VIRAL HEPATITIS

Kolářová M., Spring 2018

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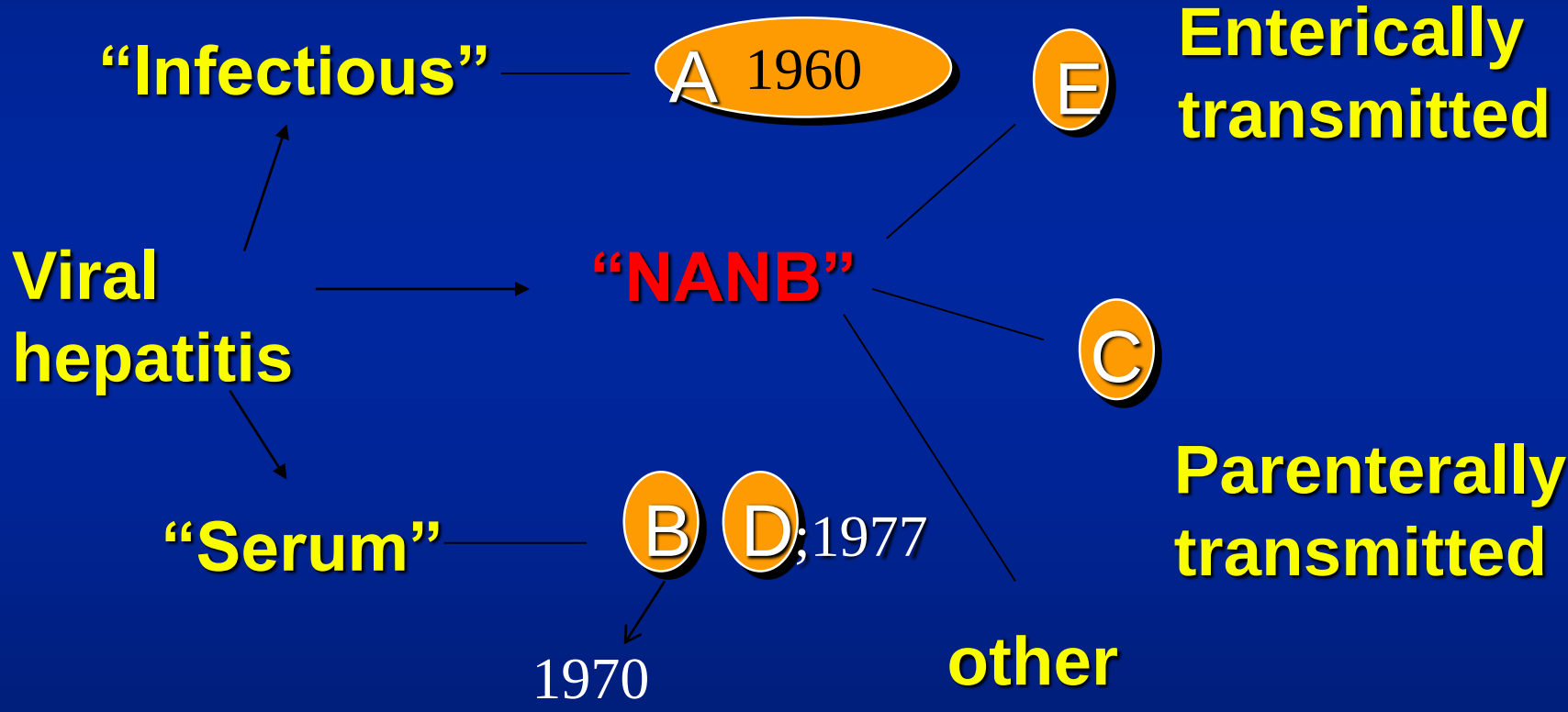
CENTERS FOR DISEASE CONTROL AND PREVENTION

VIRAL HEPATITIS

HISTORICAL PERSPECTIVE



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VIRAL HEPATITIS A

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Clinical Criteria

Any person with a discrete onset of symptoms (e.g. fatigue, abdominal pain, loss of appetite, intermittent nausea and vomiting)

AND

At least one of the following three:

- — Fever
- — Jaundice
- — Elevated serum aminotransferase levels

Laboratory Criteria

- At least one of the following three:
- — Detection of hepatitis A virus nucleic acid in serum or stool
- — Hepatitis A virus specific antibody response
- — Detection of hepatitis A virus antigen in stool

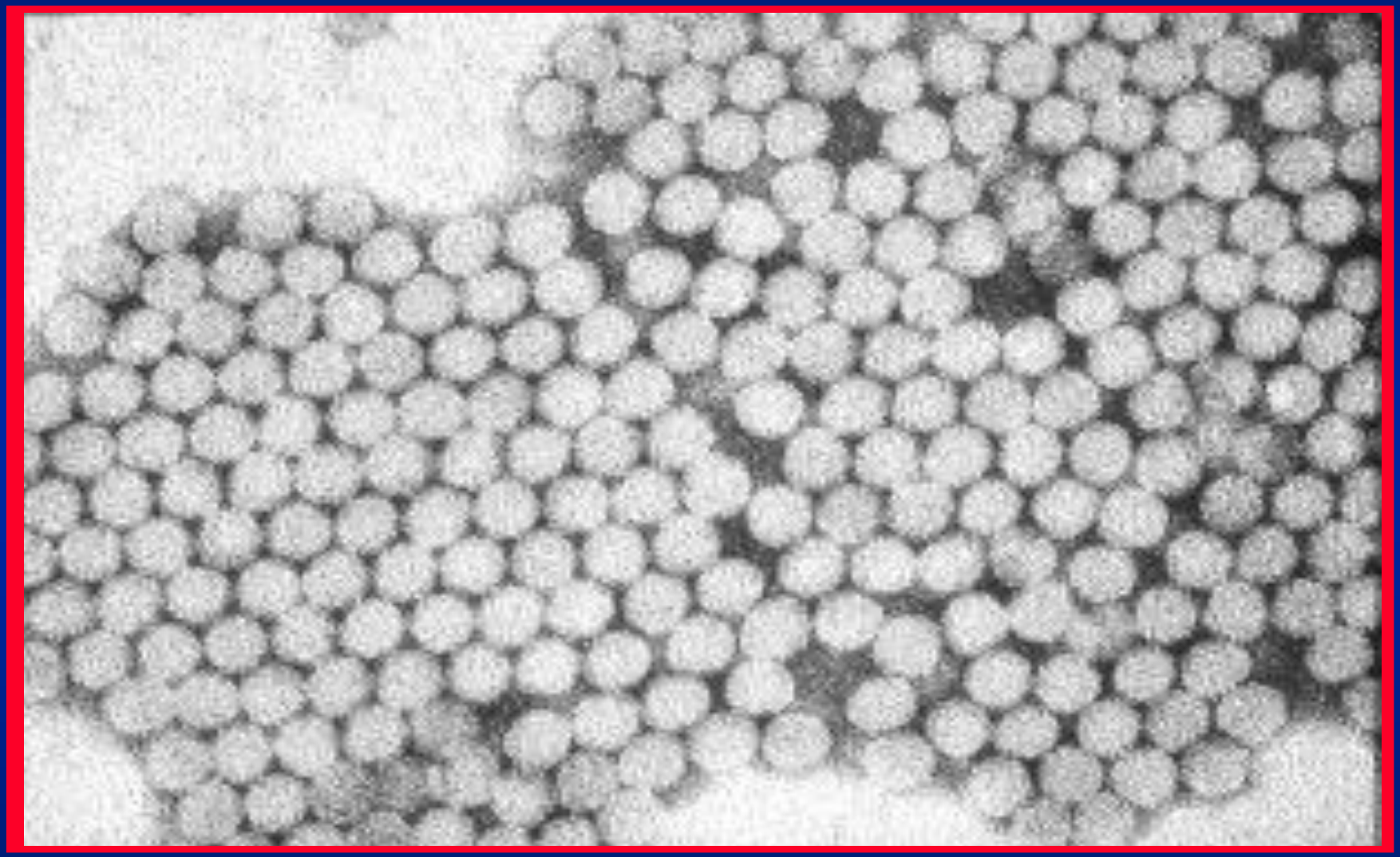
Epidemiological Criteria

- At least one of the following four:
- — Human to human transmission
- — Exposure to a common source
- — Exposure to contaminated food/drinking water
- — Environmental exposure

- **Case Classification**

- A. **Possible case NA** (not applicable)
- B. **Probable case**
- Any person meeting the clinical criteria and with an epidemiological link
- C. **Confirmed case**
- Any person meeting the clinical and the laboratory criteria

HEPATITIS A VIRUS



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HEPATITIS A VIRUS

- RNA Picornavirus
  - Single serotype worldwide
  - Acute disease and asymptomatic infection
- No chronic infection
  - Protective antibodies develop in response to infection - confers lifelong immunity

HEPATITIS A - CLINICAL FEATURES

- Jaundice by age group:
  - <6 yrs: <10%
  - 6-14 yrs: 40%-50%
  - >14 yrs: 70%-80%
- Rare complications:
  - Fulminant hepatitis
  - Cholestatic hepatitis
  - Relapsing hepatitis
- Incubation period:
  - Average 30 days
  - Range 15-50 days
- Chronic sequelae: None

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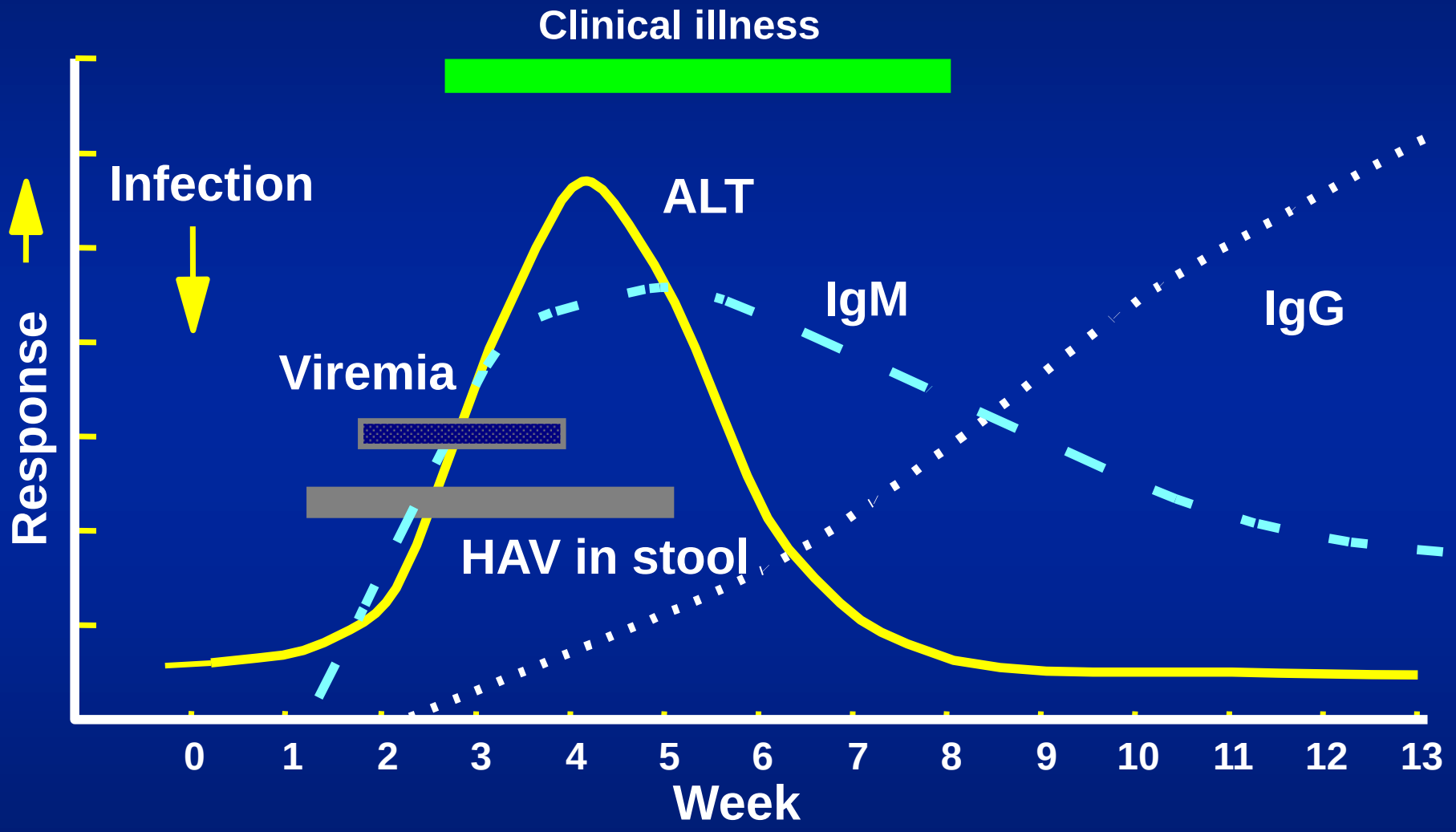
EVENTS IN HEPATITIS A VIRUS INFECTION



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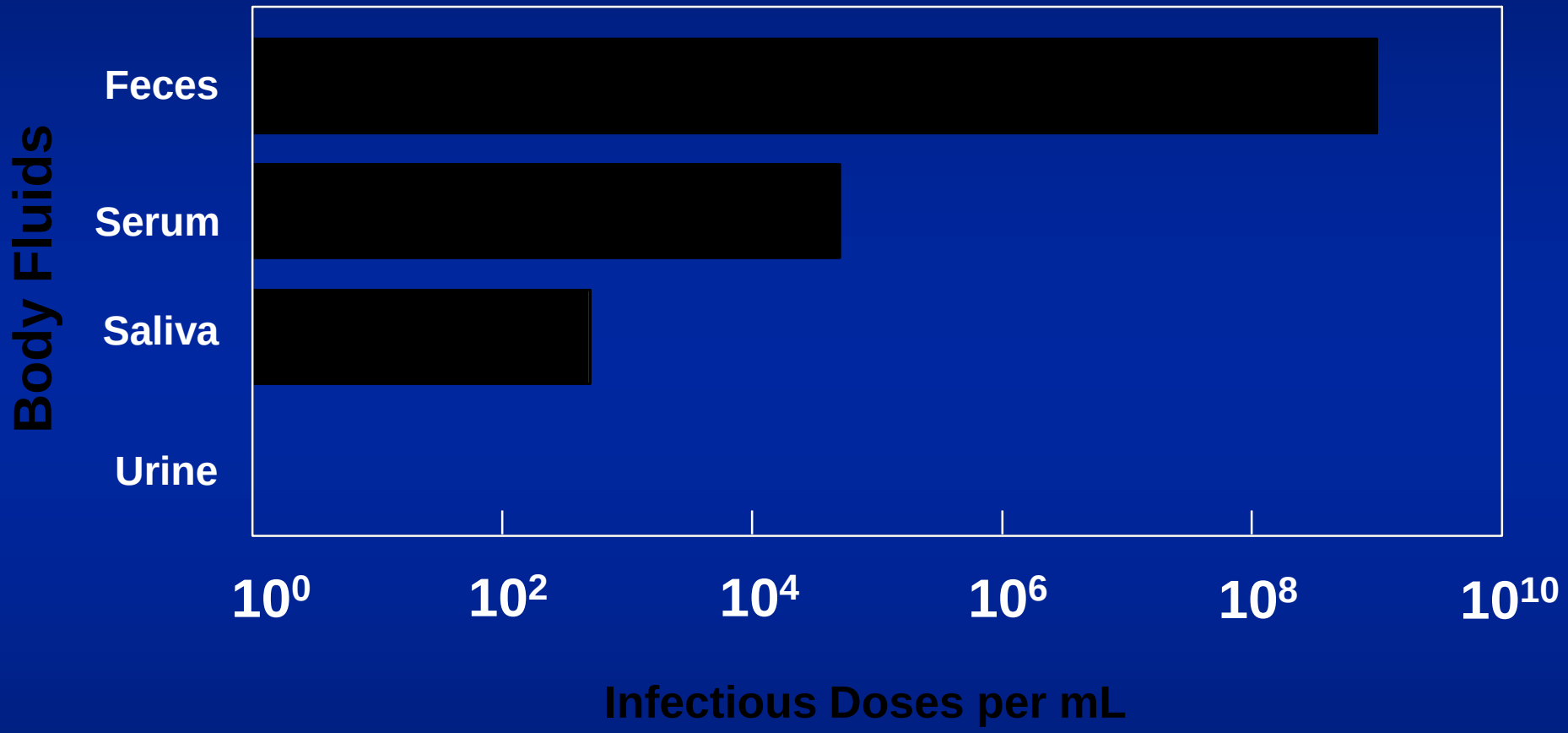
CONCENTRATION OF HEPATITIS A VIRUS IN VARIOUS BODY FLUIDS



Source: Viral Hepatitis and Liver Disease 1984;9-22
J Infect Dis 1989;160:887-890

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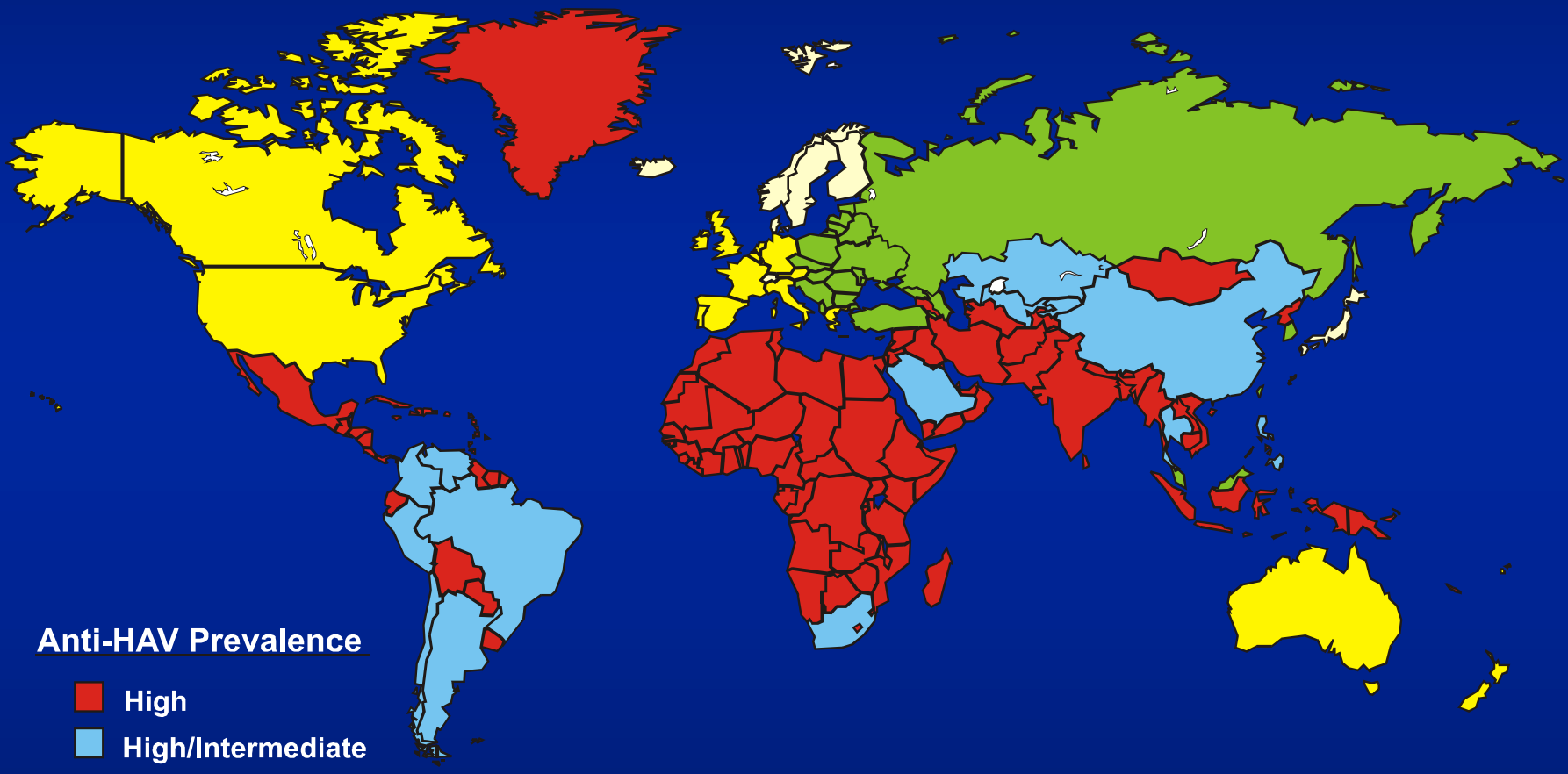
GEOGRAPHIC DISTRIBUTION OF HEPATITIS A VIRUS INFECTION



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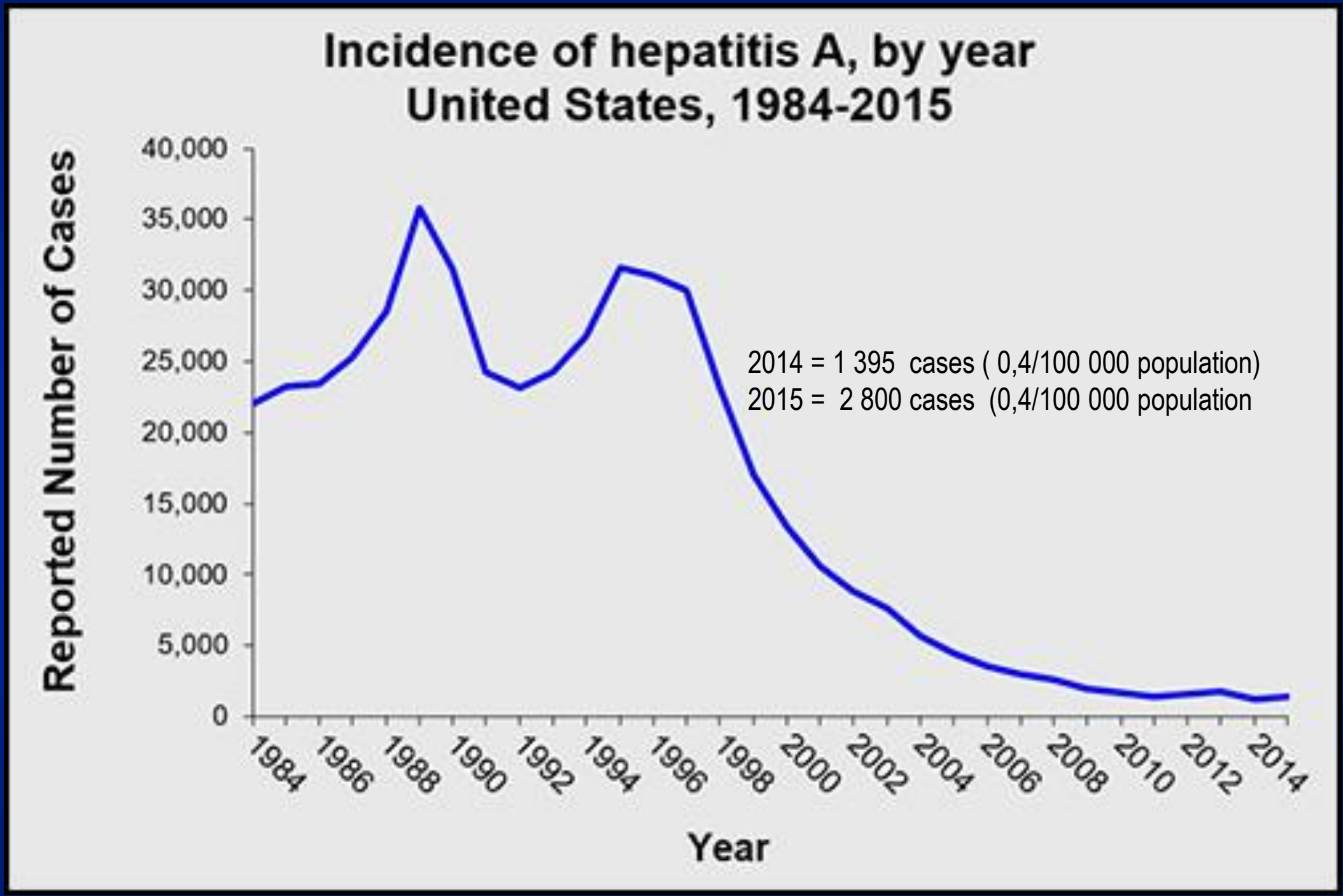
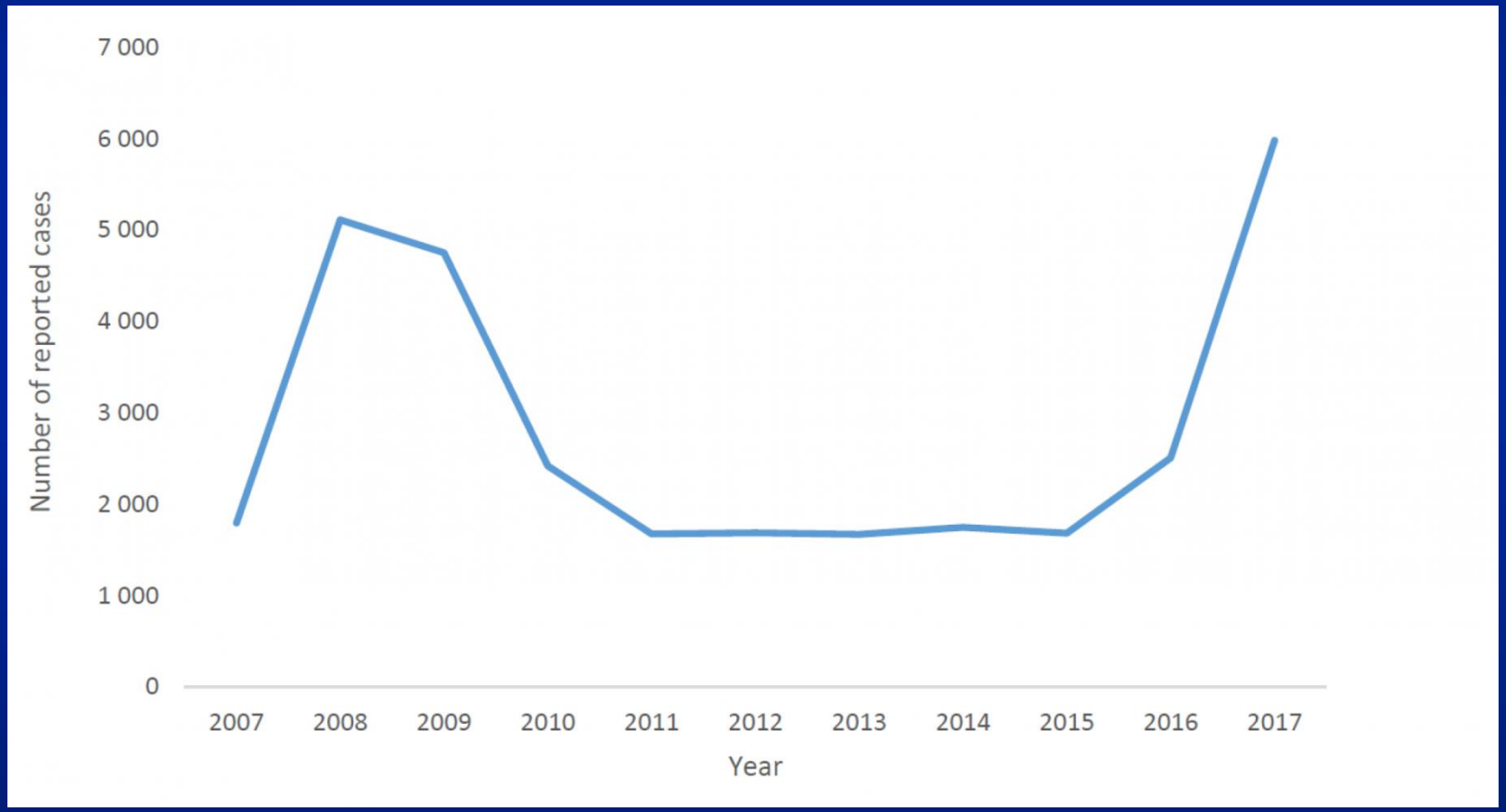

Incidence of hepatitis A, by year
United States, 1984-2015
Reported Number of Cases
40,000
35,000
30,000
25,000
20,000
15,000
10,000
5,000
0
1984
1986
1988
1990
1992
1994
1996
1998
2000
2002
2004
2006
2008
2010
2012
2014
Year
2014 = 1 395 cases (0,4/100 000 population)
2015 = 2 800 cases (0,4/100 000 population

VHA – TESSY (The European Surveillance System)



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HEPATITIS A VIRUS TRANSMISSION

- **Close personal contact**
  (e.g., household contact, sex contact, child day-care centers)
- **Contaminated food, water**
  (e.g., infected food handlers)
- **Blood exposure (rare)**
  (e.g., injection drug use, rarely by transfusion)

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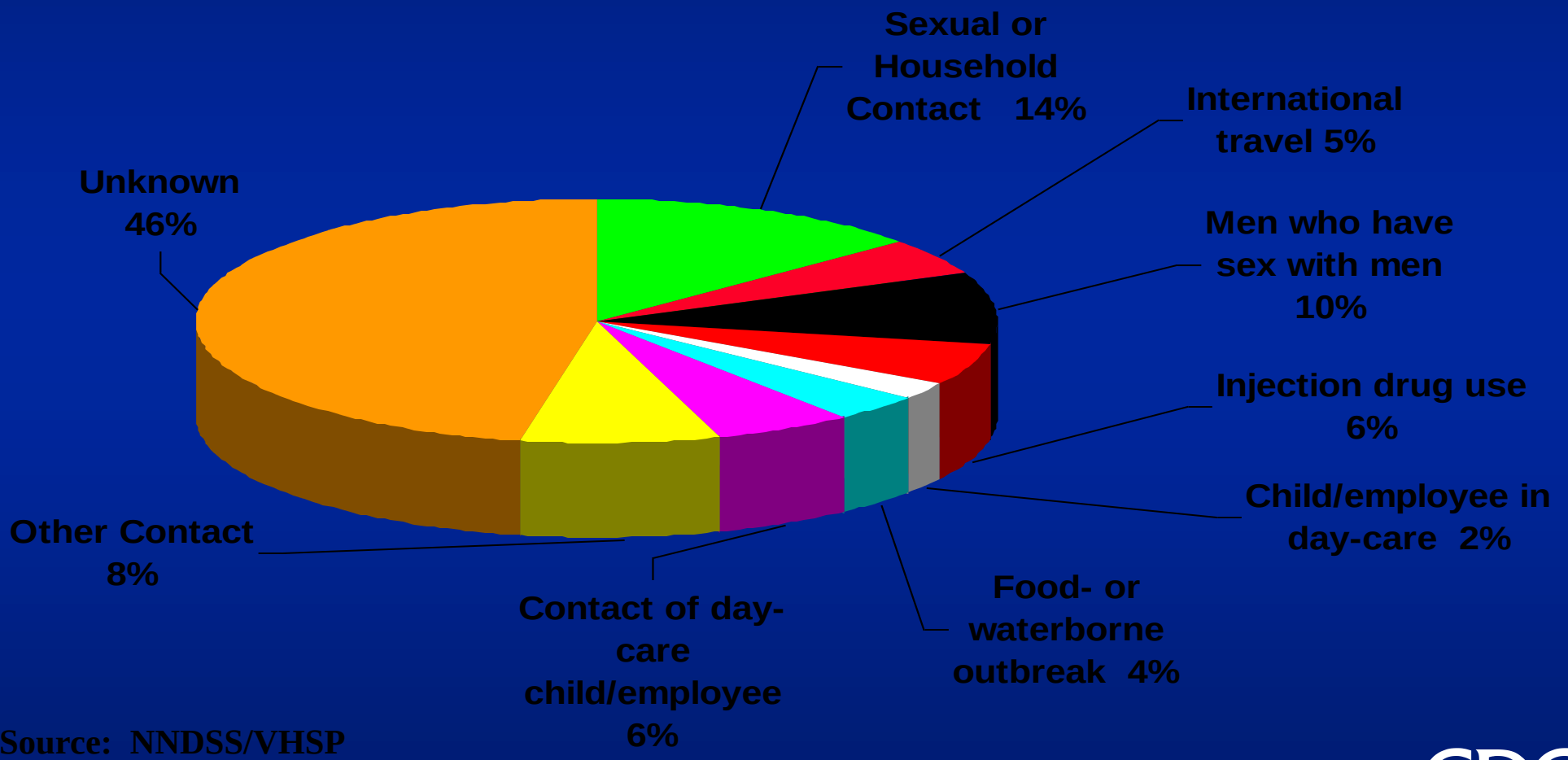
RISK FACTORS ASSOCIATED WITH REPORTED HEPATITIS A, 1990-2000, UNITED STATES



Source: NNDSS/VHSP

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PREVENTING HEPATITIS A

- **Hygiene (e.g., hand washing)**
- **Sanitation (e.g., clean water sources)**
- **Hepatitis A vaccine (pre-exposure)**
- **Immune globulin (pre- and post-exposure)**

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PREPARATION OF INACTIVATED HEPATITIS A VACCINES

- Cell culture adapted virus grown in human fibroblasts
- Purified product inactivated with formalin
- Adsorbed to aluminum hydroxide adjuvant

HEPATITIS A VACCINES

- **Highly immunogenic**
  - **97%-100% of children, adolescents, and adults have protective levels of antibody within 1 month of receiving first dose; essentially 100% have protective levels after second dose**

- **Highly efficacious**
  - **In published studies, 94%-100% of children protected against clinical hepatitis A after equivalent of one dose**

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DURATION OF PROTECTION AFTER HEPATITIS A VACCINATION

- **Persistence of antibody**
  - **At least 5-8 years among adults and children**
- **Efficacy**
  - **No cases in vaccinated children at 5-6 years of follow-up**
- **Mathematical models of antibody decline suggest protective antibody levels persist for at least 20 years**
- **Other mechanisms, such as cellular memory, may contribute**

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VIRAL HEPATITIS B

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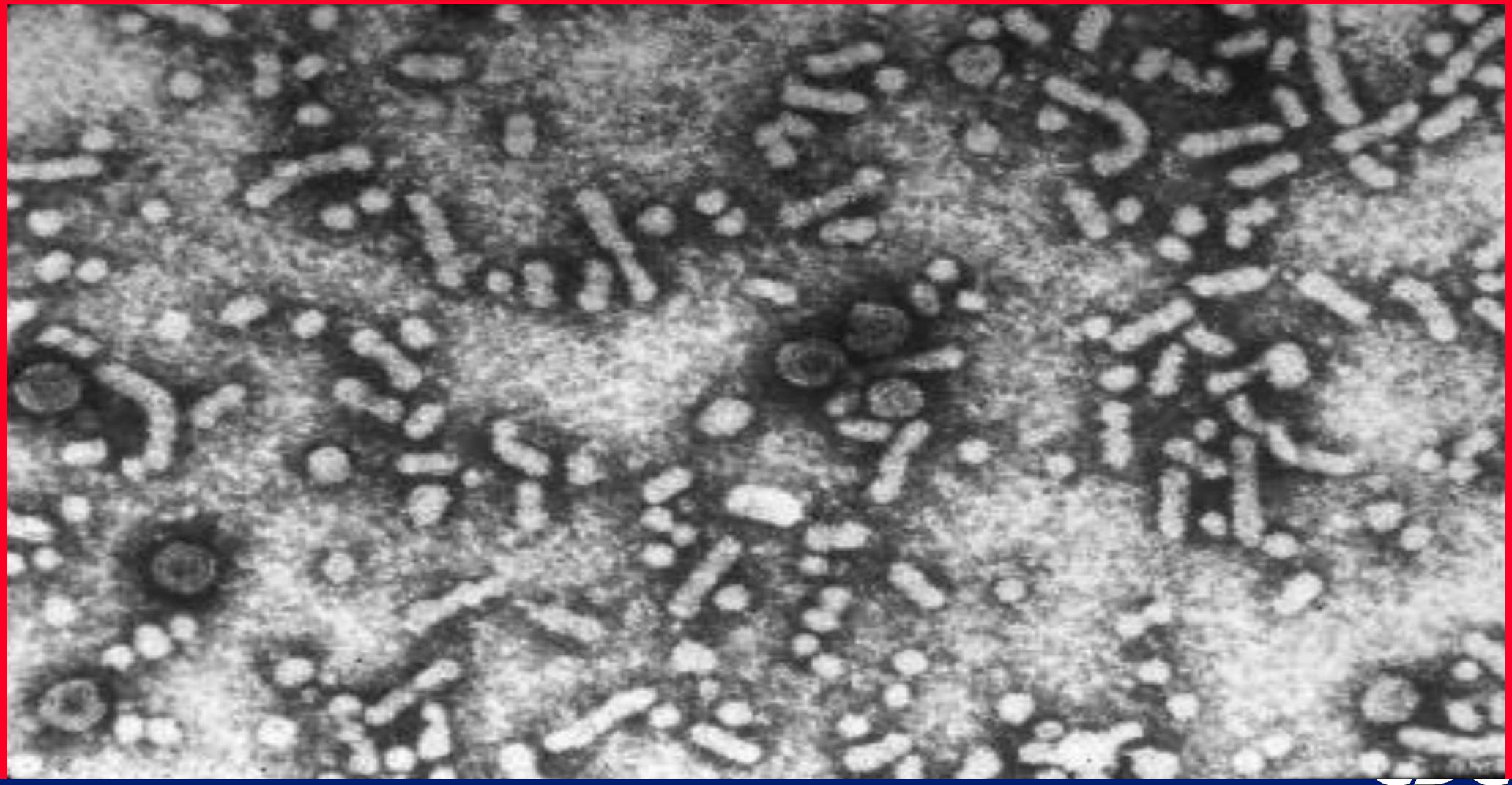
The hepatitis_ B virus is a DNA virus belonging to the Hepadnaviridae family of viruses.



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EU Definition VHB

- HEPATITIS B (Hepatitis B virus)
- **Clinical Criteria**
- Not relevant for surveillance purposes
- **Laboratory Criteria**
- Positive results of at least one or more of the following tests or combination of tests:
- — IgM hepatitis B core antibody (anti-HBc IgM)
- — Hepatitis B surface antigen (HBsAg)
- — Hepatitis B e antigen (HBeAg)
- — Hepatitis B nucleic acid (HBV-DNA)
- **Epidemiological Criteria**
- Not relevant for surveillance purposes
- **Case Classification**
- A. **Possible case** NA
- B. **Probable case** NA
- C. **Confirmed case**
- Any person meeting the laboratory criteria

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VIRAL HEPATITIS TYPE B

Etiology:

Hepatitis B virus, HBV, Hepadnavirus, the so-called Dane particle with a core (formed by DNA, DNA polymerase, and a nucleocapsid protein with the hepatitis B core antigen (HBcAg) and a coat of hepatitis B surface antigen (HBsAg)). The whole virus is infectious with a diameter of 42 nm.

The source of infection

Two months in the ende of incubation period, the sick or carriers.

Route of transmission

Parenteral transmission - blood, blood products and inoculation of the infectious material are of principal significance in the transmission.

Professional risk to medical personnel (injury by needle - transmission in 7 - 30 %, contaminated instruments, blood transfusions - transmission in 90 %).

i.v. drug addicts - injury during tattooing, possibly other minute injuries of the skin and mucosa.

By **sexual intercourse** in homosexuals, bisexuals, and prostitutes.

Vertical - perinatal transmission from mother to child when the mother is the virus carrier or the sick person. About 95 % of newborns infect intranatally and 5 % intrauterinely.

Susceptibility

General

Preventive measures: ⇩

VIRAL HEPATITIS TYPE B

Preventive measures:

Health education - to emphasize the extent of risk
Observance of epidemic measures in medical establishments.
Handling biological material and contaminated instruments,
consistent disinfection and sterilization,
application of single-use needles and syringes,
use of closed hemodialysis systems,
smoking and drinking in workplaces with biological material is forbidden.
Postexposure prophylaxis - passive and active immunization (newborns).
Examination of blood-donors - exclusion of HBsAg carriers from blood donation
Designation and inspection of sanitary-epidemic
measures in non-medical establishments (hair-dressing salons, barber shops, etc.)
Active immunization in persons with a high risk of infection (stated by public notice)
.
.

Estimate: more than 10 million Europeans suffer from chronic viral hepatitis.

The prevalence of HBV is estimated to be around 0.9% and of HCV about 1.1% in the EU/EEA, with an estimated total of 4.7 million chronic HBV cases and 5.6 million HCV cases.

Overall, countries in the eastern and southern part of the EU/EEA were found to have a higher HBV and HCV prevalence than countries in the northern and western parts.

The HBV prevalence ranged from 0.1% in Ireland to 4.4% in Romania, while the report found that the prevalence of anti-HCV ranges from 0.1% in Belgium, Ireland and the Netherlands, to 5.9% in Italy. As expected, groups at higher risk of hepatitis infection, such as people who inject drugs, prisoners and certain migrant groups were found to have higher prevalence, compared to the general population.

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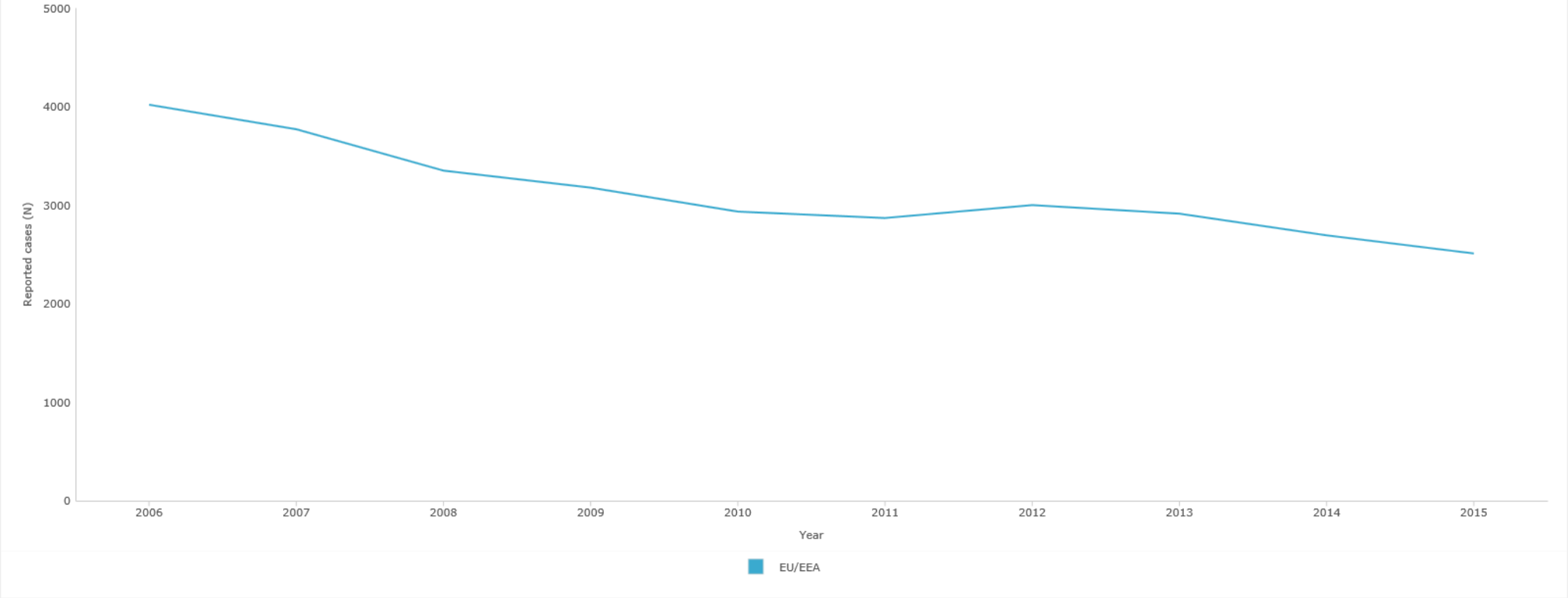
Surveillance Atlas of Infectious Diseases

Hepatitis B | Acute cases | Reported cases | 2015



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The symptoms can vary greatly and many of those infected with HBV never develop any symptoms at all.

Those who do get symptoms (30-50% of cases) usually suffer from tiredness, loss of appetite, abdominal discomfort, nausea, vomiting and fever. The vast majority of healthy adults who get acute hepatitis B will recover with no liver damage in 4–12 weeks but the death rate can reach 2% in the elderly.

Chronic infection is most likely to develop in young babies.

Hepatitis B – Clinical Features

* Incubation period: Average 60-90 days
  Range 45-180 days
* Clinical illness (jaundice): <5 yrs, <10%
  >5 yrs, 30%-50%
* Acute case-fatality rate: 0.5%-1%
* Chronic infection: <5 yrs, 30%-90%
  >5 yrs, 2%-10%
* Premature mortality from chronic liver disease: 15%-25%

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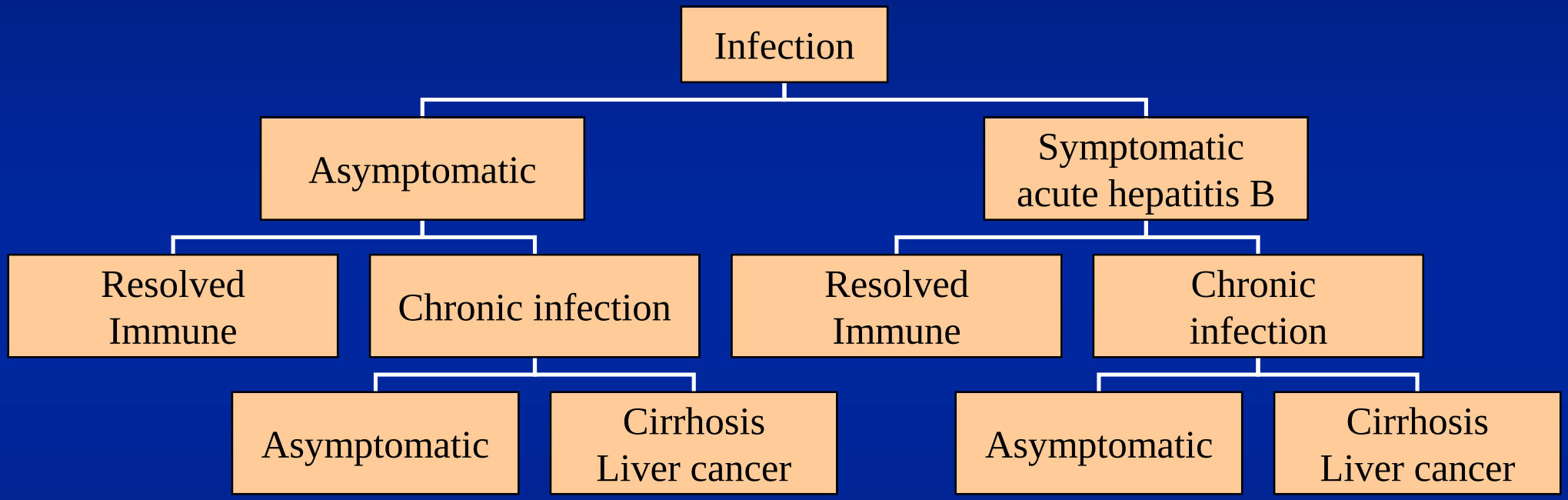
Outcome of HBV Infection



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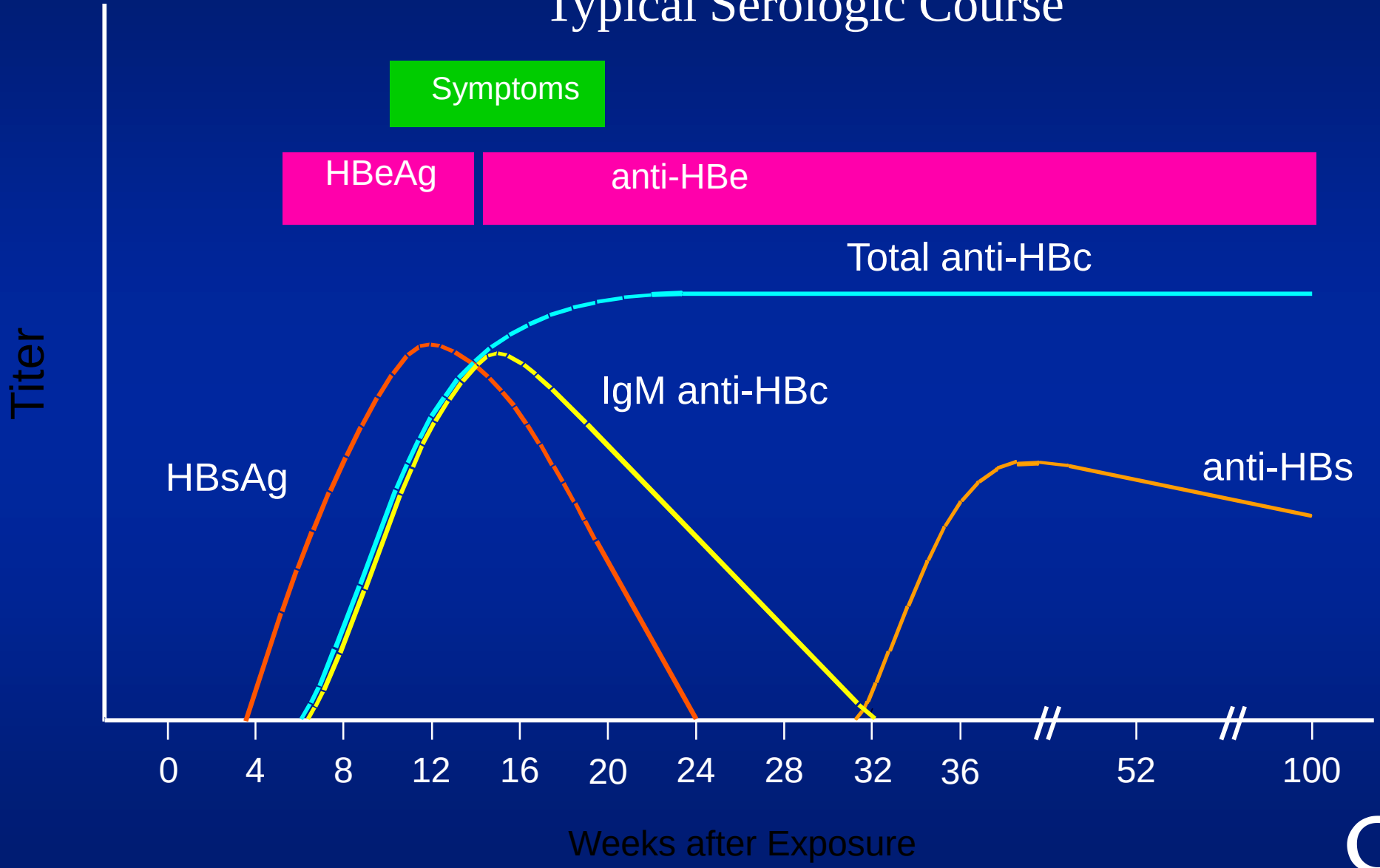
Acute Hepatitis B Virus Infection with Recovery

Typical Serologic Course



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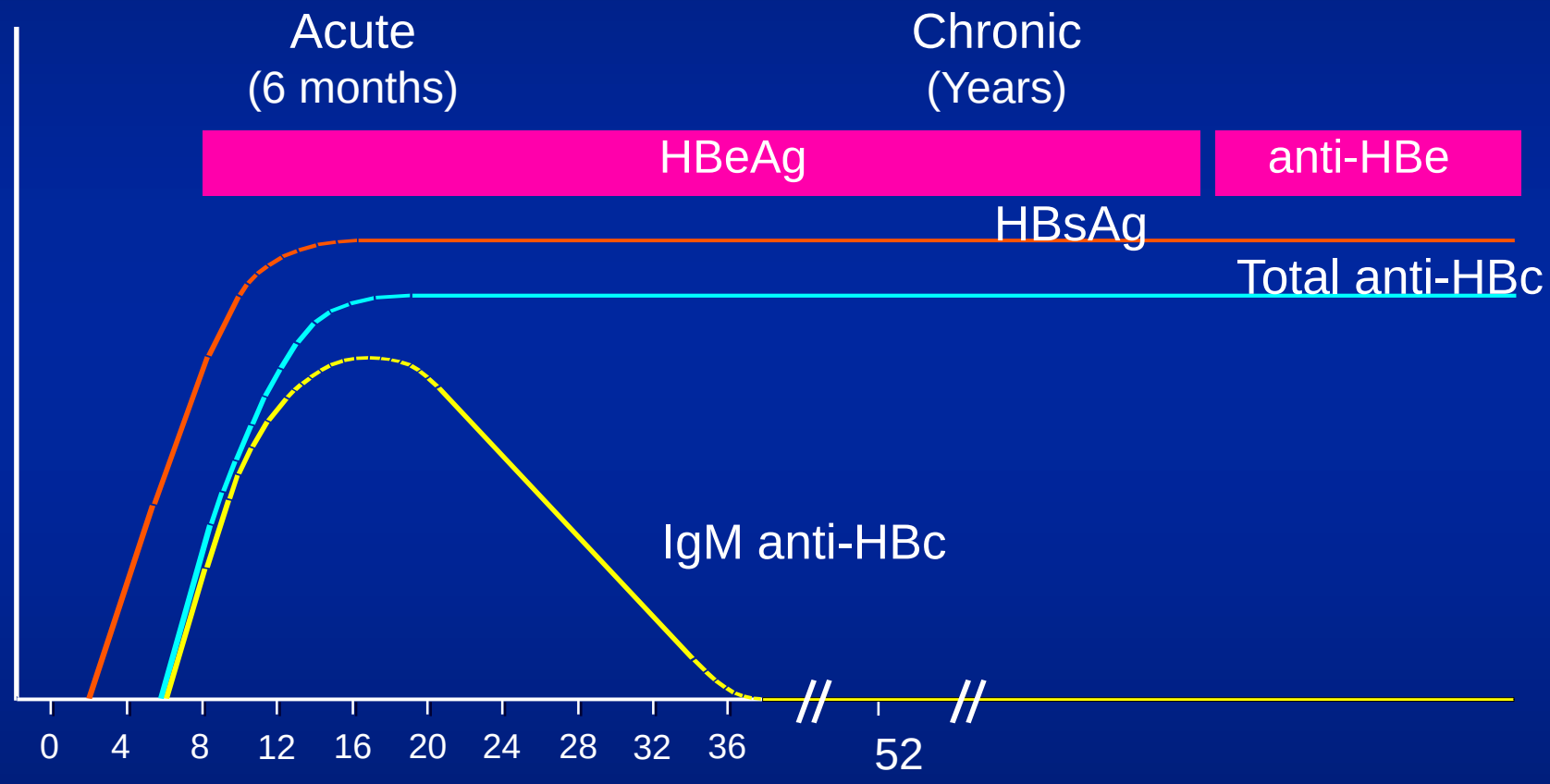
Progression to Chronic Hepatitis B Virus Infection

Typical Serologic Course



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HBV Modes of Transmission

- Sexual
- Parenteral
- Perinatal

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Concentration of HBV in Various Body Fluids

High	Moderate	Low/Not Detectable
blood	semen	urine
serum	vaginal fluid	feces
wound exudates	breast milk	sweat
		tears

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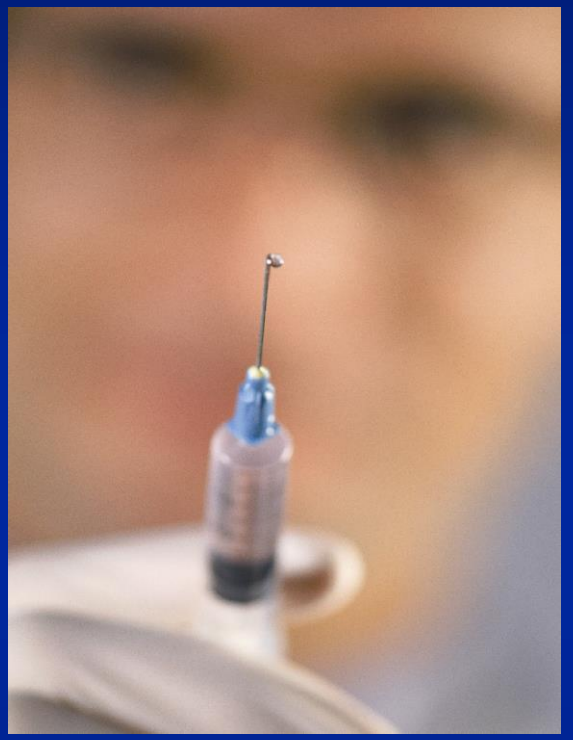
Elimination of HBV Transmission,

Strategy

- Prevent perinatal HBV transmission
- Routine vaccination of all infants
- Vaccination of children in high-risk groups
- Vaccination of adolescents
  - all children up through age 18
- Vaccination of adults in high-risk groups



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Hepatitis B Vaccine

- Licensed in 1982; currently recombinant (in US)
- 3 dose series, typical schedule 0, 1-2, 4-6 months - no maximum time between doses (no need to repeat missed doses or restart)
- Protection ~30-50% dose 1; 75% - 2; 96% - 3;
- lower in older, immunosuppressive illnesses (e.g., HIV, chronic liver diseases, diabetes), obese, smokers

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Hepatitis B Vaccination ACIP Recommendations

- Routine infant
- Ages 11-15 “catch up”, and through age 18(VFC eligible)
- Over 18 – high risk
  - **Occupational risk (HCWs)**
  - **Hemodyalisis patients**
  - **All STD clinic clients**
  - **Multiple sex partners or prior STD**
  - **Inmates in Correctional settings**
  - **MSM**
  - **IDU**
  - **Institution for developmental disability**
- Pre-vaccination testing – if cost effective
- Post-vaccination testing – 1-2 months after last shot, if establishing response critical (HCW)

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VIRAL HEPATITIS C

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EU Definition VHC

- HEPATITIS C (Hepatitis C virus)
- **Clinical Criteria**
- Not relevant for surveillance purposes
- **Laboratory Criteria**
- At least one of the following three:
- — Detection of hepatitis C virus nucleic acid (HCV RNA)
- — Detection of hepatitis C virus core antigen (HCV-core)
- — Hepatitis C virus specific antibody (anti-HCV) response confirmed by a confirmatory (e.g. immunoblot) antibody test in persons older than 18 months without evidence of resolved infection)
- **Epidemiological Criteria** NA
- **Case Classification**
- A. **Possible case** NA
- B. **Probable case** NA
- C. **Confirmed case**
- Any person meeting the laboratory criteria

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VIRAL HEPATITIS TYPE C

Etiology: Hepatitis C virus is a RNA-virus measuring 50 nm. It is classed into a separate genus, Hepacavirus of the Flaviviridae family.

The source of infection — Long-term in viremia (in the ende IP), chronic infections.

Route of transmission — Parenteral transmission. Sporadically, vertical and sexual transmissions were reported carrier or the sick person.

Susceptibility — Susceptibility is general.

Preventive measures:
The same as for HBV, exclusive immunization.

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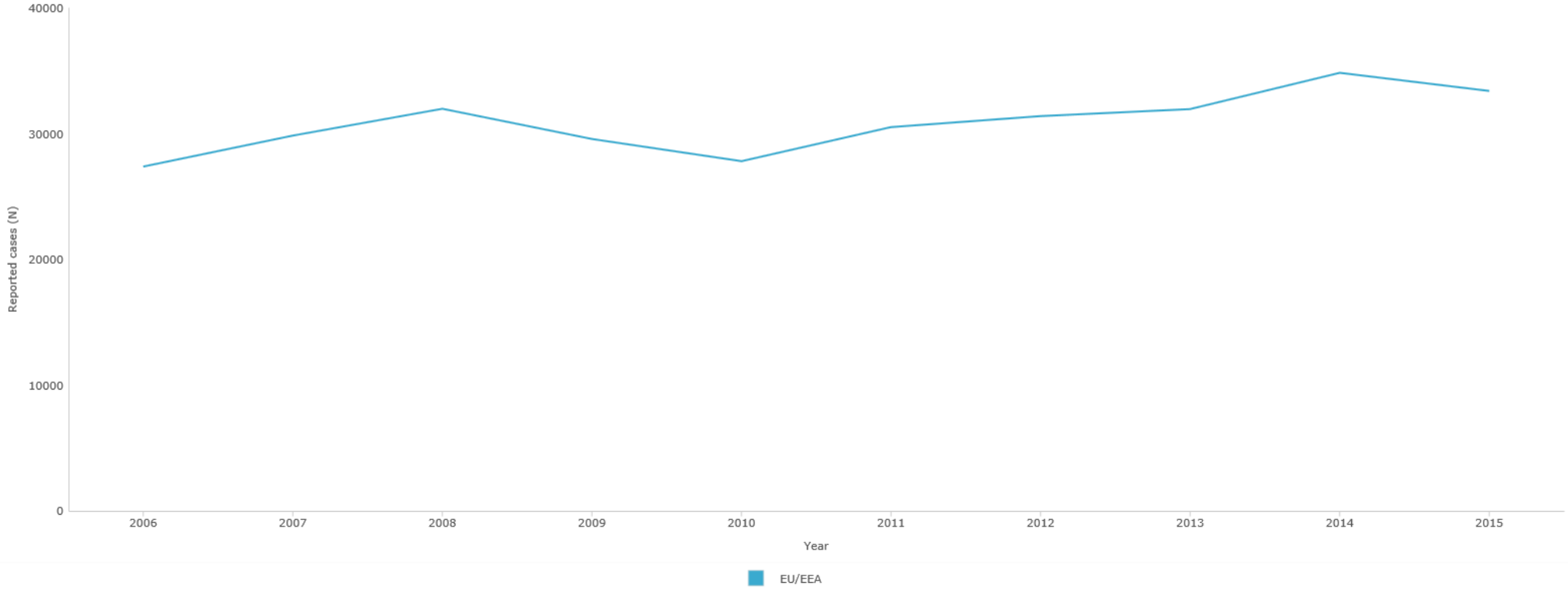
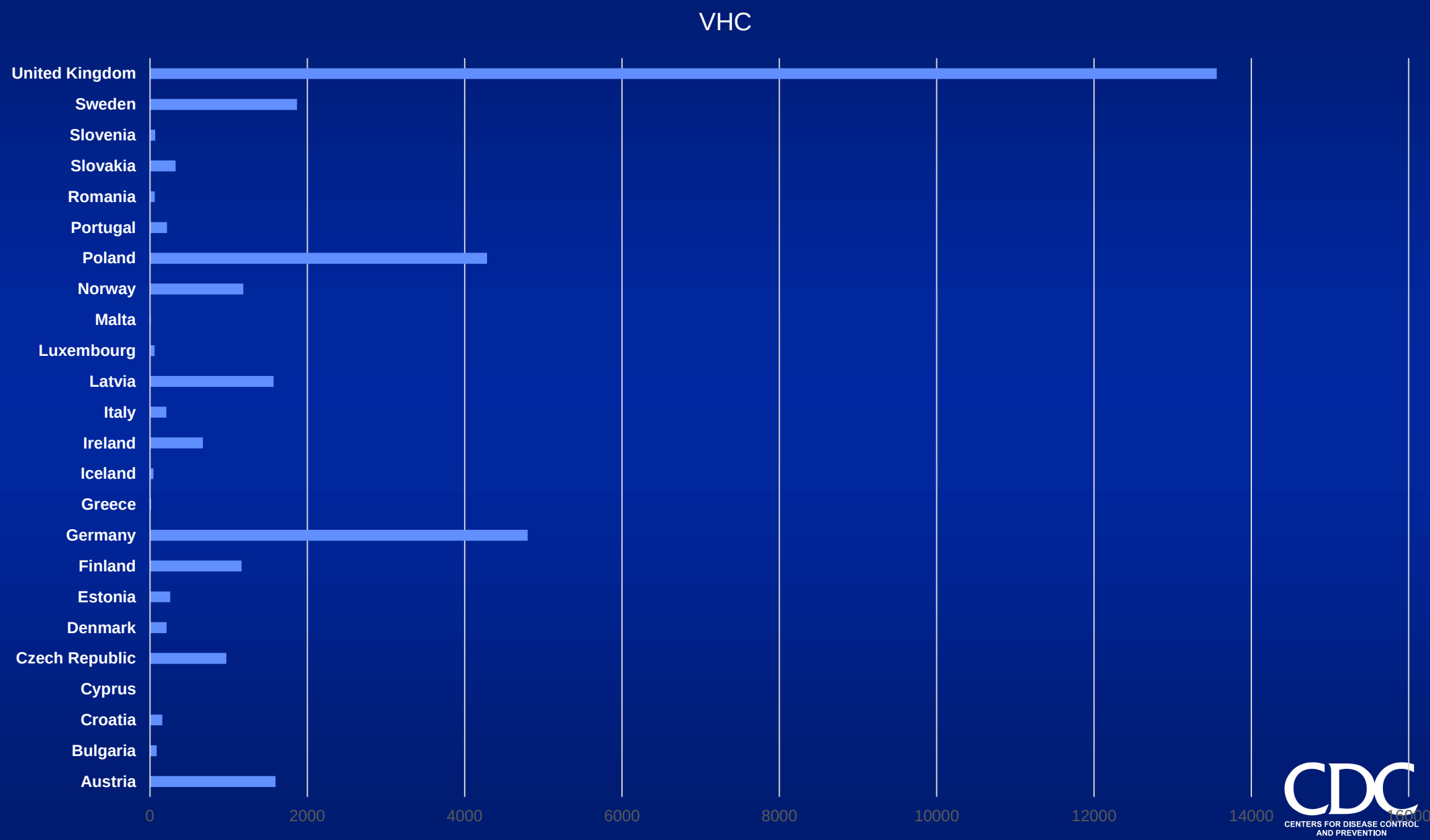
Surveillance Atlas of Infectious Diseases

Hepatitis C | All cases (for countries reporting both acute and chronic cases) | Reported cases | 2015





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Features of Hepatitis C Virus Infection

Incubation period		Average 6-7 weeks Range 2-26 weeks
Acute illness (jaundice)		Mild (≤20%)
Case fatality rate		Low
Chronic infection		60%-85%
Chronic hepatitis	**Age-related**	10%-70% (most asx)
Cirrhosis		<5%-20%

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Chronic Hepatitis C
Factors Promoting Progression or Severity

- Increased alcohol intake
- Age > 40 years at time of infection
- HIV co-infection
- Other
  - Male gender
  - Chronic HBV co-infection

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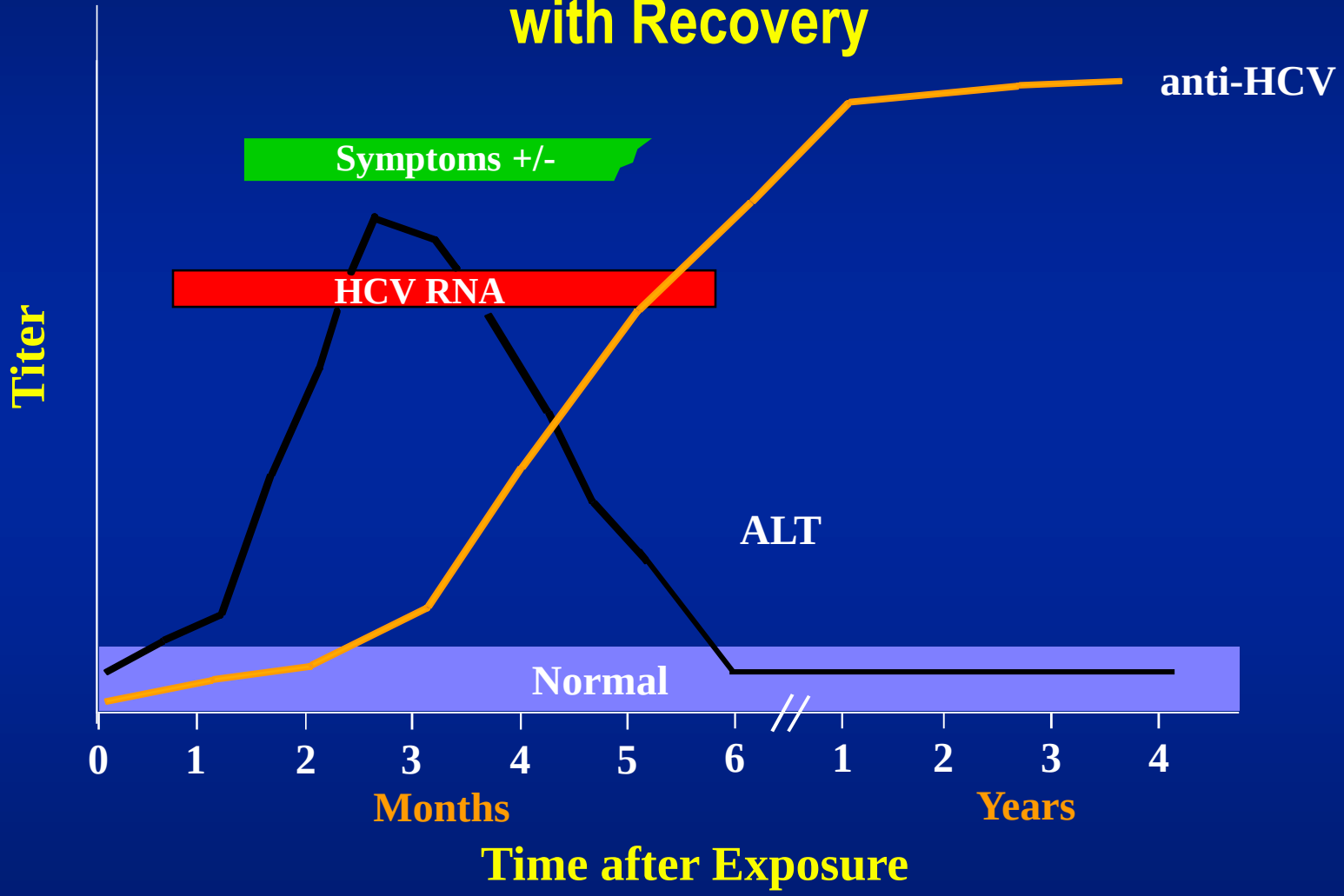
Serologic Pattern of Acute HCV Infection with Recovery



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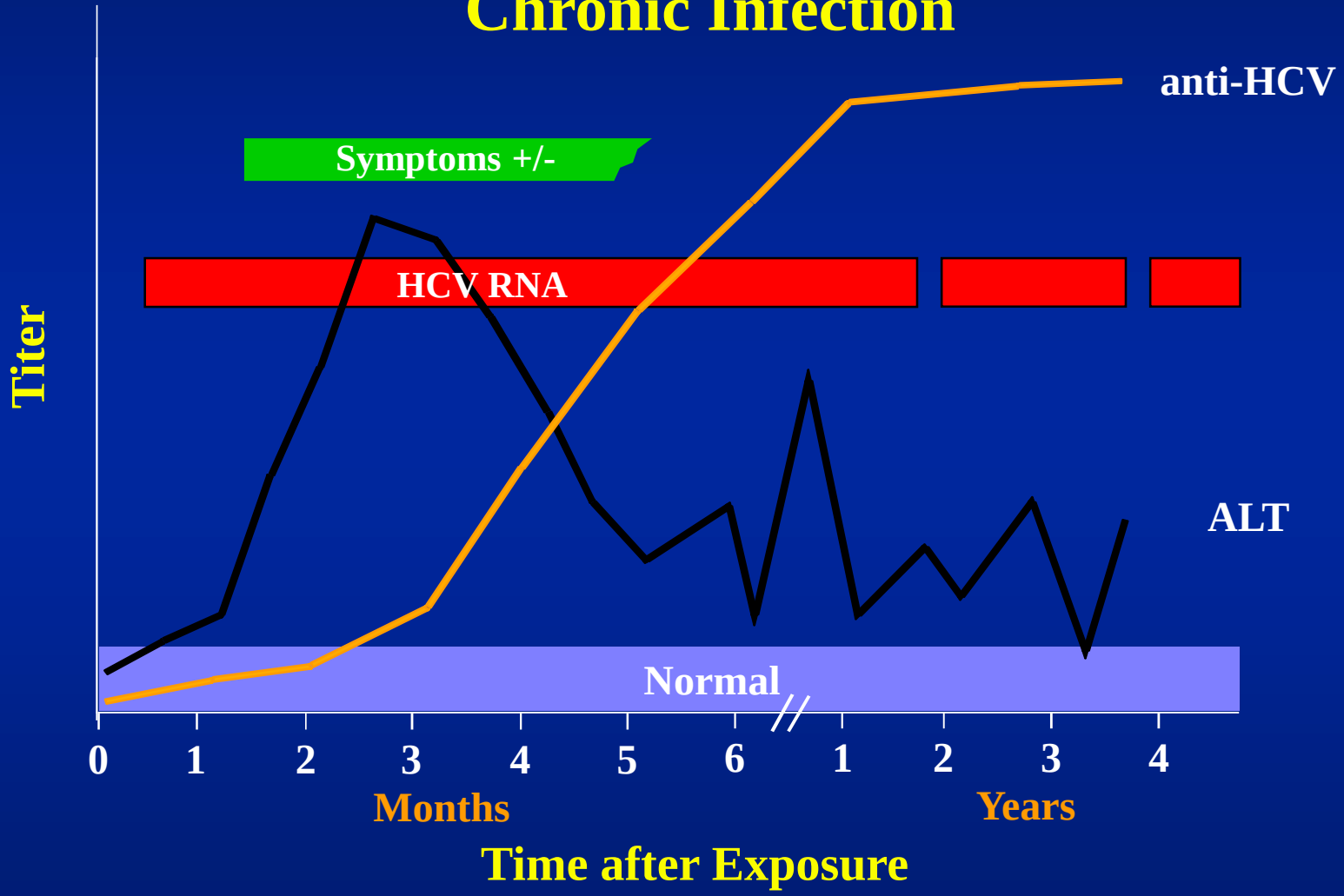
Serologic Pattern of Acute HCV Infection with Progression to Chronic Infection



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Exposures Known to Be Associated With HCV Infection

- Injecting drug use
- Transfusion, transplant from infected donor
- Occupational exposure to blood
  - Mostly needle sticks
- Iatrogenic (unsafe injections)
- Birth to HCV-infected mother
- Sex with infected partner
  - Multiple sex partners

Injecting Drug Use and HCV Transmission

- Highly efficient
  - Contamination of drug paraphernalia, not just needles and syringes
- Rapidly acquired after initiation
  - 30% prevalence after 3 years
  - >50% after 5 years
- Four times more common than HIV

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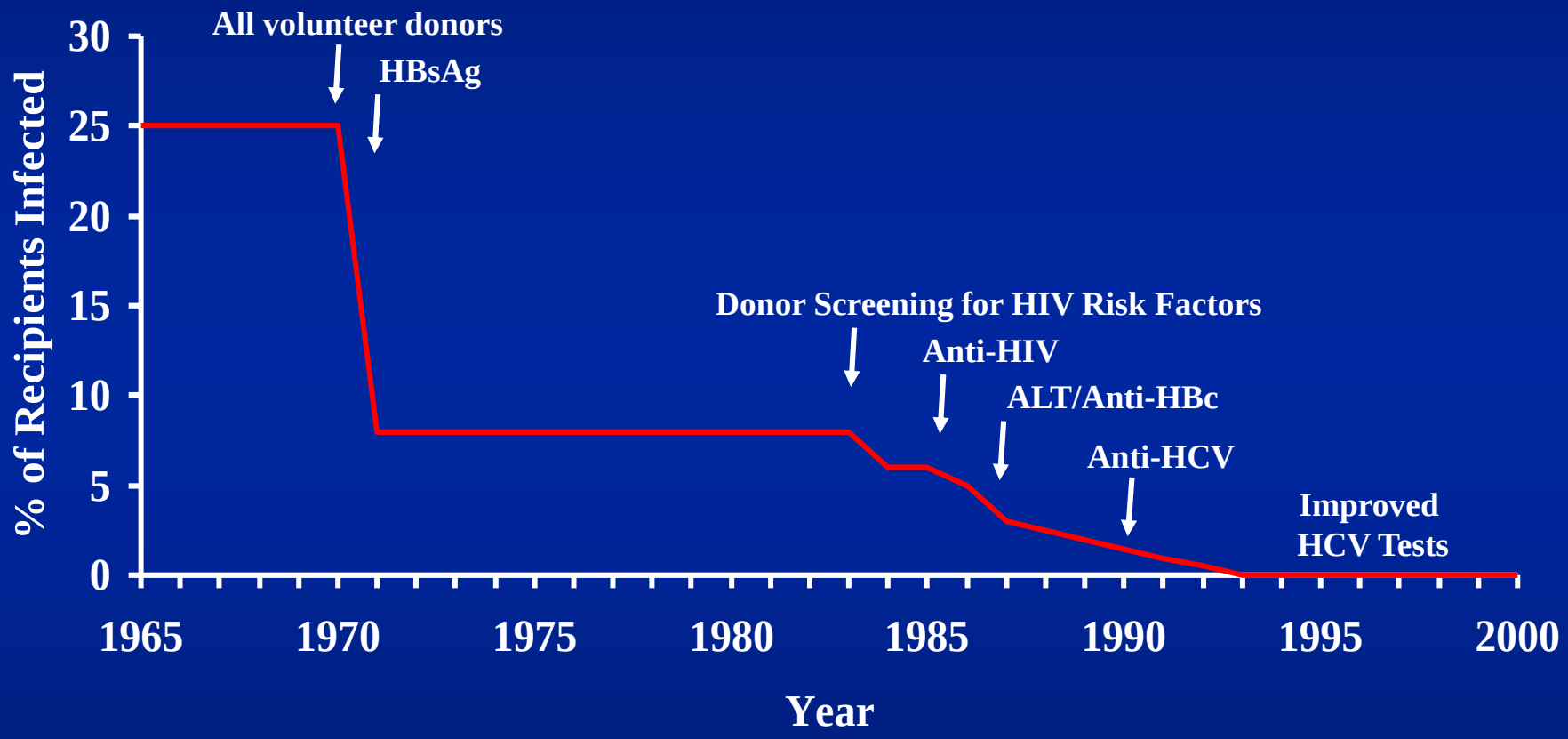
Posttransfusion Hepatitis C



Adapted from HJ Alter and Tobler and Busch, Clin Chem 1997

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Occupational Transmission of HCV

- Inefficient by occupational exposures
- Average incidence 1.8% following needle stick from HCV-positive source
  - Associated with hollow-bore needles
- Case reports of transmission from blood splash to eye; one from exposure to non-intact skin
- Prevalence 1-2% among health care workers
  - Lower than adults in the general population
  - 10 times lower than for HBV infection

HCV Related to Health Care Procedures

- Recognized primarily in context of outbreaks
  - Chronic hemodialysis
  - Hospital inpatient setting
  - Private practice setting
  - Home therapy
- Unsafe injection practices
  - Reuse of syringes and needles
  - Contaminated multiple dose medication vials

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Perinatal Transmission of HCV

- Transmission only from women HCV-RNA positive at delivery
  - Average rate of infection 6%
  - Higher (17%) if woman co-infected with HIV
  - Role of viral titer unclear
- No association with
  - Delivery method
  - Breastfeeding
- Infected infants do well
  - Severe hepatitis is rare

Sexual Transmission of HCV

- Case-control, cross sectional studies
  - Infected partner, multiple partners, early sex, non-use of condoms, other STDs, sex with trauma, BUT
  - MSM no higher risk than heterosexuals
- Partner studies
  - Low prevalence (1.5%) among long-term partners
    - infections might be due to common percutaneous exposures (e.g., drug use), BUT
  - Male to female transmission more efficient
    - more indicative of sexual transmission

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Sexual Transmission of HCV

- Occurs, but efficiency is low
  - Rare between long-term steady partners
  - Factors that facilitate transmission between partners unknown (e.g., viral titer)
- Accounts for 15-20% of acute and chronic infections
- Sex is a common behavior
  - Large chronic reservoir provides multiple opportunities for exposure to potentially infectious partners

Household Transmission of HCV

- Rare but not absent
- Could occur through percutaneous/mucosal exposures to blood
  - Contaminated equipment used for home therapies
    - IV therapy, injections
  - Theoretically through sharing of contaminated personal articles (razors, toothbrushes)

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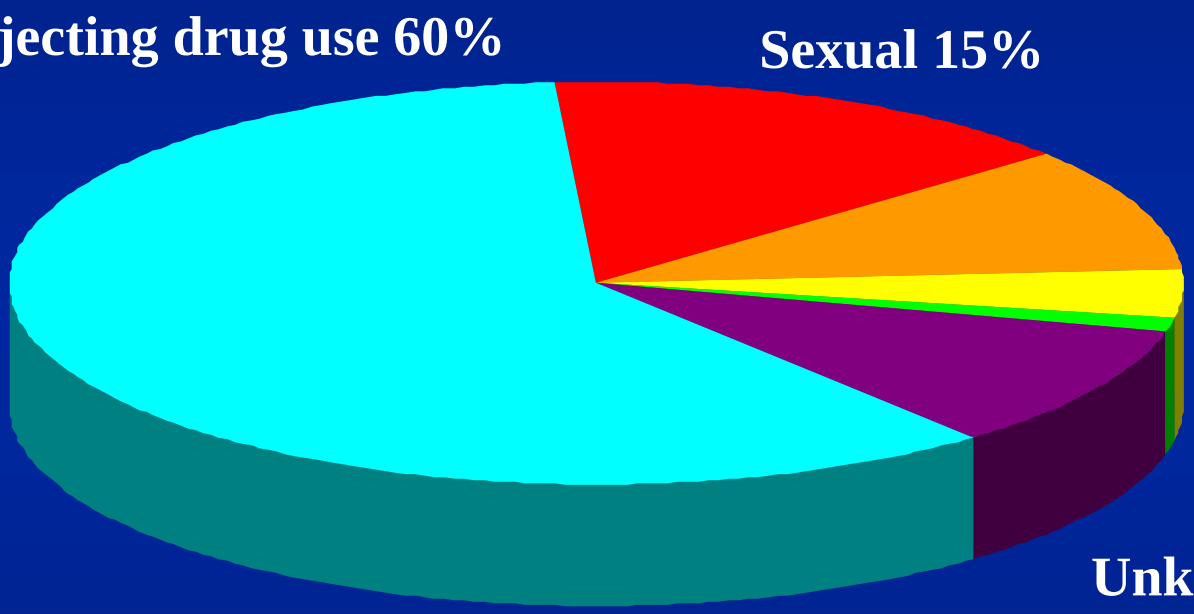
Other Potential Exposures to Blood

- No or insufficient data showing increased risk
  - intranasal cocaine use, tattooing, body piercing, acupuncture, military service
- No associations in acute case-control or population-based studies
- Cross-sectional studies in highly selected groups with inconsistent results
  - Temporal relationship between exposure and infection usually unknown
  - Biologically plausible, but association or causal relationship not established

Sources of Infection for Persons With Hepatitis C



*** Nosocomial; iatrogenic; perinatal**

Source: Centers for Disease Control and Prevention

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Reduce or Eliminate Risks for Acquiring HCV Infection

- Screen and test donors
- Virus inactivation of plasma-derived products
- Risk-reduction counseling and services
  - Obtain history of high-risk drug and sex behaviors
  - Provide information on minimizing risky behavior, including referral to other services
  - Vaccinate against hepatitis A and/or hepatitis B
- Safe injection and infection control practices

MMWR 1998;47 (No. RR-19)

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Reduce Risks for Disease Progression and Further Transmission

- Identify persons at risk for HCV and test to determine infection status
  - Routinely identify at risk persons through history, record review
- Provide HCV-positive persons
  - Medical evaluation and management
  - Counseling
    - Prevent further liver damage
    - Prevent transmission to others

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HCV Testing Routinely Recommended

Based on increased risk for infection

- Ever injected illegal drugs
- Received clotting factors made before 1987
- Received blood/organs before July 1992
- Ever on chronic hemodialysis
- Evidence of liver disease

Based on need for exposure management

- Healthcare, emergency, public safety workers after needle stick/mucosal exposures to HCV-positive blood
- Children born to HCV-positive women

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Postexposure Management for HCV

- IG, antivirals not recommended for prophylaxis
- Follow-up after needlesticks, sharps, or mucosal exposures to HCV-positive blood
  - Test source for anti-HCV
  - Test worker if source anti-HCV positive
    - Anti-HCV and ALT at baseline and 4-6 months later
    - For earlier diagnosis, HCV RNA at 4-6 weeks
  - Confirm all anti-HCV results with RIBA
- Refer infected worker to specialist for medical evaluation and management

Routine HCV Testing of Uncertain Need

Not confirmed as risk factor/prevalence low or unknown

- Recipients of transplanted tissue
- Intranasal cocaine or other non-injecting illegal drug users
- History of tattooing, body piercing

Confirmed risk factor but prevalence of infection low

- History of STDs or multiple sex partners
- Long-term steady sex partners of HCV-positive persons

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Mother-to-Infant Transmission of HCV

- Postexposure prophylaxis not available
- No need to avoid pregnancy or breastfeeding
  - Consider bottle feeding if nipples cracked/bleeding
- No need to determine mode of delivery based on HCV infection status
- Test infants born to HCV-positive women
  - >15-18 months old
  - Consider testing any children born since woman became infected
  - Evaluate infected children for CLD

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Sexual Transmission of HCV

Persons with One Long-Term Steady Sex Partner

- Do not need to change their sexual practices
- Should discuss with their partner
  - Risk (low but not absent) of sexual transmission
  - Counseling and testing of partner should be individualized
    - May provide couple with reassurance
    - Some couples might decide to use barrier precautions to lower limited risk further

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Sexual Transmission of HCV

Persons with High-Risk Sexual Behaviors

- At risk for sexually transmitted diseases, e.g., HIV, HBV, gonorrhea, chlamydia, etc.
- Reduce risk
  - Limit number of partners
  - Use latex condoms
  - Get vaccinated against hepatitis B
  - MSMs also get vaccinated against hepatitis A

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Other Transmission Issues

- HCV not spread by kissing, hugging, sneezing, coughing, food or water, sharing eating utensils or drinking glasses, or casual contact
- Do not exclude from work, school, play, child-care or other settings based on HCV infection status

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VIRAL HEPATITIS D

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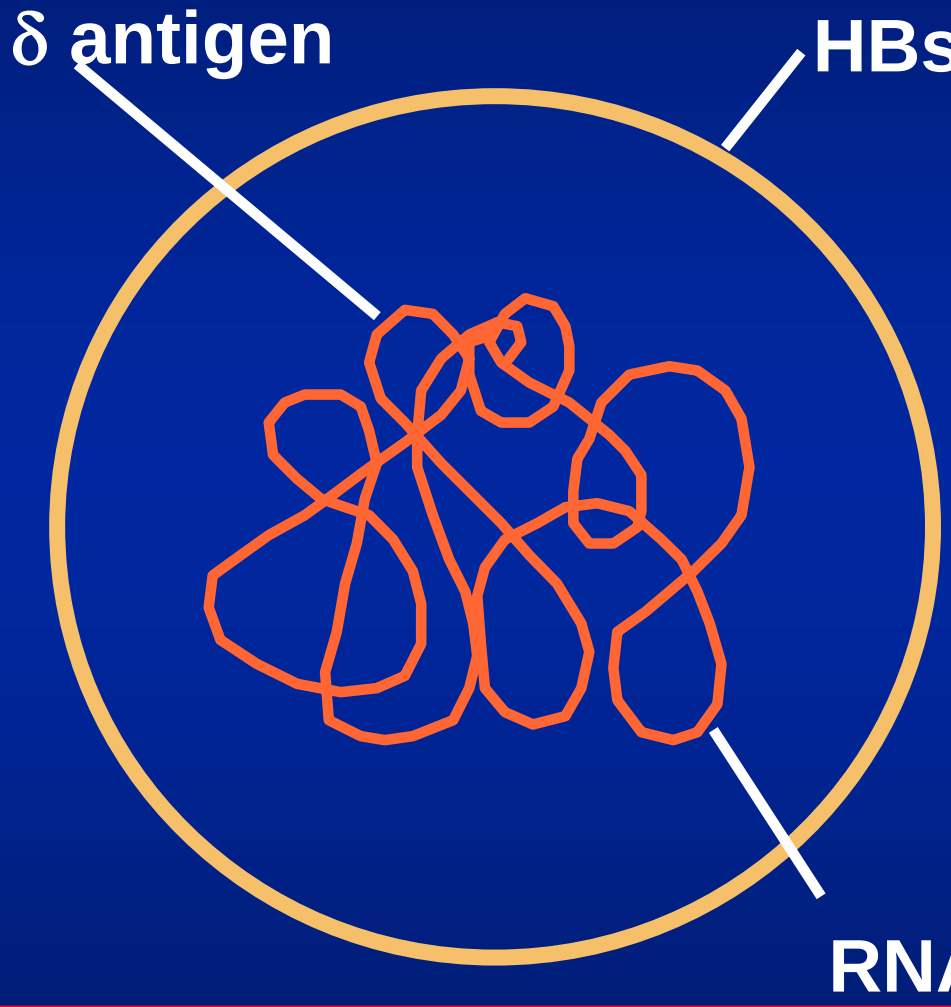
Hepatitis D (Delta) Virus



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Hepatitis D - Clinical Features

- Coinfection
  - severe acute disease
  - low risk of chronic infection
- Superinfection
  - usually develop chronic HDV infection
  - high risk of severe chronic liver disease

Hepatitis D Virus
Modes of Transmission

- Percutanous exposures
  - –injecting drug use
- Permucosal exposures
  - –sex contact

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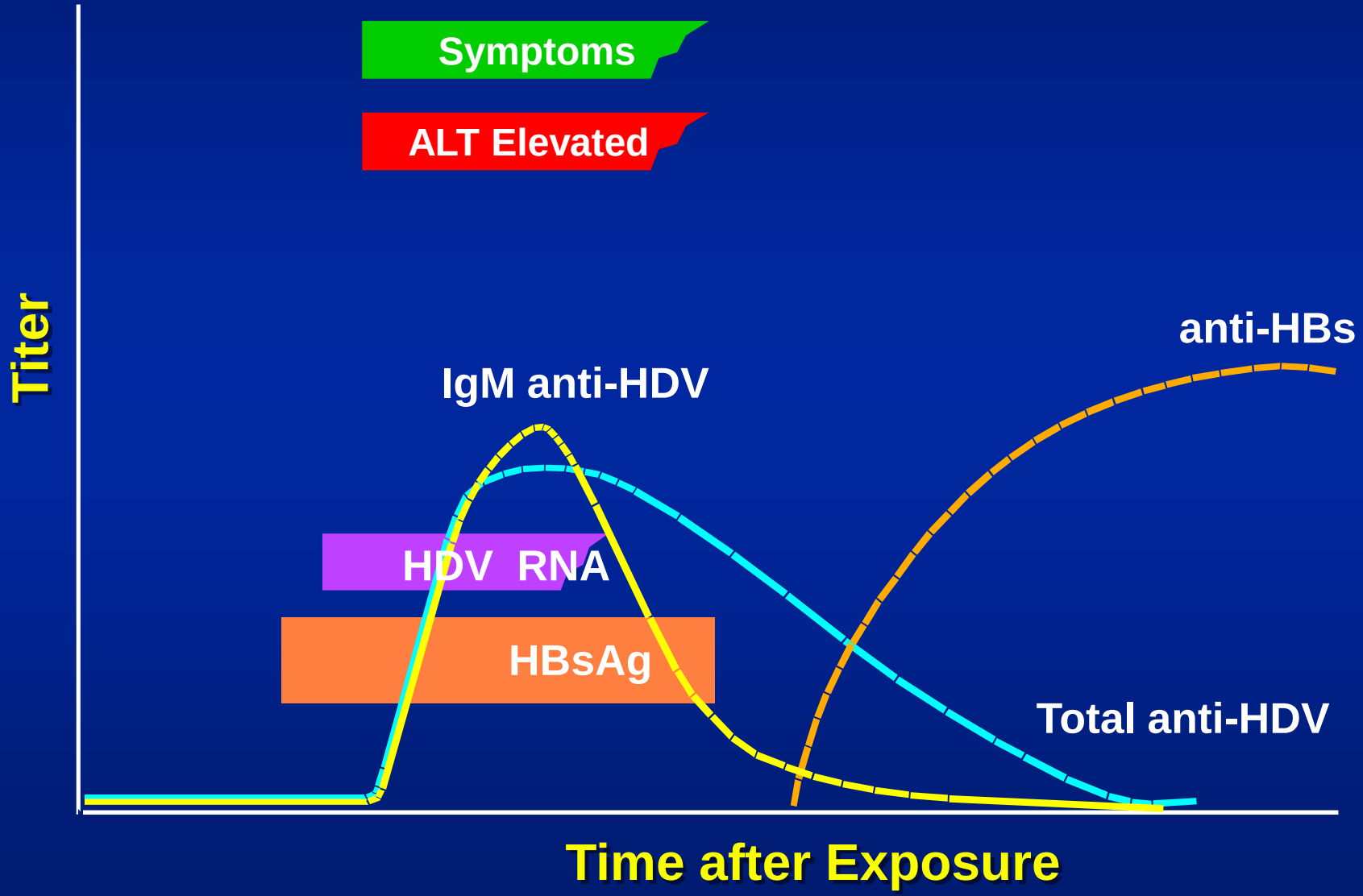
HBV - HDV Coinfection

Typical Serologic Course



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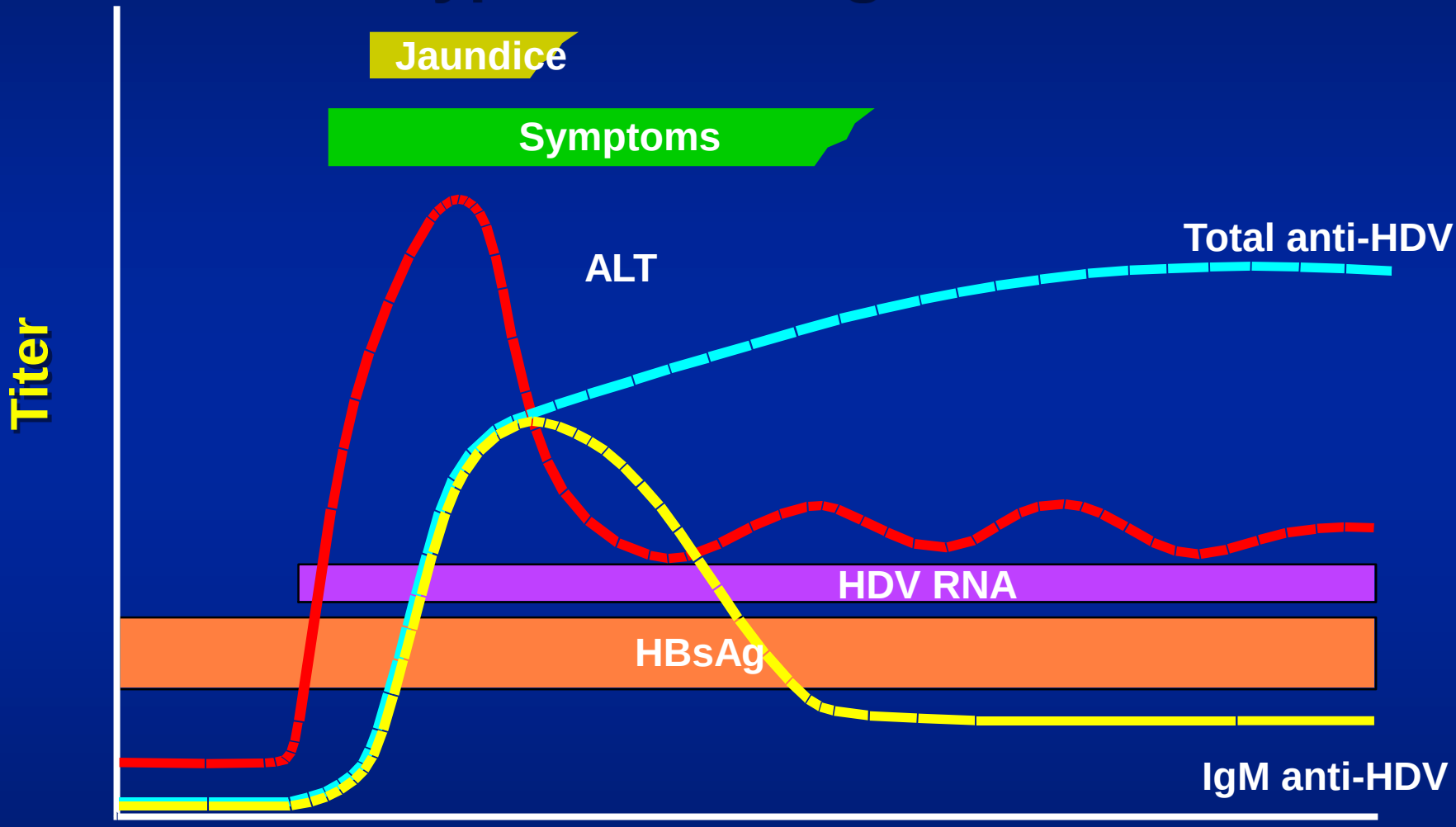
HBV - HDV Superinfection

Typical Serologic Course



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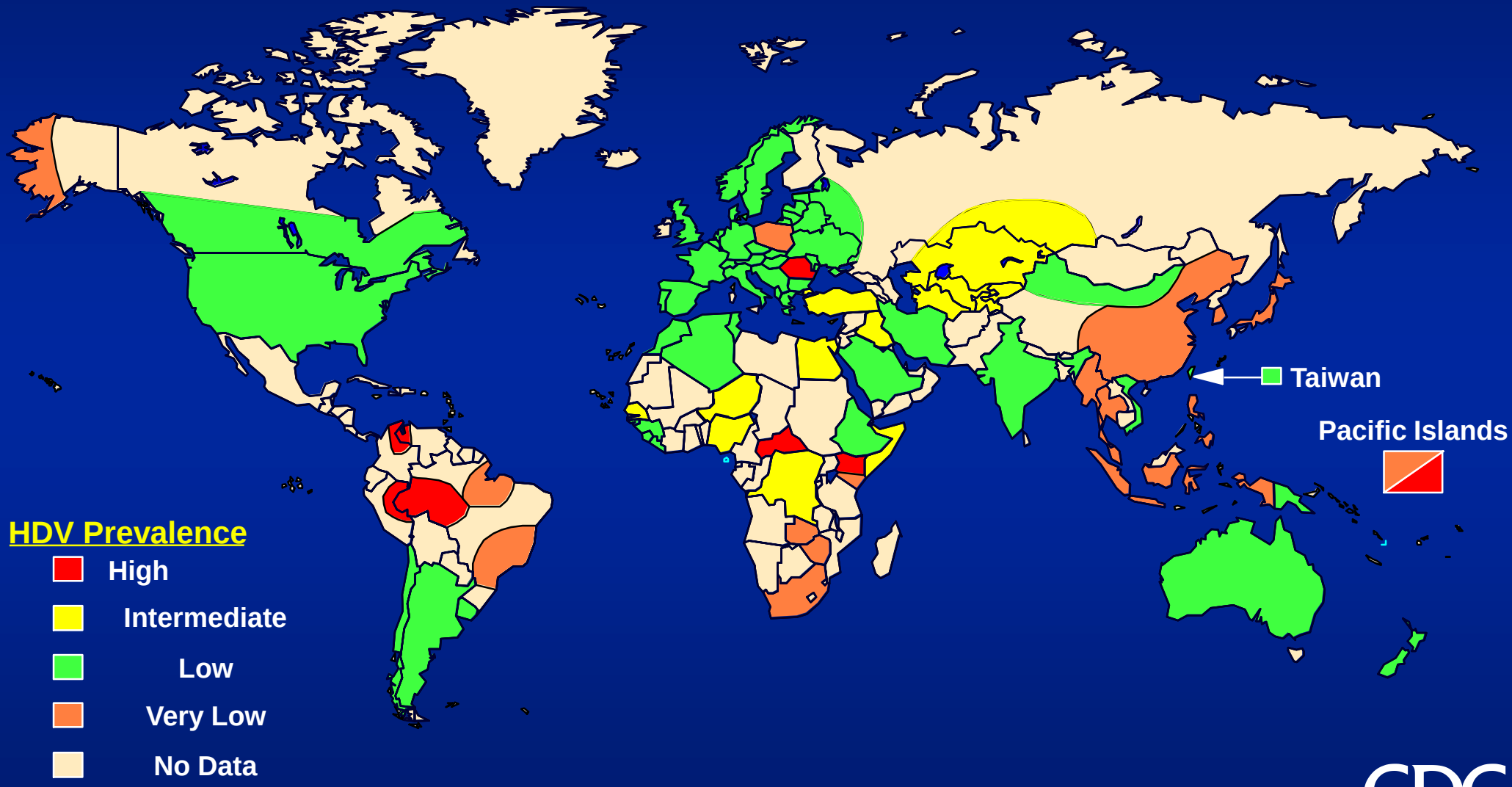
Geographic Distribution of HDV Infection



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Hepatitis D - Prevention

- HBV-HDV Coinfection

  Pre or postexposure prophylaxis to prevent HBV infection

- HBV-HDV Superinfection

  Education to reduce risk behaviors among persons with chronic HBV infection

VIRAL HEPATITIS E

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Hepatitis E is caused by the Hepatitis E virus (HEV), a positive-stranded RNA virus of the *Hepeviridae* family genus Orthohepevirus, comprises 4 species, Orthohepevirus A–D. Orthohepevirus A contains 7 genotypes (HEV-1–7).

Genotypes 1 and 2 infect humans only, while genotypes 3, and 4 are zoonotic and can infect humans and other mammals; genotypes 5 and 6 infect animals only. HEV-7 has been recently detected in a dromedary camels and transmitted to an immunosuppressed patient in the Middle East.

In Europe, autochthonous infections are mostly related to HEV-3; however, sporadically also infections with other genotypes can be detected that are either locally acquired (HEV-4) or travel-associated.

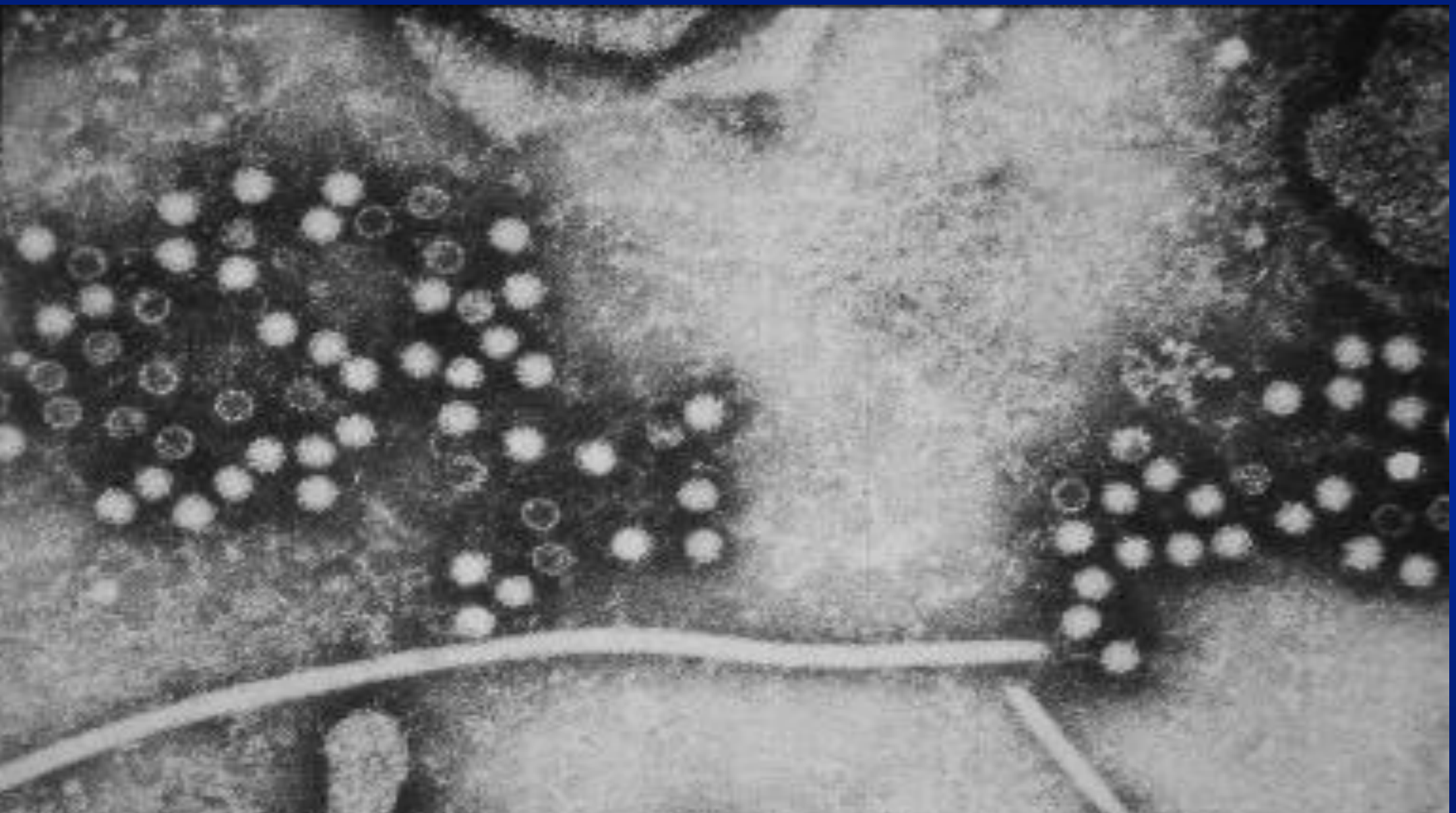
HEV infection in humans is mostly an asymptomatic infection. The majority of cases do not develop any symptoms but seroconvert.

In acute cases the infection causes a self-limiting hepatitis initially with fatigue, asthenia, nausea, fever and jaundice. Other signs can be elevated liver enzyme levels and abnormal liver function tests, abdominal pain and hepatosplenomegaly.

HEV-1 and -2, endemic in African and Asian countries, can cause severe disease and fulminant hepatitis particularly in pregnant women, with up to 21% mortality.

In Europe, where HEV-3 is endemic, the infection is not associated with severe disease in pregnant women and thus they are not considered as risk group.

Hepatitis E Virus



Hepatitis E - Clinical Features

- Incubation period: Average 40 days
  Range 15-60 days
- Case-fatality rate: Overall, 1%-3%
  Pregnant women, 15%-25%
- Illness severity: Increased with age
- Chronic sequelae: None identified

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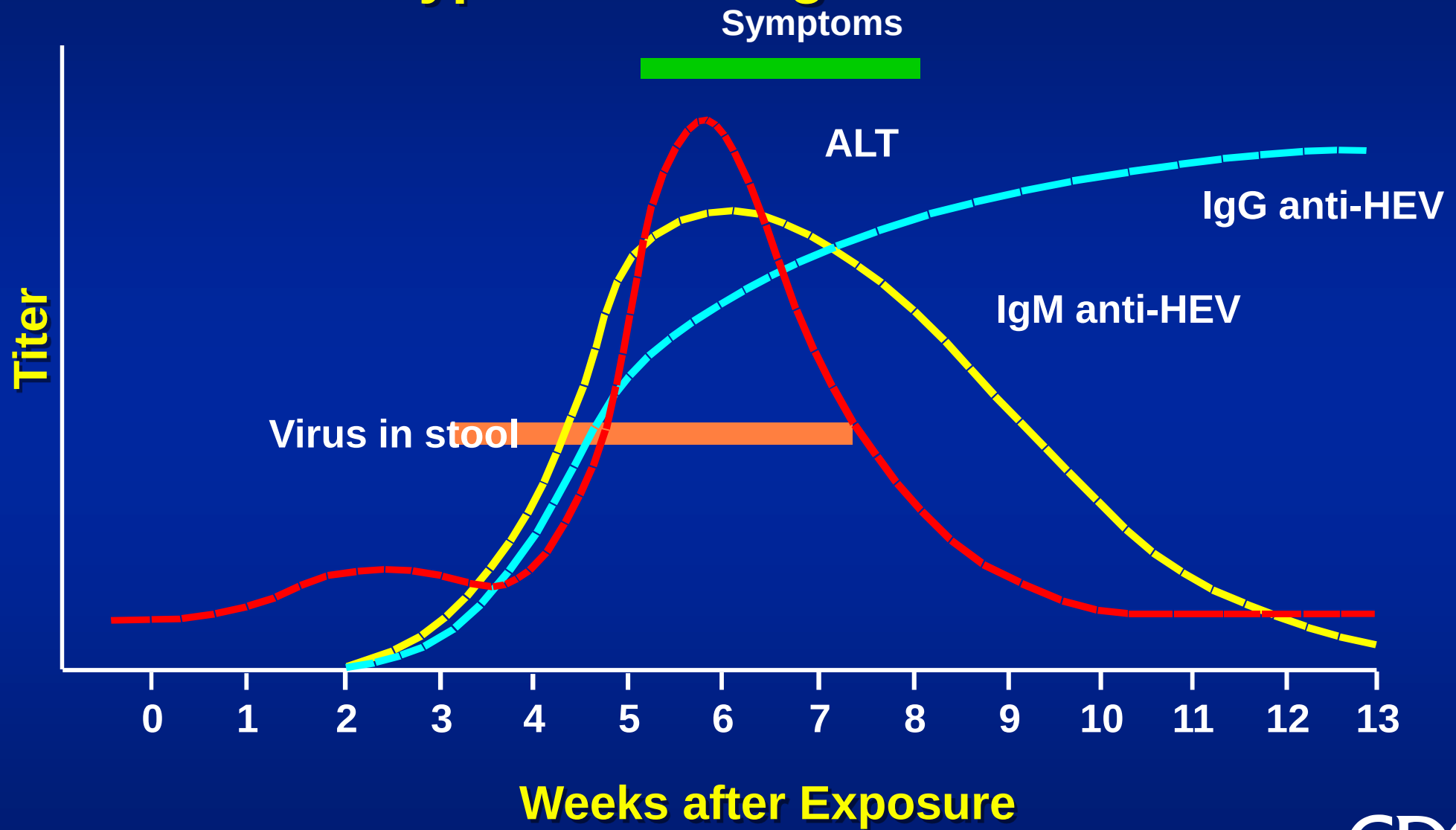
Hepatitis E Virus Infection

Typical Serologic Course



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Hepatitis E - Epidemiologic Features

- Most outbreaks associated with fecally contaminated drinking water
- Minimal person-to-person transmission
- U.S. cases usually have history of travel to HEV-endemic areas

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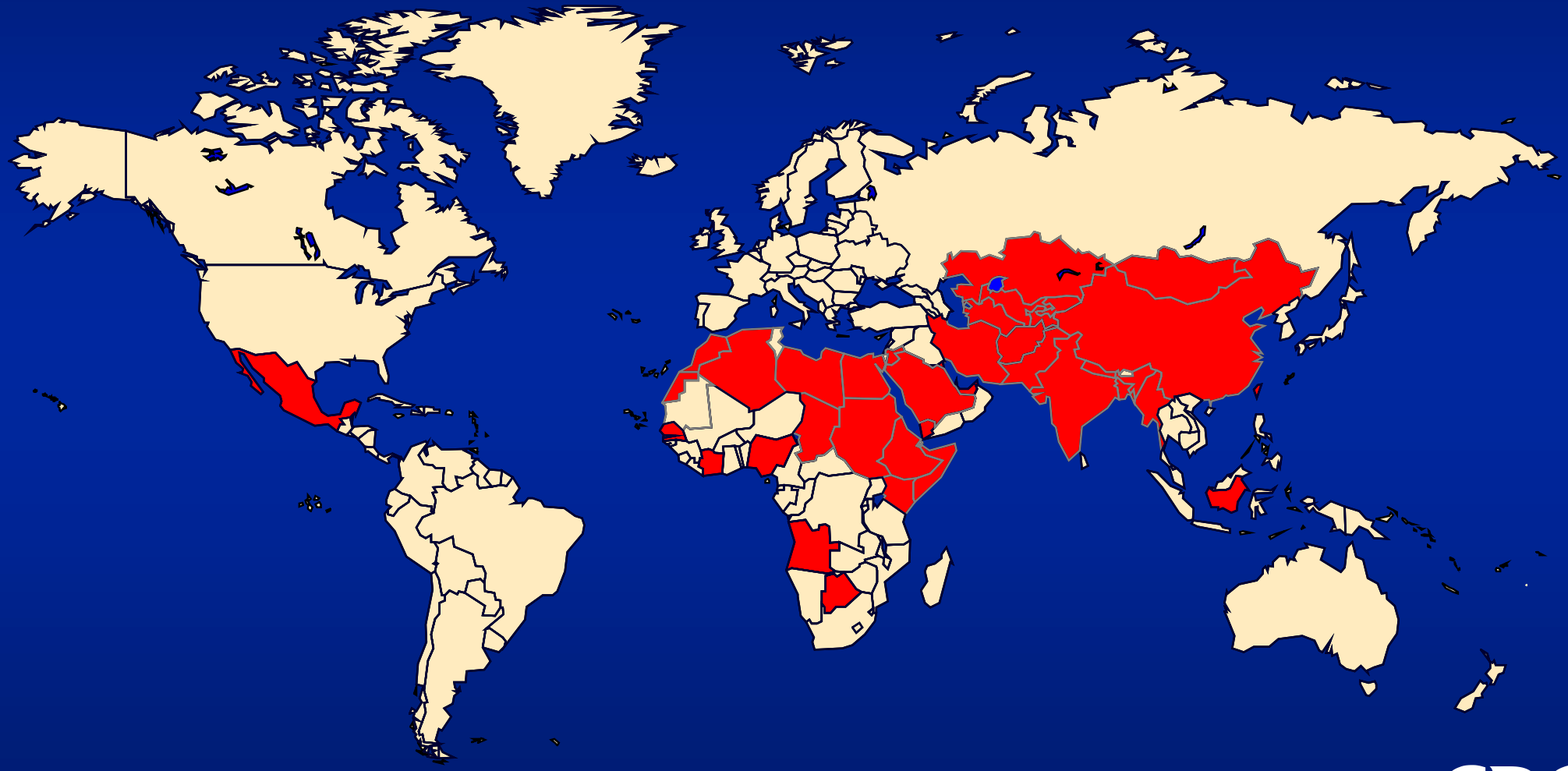
Geographic Distribution of Hepatitis E

Outbreaks or Confirmed Infection in >25% of Sporadic Non-ABC Hepatitis



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Prevention and Control Measures for Travelers to HEV-Endemic Regions

- **Avoid drinking water (and beverages with ice) of unknown purity, uncooked shellfish, and uncooked fruit/vegetables not peeled or prepared by traveler**
- **IG prepared from donors in Western countries does not prevent infection**
- **Unknown efficacy of IG prepared from donors in endemic areas**
- **Vaccine?**

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Key characteristics of HAV, HBV, HCV, HDV, HEV

	A	B	C	D	E
Causative agent	Picornaviridae	Hepadnaviridae	Raviviridae	Deltaviridae	Hepeviridae
	RNA	DNA	RNA	RNA	RNA
Incubation period	2 – 6 weeks	2 - 6 months	2 - 6 months	3-7 weeks	2 - 10 weks
Characteristic of acute hepatitis	Case fatality increases with age	Acute hepatitis more common in adults	Acute hepatitis uncommon, almost never fulminant	Superinfection with HDV in chronic heptitis B may lead to fulminnat disease	High case fatality in pregnant women -10-20 %; other 1 -2 %
Biomarker of recent infection	IgM anti-HAV	IgM anti-HBc	None	IgM anti-HDV	IgM anti-HEV
Chronic infection	none	Chronic infection leading to sequelae	Chronic infection leading to sequelae	Chronic hepatitis that copmlicated chronic hepatitis B	Very rare
Cirrhosis and hepatocelular Ca	No	Yes; 0,1 -1,0 % are fulminant	Yes; 50 % can be fulminant	Yes; 5 - 20 % can be fulminant	NO
The period of infectivity	last 2 weeks of incubation period	last 2 months of incubation period	last 2 months of incubation period	??	??
	first day of acute stage	entire period of acute stage	entire period of acute stage		
		chronic disease, carriers	chronic disease, carriers		
Infectious biological material	faeces	blood	blood	blood	faeces
	viremia - 1. day of illnes	genital secretions	genital secretions		meat of animals
Mode of transmission	Person-to person	Perinatal	Blodborne	Blodborne	Waterborne
	Foodborne	Bloodborne	Perinatal		Foodborne
	Waterborne	Sexual	Sexual		Person-to person
	Inactivated hepatitis A vaccines are	Active (recombinant			Vaccine licensed in China;