VIRAL HEPATITIS

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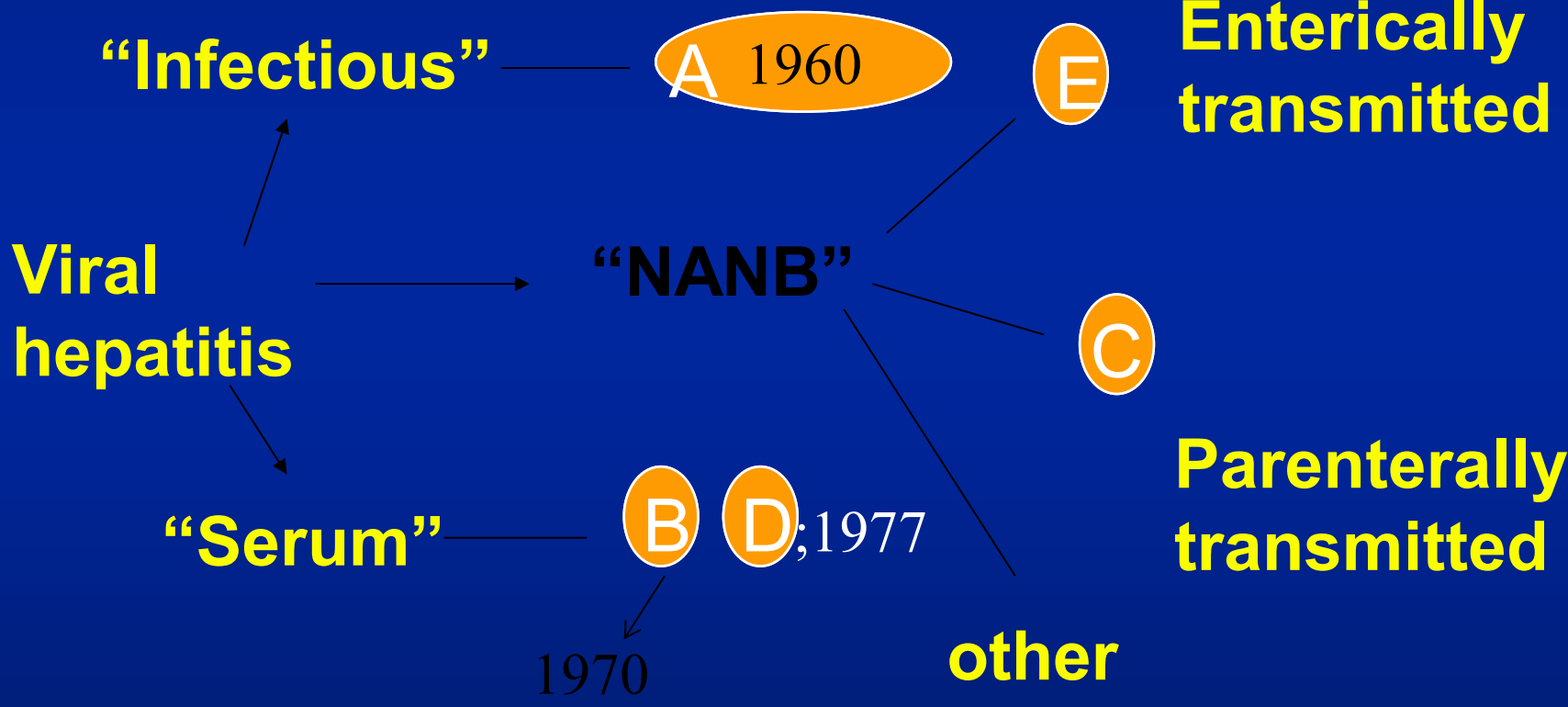
VIRAL HEPATITIS

HISTORICAL PERSPECTIVE



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VIRAL HEPATITIS A

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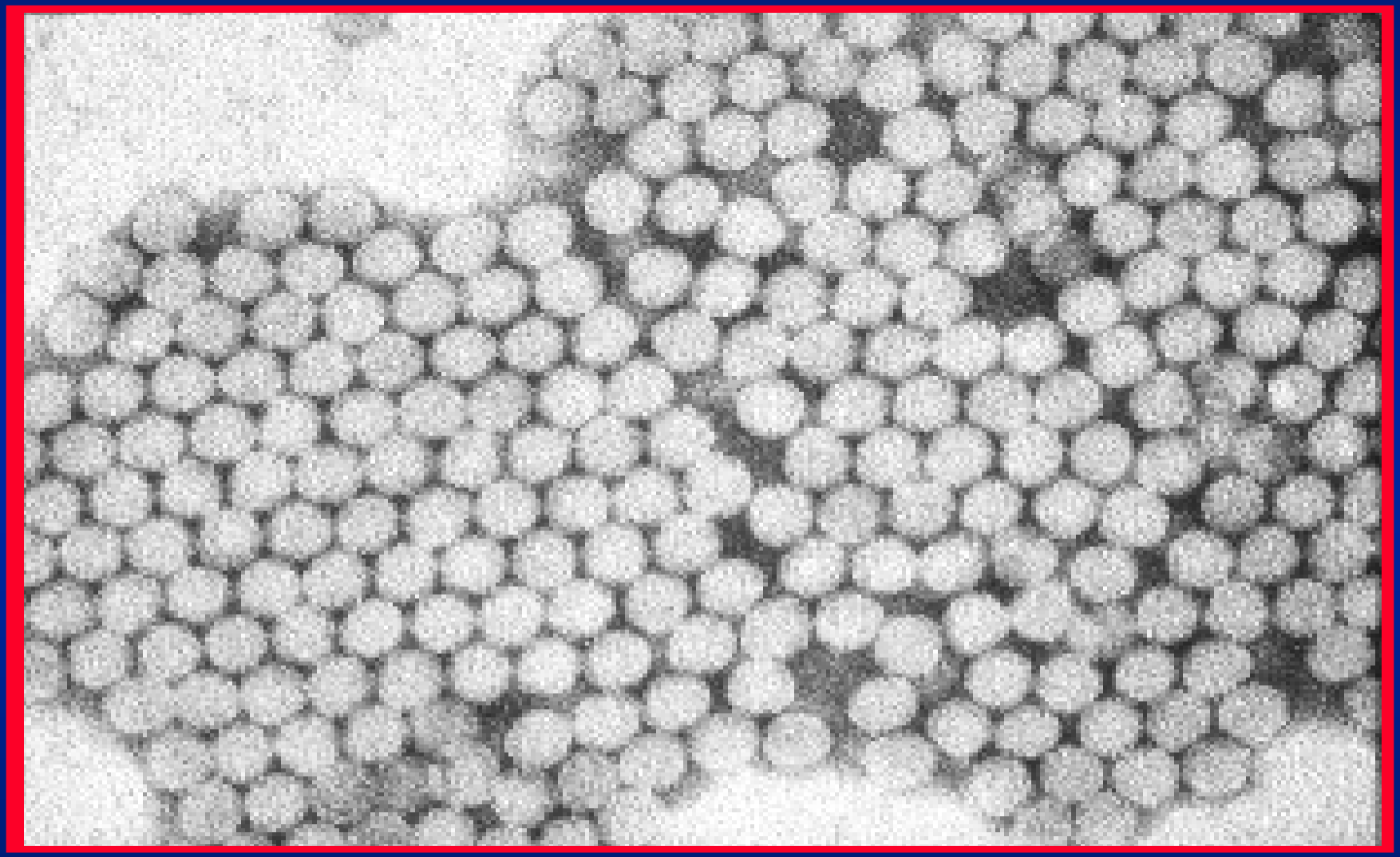
HEPATITIS A VIRUS



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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

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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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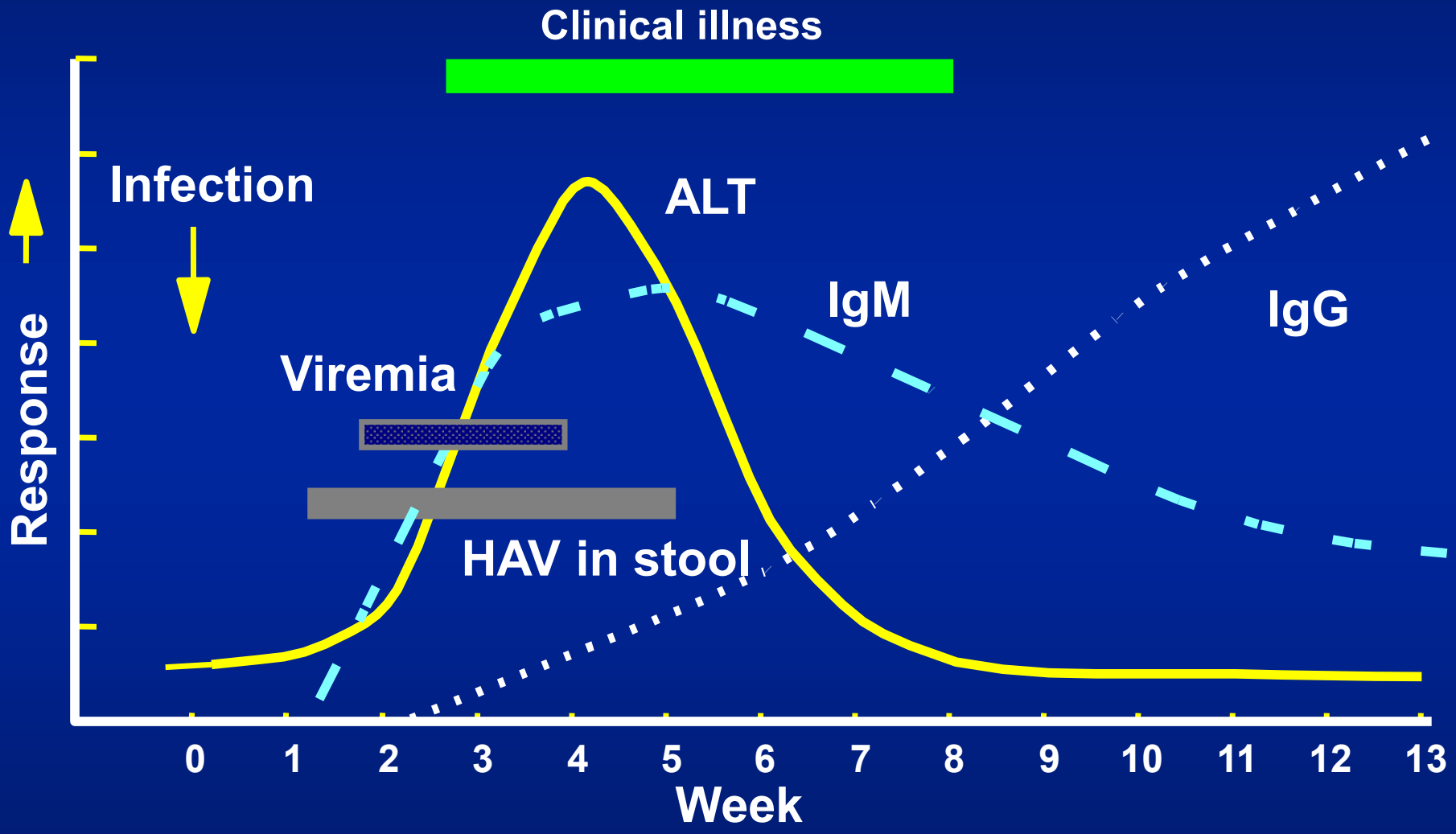
EVENTS IN HEPATITIS A VIRUS INFECTION



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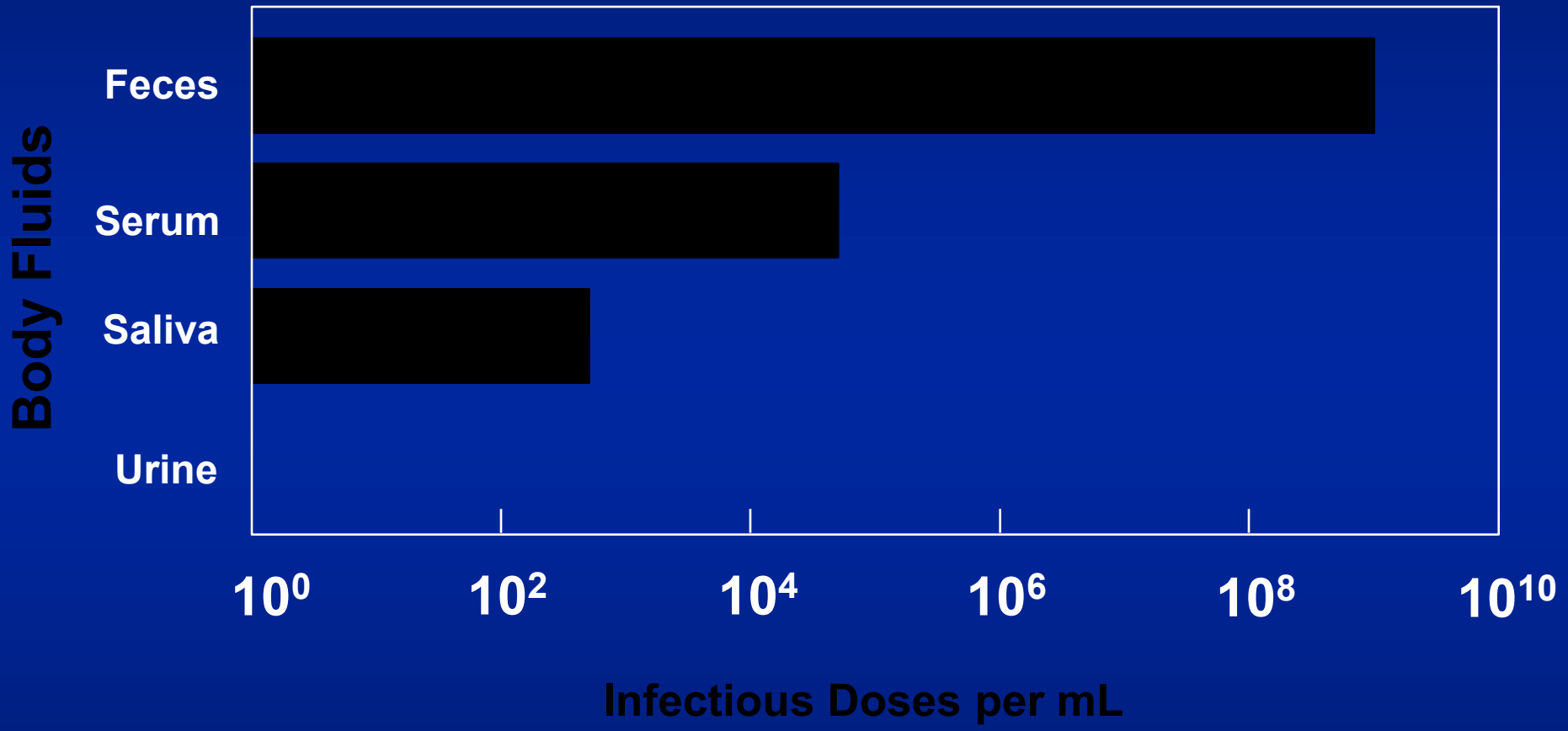
CONCENTRATION OF HEPATITIS A VIRUS IN VARIOUS BODY FLUIDS



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

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Is estimated that in 2013 HAV caused 14 900 deaths.

The severity of clinical disease associated with HAV infection increases with increasing age; jaundice occurs among less than:

- 10% of children younger than 6 years of age,
- 40%-50% of older children, and
- 70%-80% of adults.

Complications of hepatitis A include fulminant hepatitis, in which the case fatality rate can be greater than 50% despite medical interventions such as liver transplantation; cholestatic hepatitis, with very high bilirubin levels that can persist for months; and relapsing hepatitis, in which exacerbations can occur weeks to months after apparent recovery. Chronic infection does not occur following HAV infection.

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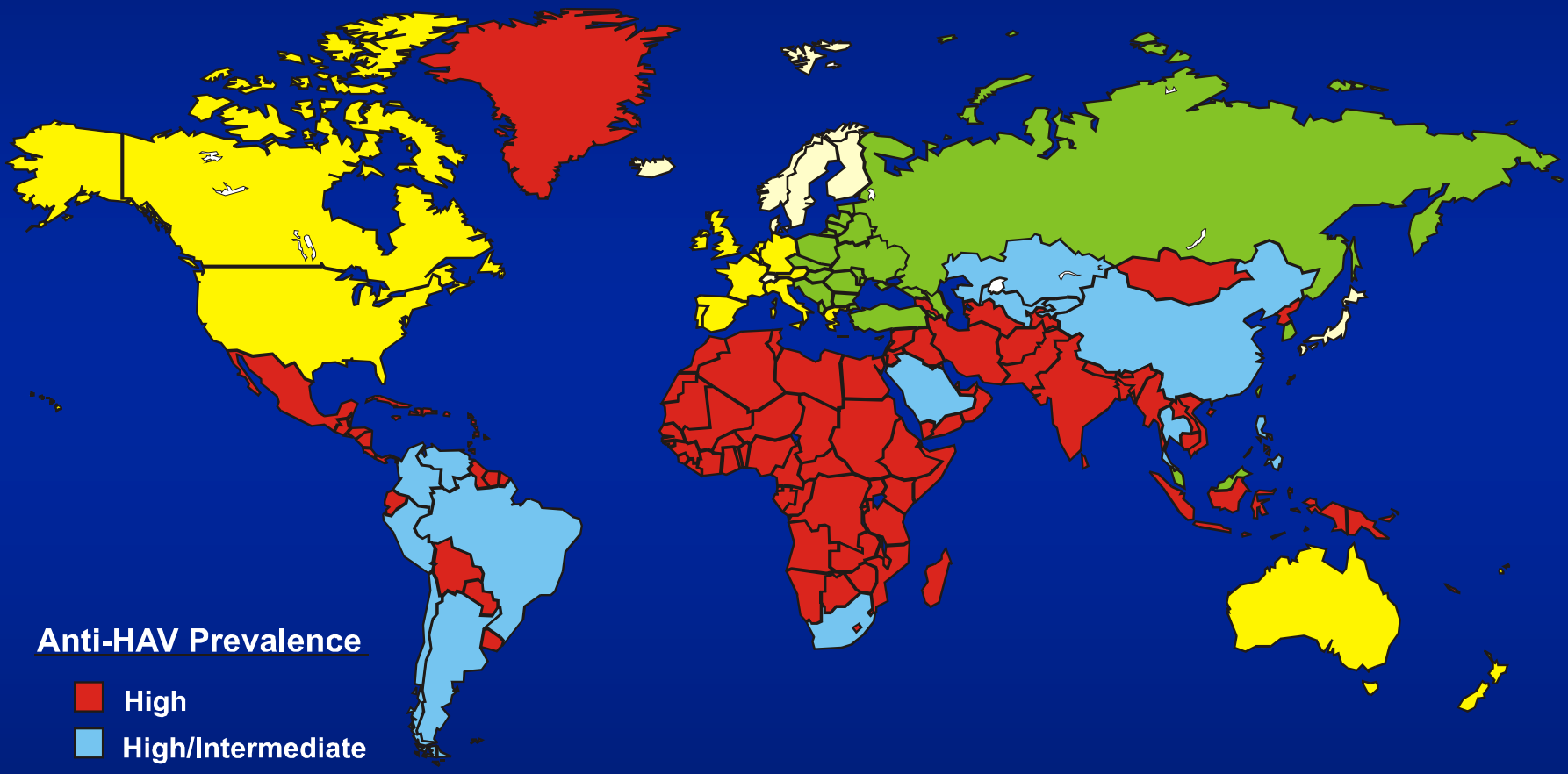
GEOGRAPHIC DISTRIBUTION OF HEPATITIS A VIRUS INFECTION



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ACUTE HEPATITIS A CASE DEFINITION FOR SURVEILLANCE

- **Clinical criteria**

  An acute illness with:
  - discrete onset of symptoms (e.g. fatigue, abdominal pain, loss of appetite, intermittent nausea, vomiting), **and**
  - jaundice or elevated serum aminotransferase levels

- **Laboratory criteria**
  - IgM antibody to hepatitis A virus (anti-HAV) positive

- **Case Classification**
  - Confirmed. A case that meets the clinical case definition and is laboratory confirmed or a case that meets the clinical case definition and occurs in a person who has an epidemiologic link with a person who has laboratory-confirmed hepatitis A (i.e., household or sexual contact with an infected person during the 15-50 days before the onset of symptoms).

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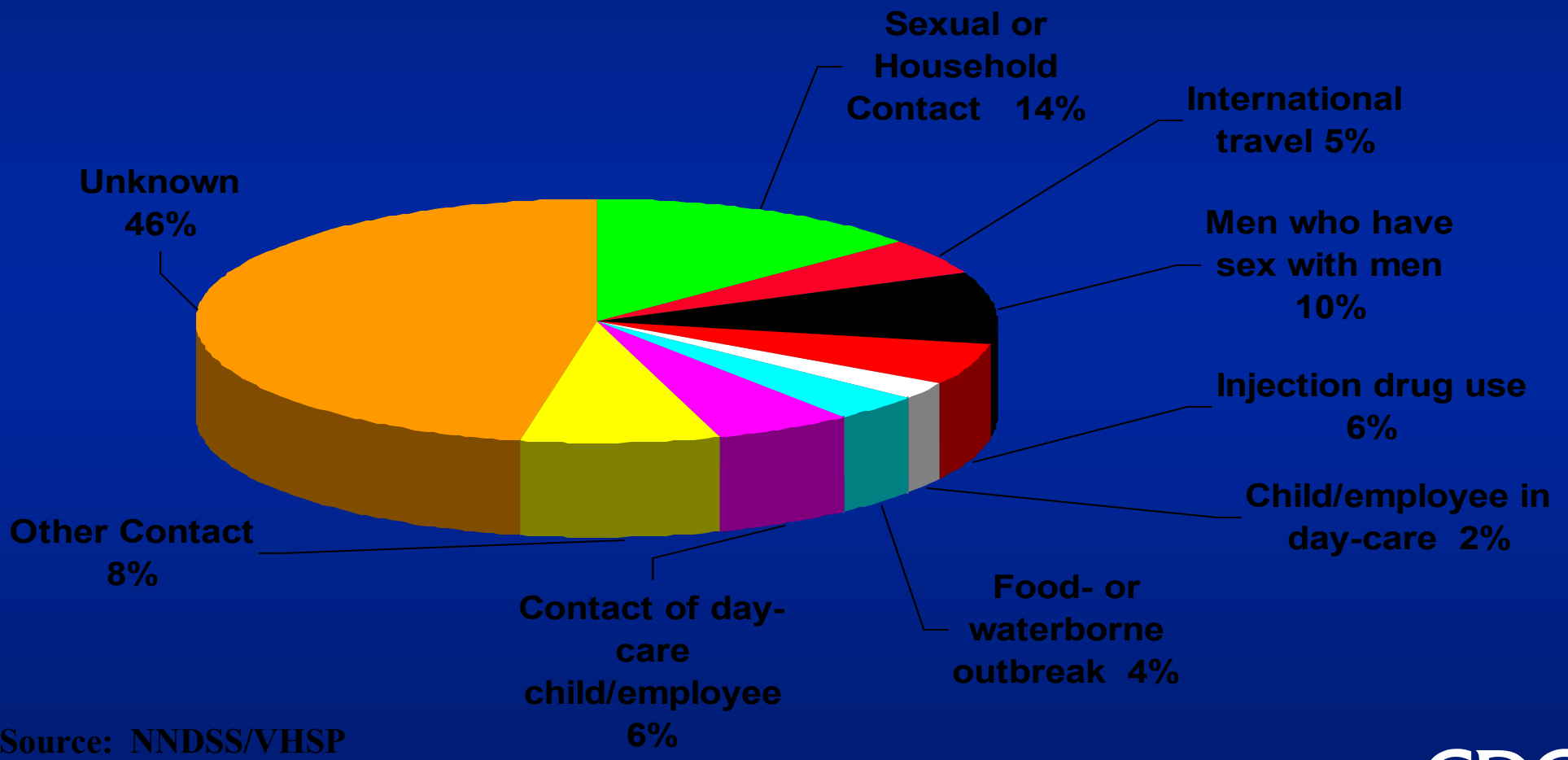
RISK FACTORS ASSOCIATED WITH REPORTED HEPATITIS A, 1990-2000, UNITED STATES



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

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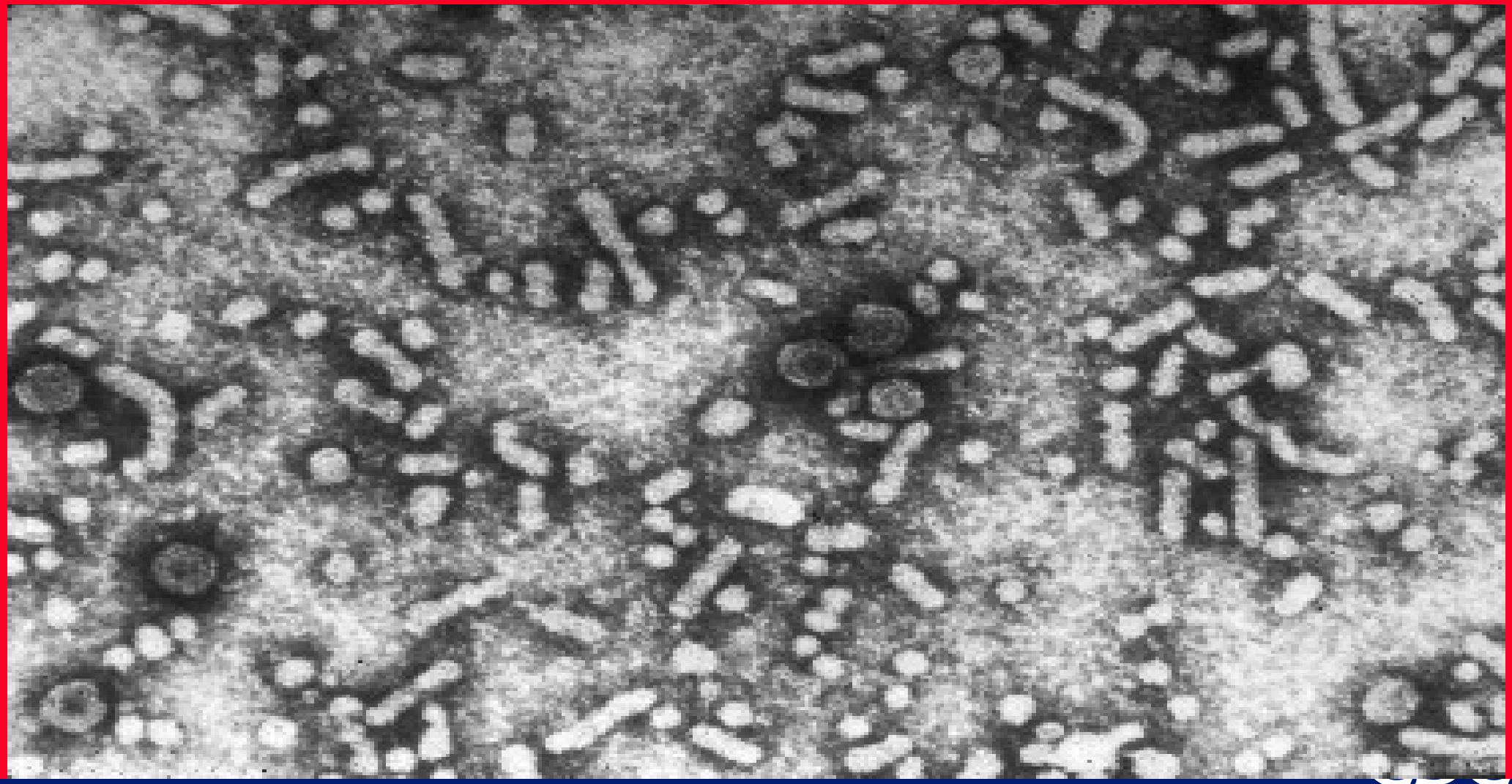
The hepatitis_ B virus is a DNA virus belonging to the Hepadnaviridae family of viruses.



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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: ⇩

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)
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AND PREVENTION

The disease occurs worldwide.

In 2013, HBV caused:

- 686 000 deaths, including 68 600 deaths from fulminant hepatitis,
- 300 000 deaths from hepatocellular carcinoma
- 317 400 deaths from cirrhosis

with a very high burden among an estimated 280 million carriers (prevalence 3,7 %).

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.

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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.

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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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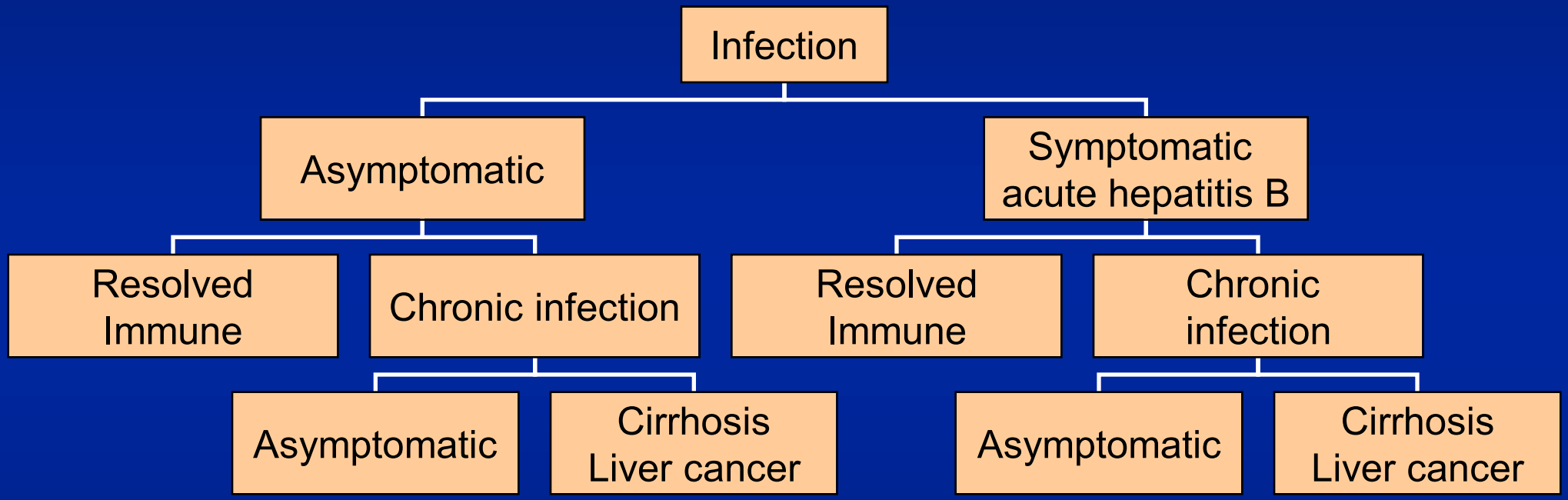
Outcome of HBV Infection



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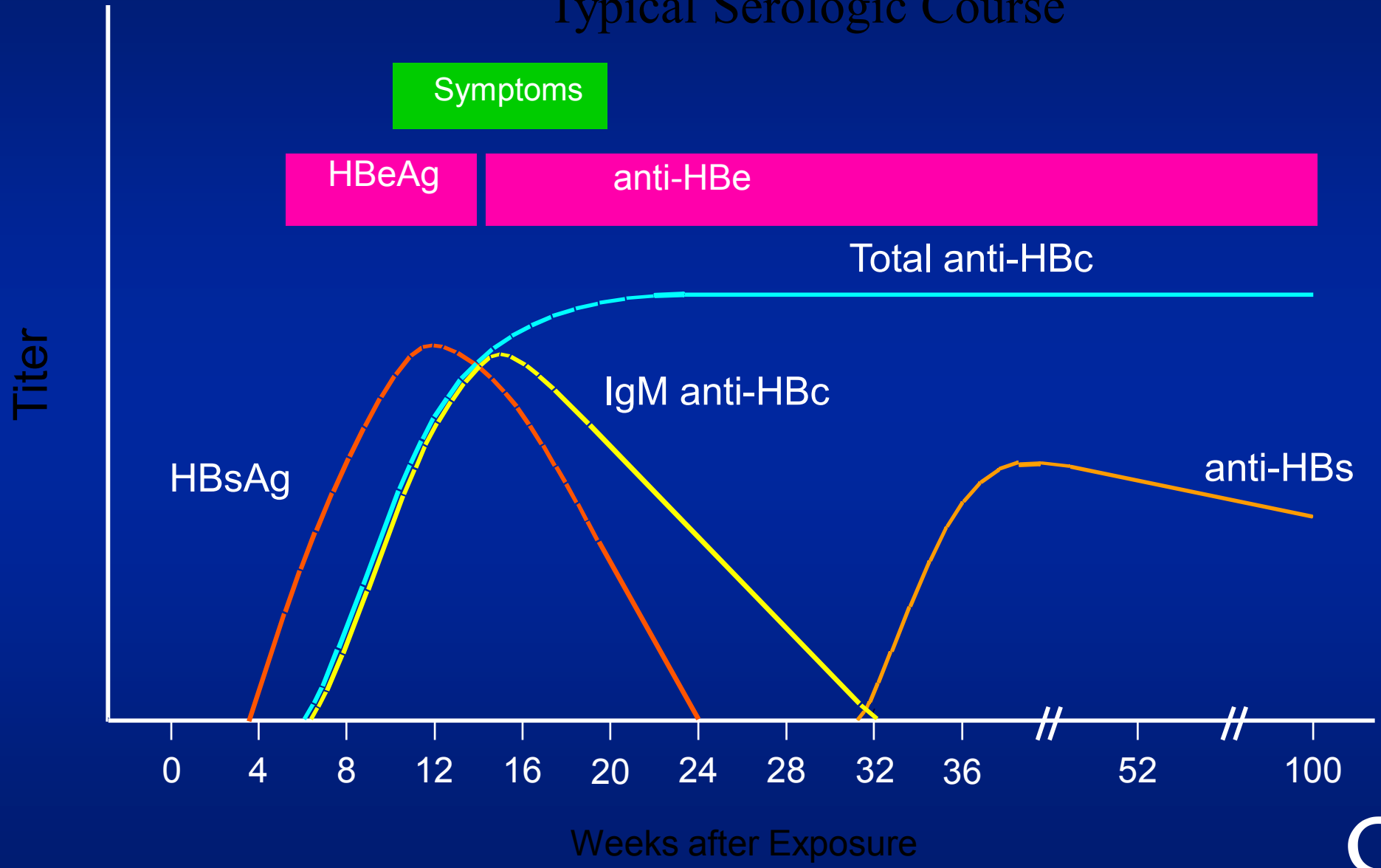
Acute Hepatitis B Virus Infection with Recovery

Typical Serologic Course



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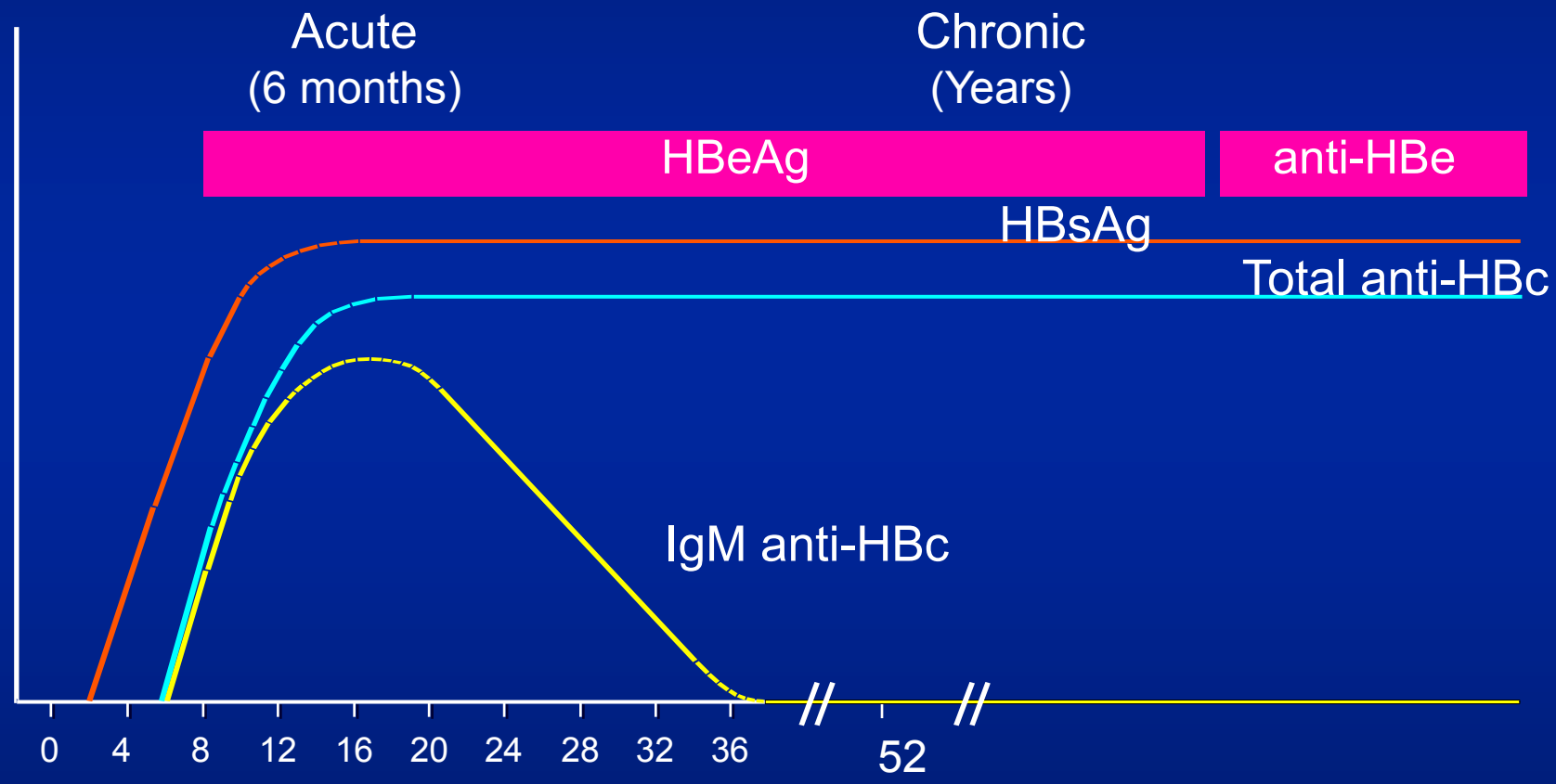
Progression to Chronic Hepatitis B Virus Infection

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	saliva	sweat
		tears
		breast milk

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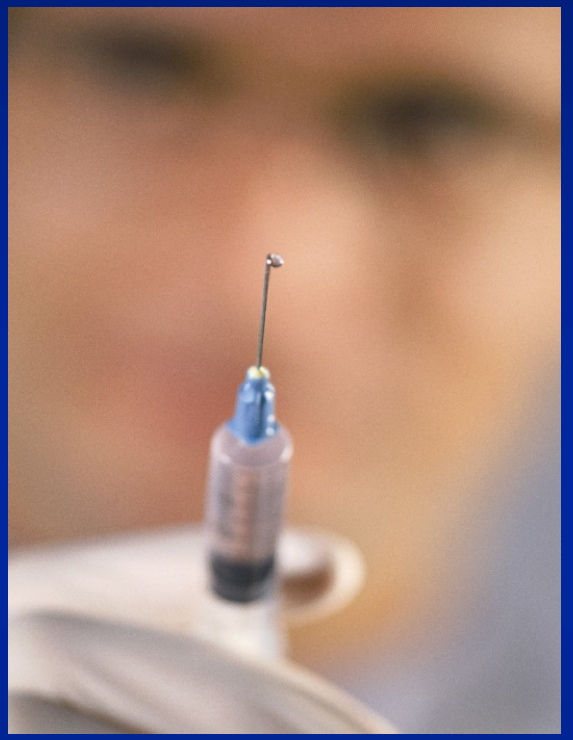
Elimination of HBV Transmission, United States

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)
- 2 dose series (adult dose) licensed by FDA for 11-15 year olds (Merck)
- 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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VIRAL HEPATITIS TYPE C B

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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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	10%-70% (most asx)
Cirrhosis	<5%-20%
Mortality from CLD	1%-5%

Age-related

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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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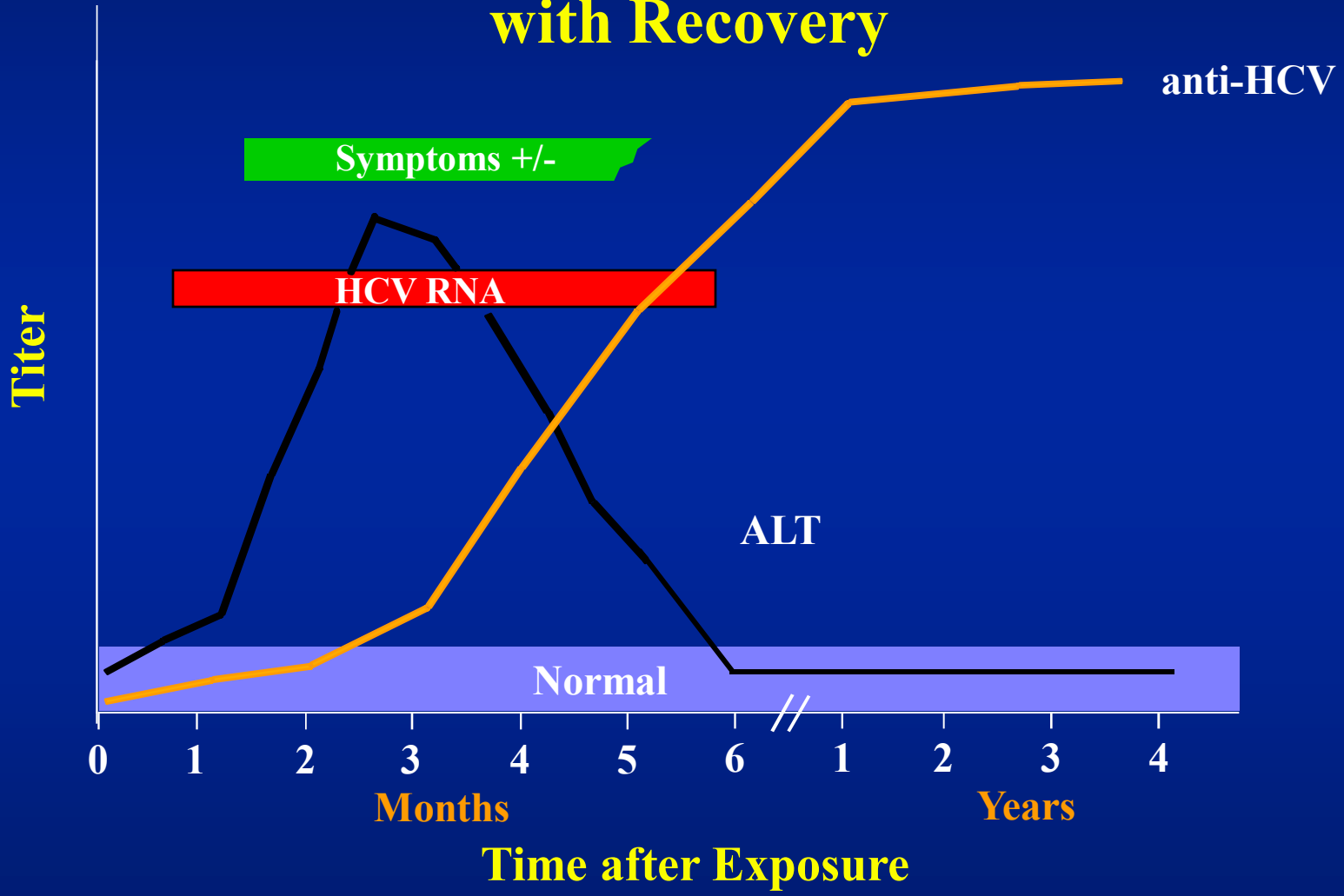
Serologic Pattern of Acute HCV Infection with Recovery



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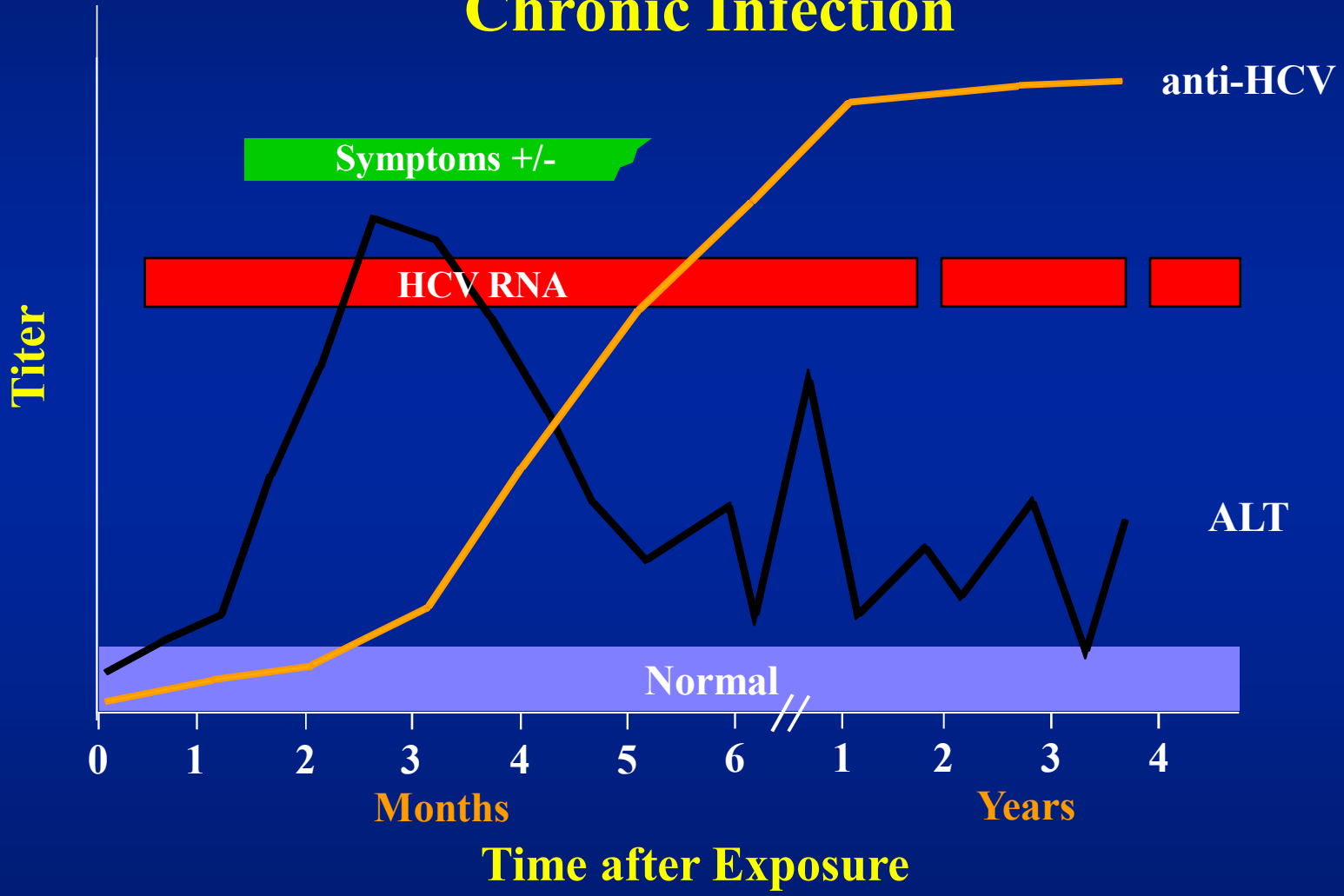
Serologic Pattern of Acute HCV Infection with Progression to Chronic Infection



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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

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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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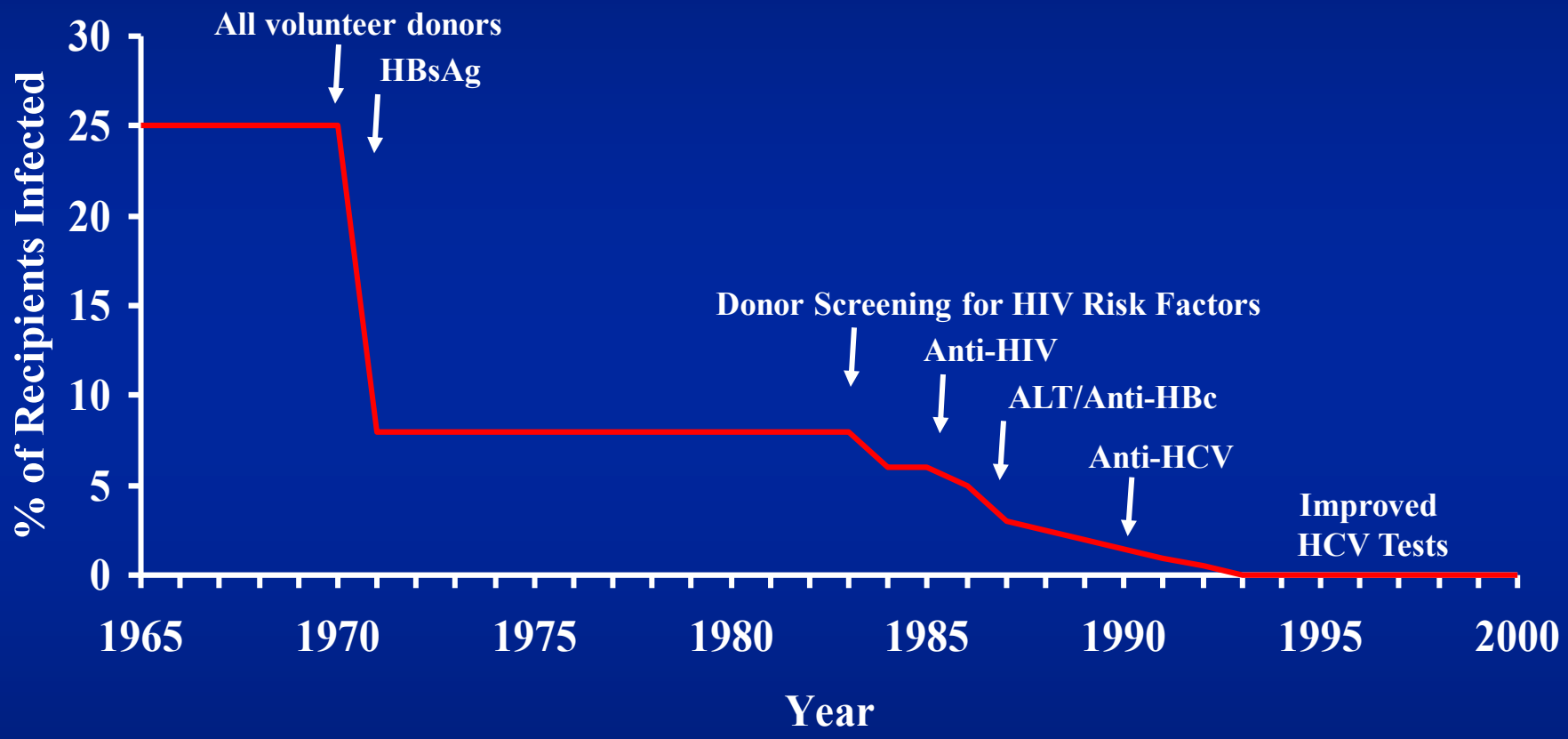
Posttransfusion Hepatitis C



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

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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

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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

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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

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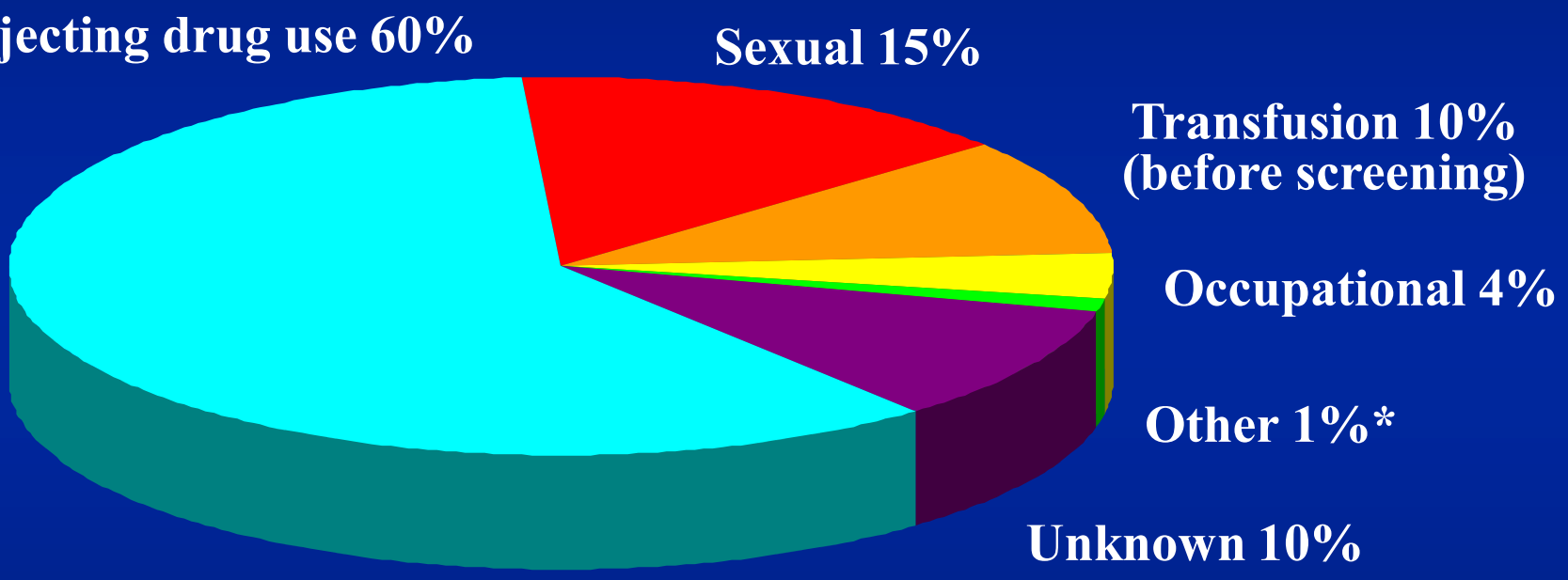
Sources of Infection for Persons With Hepatitis C



* 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

MMWR 1998;47 (No. RR-19)

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

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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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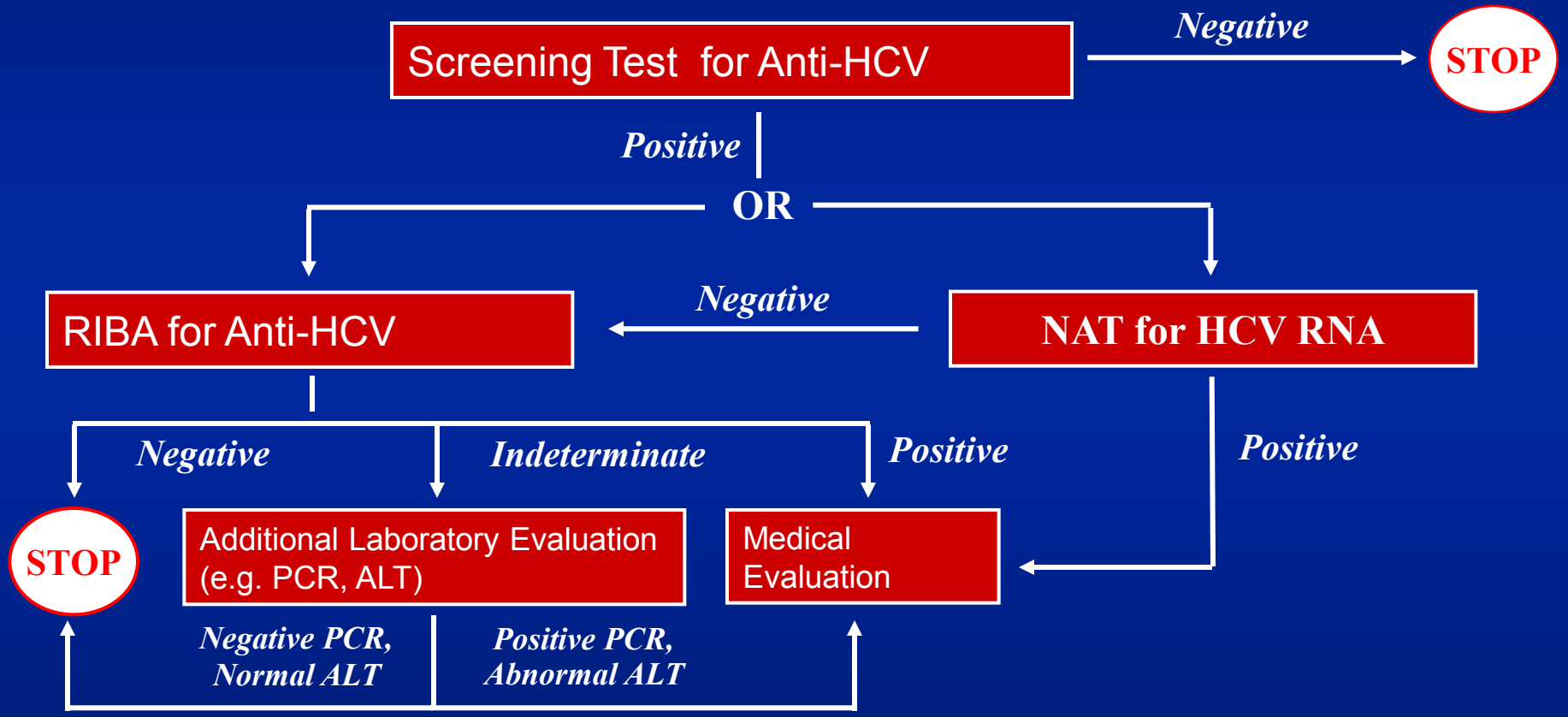
HCV Infection Testing Algorithm for Diagnosis of Asymptomatic Persons



Source: MMWR 1998;47 (No. RR 19)

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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

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

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

VIRAL HEPATITIS D

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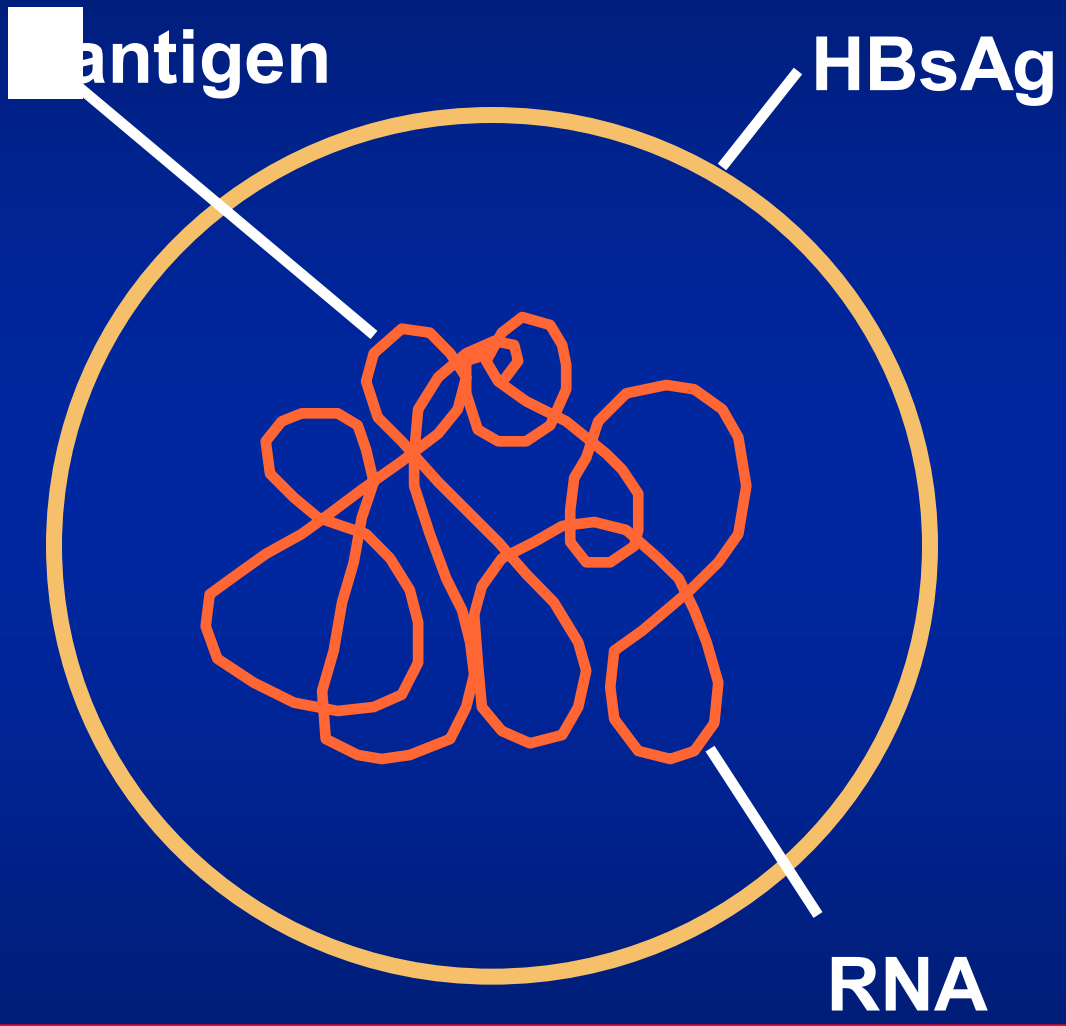
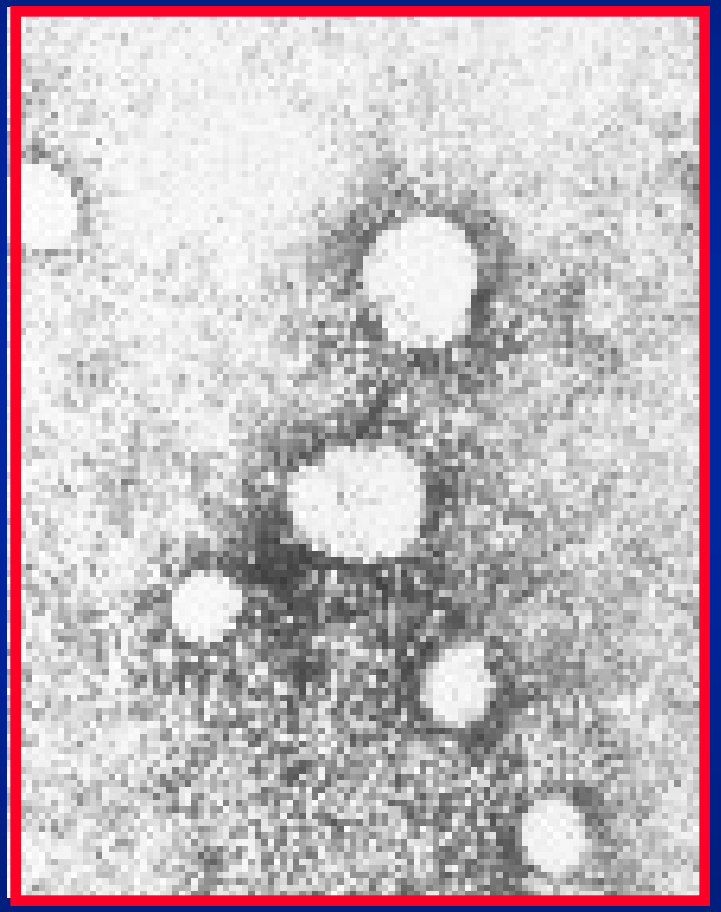
Hepatitis D (Delta) Virus





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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

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Hepatitis D Virus
Modes of Transmission

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

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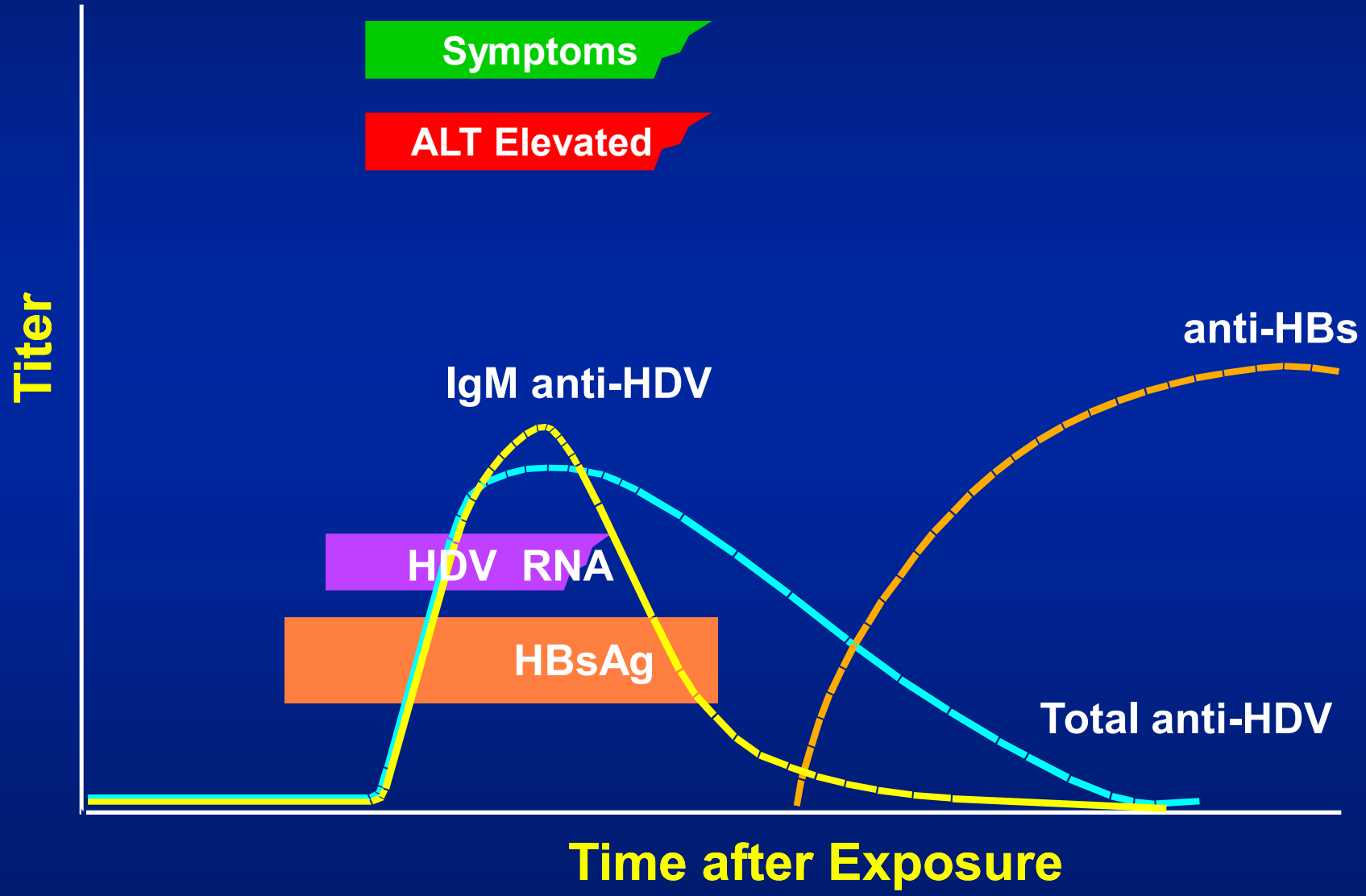
HBV - HDV Coinfection

Typical Serologic Course



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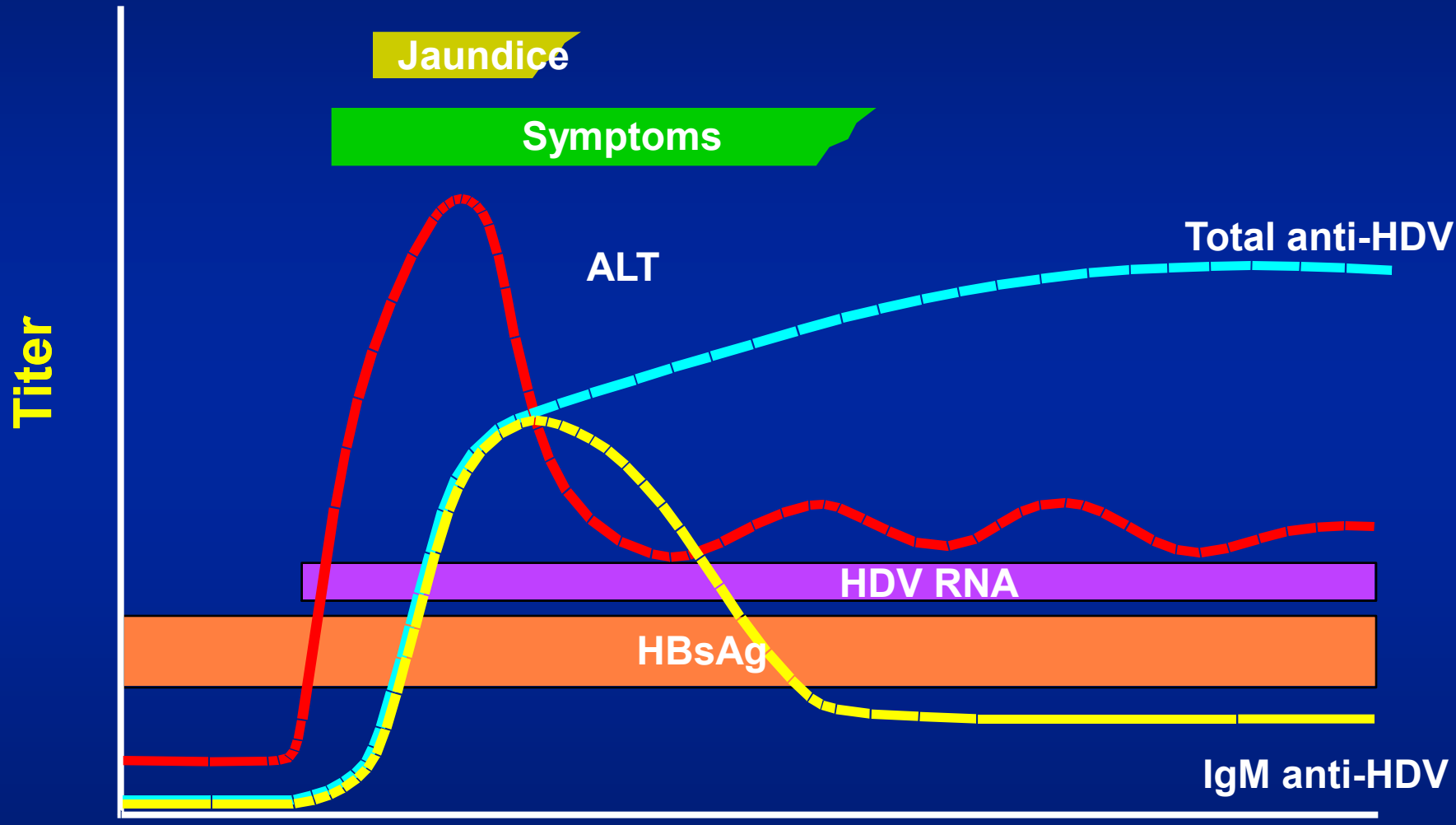
HBV - HDV Superinfection

Typical Serologic Course



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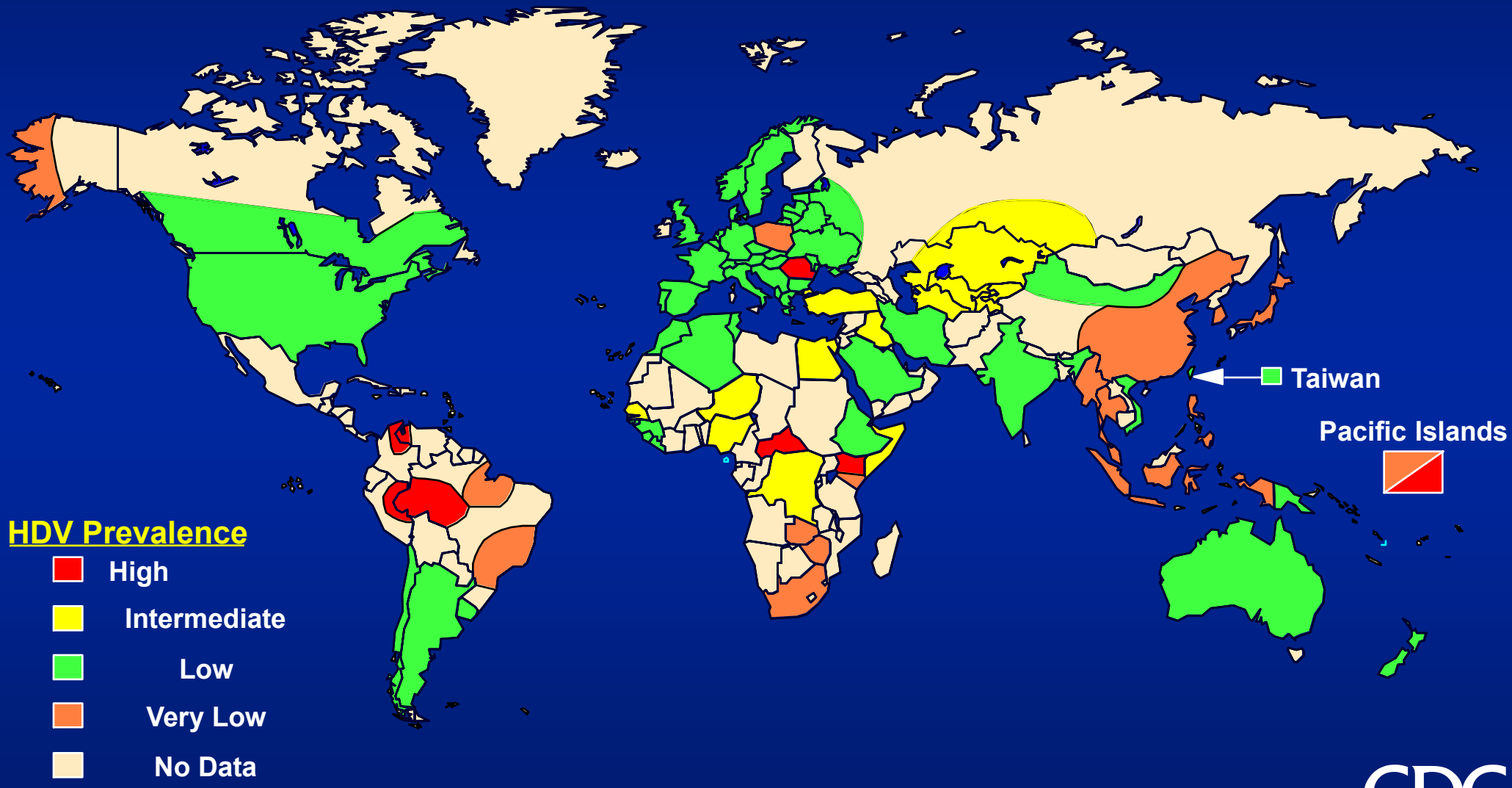
Geographic Distribution of HDV Infection



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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

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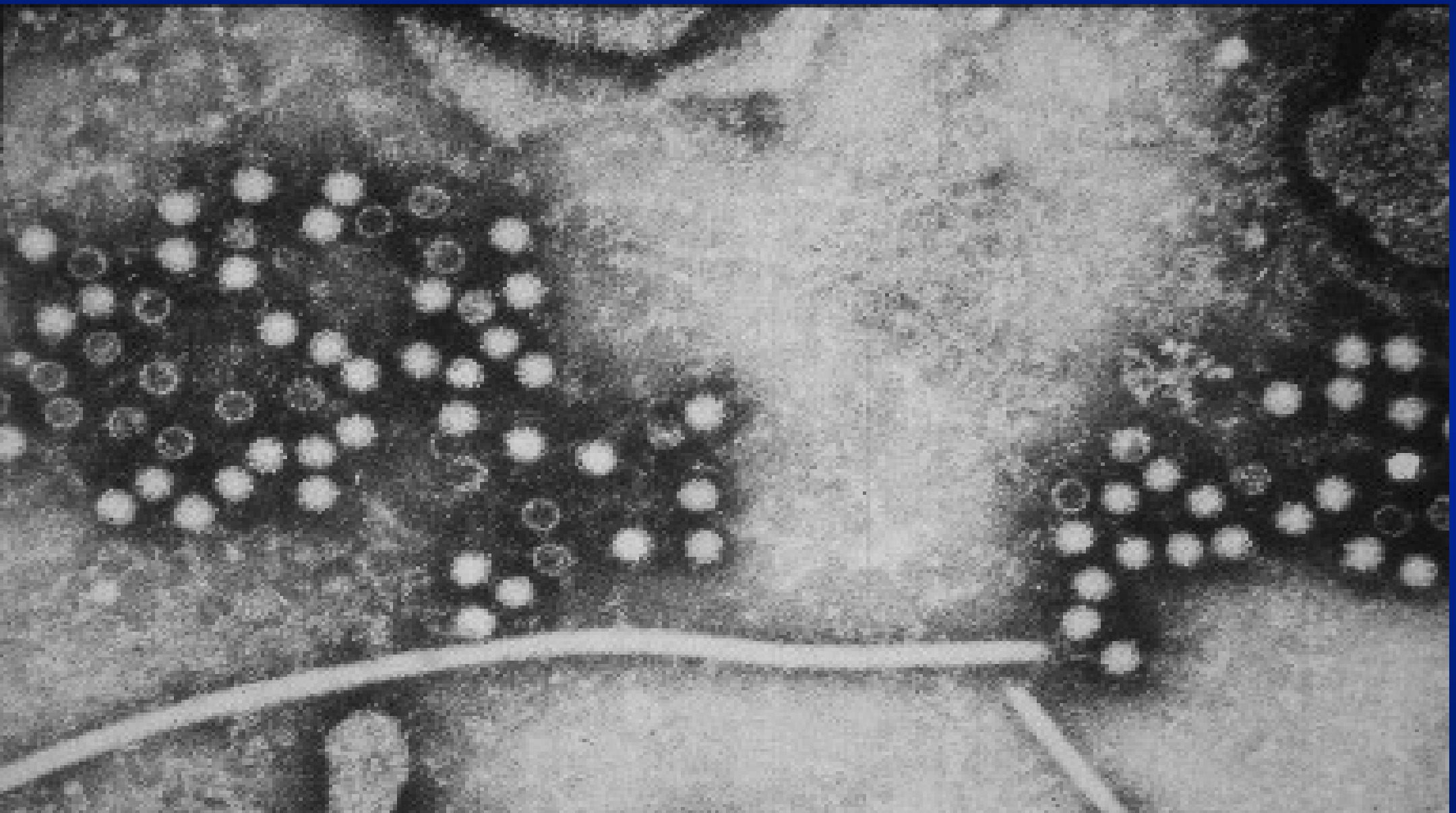
Hepatitis E Virus



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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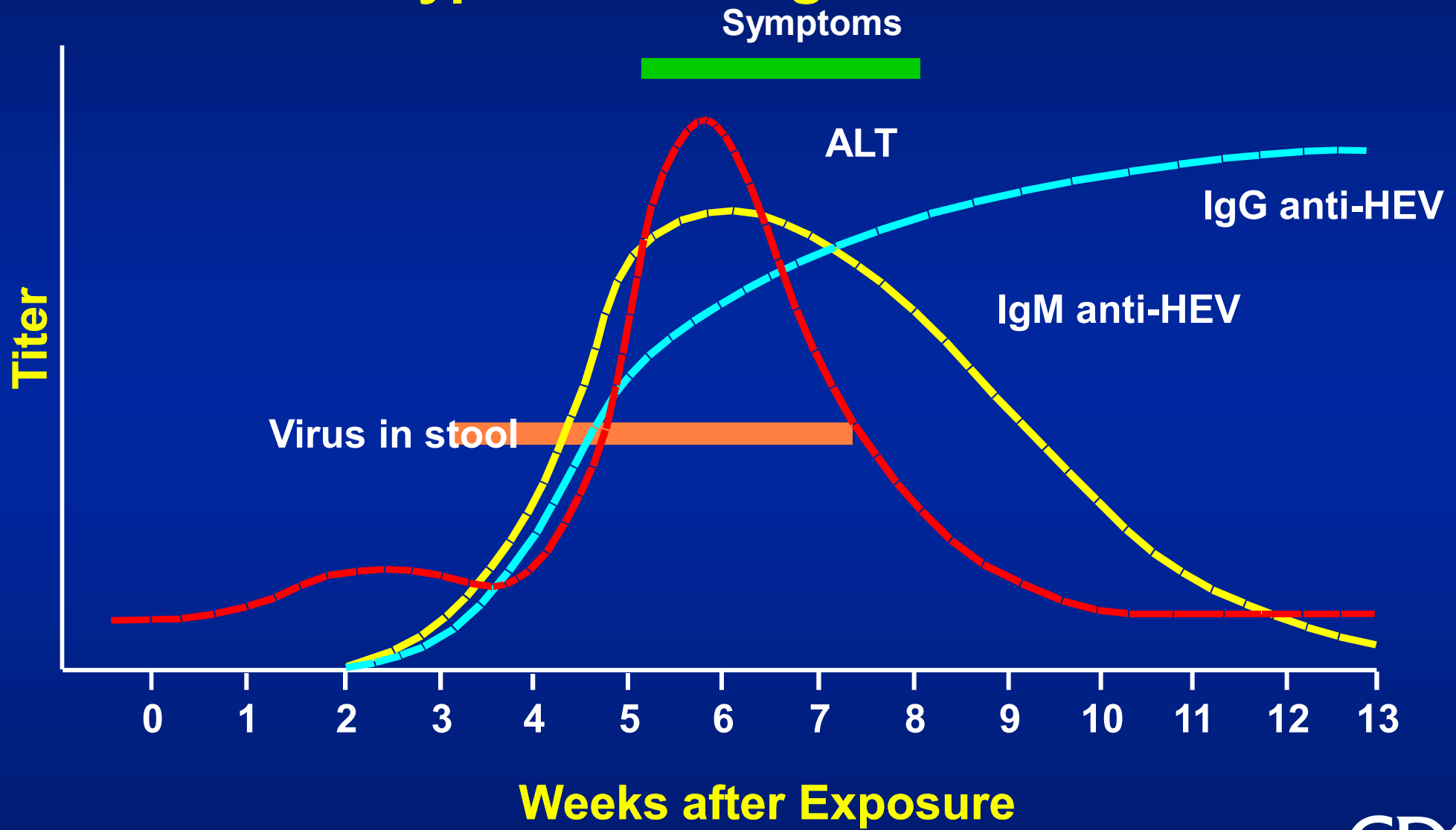
Hepatitis E Virus Infection

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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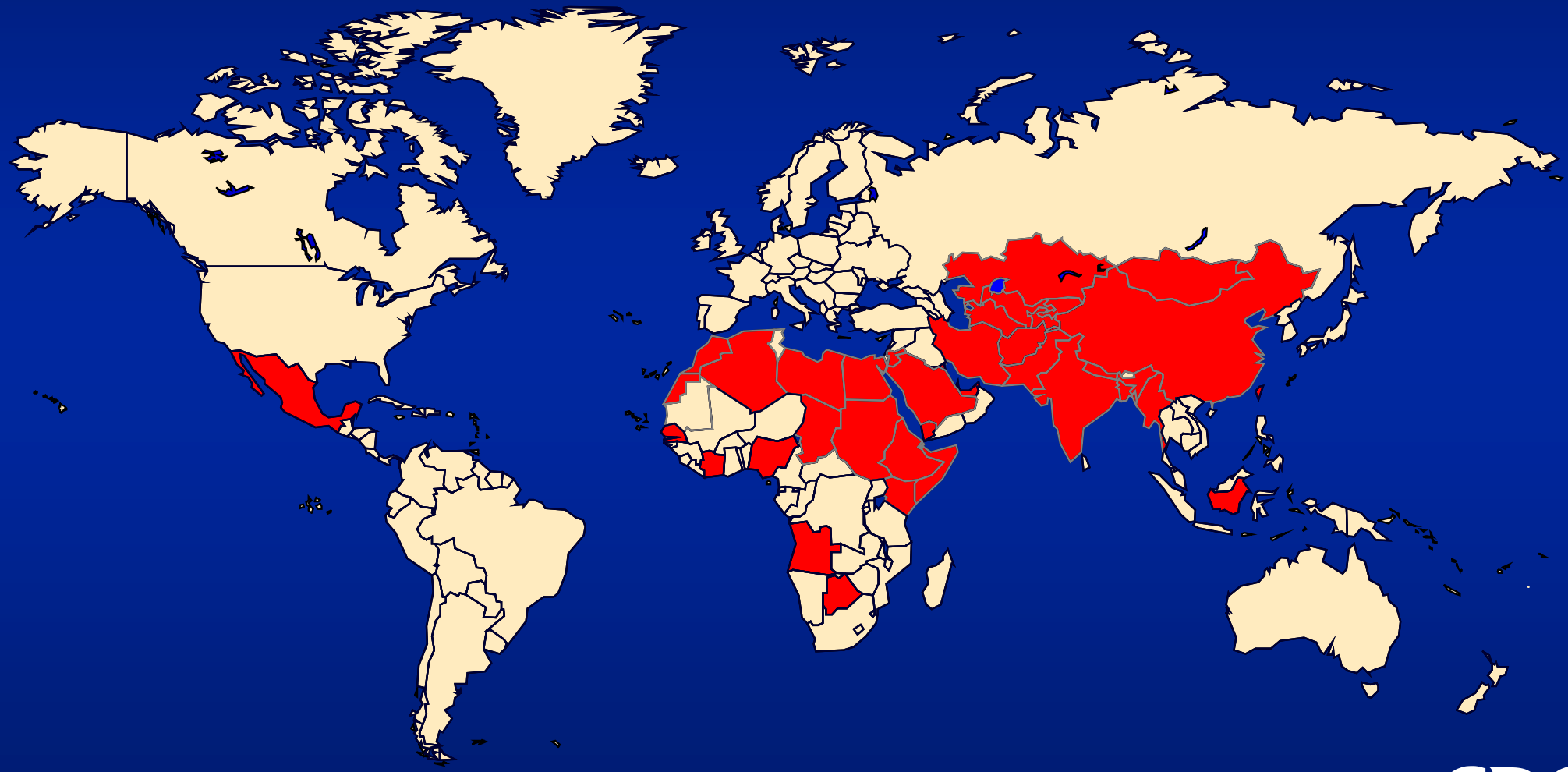
Geographic Distribution of Hepatitis E

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;