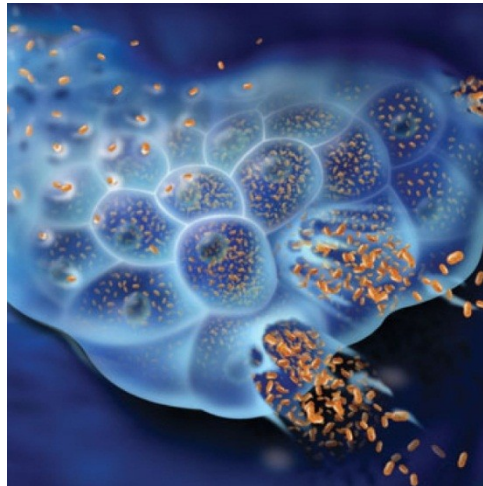


Viral Hepatitis

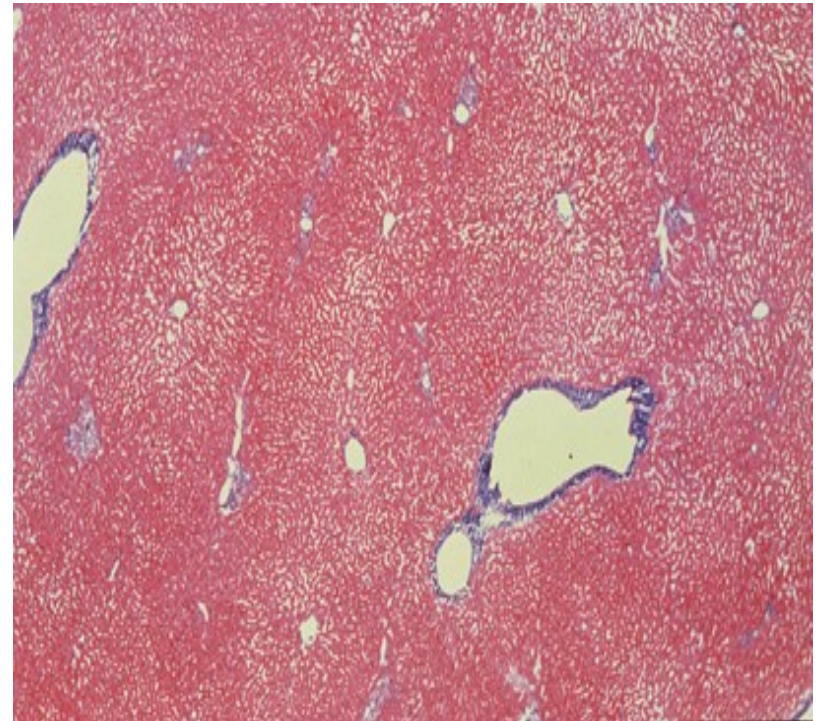
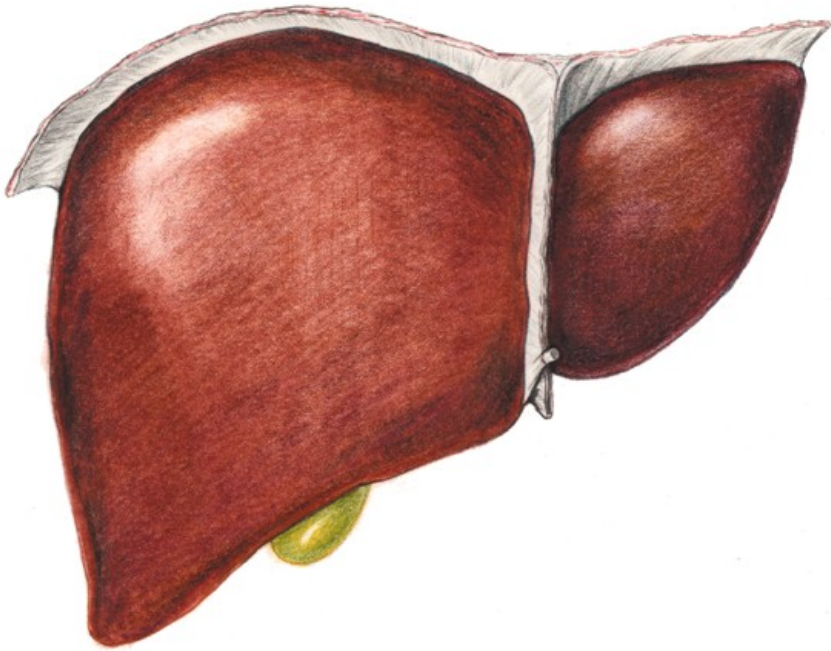


prof. MUDr. Petr Husa, CSc.
Klinika infekčních chorob, FN Brno

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

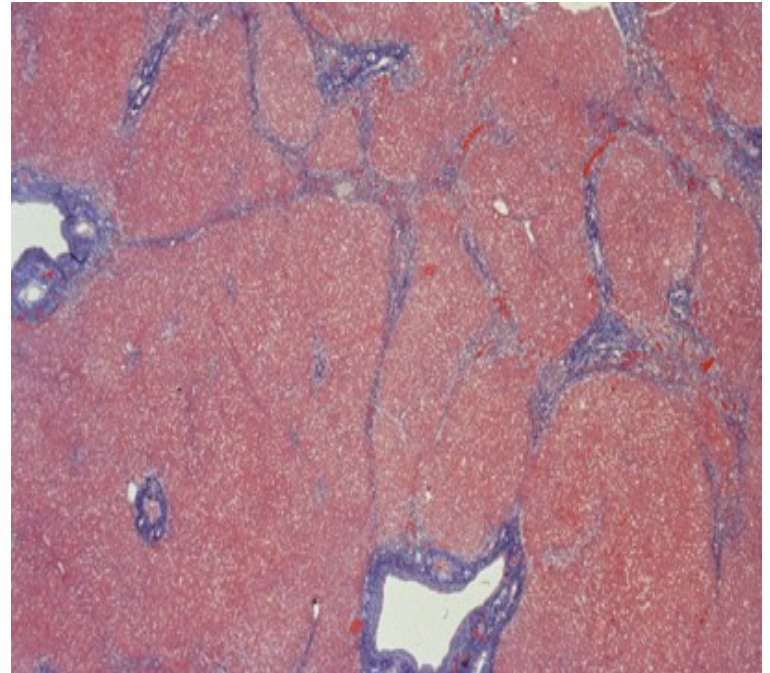
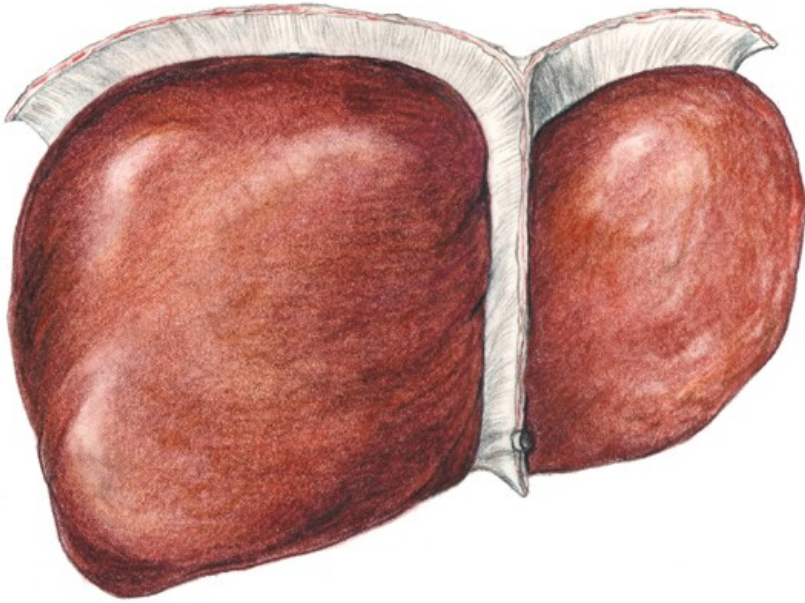
Healthy liver



Normal Biopsy



Liver fibrosis



Mild Fibrosis

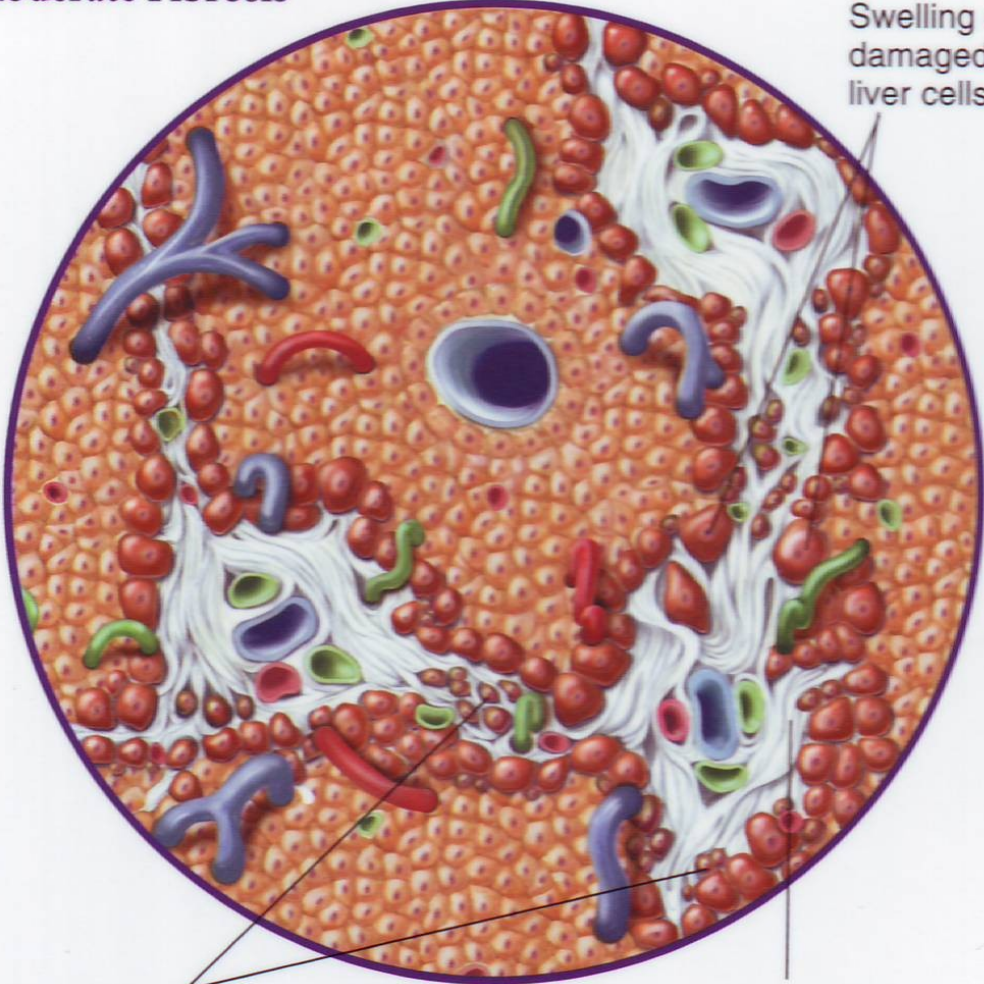
Mild swelling and inflammation of
damaged liver cells around portal areas

Development of
scar tissue (fibrosis)



Normal hepatocytes
(liver cells)

Moderate Fibrosis

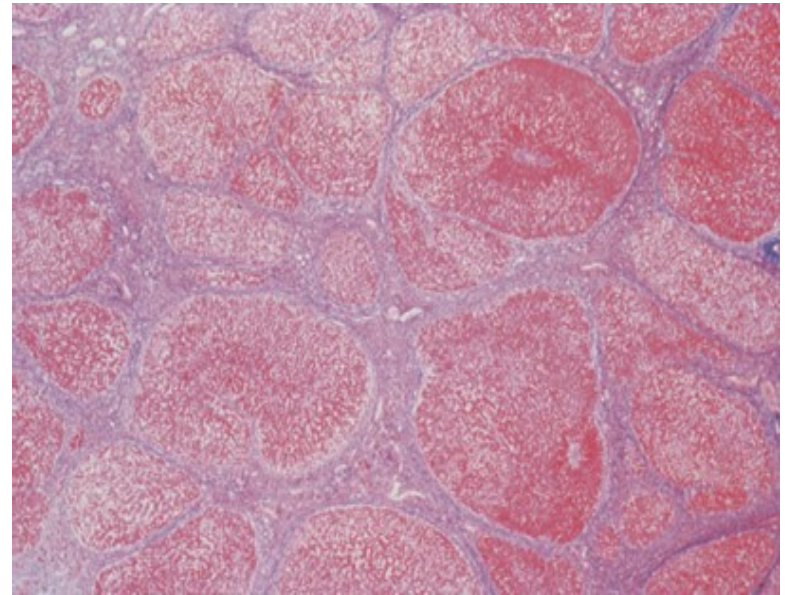
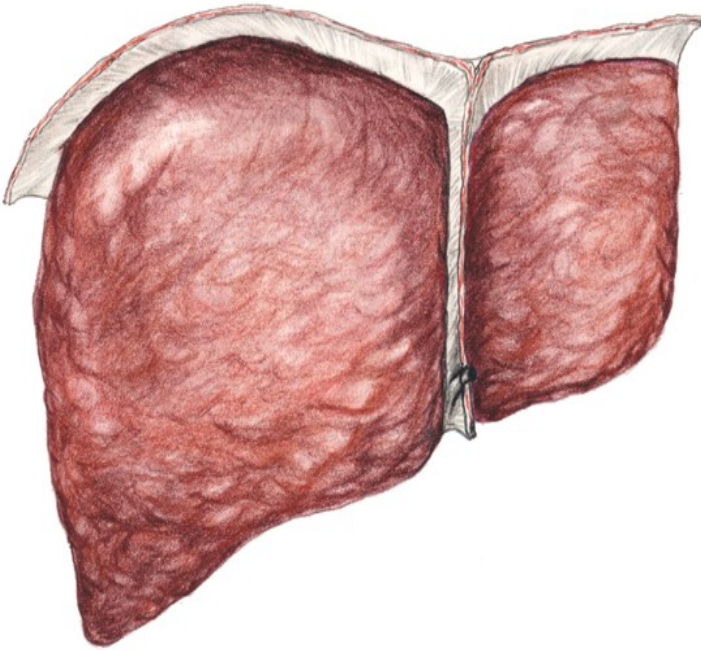


Swelling of
damaged
liver cells

Necrosis of liver cells

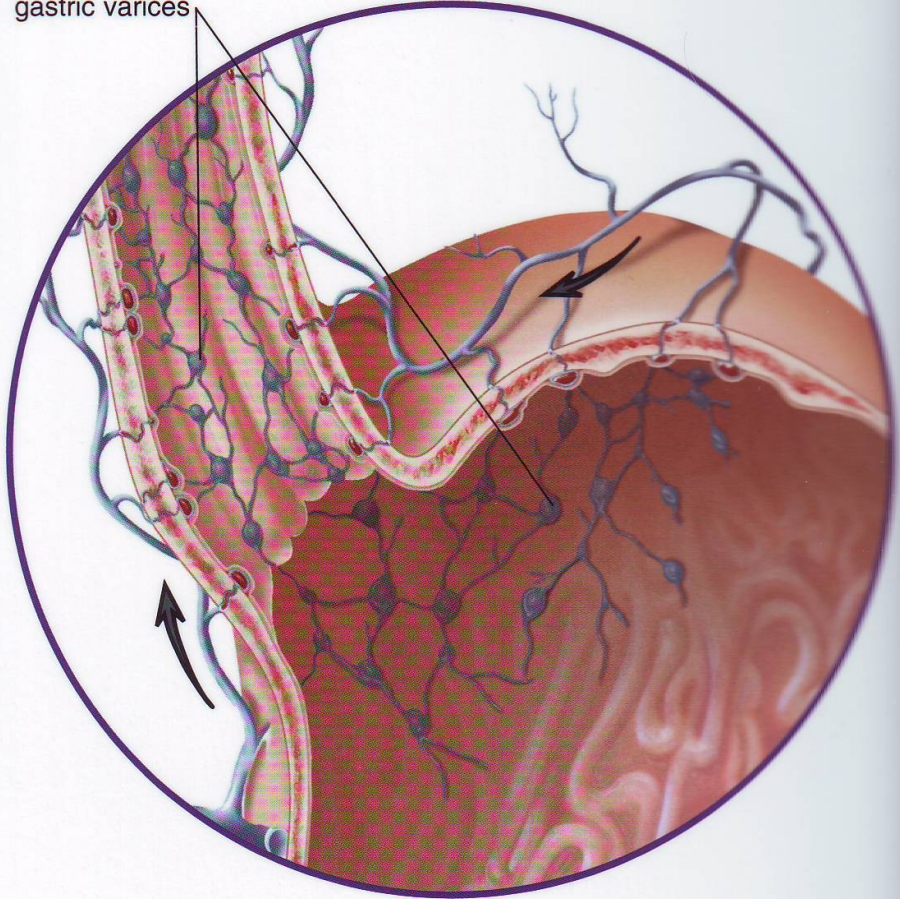
Fibrosis extending
between portal areas

Liver cirrhosis

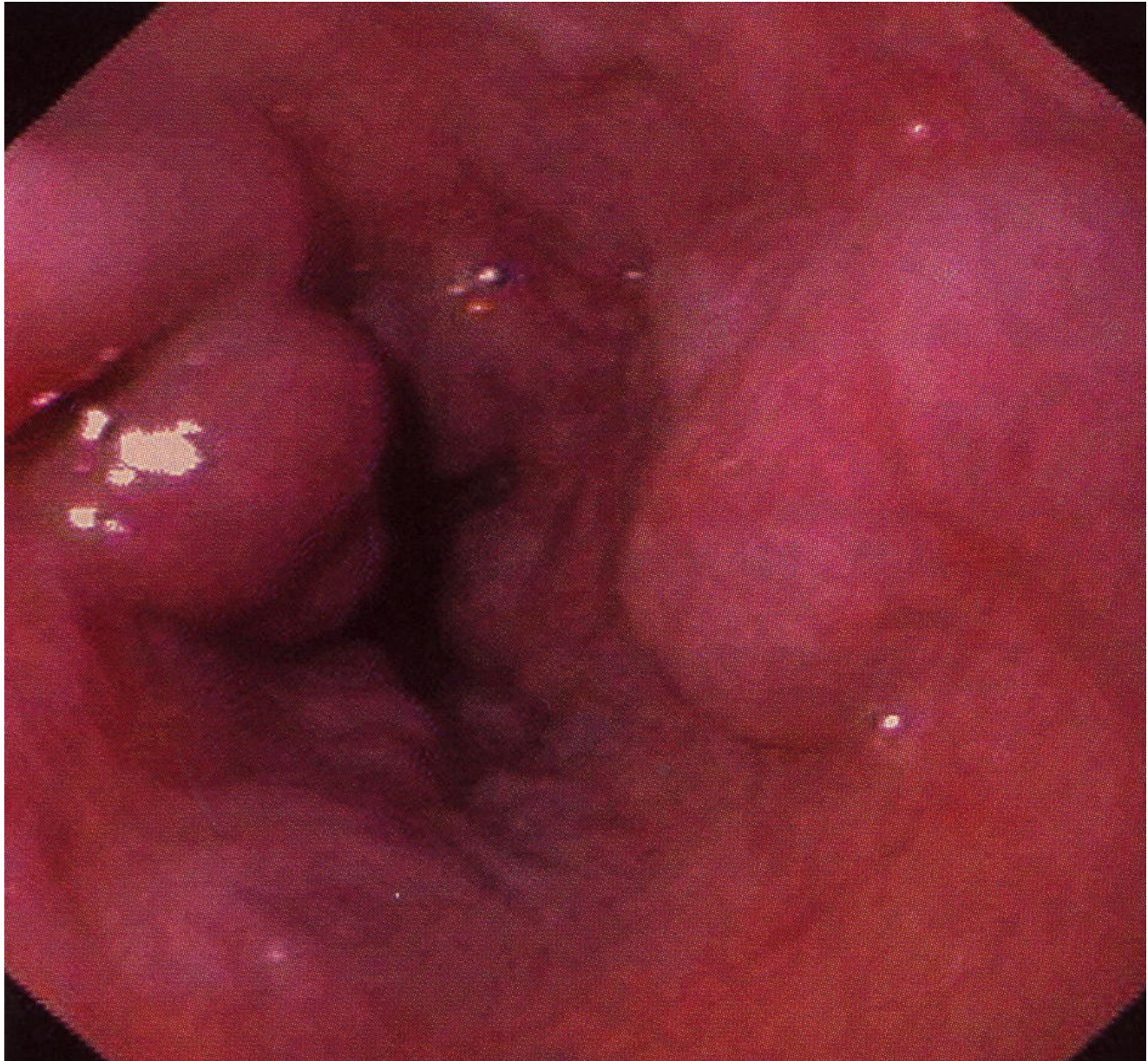


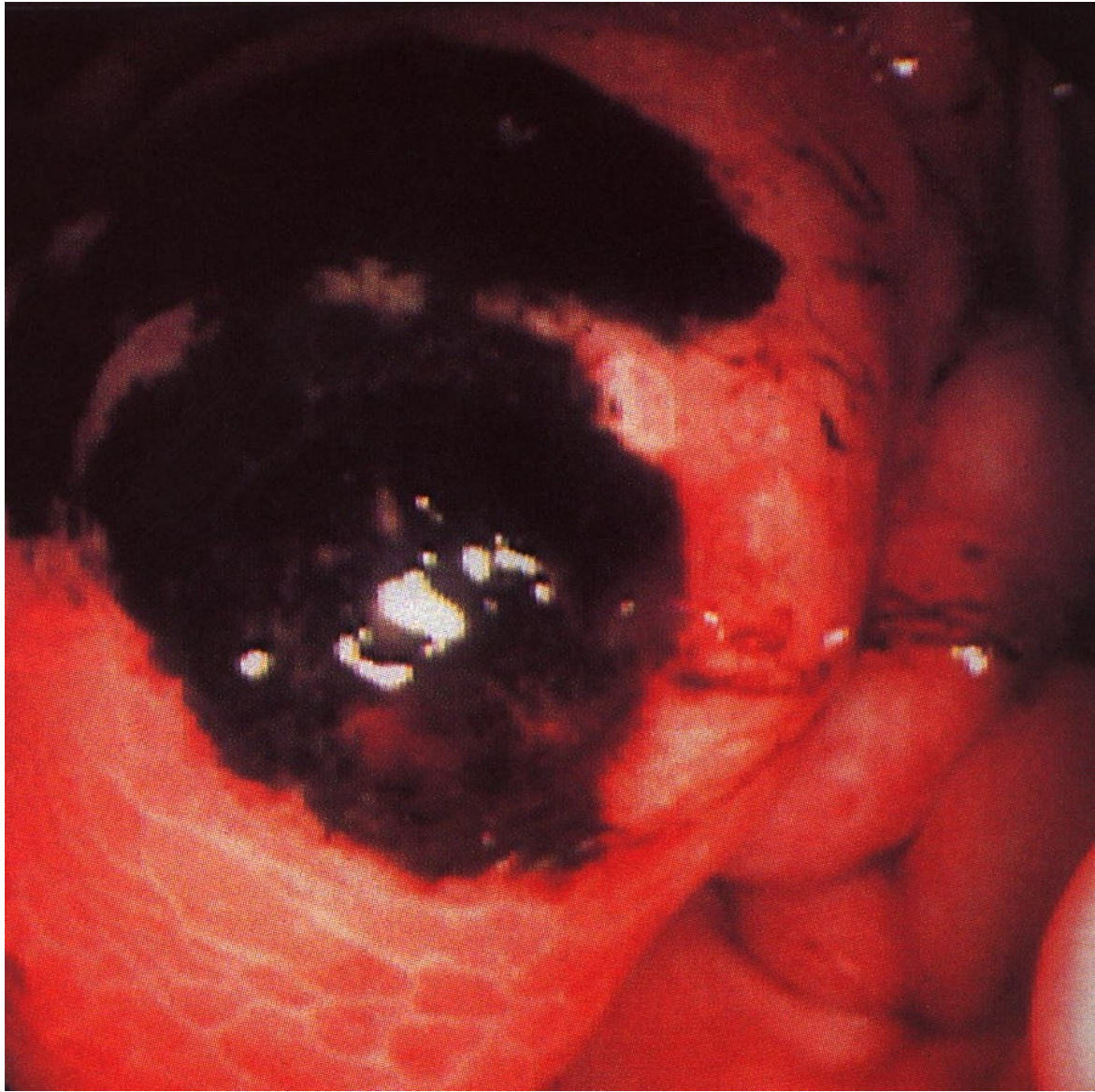
Development of Varices

Esophageal and gastric varices





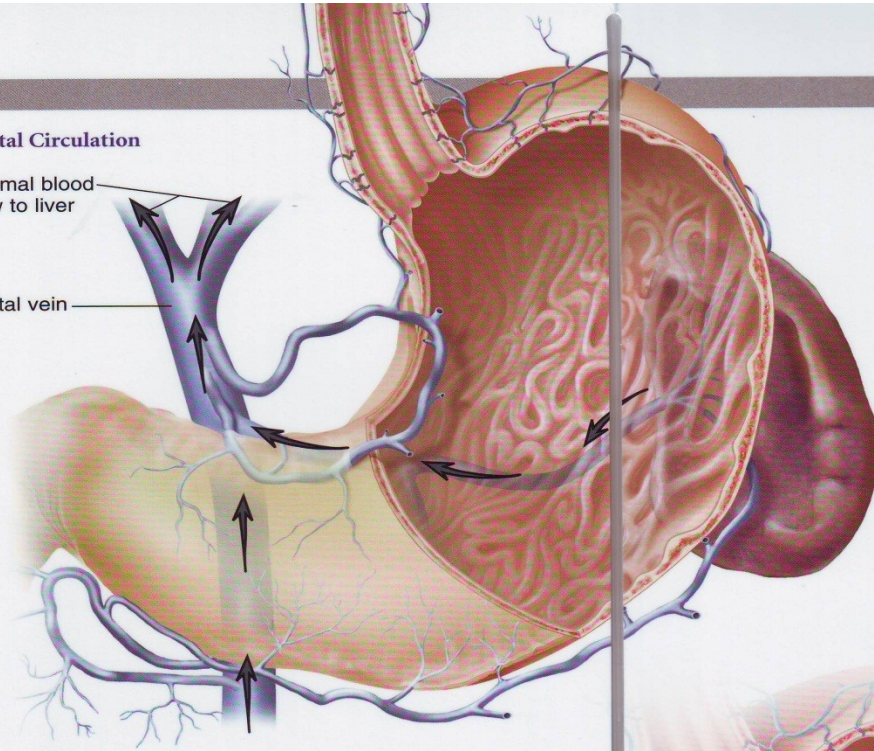




Portal Circulation

Normal blood flow to liver

Portal vein

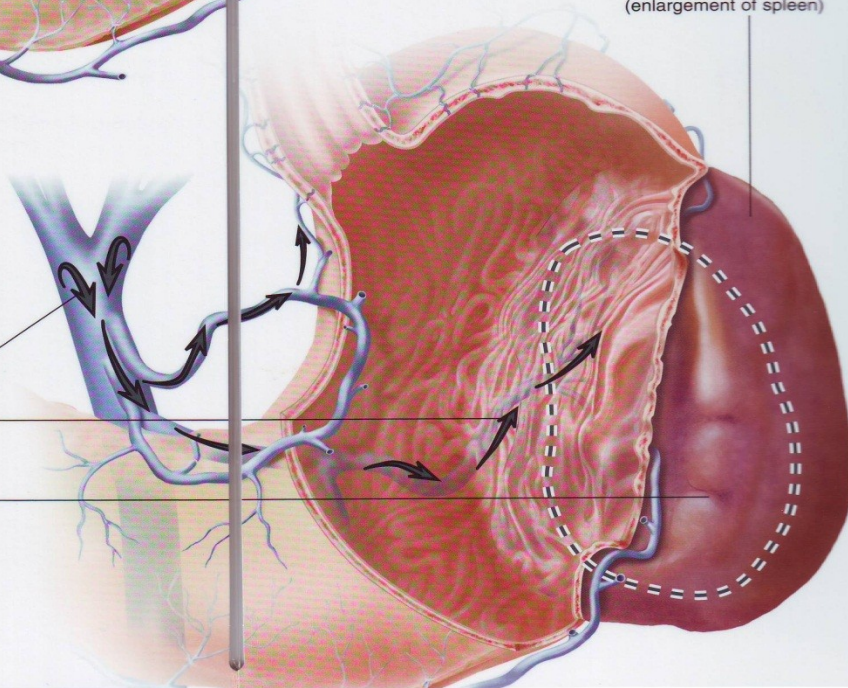


Splenomegaly
(enlargement of spleen)

Portal Hypertension

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

Size of normal spleen

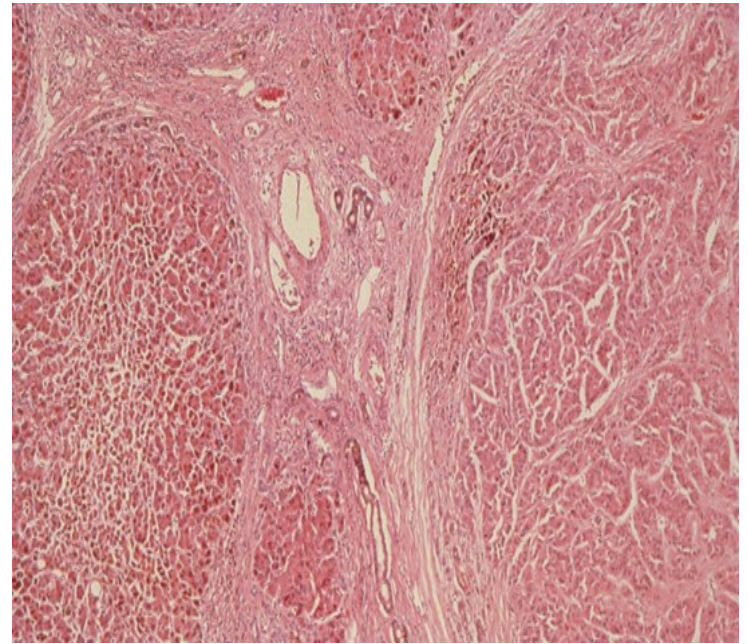
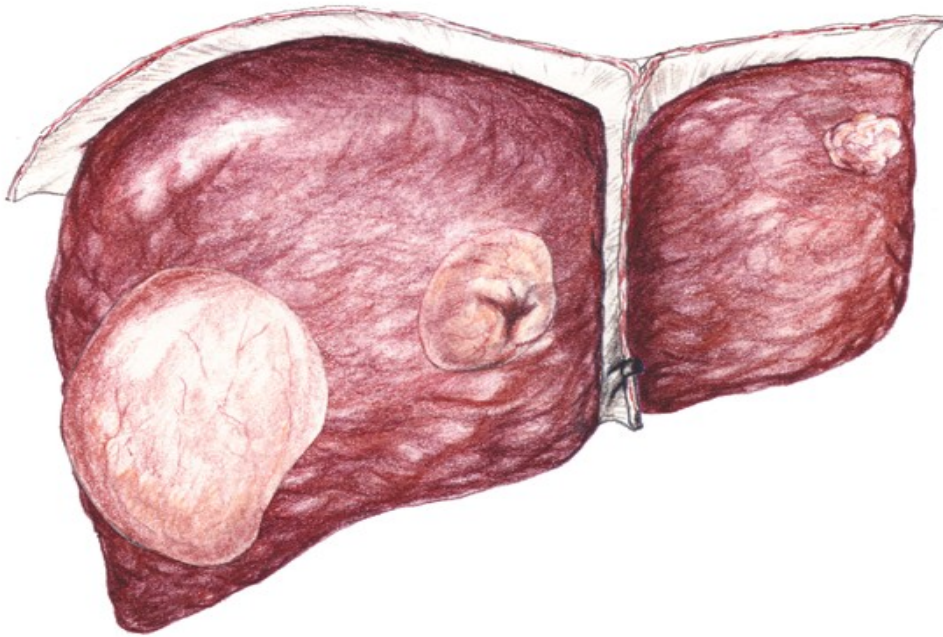








Hepatocellular carcinoma

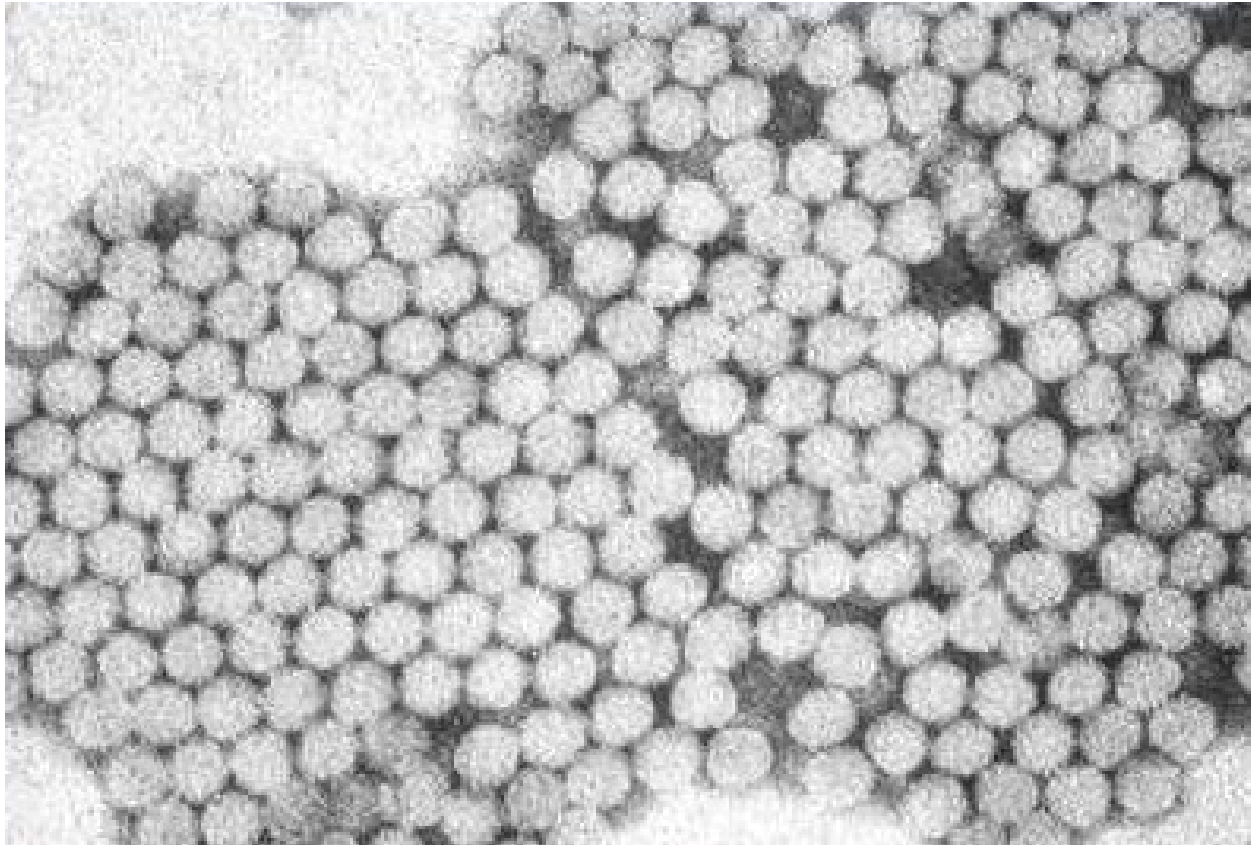




Viral hepatitis in CR 2008-2017

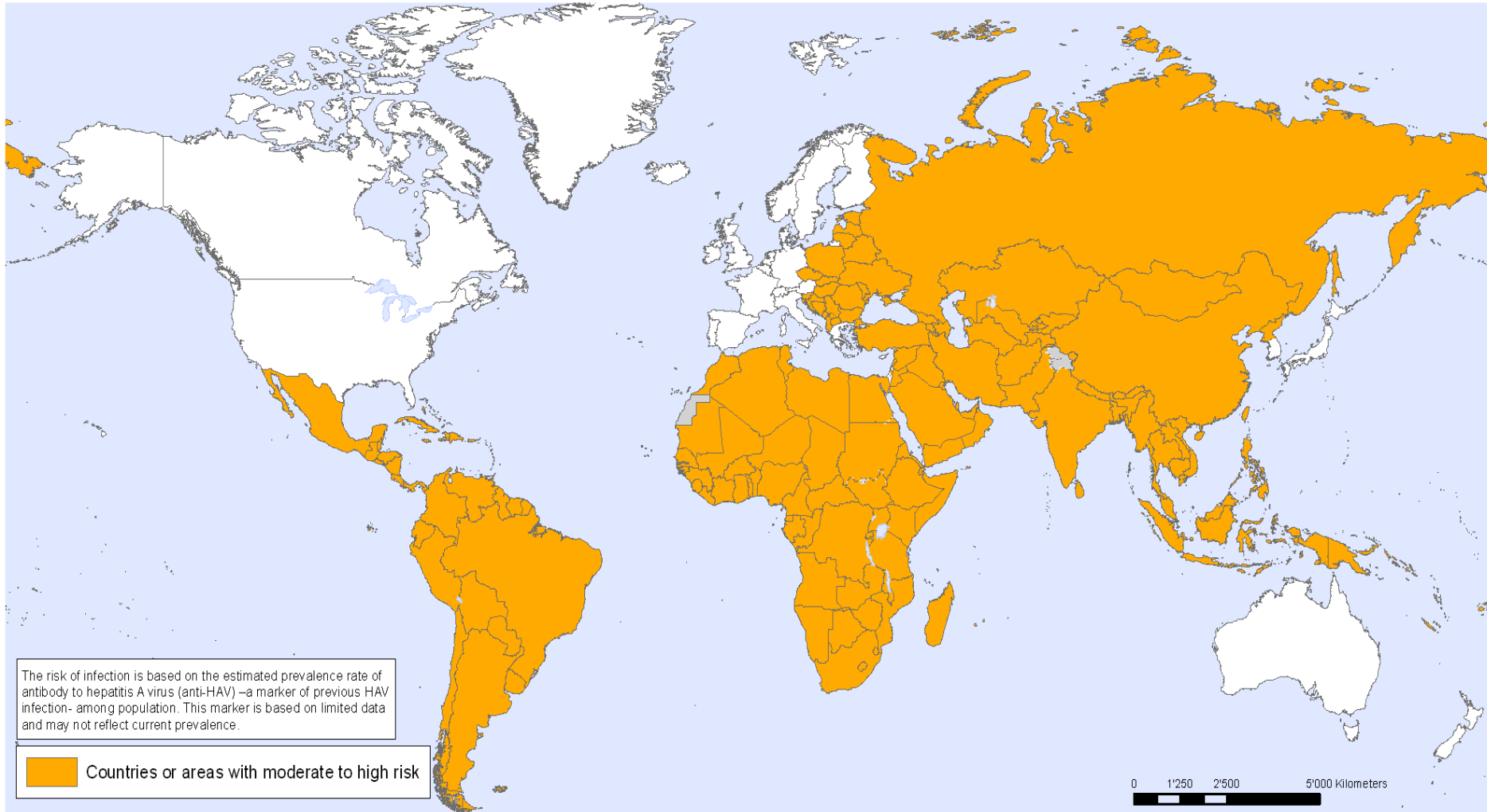
	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
VH A	1104	862	264	284	348	673	723	930	772	211
acute VH B	247	244	192	154	133	105	90	73	85	54
chronic VH B	201	136	162	147	147	193	193	208	248	269
VH C	836	709	812	794	873	867	945	1103	992	1050
VH E	99	72	163	258	218	299	409	339	344	272

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



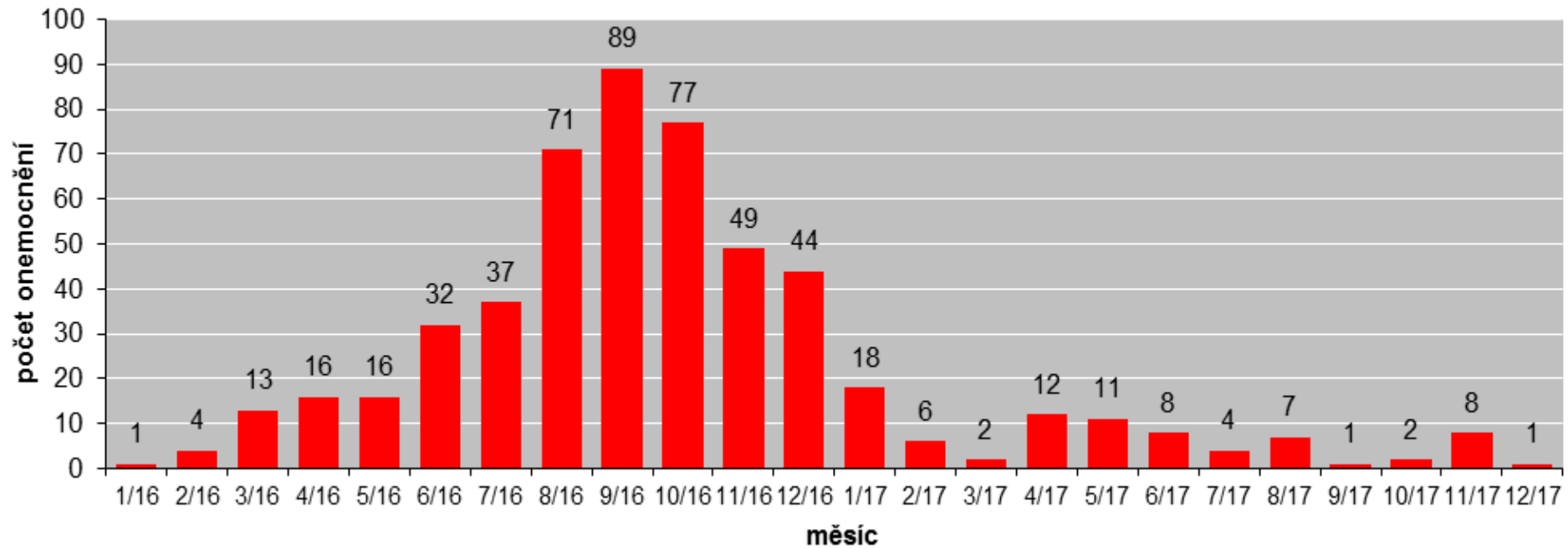
The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers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

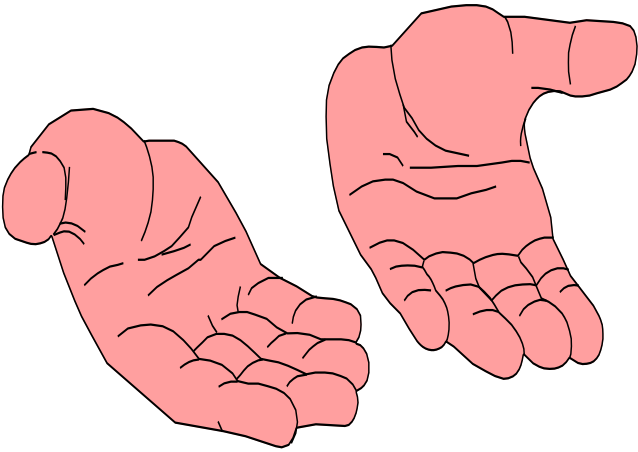
Data Source: World Health Organization. Jacobsen KH, Wiersma ST. Hepatitis A virus seroprevalence by age and world region, 1990 and 2005. *Vaccine* 2010 Sep;28(41):6653-7
Map Production: Public Health Information and Geographic Information Systems (GIS) World Health Organization



© WHO 2012. All rights reserved.

HAV epidemic in the South Moravia 2016-2017



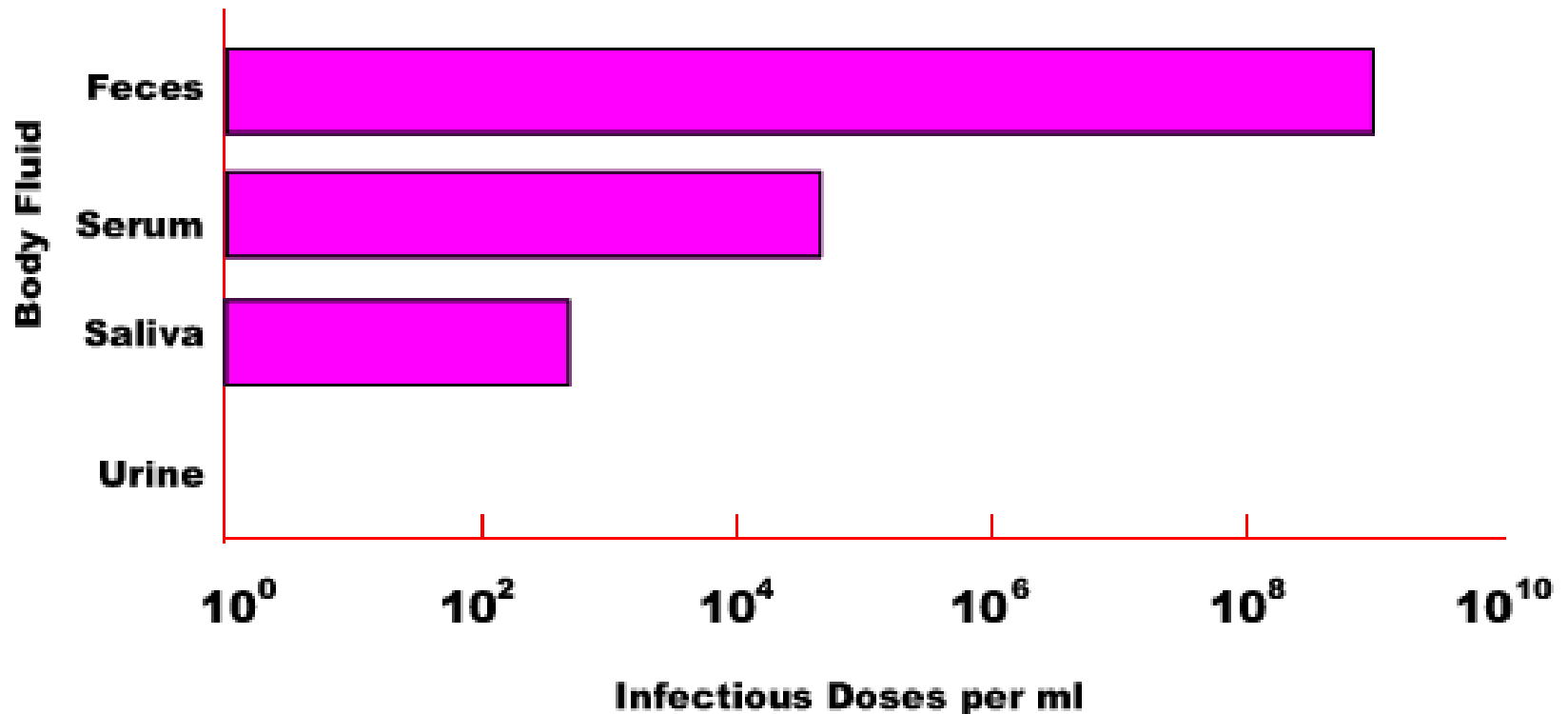


Epidemiology

- 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

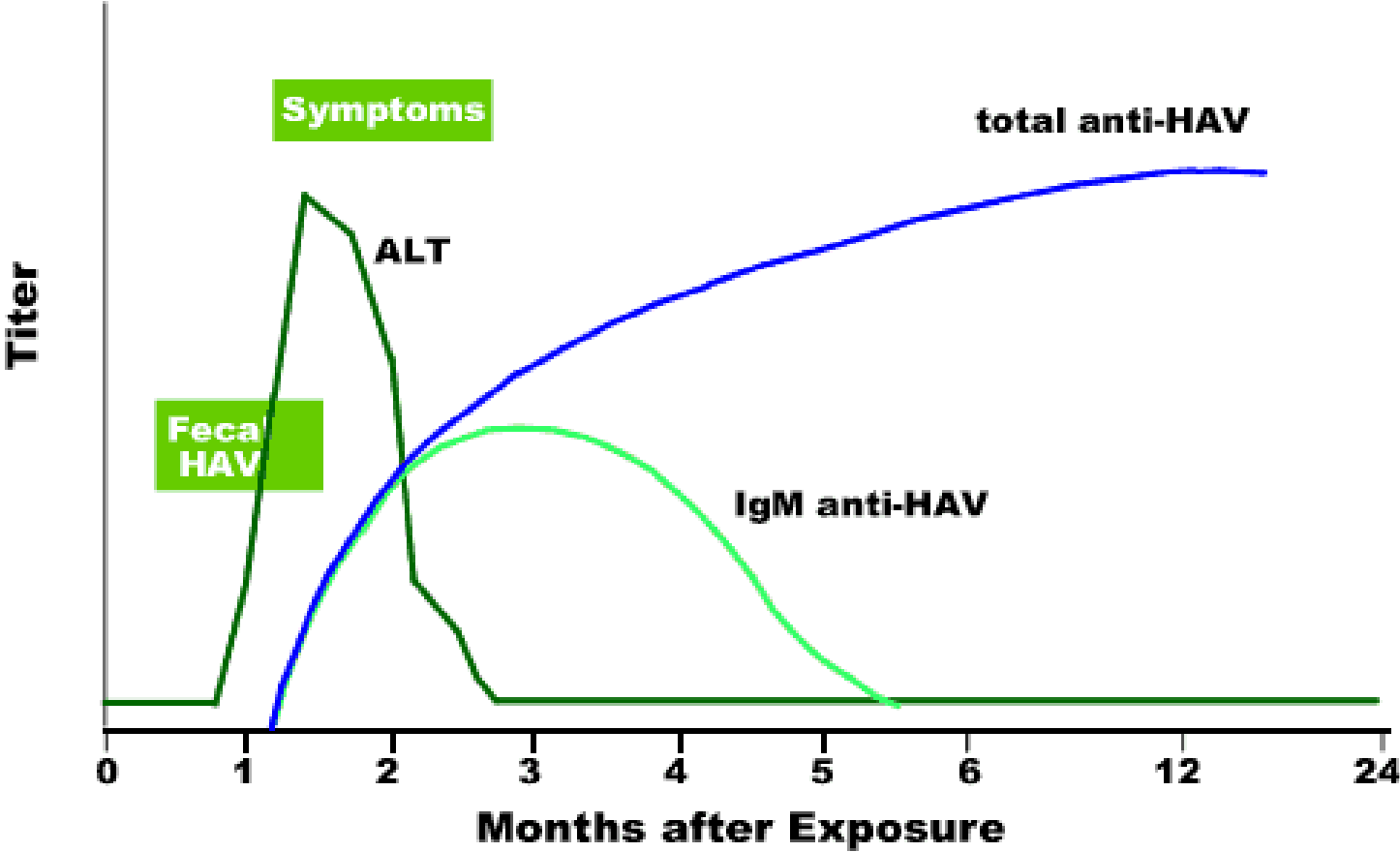
Concentration of Hepatitis A Virus in Various Body Fluids



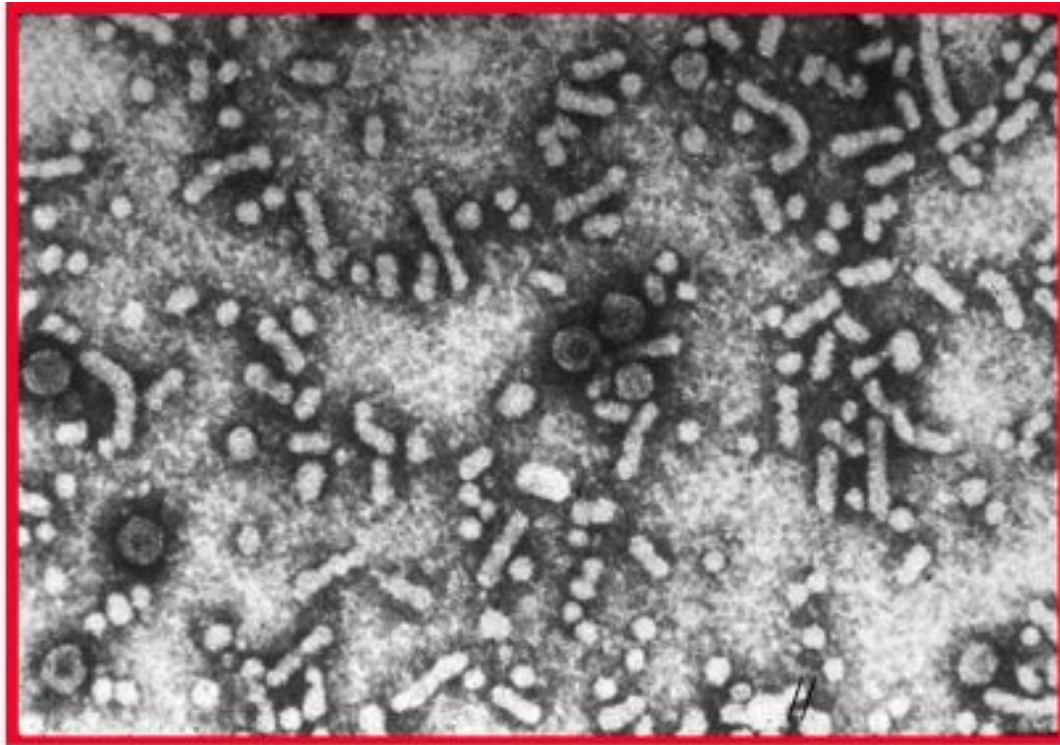
Source: Viral Hepatitis and Liver Disease 1984;9-2
J Infect Dis 1989; 160:887-890

Hepatitis A Virus Infection

Typical Serologic Course



Hepatitis B Virus (HBV)



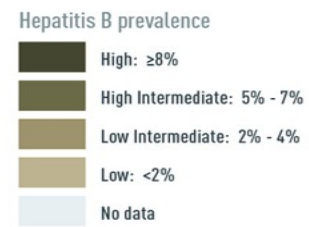
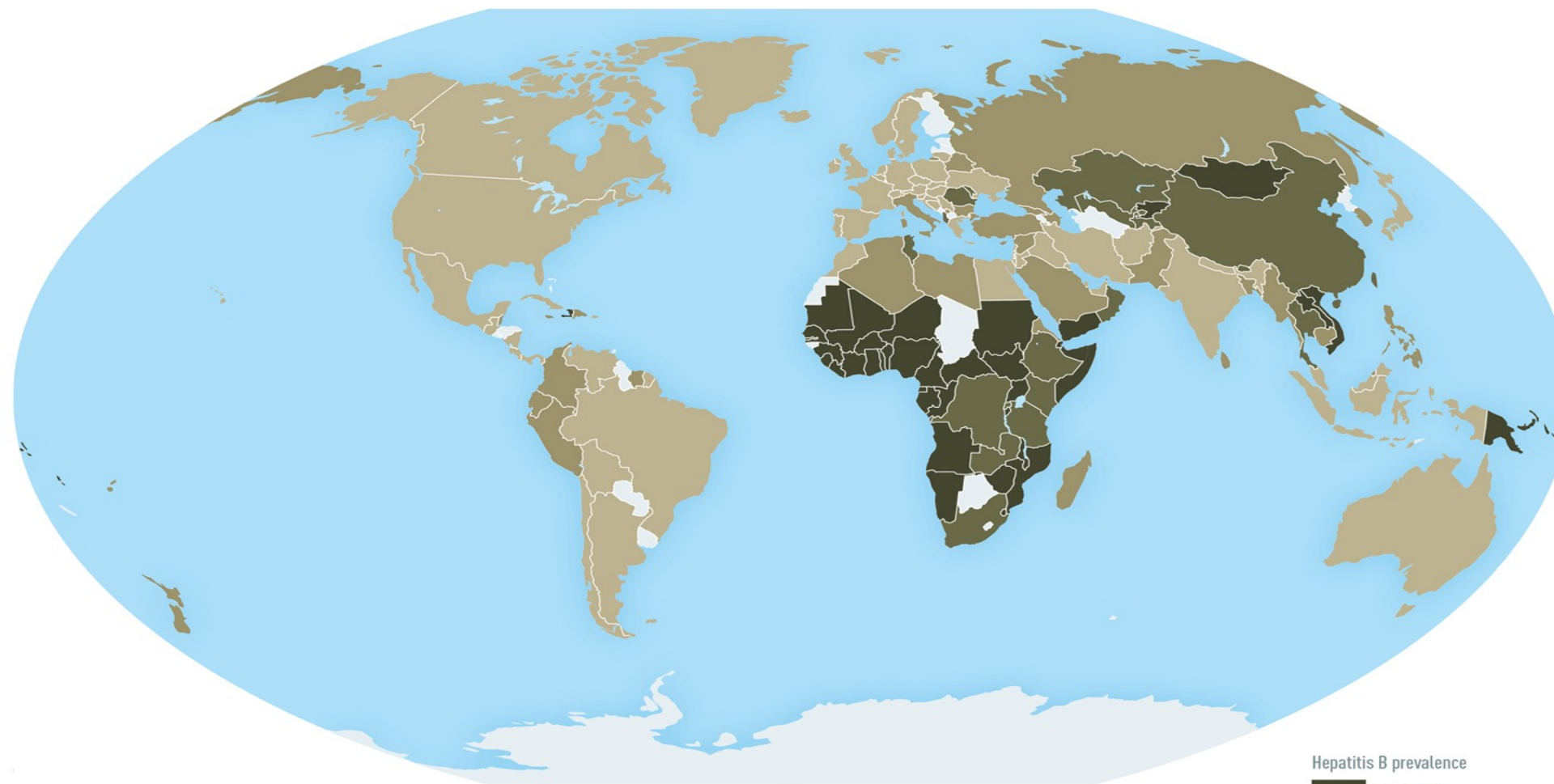
Family Hepadnaviridae, genus *Orthohepadnavirus*, enveloped DNA, 42 nm,
9 genotypes (A-I), Europe A,D, Asia B,C, several subtypes

Global significance of HEP B

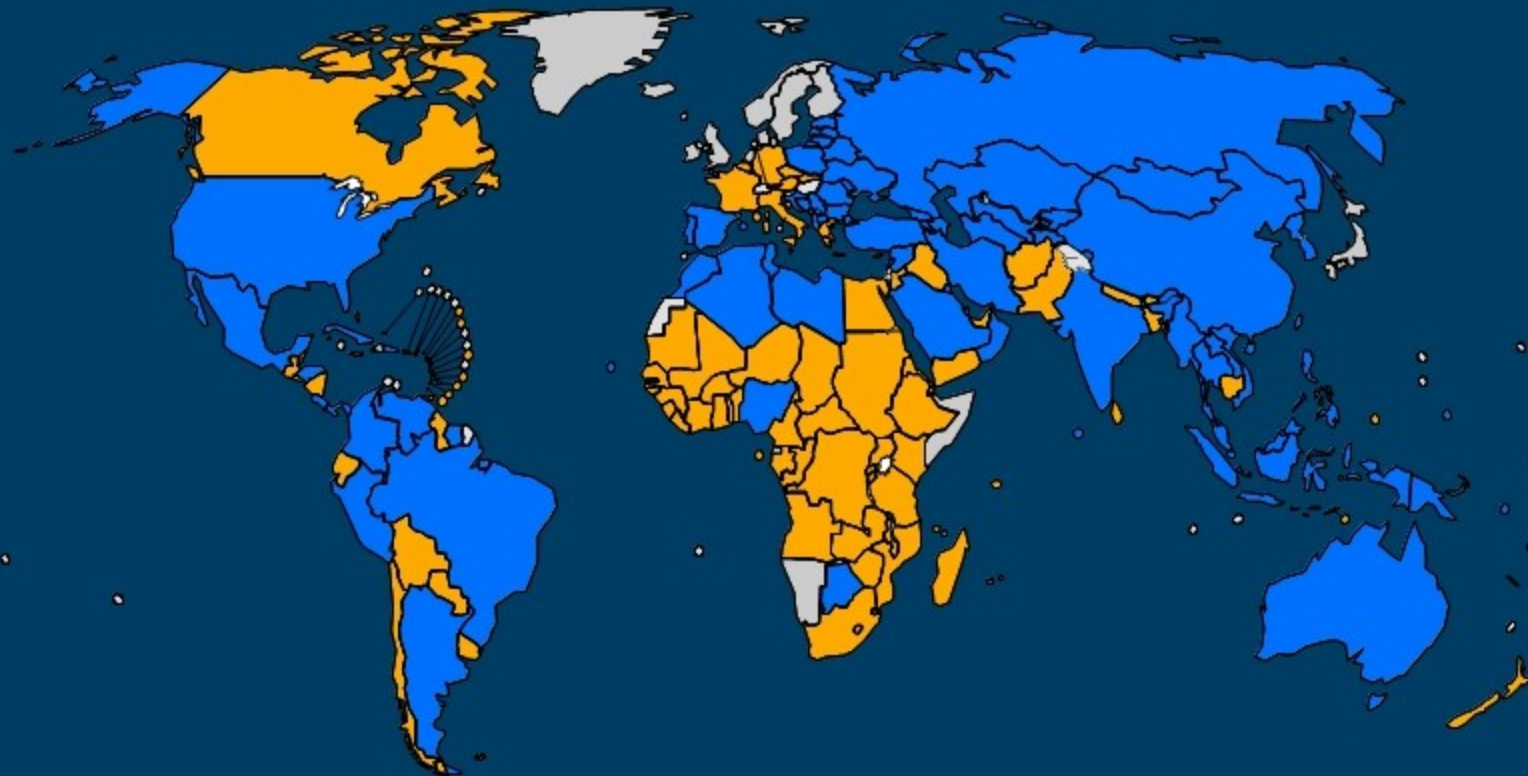
- One of the biggest global health problems
- ✓ More than 2 billions of infections during the life
- ✓ 240 million chronic carriers
- ✓ 686 000 deaths annually due to LC or HCC (2013, increase about one third since 1990)
- ✓ Indication for 5-10 % liver transplantations globally
- ✓ 50 thousand death 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

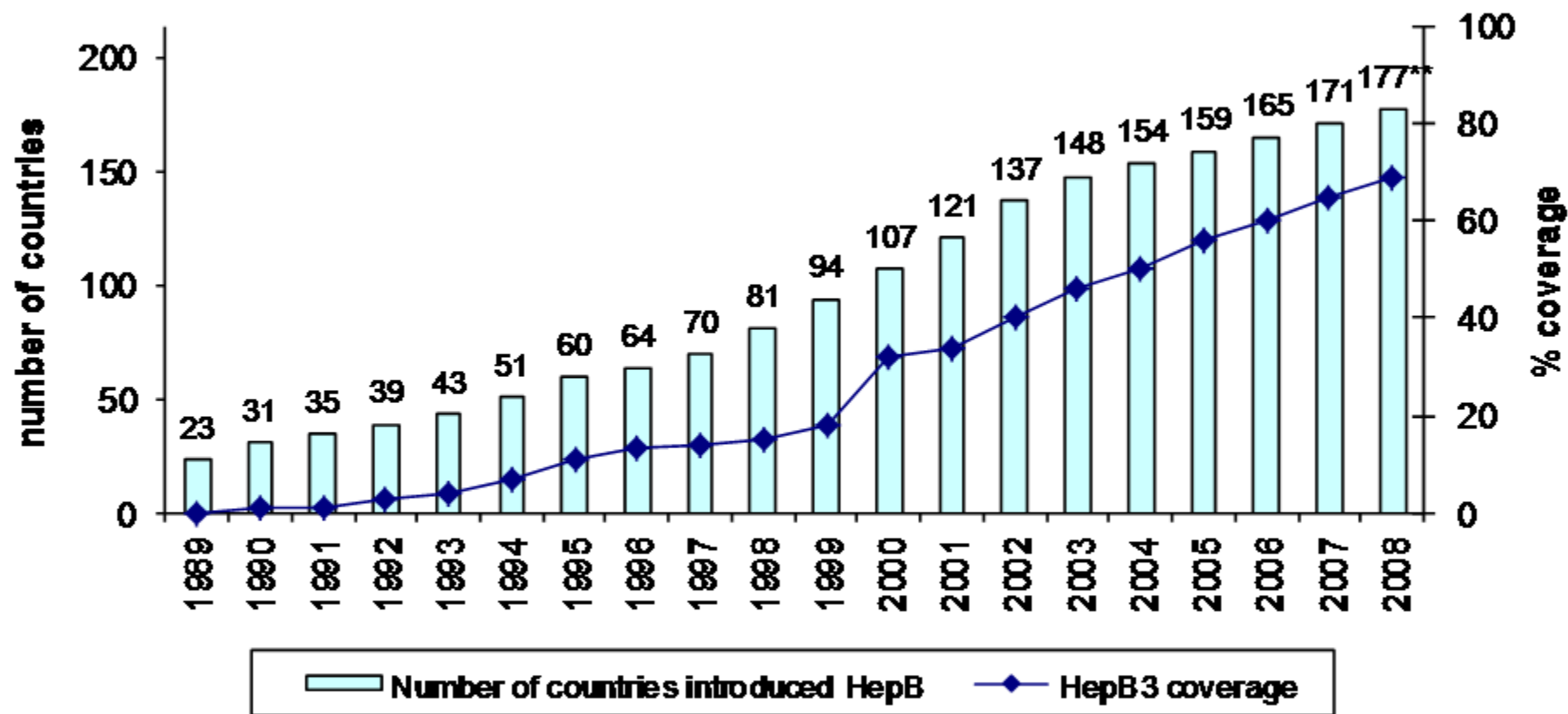
-  No HepB (16 countries¹ or 8%)
-  HepB no Birth Dose (92 countries² or 48%)
-  HepB with Birth Dose (85 countries³ or 44%)

¹includes three countries with adolescent immunization
²includes 81 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 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.
© WHO 2009. All rights reserved.



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 %

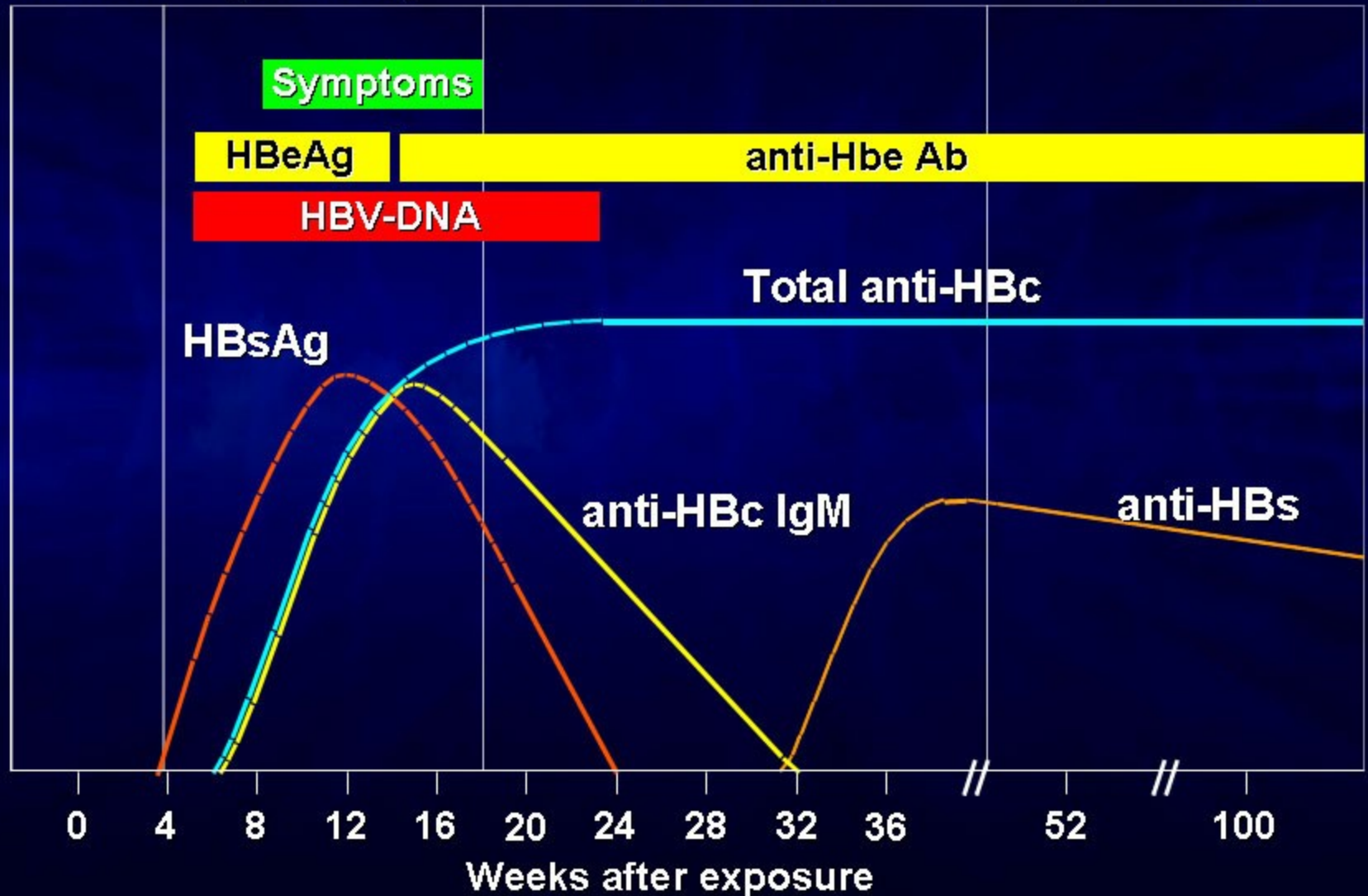
Acute Hepatitis B

Incubation
4-12 weeks

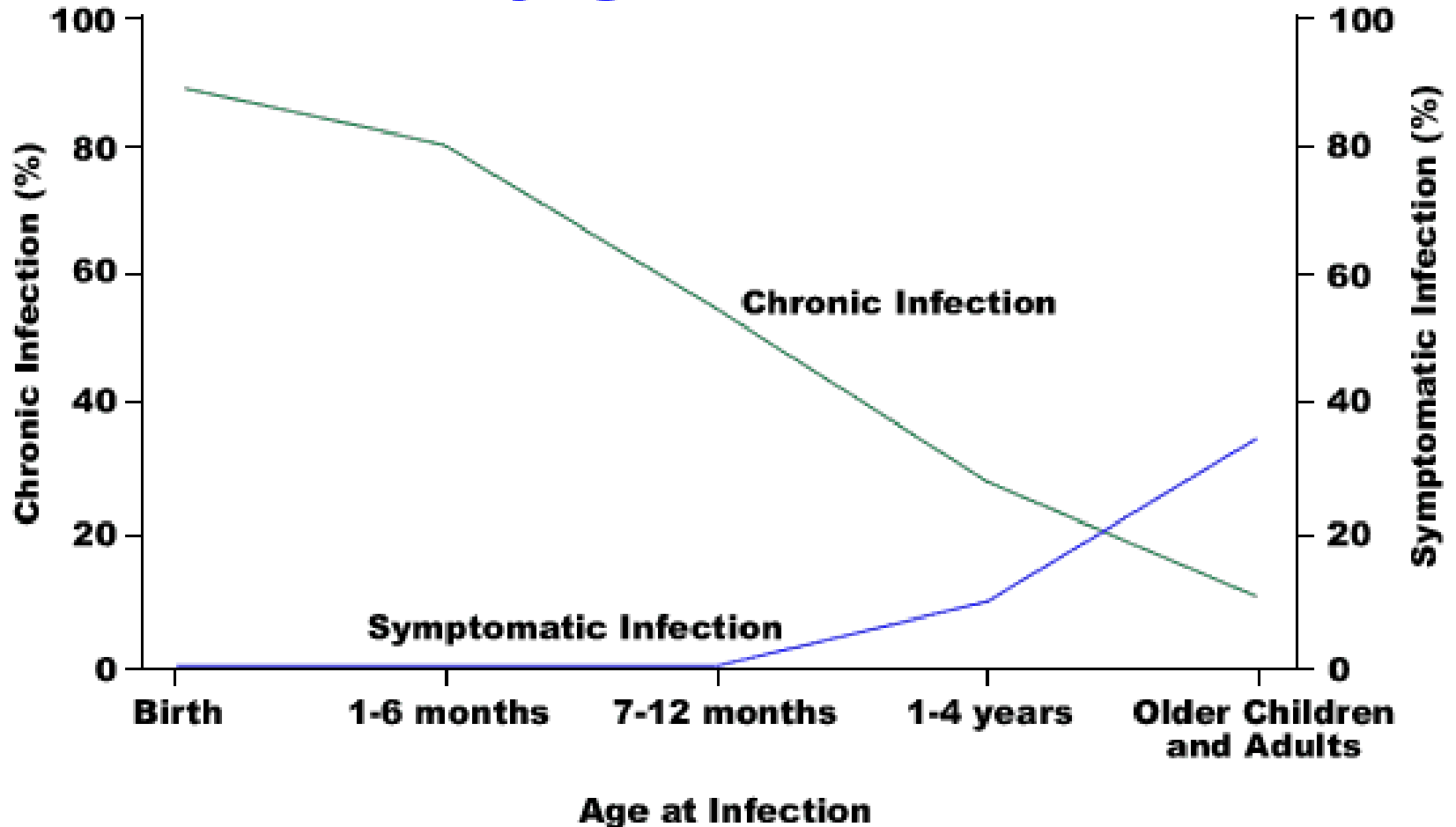
Acute infection
(2-12 weeks)

Early recovery
(12-24 weeks)

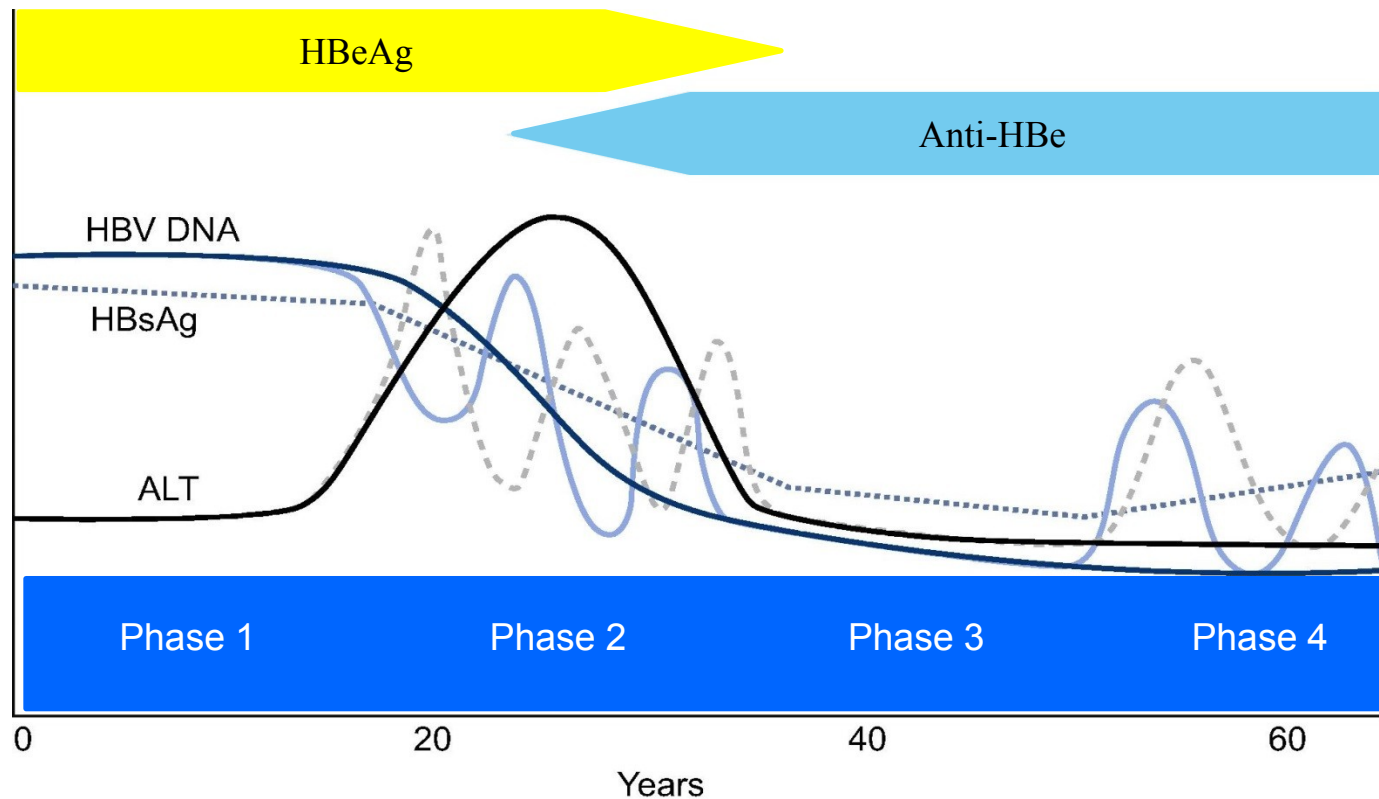
Recovery
(24-48 weeks)



Outcome of Hepatitis B Virus Infection by Age at Infection



Phases of chronic HBV infection



Nomenclature

HBeAg-positive
chronic HBV **infection**

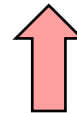
HBeAg-positive
chronic **hepatitis**

HBeAg-negative
chronic HBV **infection**

HBeAg-negative
chronic **hepatitis**

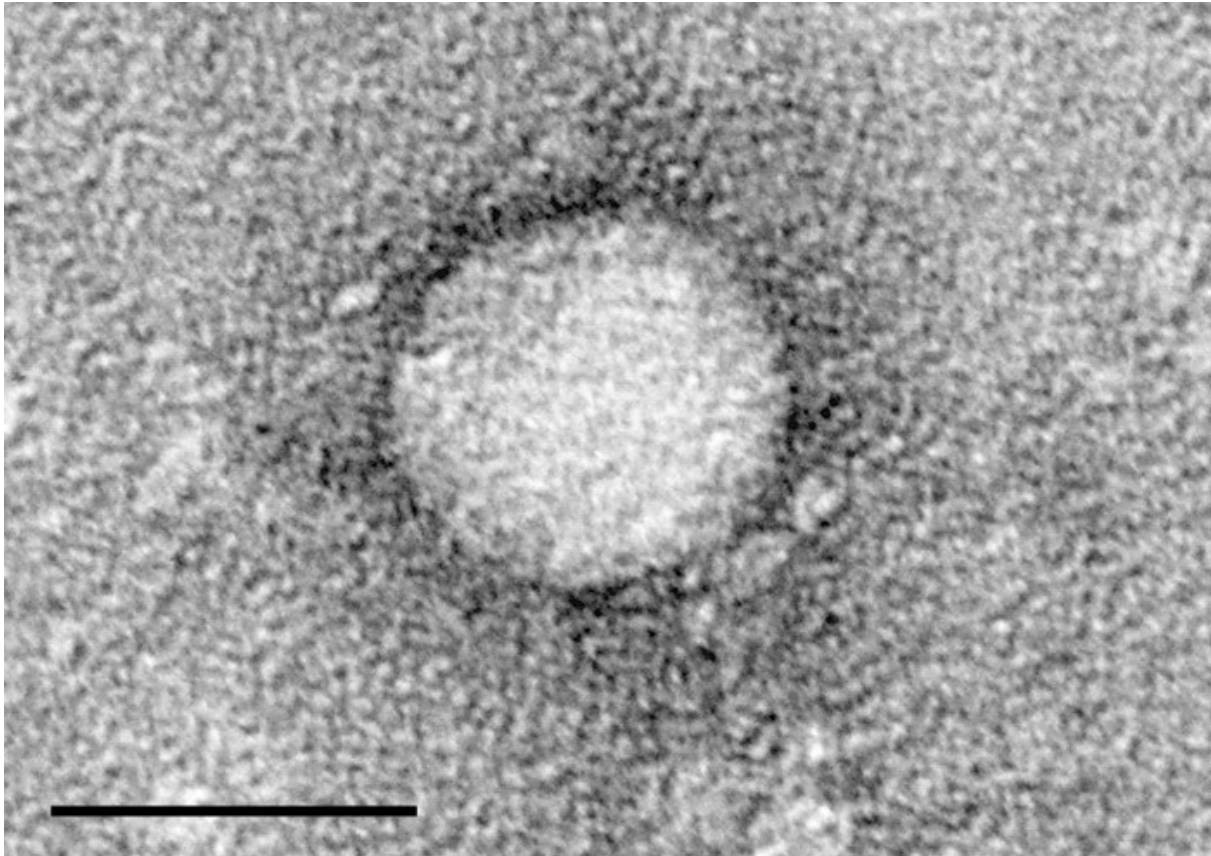


treatment



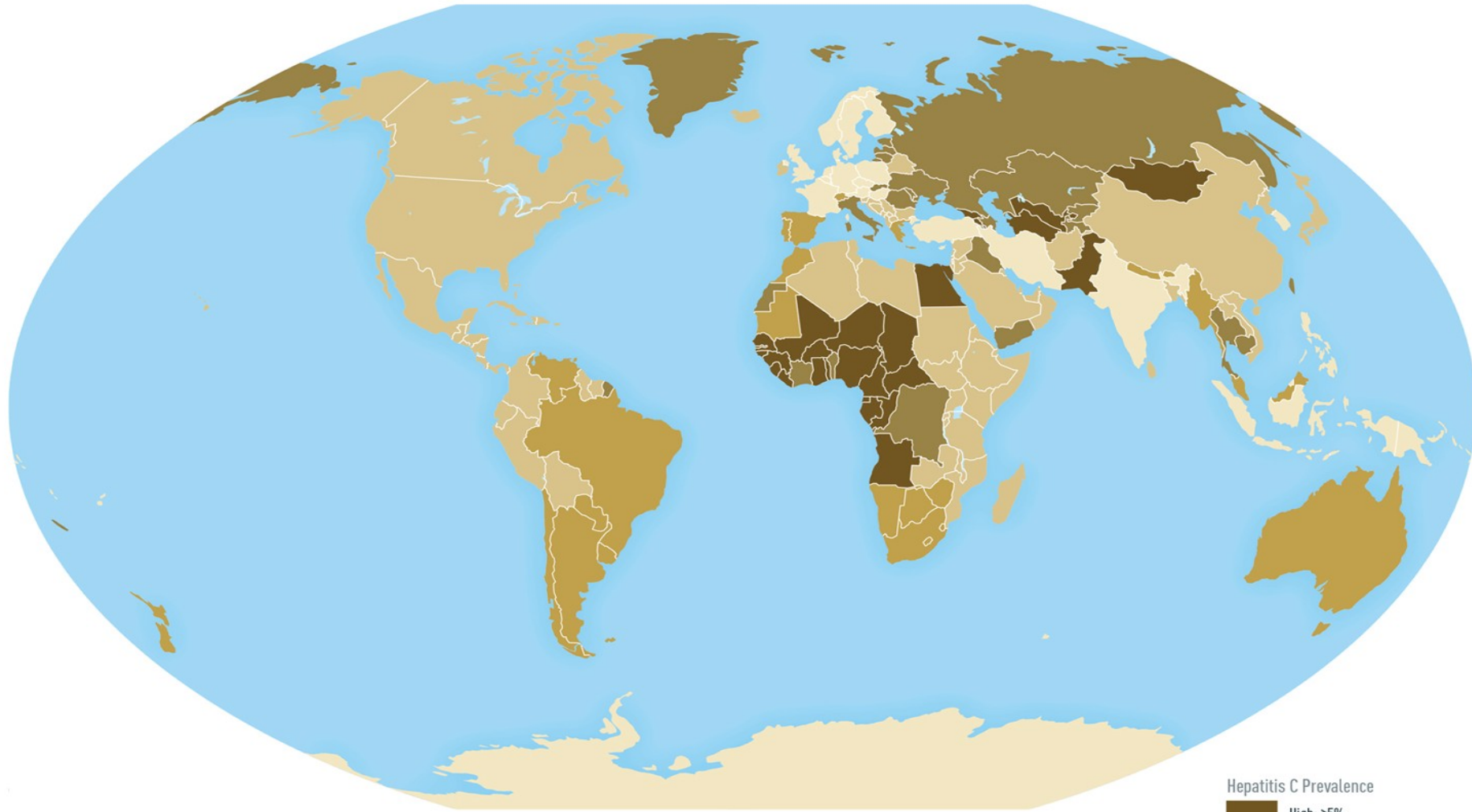
treatment

Hepatitis C virus (HCV)



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

Chronic HCV infection (CDC 2017)



Distribution of HCV genotypes



Hepatitis C

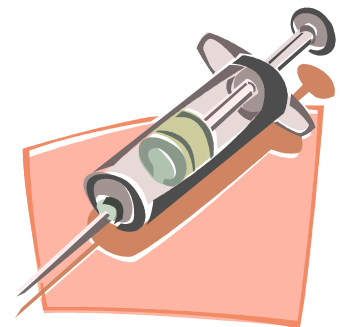
- Significant global health problem
- ✓ 70-80 million persons worldwide are chronically infected with HCV
- ✓ In well-developed countries about 20 % of all acute hepatitis, 70 % chronic hepatitis, 40 % cirrhosis, 60 % HCC and indication to 30 % liver transplantations
- In Czech Republic
- ✓ prevalence 0.2 % (2001), current estimations 0.4-0.5 %
- No vaccine, no hyper-immune immunoglobulin

Epidemiology of HEP C

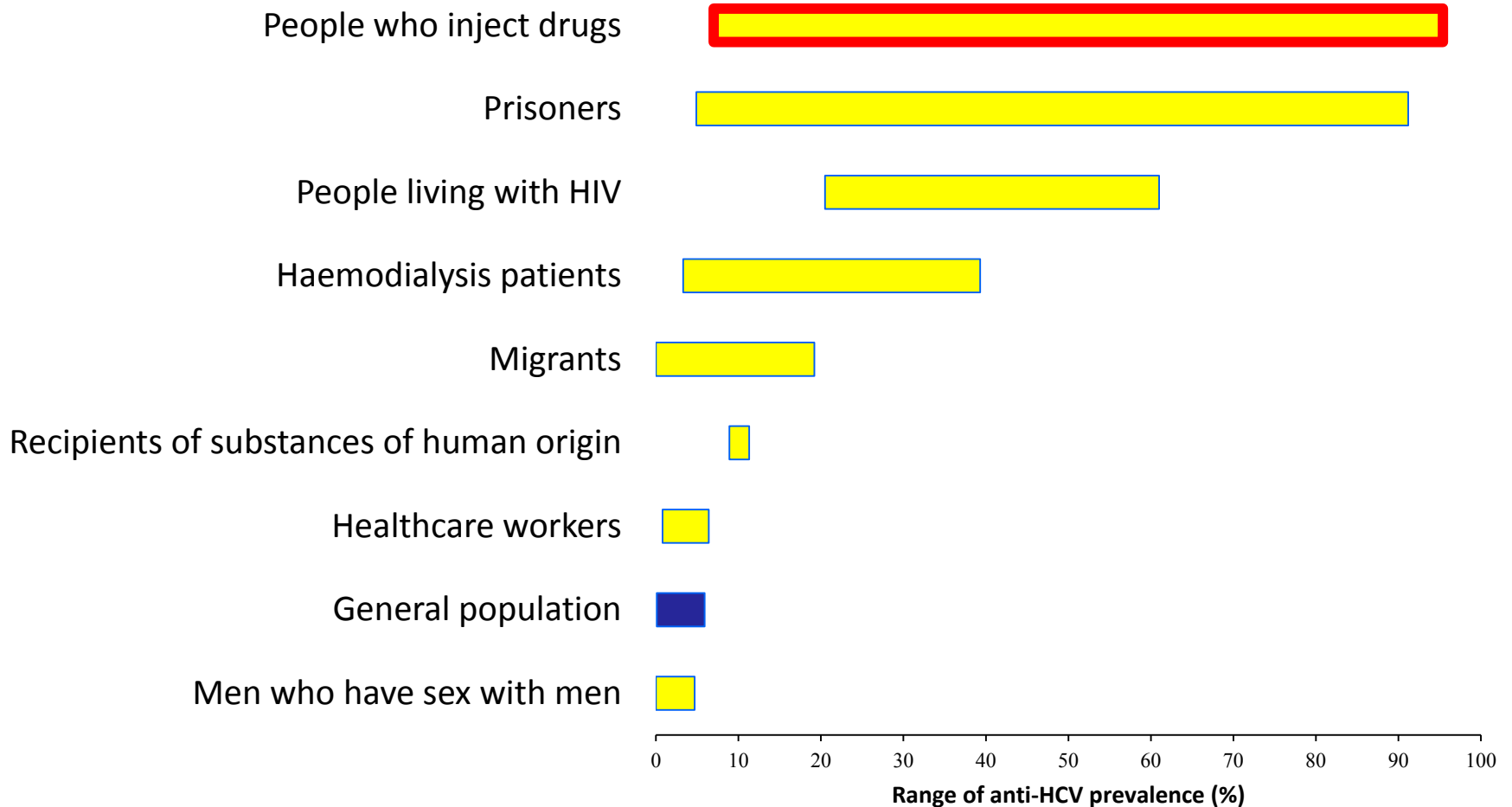
- Transmission:
 - ✓ blood and blood products
 - ✓ sharing of used injection needles and syringes
 - ✓ sexually (rare)
 - ✓ vertically (rare)
- Who is in the highest risk of HCV infection at present?
 - ✓ intravenous drug abusers
- Infection is frequently diagnosed in chronic stage

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

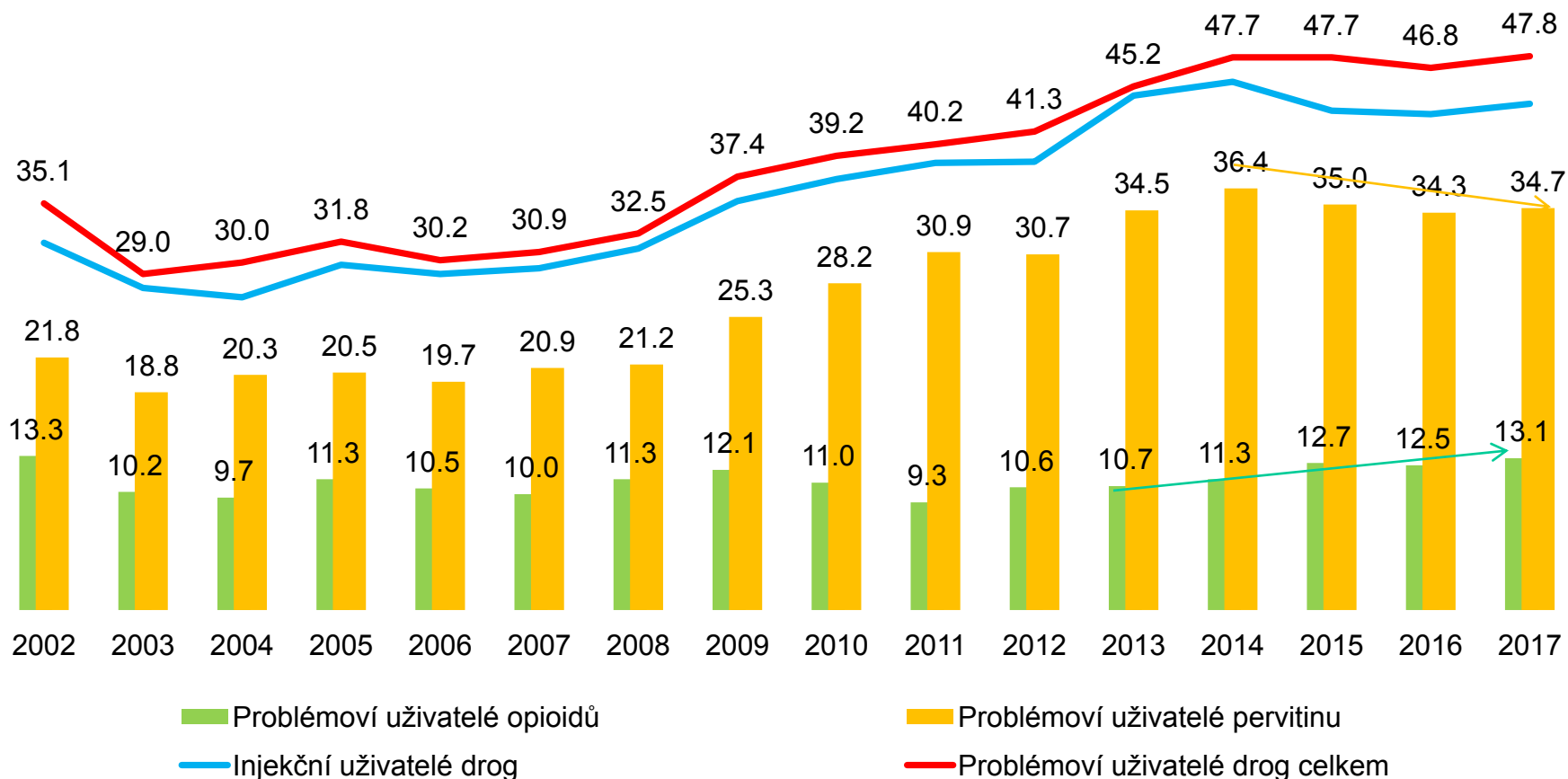


HCV prevalence in risk groups of inhabitants in EU/EEA countries



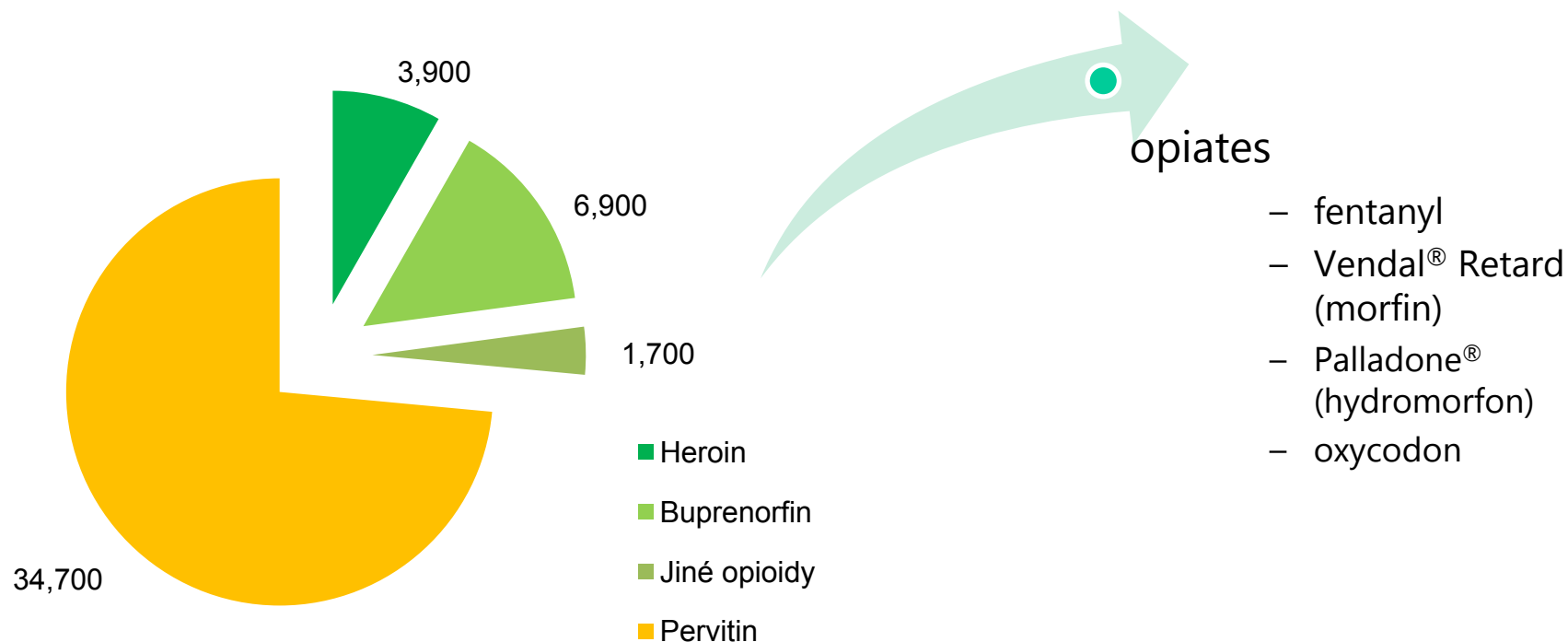
Problematic drug abusers in the CR (2017)

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

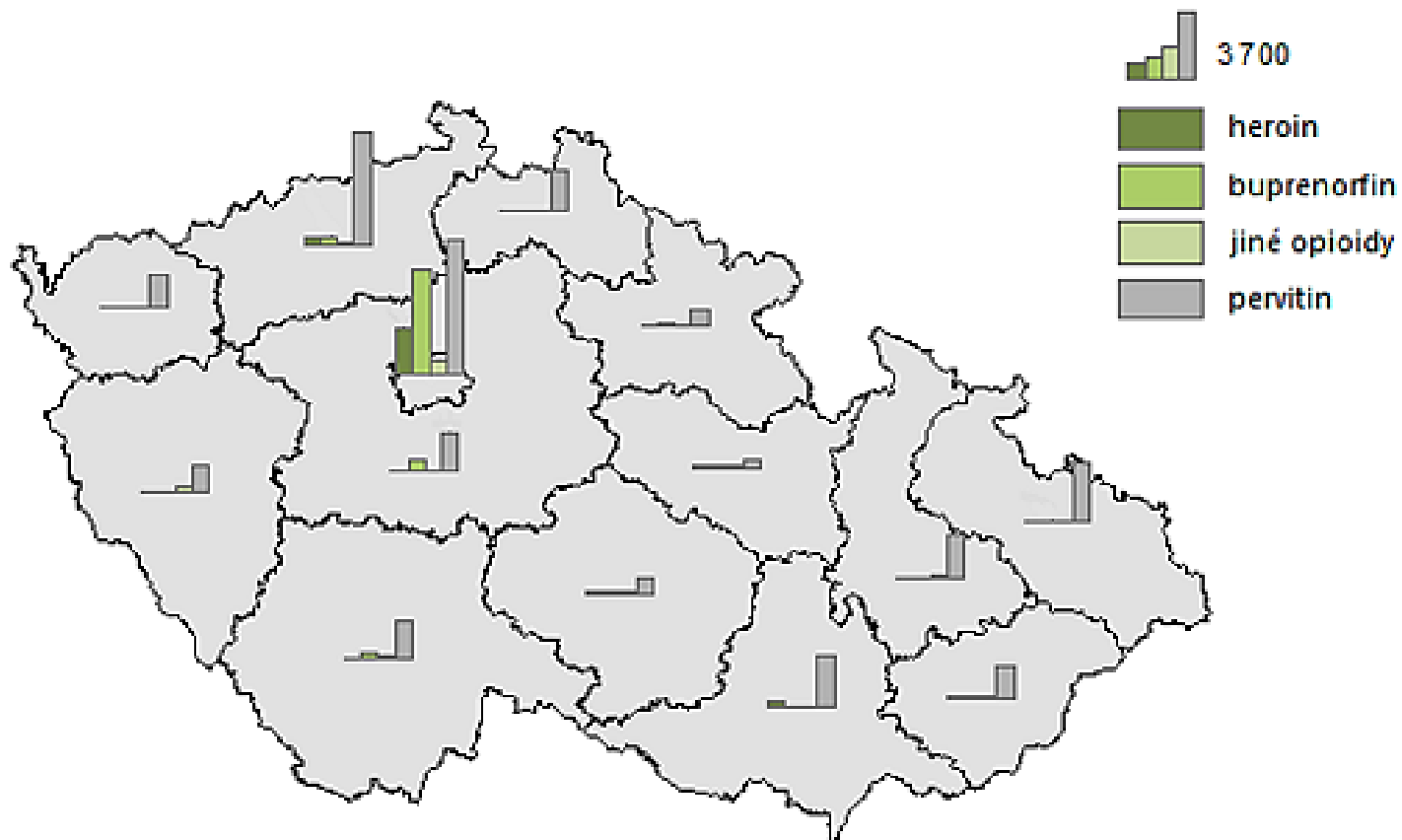


Problematic drug abusers in the CR (2017)

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

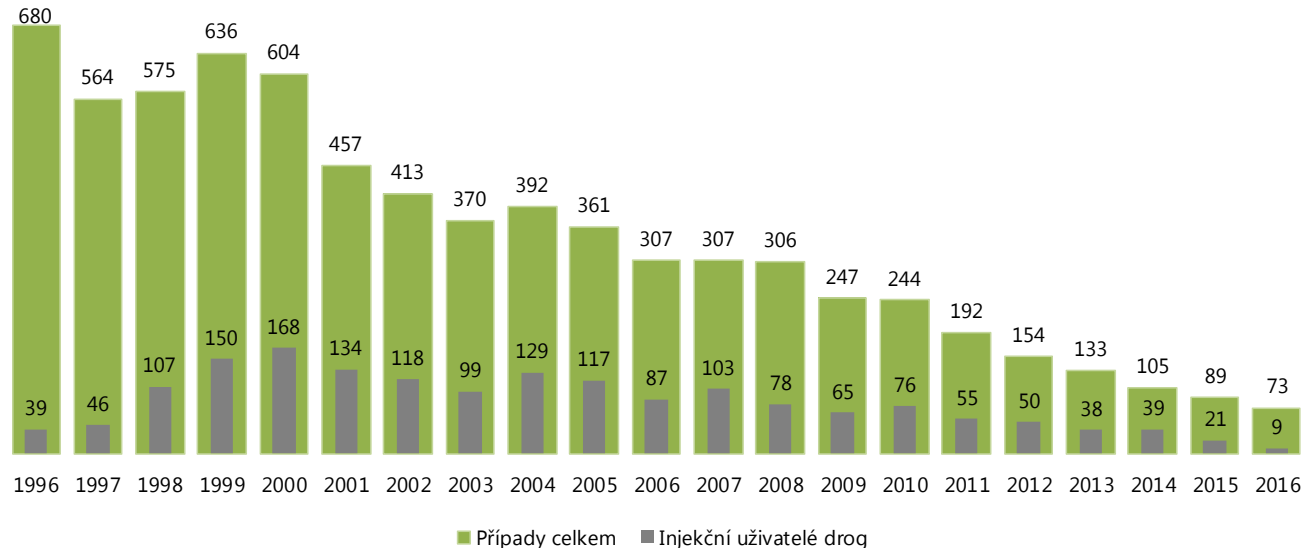


Opiates and pervitin abus

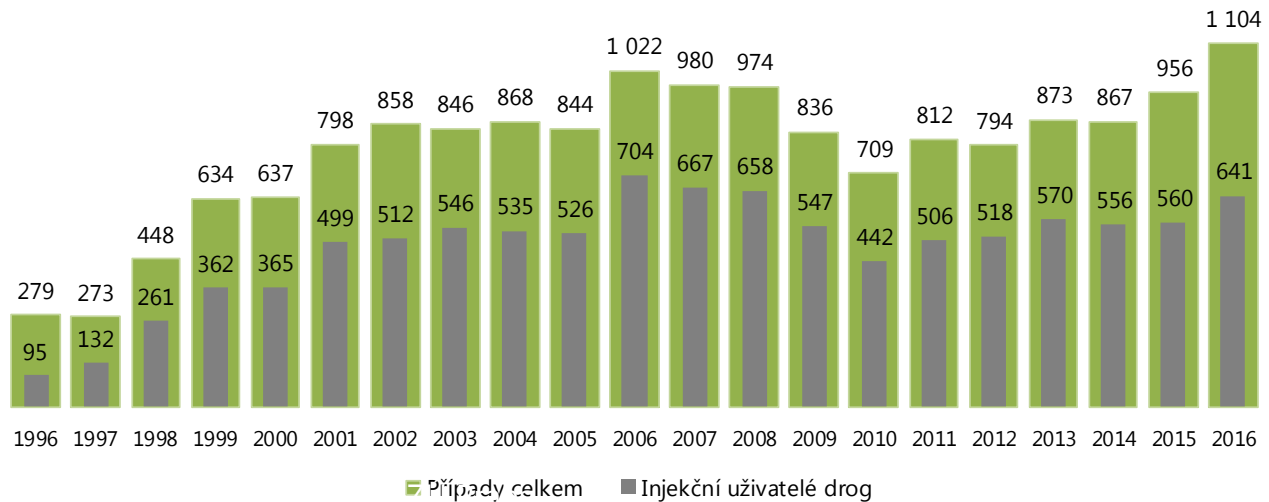


Infectious diseases in IUDs – new cases 1996-2016

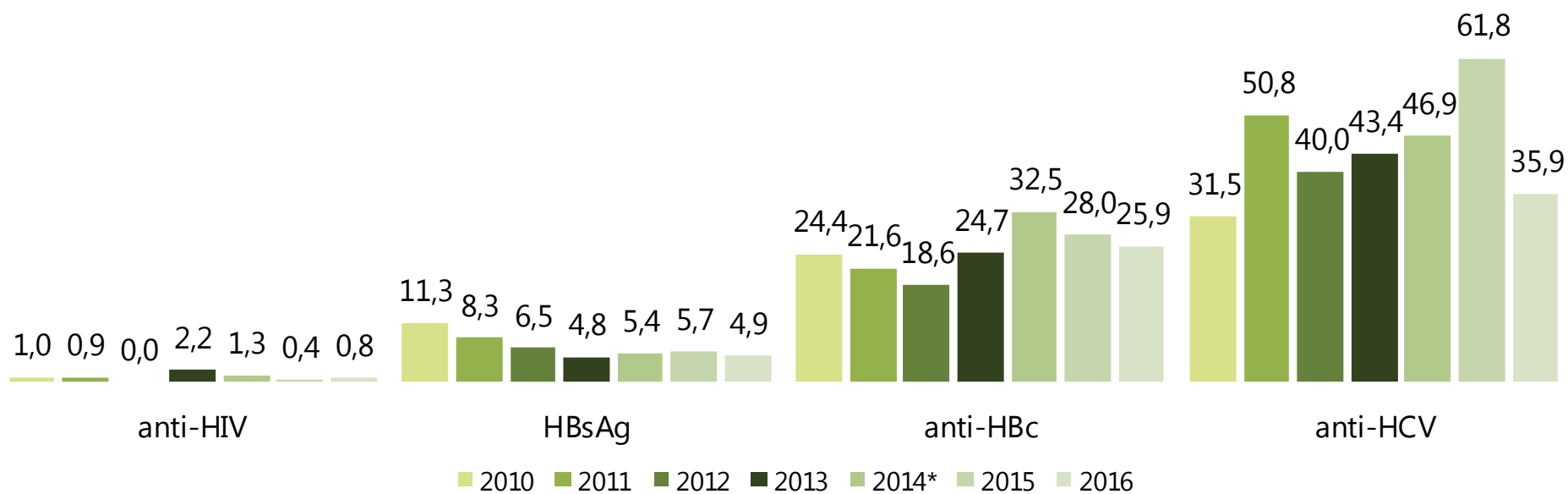
Acute HBV



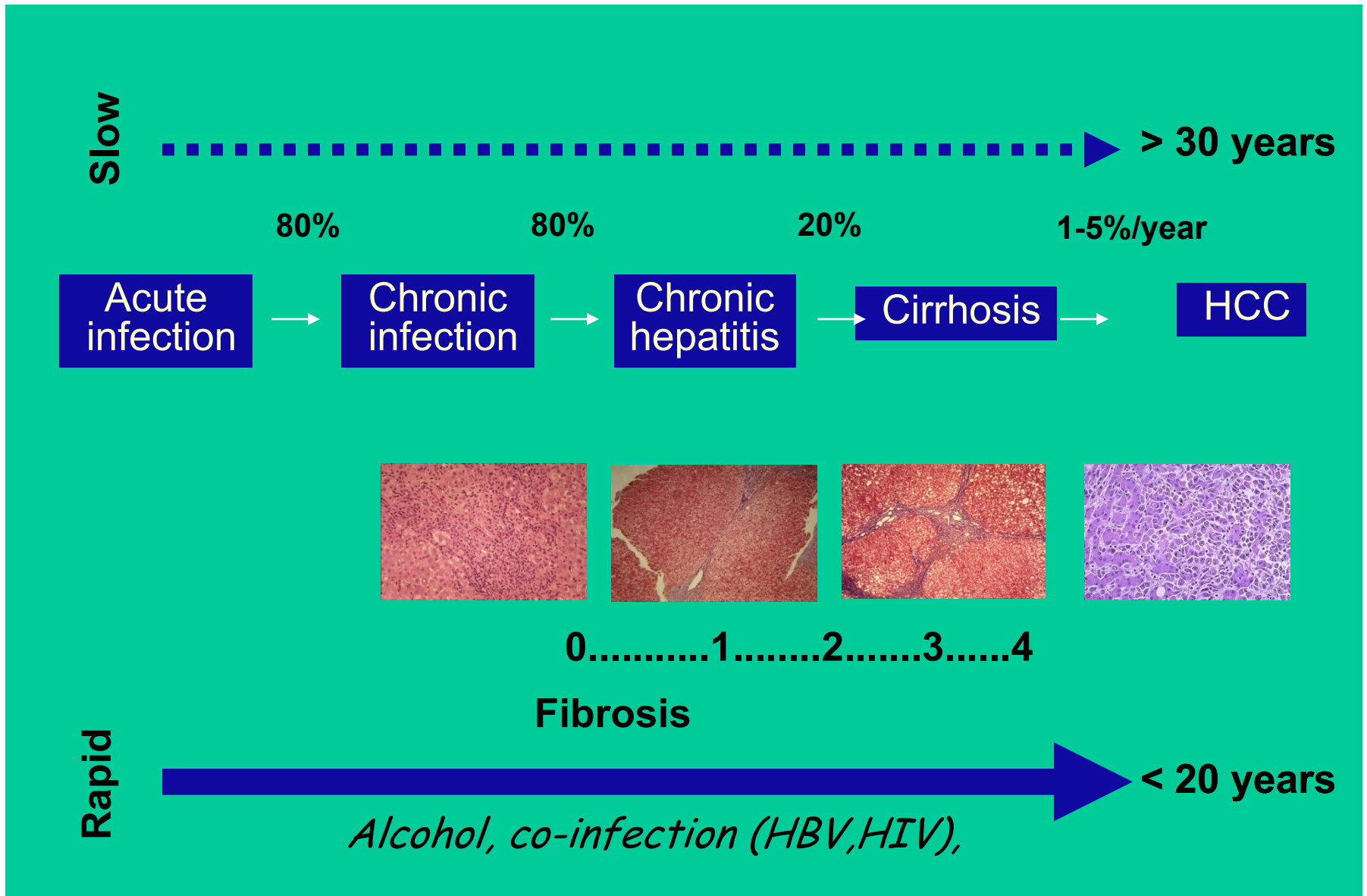
Acute and chronic HCV



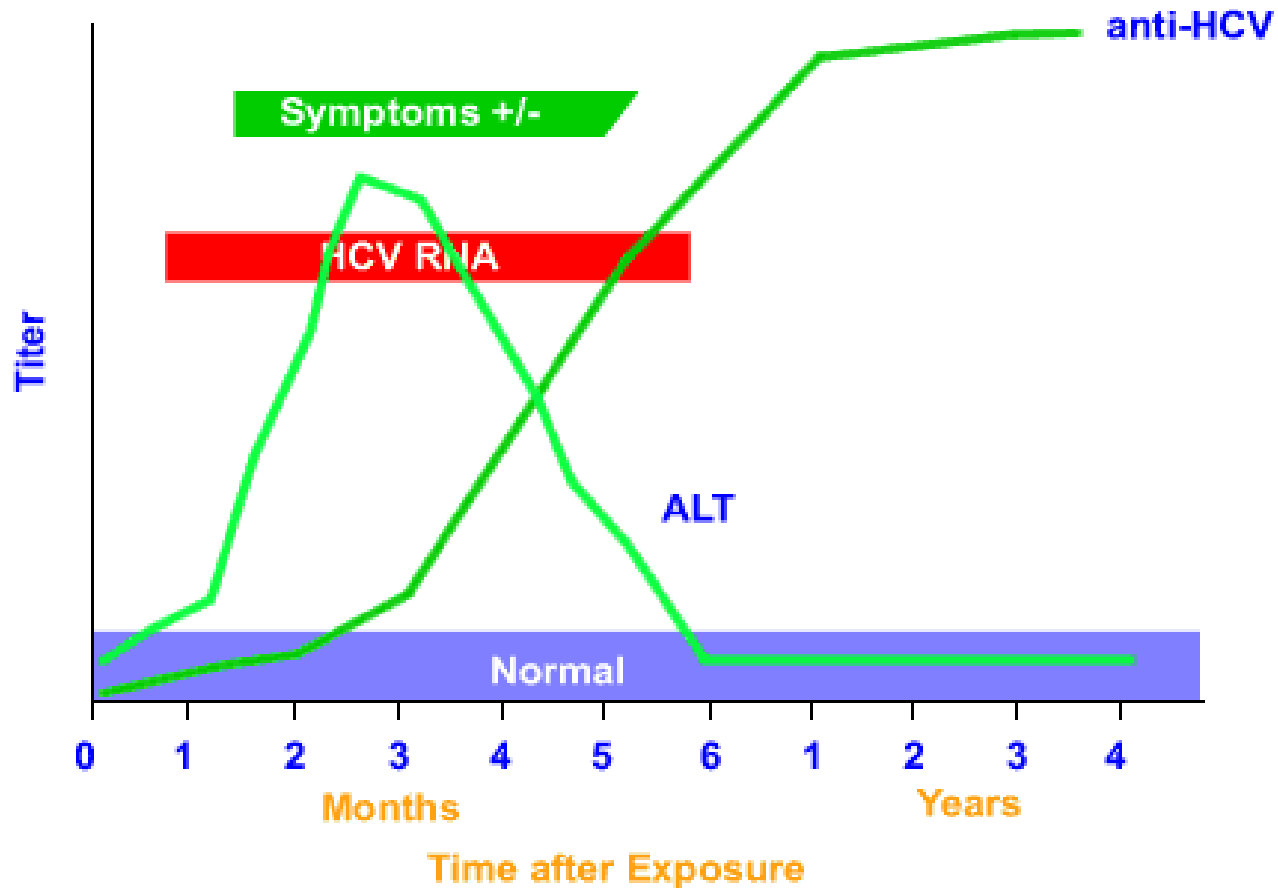
Infectious diseases in IUD in prison (%)



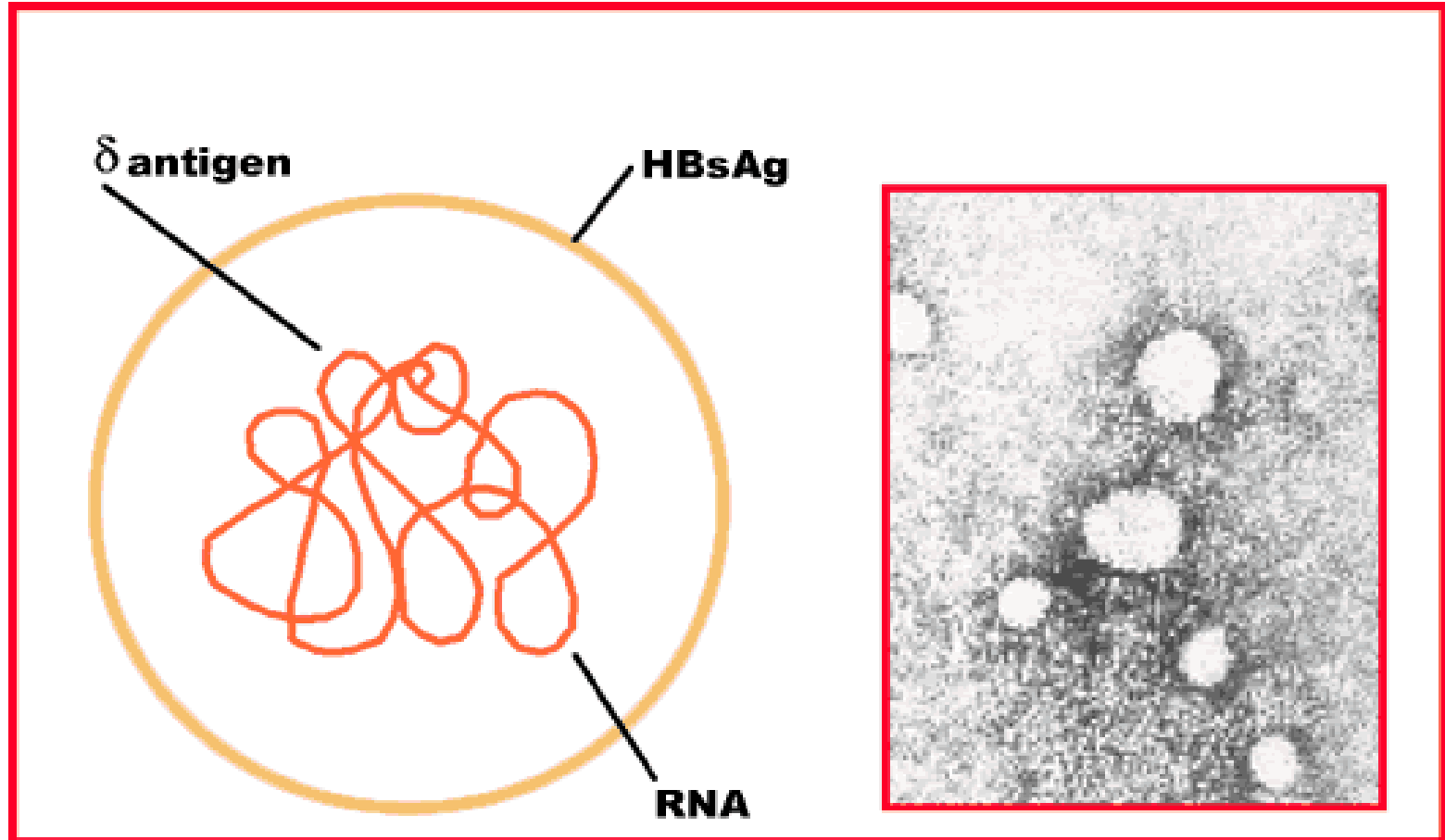
Clinical course of HCV infection



Diagnosis of HCV infection



Hepatitis D Virus (HDV)



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

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

1980s

-  **Endemic**
 -  **In risk groups**
- Drug addicts*



Rizzetto M. EASL 2009

Epidemiology of HDV in Europe

2009



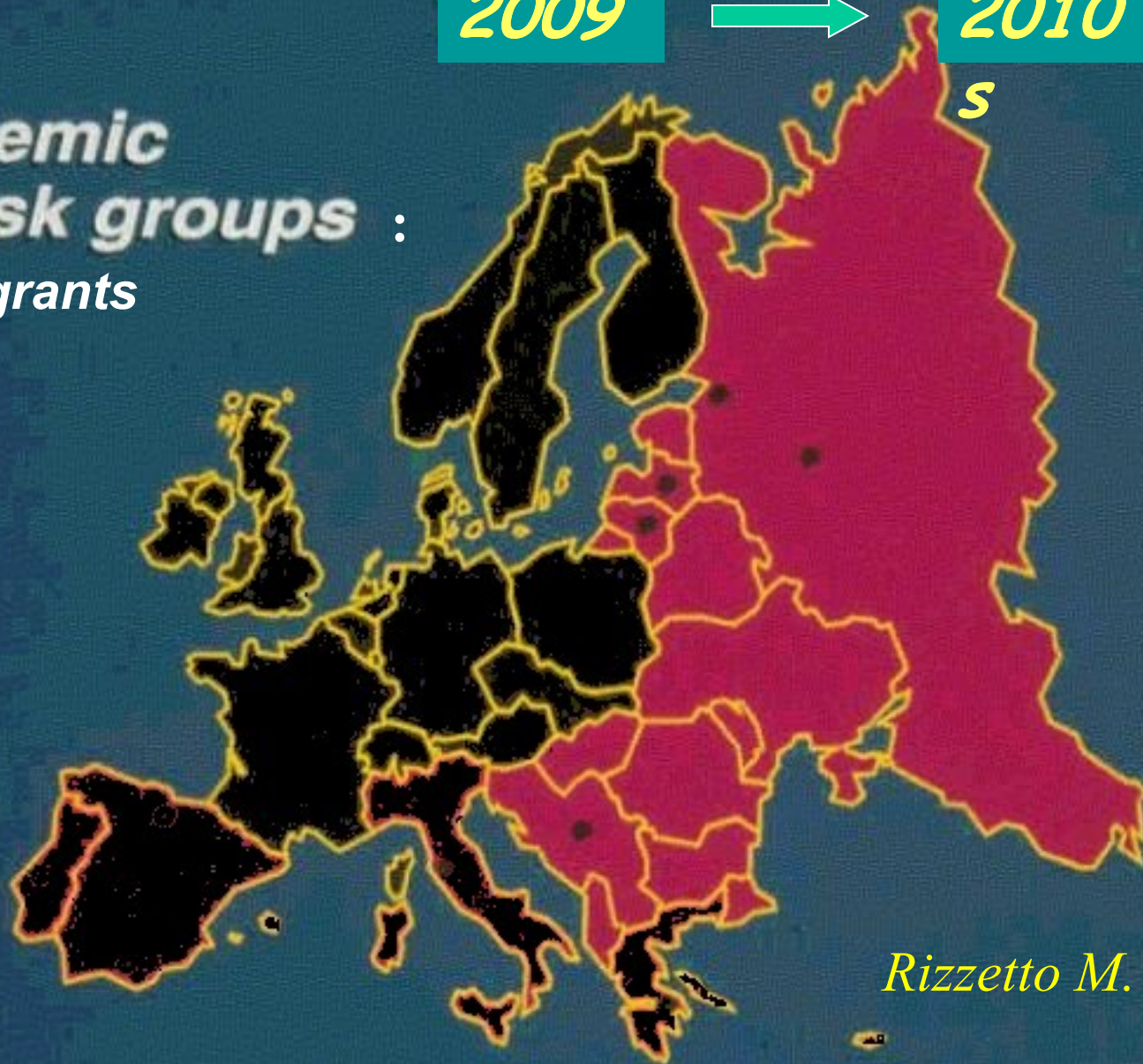
2010

5

 **Endemic**

 **In risk groups** :

- *immigrants*



Rizzetto M. EASL 2009

Significant incidence and prevalence (since 2006)

PAKISTANI¹

INDIA²

MONGOLIA³

IRAN⁴

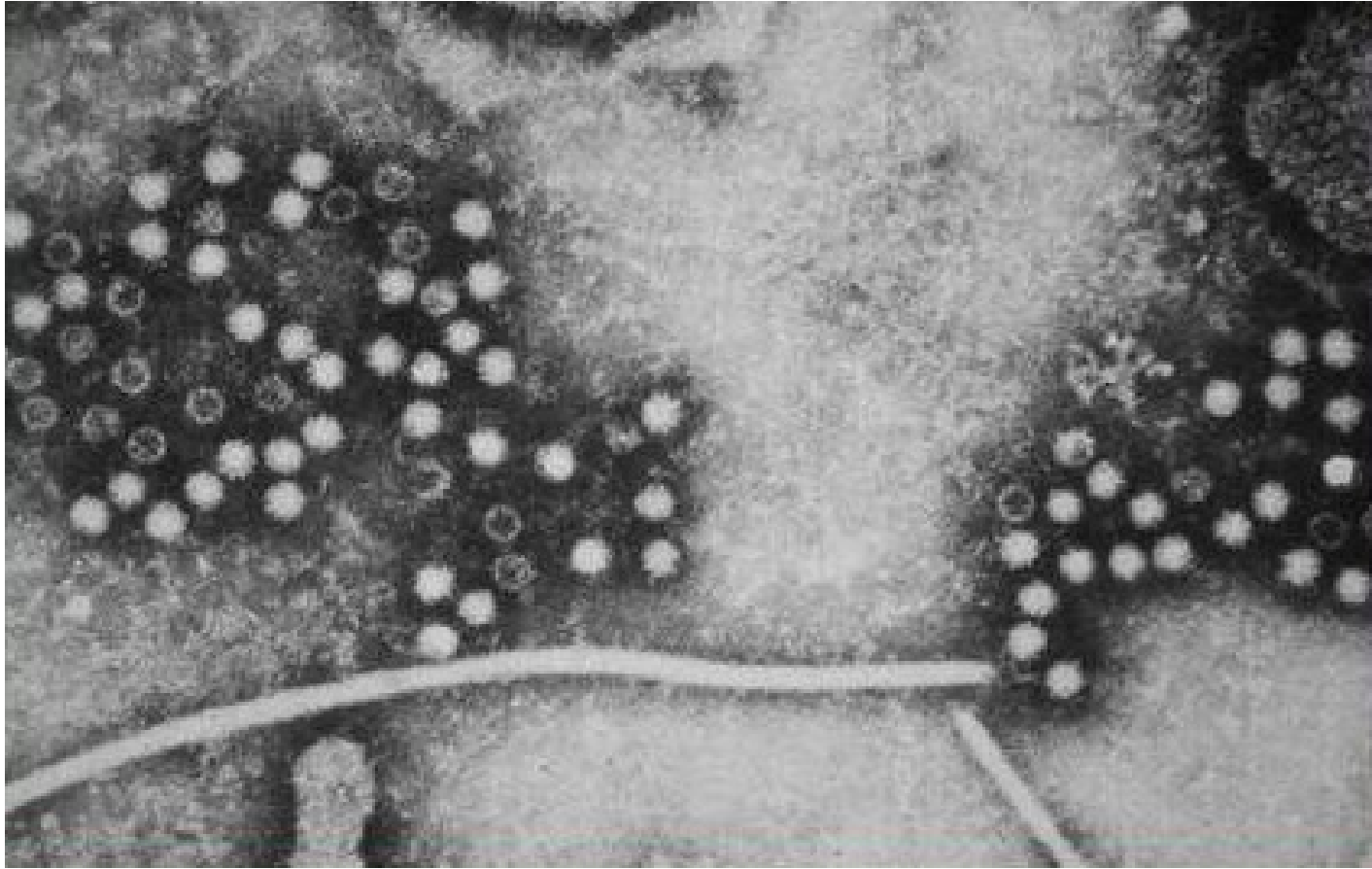
VIETNAM⁵

TAJIKISTAN⁶

TUNISIA⁷

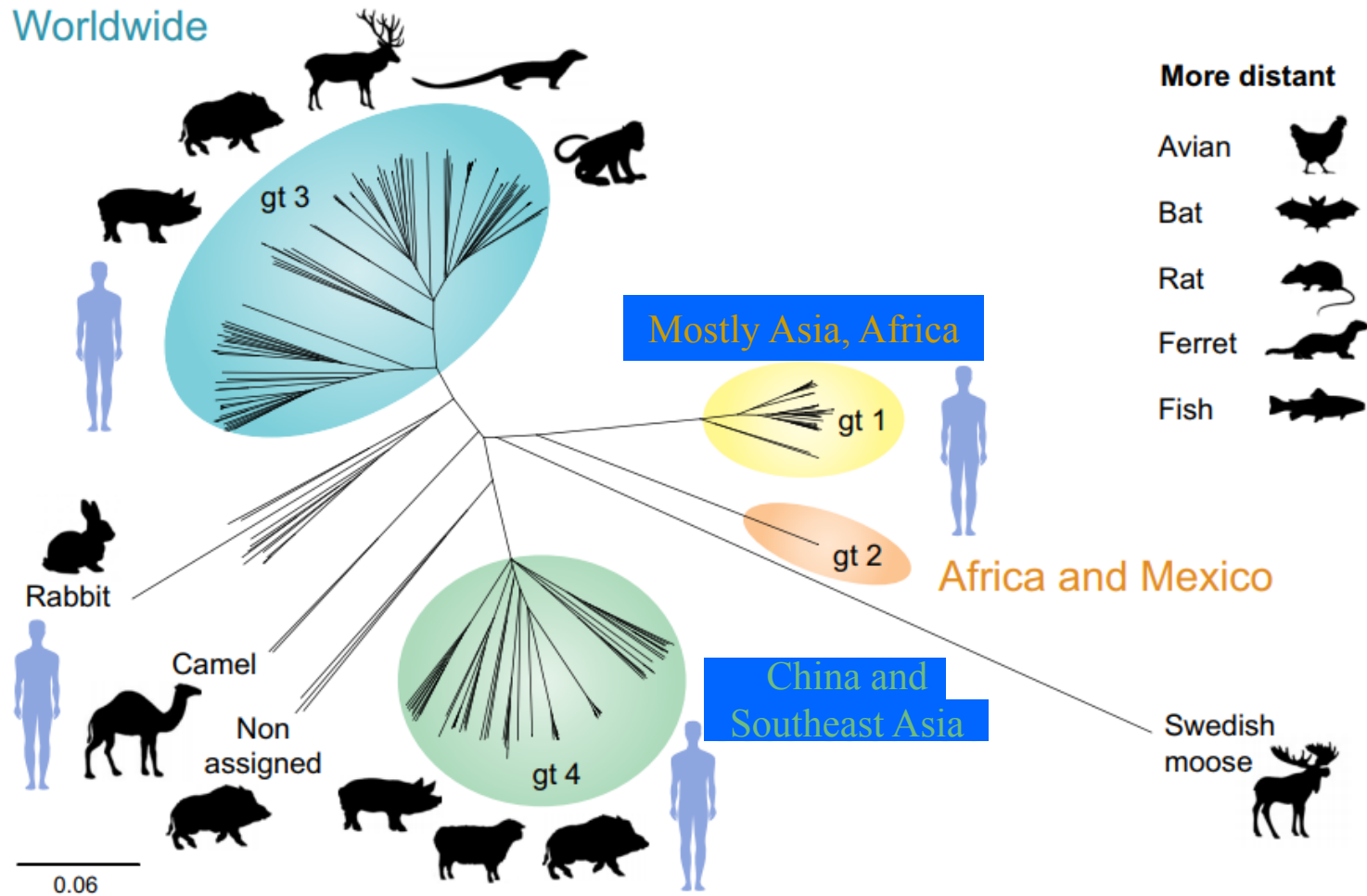
MAURETANIA⁸

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

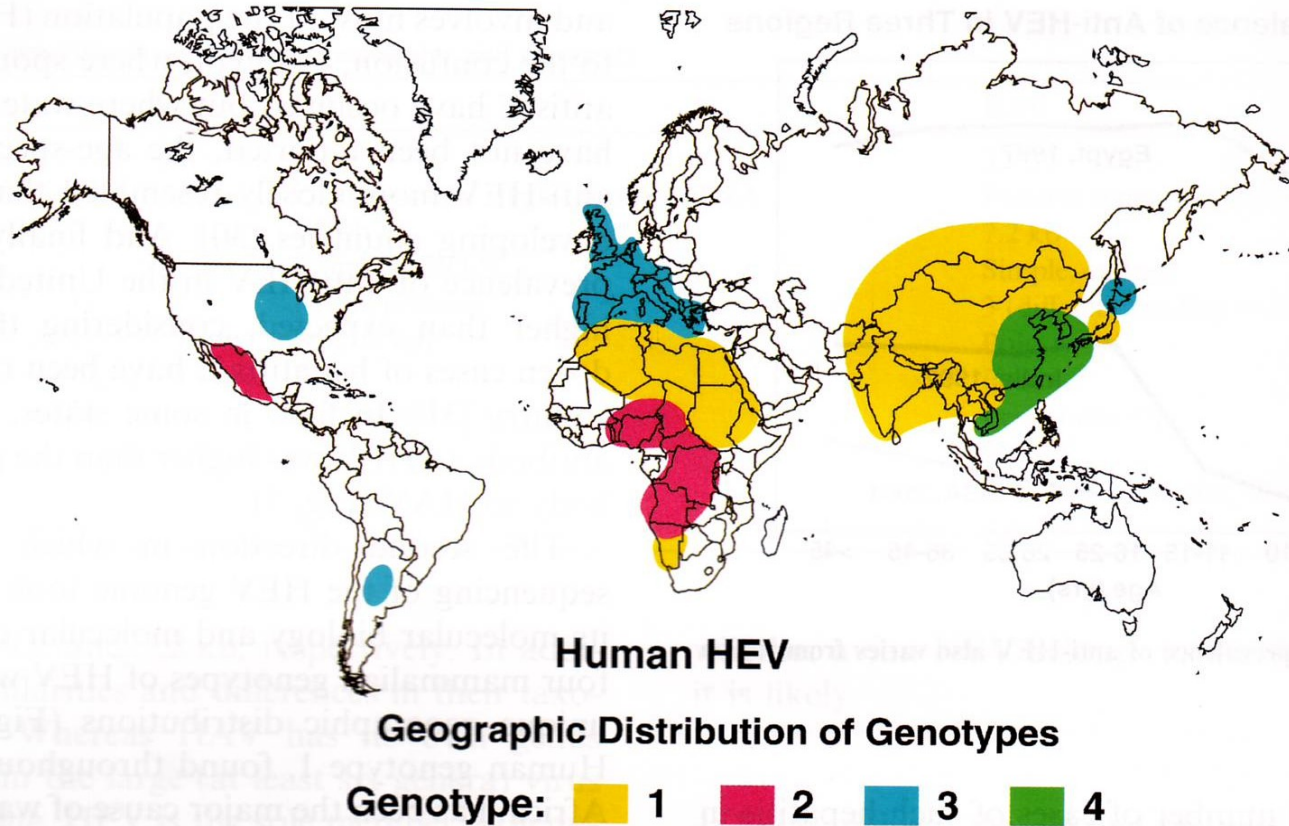


Fig. 4. Each of the four genotypes of HEV that infect humans has a distinct, and in some cases, overlapping geographic distribution.

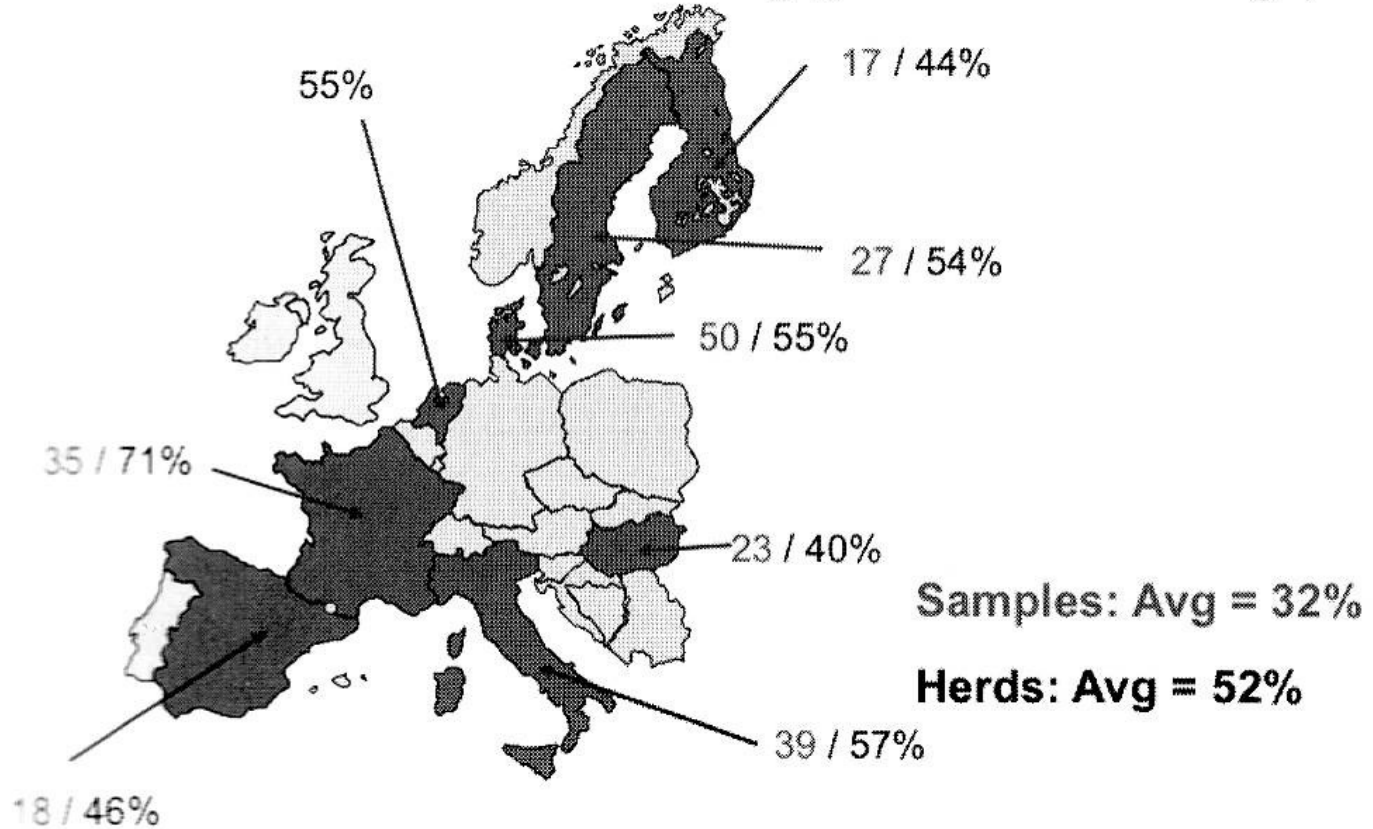
Infection with G-1,2 HEV

- 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 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)

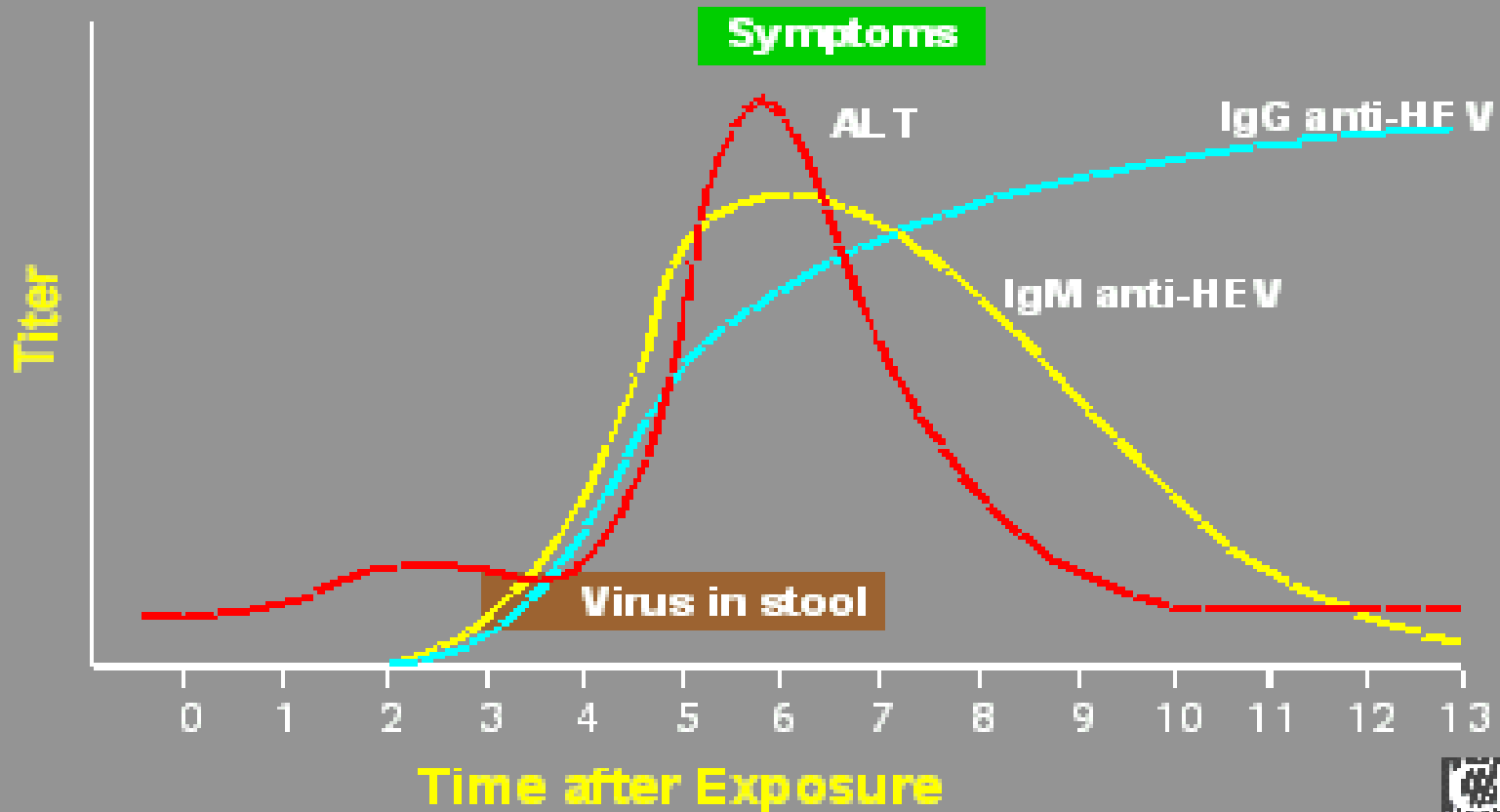


Figatellu – sausage with raw pork liver



Hepatitis E Virus Infection

Typical Serological Course



Rapid progression of chronic hepatitis E

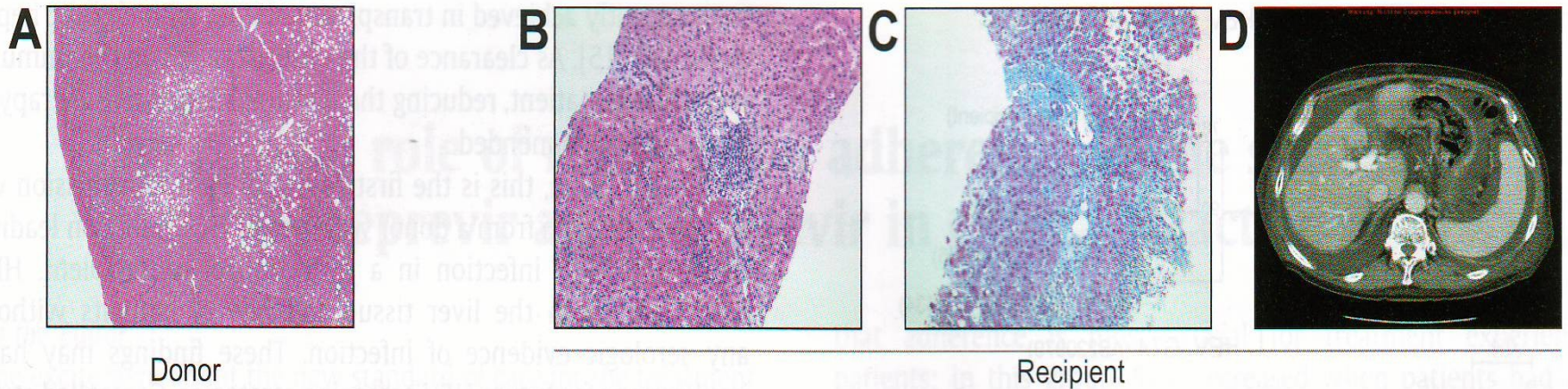


Fig. 1. Histologic assessment of the liver tissue before and after OLT and CT scan after OLT. (A) The liver tissue of the donor revealed absence of significant signs of chronic hepatitis but vesicular fatty liver disease was diagnosed. (B) Second biopsy. One hundred and fifty days after OLT, chronic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

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 disoproxil
 - ✓ entecavir
 - ✓ tenofovir alafenamid (?)
 - ✓ lamivudin
- Interferon alfa (standard or pegylated) is absolutely contra-indicated – danger of acute liver failure!

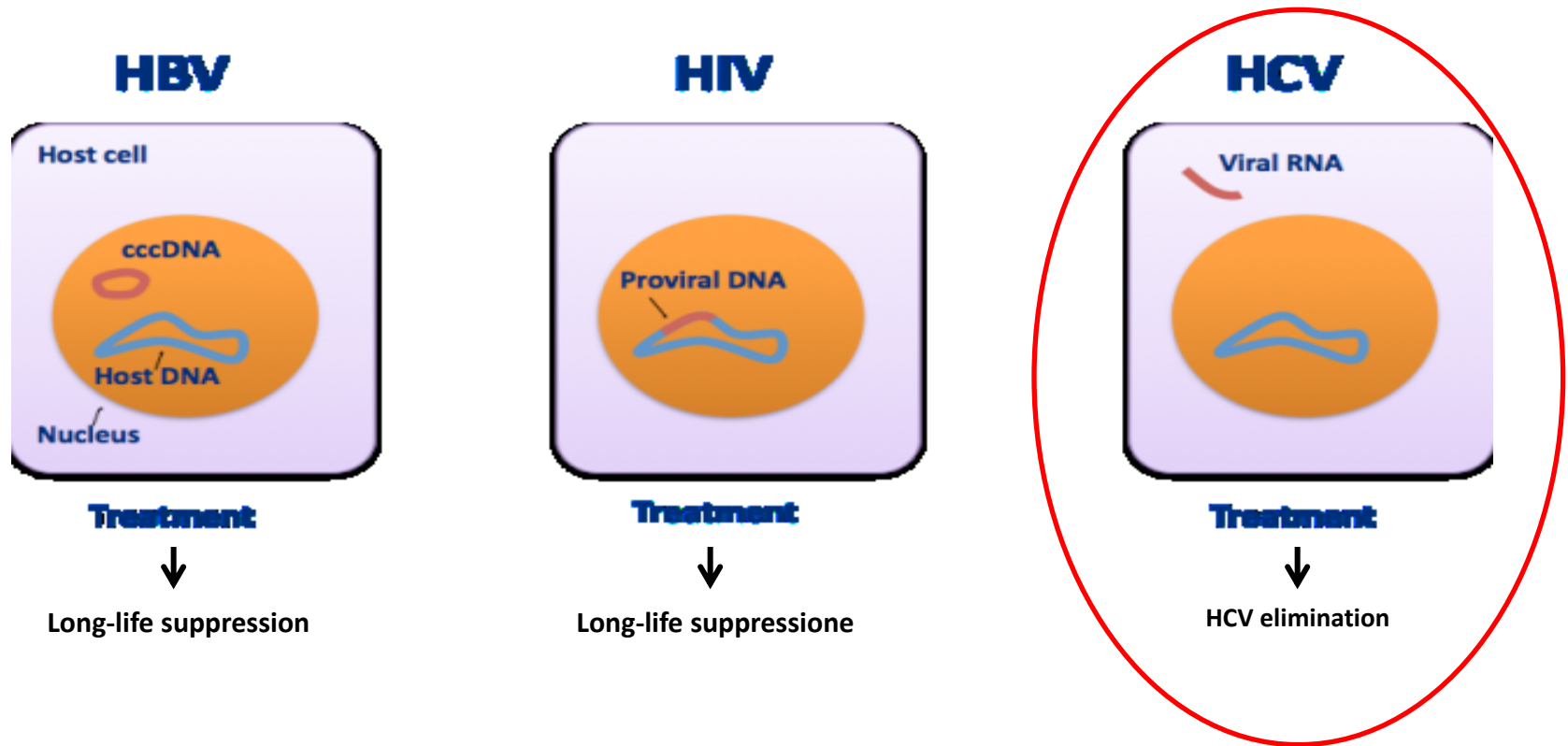
Current possibilities of treatment of chronic HEP B

- 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

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 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