Viral Hepatitis

Dr. Abdulwahhab S. Abdullah

CABM, FICMS-G&H

PROF. DR. SABEHA ALBAYATI

CABM,FRCP

Viral hepatitis

- *Viral hepatitis must be considered in any patient presenting with hepatitis on LFTs (high ALT & AST).*
- *Viral hepatitis is usually caused by 2 enterally-transmitted and 2 parenterally-transmitted hepatitis viruses.*
- *The enterically-transmitted viruses (hepatitis A and hepatitis E) cause acute self-limited hepatitis.*
- *The parenterally-transmitted viruses (hepatitis B and C) can cause acute or chronic hepatitis.*

Causes of viral hepatitis

- *Common:* *Hepatitis A*
  Hepatitis B (± D)
  Hepatitis C
  Hepatitis E

- *Less common:* *Cytomegalovirus*
  Epstein–Barr virus

- *Rare:* *Herpes simplex*
  Yellow fever

Clinical features of acute viral hepatitis

Acute viral hepatitis can be: *Asymptomatic*
Anicteric
Icteric (jaundice)

A typical episode includes:

- *Prodromal period (few days to 2 weeks): malaise, nausea, anorexia.*
- *Icteric period (1-4 weeks): jaundice heralded by darkening of urine often with improvement of prodromal symptoms.*
- *Recovery period (few weeks to several months): rapid in children, slow in adults*

Clinical features of acute viral hepatitis

Signs may include Jaundice, tender hepatomegaly, splenomegaly, and cervical lymphadenopathy.

Possible complications include:

- *Acute liver failure (especially HEV in pregnancy)*
- *Chronic liver disease & cirrhosis (HBV & HCV)*
- *Prolonged cholestasis (HAV & HEV)*
- *Relapses (especially HAV)*
- *Aplastic anemia*

Lab tests in acute viral hepatitis

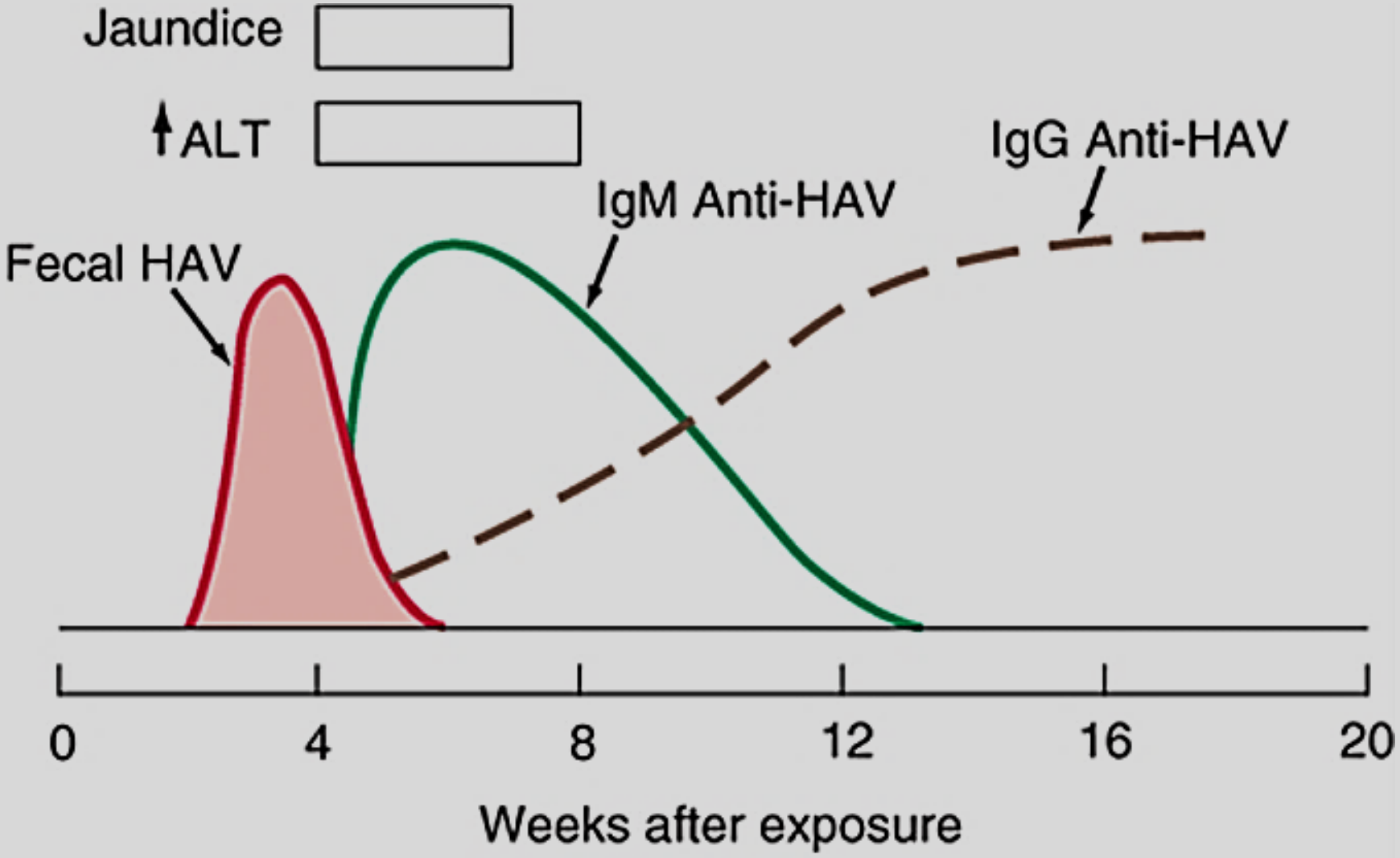
- *Hepatitic pattern of LFTs (ALT and AST several hundreds to several thousands U/L and ALP less than 2-3 times the upper limit of normal).*
- *PT (INR) indicates the severity of hepatitis, and PT >25 sec usually indicates acute liver failure.*
- *CBC may only show relative lymphocytosis.*
- *Serological tests (IgM Ab) confirm the diagnosis.*

Management of acute viral hepatitis

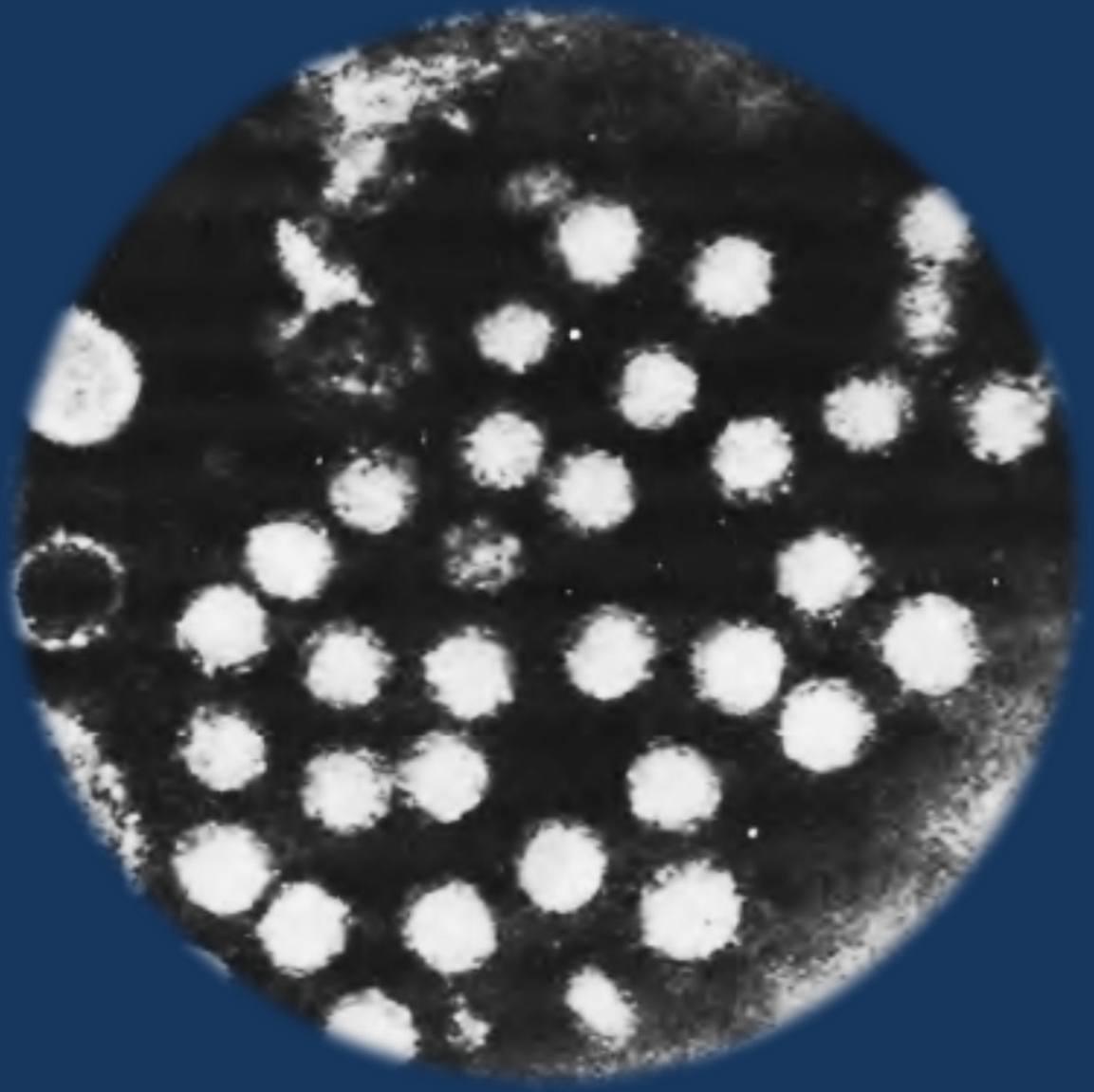
- *Outpatient supportive therapy is appropriate for most patients. Antivirals are not used.*
- *Hepatotoxic drugs (e.g. paracetamol), sedatives, and alcohol should be avoided.*
- *No special diet is recommended.*
- *Elective surgery must be postponed after recovery.*
- *Persistent nausea/vomiting, any mental confusion, and prolonged PT warrants hospitalization.*
- *Liver transplantation may be indicated in patients with the rare complication of fulminant hepatitis.*

Hepatitis A

- *Hepatitis A virus (HAV) is the commonest cause of acute viral hepatitis.*
- *HAV is an RNA picornavirus (enterovirus).*
- *HAV is highly infectious, transmitted feco-orally with an average incubation period of 2-4 weeks.*
- *Infection is more common in overcrowded areas with poor hygiene and sanitation.*
- *HAV is present in stool for 2 weeks before and 2 weeks after onset of symptoms with maximal infectivity just before the onset of jaundice.*



Source: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine, 18th Edition*: www.accessmedicine.com



Electron microscopy of hepatitis A virions in feces. These are shown as 27 nm spheres. (× 250 000.)

Hepatitis A

- *The presence and severity of symptoms depend on the patient's age:*

About 70% of adults develop symptoms, including jaundice. In contrast, only 10-30% of children <6 years old develop symptoms, which usually are non-specific and flu-like without jaundice.

Mortality (fulminant hepatitis) occur in 0.1% of patients aged <14 yr and in 2% of those >40 yr.

Investigations in hepatitis A

- *Liver biochemistry:*

Prodromal stage:
Serum bilirubin is normal (bilirubinuria may be found).
Serum ALT & AST is elevated.

Icteric stage:
Serum bilirubin is elevated and ALP is usually <3x ULN.
ALT reach a peak 1–2 days after onset of jaundice.

After jaundice subsides, ALT & AST may remain elevated for some weeks and occasionally for up to 6 months.

Investigations in hepatitis A

- *Hematological tests:*

Leucopenia with a relative lymphocytosis.
Very rarely Coombs'-positive hemolysis or aplastic anemia.
PT is prolonged in severe cases.
ESR is raised.

- *Viral markers:*

IgM anti-HAV is diagnostic of acute hepatitis A.

IgG anti-HAV denotes past exposure and immunity.

Course and prognosis of hepatitis A

- *Prognosis is excellent in most patients.*
- *Mortality in young adults is 0.1% but it increases with age.*
- *Recovery may be complicated by relapse of the hepatitis in 5-15% of cases followed by resolution.*
- *Adult patients may have a prolonged cholestatic phase with elevated ALP for up to several months.*
- *Patients with underlying chronic liver disease and the elderly with comorbidities may have a serious or life-threatening disease course.*

Prevention of hepatitis A

- *In the community, improving social conditions of overcrowding, poor hygiene and sanitation is vital.*
- *Active immunization with inactivated vaccine, especially during outbreaks, and for people at risk of severe disease, such as the elderly and patients with chronic hepatitis B or C is recommended.*
- *Passive immunization (post-exposure prophylaxis) of close contacts within 2 weeks using immune serum globulin can prevent secondary spread of HAV.*

Hepatitis E

- *Hepatitis E is caused by an RNA virus that is endemic in India and the Middle East.*
- *Transmission, clinical features, diagnosis and management of HEV are similar to that of HAV.*
- *HEV vaccine has been developed recently.*
- *HEV differs from HAV in two aspects:*

1. *High mortality (20%) reported in pregnancy.*
2. *Chronic infection reported in some immune-compromised patients.*


Take a deep breath
It calms the mind

What is "chronic hepatitis"?

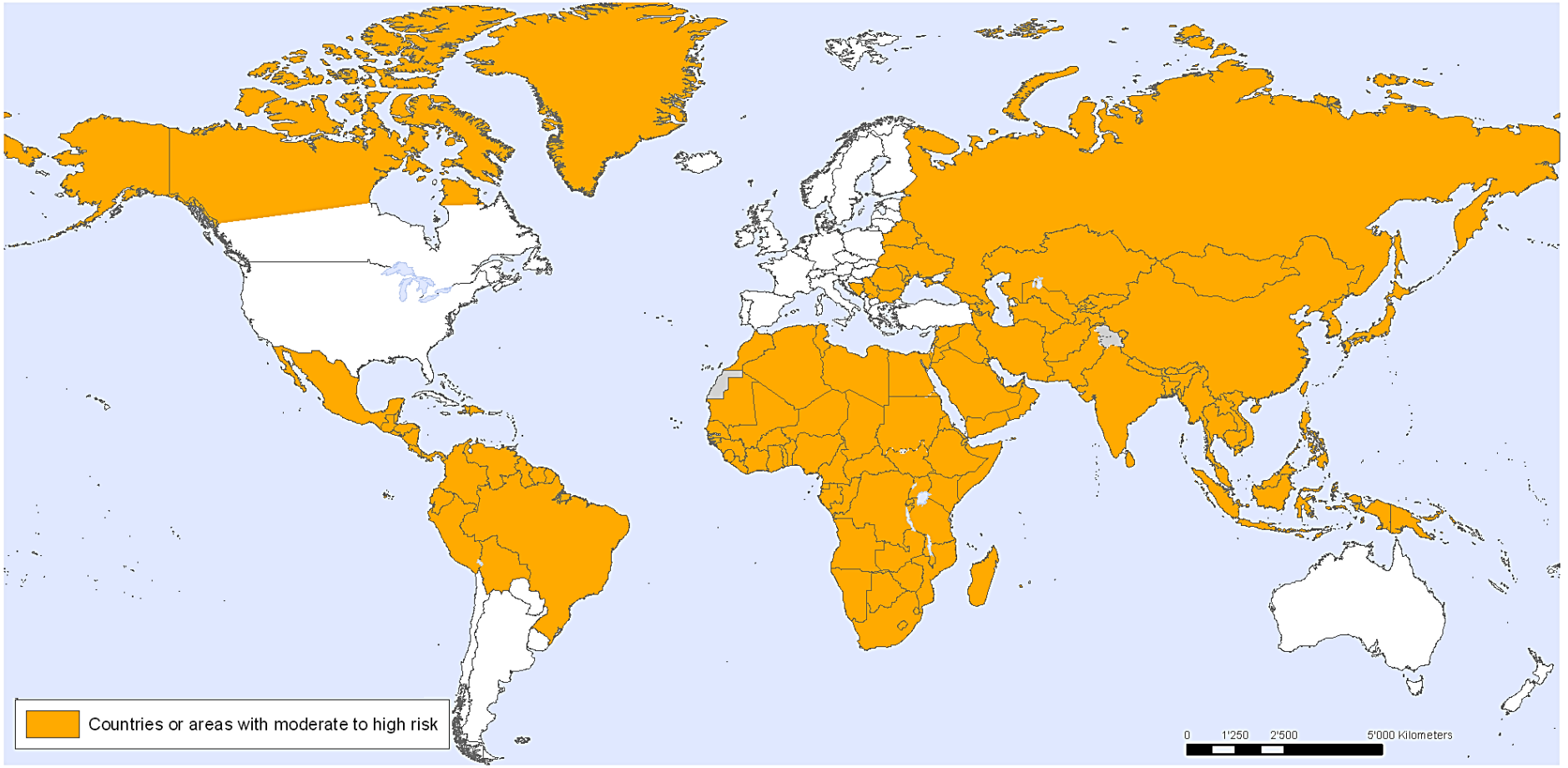
- *Chronic hepatitis is a liver disorder in which hepatic necroinflammatory activity continues for at least 6 months.*
- *Hepatitis B and C are the most common causes of chronic hepatitis worldwide.*
- *Patients with chronic viral hepatitis are usually asymptomatic until they develop cirrhosis.*

Hepatitis B
What's the size of the problem?

- *Globally, hepatitis B is a major cause of cirrhosis (chronic liver disease), fulminant hepatitis (acute liver failure), and hepatocellular cancer, with over 1 million deaths annually.*

- *Prevalence of chronic hepatitis B varies geographically (0.5-2% in Western Europe and USA and 10-20% in parts of Africa, the Middle East and the Far East).*

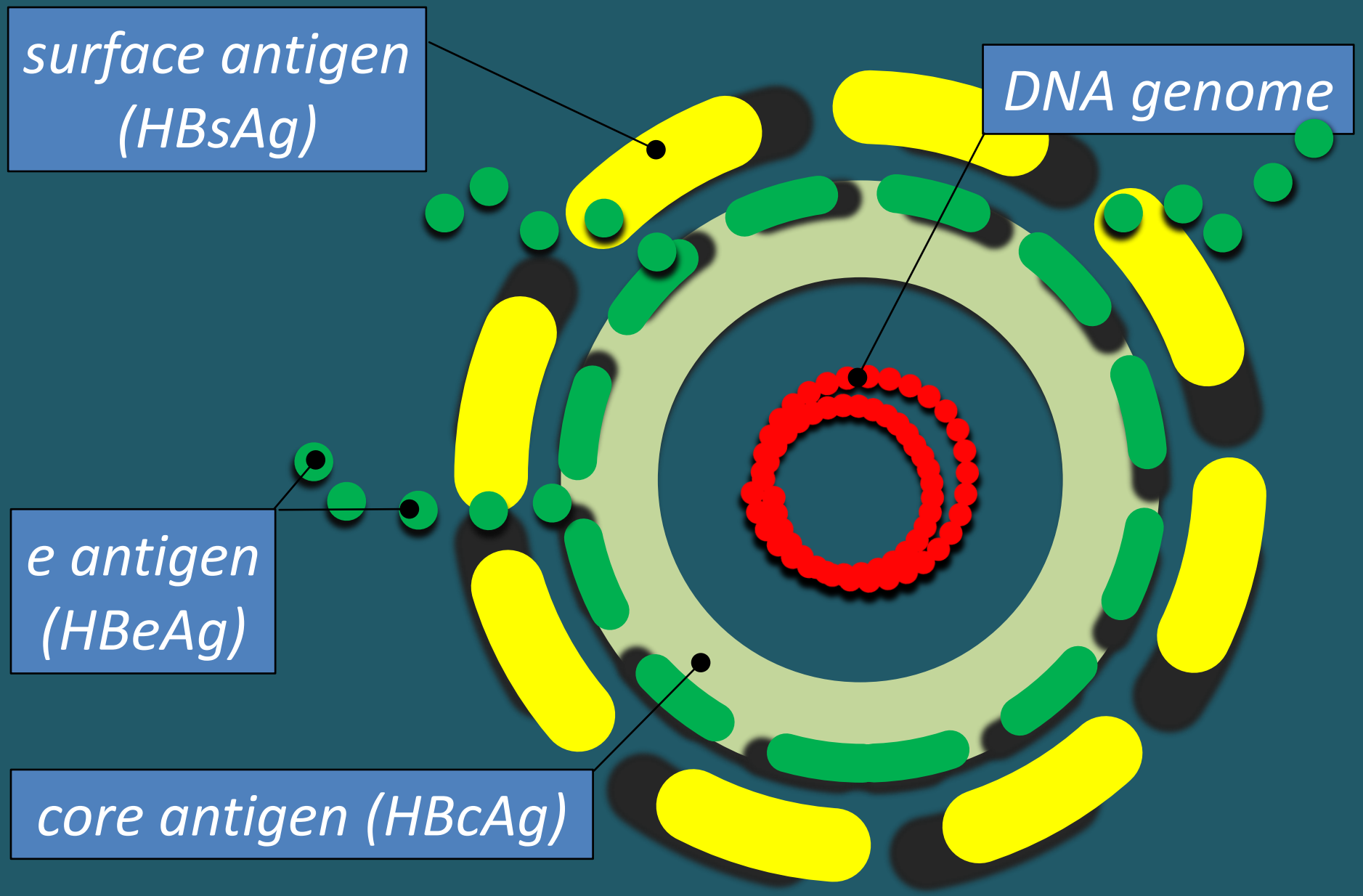
Hepatitis B, countries or areas at risk

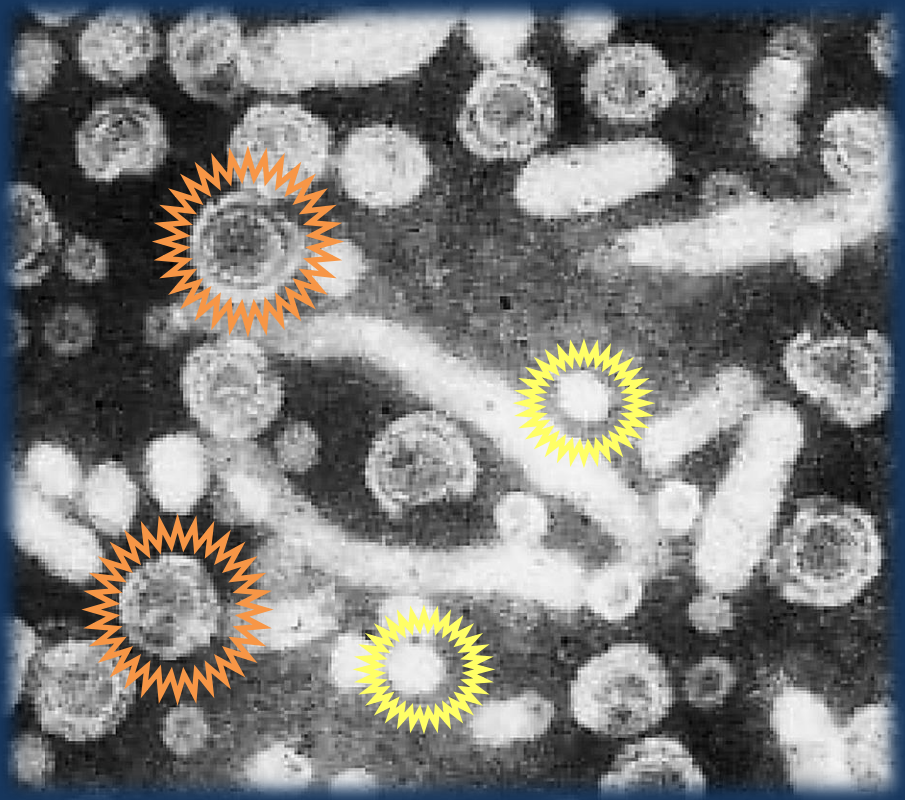


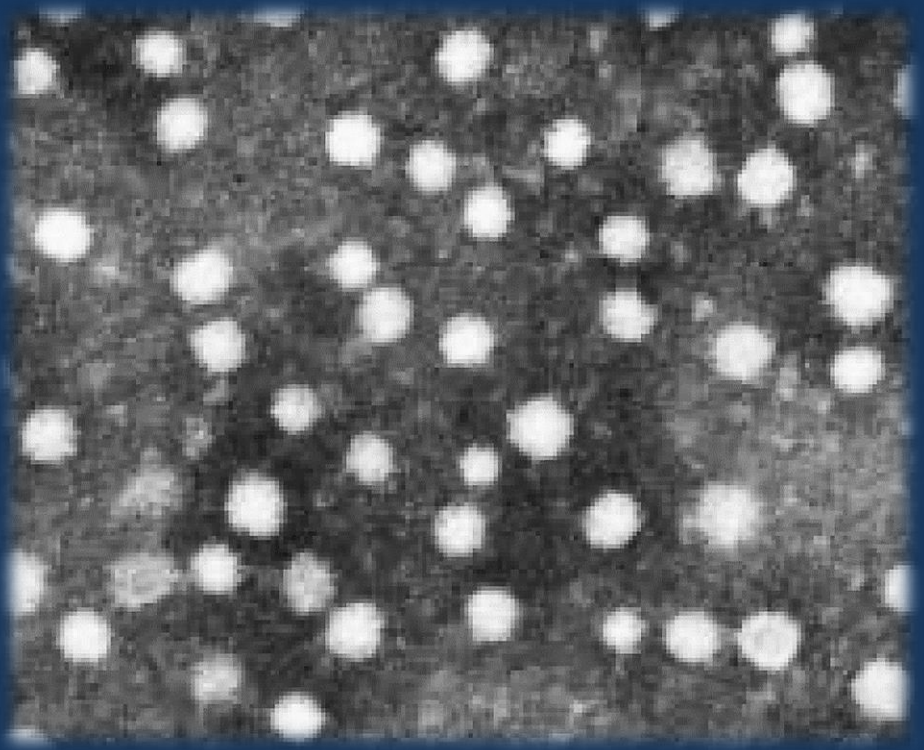
Data Source: World Health Organization/CDC
Map Production: Public Health Information and Geographic Information Systems (GIS)
World Health Organization

World Health Organization

Structure of HBV (Dane particle)







How is HBV transmitted?

- *Perinatal (mother to child at birth)*
- *Close contact among young children*
- *Sexual*
- *Contaminated needles and tools (iv drug use, tattooing, acupuncture, razors, etc..)*
- *Infected unscreened blood products (rare)*

How is HBV transmitted?

The main route of transmission varies by geographical region:

- *In high-prevalence areas:*
  - *vertical (perinatal)*
  - *horizontal (close contact among toddlers)*
- *In low-prevalence areas:*
  - *sexual*
  - *iv drug abuse*

Does HBV cause acute or chronic infection?

- *Upon exposure to HBV, the risk of progression from acute to chronic infection is inversely related to the patient's **age** at time of infection:*

Risk of chronic HBV infection

Rate of chronic infection	Age at time of infection

Risk of chronic HBV infection

Rate of chronic infection	Age at time of infection
90-95%	at birth

Risk of chronic HBV infection

Rate of chronic infection	Age at time of infection
90-95%	at birth
20-50%	children < 5 years-old

Risk of chronic HBV infection

Rate of chronic infection	Age at time of infection
90-95%	at birth
20-50%	children < 5 years-old
1-10%	Older children and adults

What are the possible clinical presentations of hepatitis B?

- *Silent chronic infection is common in children while symptomatic acute infection often occur in adults.*
- *Acute hepatitis B: Jaundice, malaise, and RUQ pain may develop 1-4 months after infection.*
- *Acute (fulminant) liver failure is rare (up to 1% of adults).*
- *Chronic hepatitis B: defined by persistent HBsAg in serum for >6 months. Patients are usually asymptomatic until cirrhosis develops.*

What are the complications and prognosis of chronic hepatitis B?

- *Cirrhosis and decompensation (chronic liver failure), such as ascites, variceal bleeding, encephalopathy, etc…*
- *Hepatocellular carcinoma (usually in cirrhotics)*
- *Other: Membranous glomerulonephritis*
  Polyarteritis nodosa (vasculitis)

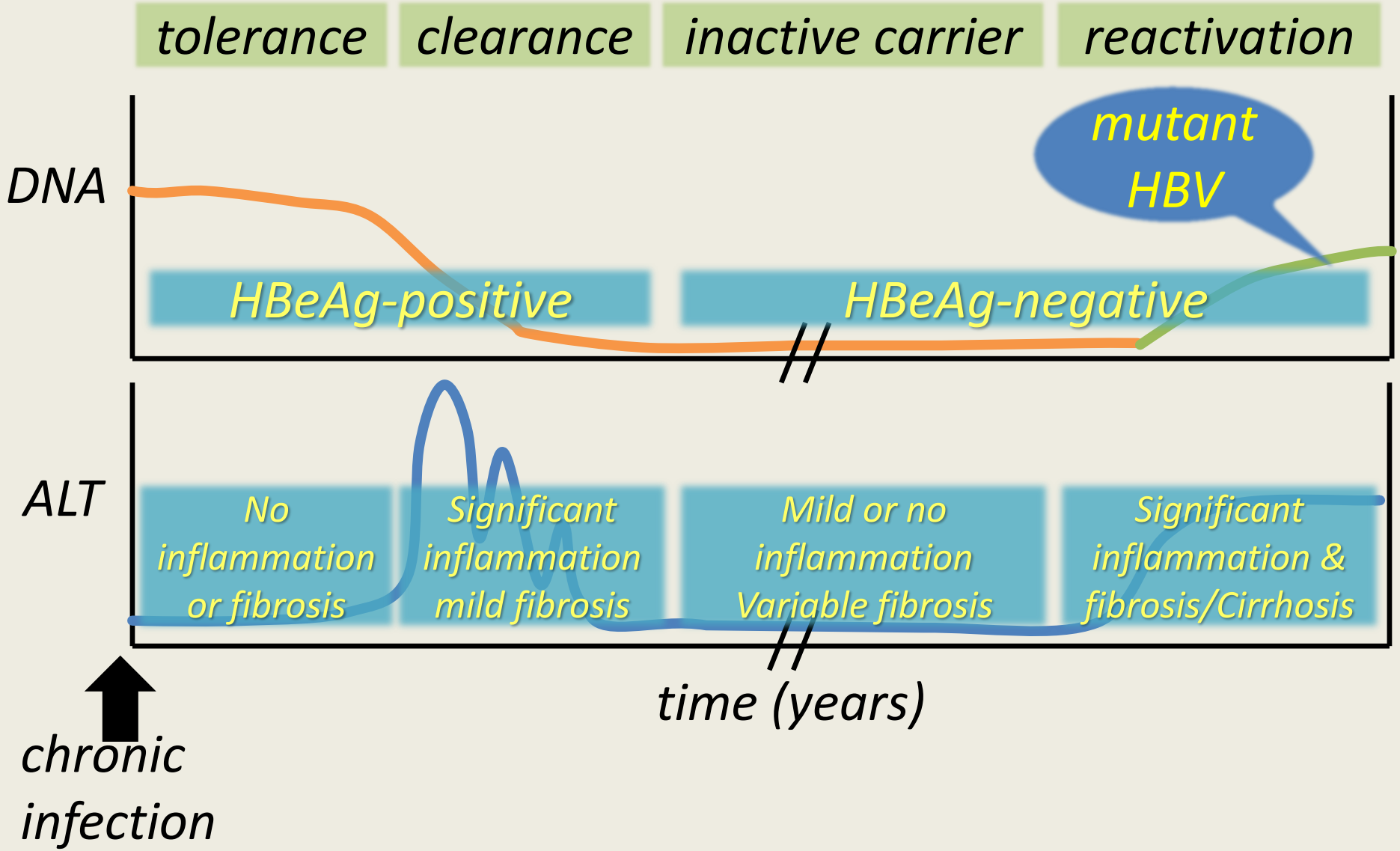
How to diagnose hepatitis B?

Surface antigen (HBsAg)	*Current infection (6/12?)*
Surface antibody (anti-HBs)	*Immunity (anti-HBc?)*
IgM core antibody (IgM anti-HBc)	*Recent infection (flare?)*
IgG core antibody (IgG anti-HBc)	*Remote infection (HBsAg?)*
e antigen (HBeAg)	*High replication (always)*
e antibody (anti-HBe)	*?Low replication (DNA?)*
HBV DNA (viral load)	
>20,000 IU/L	*High replication (HBeAg±)*
<20,000 IU/L	*Low replication (HBeAg-)*

What is the natural history of chronic hepatitis B?

- *Chronic HBV infection is a dynamic process that can be divided into 4 phases. These are not necessarily sequential and not all patients will go through all of them.*

- *HBV is not directly cytopathic but a prolonged ineffective immune response in patients with chronic hepatitis B can mediate liver damage.*


tolerance
clearance
inactive carrier
reactivation
DNA
mutant HBV
HBeAg-positive
HBeAg-negative
ALT
No inflammation or fibrosis
Significant inflammation mild fibrosis
Mild or no inflammation Variable fibrosis
Significant inflammation & fibrosis/Cirrhosis
time (years)
chronic infection

How to manage a patient with acute hepatitis B?

- *Supportive care and monitoring for acute liver failure (<1%). Antivirals are usually not used.*
- *Full recovery expected in 90-95% of immune-competent adults and remaining 5-10% develop chronic infection that usually persists for life.*
- *Resolution occurs within 6/12 and is shown by:*

  HBsAg (-), HBeAg (-), anti-HBs (+)
- *Progression to chronicity is shown on follow up by:*

  HBsAg (+) for >6/12 ***or*** *HBeAg (+) for >3/12*

How to manage a patient with chronic hepatitis B?

- *The goal is to prevent cirrhosis and cancer (HCC) by clearing HBsAg but this is **not** yet achievable.*
- *Current aims: HBeAg seroconversion (if HBeAg+)*

  low or undetectable HBV DNA

  normal serum ALT
- *Treatment is indicated for patients with:*

  *-high viral load **and***

  *-active hepatitis (↑ALT **or** significant inflammation & fibrosis on liver biopsy)*

Which drugs are used for chronic hepatitis B?

- *Monotherapy with 1 of 2 types of drugs is used:*

a. nucleos(t)ide analogues (single daily oral tab):

Best for HBeAg- patients and those with cirrhosis

***Entecavir** or **Tenofovir**: 1st choice but expensive*

***Lamivudine**: cheaper but resistance is a problem*

Adefovir,Telbivudine: expensive & not so effective

b. pegylated interferon-α (weekly s.c. injection):

Best for pre-cirrhotics with HBeAg+ and ↑ALT.

Side effects is the main problem.

How to prevent hepatitis B?

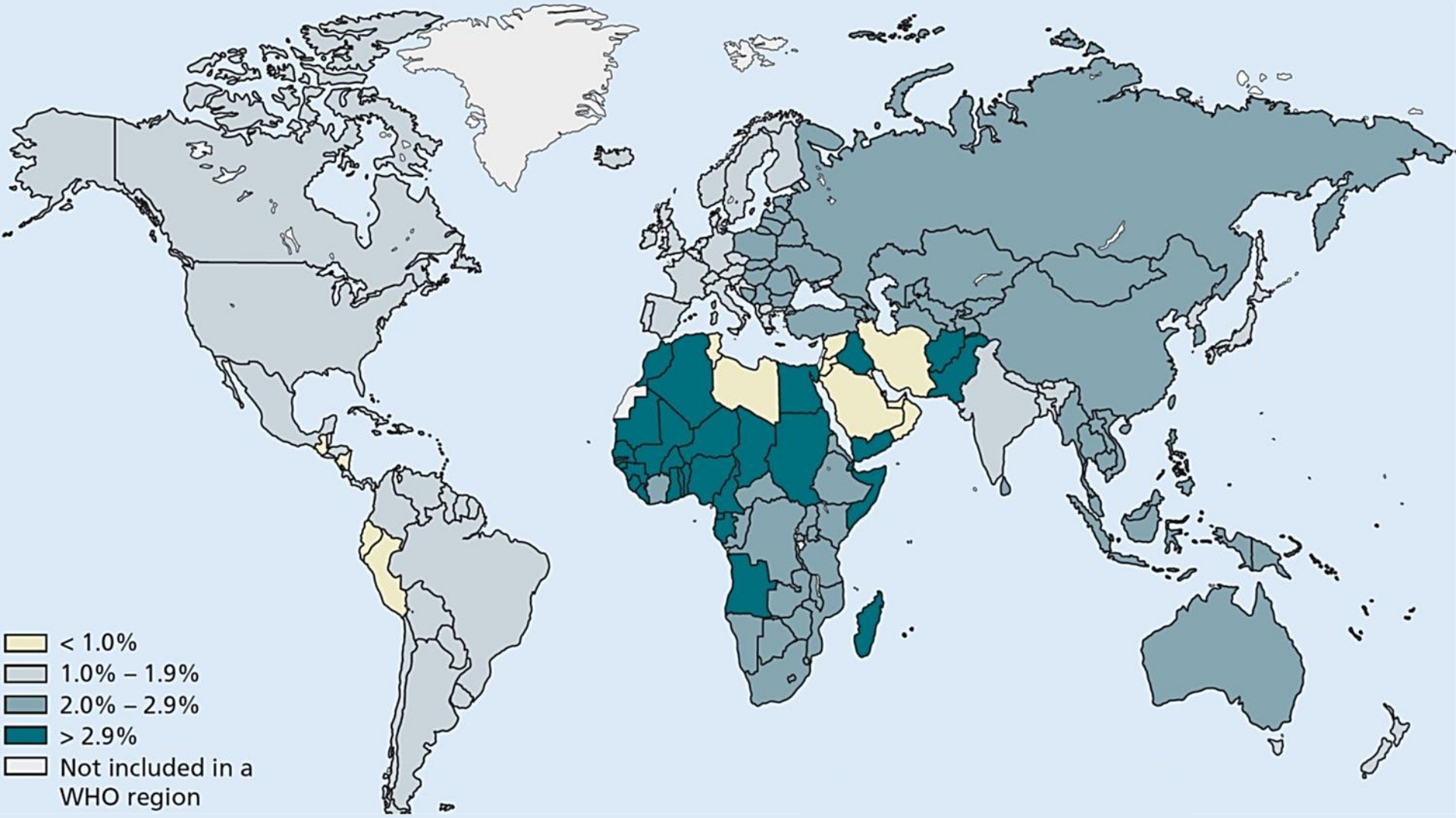
- *Avoiding risky behaviors*
- *Active immunization (vaccine) for:*
  - *all newborns*
  - *all "at risk" persons*
  - *patients with chronic liver disease*
- *Post-exposure prophylaxis with active-passive immunization (vaccine & immune globulin) in e.g.:*
  - *needle-stick injury from HBsAg+ patient*
  - *neonate of HBsAg+ mother*
  - *sexual partner of HBsAg+ patient*

What about hepatitis D?

- *HDV is an RNA-defective virus that has no independent existence (requires HBV to replicate) and has the same sources and modes of spread.*
- *Can be acquired as coinfection or superinfection and can be acute or chronic.*
- *Cirrhosis is more frequent & rapid with chronic hepatitis B+D than with chronic hepatitis B alone.*
- *Diagnosis is by serum anti-HDV (IgM & IgG).*
- *Prevention of hepatitis B prevents hepatitis D.*

What about Hepatitis C?

- *HCV is an RNA flavivirus that has a worldwide distribution & is a major cause of cirrhosis & HCC.*
- *Initial infection is usually clinically silent & leads to chronic infection in 80% of cases who will stay mostly asymptomatic until cirrhosis develops.*
- *Exposure to infected blood & blood products is the most important mode of transmission.*
- *Sexual & perinatal transmission is uncommon.*
- *Males, alcoholics, and HIV-coinfected patients has more aggressive disease course.*



Estimated HCV prevalence by region. (Source: Perz J *et al* ., unpublished data. Centers for Disease Control, **2002**.)

How to diagnose HCV infection?

- *Screening is by serum anti-HCV antibody and confirmation is by serum HCV RNA (PCR).*
- *Anti-HCV Ab persist even after HCV clearance, whether spontaneous or post-treatment.*
- *HCV genotype has no effect on natural course of disease but affect therapeutic response.*
- *LFTs may be normal or show fluctuating ALT.*
- *ALT & AST in hepatitis C are poor predictors of liver damage and cirrhosis may be present with normal ALT & AST.*

How to treat chronic hepatitis C?

- *The aim is to achieve a sustained viral response evidenced by undetectable HCV RNA 12 or 24 weeks after completion of therapy (SVR12 or SVR24).*
- *Traditional HCV therapy (weekly s.c. peg IFN-α injections with daily oral ribavirin) has now been replaced by more effective and convenient oral regimens using direct acting antiviral drugs (DAAs).*
- *No active or passive immunization against HCV is available yet.*

What about liver transplantation for hepatitis B and C?

- *In chronic viral hepatitis, liver transplantation is only indicated for decompensated end-stage cirrhosis and certain patients with early HCC.*
- *HCV almost always recurs in the allograft but current IFN-free regimens can effectively eradicate the virus in pre- and post-transplant patients.*
- *Recurrent HBV post-transplant is markedly reduced by pre-transplant antiviral drugs and post-transplant drugs and immunoglobulin.*

Thank you