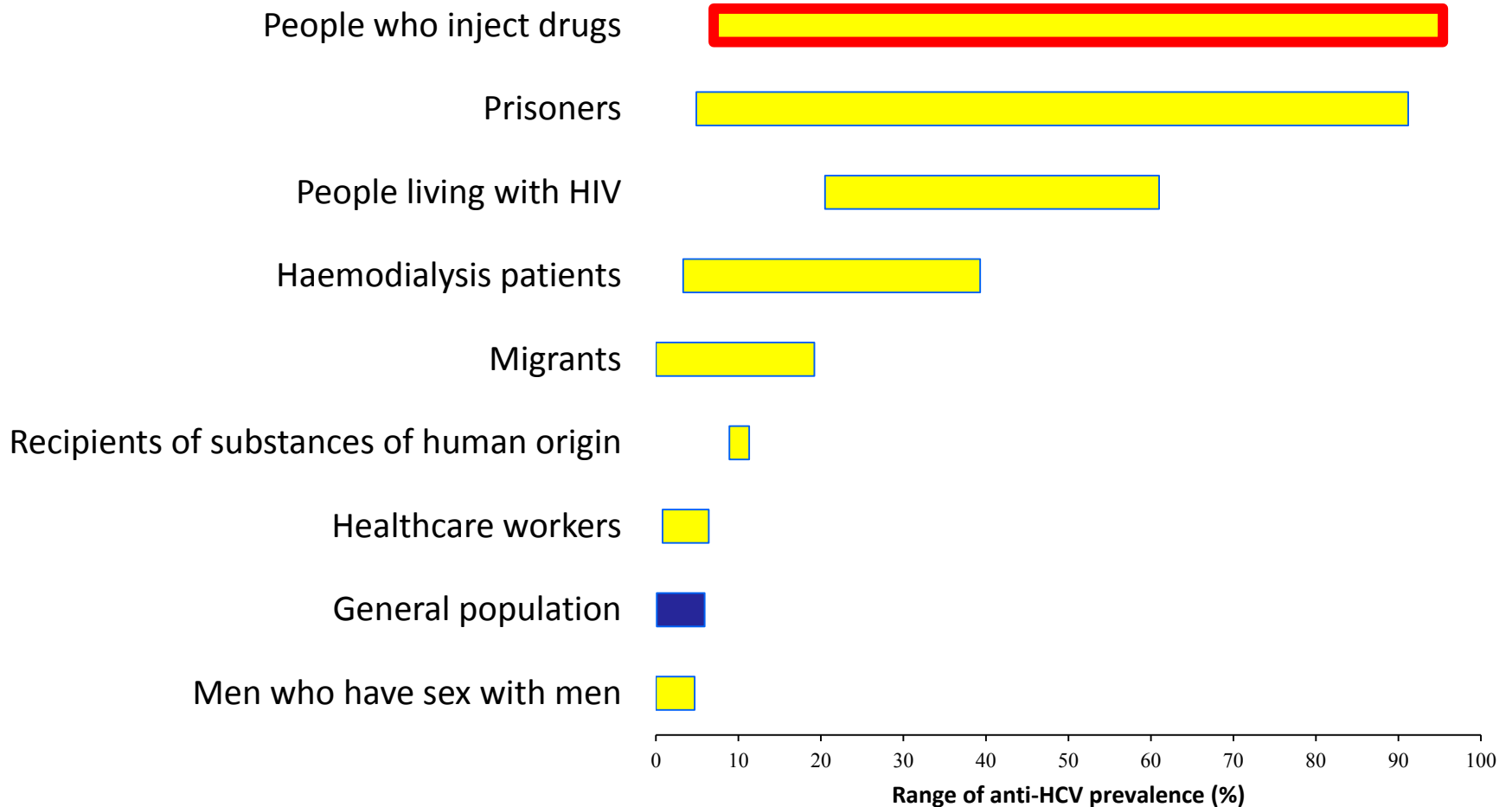
Distribution of HCV genotypes and subtypes



Risk groups of inhabitants for HCV infection

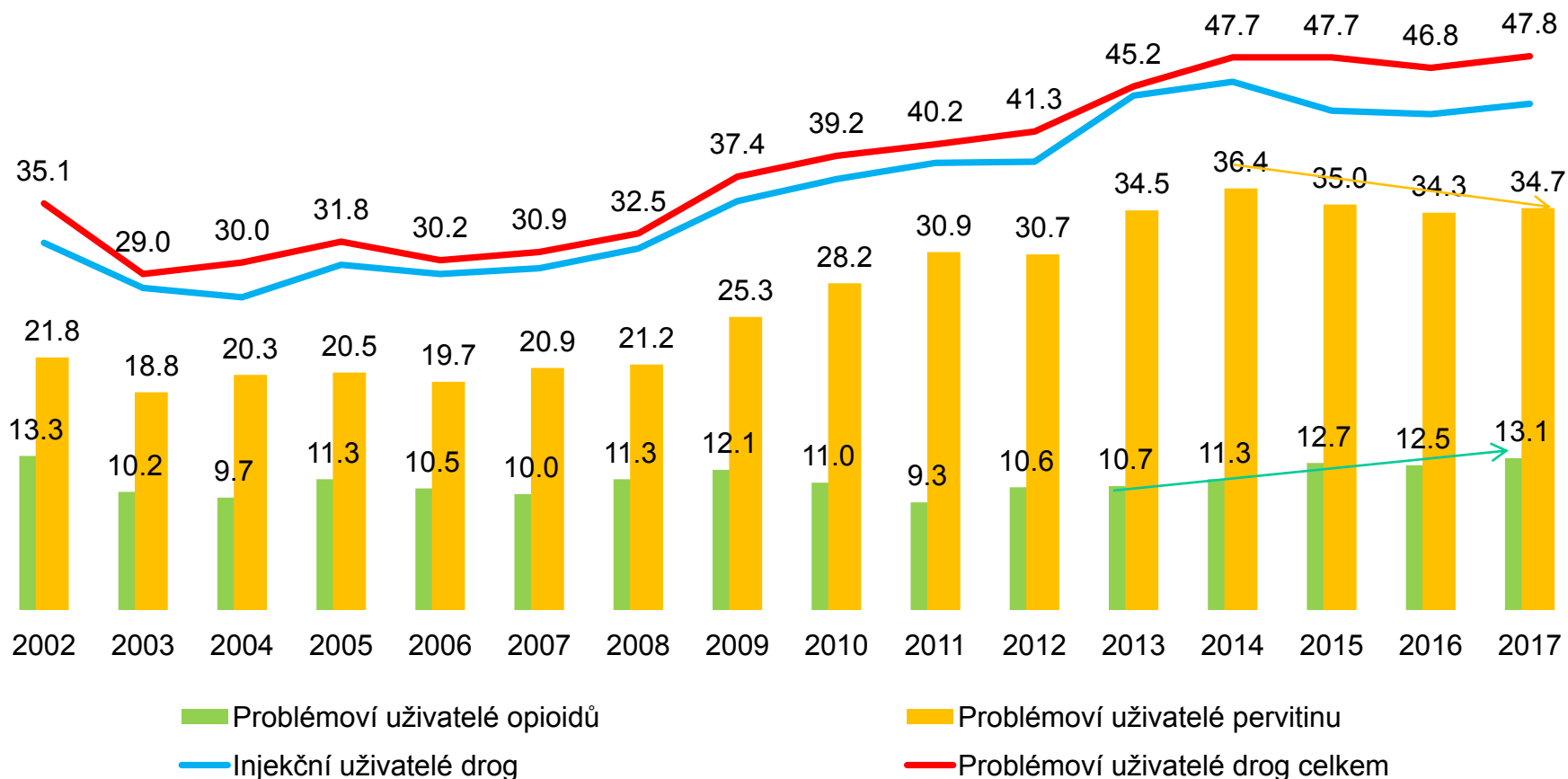


HCV prevalence in risk groups of inhabitants in EU/EEA countries



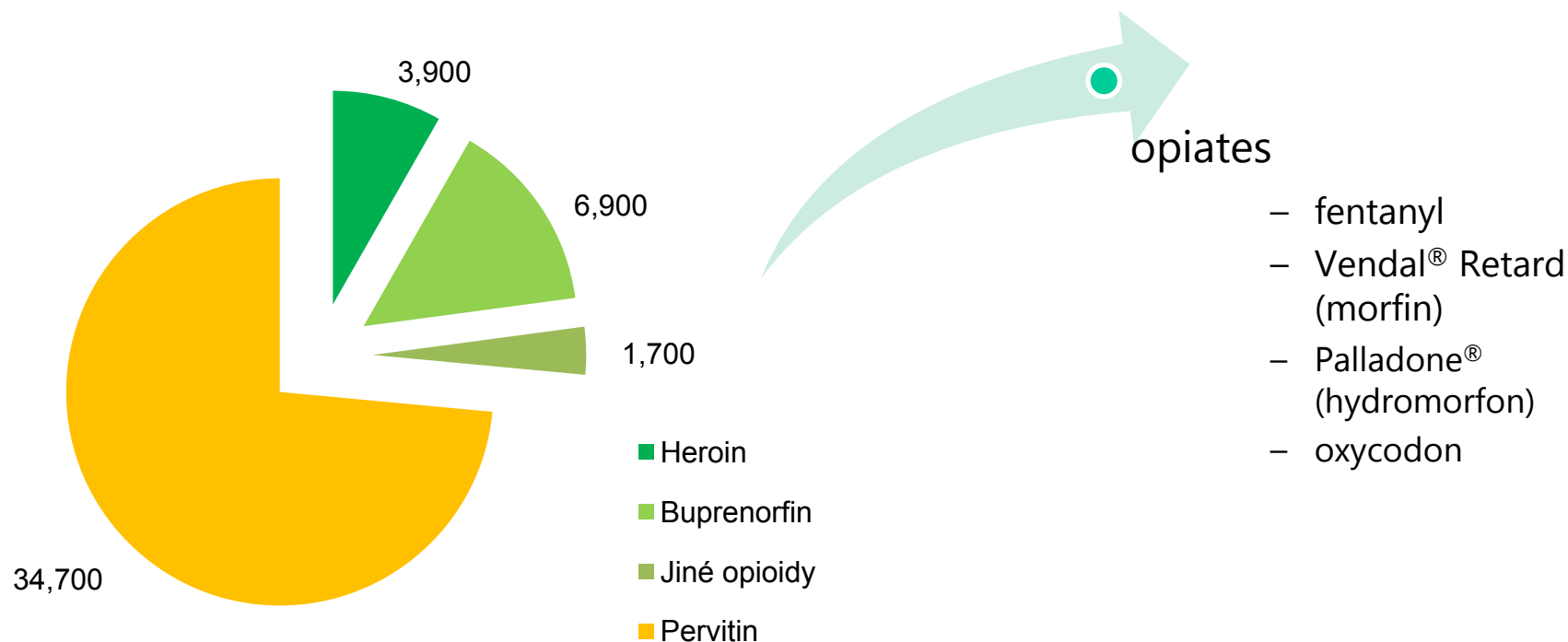
Problematic drug abusers in the CR (2017)

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

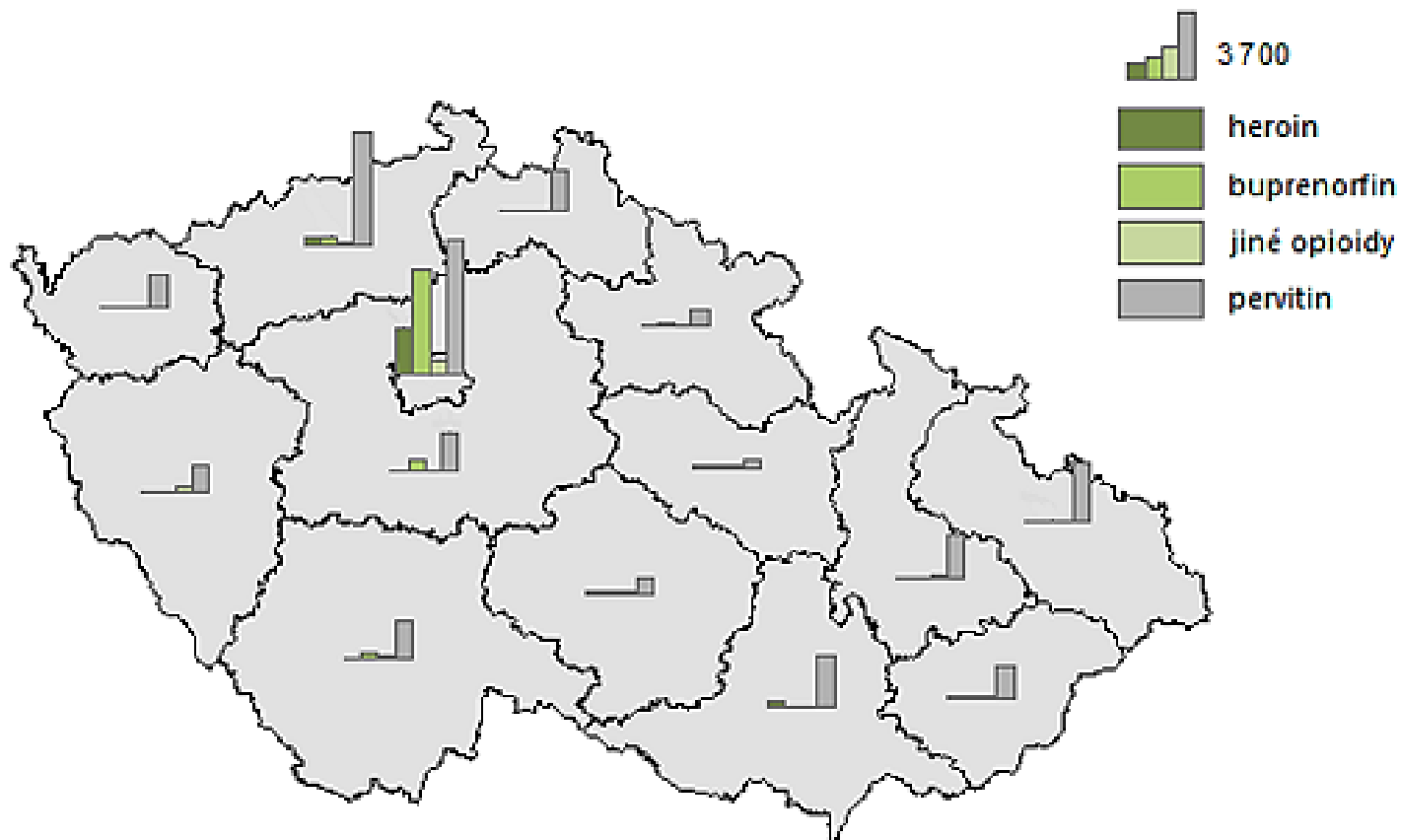


Problematic drug abusers in the CR (2017)

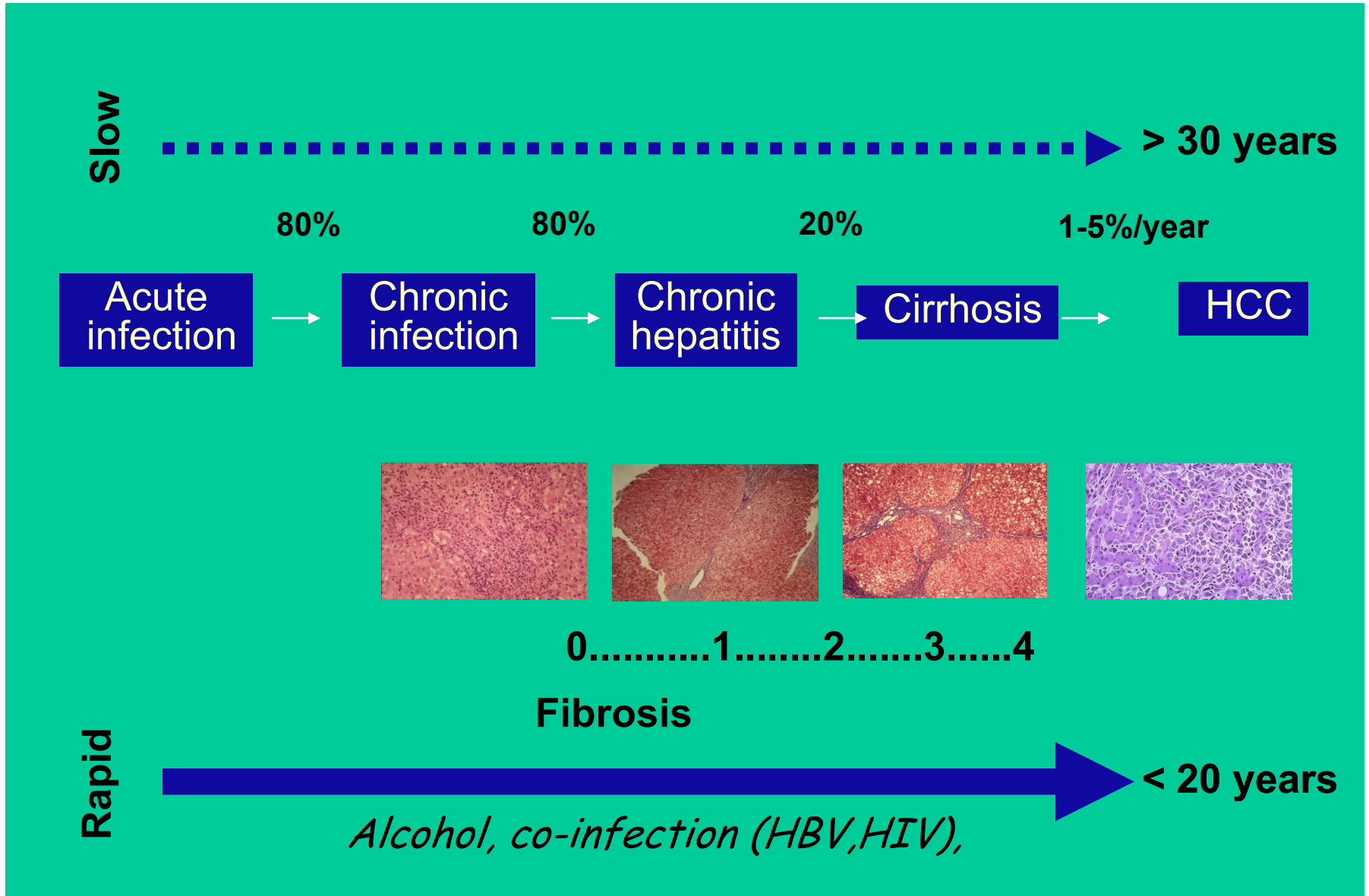
2017 - Estimation in the CR - 47 800 problematic drug abusers, about 90 % intravenous



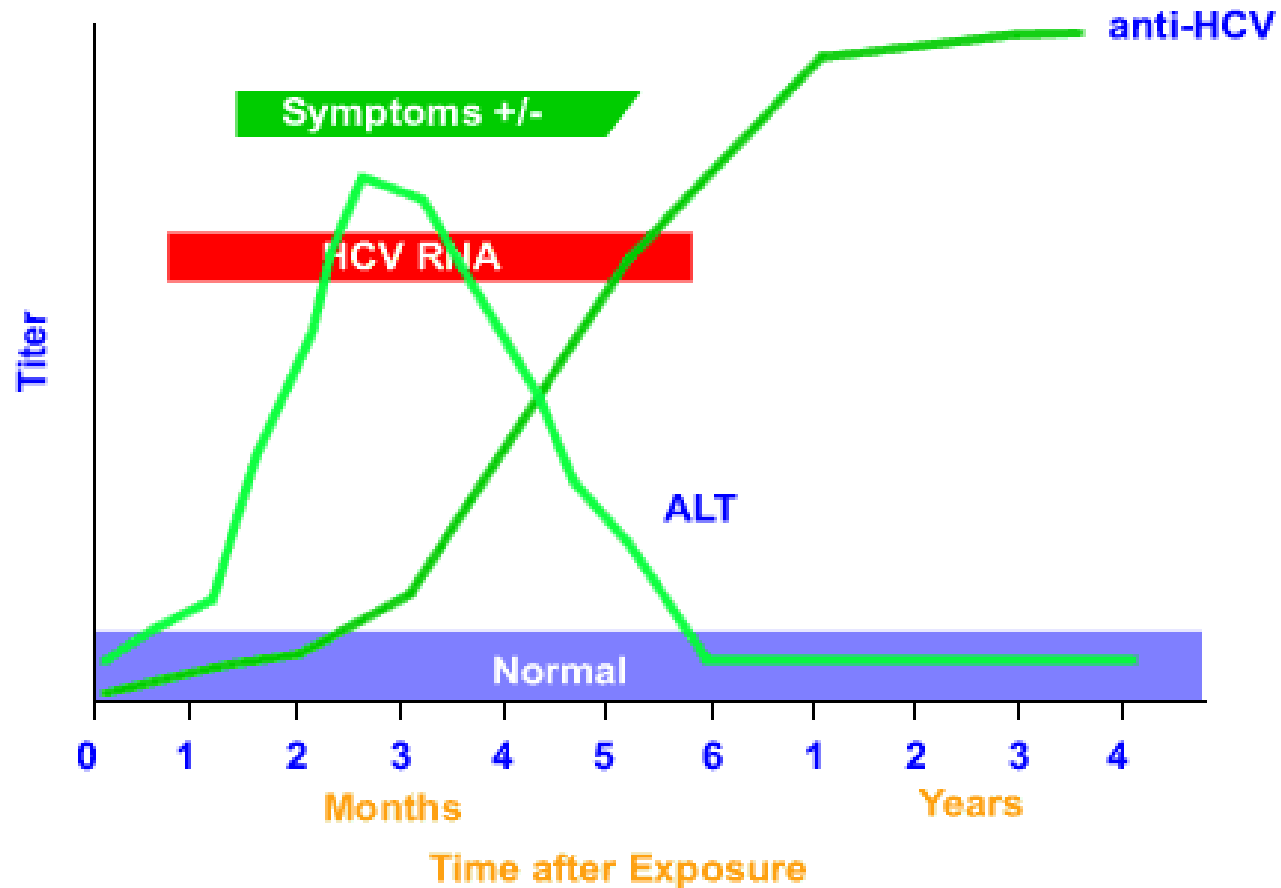
Opiates and pervitin abus



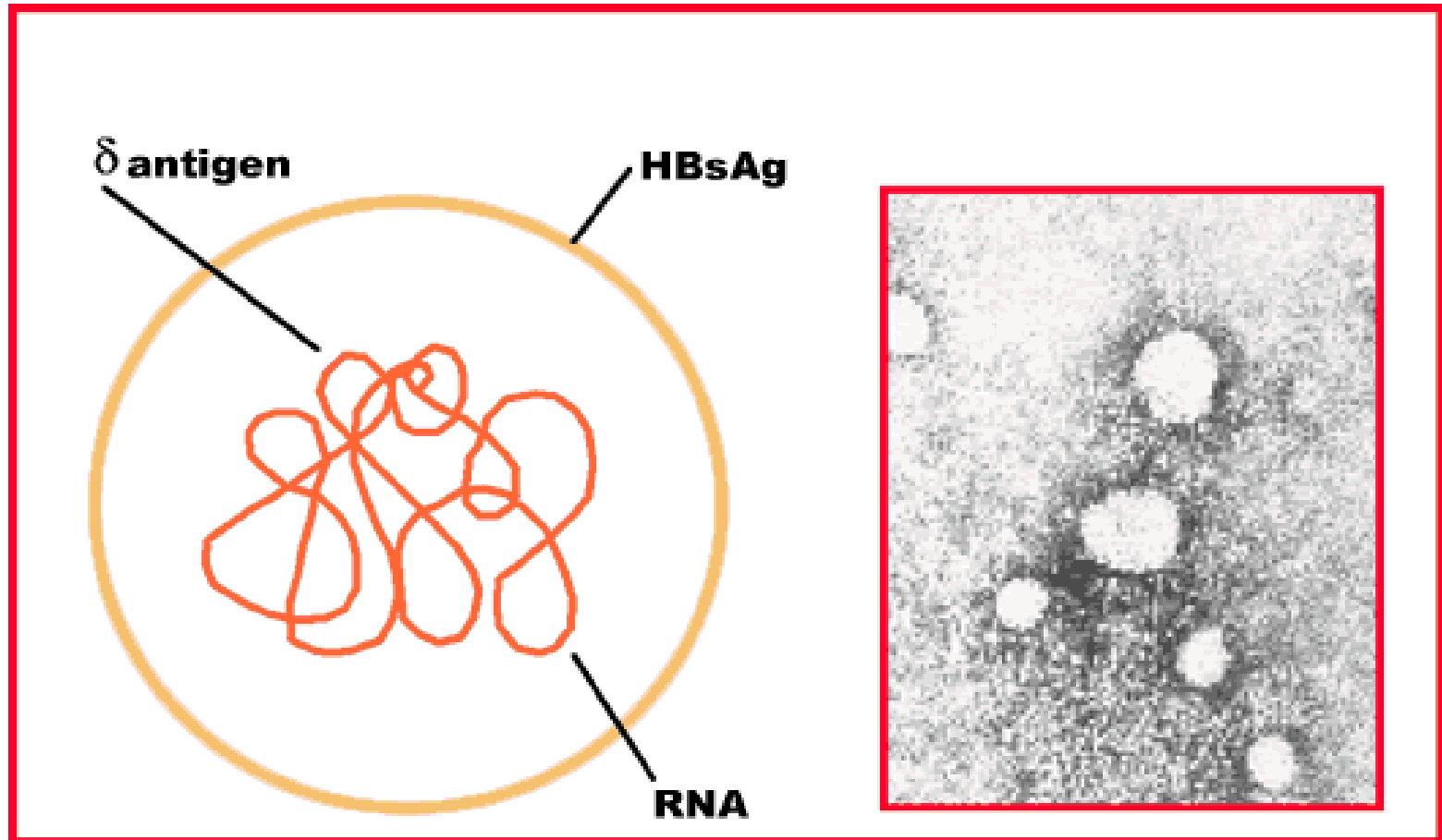
Clinical course of HCV infection



Diagnosis of HCV infection



Hepatitis D (Delta) Virus (HDV)



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

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

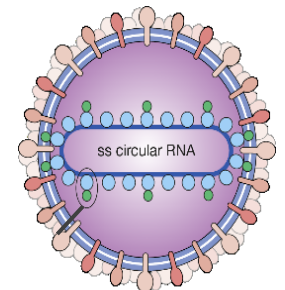
Increased risk of cirrhosis/HCC and higher mortality vs HBV

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

2009



2010

5

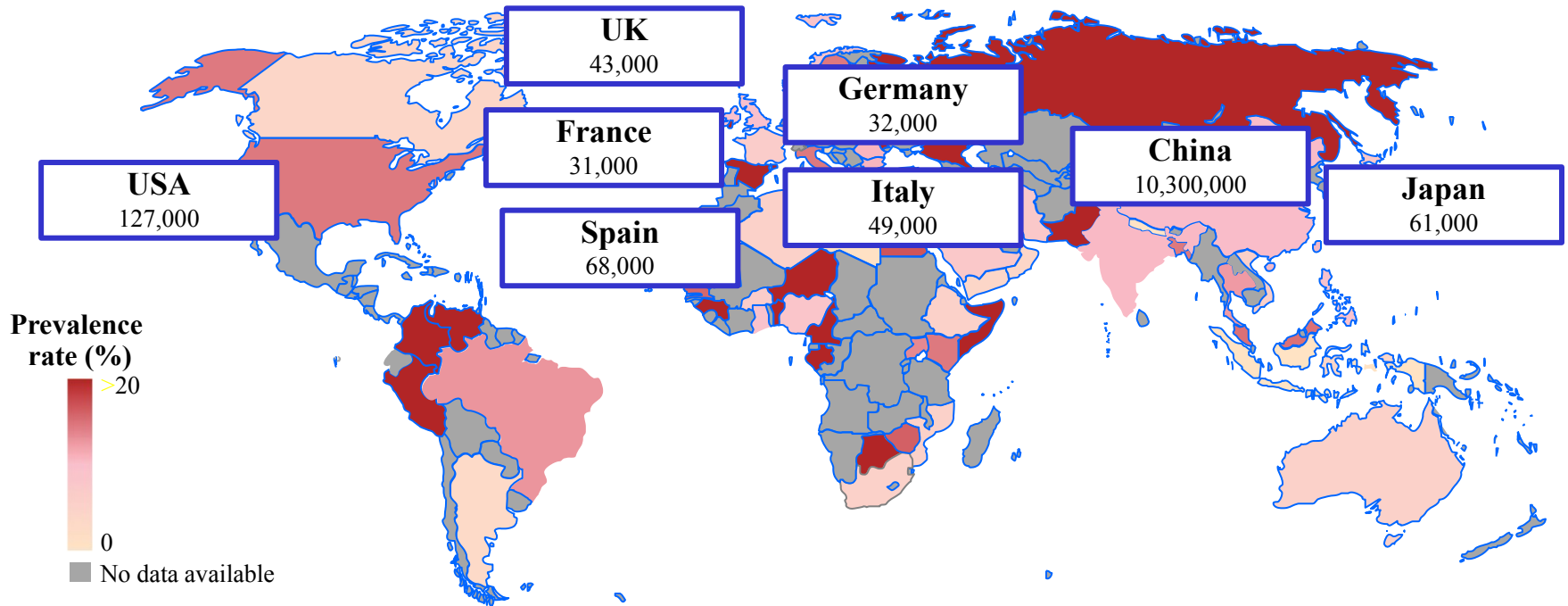
-  **Endemic**
-  **In risk groups**
Immigrants



Rizzetto M. EASL 2009

Estimated number of individuals with HDV in selected countries

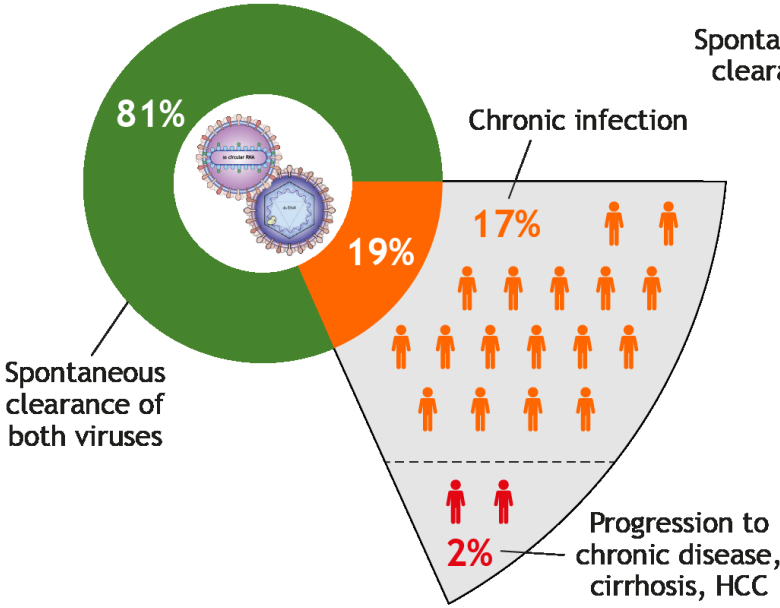
An estimated 48-60 million people are infected with HDV worldwide



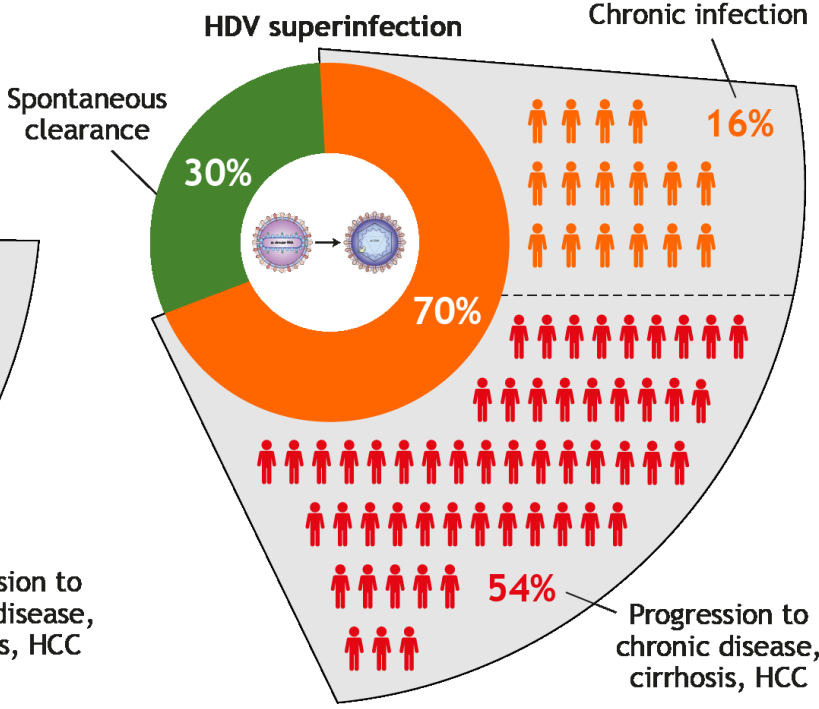
Numbers shown are patient numbers, ie prevalence of HDV in HBsAg-positive patients.
HBsAg: hepatitis B surface antigen; HDV: hepatitis delta virus.

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

Simultaneous HBV/HDV coinfection

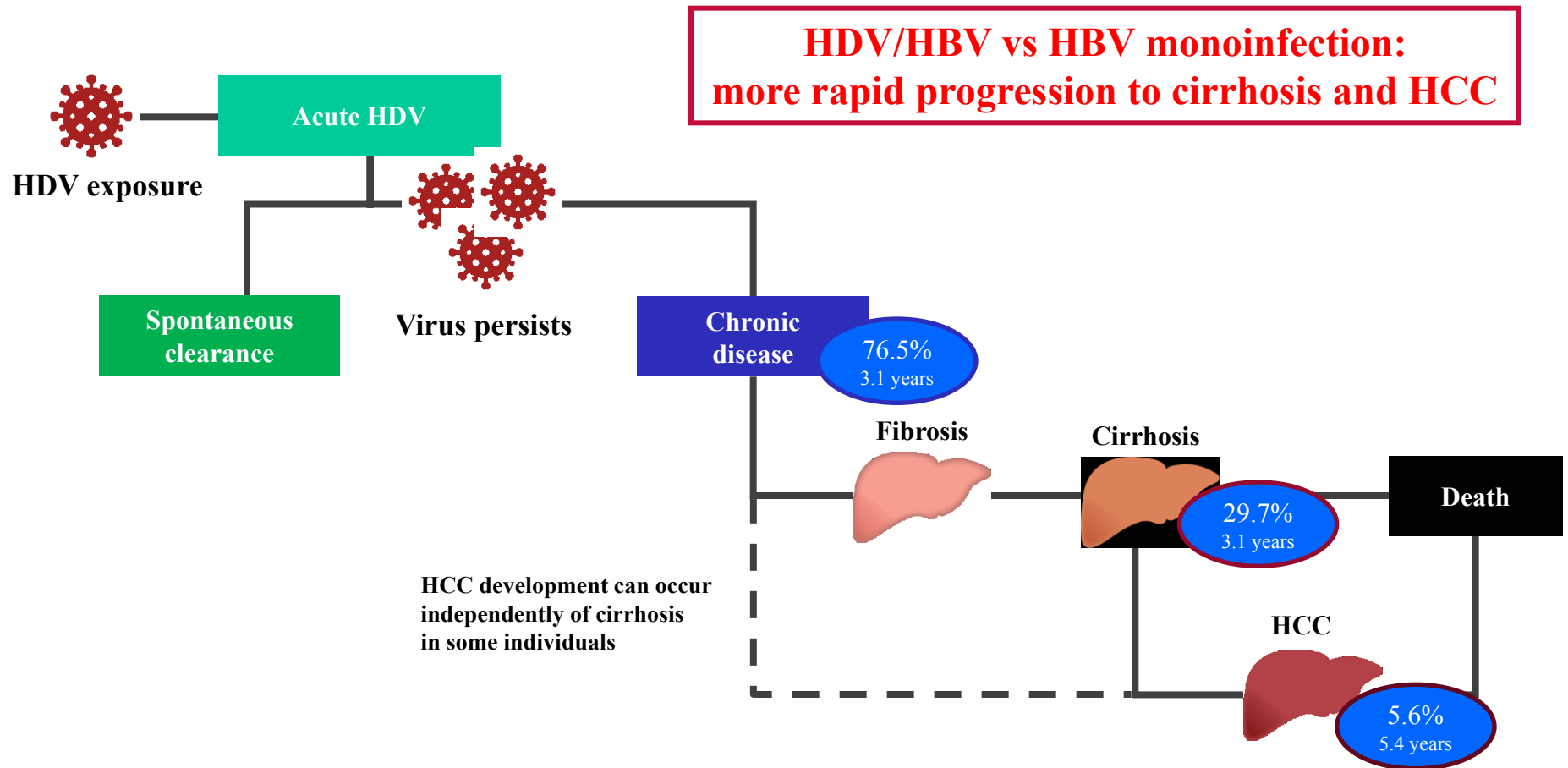


HDV superinfection

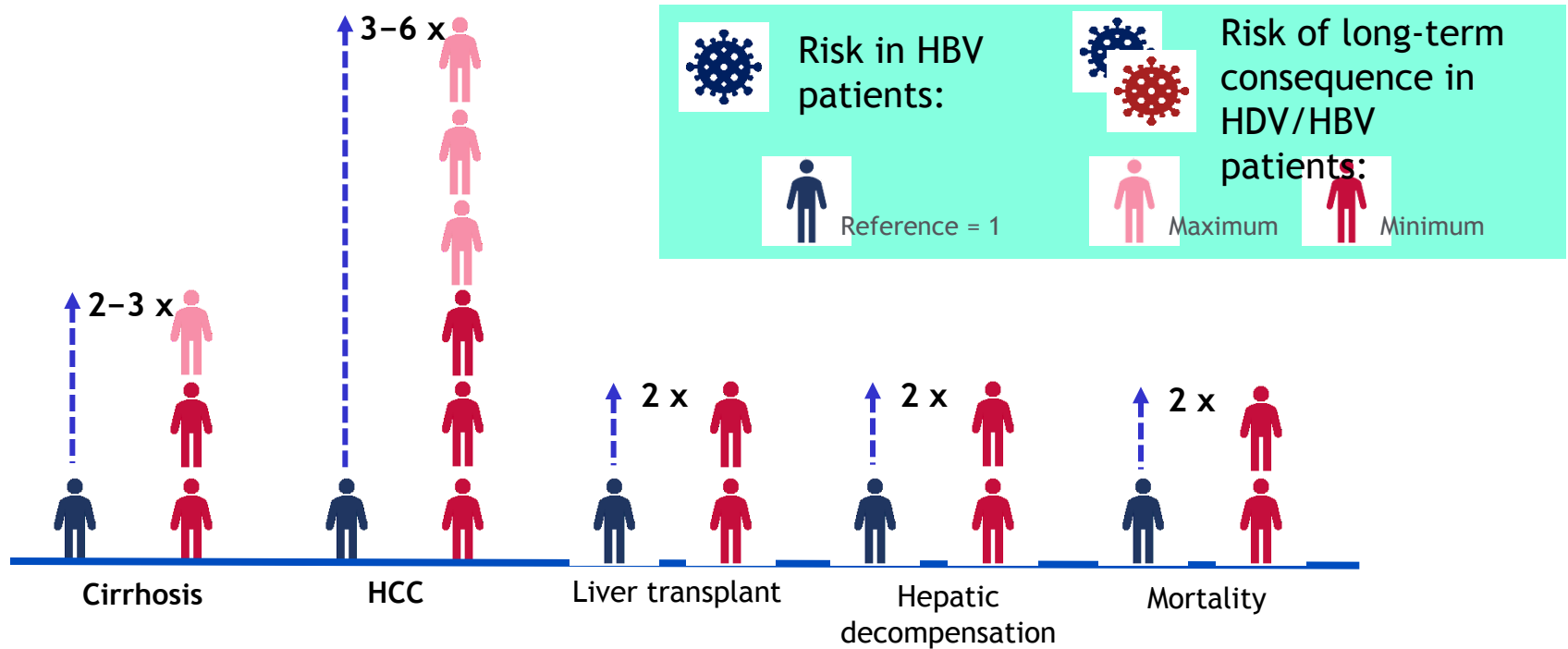


Data presented are based on estimates of HDV prevalence and disease progression rates determined in a large global epidemiology analysis.
HBV: hepatitis B virus; HCC: hepatocellular carcinoma; HDV: hepatitis delta virus.

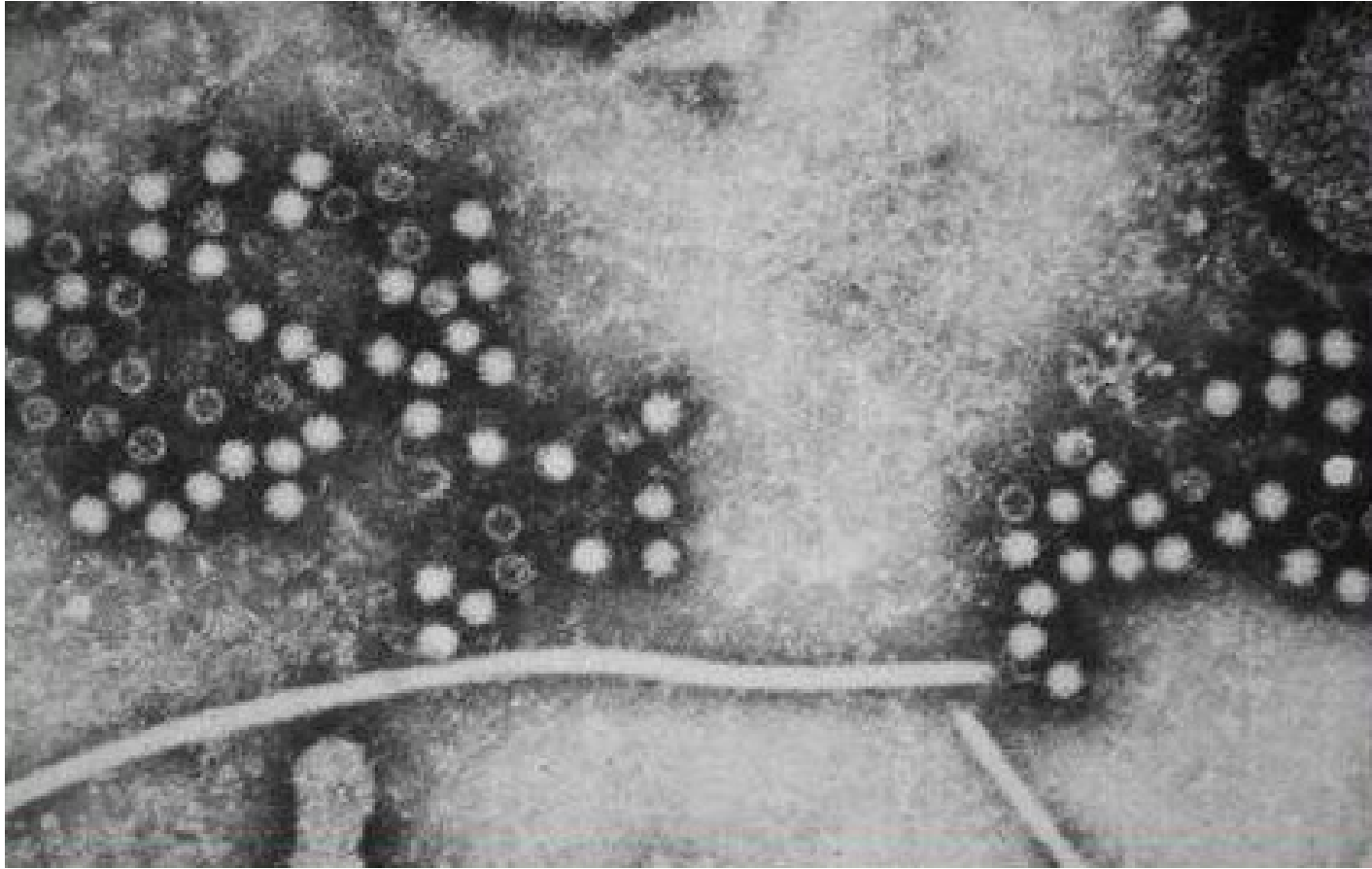
Clinical course of hepatitis delta



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

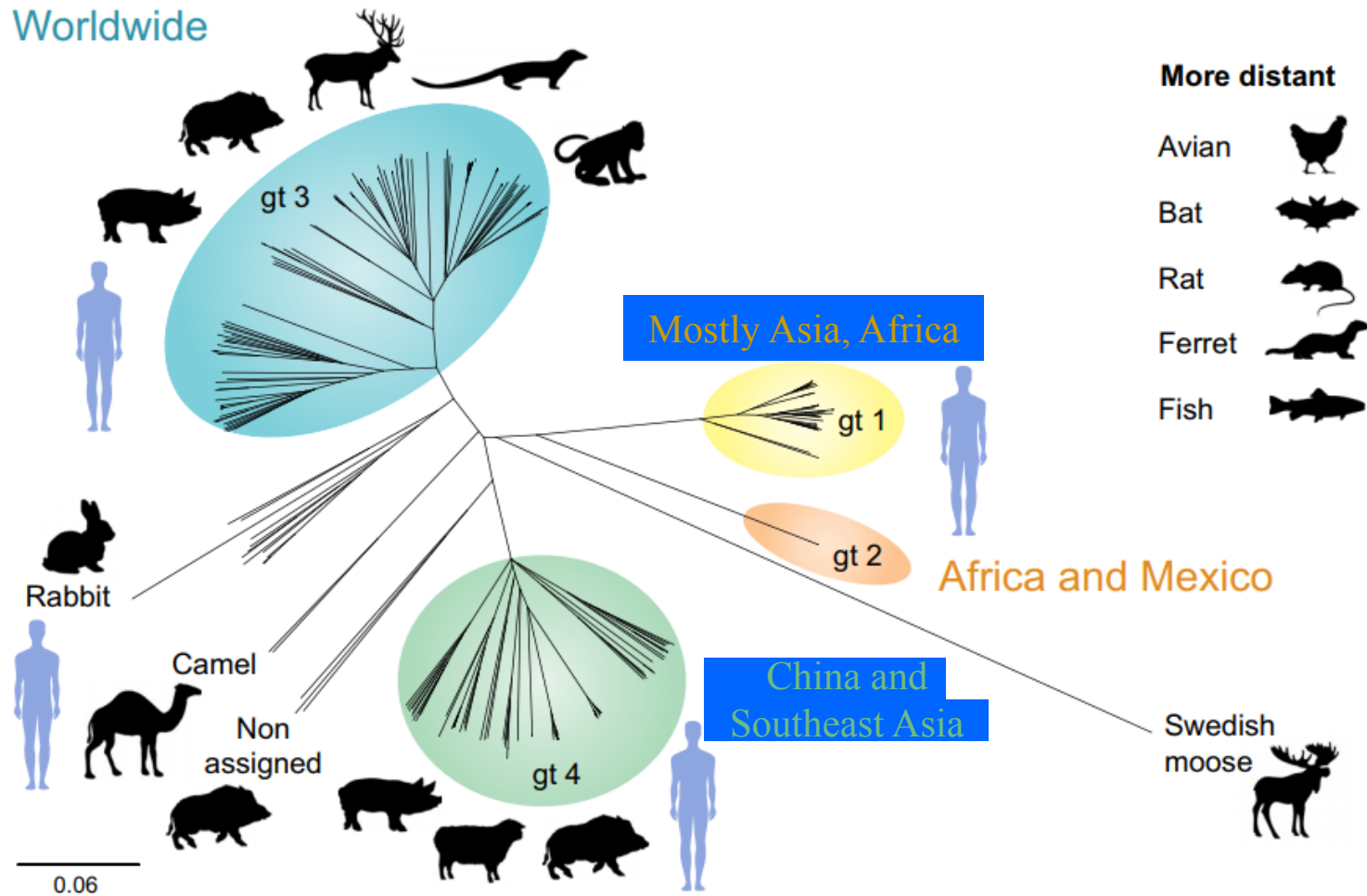


Hepatitis E virus

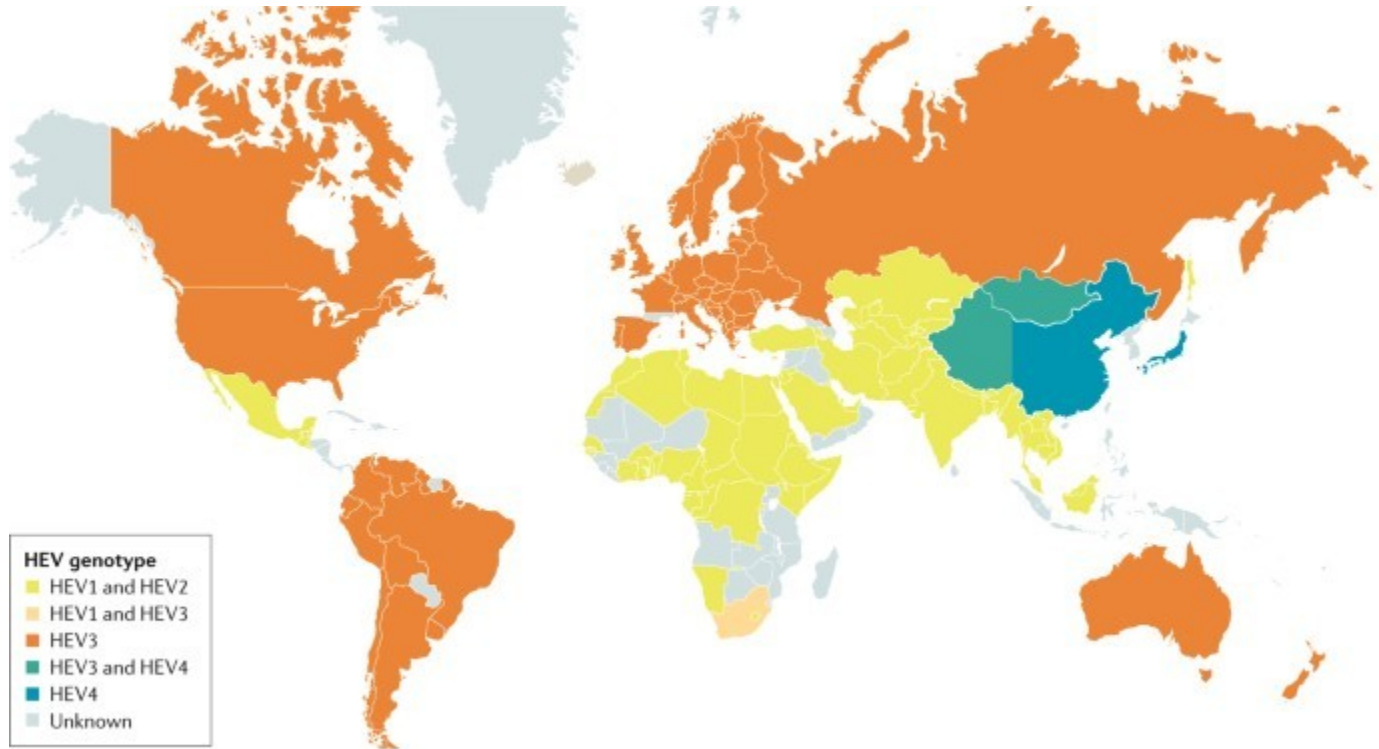


Non-enveloped RNA virus, family Hepeviridae, *genus Orthohepevirus*, 27-34 nm, 8 genotypes (1-8), human infections by G1-4

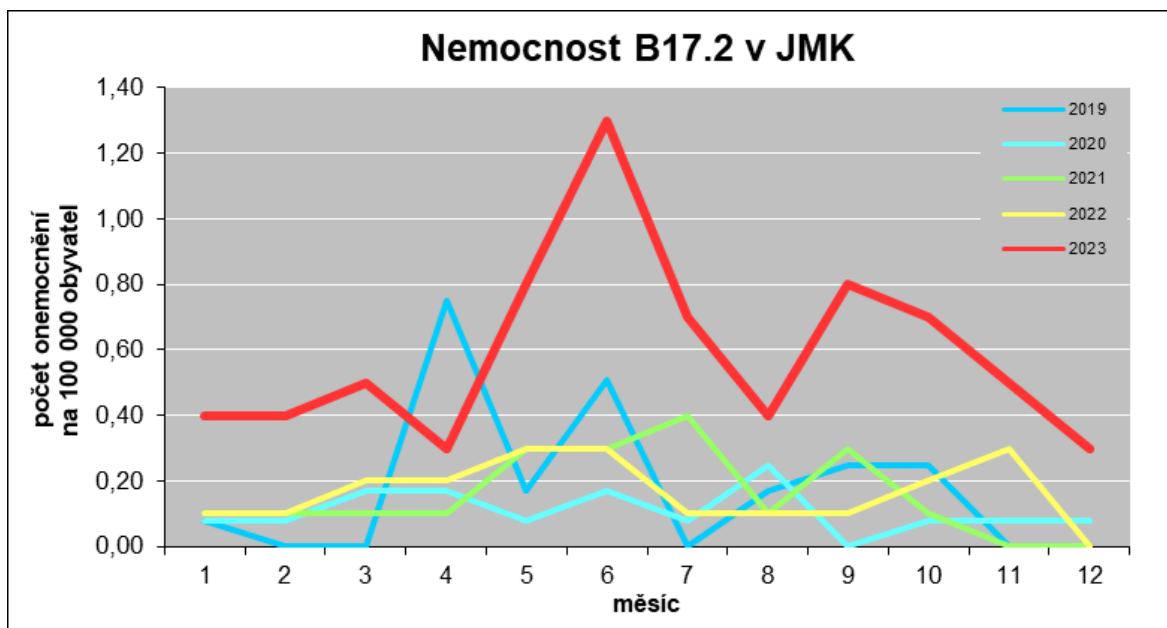
Phylogenetic relationship of hepeviruses identified in various hosts



HEV genotypes (1-4)



Hepatitis E in South Moravia 2019-2023



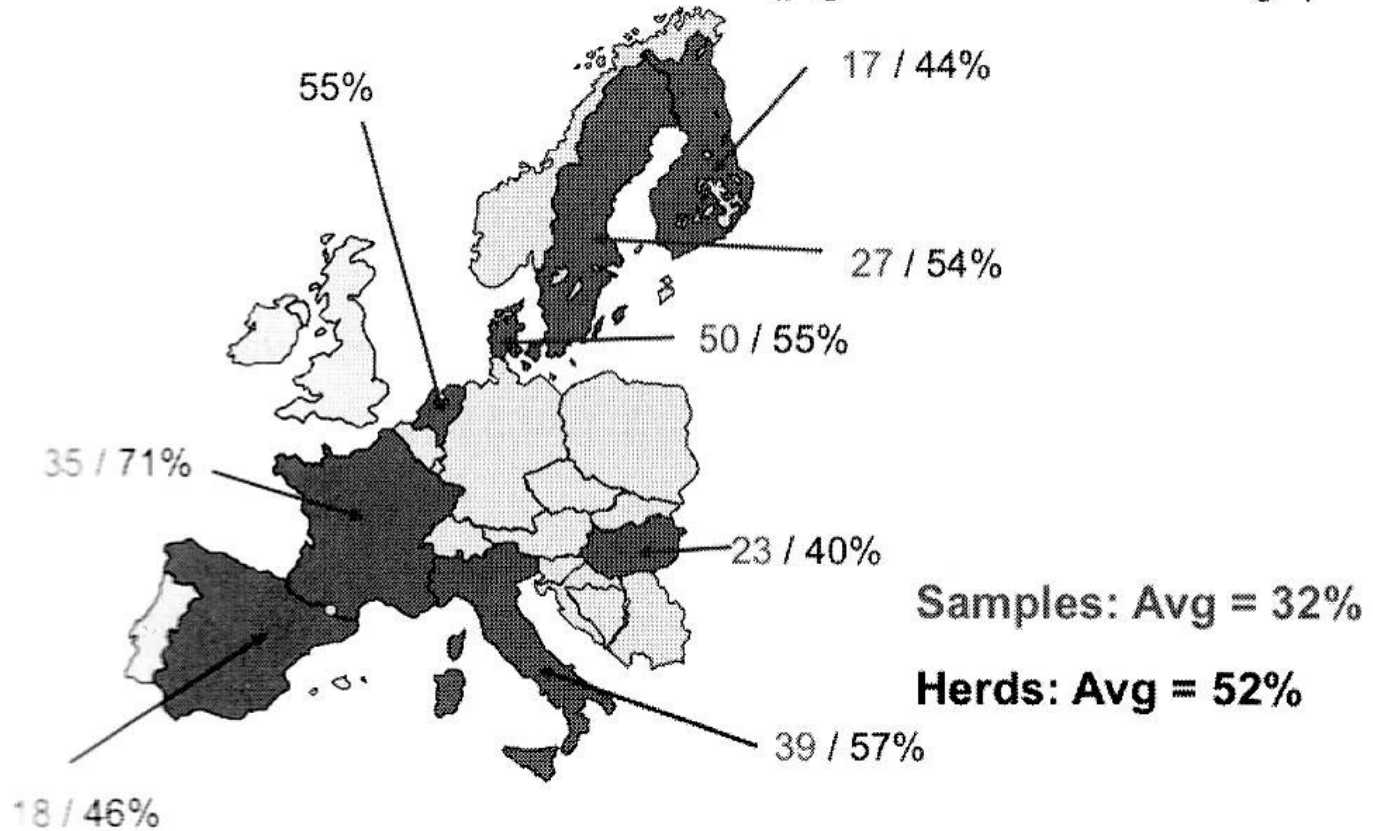
Infection with G-1,2 HEV

- 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

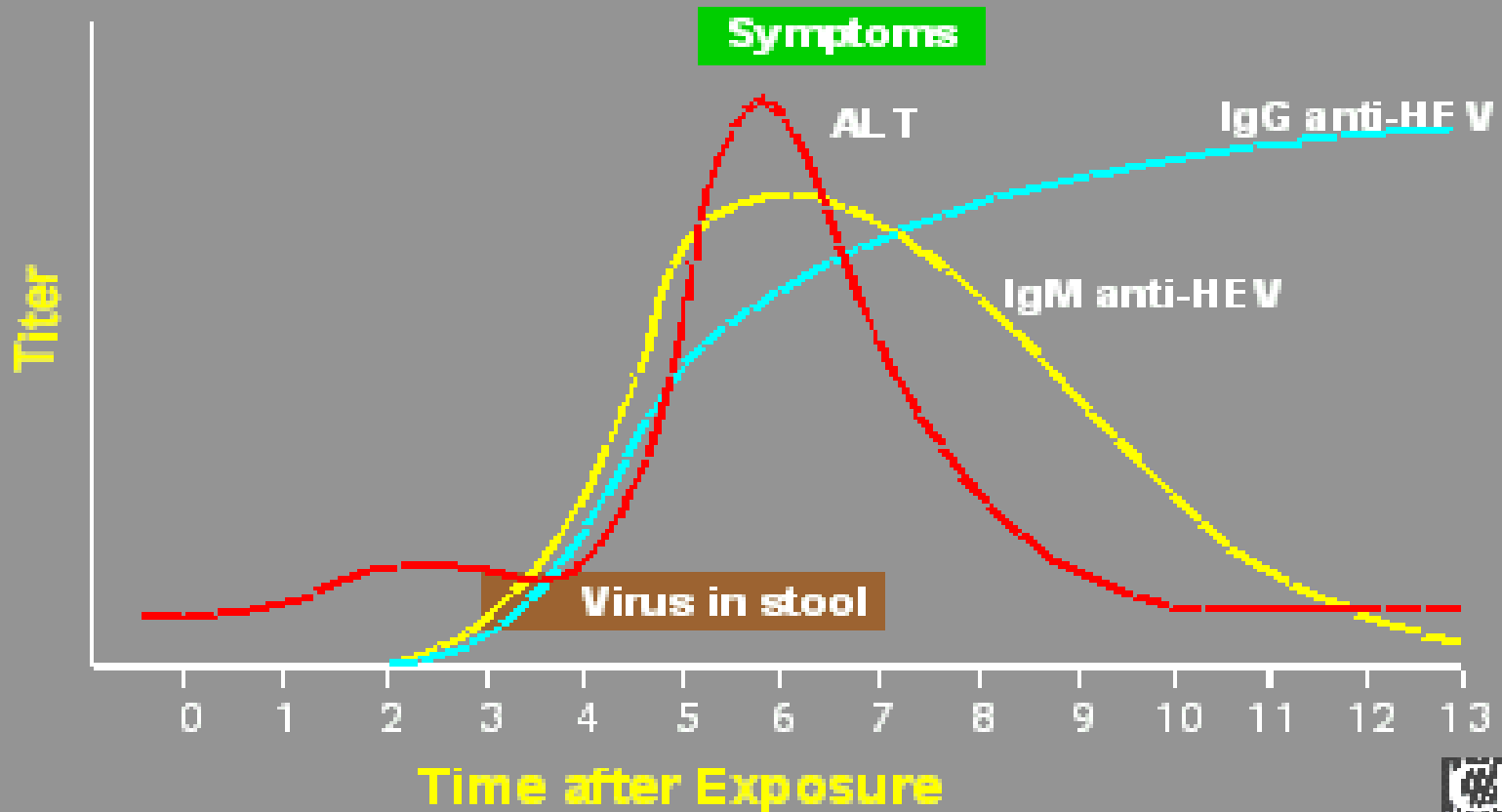
- Both human and zoonotic infection
- Pigs are the main reservoir (venison as well)
- G-3 – worldwide distribution, G-4 – China a southeast Asia
- ≥ 2 million locally acquired HEV infections/year in Europe (G-3), mostly asymptomatic (minimally 95 %), tend to affect older males
- Possibility of chronic 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)



Hepatitis E Virus Infection

Typical Serological Course



Rapid progression of chronic hepatitis E

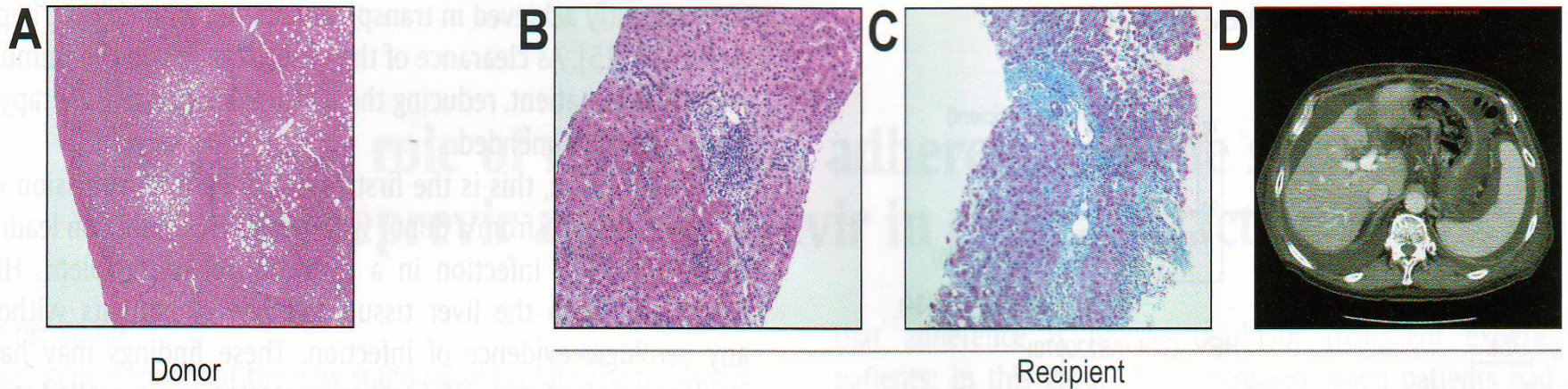


Fig. 1. Histologic assessment of the liver tissue before and after OLT and CT scan after OLT. (A) The liver tissue of the donor revealed absence of significant signs of chronic hepatitis but vesicular fatty liver disease was diagnosed. (B) Second biopsy. One hundred and fifty days after OLT, chronic 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 hepatotoxic drugs
 - ✓ diet (?)
 - ✓ supportive treatment (silymarin, essential phospholipids) (?)
 - ✓ antivirals for complicated acute HEP B and E

Therapy of acute HEP B

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

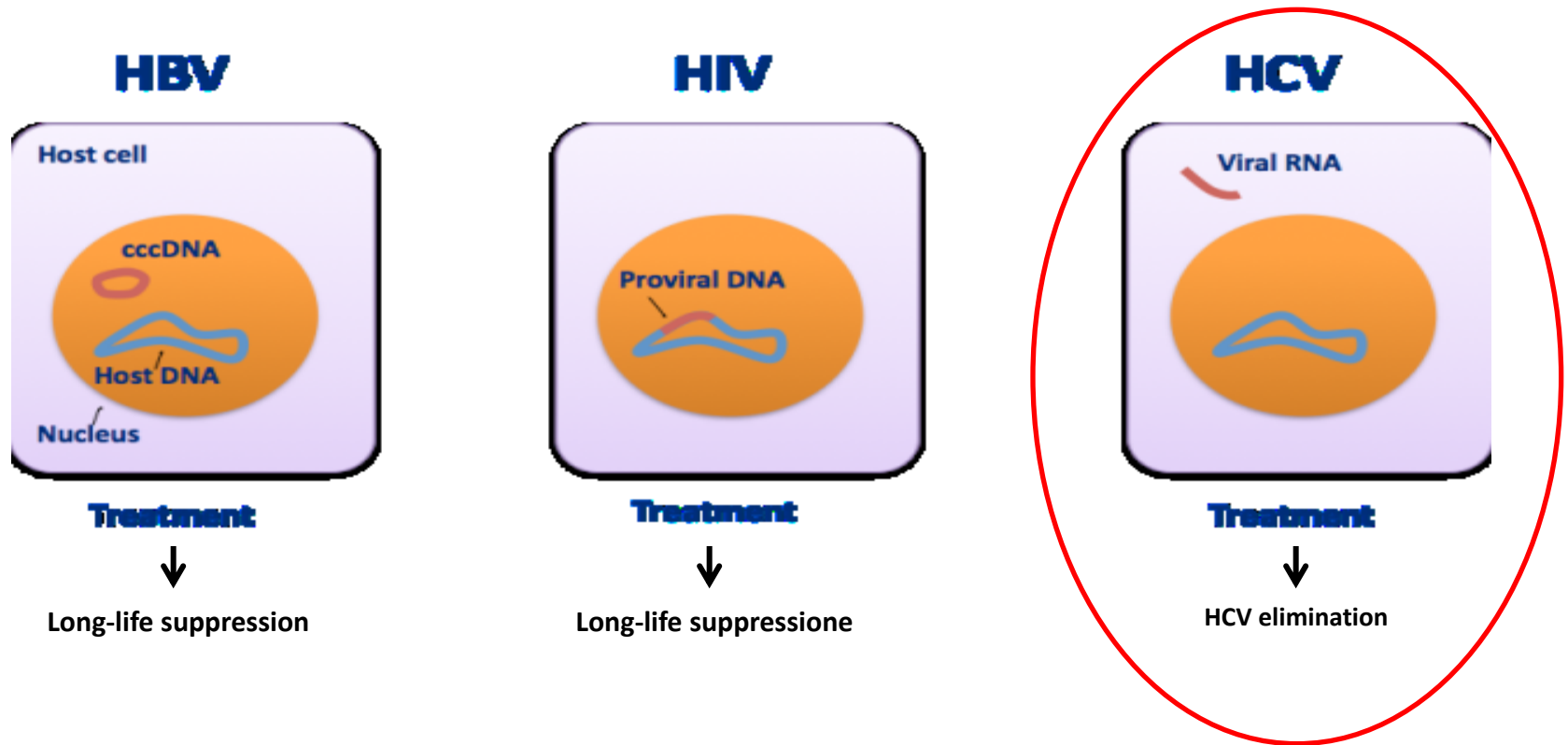
Current possibilities of treatment of chronic HEP B

- 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

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 immunosuppression – 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