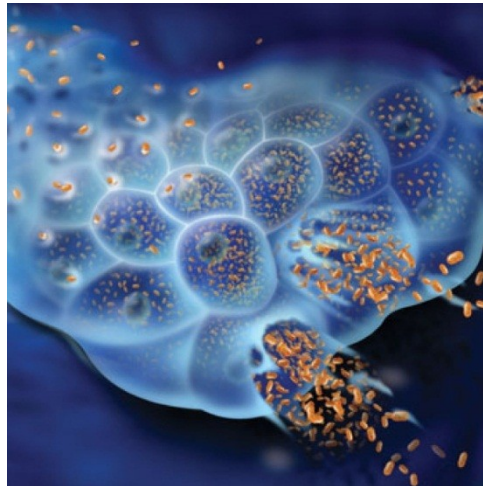


# Viral Hepatitis

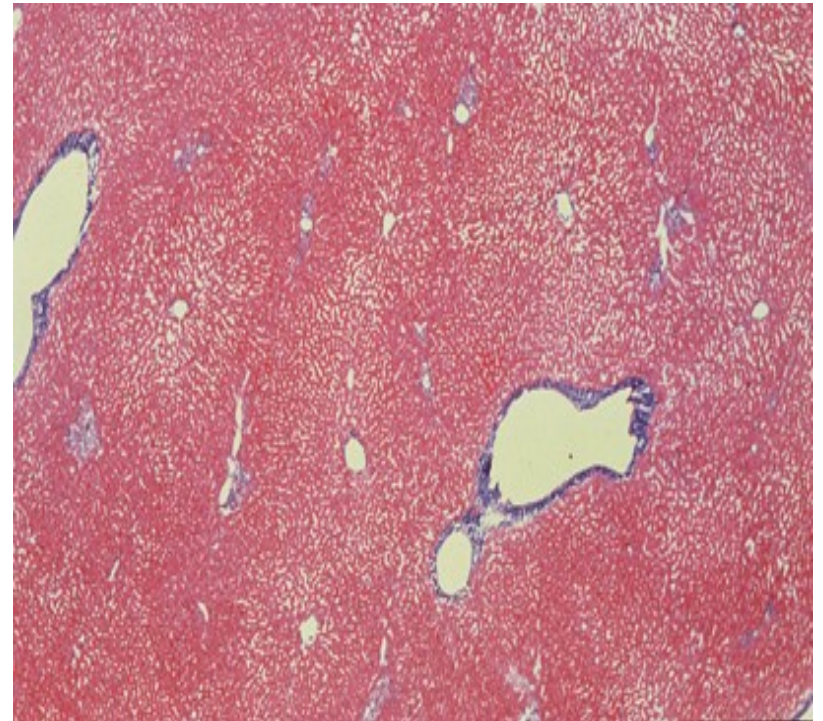
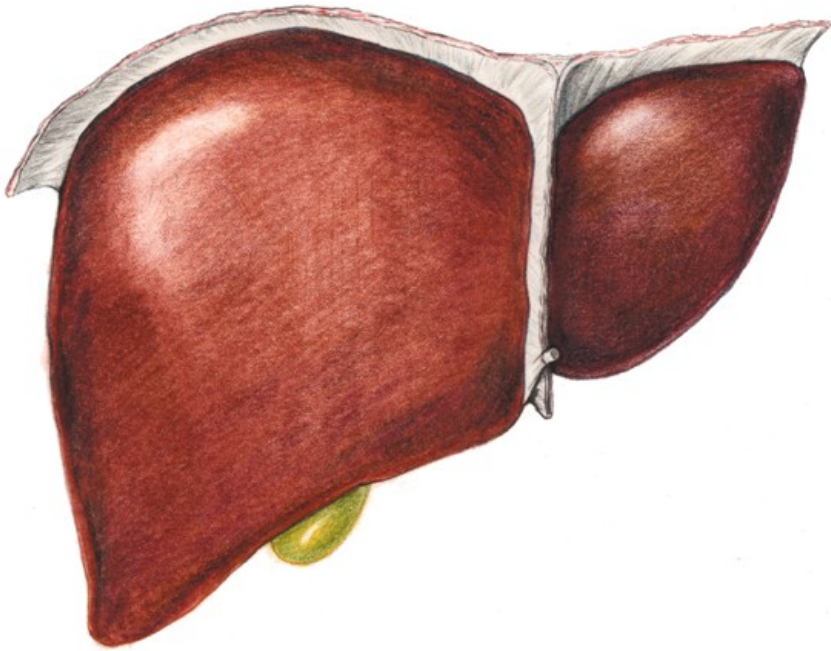


prof. MUDr. Petr Husa, CSc.  
Klinika infekčních chorob, FN Brno

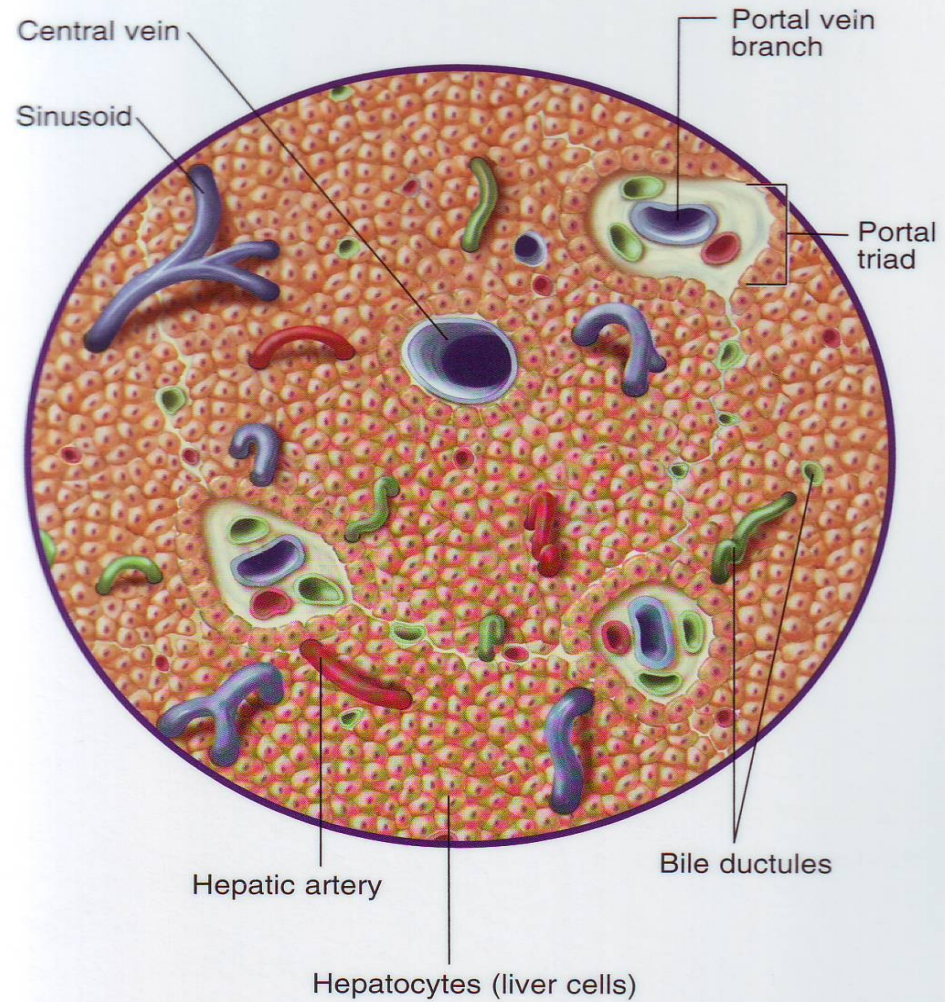
# Viral Hepatitis

- 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

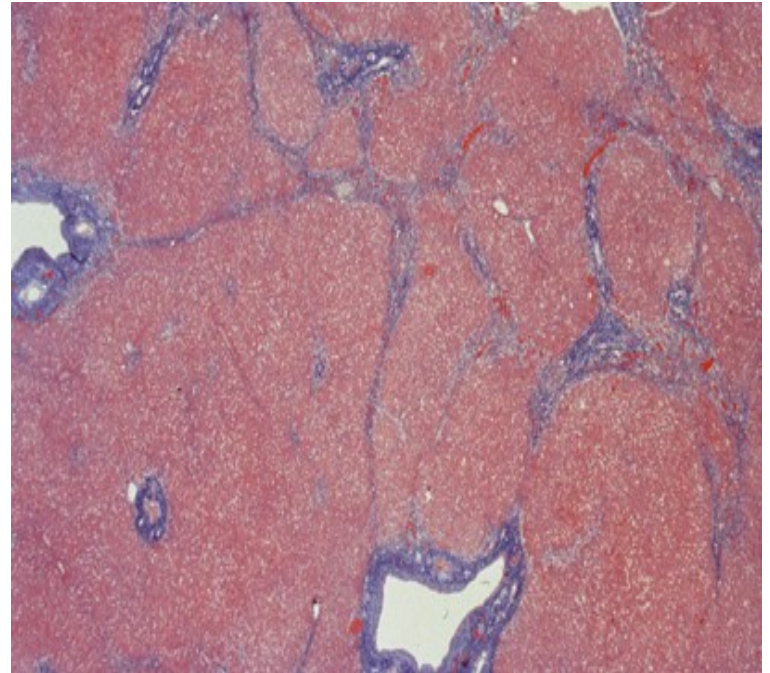
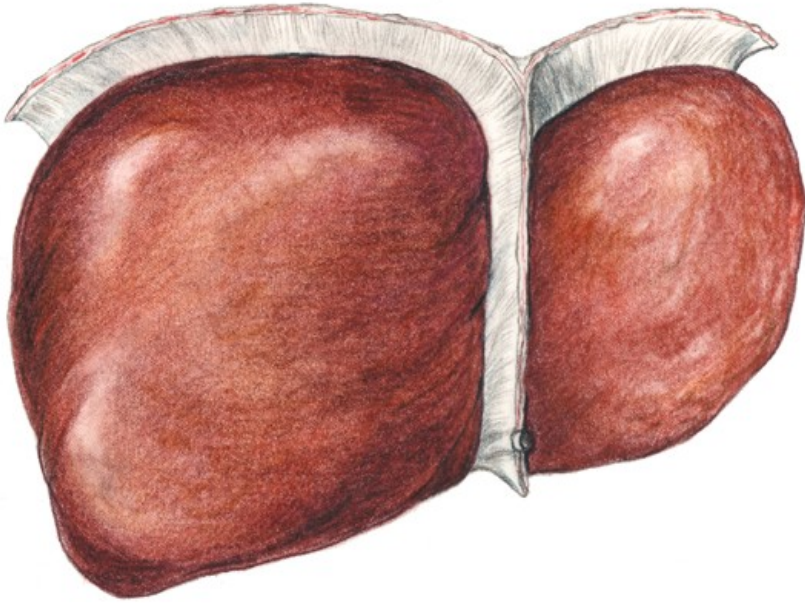
# Healthy liver



## Normal Biopsy



# Liver fibrosis



## Mild Fibrosis

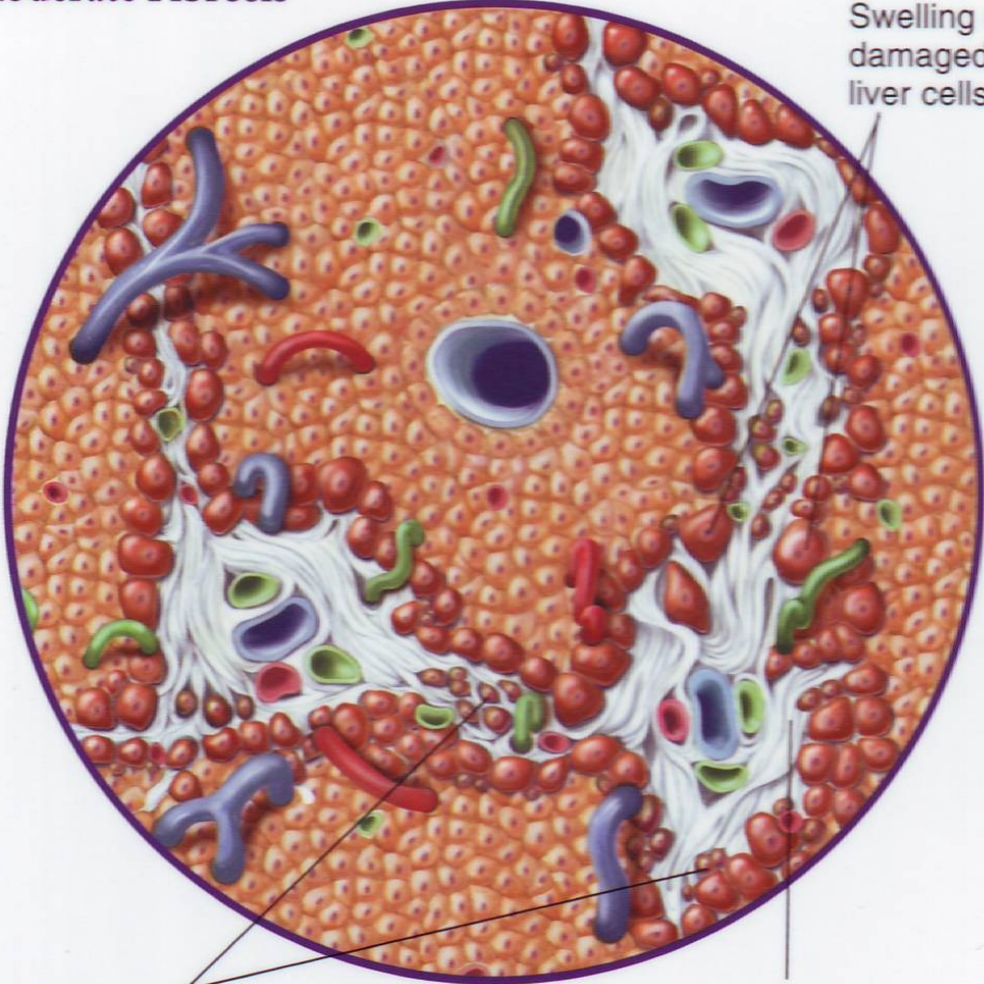
Mild swelling and inflammation of  
damaged liver cells around portal areas

Development of  
scar tissue (fibrosis)



Normal hepatocytes  
(liver cells)

Moderate Fibrosis

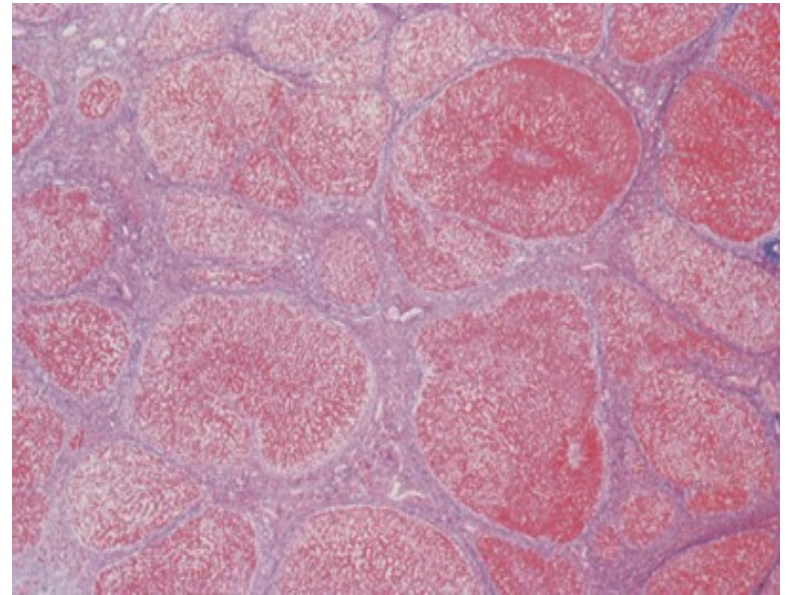
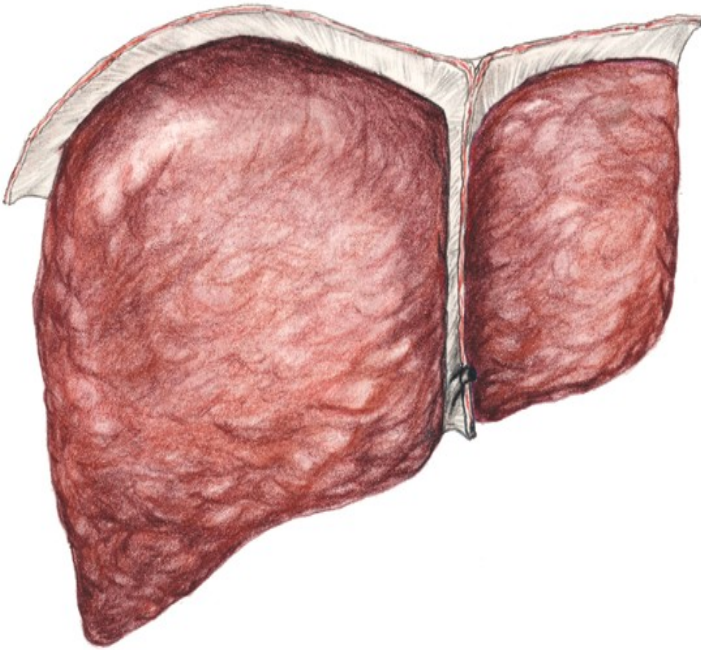


Swelling of  
damaged  
liver cells

Necrosis of liver cells

Fibrosis extending  
between portal areas

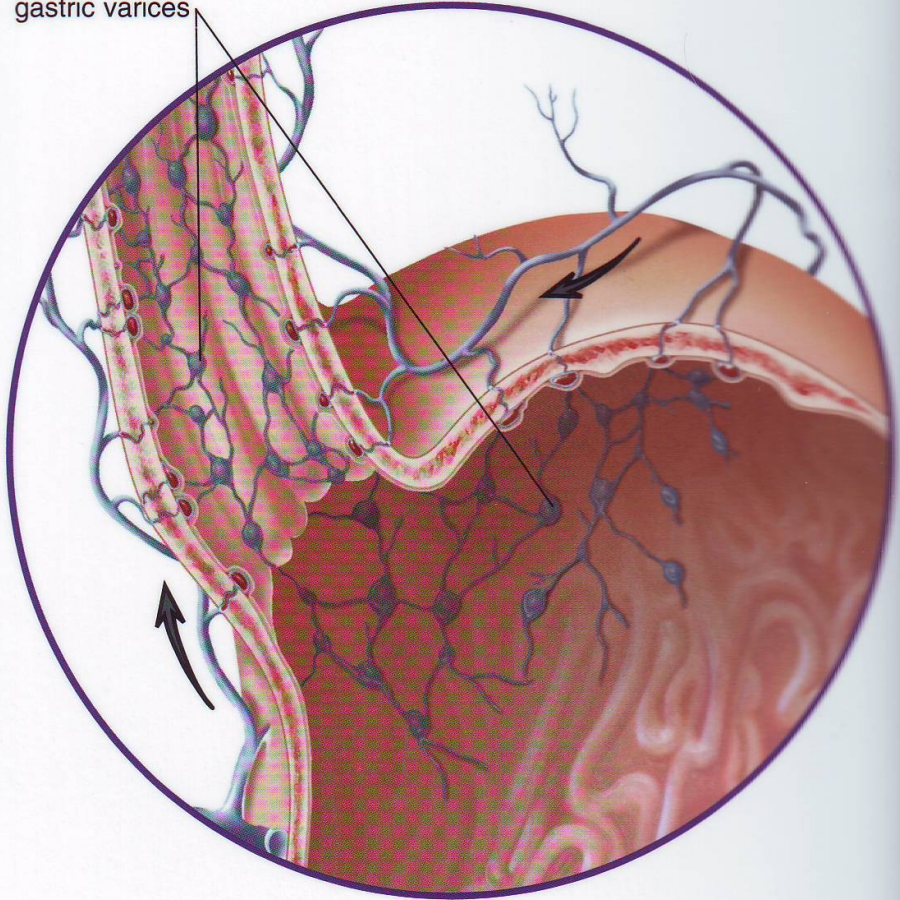
# Liver cirrhosis

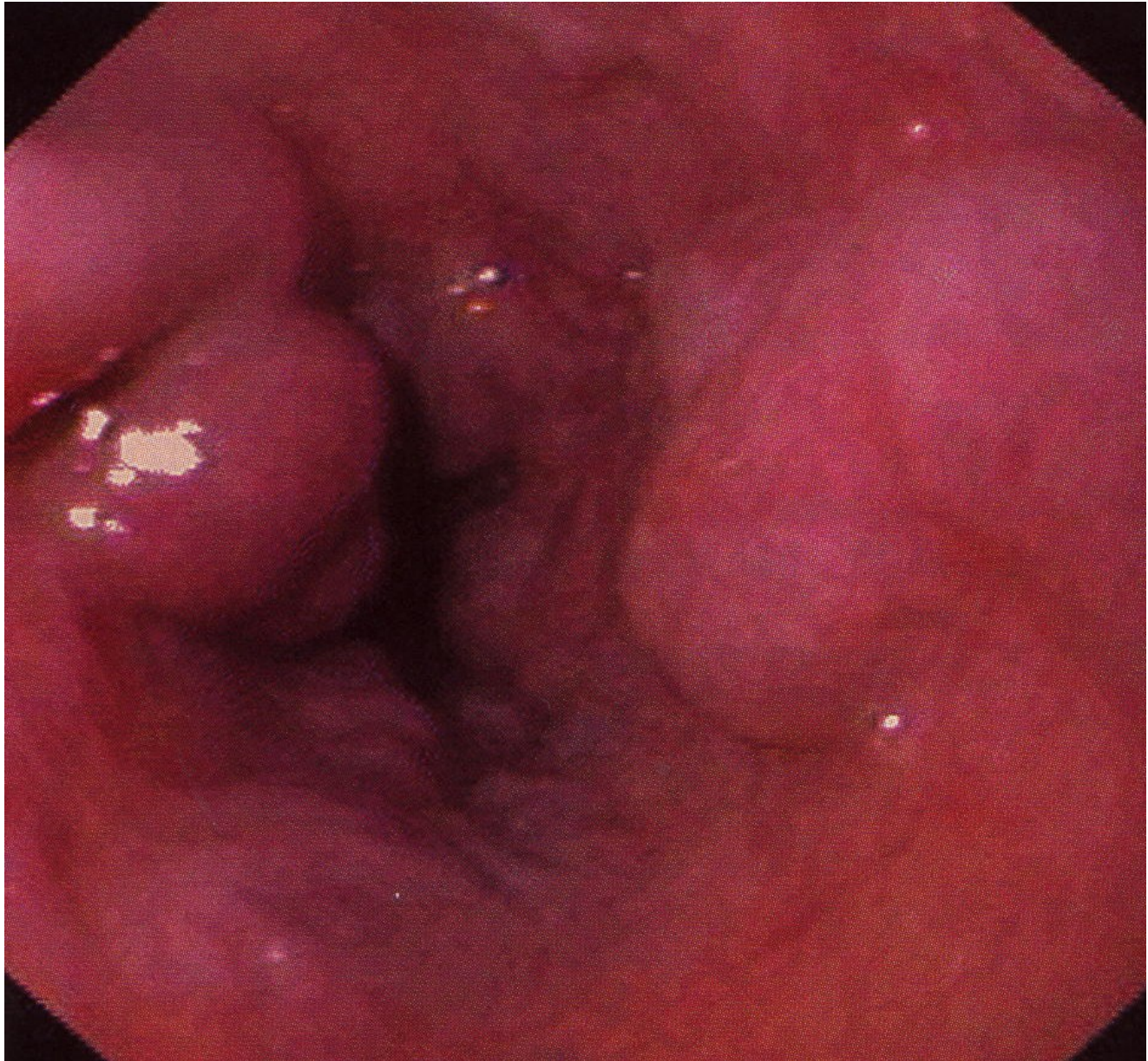


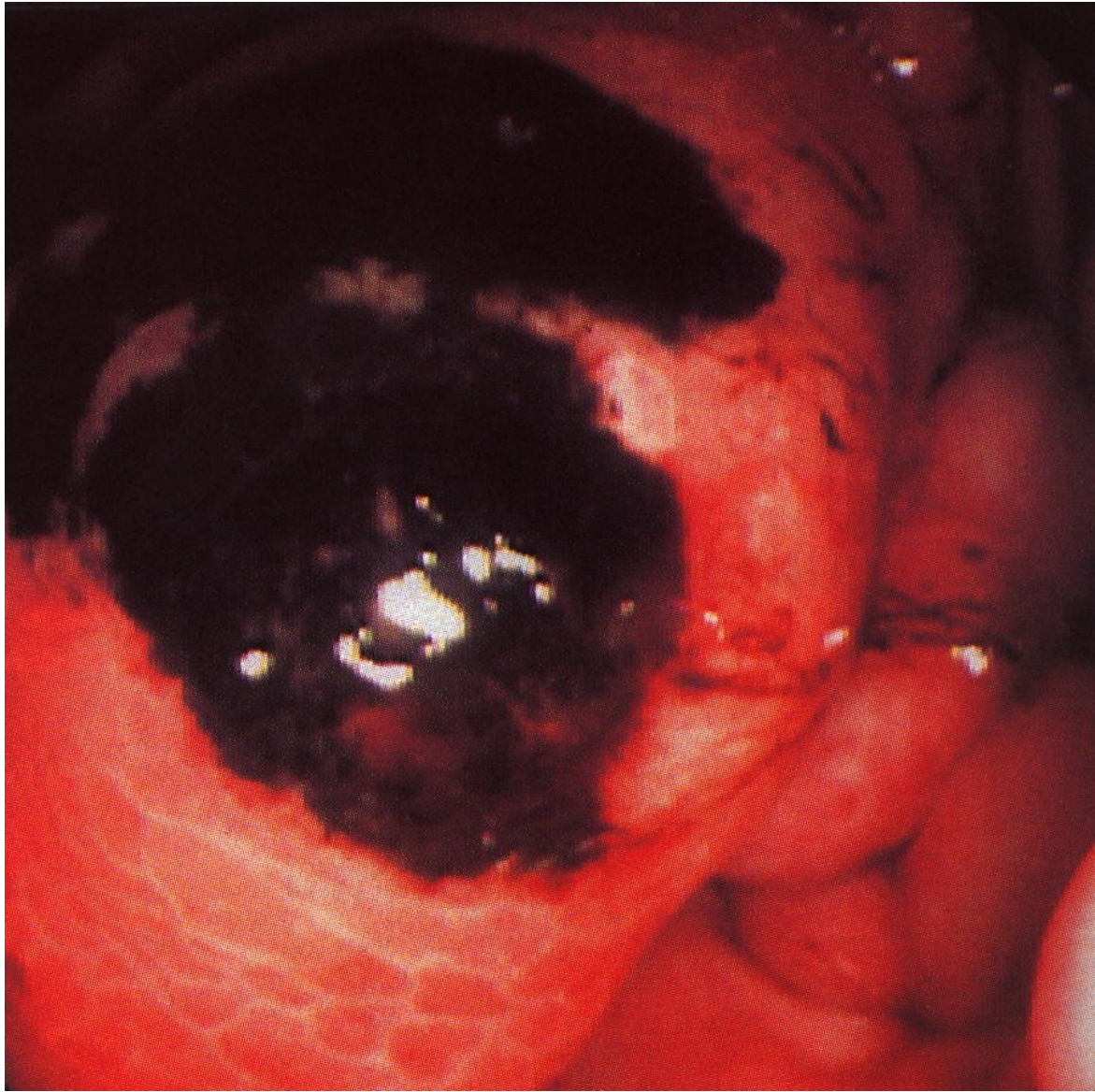


# Development of Varices

Esophageal and gastric varices



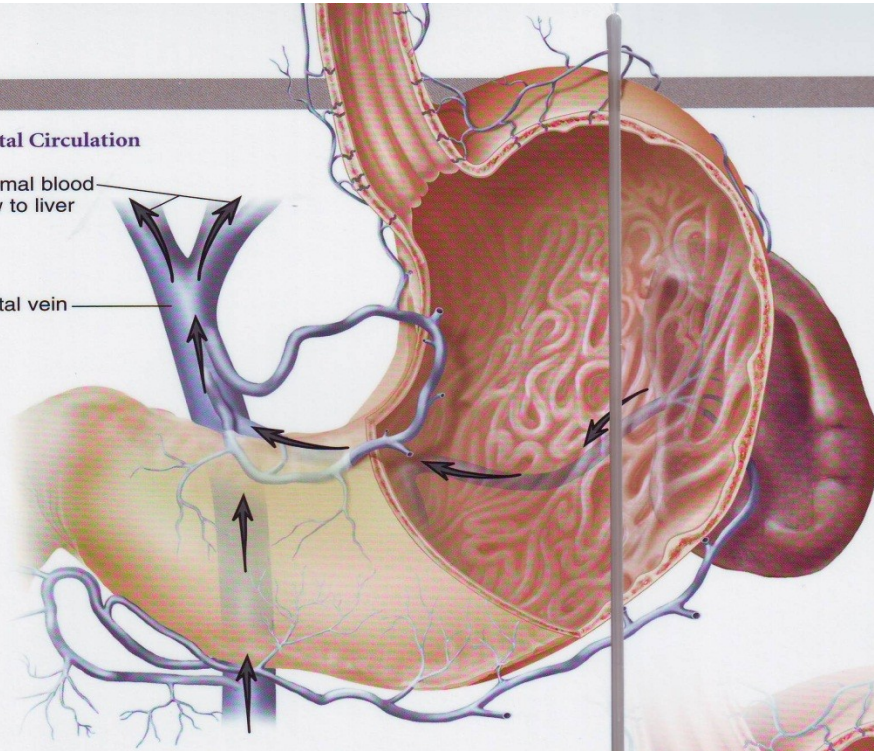




**Portal Circulation**

Normal blood flow to liver

Portal vein

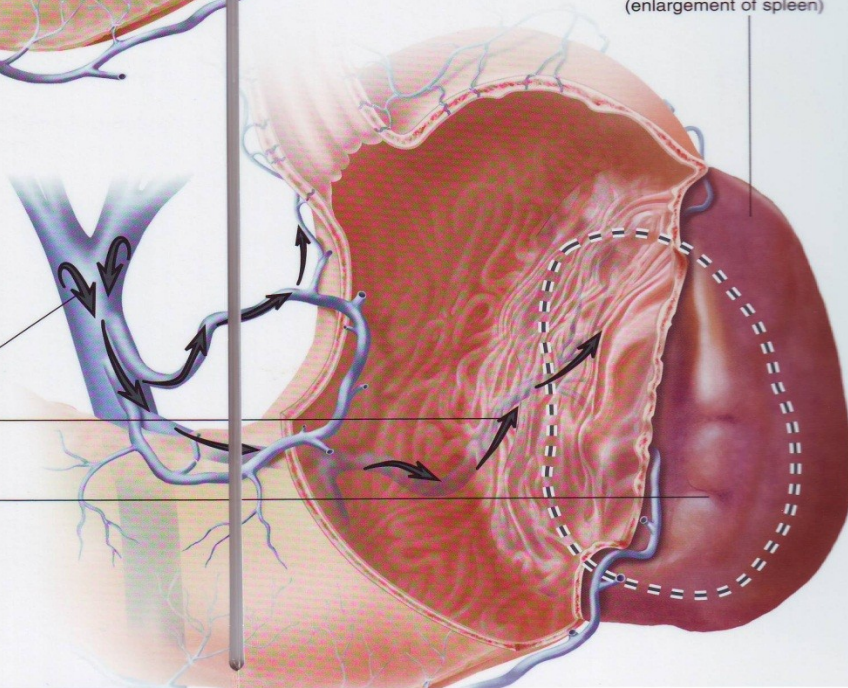


Splenomegaly  
(enlargement of spleen)

**Portal Hypertension**

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

Size of normal spleen

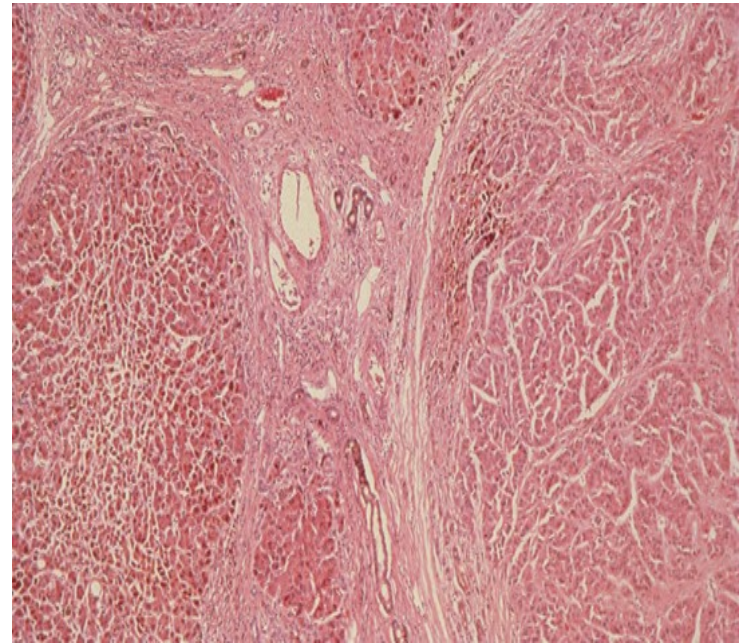
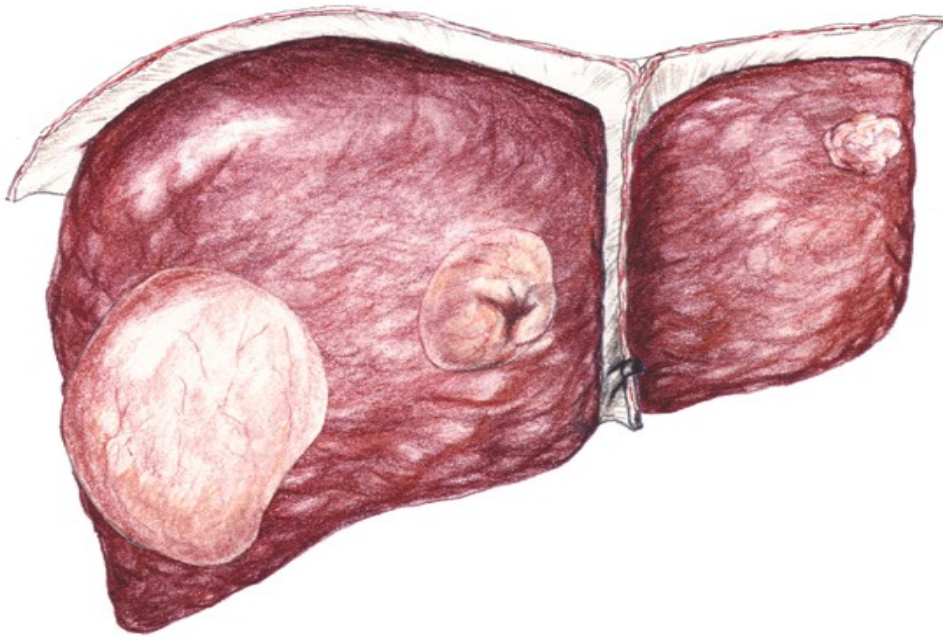








# Hepatocellular carcinoma



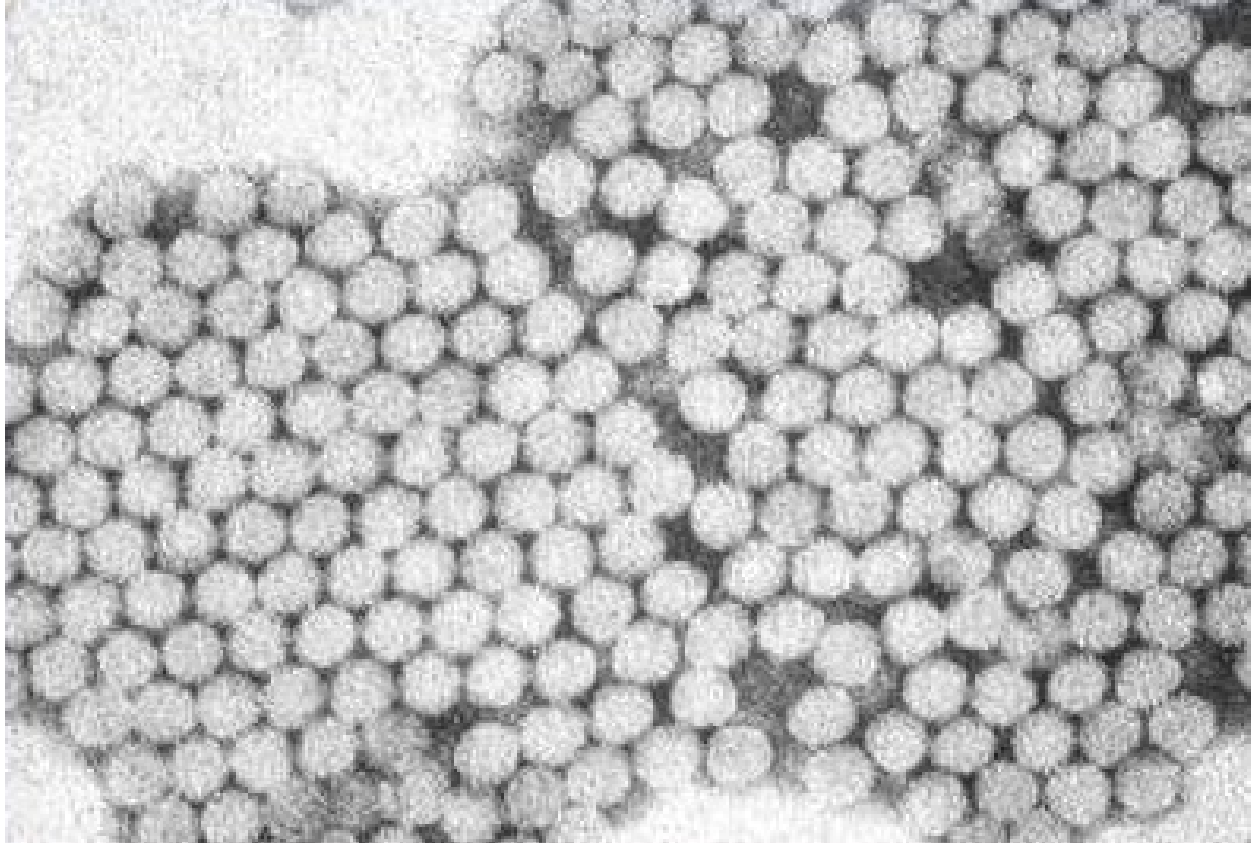




# Viral hepatitis in CR 2011-2020

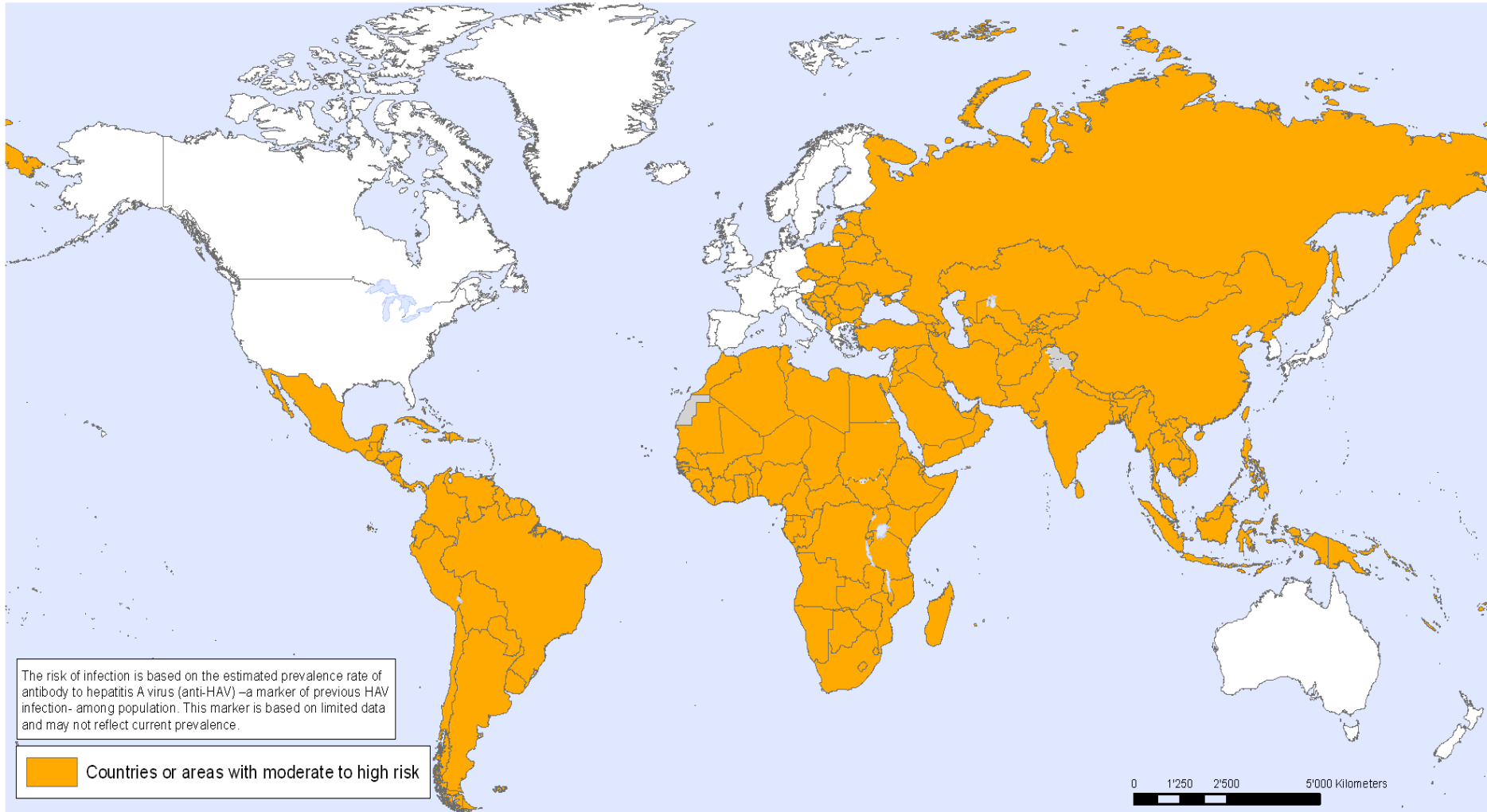
	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
<b>VH A</b>	264	284	348	673	723	930	772	211	240	183
<b>acute VH B</b>	192	154	133	105	90	73	85	54	41	27
<b>chronic VH B</b>	162	147	147	193	193	208	248	269	276	142
<b>VH C</b>	812	794	873	867	945	1103	992	1050	1138	771
<b>VH E</b>	163	258	218	299	409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

# 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



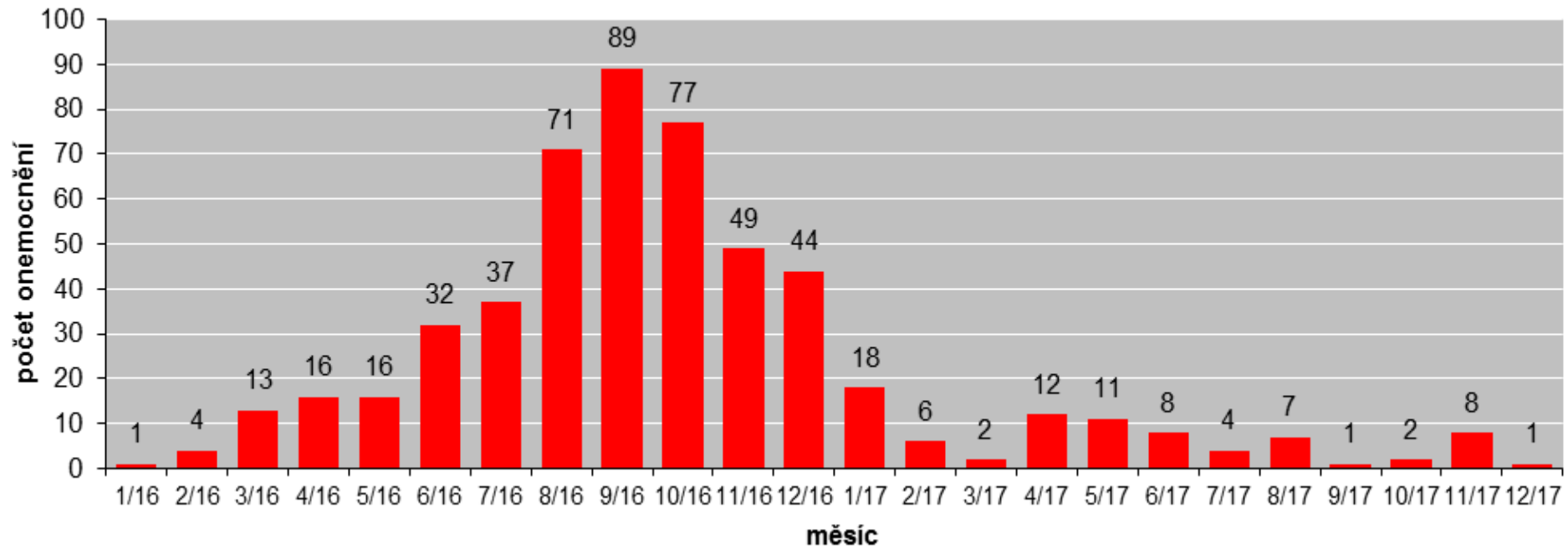
The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers 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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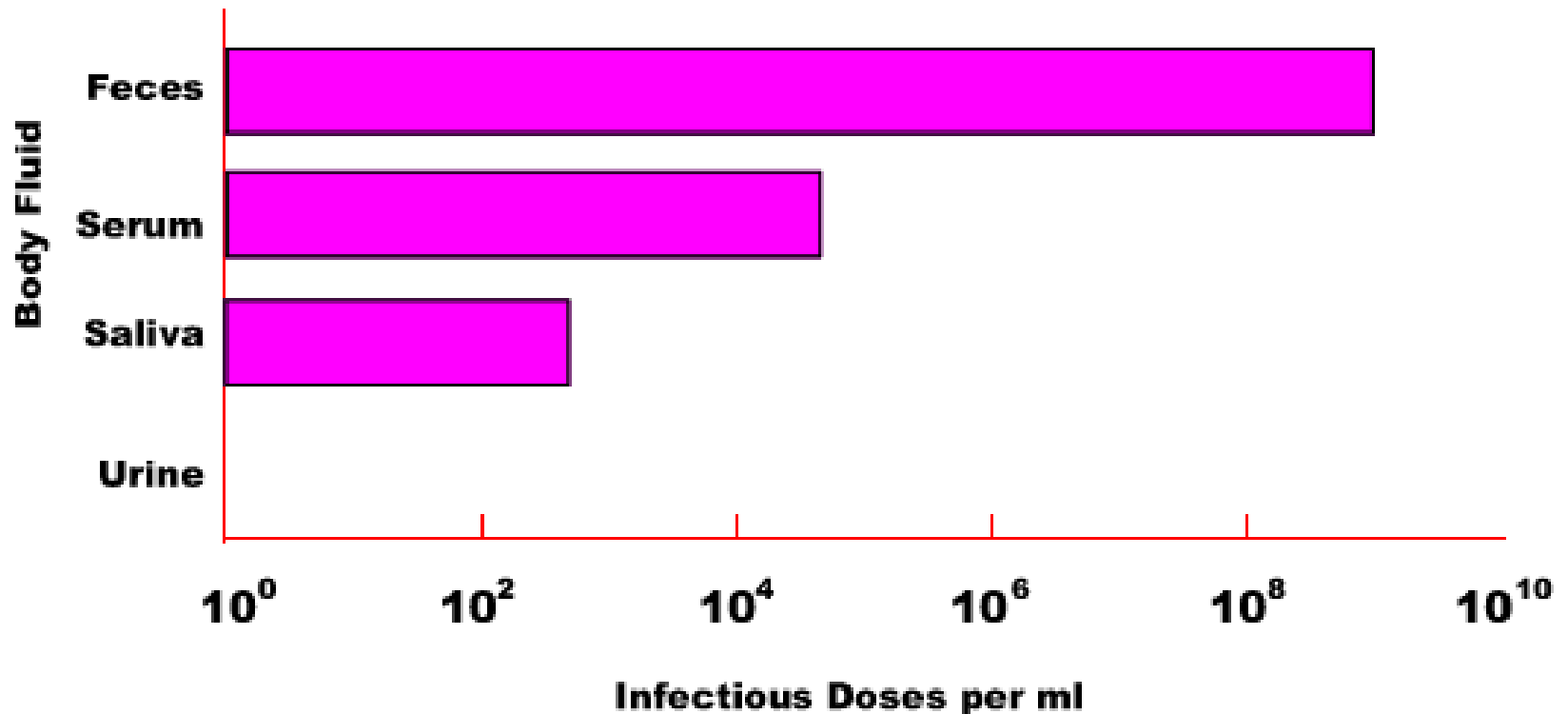
# HAV epidemic in the South Moravia 2016-2017



# 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

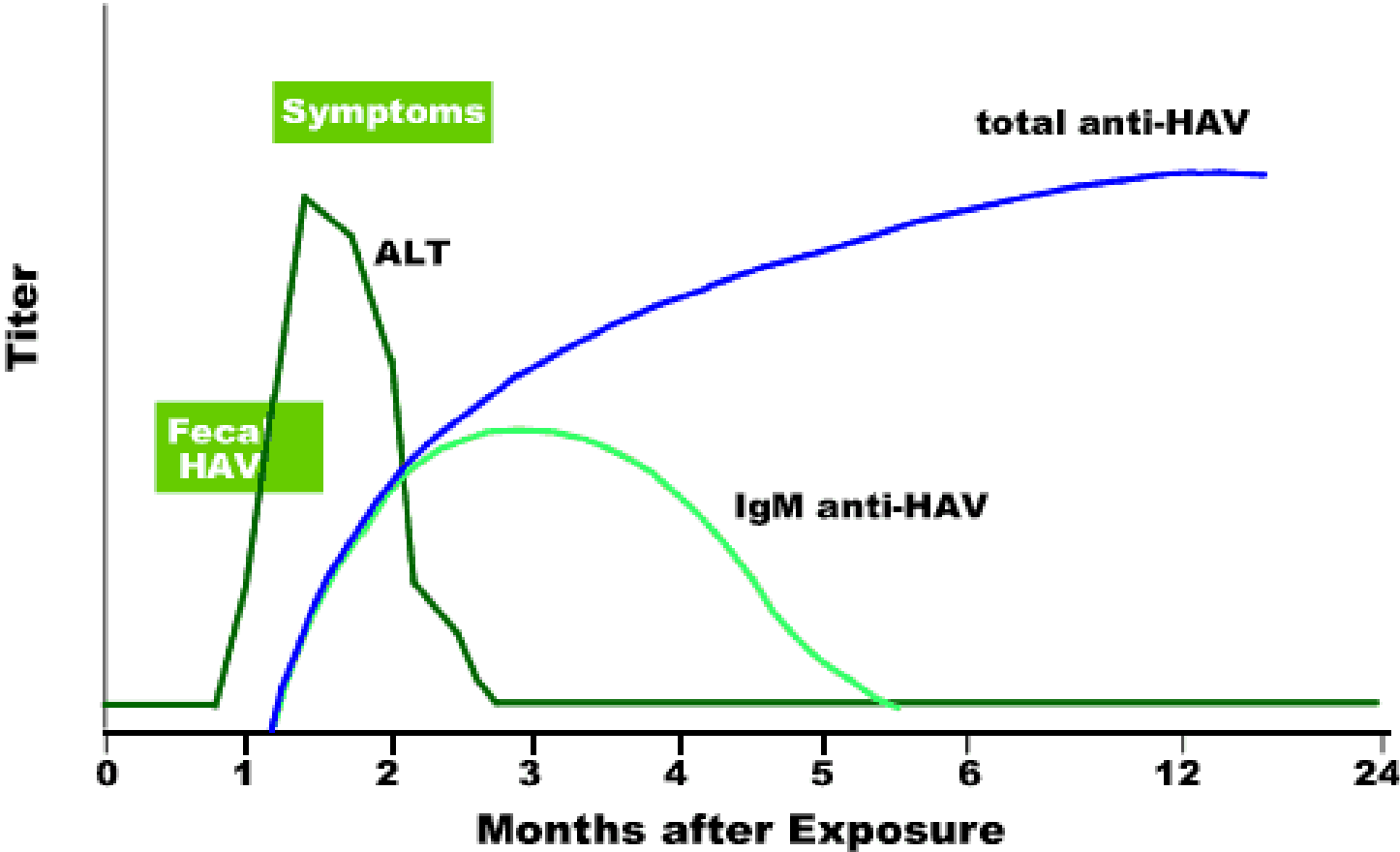
## Concentration of Hepatitis A Virus in Various Body Fluids



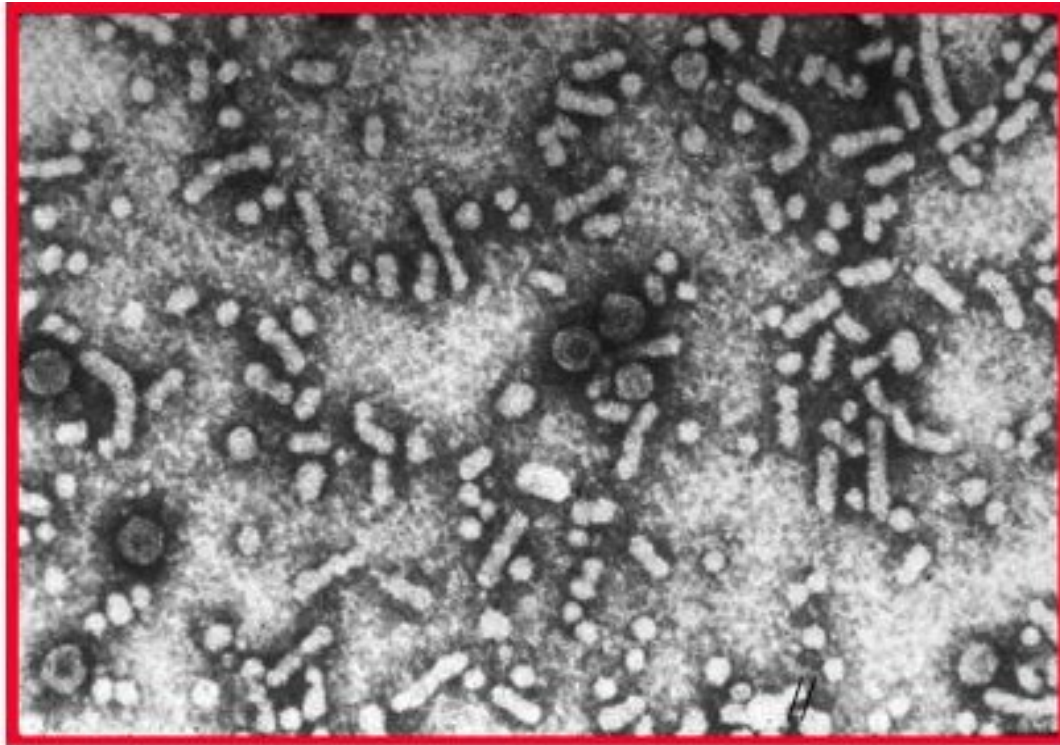
Source: Viral Hepatitis and Liver Disease 1984;9-2  
J Infect Dis 1989; 160:887-890

# Hepatitis A Virus Infection

## Typical Serologic Course



# Hepatitis B Virus (HBV)

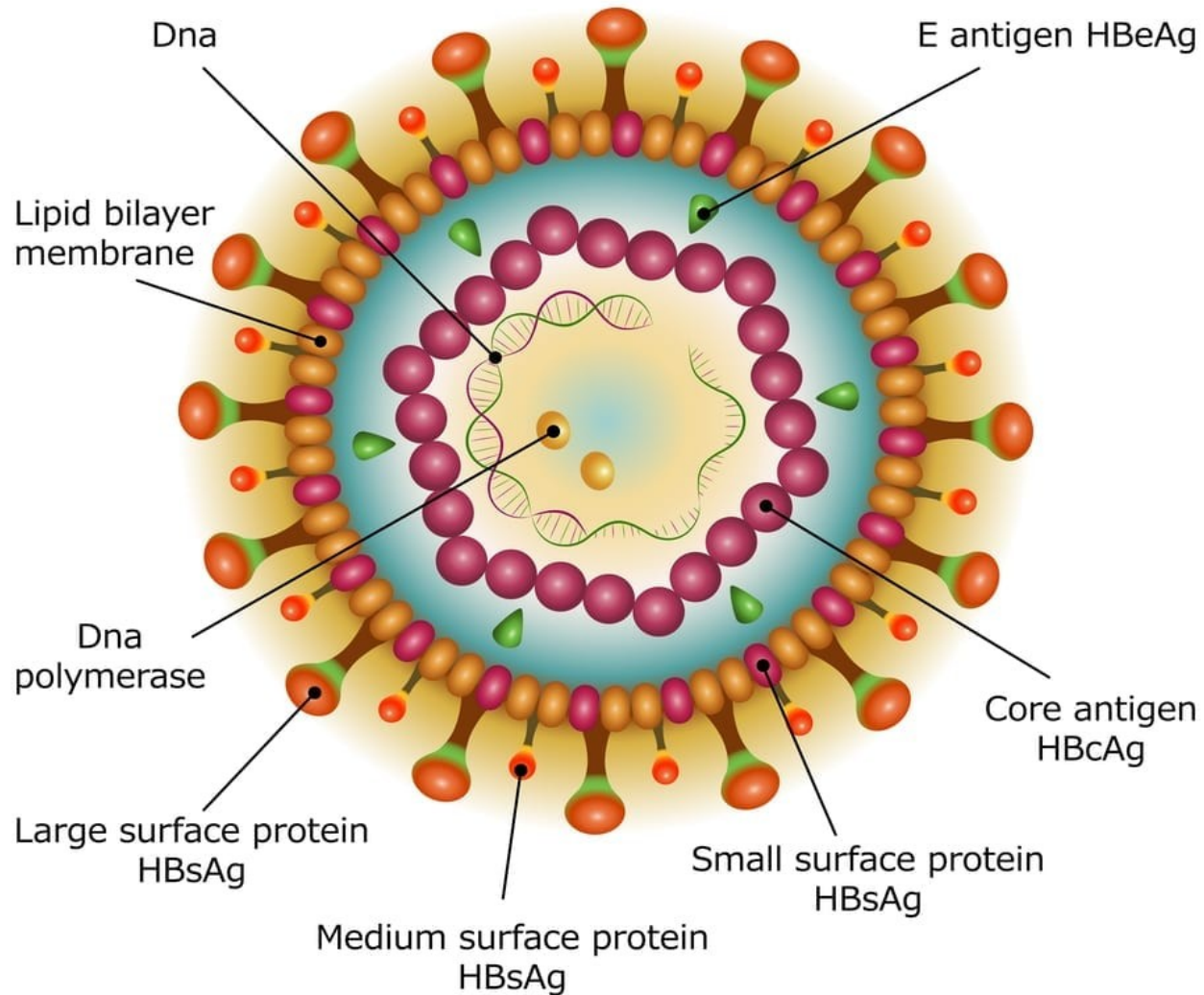


Family Hepadnaviridae, genus *Orthohepadnavirus*, enveloped DNA, 42 nm,  
9 genotypes (A-I), Europe A,D, Asia B,C, several subtypes



# Hepatitis B Virus

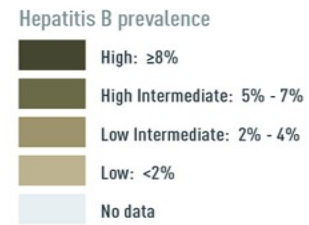
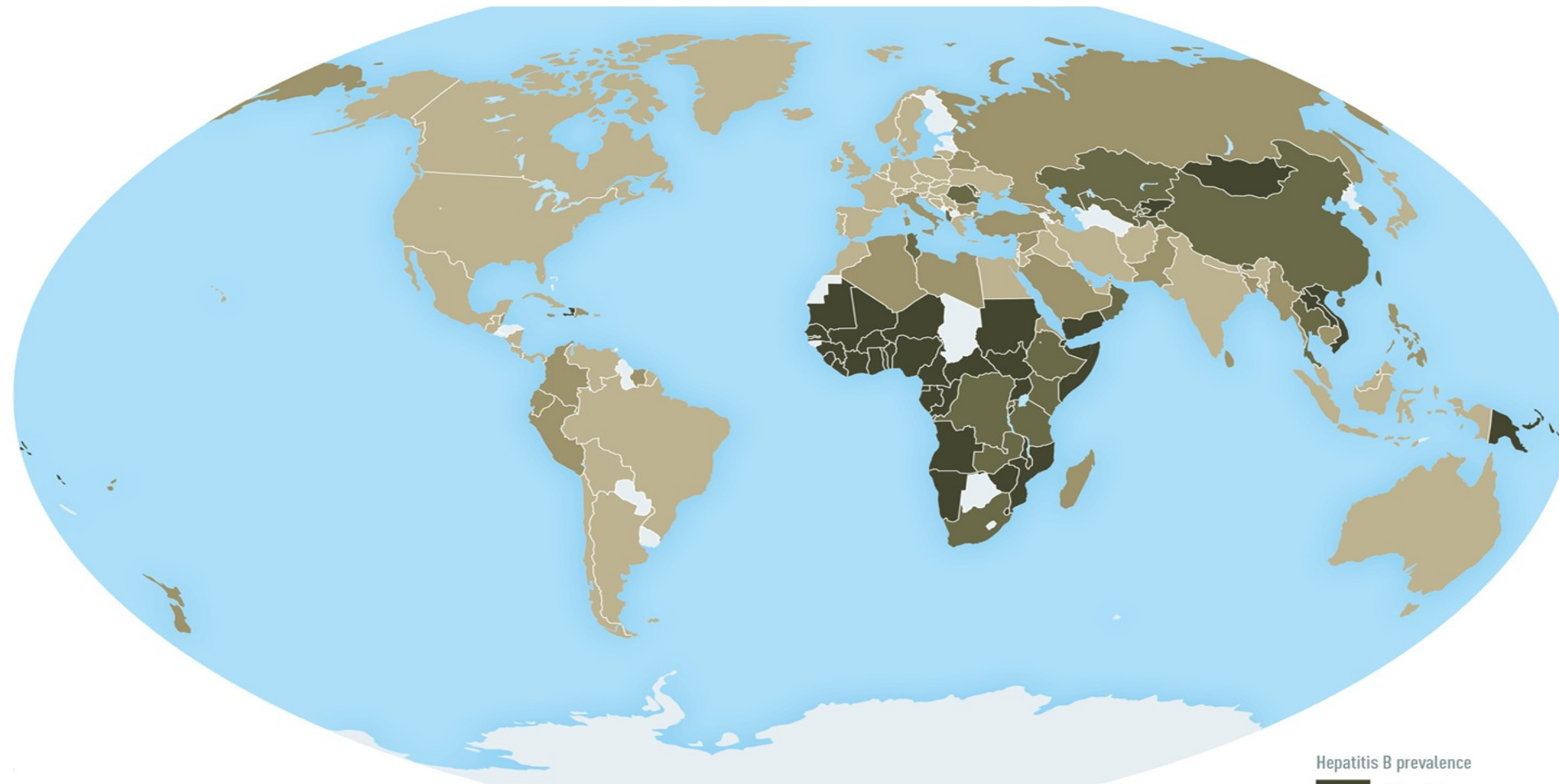
Baltimore Group VII (dsDNA-RT)



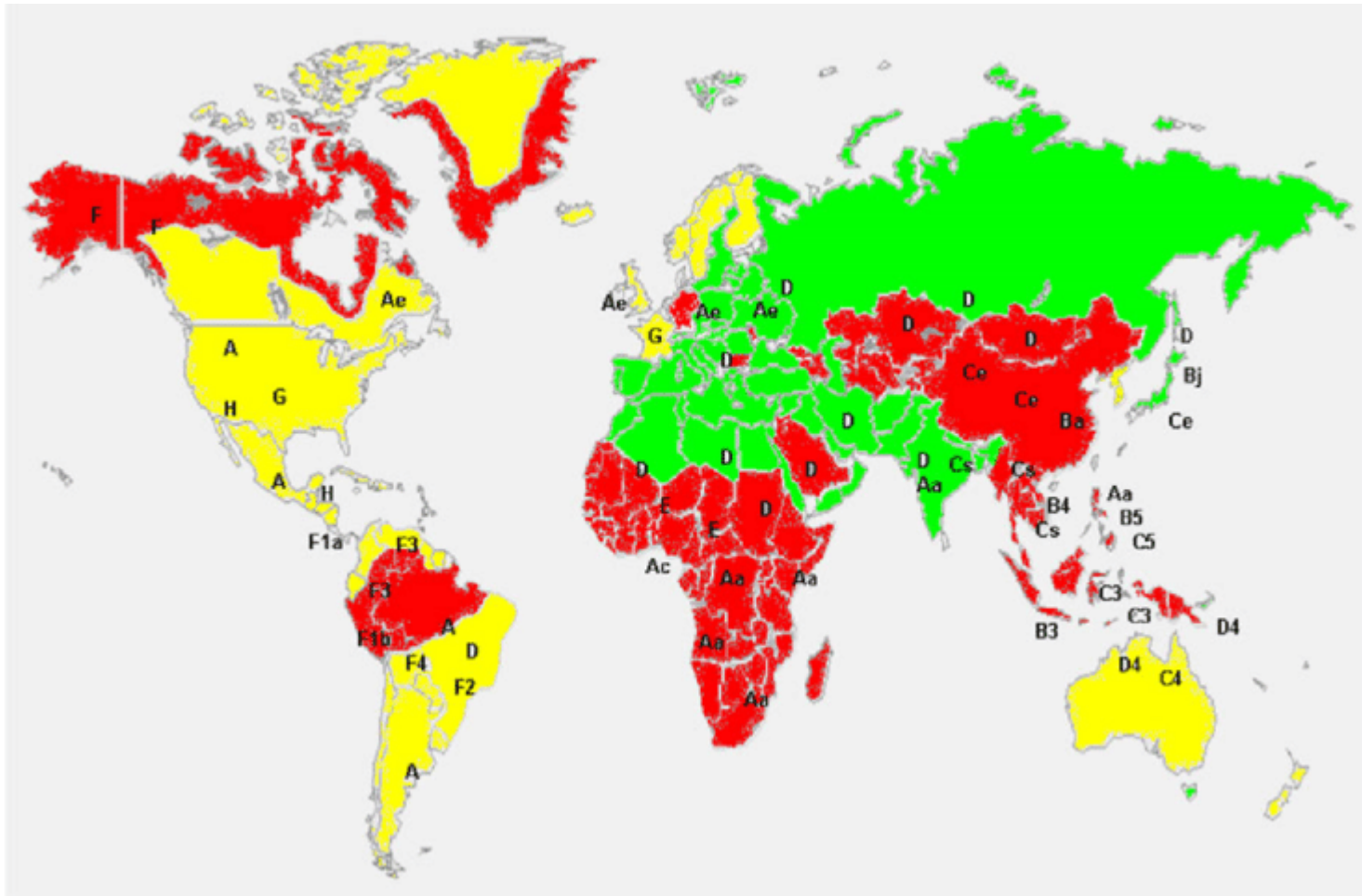
# Global significance of HEP B

- 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

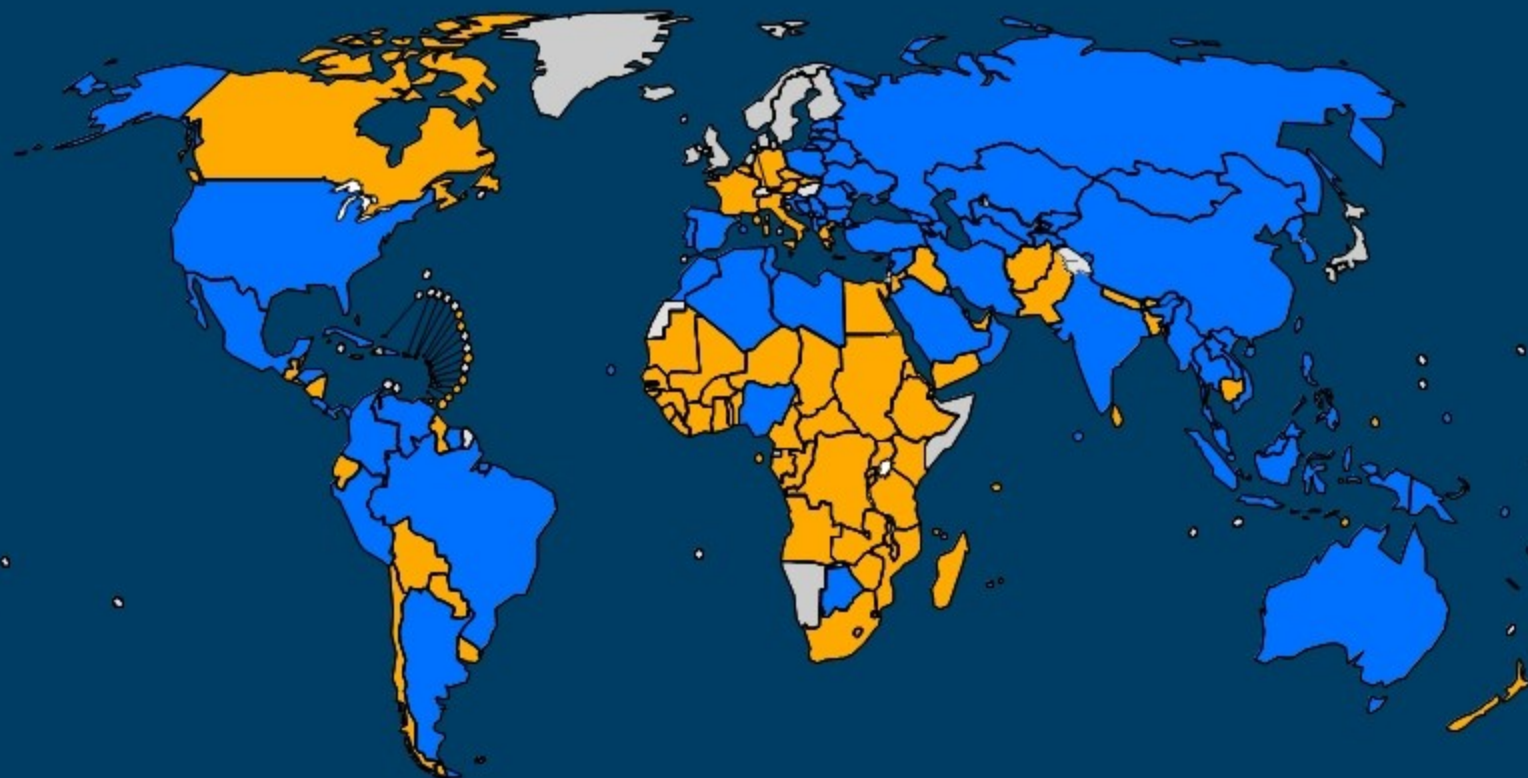
# Chronic HBV infection (CDC 2020)






# 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

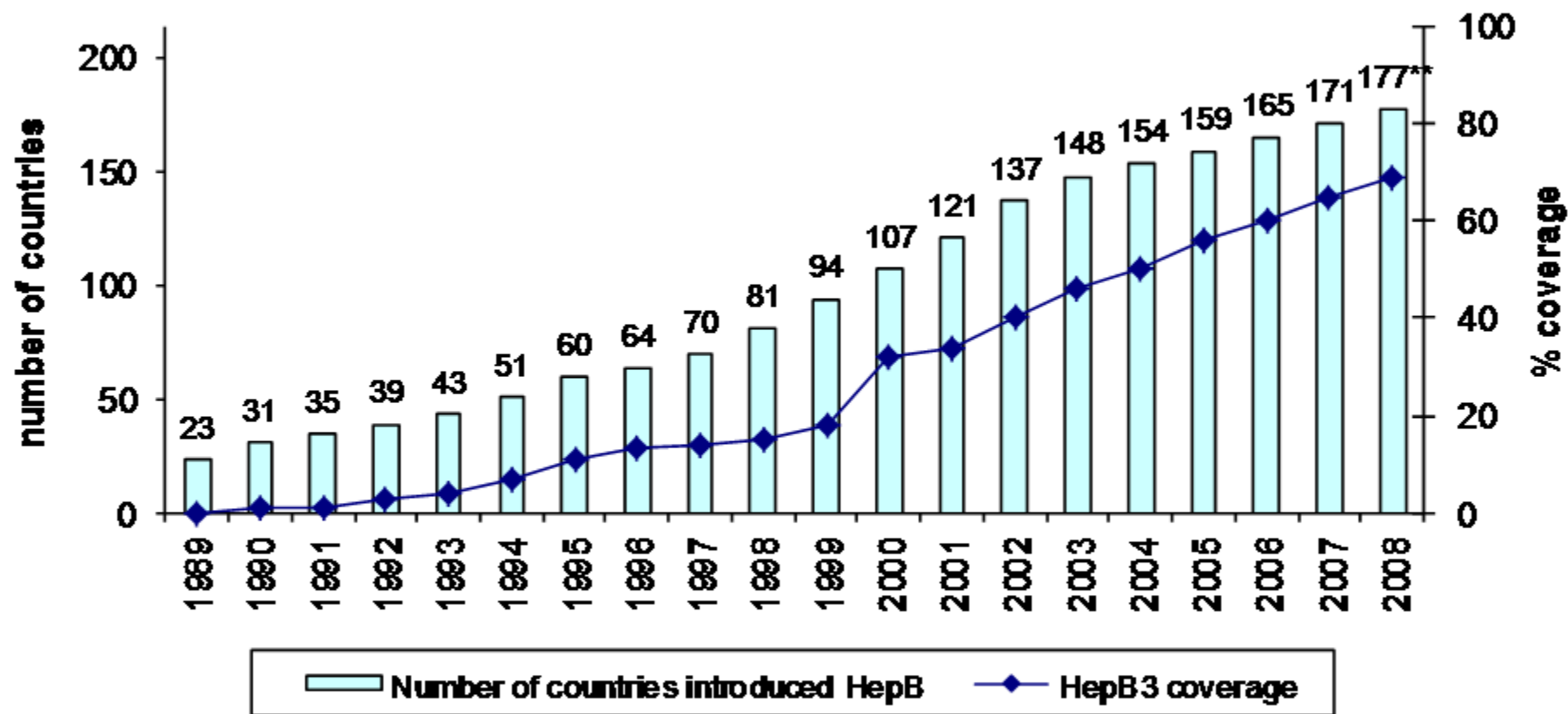
-  No HepB (16 countries<sup>1</sup> or 8%)
-  HepB no Birth Dose (92 countries<sup>2</sup> or 48%)
-  HepB with Birth Dose (85 countries<sup>3</sup> or 44%)

<sup>1</sup>includes three countries with adolescent immunization  
<sup>2</sup>includes 81 countries with partial introduction  
<sup>3</sup>includes India with partial introduction

The boundaries and names shown and the designations used on this map do not imply the endorsement of any specific viewpoint or the position 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 %

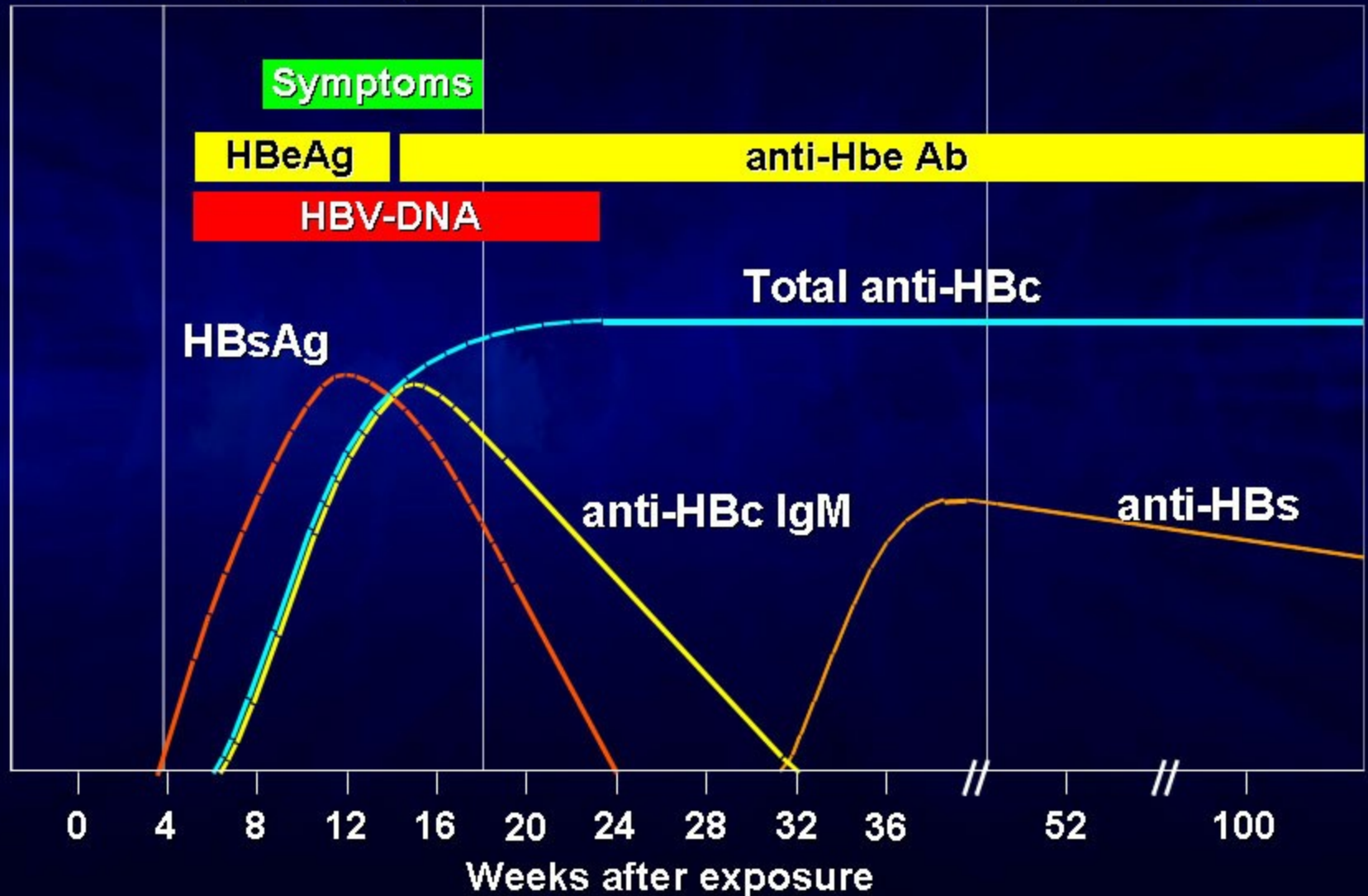
# Acute Hepatitis B

Incubation  
4-12 weeks

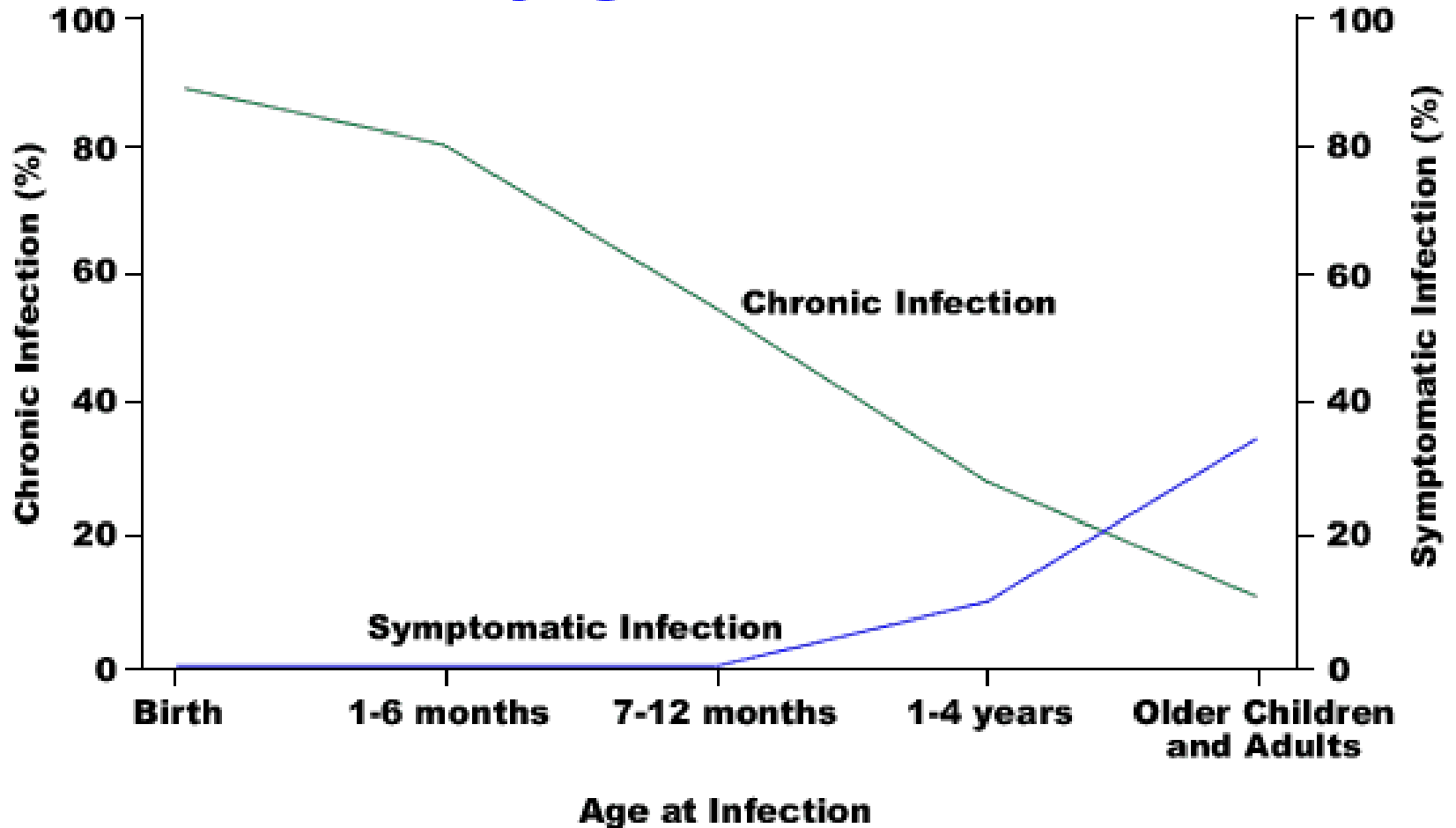
Acute infection  
(2-12 weeks)

Early recovery  
(12-24 weeks)

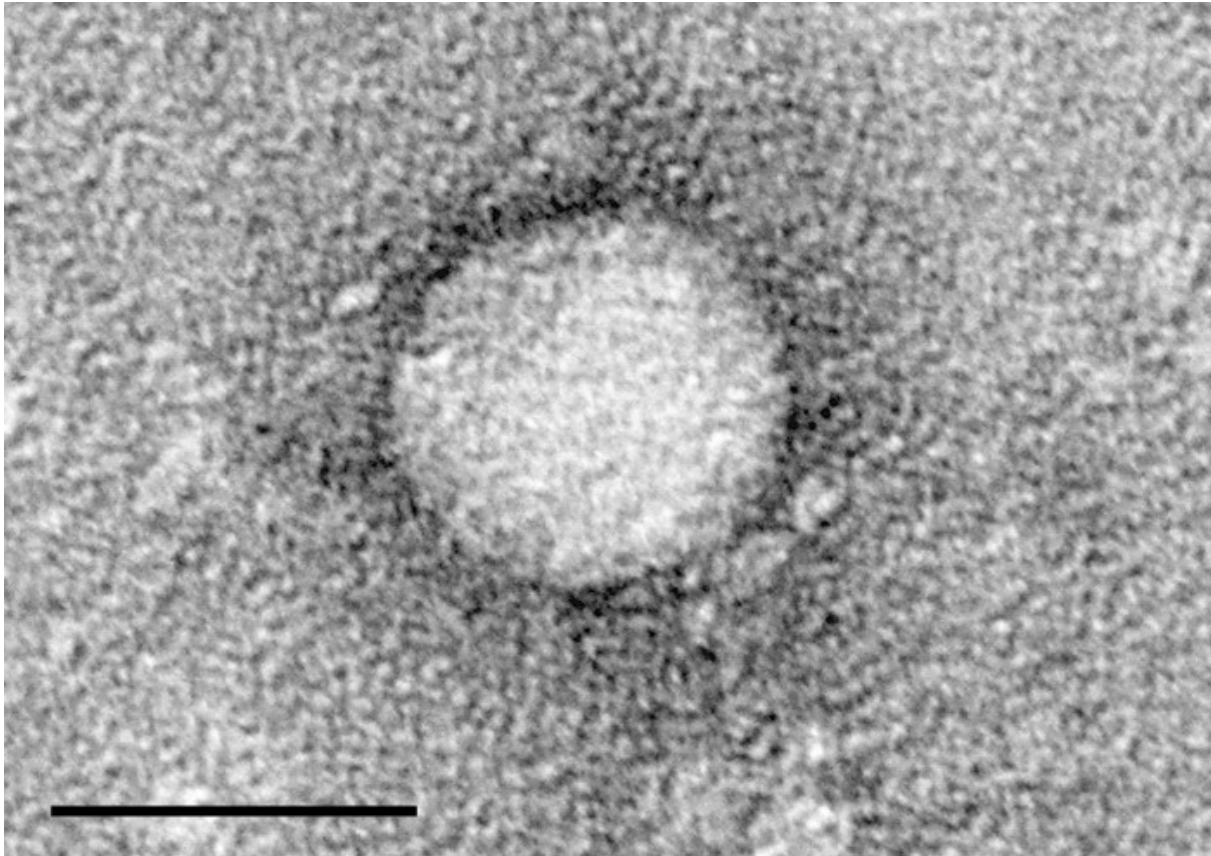
Recovery  
(24-48 weeks)



## Outcome of Hepatitis B Virus Infection by Age at Infection

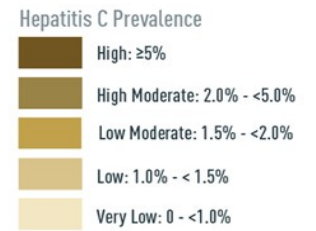
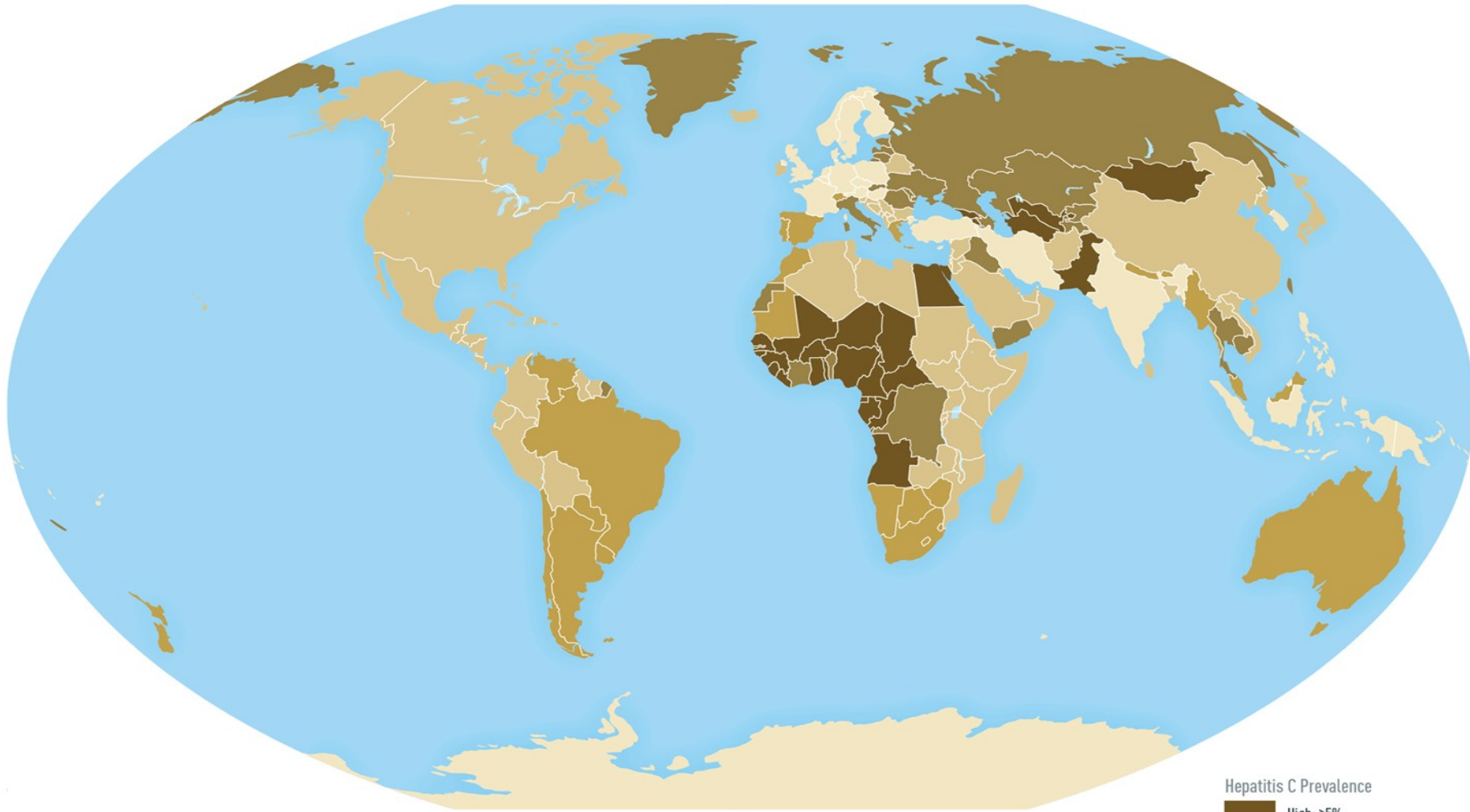


# Hepatitis C Virus (HCV)

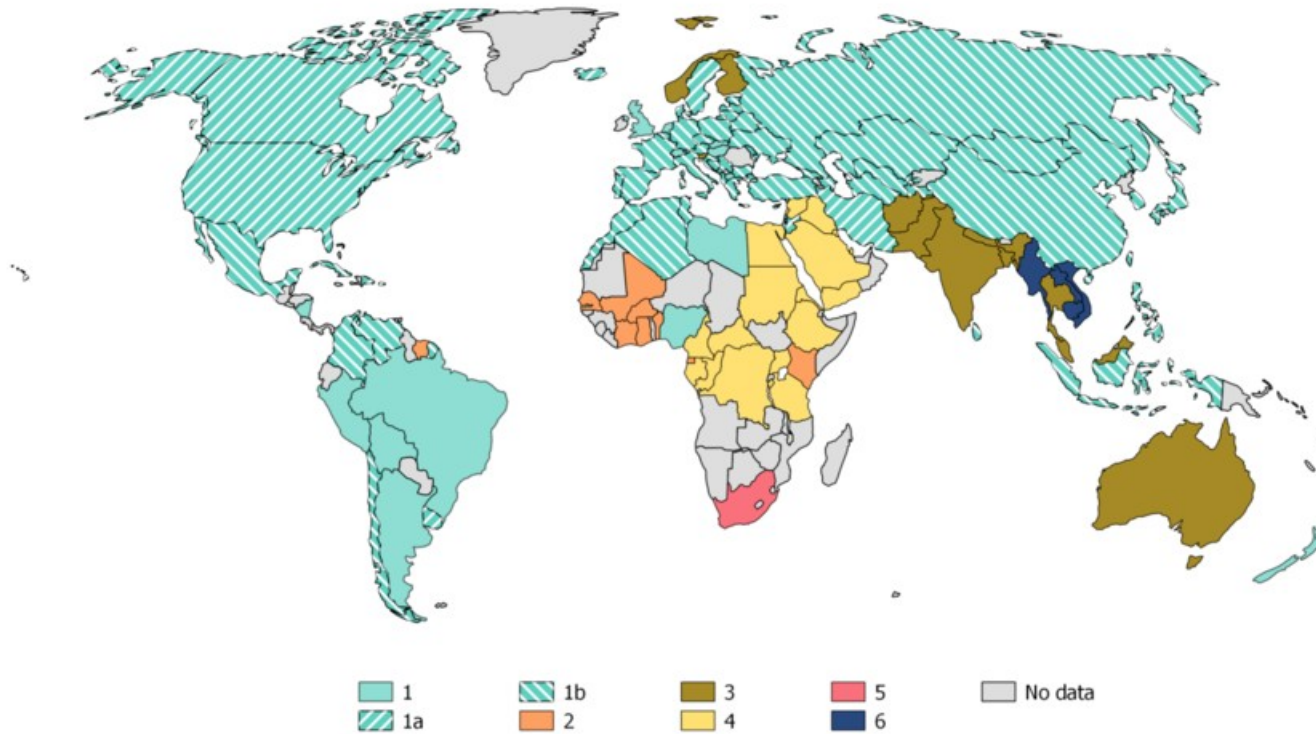


Family Flaviviridae, genus *Hepacivirus*, enveloped RNA virus 60 nm,  
8 genotypes (1-8), many subtypes (a...)

# Chronic HCV infection (CDC 2020)



# HCV genotypes distribution



# Hepatitis C

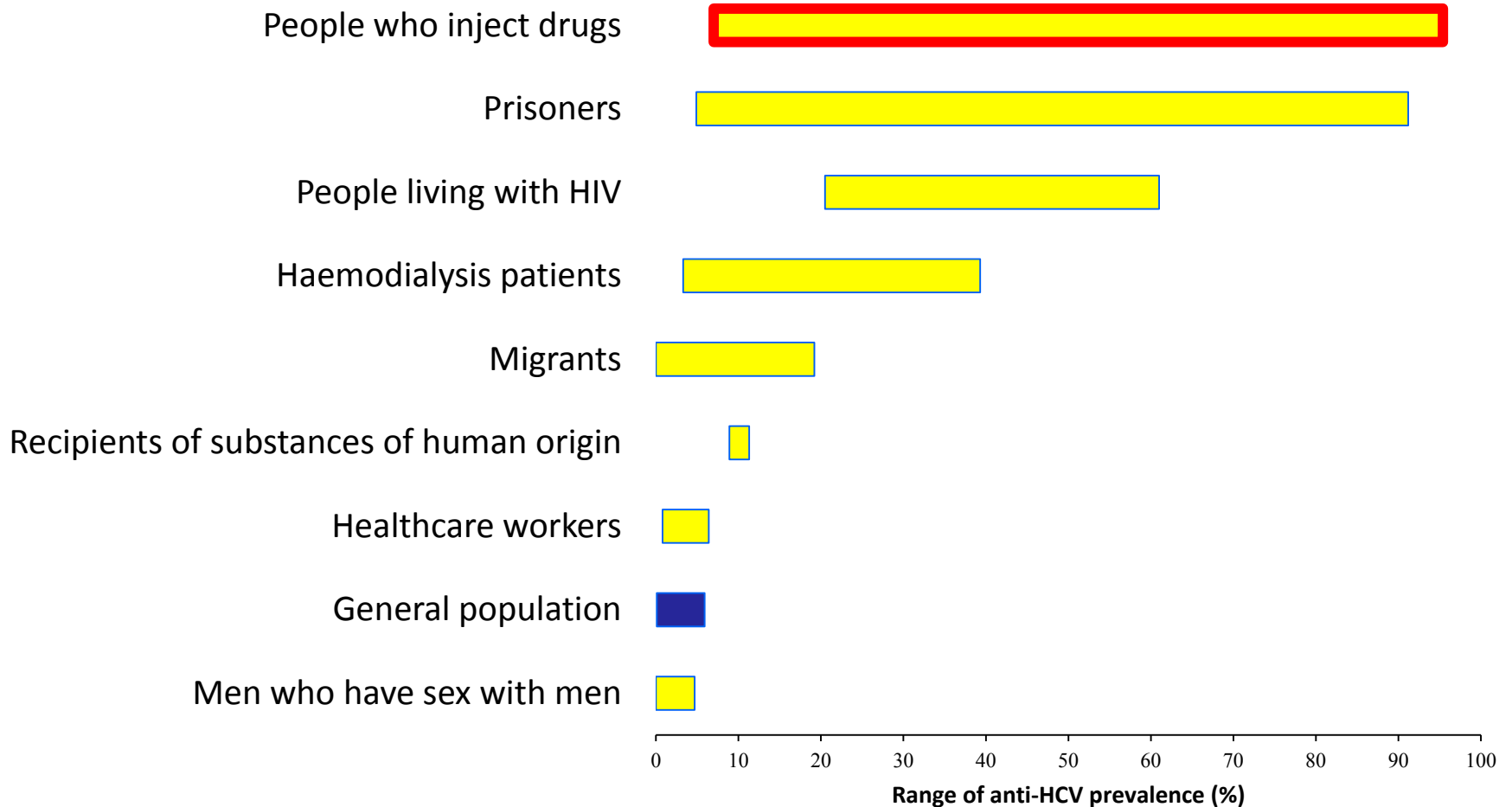
- Significant global health problem
- ✓ 70-80 million persons worldwide are chronically infected with HCV
- ✓ In well-developed countries about 20 % of all acute hepatitis, 70 % chronic hepatitis, 40 % cirrhosis, 60 % HCC and indication to 30 % liver transplantations
- In Czech Republic
- ✓ prevalence 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

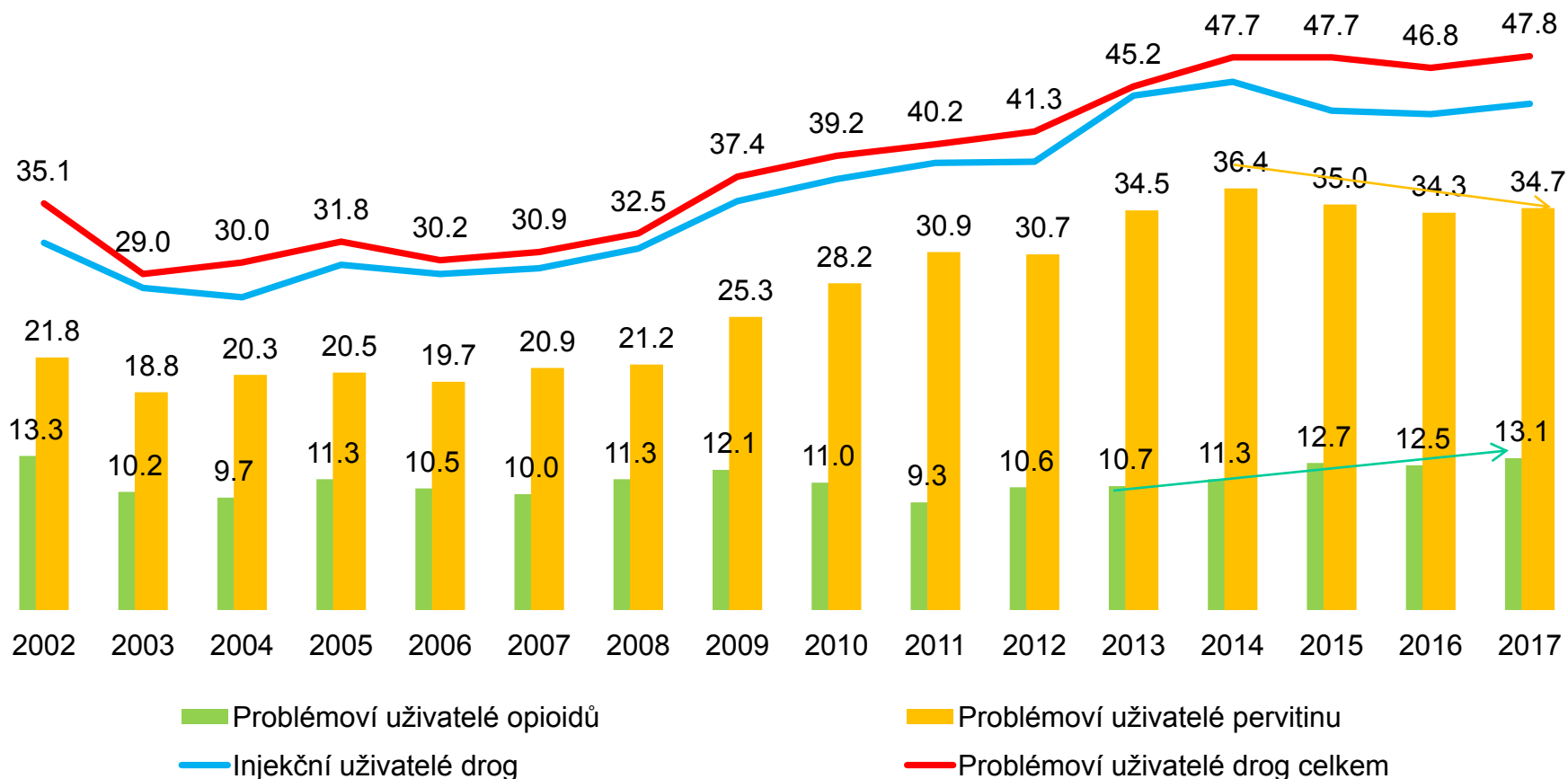


# HCV prevalence in risk groups of inhabitants in EU/EEA countries



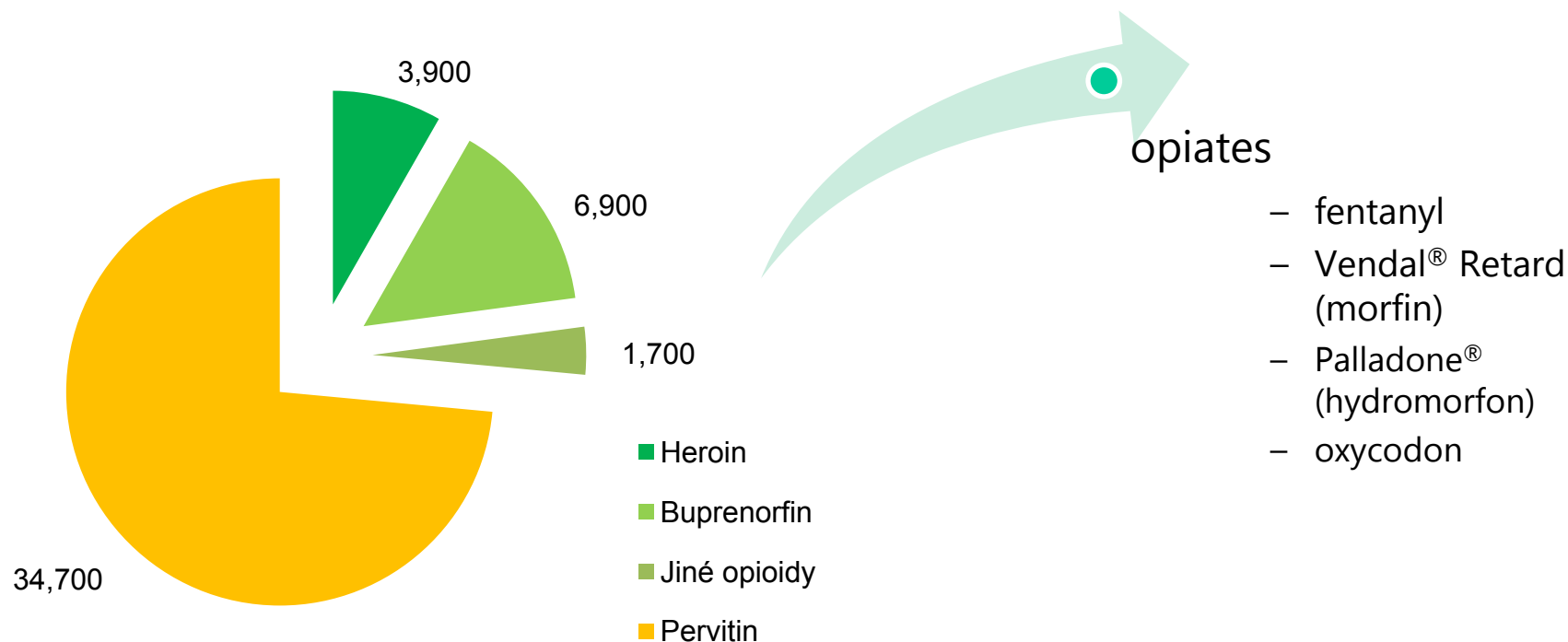
# Problematic drug abusers in the CR (2017)

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

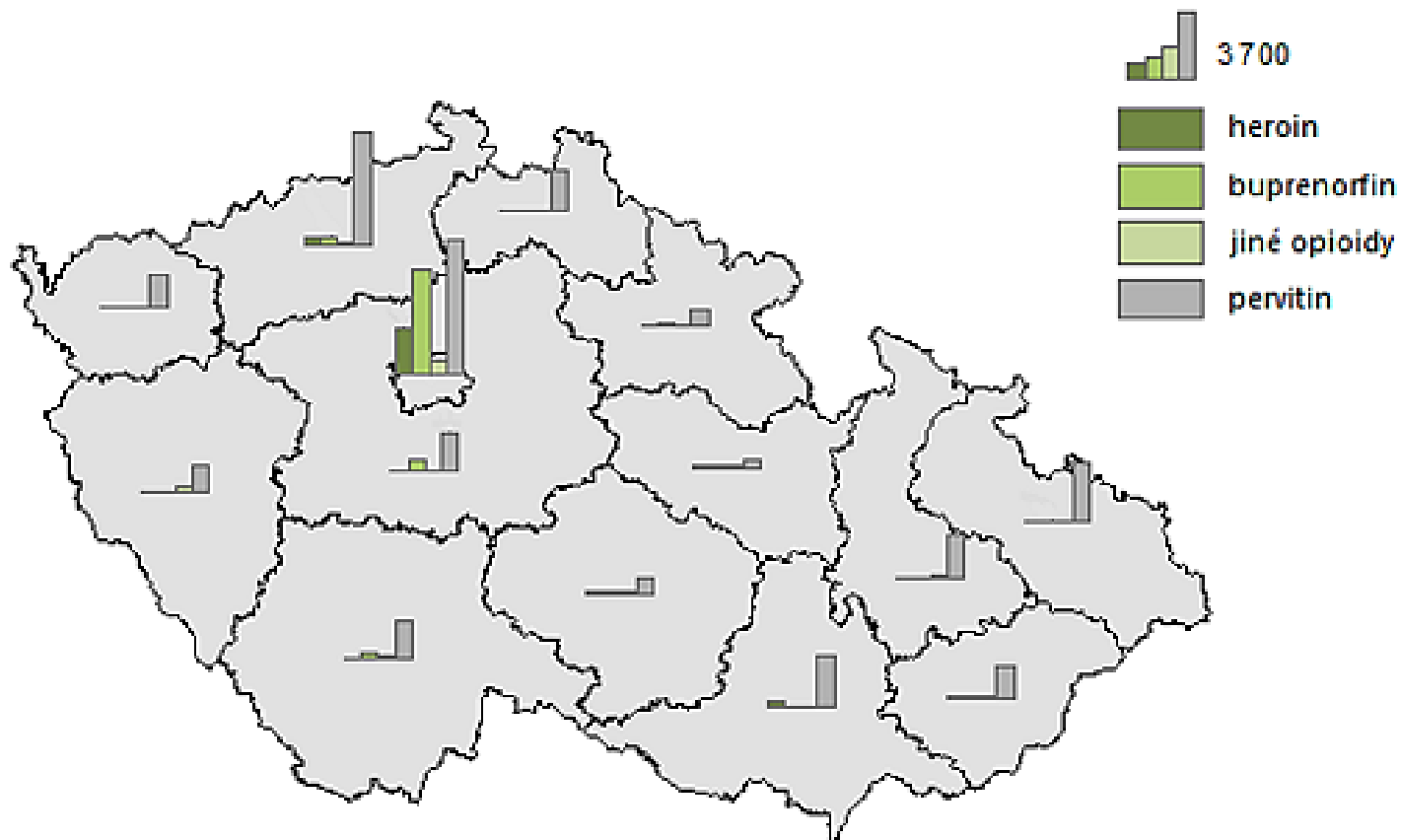


# Problematic drug abusers in the CR (2017)

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

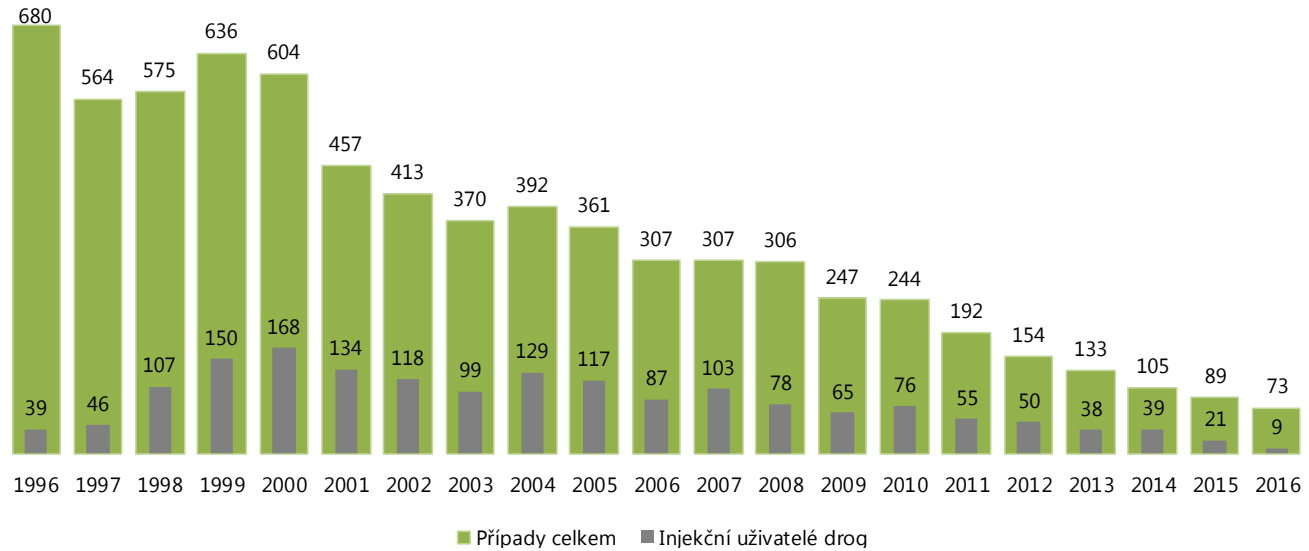


# Opiates and pervitin abus

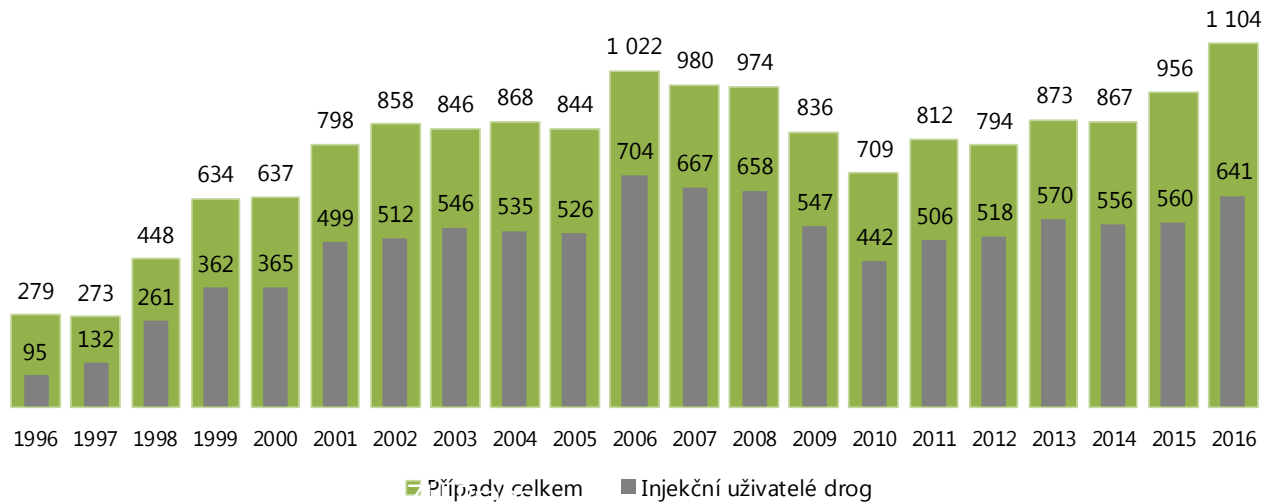


# Infectious diseases in IUDs – new cases 1996-2016

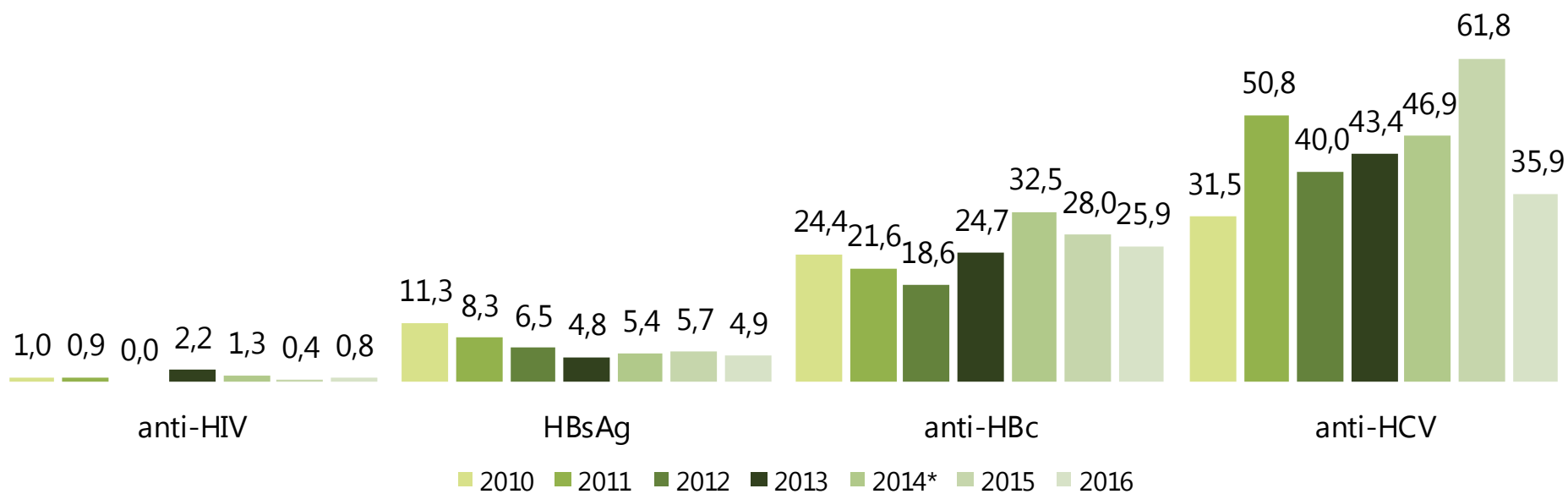
*Acute HBV*



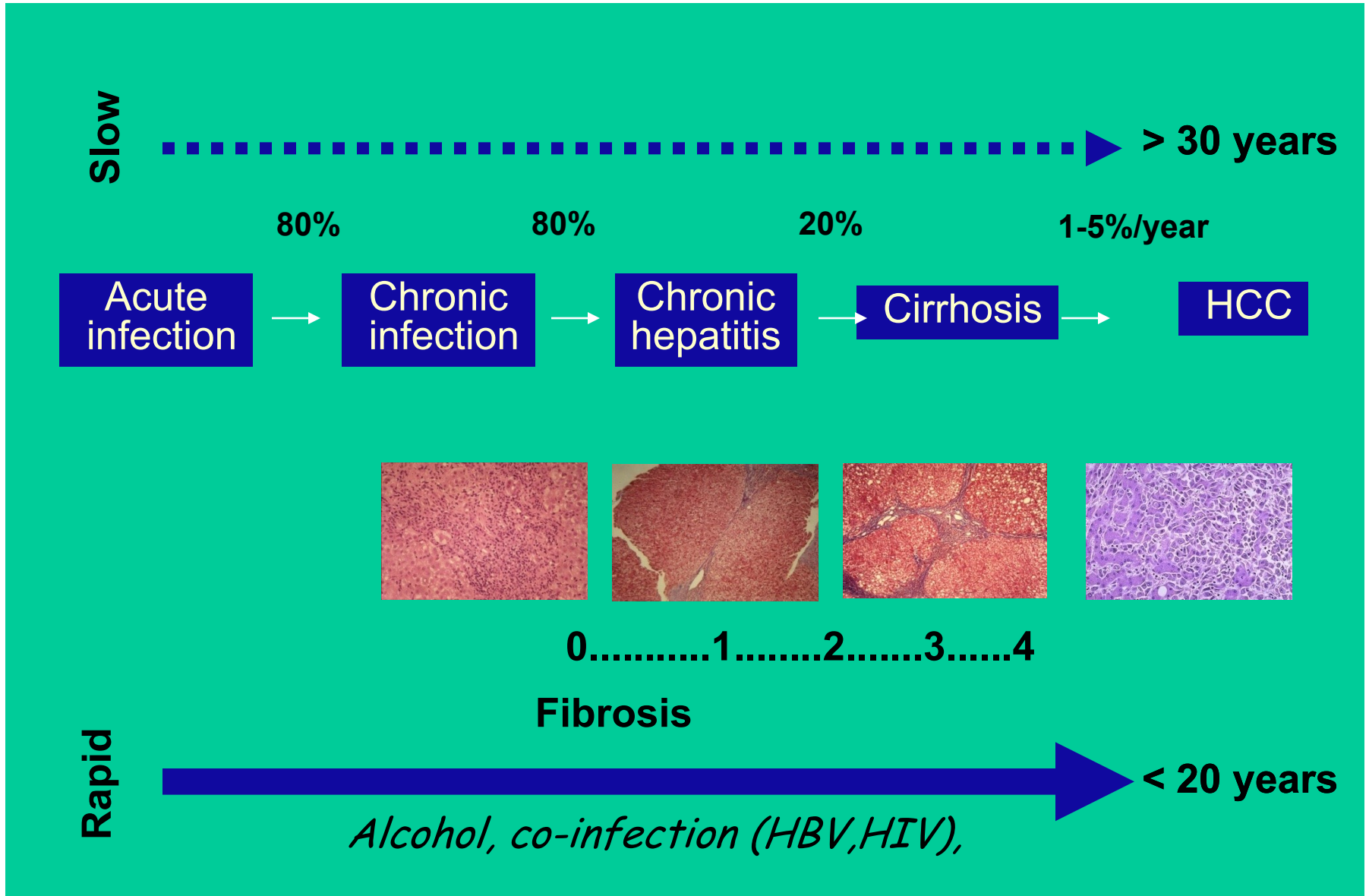
*Acute and chronic HCV*



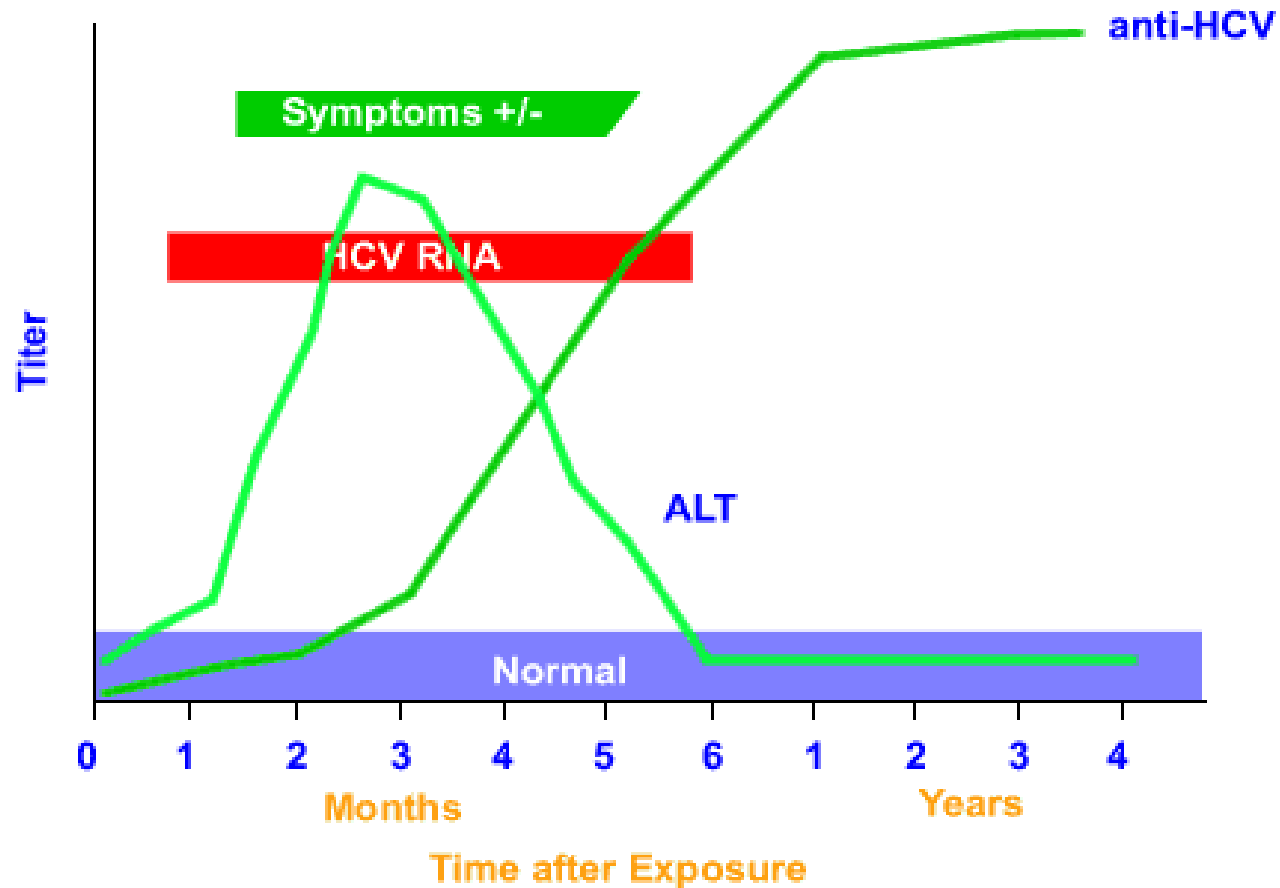
# Infectious diseases in IUD in prison (%)



# Clinical course of HCV infection

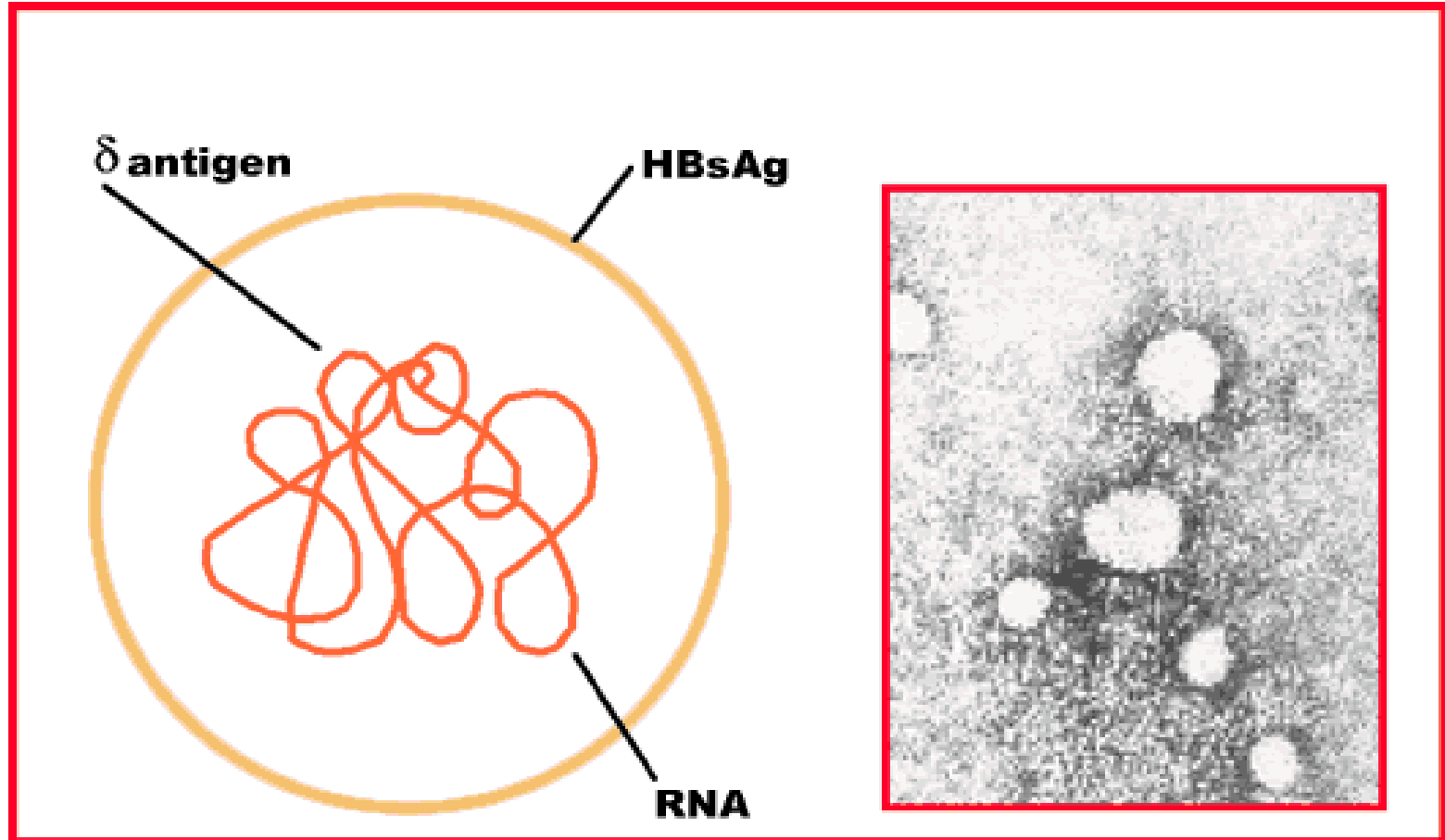


# Diagnosis of HCV infection





# 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

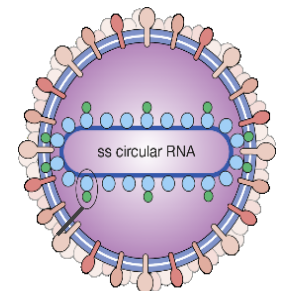
Increased risk of cirrhosis/HCC and higher mortality vs HBV

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

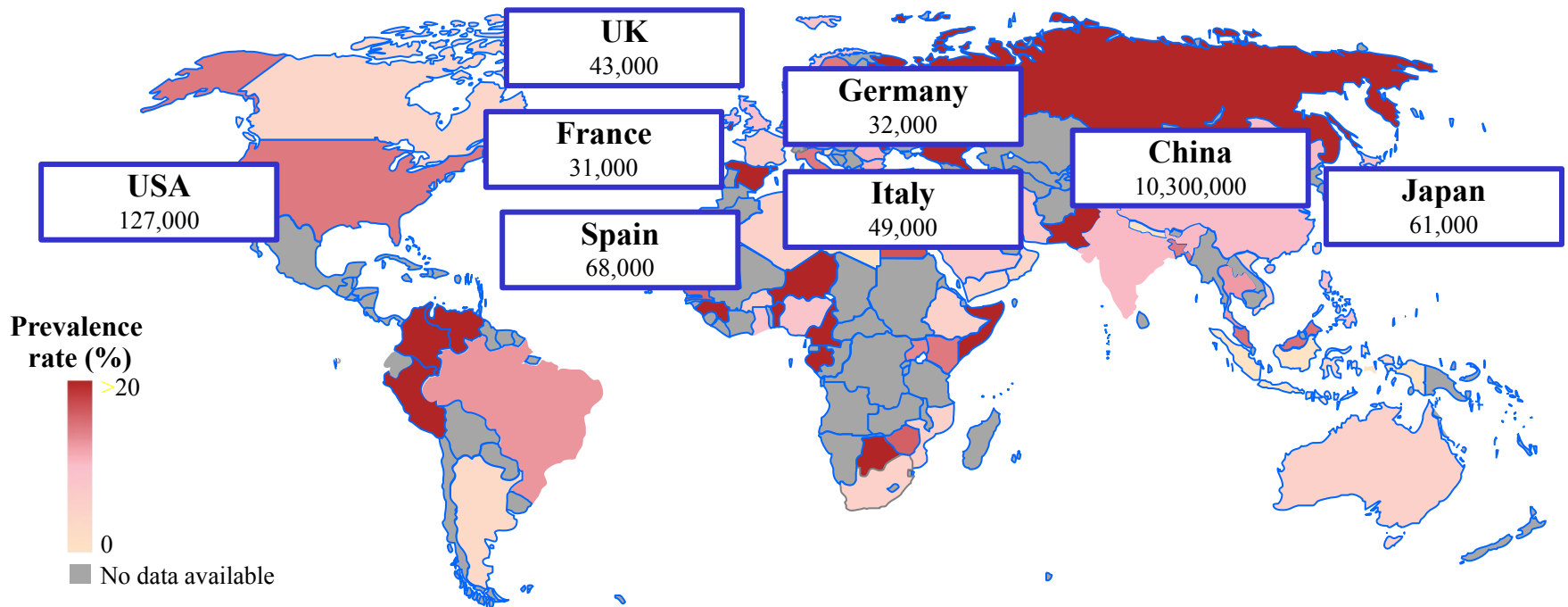
-  **Endemic**
-  **In risk groups**  
*Immigrants*



*Rizzetto M. EASL 2009*

# Estimated number of individuals with HDV in selected countries

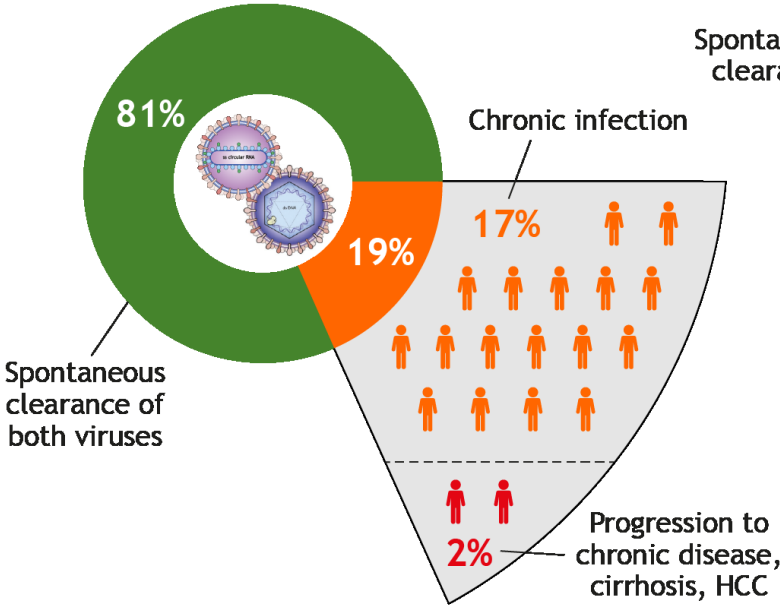
An estimated 48-60 million people are infected with HDV worldwide



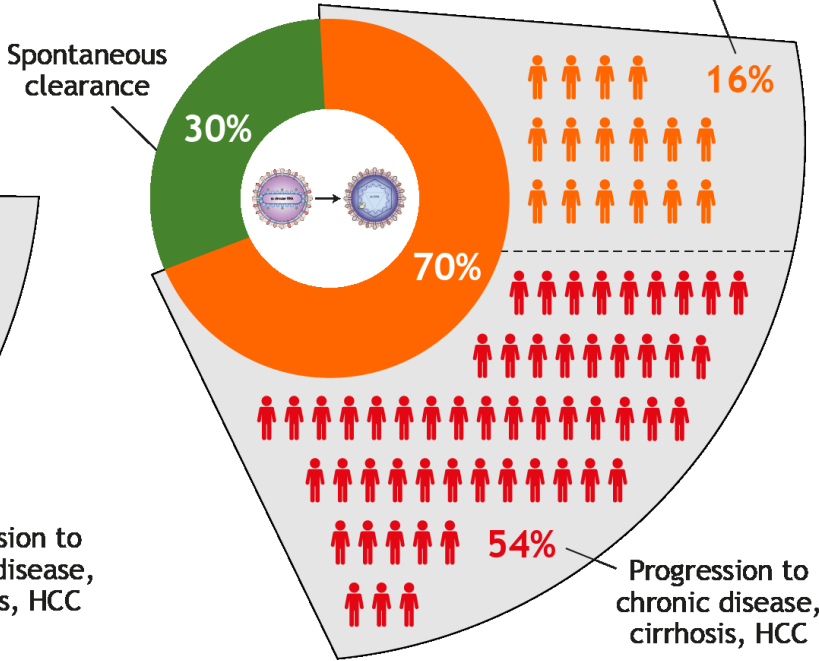
Numbers shown are patient numbers, ie prevalence of HDV in HBsAg-positive patients.  
HBsAg: hepatitis B surface antigen; HDV: hepatitis delta virus.

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

Simultaneous HBV/HDV coinfection

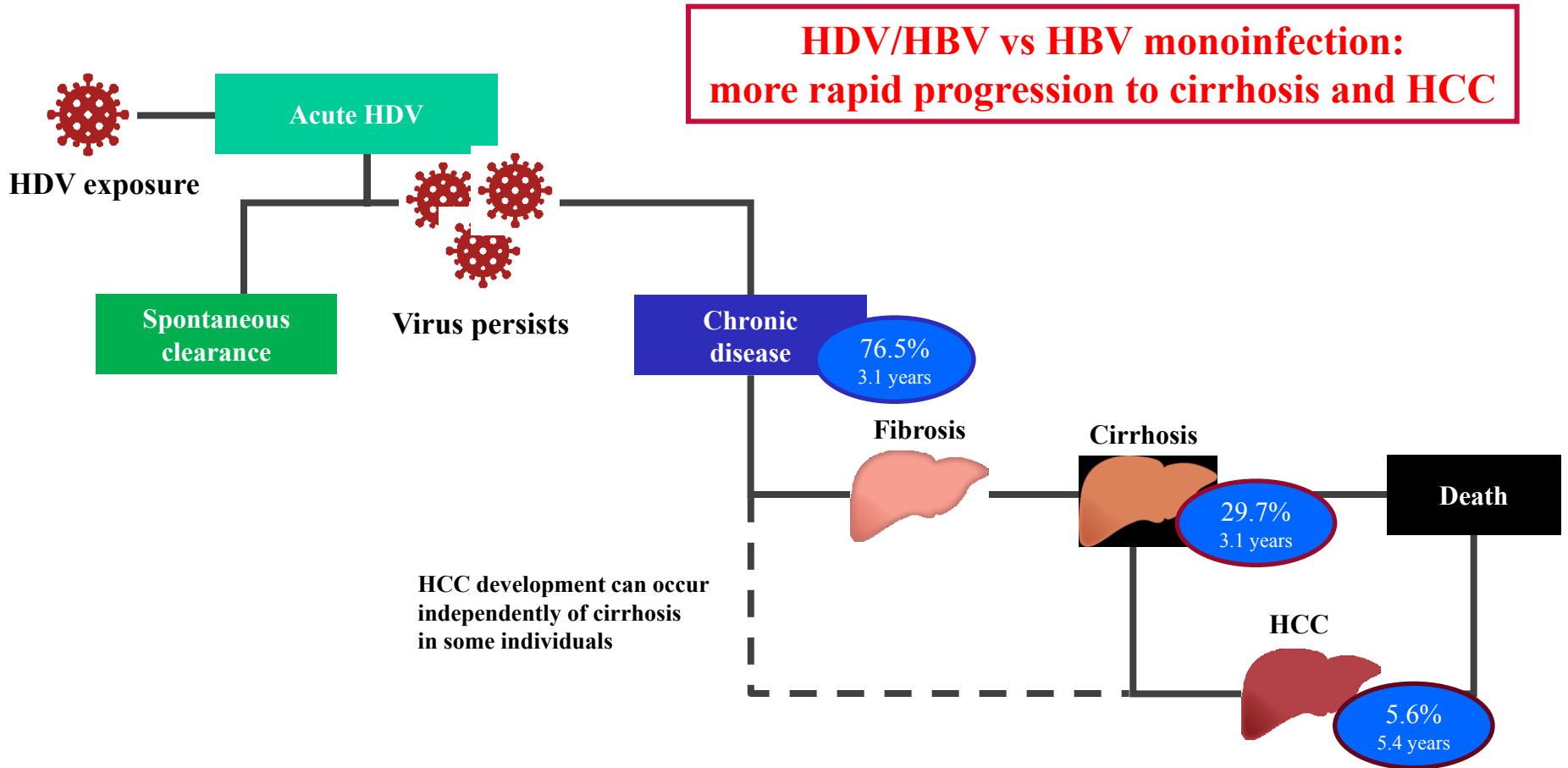


HDV superinfection

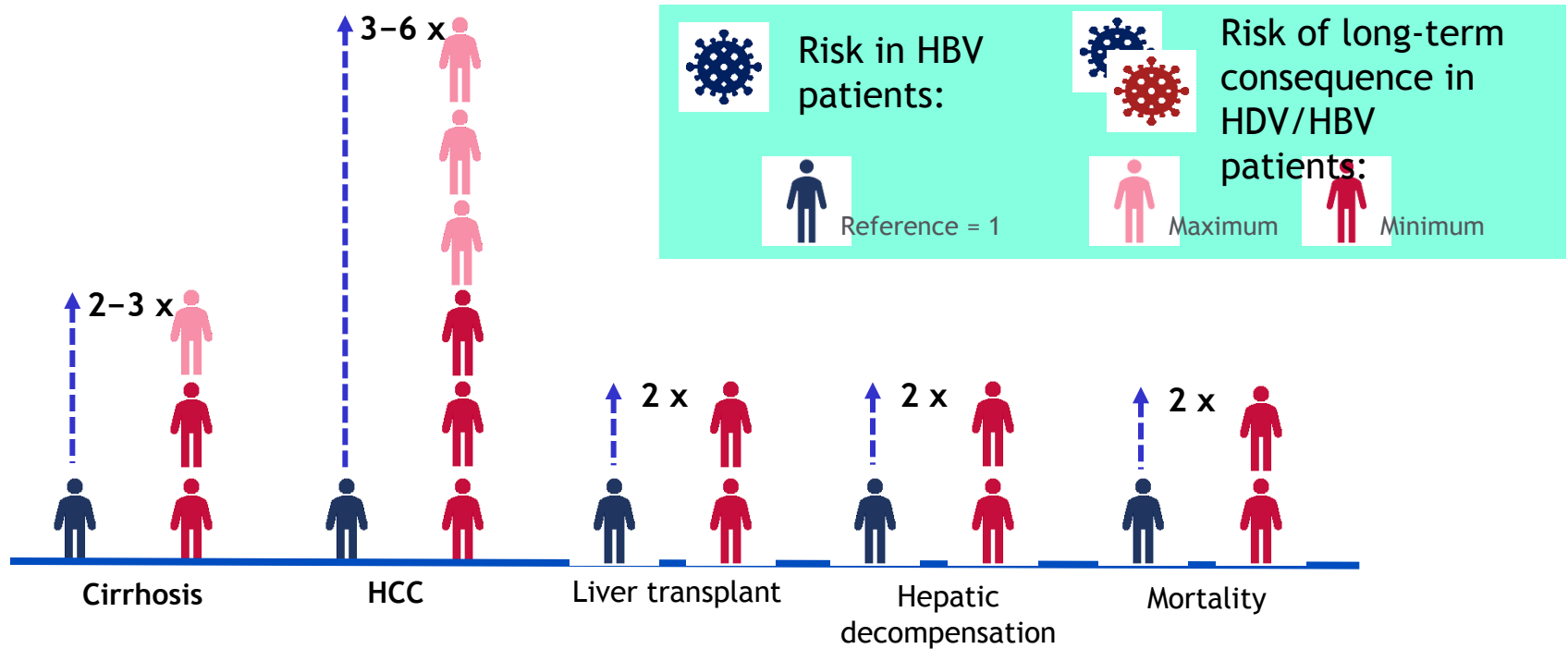


Data presented are based on estimates of HDV prevalence and disease progression rates determined in a large global epidemiology analysis.  
HBV: hepatitis B virus; HCC: hepatocellular carcinoma; HDV: hepatitis delta virus.

# Clinical course of hepatitis delta

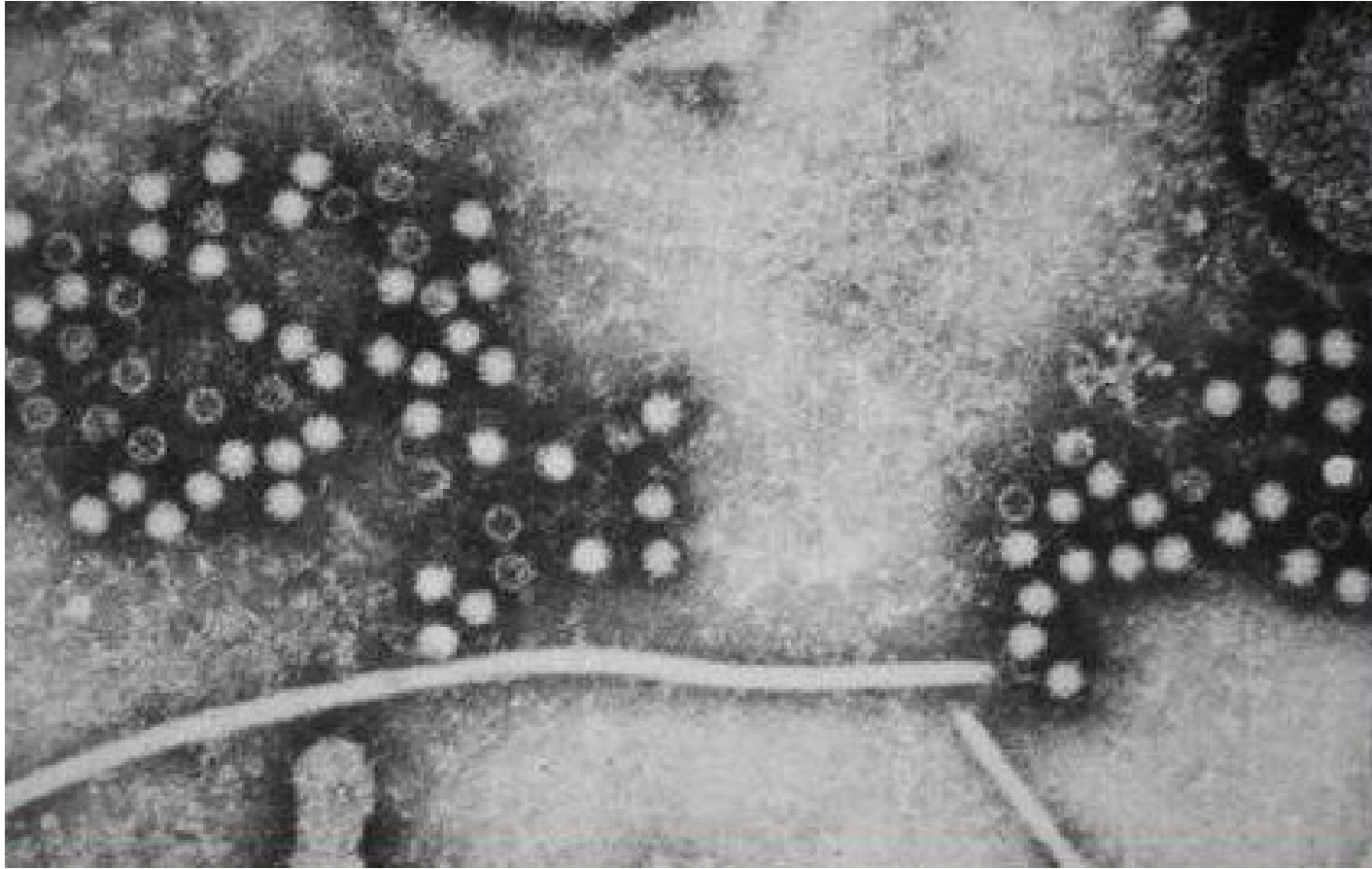


# Increased risk of long-term consequences of viral hepatitis in HBV/HDV patients versus HBV mono-infection



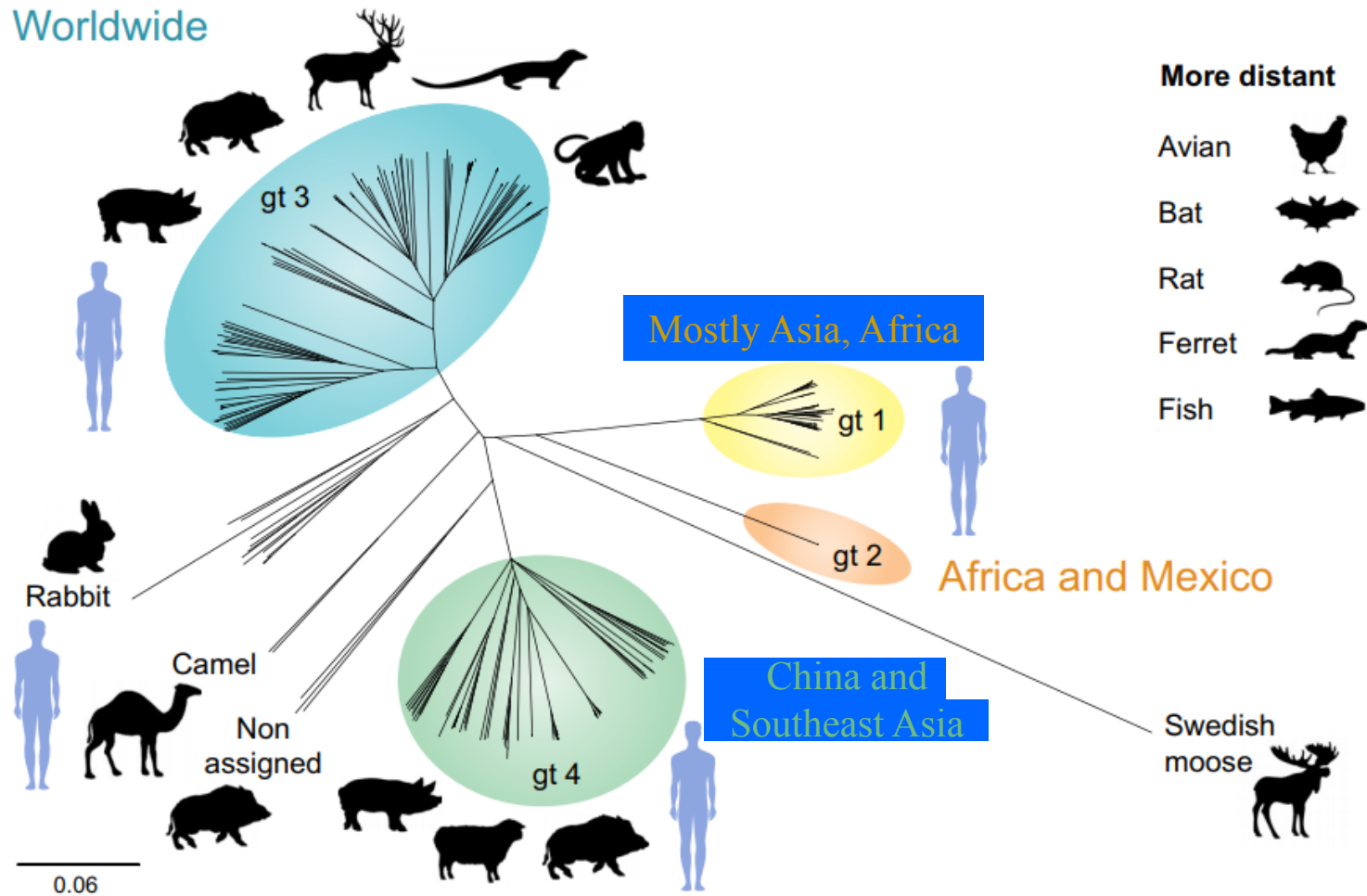


# Hepatitis E virus

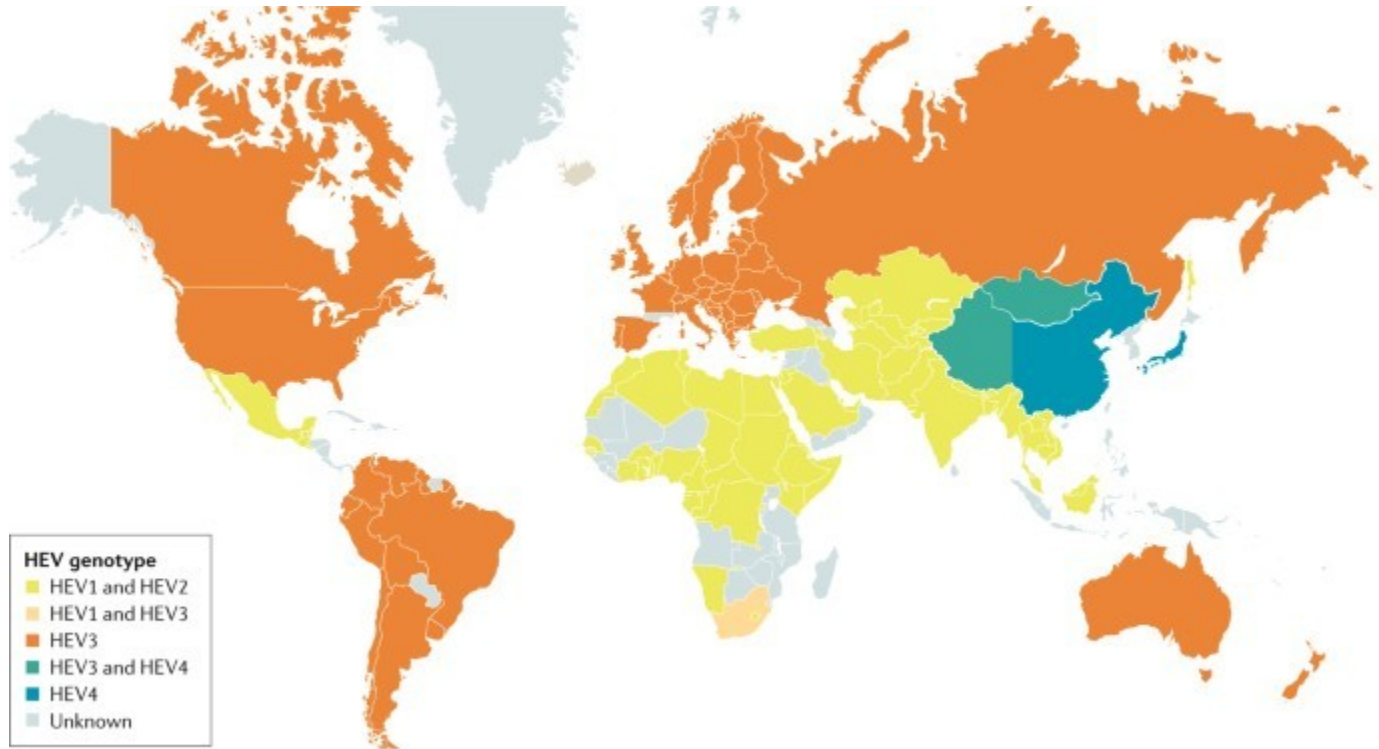


Non-enveloped RNA virus, family Hepeviridae, *genus Orthohepevirus*, 27-34 nm, 8 genotypes (1-8), human infections by G1-4

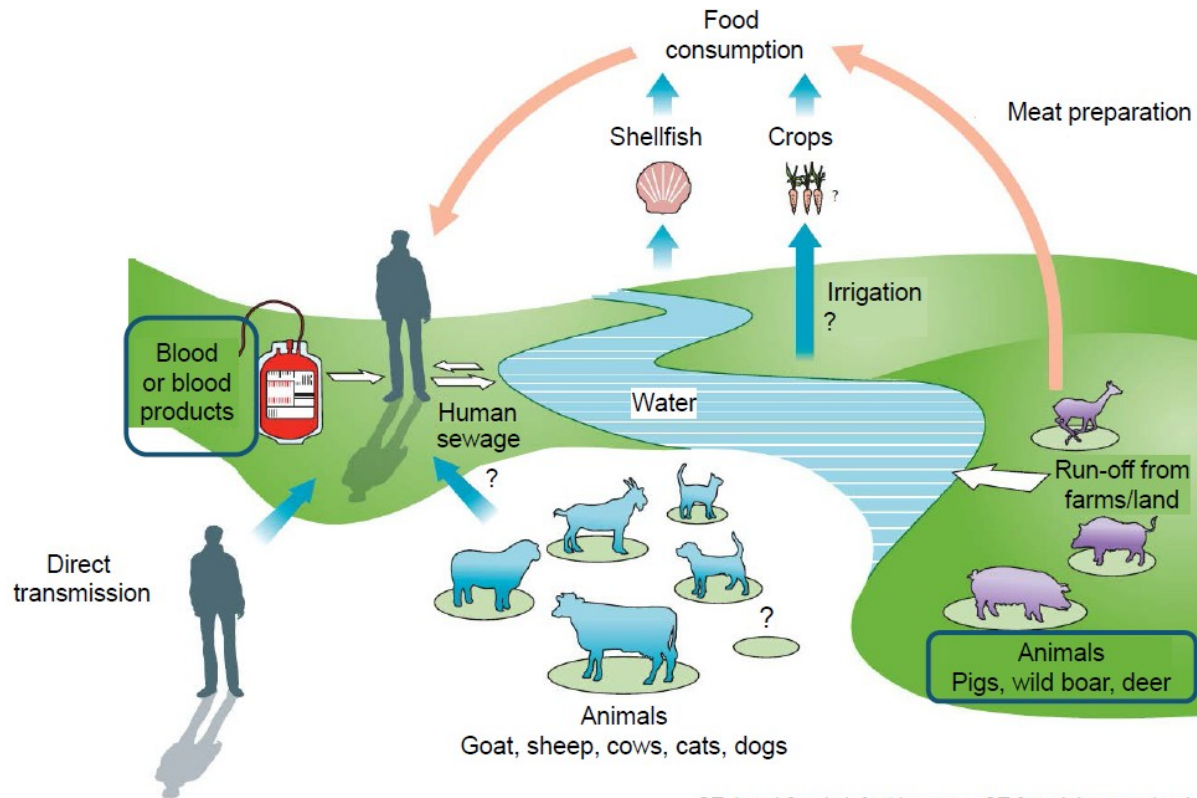
# Phylogenetic relationship of hepeviruses identified in various hosts



# HEV genotypes (1-4)

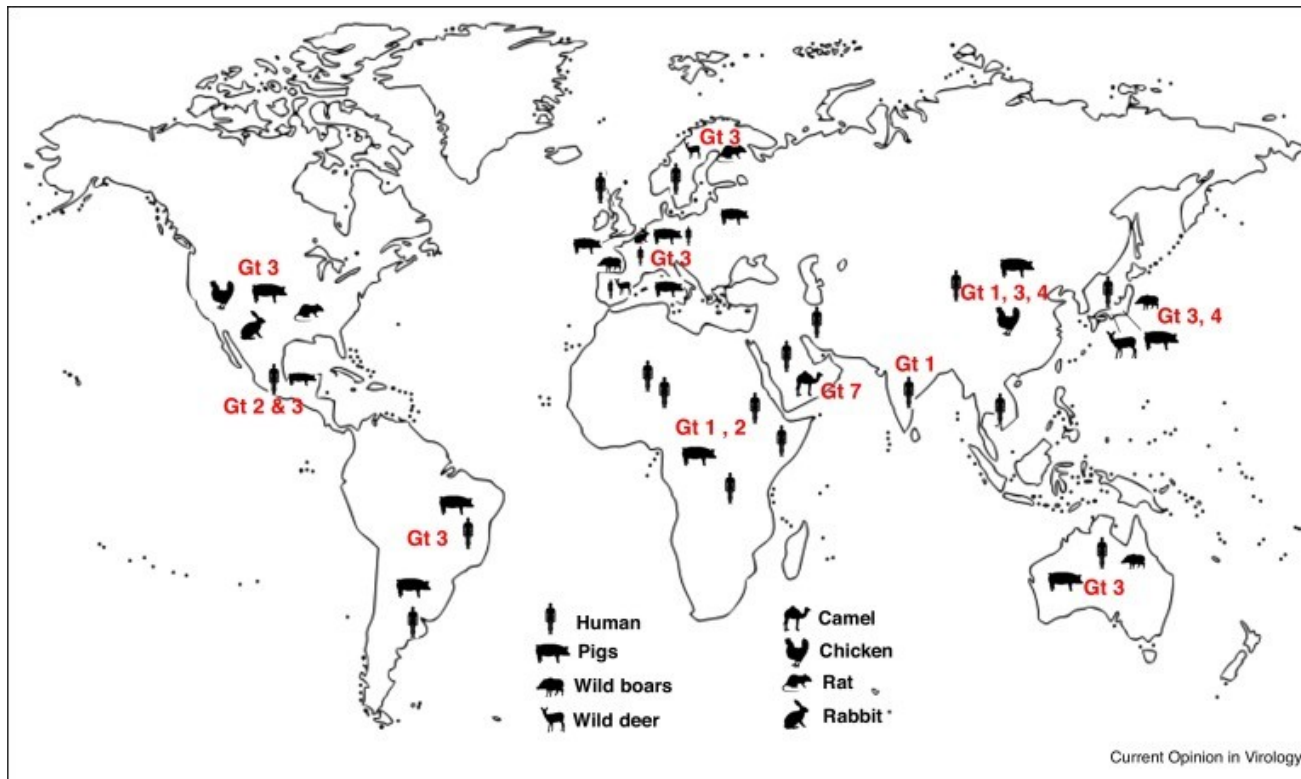


# Transmission of HEV



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



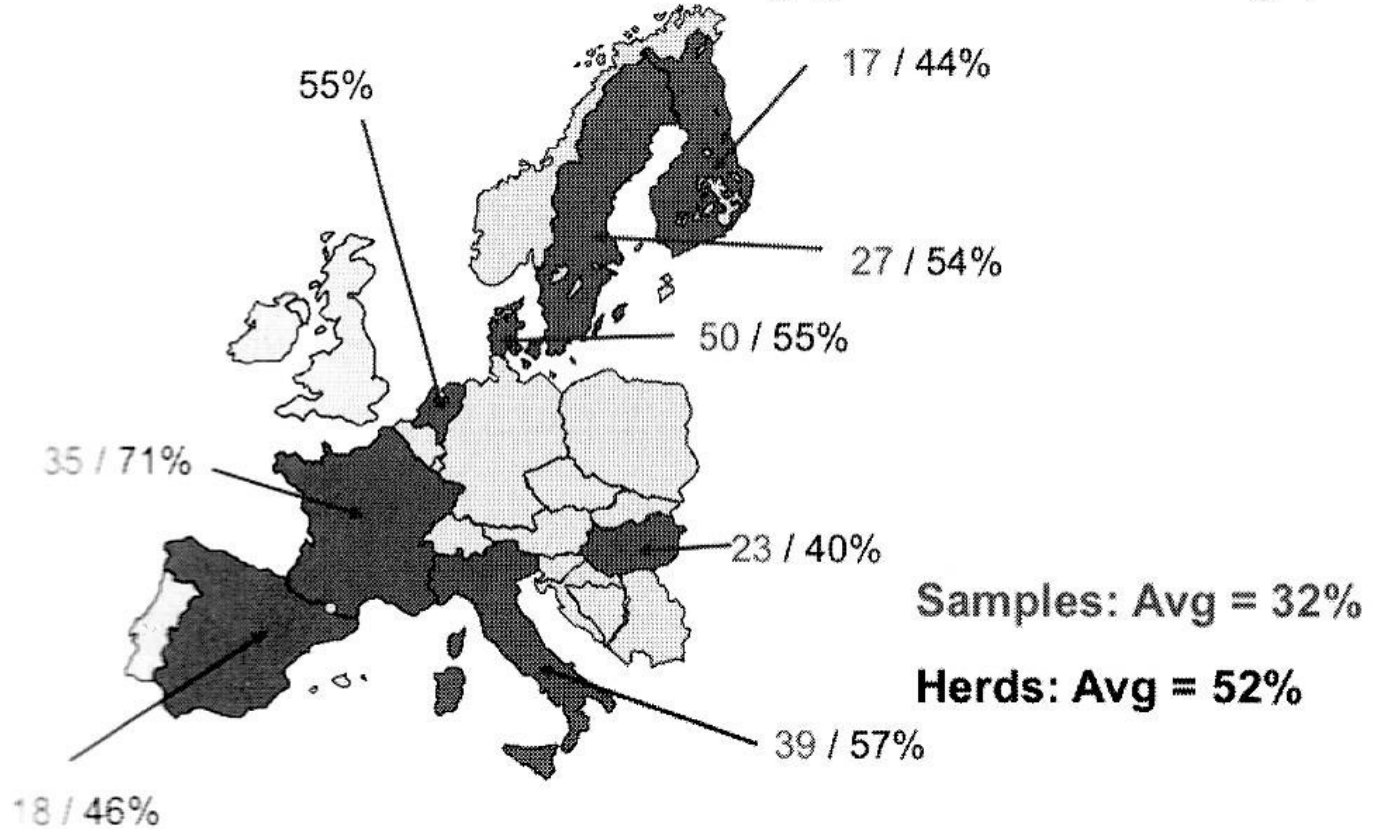
# Infection with G-1,2 HEV

- 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
- $\geq 2$  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)



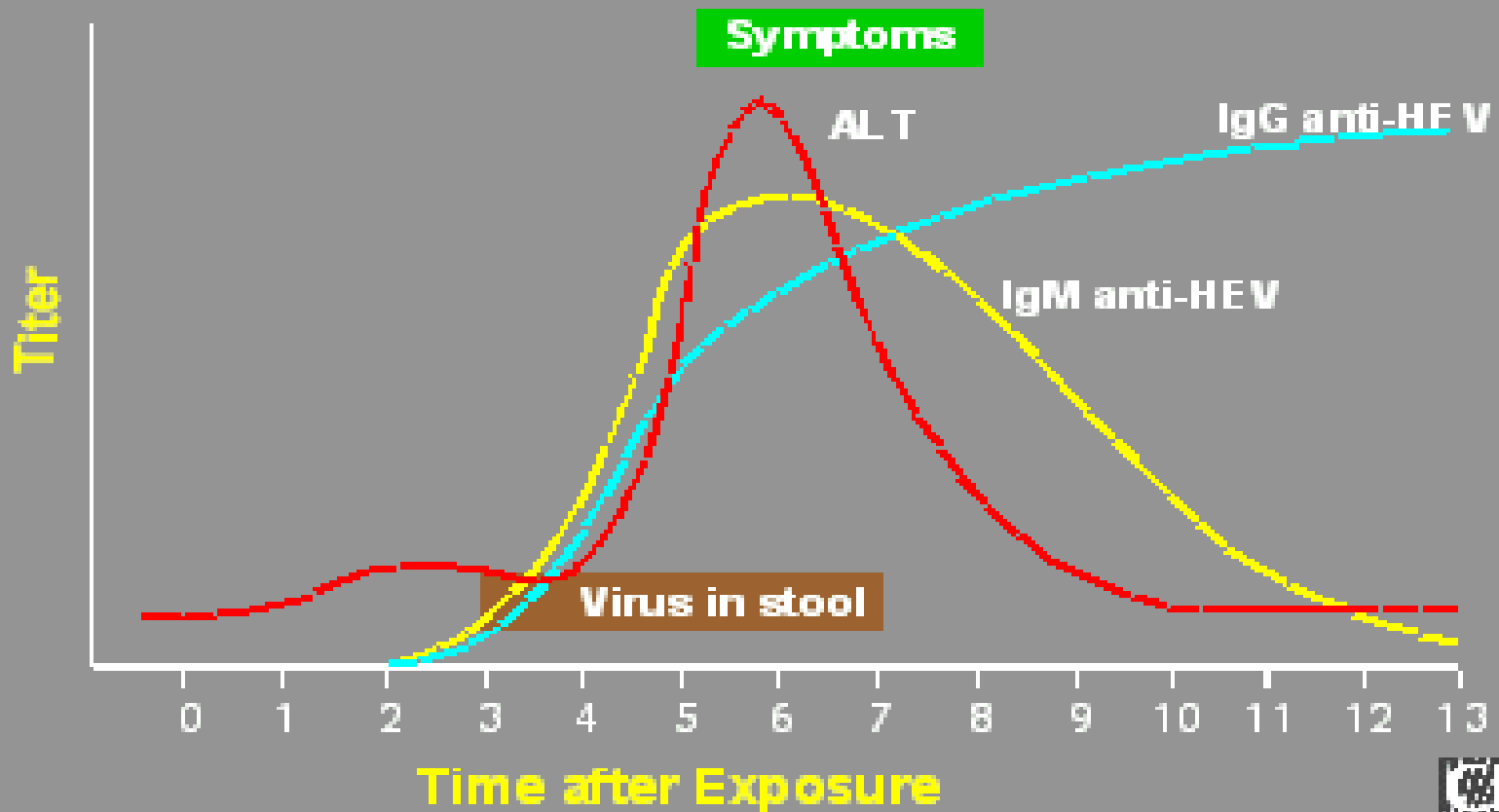


# Figatellu – sausage with raw pork liver

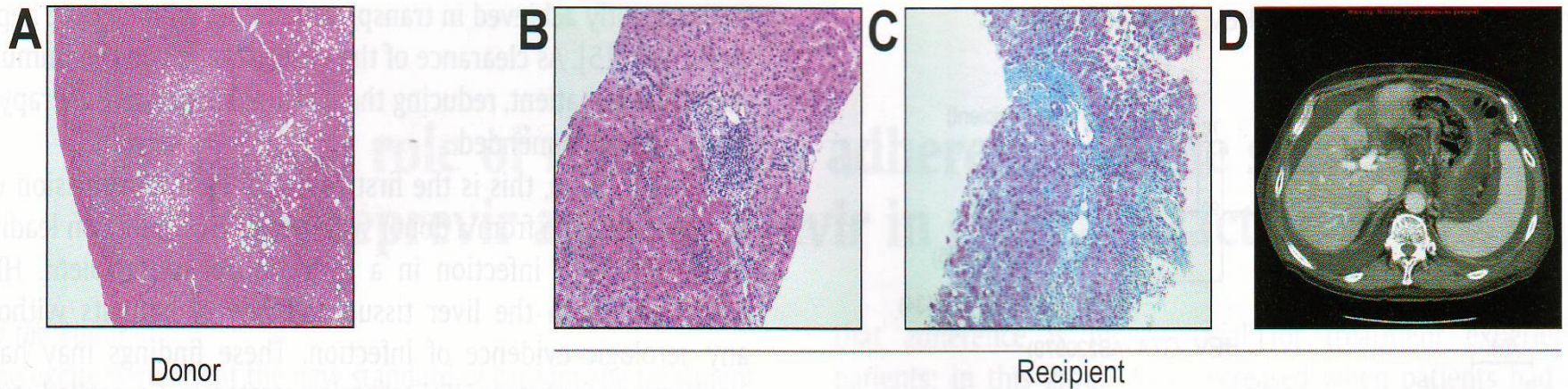


# Hepatitis E Virus Infection

## 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 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

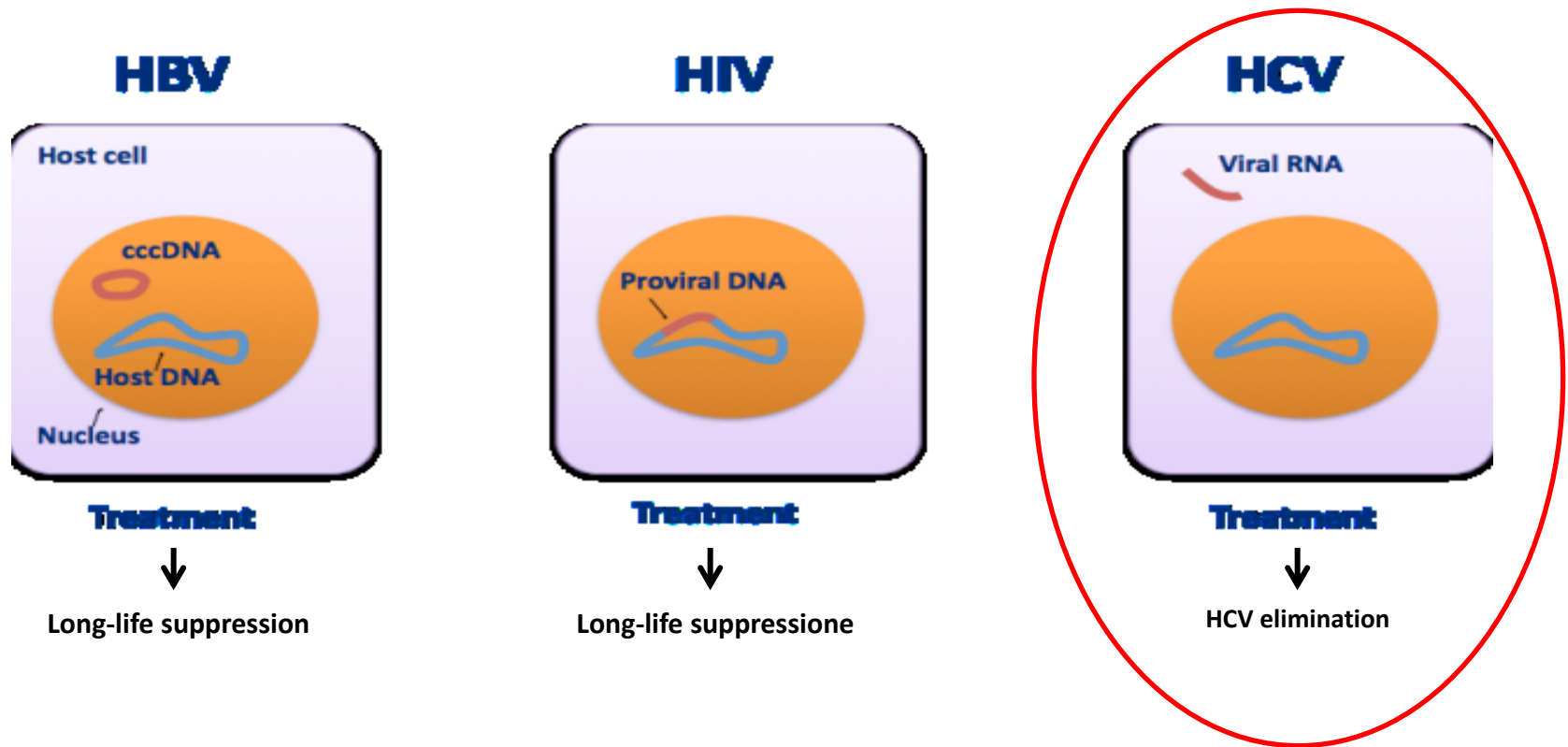
# Current possibilities of treatment of chronic HEP B

- 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](mailto:phusa@fnbrno.cz)**