Viral Hepatitis A-E

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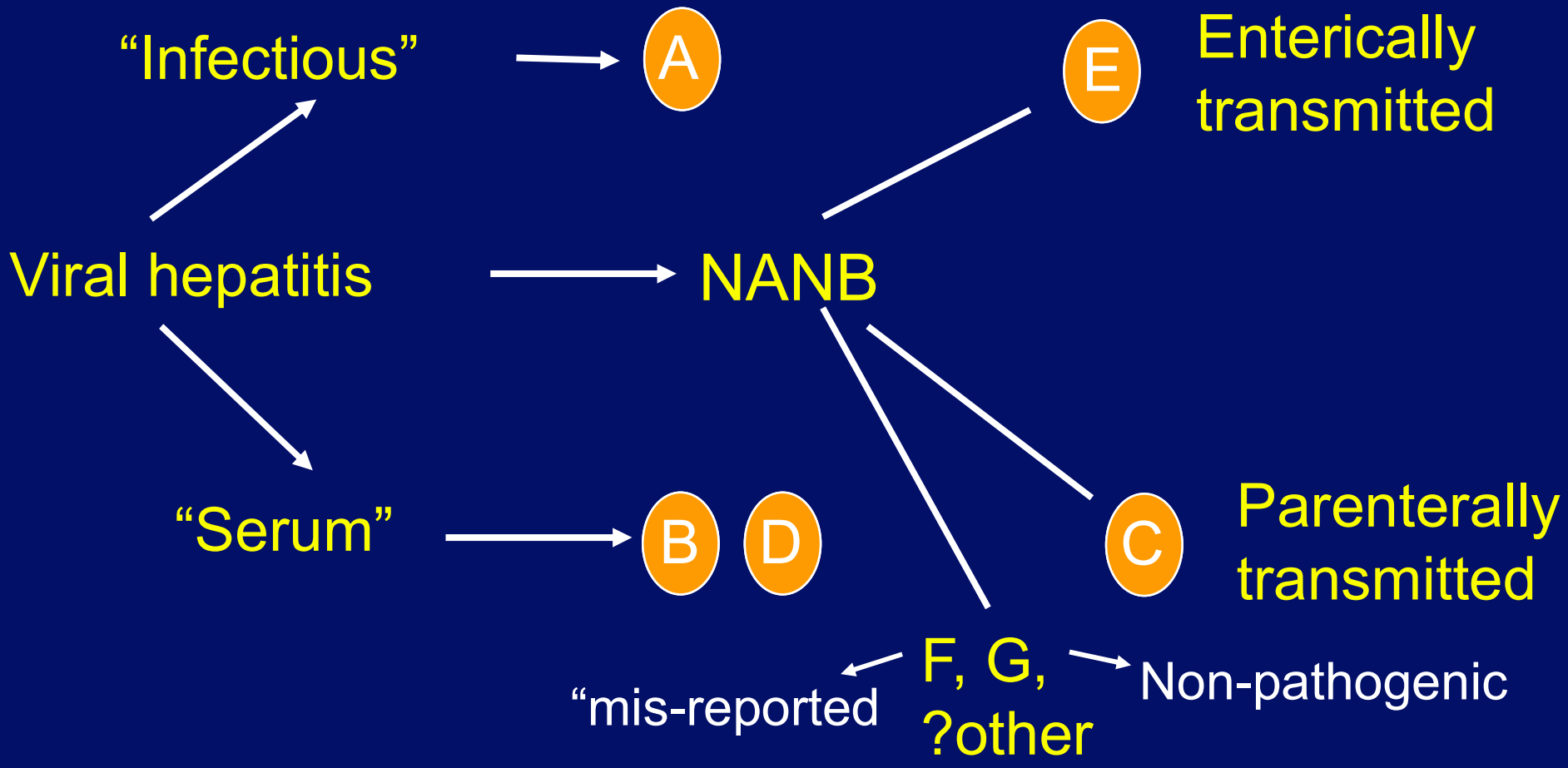
Viral Hepatitis - Overview

- Primary infection of the liver caused by at least five unrelated viruses: A, B, C, D, E
- HAV and HEV
  - Fecal-oral route
  - Acute self-limited disease; no chronic infection
- HBV, HCV, HDV
  - Percutaneous or mucosal exposures to blood
  - Chronic infection – major causes of cirrhosis and hepatocellular carcinoma worldwide

Viral Hepatitis – Historical Perspective



Viral Hepatitis - Overview

	Type of Hepatitis				
	A	**B**	**C**	**D**	**E**
Source of virus	feces	blood/ blood-derived body fluids	blood/ blood-derived body fluids	blood/ blood-derived body fluids	feces
Route of transmission	fecal-oral	percutaneous permucosal	percutaneous permucosal	percutaneous permucosal	fecal-oral
Chronic infection	no	yes	yes	yes	no
Prevention	pre/post-exposure immunization	pre/post-exposure immunization	blood donor screening; risk behavior modification	pre/post-exposure immunization; risk behavior modification	ensure safe drinking water

Clinical Features of Hepatitis

Common

- malaise
- anorexia
- nausea & vomiting
- fever
- jaundice
- abdominal pain
- hepatomegaly

Less Common

- diarrhea
- arthralgias
- pruritis
- rash

Enterically Transmitted Viral Hepatitis

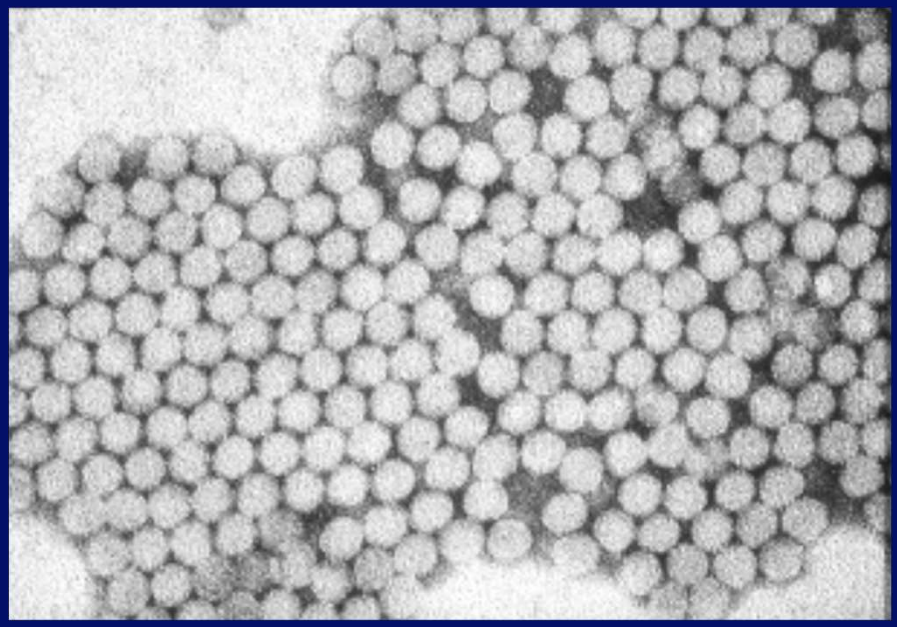
Hepatitis A—Highlights

- Estimated 1.4 million clinical cases of hepatitis A annually worldwide
- Tens of millions of hepatitis A virus infections occur each year
- Universal childhood vaccination effective in countries with varying endemic rates
  - Reduces morbidity and mortality
  - However, incidence in US stable 2011-2016, then increasing

Wasley A, Epidemiologic Reviews 2006;
https://www.cdc.gov/hepatitis/hav/havfaq.htm#general

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
- Vaccine preventable



Transmission of Hepatitis A Virus

- Fecal-oral transmission leads to spread between close contacts
- Incubation period, 15-50 days (average: 28 days)
- Greatest period of communicability: 2 weeks before onset of jaundice
- Stable in environment for months

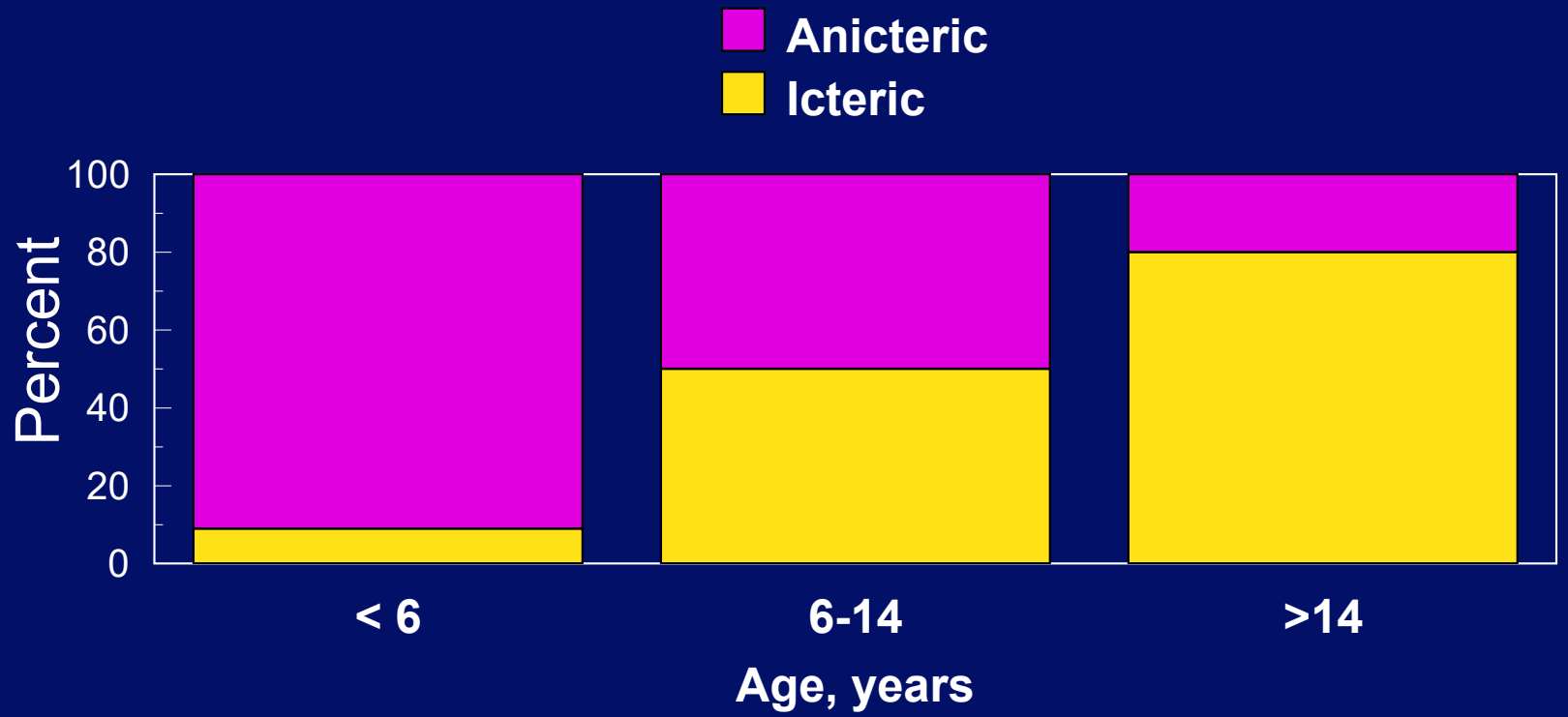
Transmission of Hepatitis A Virus

- Close personal contact
  (e.g., household contact, sex contact)
- Contaminated food (water)
  (e.g., infected food handlers, produce)
- Blood exposure **(uncommon)**
  (e.g., injecting drug use, transfusion)

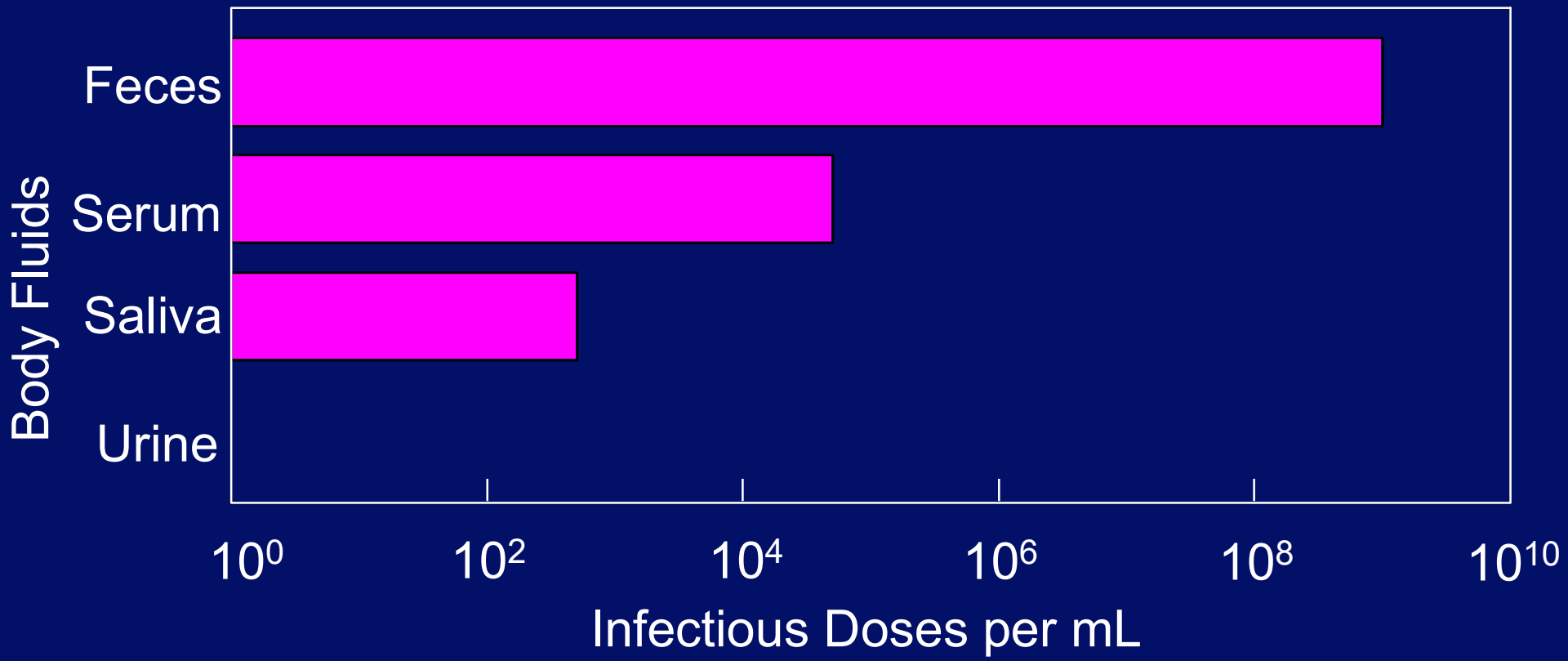
Hepatitis A - Clinical Features

Incubation period	Average 30 days Range 15-50 days
Jaundice by age	<6 yrs <10% 6-14 yrs 40%-50% >14 yrs 70%-80%
Case fatality rate	0.3% (0.2%-2.0%)
Complications	Fulminant; cholestatic; relapsing
Chronic sequelae	None (prolonged shedding in neonates and immunocompromised)

Relative Frequency of Jaundice with Hepatitis A, by Age

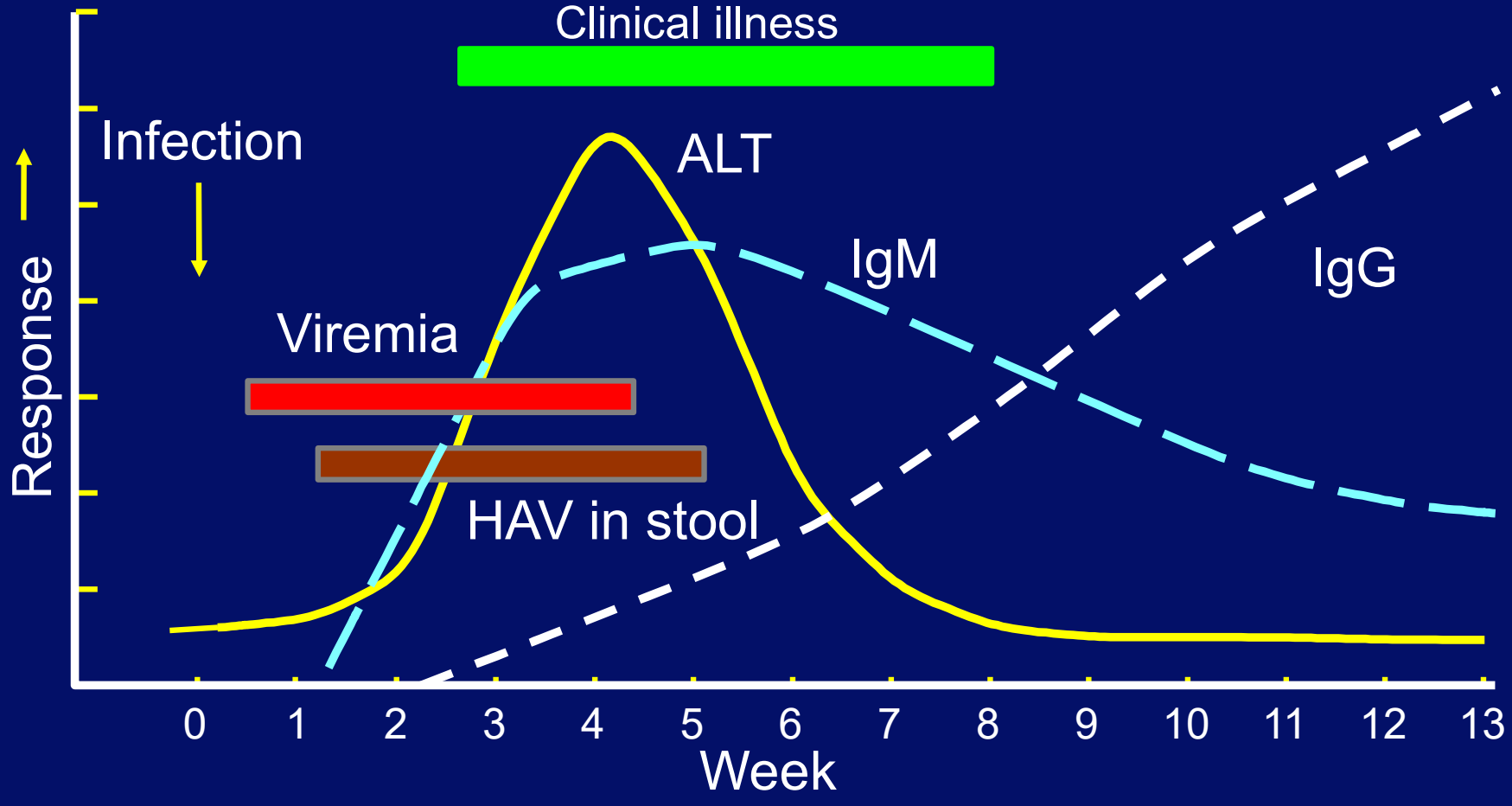


Concentration of Hepatitis A Virus in Various Body Fluids

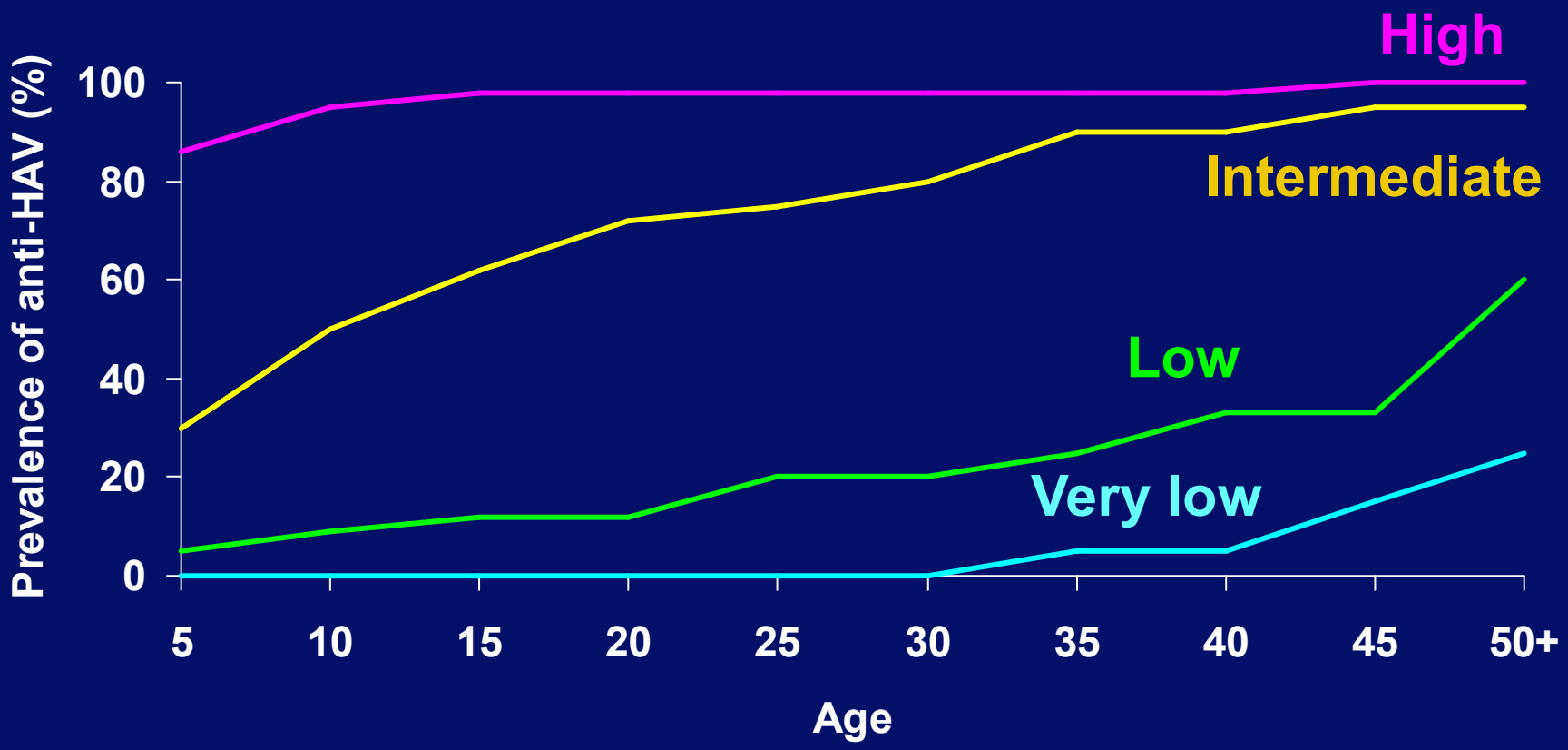


Source: Viral Hepatitis and Liver Disease 1984;9-22; J Infect Dis 1989;160:887-890

Events in Hepatitis A Virus Infection



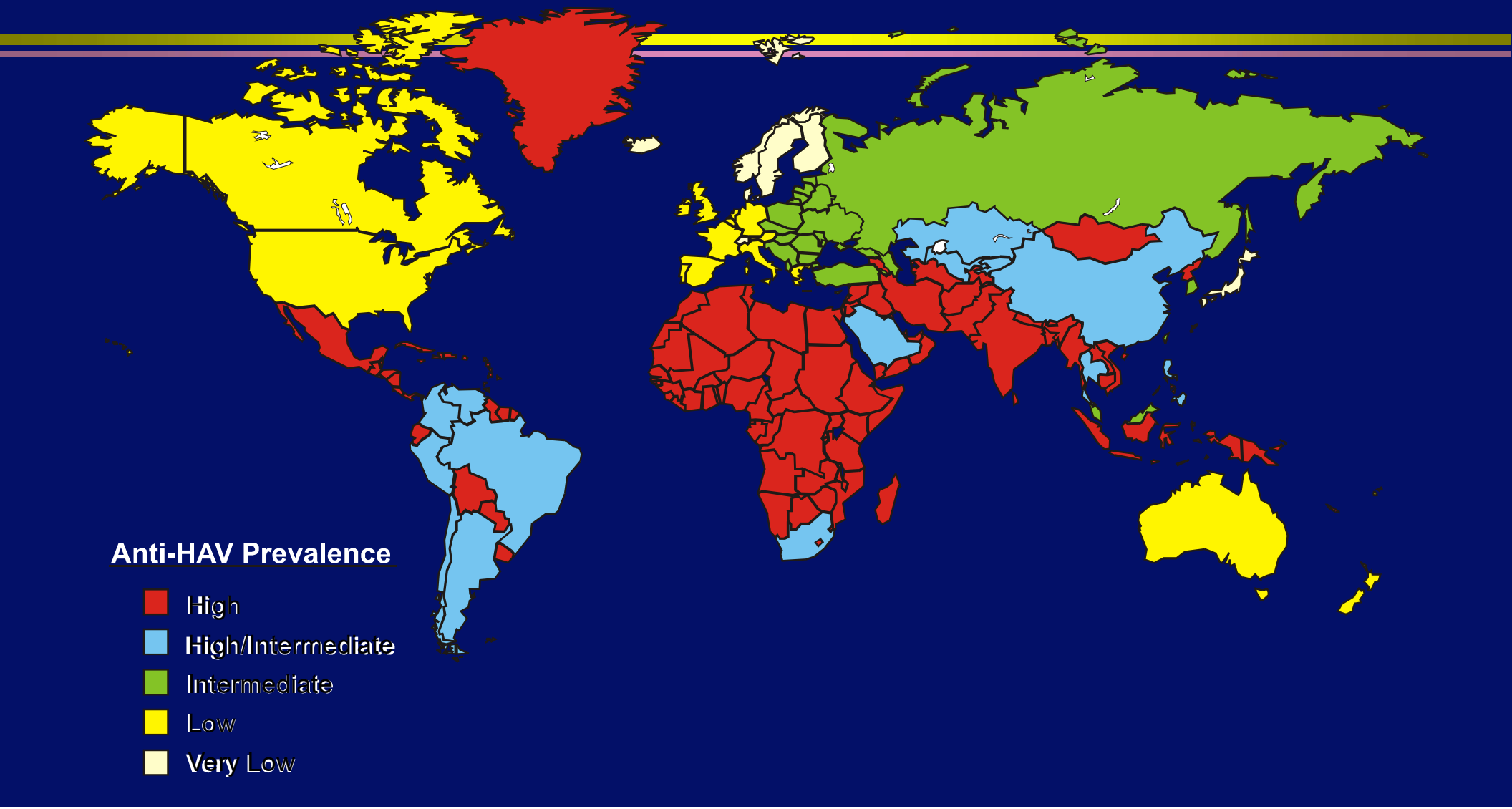
Patterns of Hepatitis A Virus Infection Worldwide



Hepatitis A Virus Transmission
Global Patterns

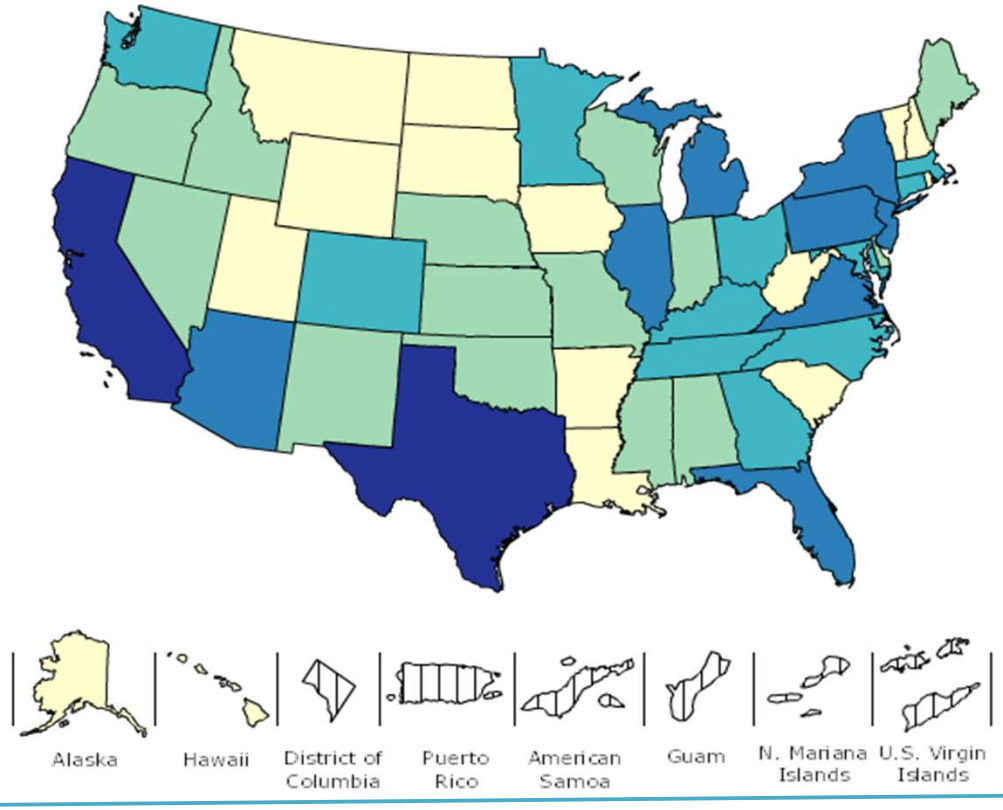
Endemicity	Disease Rate	Age at Infection	Transmission patterns
High	Low	Early childhood	Person to person; outbreaks uncommon
Intermediate	High	Late childhood/ young adults	Person to person; food and waterborne outbreaks
Low	Low to high	Late childhood/ young adults	Person to person; food and waterborne outbreaks
Very low	Very low	Adults	Travelers; outbreaks uncommon

Global Patterns of Hepatitis A Endemicity



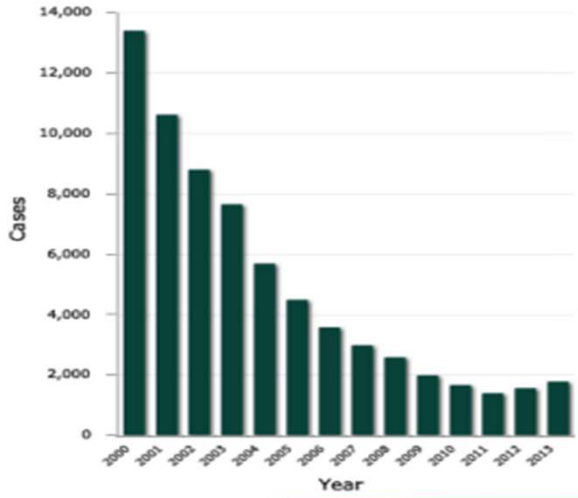
Acute Viral Hepatitis A (2013)

All races/ethnicities | Both sexes | Change over time (2000-2013) | All age groups | By State



Legend classified using quantiles according to 2000-2013 data.

National Data By Year



Disclaimer: This is a user-generated report. The findings and conclusions are those of the user and do not necessarily represent the views of the CDC.

Data Source: Query and graphics are based on viral hepatitis surveillance data. Data may include a combination of the following: acute viral hepatitis A, hepatitis B, and hepatitis C; by state and year; shown in numbers. **For more info, see:** Viral Hepatitis Surveillance Notes.

Notes: Viral Hepatitis case report data are submitted from all 50 states and the District of Columbia for the years 2000 to 2013. These data are summarized by disease, year, age group, sex, and race/ethnicity. **For more info, see:** Viral Hepatitis Surveillance Notes **Suggested citation:** Centers for Disease Control and Prevention (CDC) NCHHSTP Atlas. Accessed on 01/26/2016.

Epidemiologic Features of Hepatitis A in the United States

- Wide geographic and temporal variation in incidence
  - Areas with highest rates account for most reported cases
- Most disease occurs in the context of community-wide outbreaks
- Infection transmitted from person to person in households and extended family settings
  - Facilitated by asymptomatic infection among children
- Groups at increased risk can be identified
  - Specific factor varies
  - Do not account for majority of cases
- No risk factor identified for 30%-40% of cases

TABLE 3. Categories of persons with increased risk for hepatitis A virus infection or severe disease from hepatitis A virus infection*

Type of risk	Risk category	Examples
Increased risk for HAV infection	Close personal contacts of persons with HAV infection†	Household contacts Caretakers Sexual contacts Persons who anticipate close personal contact with an international adoptee
	Occupational risk	Persons working with nonhuman primates Persons working with clinical or nonclinical material containing HAV in a research laboratory
	Persons who use drugs Persons in settings where services to adults are provided	Persons who use injection or noninjection drugs (i.e., all those who use illegal drugs) Group settings for persons with developmental disabilities Homeless shelters Syringe services programs Correctional facilities during outbreaks
	International travelers	Persons traveling to or working in countries with high or intermediate HAV endemicity
Increased risk for severe disease from HAV infection	Immunocompromised persons	Congenital or acquired immunodeficiency HIV infection Chronic renal failure, undergoing dialysis Solid organ, bone marrow, or stem cell transplant recipients Persons with diseases requiring treatment with immunosuppressive drugs/biologics (e.g., tumor necrosis alpha inhibitors), long-term systemic corticosteroids, radiation therapy
	Persons with chronic liver disease	Hepatitis B virus infection Hepatitis C virus infection Cirrhosis (any etiology) Fatty liver disease (hepatic steatosis) Alcoholic liver disease Autoimmune hepatitis Alanine aminotransferase or aspartate amino transferase level more than twice the upper limit of normal or persistently elevated for 6 months
	Age	Adults aged >40 years

Abbreviations: HAV = hepatitis A virus; HIV = human immunodeficiency virus.

* Not all risk categories include persons recommended for routine hepatitis A vaccination (Box). Providers should assess the risk for HAV infection or severe disease from HAV infection when making decisions regarding the provision of postexposure prophylaxis or revaccination (Table 4). Providers should consider vaccination in settings providing services to adults at risk for HAV infection (see Implementation Strategies and Hepatitis A Vaccination During Outbreaks).

† Excludes health care personnel using appropriate personal protective equipment.

ACIP 2020; www.cdc.gov/mmwr/volumes/69/rr/pdfs/rr6905a1-H.pdf

SAFETY OF HEPATITIS A VACCINE

- Most common side effects
  - Soreness/tenderness at injection site - 50%
  - Headache - 15%
  - Malaise - 7%

- No severe adverse reactions attributed to vaccine
- Safety in pregnancy not determined – risk likely low
- Contraindications - severe adverse reaction to previous dose or allergy to a vaccine component
- No special precautions for immunocompromised persons

Immunogenicity of Inactivated Hepatitis A Vaccines

- 2-dose series 6-18 months apart (dosage varies by manufacturer)
- 95%-100% had protective levels of antibody one month after receiving one dose
- 100% had protective levels of antibody one month after receiving second dose with high geometric mean titers

HEPATITIS A VACCINES

TABLE 1. Vaccines used to prevent hepatitis A virus infection

Vaccine	Trade name (manufacturer)	Age group (yrs)	Dosage	Route	Schedule	Booster
HepA, inactivated (2 doses)	Havrix (GlaxoSmithKline)	1–18	0.5 mL (720 ELISA units inactivated HAV)	IM	0, 6–12 months	None
		≥19	1 mL (1,440 ELISA units inactivated HAV)	IM	0, 6–12 months	None
HepA, inactivated (2 doses)	Vaqta (Merck)	1–18	0.5 mL (25 units HAV antigen)	IM	0, 6–18 months	None
		≥19	1 mL (50 units HAV antigen)	IM	0, 6–18 months	None
Combined HepA and HepB* (3 doses)	Twinrix (GlaxoSmithKline)	≥18 (primary)	1 mL (720 ELISA units inactivated HAV + 20 µg HBsAg)	IM	0, 1, 6 months	None
		≥18 (accelerated)	1 mL (720 ELISA units inactivated HAV + 20 µg HBsAg)	IM	0, 7, 21–30 days	12 months

Abbreviations: ELISA = enzyme-linked immunosorbent assay; HAV = hepatitis A virus; HBsAg = hepatitis B surface antigen; HepA = hepatitis A; HepB = hepatitis B; IM = intramuscular.

* Combined HepA and HepB vaccine (Twinrix) should not be used for postexposure prophylaxis.

ACIP 2020: https://www.cdc.gov/mmwr/volumes/69/rr/pdfs/rr6905a1-H.pdf

IMMUNE GLOBULIN-PROPHYLAXIS

TABLE 2. Dosage recommendations for GamaSTAN human immune globulin for preexposure and postexposure prophylaxis against hepatitis A infection

Indication	Time	Dose*	Route
Preexposure prophylaxis	Up to 1 month duration of travel	0.1 mL/kg	IM
Preexposure prophylaxis	Up to 2 months duration of travel	0.2 mL/kg	IM
Preexposure prophylaxis	≥2 months duration of travel	0.2 mL/kg (repeat every 2 months)	IM
Postexposure prophylaxis	Within 2 weeks of exposure	0.1 mL/kg	IM

Abbreviation: IM = intramuscular.

* The dosage of immune globulin is based on weight for all ages and does not have a maximum dose for protection against hepatitis A (**Source:** Grifols. Treating with GamaSTAN [immune globulin (human)] Los Angeles, CA: Grifols, 2019. https://www.hypermunes.com/en/hcp/gamastan-hepatitis-a).

ACIP 2020: https://www.cdc.gov/mmwr/volumes/69/rr/pdfs/rr6905a1-H.pdf

Prevention of Hepatitis A

- Worldwide
  - Hygiene and sanitation
    - Handwashing and clean water sources
    - Prevent contamination of fresh produce
- Low endemic countries
  - Preexposure vaccination
    - All children aged ≥1 years
    - Risk groups (travelers, MSM, illegal drug users, persons with chronic liver disease)
  - Postexposure prophylaxis (vaccine or IG)
    - Household and sex contacts
    - Common source exposure (prepared food by infected handler)

Recommendations for Hepatitis A Vaccine and Immune Globulin for Preexposure Prophylaxis

BOX. Prevention of hepatitis A virus infection in the United States: Recommendations of the Advisory Committee on Immunization Practices, 2020*

Children
All children aged 12–23 months
Unvaccinated children and adolescents aged 2–18 years

Persons at increased risk for HAV infection
International travelers
Men who have sex with men
Persons who use injection or noninjection drugs (i.e., all those who use illegal drugs)
Persons with occupational risk for exposure
Persons who anticipate close personal contact with an international adoptee
Persons experiencing homelessness

Persons at increased risk for severe disease from HAV infection
Persons with chronic liver disease
Persons with human immunodeficiency virus infection

Other persons recommended for vaccination
Pregnant women at risk for HAV infection or severe outcome from HAV infection
Any person who requests vaccination

Vaccination during outbreaks
Unvaccinated persons in outbreak settings who are at risk for HAV infection or at risk for severe disease from HAV

Implementation strategies for settings providing services to adults
Persons in settings that provide services to adults in which a high proportion of those persons have risk factors for HAV infection

Hepatitis A vaccination is no longer recommended by ACIP
Persons who receive blood products for clotting disorders (e.g., hemophilia)

* See the Recommendations for Hepatitis A Vaccine and Immune Globulin for Preexposure Prophylaxis section in this report for additional information.

ACIP 2020: https://www.cdc.gov/mmwr/volumes/69/rr/pdfs/rr6905a1-H.pdf

Hepatitis E Virus (HEV)

Hepatitis E—Highlights

Like HAV

- Fecal-oral
- Acute self-limiting infection
  - Exception—may persist in immunologically compromised host
- Vaccine preventable

Unlike HAV

- Incubation period ~10 days longer
- Clinical response dose-dependent
  - Not age dependent
  - Infection rare in children and household contacts
- Higher mortality overall
  - Much higher in pregnant women
- Sporadic disease very rare in developed countries, Ab relatively common
  - Not always associated with travel*
  - *Zoonotic* source

Purcell RH, Emerson SU, J Hepatology 2008

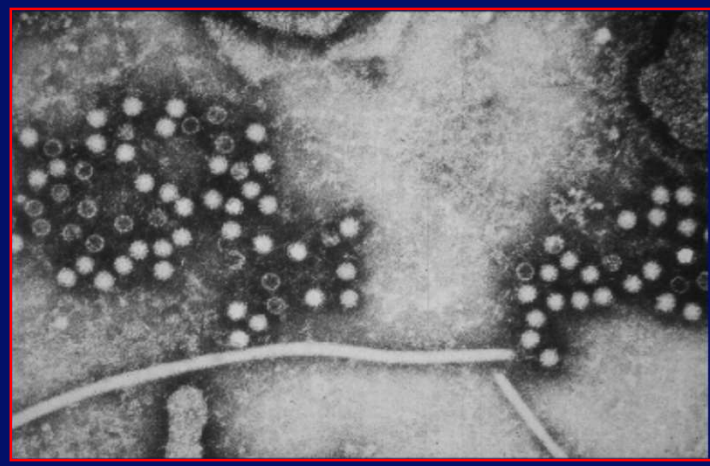
* Autochthonous

First Recognized Outbreak of Hepatitis E New Delhi, India (1956)

- 35,000 cases acute jaundice
- City water system contaminated by sewage
- Highest attack rate persons 15-40 years old
- Case-fatality rate 10.5% among pregnant women
- Originally thought to be hepatitis A

History

- 1983 human challenge experiment
  - Ingested pooled stool from outbreak-related cases
  - Developed acute non-A, non-B hepatitis
  - Excretion of virus-like particles
  - Stool infectious for non-human primates
- Classified enterically-transmitted NANB hepatitis
- 1990 HEV genome cloned
  - Classified as calicivirus



Diagnosis of Acute Hepatitis E

- Clinical illness indistinguishable from other types of acute viral hepatitis (A, B, C, D,….)
- Definitive diagnosis requires laboratory confirmation
- Serology:
  - IgM anti-HEV, IgG anti-HEV
  - Acute infection - good sensitivity and specificity
  - Prevalent infection - discordance between tests
- Research labs
  - HEV RNA by PCR (serum, stool, liver)
  - HEVAg by immunofluorescent probe (liver)

Hepatitis E - Clinical Features

Incubation period	Average 40 days; Range 15-60 days
Clinical illness	Case/infection ratio and severity increase with age
Chronic sequelae	None (“chronic” viremia recently reported in transplant patients)
Case-fatality rate	Overall 1-3% Pregnant women 15-20%
Factors related to increased severity	Chronic liver disease, large inoculum, pregnancy

Hepatitis E in Pregnancy

- Reasons for poor outcomes are unclear
- Most severe in 3rd trimester
  - 1/2: asymptomatic or mild HEV infection
  - 1/2: acute HE
    - 1/3 have FHF (fulminant hepatic failure, in resource-poor settings: high mortality)
    - 2/3 preterm delivery
    - High rates of obstetric complications
- Vertical transmission is common with 3rd trimester
  - Rate 33%-100%
  - Clinical outcome in infants is highly variable
    - Asymptomatic infection to hepatic necrosis
    - Hypoglycemia and hypothermia associated with mortality

Treatment

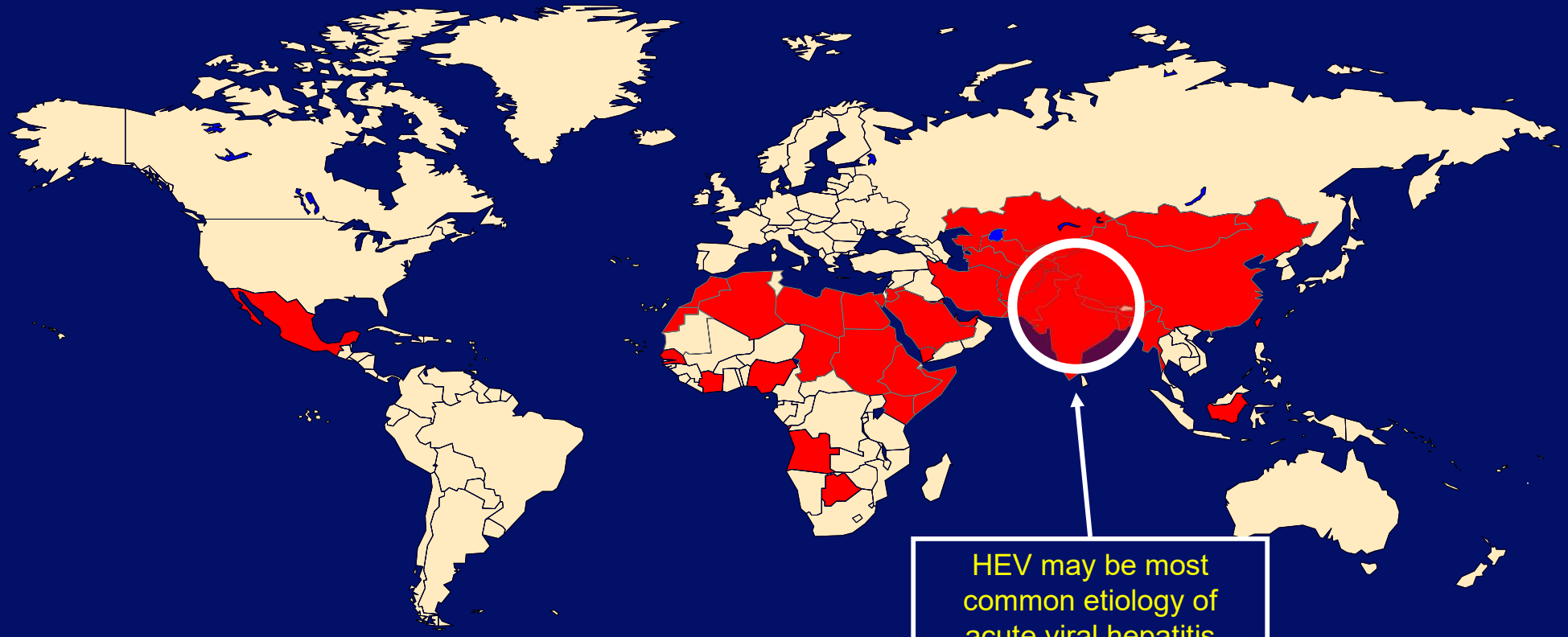
- Supportive
- No specific antiviral therapy
- Acute HE in pregnant women
  - No published data on potential benefits of early delivery
- No U.S. approved vaccine

Epidemiologic Features of HEV

- Responsible for sporadic cases of acute hepatitis and outbreaks
- Mode of transmission fecal-oral
  - Recent report of solid organ transplant-related
- Pattern
  - Outbreaks - fecally contaminated drinking water
  - Sporadic cases - not known
- Highest attack rate in young adults
- Minimal person-to-person transmission
- Animal reservoir

Geographic Distribution of HEV

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



“Endemic” Countries

- Outbreaks
  - Waterborne
  - Flooding, disruptions in water systems
- Sporadic Hepatitis E
  - HEV accounts for a variable proportion of acute viral hepatitis
  - Source of transmission not clear

“Non-Endemic” Countries

- No outbreaks
- Sporadic HE
  - Travel-related
    - Most commonly after travel to Asia, especially India and China
  - Domestically acquired
    - Rare
    - Source unknown

Prevention of Hepatitis E

- Treatment - None
- Vaccine (not approved in US) – effective, high-risk populations
- Immune globulin - Not effective
- Clean and reliable water supply
  - Virus probably inactivated by boiling
  - Effect of chlorination not known
- Proper sanitation (e.g., safe disposal of human and animal sewage)

Bloodborne Viral Hepatitis

Hepatitis B Virus

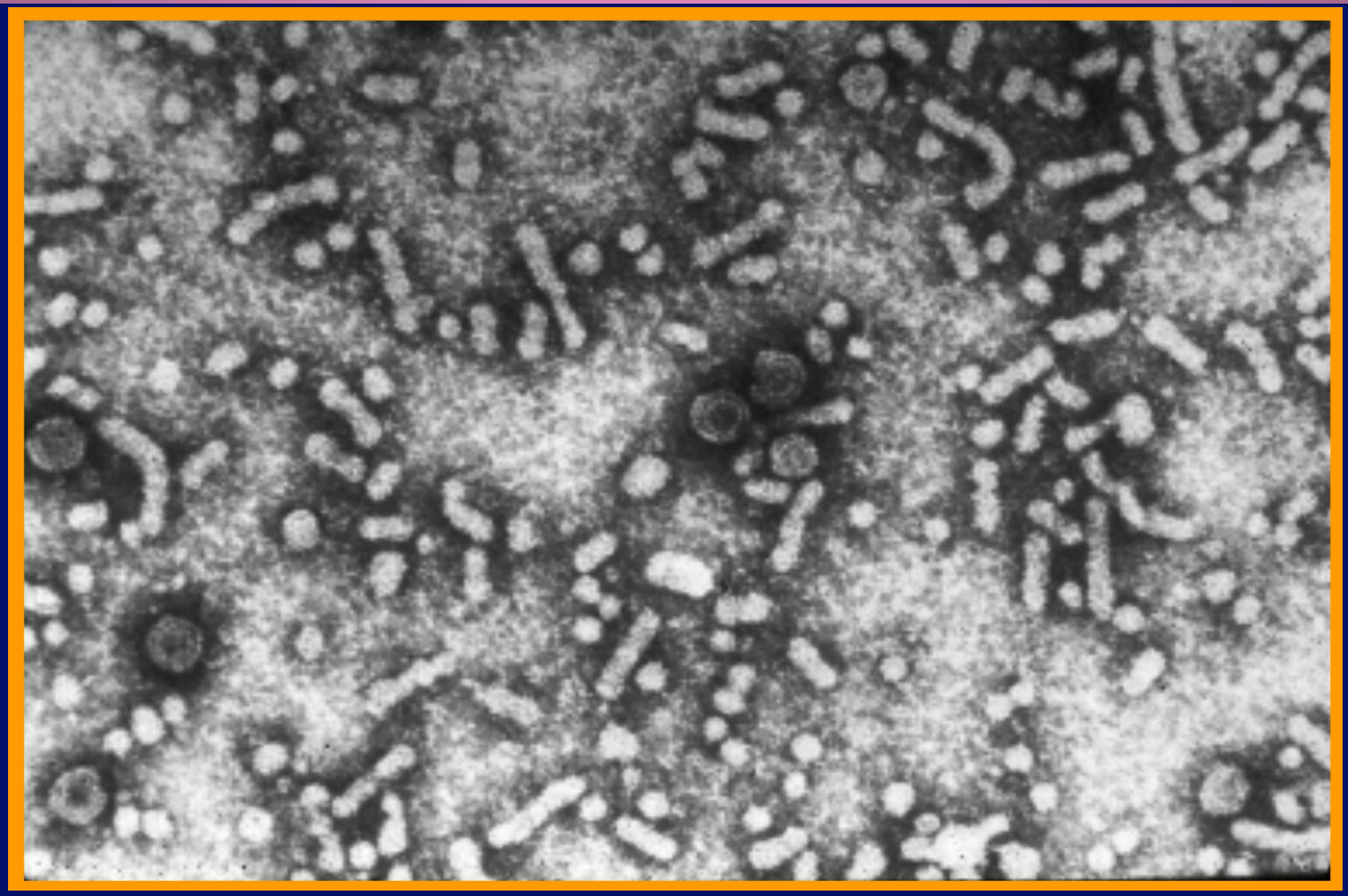
Hepatitis C Virus

Hepatitis D Virus

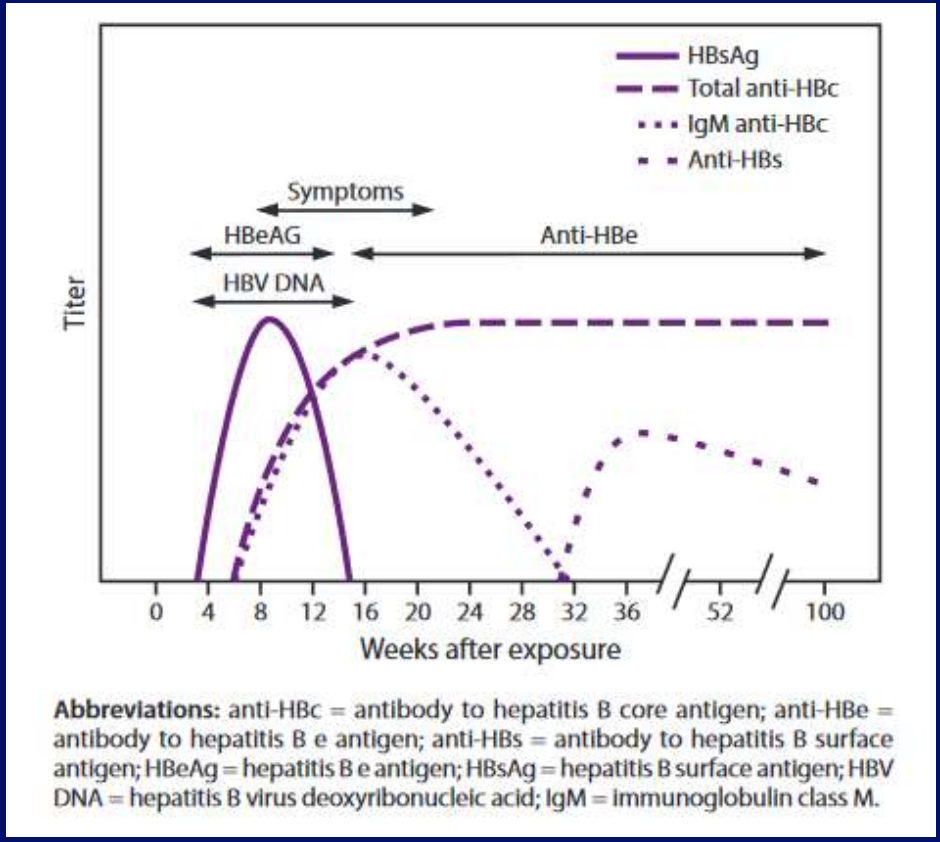
Bloodborne Viral Hepatitis
HBV and HCV—Highlights

- HBV
  - Status of universal childhood immunization
- HBV and HCV
  - Transfusion Safety
  - Injection Safety
  - Changing epidemiology
  - Chronic disease burden

Hepatitis B Virus



Acute hepatitis B virus infection with recovery



Abbreviations: anti-HBc = antibody to hepatitis B core antigen; anti-HBe = antibody to hepatitis B e antigen; anti-HBs = antibody to hepatitis B surface antigen; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; HBV DNA = hepatitis B virus deoxyribonucleic acid; IgM = immunoglobulin class M.

ACIP, 2018: https://www.cdc.gov/mmwr/volumes/67/rr/pdfs/rr6701-H.pdf

Typical interpretation of test results for hepatitis B virus infection

HBsAg	Total anti-HBc	IgM anti-HBc	Anti-HBs	HBV DNA	Interpretation
-	-	-	-	-	Never infected
+	-	-	-	+ or -	Early acute infection; transient (up to 18 days) after vaccination
+	+	+	-	+	Acute infection
-	+	+	+ or -	+ or -	Acute resolving infection
-	+	-	+	-	Recovered from past infection and immune
+	+	-	-	+	Chronic infection
-	+	-	-	+ or -	False-positive (i.e., susceptible); past infection; "low-level" chronic infection; or passive transfer of anti-HBc to infant born to HBsAg-positive mother
-	-	-	+	-	Immune if anti-HBs concentration is ≥10 mIU/mL after vaccine series completion; passive transfer after hepatitis B immune globulin administration

Abbreviations: - = negative; + = positive; anti-HBc = antibody to hepatitis B core antigen; anti-HBs = antibody to hepatitis B surface antigen; HBsAg = hepatitis B surface antigen; HBV DNA = hepatitis B virus deoxyribonucleic acid; IgM = immunoglobulin class M.

ACIP, 2018: https://www.cdc.gov/mmwr/volumes/67/rr/pdfs/rr6701-H.pdf

Ten Leading Causes of Infectious Disease Deaths Worldwide (2000)

Disease	Deaths per Year
Lower resp tract infections	~3.5 million
HIV/AIDS	~3.0 million
Diarrheal diseases	~2.2 million
Tuberculosis	~2.0 million
Malaria	~1-3 million
Measles	~888,000
Hepatitis B	~750,000
Pertussis	~355,000
Neonatal tetanus	~300,000
Hepatitis C	~ 250,000

Source: CDC, WHO, UNICEF, UNAIDS

Global and US Disease Burden from Bloodborne Viral Infections

	Estimated No. Chronic Infections	
	Global	US
HBV	370 million	1.25 million
HCV	130 million	3-4 million
HIV	40 million	1 million
HIV / HBV	(3–4 million)	(250,000)
HIV / HCV	(4–5 million)	(40-50,000)

Sources: WHO and CDC, unpublished data.

Features of HBV & HCV Infection

	HBV	HCV
Virus Classification	DNA	RNA
	Hepadnavirus	Flavivirus
Incubation period – average	8–12 wks	6–7 wks
– range	6–26 wks	2–26 wks
Specific serologic markers		
acute infection	Yes	No
active infection	Yes	No
chronic infection	Yes	No
Clinical illness (jaundice)	30%–50%	20%
Chronic infection	90% (infants)	~70%
	5–10% (adults)	
Mortality from CLD, cirrhosis, HCC	25%	1-5%

Relative Efficiency of Transmission by Type of Exposure

Type of exposure	Efficiency of transmission		
to infected source	HBV	HCV	HIV
Transfusion	++++	++++	++++
Injecting drug use	++++	++++	++++
Unsafe injections	+++	+++	++
Needlestick	+++	+	<+
Sexual	+++	+	+++
Perinatal	++++	++	+++
Non-intact skin	++	+/-	+/-

Relative Infectivity of HBV, HCV, HIV

	HBV	HCV	HIV
Copies/mL	10^{8-9}	10^{5}	10^{3}
Environmental stability	++++	++	-
Infectious after drying at room temperature	≥7d	≥16h (<4d)	0

Bond WW, Lancet 1981;1:550-51; Kamili S, Infect Control Hosp Epi 2006.

Environmental Stability of HBV and HCV Facilitates Their Transmission

- More rapid acquisition among IDUs
  - Clean needles and syringes alone insufficient to interrupt transmission because virus can live on contaminated drug preparation equipment (i.e., cookers and cotton)
- Iatrogenic transmission
  - Virus can live in contaminated multi-dose vials and on needles and syringes

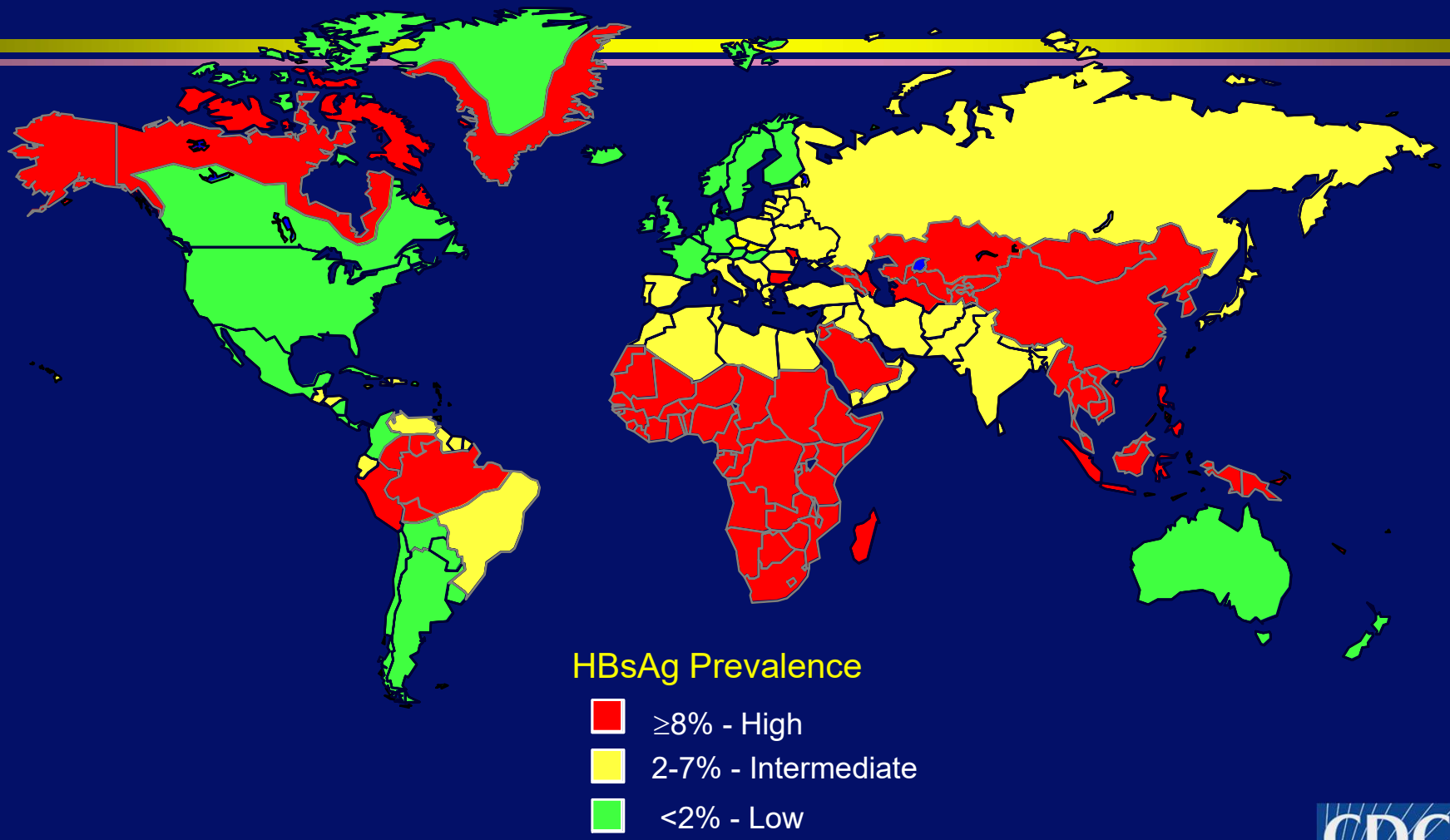
Routes of HBV Transmission

Age Group	Routes of Infection
Newborn	Mother to infant (perinatal)
Childhood	Household (non-intact skin)
Adolescent/Adult	Sexual contact
	Injecting drug use equipment
	Occupational exposures
All ages	Unsafe injections
	Transfusion from unscreened donors
	Other health care related

Global Differences in HBV Transmission Patterns

Chronic infection (% immune)	Primary Age at Infection	Primary Modes of Transmission
High ≥8% (≥60%)	Infants Young children	Perinatal, horizontal, unsafe injections, unscreened blood
Intermediate 2-7% (20-60%)	All age groups	Perinatal, horizontal, unsafe injections, sexual, IDU
Low <2% (5-20%)	Adolescents Adults	Sexual, IDU

Geographic Distribution of Chronic HBV Infection



Prevalence of chronic hepatitis B virus infection, by country

High (≥8% prevalence): Angola, Benin, Burkina Faso, Burundi, Cameroon, Central African Republic, Congo, Côte d'Ivoire, Djibouti, Equatorial Guinea, Gabon, Gambia, Ghana, Guinea, Haiti, Kiribati, Kyrgyzstan, Laos, Liberia, Malawi, Mali, Mauritania, Mongolia, Mozambique, Namibia, Nauru, Niger, Nigeria, Niue, Papua New Guinea, Senegal, Sierra Leone, Solomon Islands, Somalia, South Sudan, Sudan, Swaziland, Togo, Tonga, Uganda, Vanuatu, Vietnam, Yemen, and Zimbabwe.

Intermediate (5%–7.9% prevalence): Albania, Bhutan, Cape Verde, China, Democratic Republic of the Congo, Ethiopia, Kazakhstan, Kenya, Marshall Islands, Moldova, Oman, Romania, Rwanda, Samoa, South Africa, Tajikistan, Tanzania, Thailand, Tunisia, Tuvalu, Uzbekistan, and Zambia.

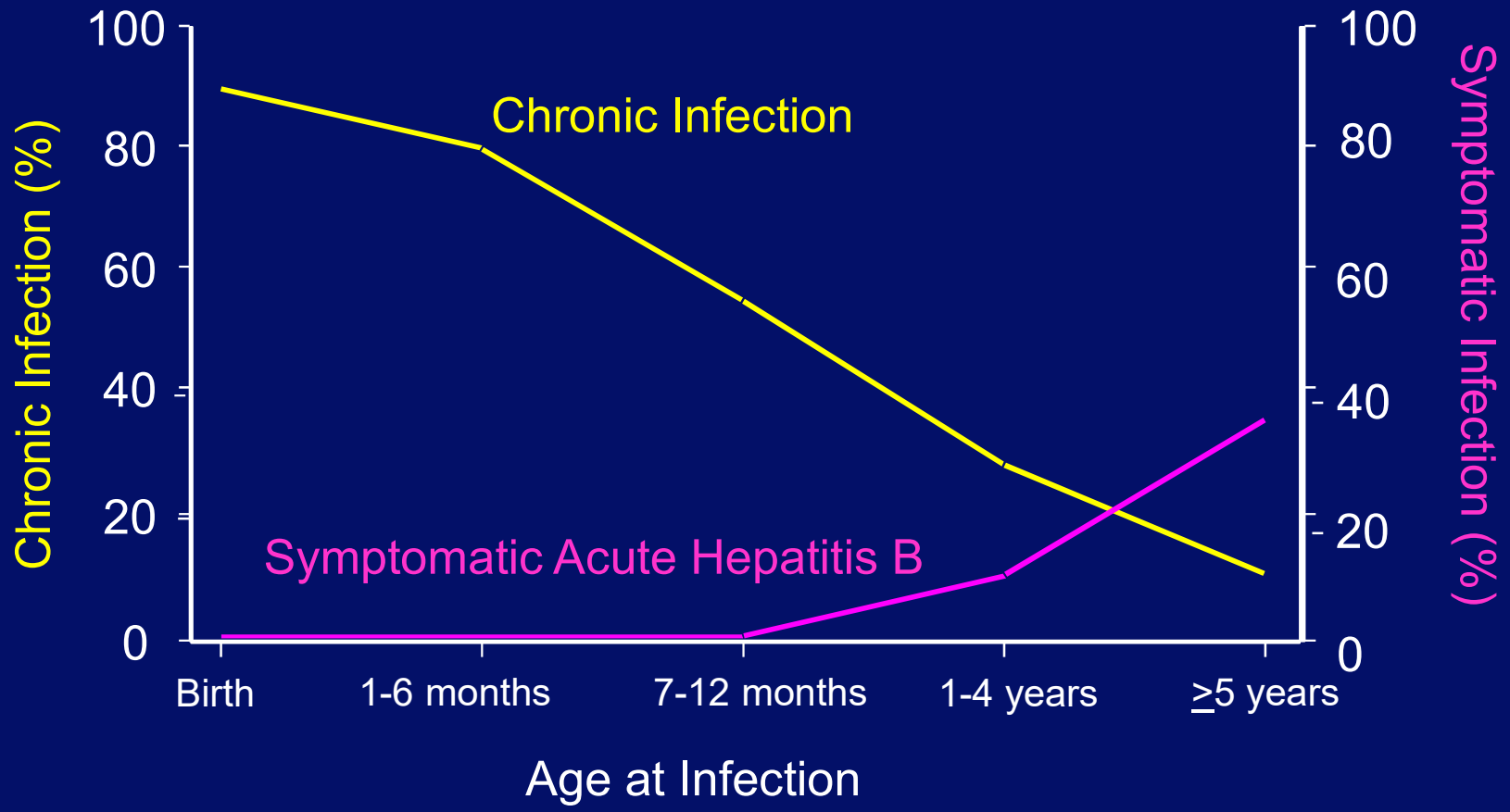
Low Intermediate (2%–4.9% prevalence): Algeria, Azerbaijan, Bangladesh, Belarus, Belize, Brunei Darussalam, Bulgaria, Cambodia, Colombia, Cyprus, Dominican Republic, Ecuador, Eritrea, Federated States of Micronesia, Fiji, Georgia, Italy, Jamaica, Kosovo, Libya, Madagascar, Myanmar, New Zealand, Pakistan, Palau, Philippines, Peru, Russia, Saudi Arabia, Singapore, South Korea, Sri Lanka, Suriname, Syria, Tahiti, and Turkey.

Low (≤1.9% prevalence): Afghanistan, Argentina, Australia, Austria, Bahrain, Barbados, Belgium, Bolivia, Bosnia and Herzegovina, Brazil, Canada, Chile, Costa Rica, Croatia, Cuba, Czech Republic, Denmark, Egypt, France, Germany, Greece, Guatemala, Hungary, Iceland, India, Indonesia, Iran, Iraq, Ireland, Israel, Japan, Jordan, Kuwait, Lebanon, Lithuania, Malaysia, Mexico, Morocco, Nepal, Netherlands, Nicaragua, Norway, Palestine, Panama, Poland, Portugal, Qatar, Serbia, Seychelles, Slovakia, Slovenia, Spain, Sweden, Switzerland, Ukraine, UK, United Arab Emirates, United States of America, and Venezuela.

No data: Andorra, Antigua and Barbuda, Armenia, The Bahamas, Botswana, Chad, Comoros, Cook Islands, Dominica, El Salvador, Finland, Grenada, Guinea-Bissau, Guyana, Honduras, Latvia, Lesotho, Lithuania, Luxembourg, Macedonia, Maldives, Malta, Mauritius, Monaco, Montenegro, North Korea, Paraguay, Saint Kitts and Nevis, Saint Lucia, Saint Vincent and the Grenadines, San Marino, Sao Tome and Principe, Timor-Leste, Trinidad and Tobago, Turkmenistan, and Uruguay.

* **Source:** CDC. Travelers health: infectious diseases related to travel. Atlanta, GA: US Department of Health and Human Services, CDC; 2017.

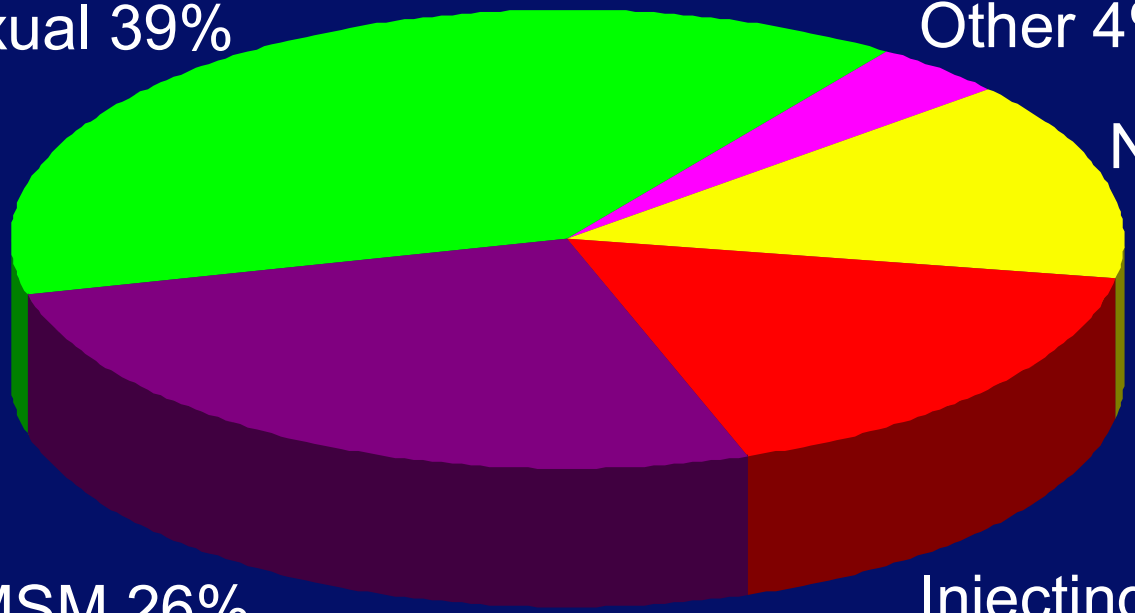
Outcome of HBV Infection by Age at Infection



Global Strategy to Prevent HBV Transmission

- Hepatitis B Vaccination
  - Routine infant vaccination (all countries)
  - Catch-up vaccination of older children/adolescents
  - Vaccination of high-risk groups
- Prevention of Iatrogenic transmission
  - Routine screening of transfused blood
    - developed countries -100% screen
    - least developed countries - 35% screen (?)
  - Safe injection practices
  - Proper infection control practices

Risk Factors Reported by Cases of Acute Hepatitis B, United States, 2000-2003



* Other - Household contact, occupational exposure, hemodialysis, institutionalization, transfusion

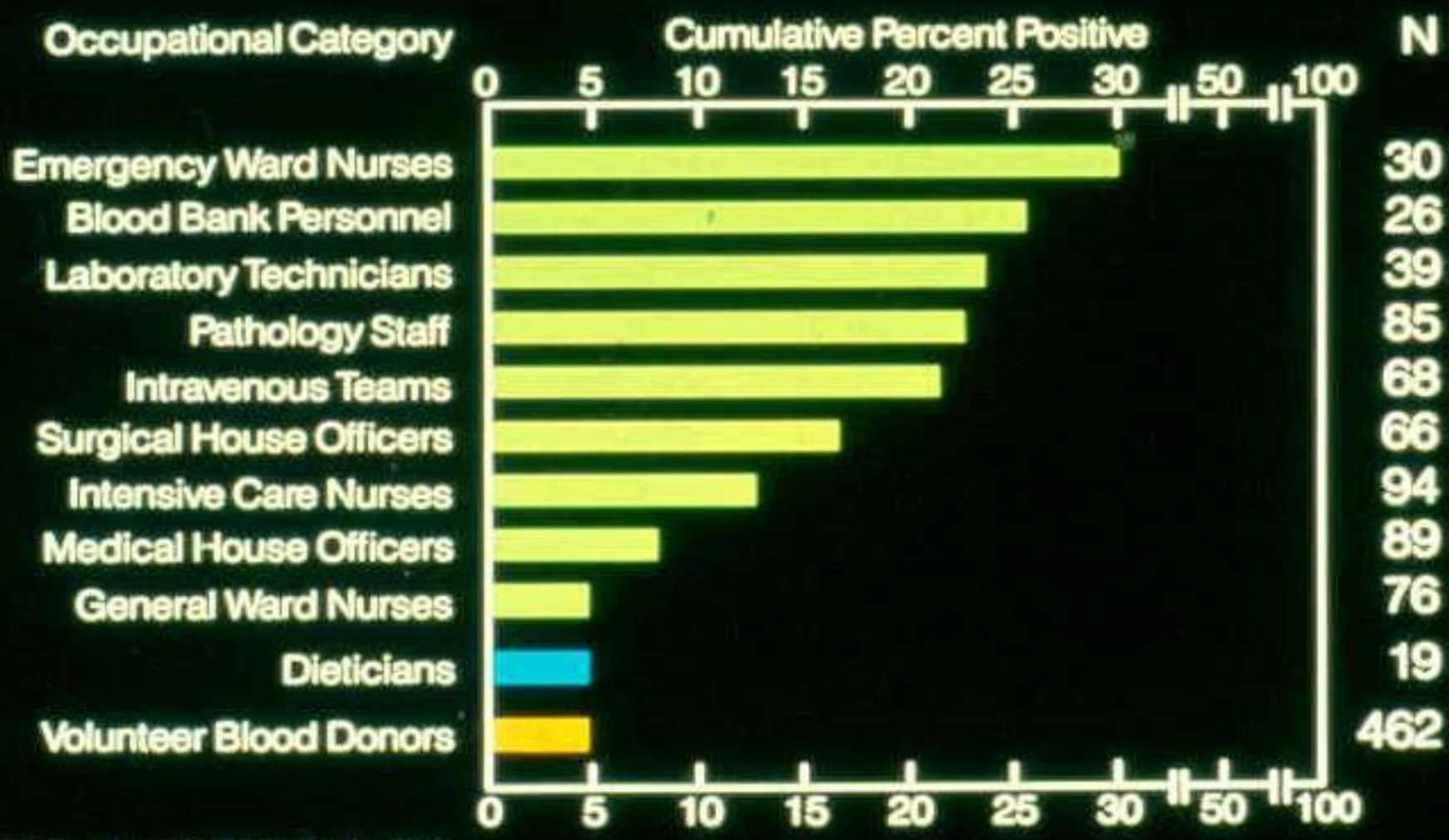
Source: Adapted from Sentinel Counties and NNDSS, CDC

Recent HBV Outbreaks Associated with Blood Glucose Monitoring

- Shared fingerstick devices
  - 1999 – VA – Assisted Living Centers – 4 cases
  - 1999 – CA – Nursing Home – 4 cases
  - 2003 – MS – Nursing Home – 15 cases
  - 2003 – CA – Assisted Living Center – 8 cases
  - 2005 – VA – Assisted Living Centers (2) – 11 cases
- Dedicated fingerstick devices
  - 1999 – CA – Skilled Nursing Facility – 5 cases
  - 2002 – CA – Subacute Hospital – 3 cases
  - 2003 – NC – Nursing Home – 11 cases

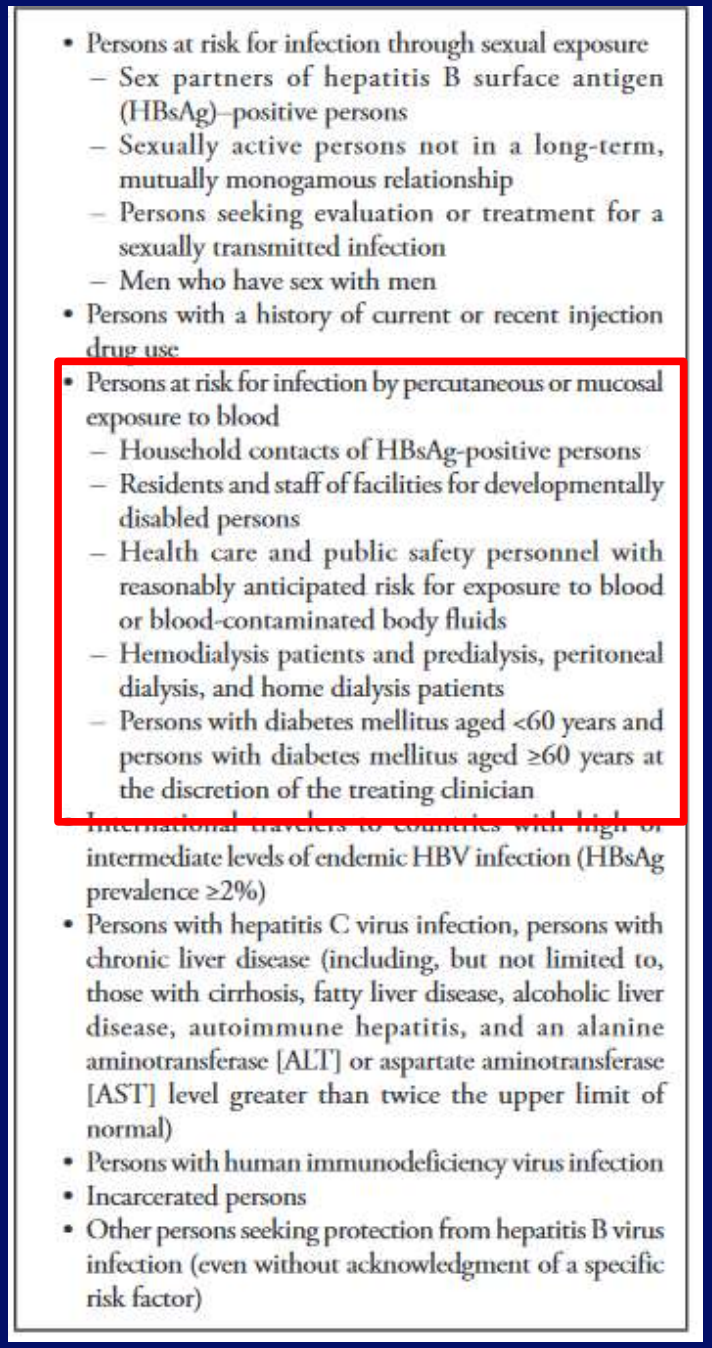
Hepatitis B in Health-Care Personnel

Prevalence of HBV Serologic Markers in 624 Hospital Personnel and 462 Nonhospital Controls



Dienstag, J. L. and Ryan, D. M., 1982

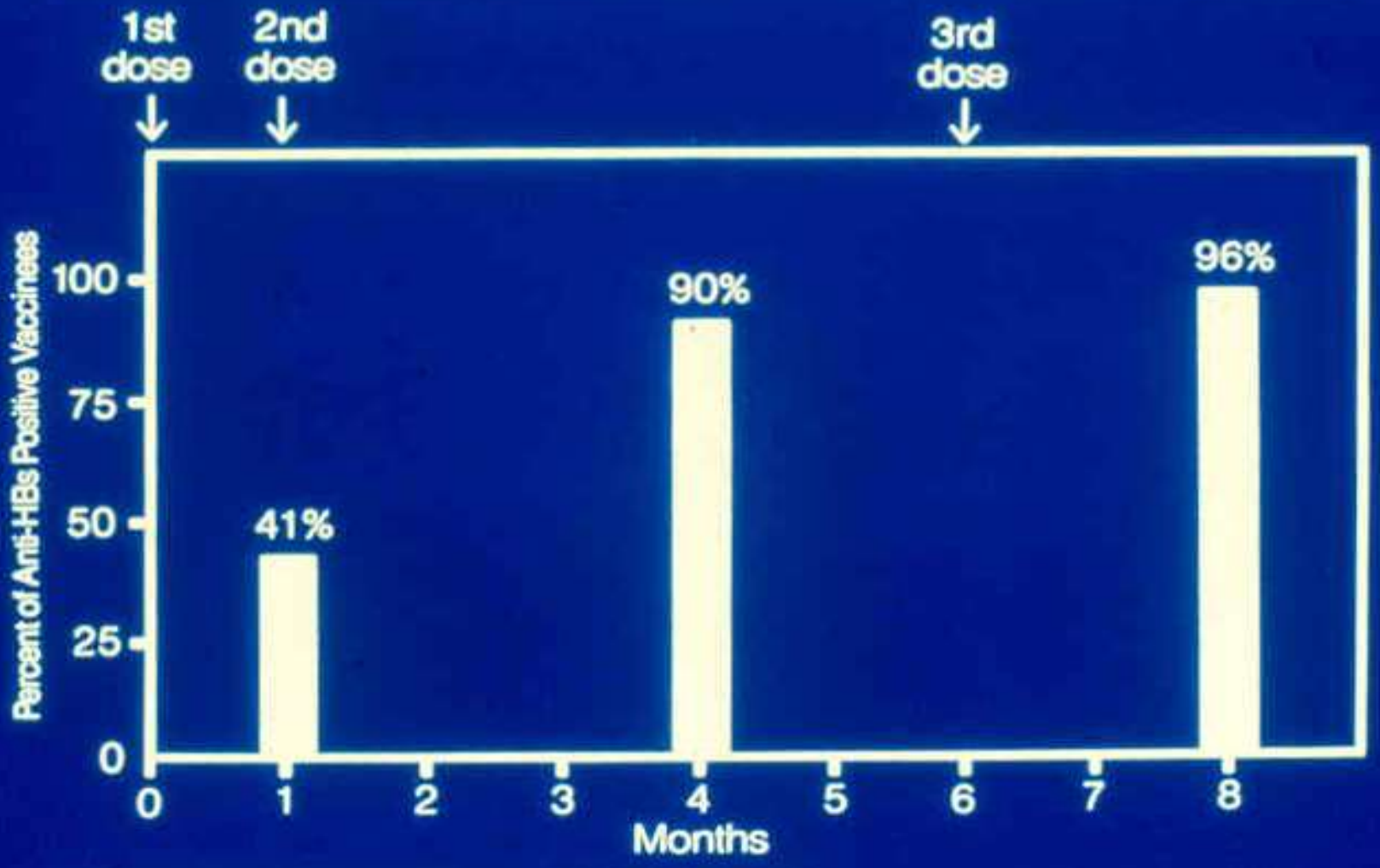
Adults who are recommended to receive hepatitis B vaccine



- Persons at risk for infection through sexual exposure
  - Sex partners of hepatitis B surface antigen (HBsAg)–positive persons
  - Sexually active persons not in a long-term, mutually monogamous relationship
  - Persons seeking evaluation or treatment for a sexually transmitted infection
  - Men who have sex with men
- Persons with a history of current or recent injection drug use
- Persons at risk for infection by percutaneous or mucosal exposure to blood
  - Household contacts of HBsAg-positive persons
  - Residents and staff of facilities for developmentally disabled persons
  - Health care and public safety personnel with reasonably anticipated risk for exposure to blood or blood-contaminated body fluids
  - Hemodialysis patients and predialysis, peritoneal dialysis, and home dialysis patients
  - Persons with diabetes mellitus aged <60 years and persons with diabetes mellitus aged ≥60 years at the discretion of the treating clinician
- International travelers to countries with high or intermediate levels of endemic HBV infection (HBsAg prevalence ≥2%)
- Persons with hepatitis C virus infection, persons with chronic liver disease (including, but not limited to, those with cirrhosis, fatty liver disease, alcoholic liver disease, autoimmune hepatitis, and an alanine aminotransferase [ALT] or aspartate aminotransferase [AST] level greater than twice the upper limit of normal)
- Persons with human immunodeficiency virus infection
- Incarcerated persons
- Other persons seeking protection from hepatitis B virus infection (even without acknowledgment of a specific risk factor)

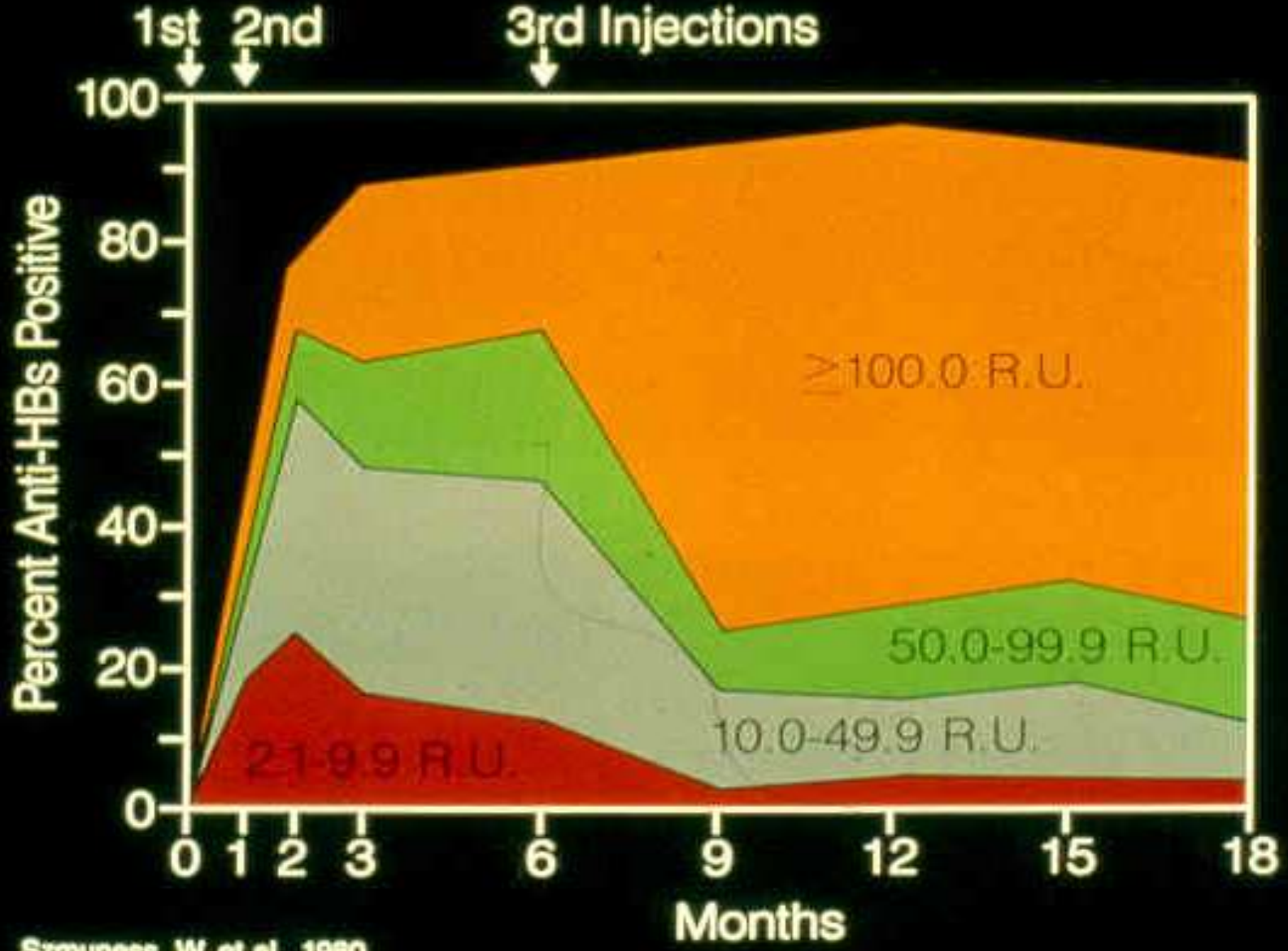
ACIP 2018; https://www.cdc.gov/mmwr/volumes/67/wr/pdfs/mm6715a5-H.pdf

Immunogenicity of Heptavax-B® (Hepatitis B Vaccine | MSD)



Adapted from Szmuness, W. et al., J. Med. Virol., 1981

Immunogenicity of Hepatitis B Vaccine



Szmuness, W. et al., 1980

Recommended doses of hepatitis B vaccine, by group and vaccine type

TABLE 4. Hepatitis B vaccine schedules for children, adolescents, and adults

Age group	Schedule* (Interval represents time in months from first dose)
Children (1–10 yrs)	0, 1, and 6 mos
	0, 1, 2, and 12 mos
Adolescents (11–19 yrs)	0, 1, and 6 mos
	0, 12, and 24 mos
	0 and 4–6 mos†
	0, 1, 2, and 12 mos
	0, 7 days, 21–30 days, 12 mos§
Adults (≥20 yrs)	0, 1, and 6 mos
	0, 1, 2, and 12 mos
	0, 1, 2, and 6 mos¶
	0, 7 days, 21–30 days, 12 mos§

ACIP 2018: https://www.cdc.gov/mmwr/volumes/67/rr/pdfs/rr6701-H.pdf

Hepatitis B Vaccine

Factor	Response	Factor	Response
Age 20-29	95%	Diabetes	70-80%
Age 30-39	90%	Liver disease	60-70%
Age 40-49	86%	Gender	Female>male
Age 50-59	71%	Obesity	Decreased
Age ≥60	47%	Smokers	Decreased
Renal Failure	50-80%	Gluteal injection	Decreased
HIV infection	50-70%		

Response is defined as ≥ 10 mIU/mL

Recommended doses of hepatitis B vaccine, by group and vaccine type

	Single-antigen vaccine				Combination vaccine			
	Recombivax		Engerix		Pediarix*		Twinrix†	
Age group (yrs)	Dose (μg)	Vol (mL)	Dose (μg)	Vol (mL)	Dose (μg)	Vol (mL)	Dose (μg)	Vol (mL)
Birth–10	5	0.5	10	0.5	10*	0.5	N/A	N/A
11–15	10§	1	N/A	N/A	N/A	N/A	N/A	N/A
11–19	5	0.5	10	0.5	N/A	N/A	N/A	N/A
≥20	10	1	20	1	N/A	N/A	20†	1
Hemodialysis patients and other immune-compromised persons								
<20	5	0.5	10	0.5	N/A	N/A	N/A	N/A
≥20	40	1	40	2	N/A	N/A	N/A	N/A

Abbreviation: N/A = not applicable.
* Pediarix is approved for use in persons aged 6 weeks through 6 years (prior to the 7th birthday).
† Twinrix is approved for use in persons aged ≥18 years.
§ Adult formulation administered on a 2-dose schedule.

ACIP 2018: https://www.cdc.gov/mmwr/volumes/67/rr/pdfs/rr6701-H.pdf

Hepatitis B Vaccine: Administration 2

- Schedule
  - 0, 1, 6 mo
  - 0, 1, 2, 12 mo (more rapid antibody rise) (Engerix)
- Pre-exposure
  - ACP: Three doses, obtain titer (1-6 mo). If antibody negative, provide up to 3 additional doses (titer 1-2 mo after each dose)
  - If no response after 6 doses, provide HBIG for exposures

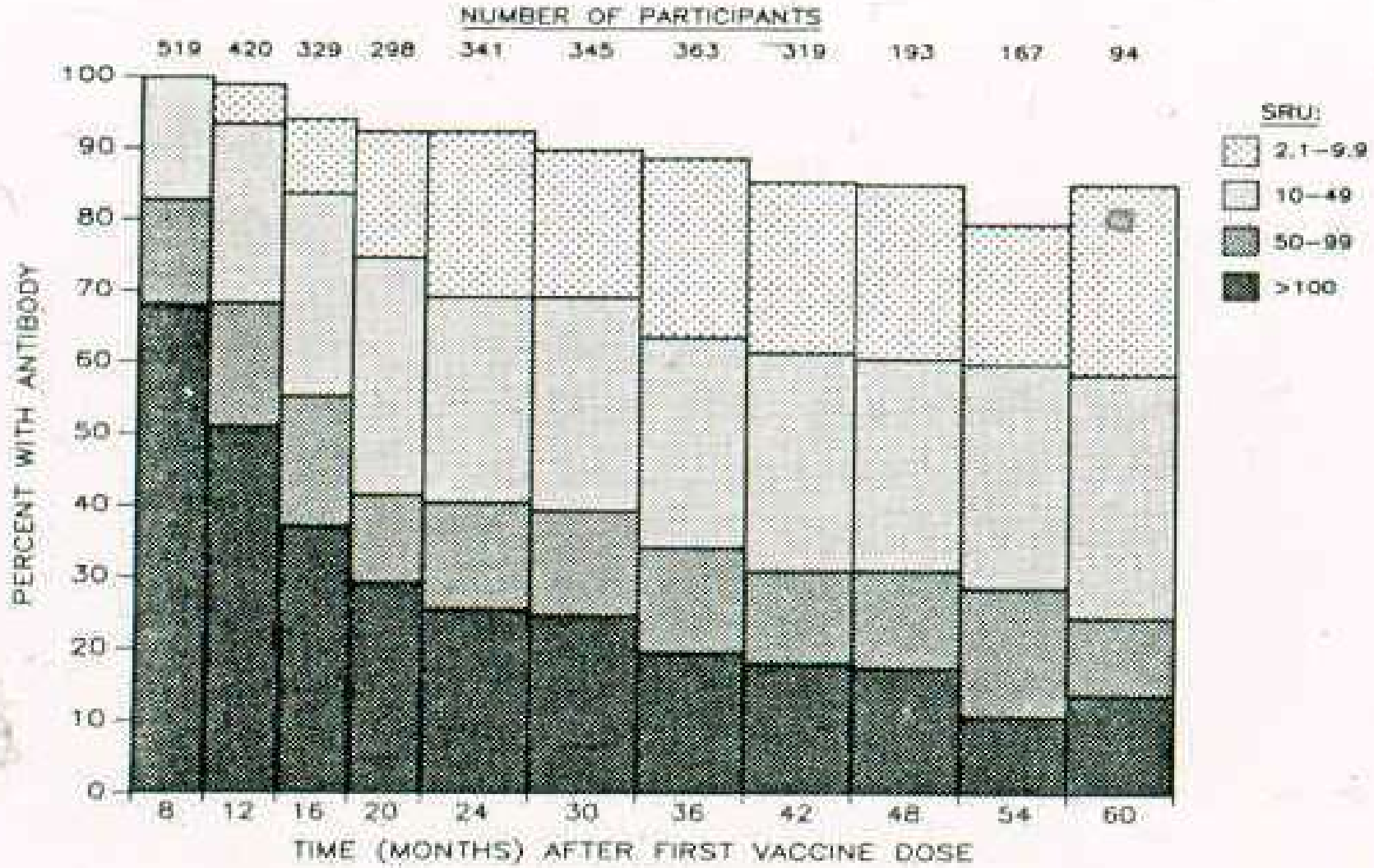
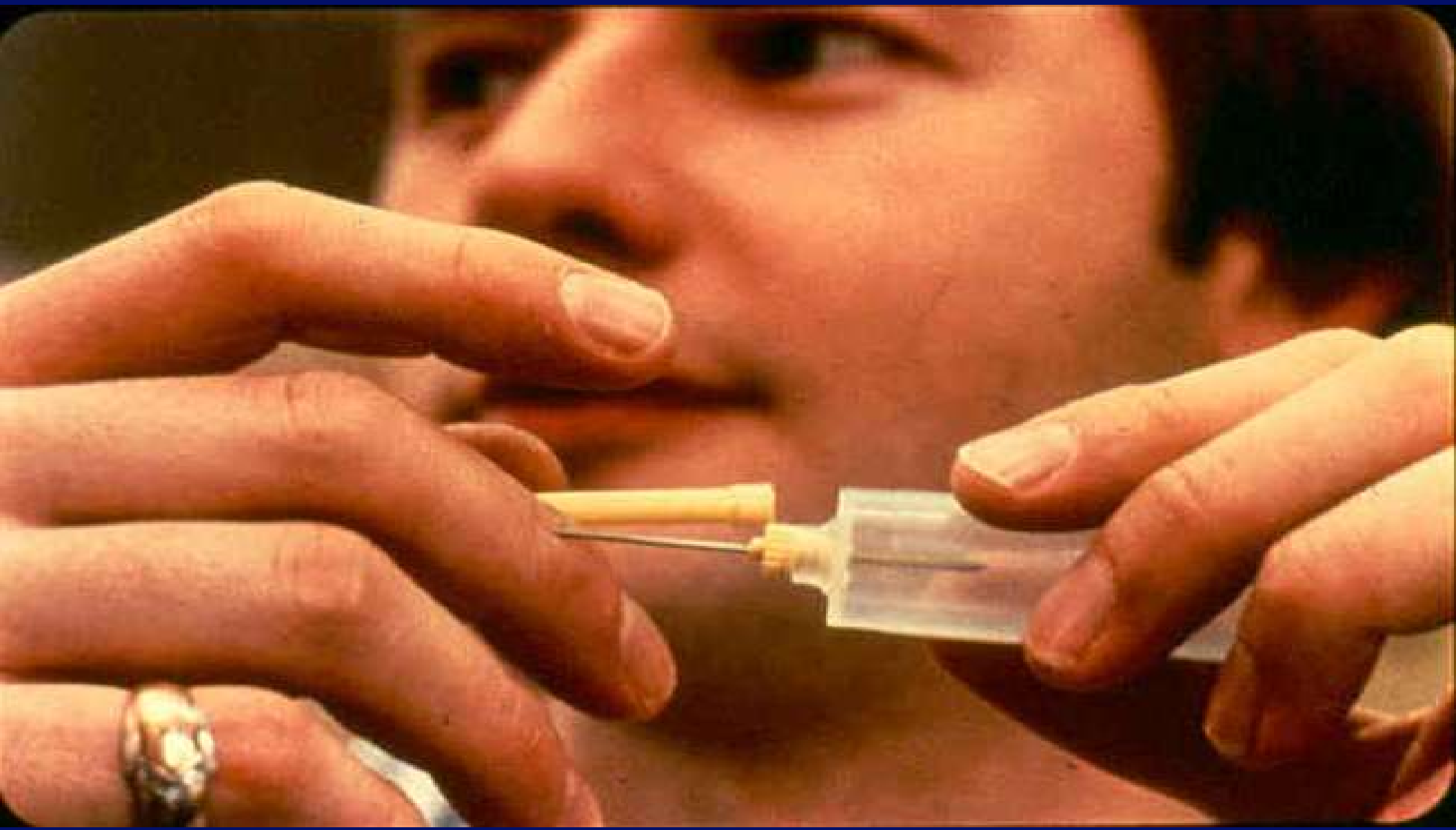


Figure 1. Long-Term Persistence of Anti-HBs in Persons in Whom Anti-HBs Levels above 9.9 SRU Developed after Standard Three-Dose Vaccination.



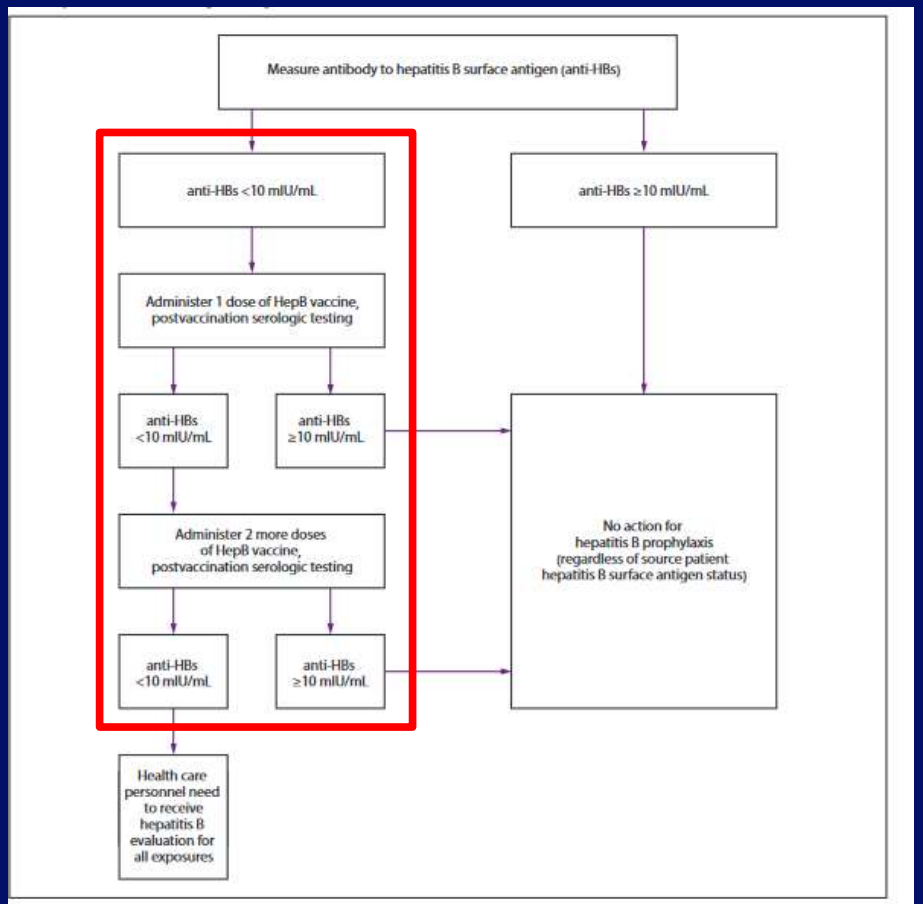
Postexposure management of health care personnel after occupational percutaneous or mucosal exposure to blood or body fluids, by health care personnel HepB vaccination and response status

	Postexposure testing		Postexposure prophylaxis		
HCP status	Source patient (HBsAg)	HCP testing (anti-HBs)	HBIG	Vaccination	Postvaccination serologic testing
Documented responder after complete series			No action needed		
Documented nonresponder after two complete series	Positive/unknown	—*	HBIG x2 separated by 1 month	—	N/A
	Negative		No action needed		
Response unknown after complete series	Positive/unknown	<10 mIU/mL	HBIG x1	Initiate revaccination	Yes
	Negative	<10 mIU/mL	None	Initiate revaccination	Yes
	Any result	≥10 mIU/mL	No action needed		
Unvaccinated/incompletely vaccinated or vaccine refusers	Positive/unknown	—	HBIG x1	Complete vaccination	Yes
	Negative	—	None	Complete vaccination	Yes

Abbreviations: anti HBs = antibody to hepatitis B surface antigen; HBIG = hepatitis B immune globulin; HBsAg = hepatitis B surface antigen; HCP = health care personnel; N/A = not applicable.
* Not indicated.

ACIP, 2018: https://www.cdc.gov/mmwr/volumes/67/rr/pdfs/rr6701-H.pdf

Pre-exposure evaluation for health care personnel previously vaccinated with complete, ≥3-dose HepB vaccine series who have not had postvaccination serologic testing*



Source: Adapted from CDC. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP). Part II: immunization of adults. MMWR 2006;55(No. RR-16).
* Should be performed 1–2 months after the last dose of vaccine using a quantitative method that allows detection of the protective concentration of anti-HBs (≥10 mIU/mL) (e.g., enzyme-linked immunosorbent assay [ELISA]).

https://www.cdc.gov/mmwr/volumes/67/rr/pdfs/rr6701-H.pdf

Serology Testing and Vaccinations

BOX 6. Persons recommended to receive serologic testing prior to vaccination*

- Household, sexual, or needle contacts of hepatitis B surface antigen (HBsAg)–positive persons†
- HIV-positive persons†
- Persons with elevated alanine aminotransferase/aspartate aminotransferase of unknown etiology†
- Hemodialysis patients†
- Men who have sex with men†
- Past or current persons who inject drugs†
- Persons born in countries of high and intermediate hepatitis B virus (HBV) endemicity (HBsAg prevalence ≥2%)
- U.S.-born persons not vaccinated as infants whose parents were born in countries with high HBV endemicity (≥8%)
- Persons needing immunosuppressive therapy, including chemotherapy, immunosuppression related to organ transplantation, and immunosuppression for rheumatologic or gastroenterologic disorders
- Donors of blood, plasma, organs, tissues, or semen

* Serologic testing comprises testing for hepatitis B surface antigen (HBsAg), antibody to HBsAg, and antibody to hepatitis B core antigen.
† Denotes persons also recommended for hepatitis B vaccination. Serologic testing should occur prior to vaccination. Serologic testing should not be a barrier to vaccination of susceptible persons. The first dose of vaccine should typically be administered immediately after collection of the blood for serologic testing.

BOX 7. Persons recommended to receive postvaccination serologic testing* following a complete series of HepB vaccination

- Infants born to hepatitis B surface antigen (HBsAg)–positive mothers or mothers whose HBsAg status remains unknown (e.g., when a parent or person with lawful custody safely surrenders an infant confidentially shortly after birth)†
- Health care personnel and public safety workers
- Hemodialysis patients and others who might require outpatient hemodialysis (e.g., predialysis, peritoneal dialysis, and home dialysis)
- HIV-infected persons
- Other immunocompromised persons (e.g., hematopoietic stem-cell transplant recipients or persons receiving chemotherapy)
- Sex partners of HBsAg-positive persons

* Postvaccination serologic testing for persons other than infants born to HBsAg-positive (or HBsAg-unknown) mothers consists of anti-HBs.
† Postvaccination serologic testing for infants born to HBsAg-positive (or HBsAg-unknown) mothers consists of anti-HBs and HBsAg. Persons with anti-HBs <10 mIU/mL after the primary vaccine series should be revaccinated. Infants born to HBsAg-positive mothers or mothers with an unknown HBsAg status should be revaccinated with a single dose of HepB vaccine and receive postvaccination serologic testing 1–2 months later. Infants whose anti-HBs remains <10 mIU/mL following single dose revaccination should receive two additional doses of HepB vaccine, followed by postvaccination serologic testing 1–2 months after the final dose. Based on clinical circumstances or family preference, HBsAg-negative infants with anti-HBs <10 mIU/mL may instead be revaccinated with a second, complete 3-dose series, followed by postvaccination serologic testing performed 1–2 months after the final dose of vaccine. For others with anti-HBs <10 mIU/mL after the primary series, administration of 3 additional HepB vaccine doses on an appropriate schedule, followed by anti-HBs testing 1–2 months after the final dose, is usually more practical than serologic testing after >1 dose of vaccine.

ACIP 2018: https://www.cdc.gov/mmwr/volumes/67/rr/pdfs/rr6701-H.pdf

HBV: POST-EXPOSURE PROPHYLAXIS

Exposed person	Source HBsAg+	Source HBsAg-	Source unknown
Unvaccinated	HBIG x 1 HBV vaccine	HBV vaccine	HBV vaccine
Vaccinated, Responder	No therapy	No therapy	No therapy
Vaccinated, Nonresponder	HBIG x 2 or HBIG x 1 & HBV vaccine	No therapy	If known high-risk source, treat as if source HBsAg+
Vaccinated, Response unknown	Obtain anti-HBs * If ok, no therapy * If low, HBIG x 1 & vaccine	No therapy	Obtain anti-HBs * If OK, no therapy * If low, vaccine booster

Adequate anti-HBs is ≥10 mIU/mL; HBIG = 0.06 mg/kg IM

Hepatitis C Virus

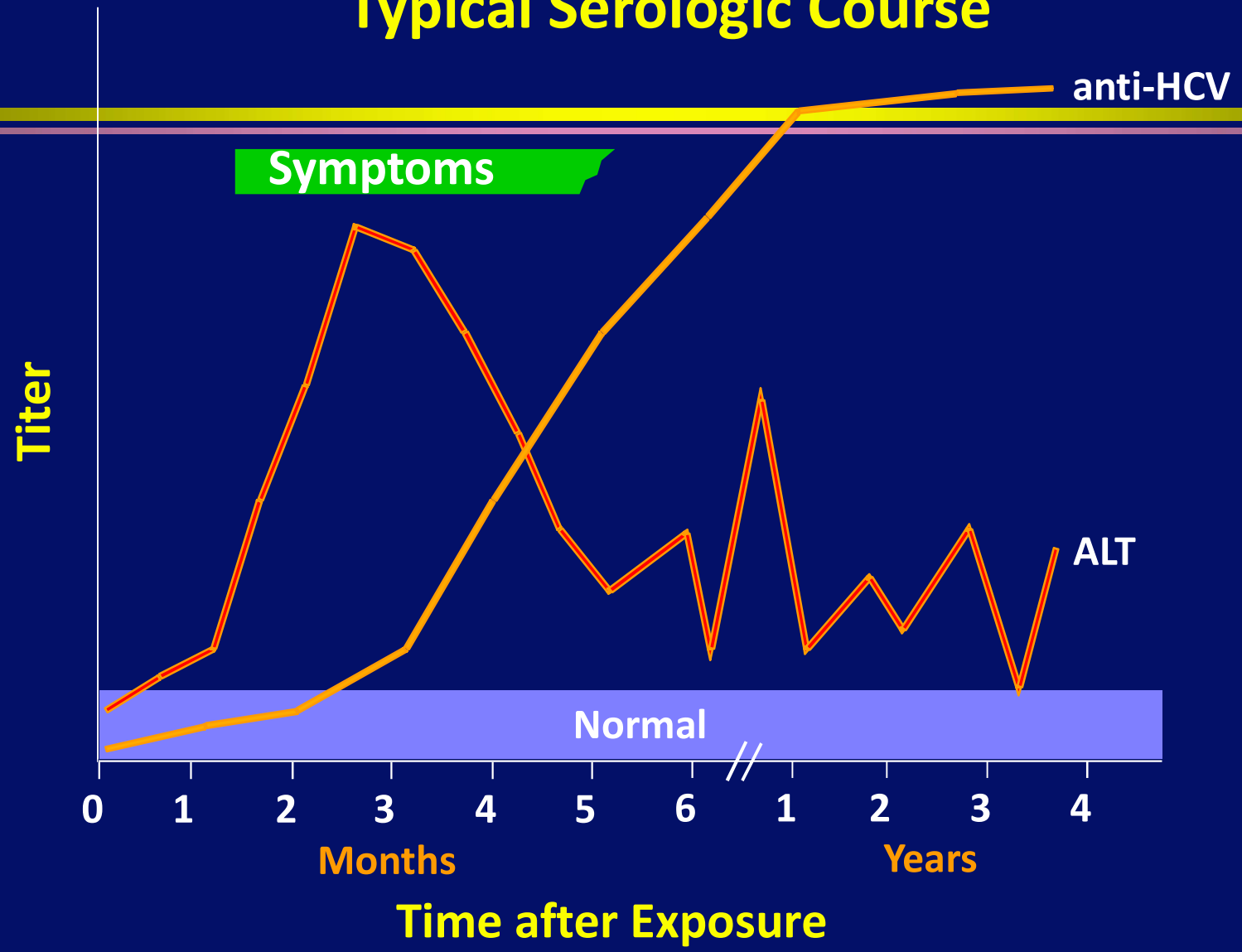
- RNA Flavivirus (Hepacivirus)
  - **Discovery using recombinant DNA technology reported in 1989**
  - **Clinical entity (non-A, non-B hepatitis) in transfused patients reported late 1960s**
  - **Target organ liver**
- Bloodborne (primarily) and sexually-transmitted
- No vaccine
  - **Mutations occur during viral replication**
  - **Substantial heterogeneity (quasi species) prevents effective neutralization**
- Treatable and curable (most people free of virus in months)

Features of Hepatitis C Virus Infection

Incubation period	Average 6-7 weeks Range 2-26 weeks
Acute illness (jaundice)	Mild (20%-30%)
Case fatality rate	Low
Chronic infection	75%-85%
Chronic hepatitis	70%
Mortality from CLD	1%-5%

Hepatitis C Virus Infection

Typical Serologic Course

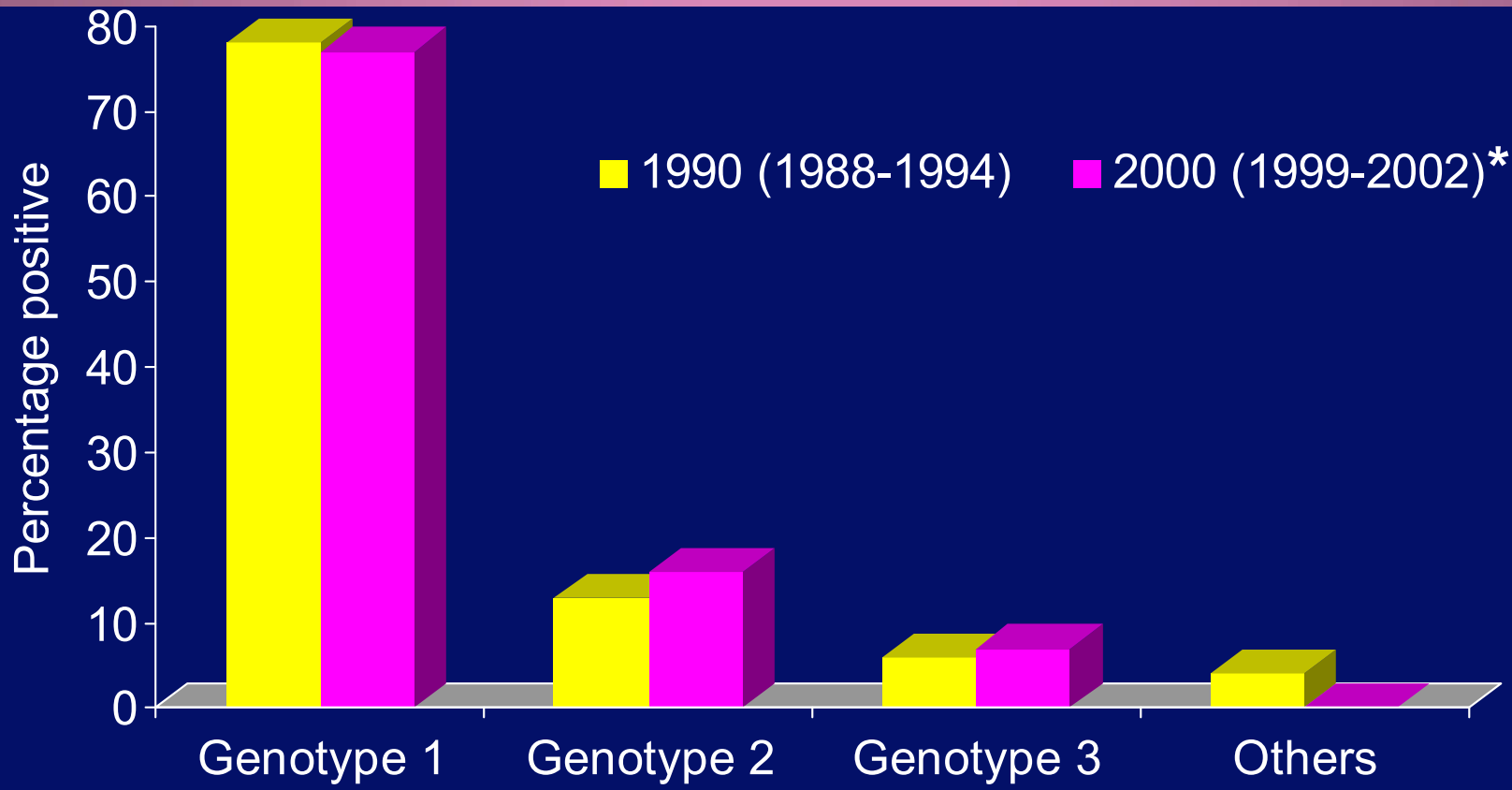


Hepatitis C Virus Infection
United States

New infections per year 1985-89	242,000
2006	20,000
Deaths from acute liver failure	Rare
Persons ever infected (1.6%)	4.1 million (3.4-4.9)*
Persons with chronic infection	3.1 million (2.5-3.7)*
HCV-related chronic liver disease	40% - 60%
Deaths from chronic disease/year	8,000-10,000

*** 95% confidence interval (data from 1999-2002)**

Distribution of HCV Genotypes in the General Population, 1990 vs. 2000, US



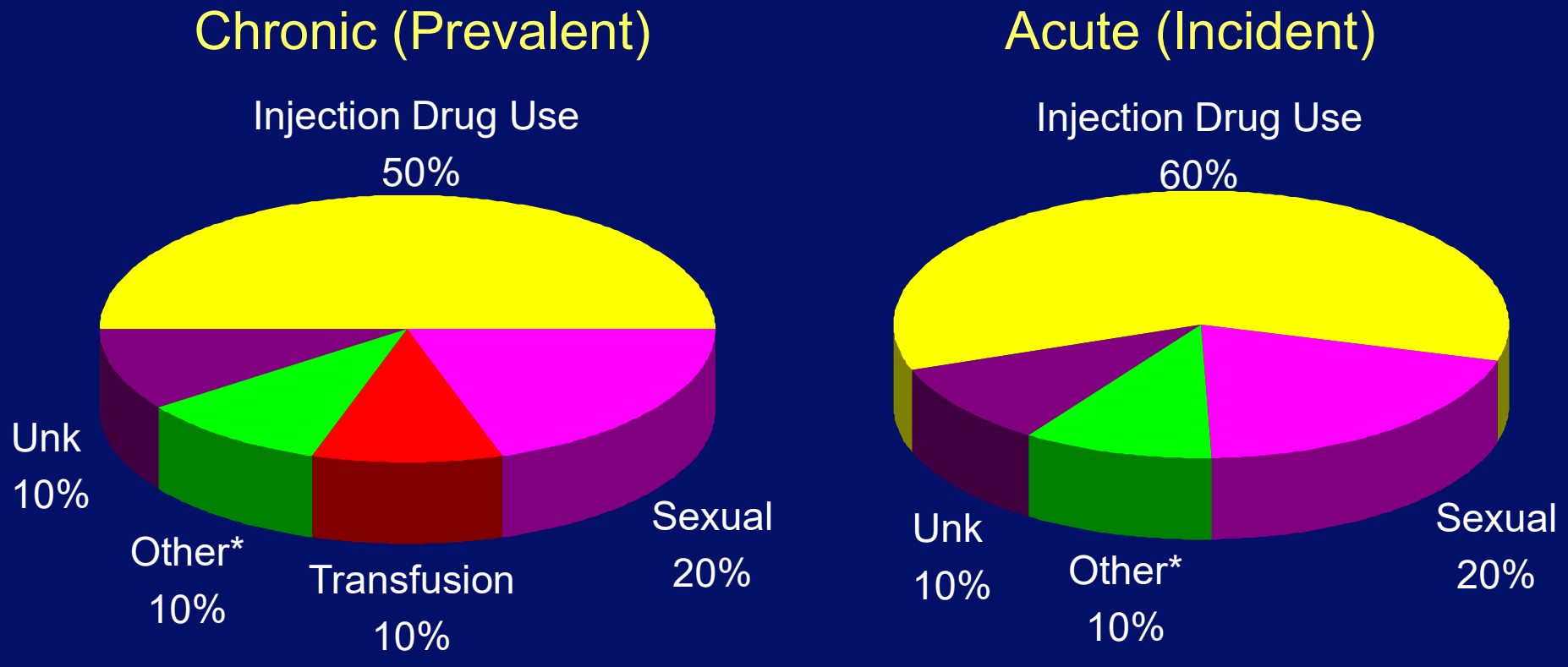
Nainan OV. Gastroenterol 2006;131:478-484

*CDC, preliminary unpublished data

Transmission of HCV

- Percutaneous
  - Injecting drug use
  - Clotting factors before viral inactivation
  - Transfusion, transplant from infected donor
  - Therapeutic (contaminated equipment, unsafe injection practices)
  - Occupational (needlestick)
- Permucosal
  - Perinatal
  - Sexual

Risk Factors For Persons with Acute or Chronic Hepatitis C 1999-2002, U.S.



* Other includes occupational, nosocomial, iatrogenic, perinatal

Armstrong GL, Ann Intern Med 2006;144:705-14; CDC Sentinel Counties, unpublished data

Iatrogenic-Related Outbreaks of HCV Infections in Developed Countries

- In- and outpatient care
  - Chronic hemodialysis, surgery, endoscopy, pain management clinic, oncology clinic, in-patient ward
- Most due to unsafe injection practices, i.e., failure to use aseptic techniques
  - Contamination of multi-dose medication vials and IV solutions
  - Reuse of syringes/needles
  - Contamination of finger stick devices
- Infected HCW rarely source
  - Usually due to self-injection of patients' narcotics

Williams IT, Clin Infect Dis 2004;38:1592-1598

Health-Care Related HCV Transmission

- Blood transfusion from unscreened donors
  - including plasma-derived products not inactivated
- Unsafe injection practices
  - inadequate sterilization of reusable needles and syringes
  - sharing of disposable needles and syringes
- Contaminated equipment
  - inadequate cleaning and disinfection
    - health care settings
    - alternative medicine practices, rituals

Global Burden of Disease Associated with Unsafe Injections

- Estimated annual incidence, 2000
  - > 20 million HBV infections
    - 30% of new infections
  - > 2 million HCV infections
    - 40% of new infections
  - > 250,000 HIV infections
    - 5% of new infections

Ezzati M et al. *Lancet. 360(9343):1347-60, 2002.*

Unsafe Injection Practices

Developing Countries

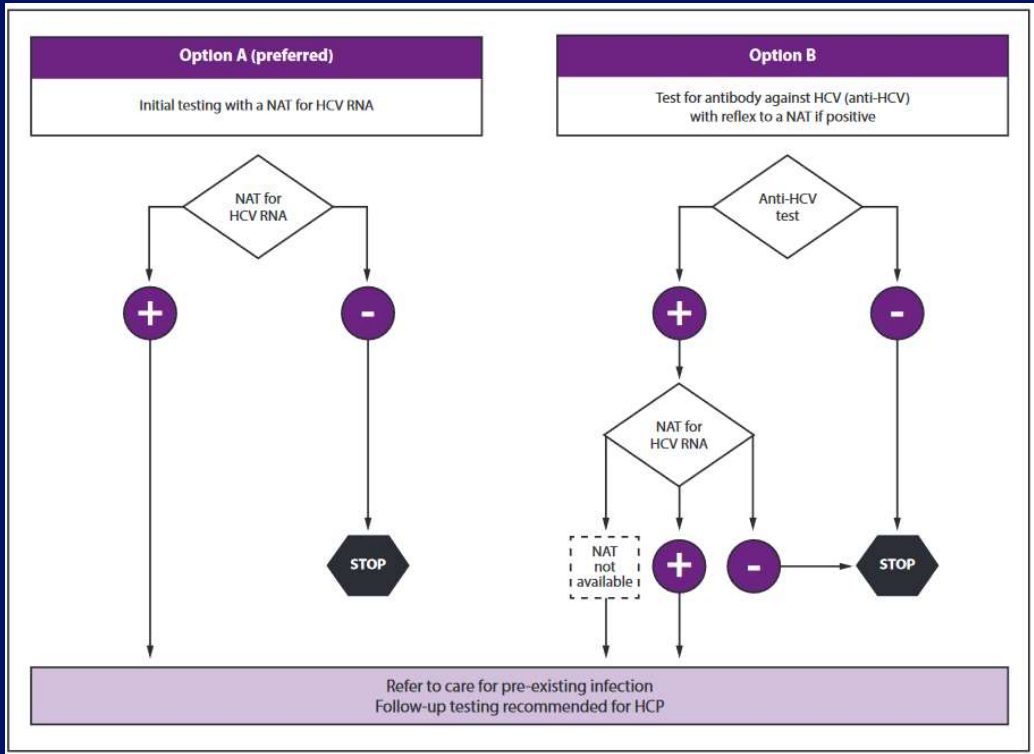
- Inadequate supplies of sterile syringes
- Inadequate sterilization of reusable syringes and needles
- Administration at home by non-professionals
- Syringes shared with others (family, neighbors)
- Overuse of therapeutic injections

Developed Countries

- Failure to use aseptic techniques
  - Reuse of same syringe and needle to administer meds to multiple patients
  - Medication preparation and blood sample handling in same area
  - Contamination of multiple dose medication vials
- Infected HCW rarely source
  - Usually due to self-injection of patients' narcotics

Children Handling Medical Waste, Bangladesh

Testing of source patients after potential exposure of health care personnel to hepatitis C virus — CDC guidance, United States, 2020*



Abbreviations: AASLD-IDSA = American Association for the Study of Liver Diseases and the Infectious Diseases Society of America; HCP = health care personnel; HCV = hepatitis C virus; NAT = nucleic acid test.

* ***Testing of the source patient should be performed as soon as possible (preferably within 48 hours) after exposure.*** Testing may follow option A (preferred), which is testing with a NAT for HCV RNA, or option B, which is testing for anti-HCV with reflex to NAT for HCV RNA if positive. If the source patient is known or suspected to have recent behaviors that increase risk for HCV acquisition (e.g., injection drug use within the previous 4 months) or if risk cannot be reliably assessed, initial testing of the source patient should include a NAT for HCV RNA. A source patient found to be positive for HCV RNA should be referred to care. Follow-up testing of HCP is recommended if the source patient is HCV RNA positive, anti-HCV positive with HCV RNA status unknown, or cannot be tested. ***Persons with detectable HCV RNA at any point*** should be referred to care consistent with current AASLD-IDSA guidelines for evaluation and treatment of all persons with acute or chronic HCV infection. Guidance for hepatitis C treatment (https://www.hcvguidelines.org) is evolving with emerging data on treatment with direct-acting antivirals.

ACIP 2020: https://www.cdc.gov/mmwr/volumes/69/rr/pdfs/rr6906a1-H.pdf

Testing of source patients after potential exposure of health care personnel to hepatitis C virus — CDC guidance, United States, 2020*

BOX. Testing of source patients and health care personnel potentially exposed to hepatitis C virus — CDC guidance, United States, 2020

Source-patient testing

- Testing of the source patient may follow option A (preferred), which is testing with a nucleic acid test (NAT) for hepatitis C virus (HCV) RNA, or option B, which is testing for anti-HCV with reflex to a NAT if positive.
- If a source patient is known or suspected to have recent behaviors that increase risk for HCV acquisition (e.g., injection drug use within the previous 4 months) or if risk cannot be reliably assessed, initial testing should include a NAT.
- Follow-up testing of health care personnel (HCP) is recommended if the source patient is HCV RNA positive, anti-HCV positive with RNA status unknown, or cannot be tested.

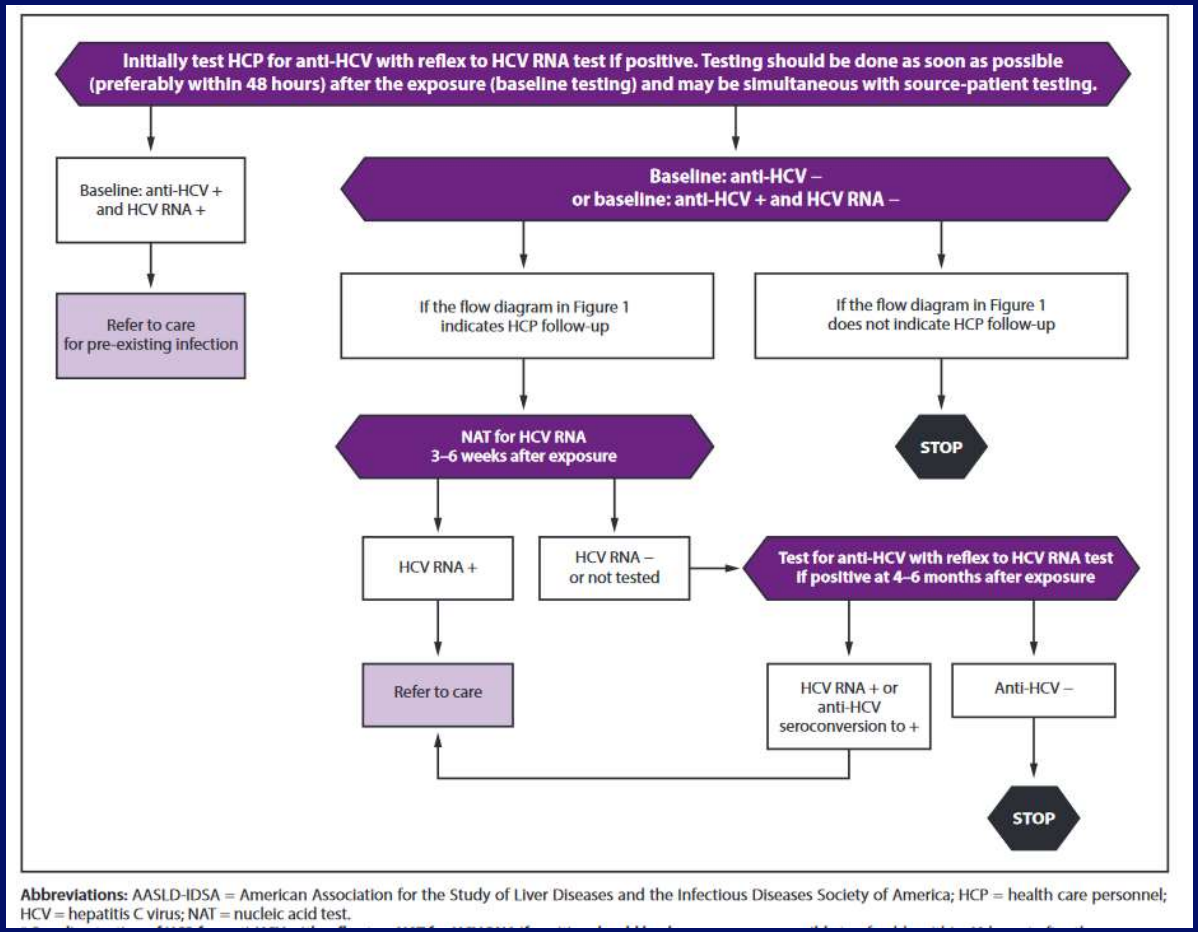
HCP testing*

- Baseline testing of HCP for anti-HCV with reflex to a NAT if positive should be conducted as soon as possible (preferably within 48 hours) after the exposure and may be simultaneous with source-patient testing.
- If follow-up testing of HCP is recommended based on the source-patient's status, test with a NAT at 3–6 weeks postexposure.
- If the HCP is NAT negative at 3–6 weeks postexposure, a final test for anti-HCV at 4–6 months postexposure is recommended.
- A source patient or HCP who is positive for HCV RNA should be referred to care.

Follow-up testing of HCP is also warranted when concerns exist about specimen integrity, including handling and storage conditions that might have compromised source-patient test results, or if they exhibit any clinical signs of HCV infection.

ACIP 2020: https://www.cdc.gov/mmwr/volumes/69/rr/pdfs/rr6906a1-H.pdf

Testing of source patients after potential exposure of health care personnel to hepatitis C virus — CDC guidance, United States, 2020*

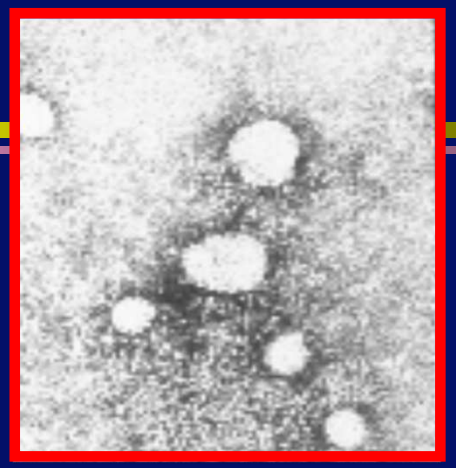


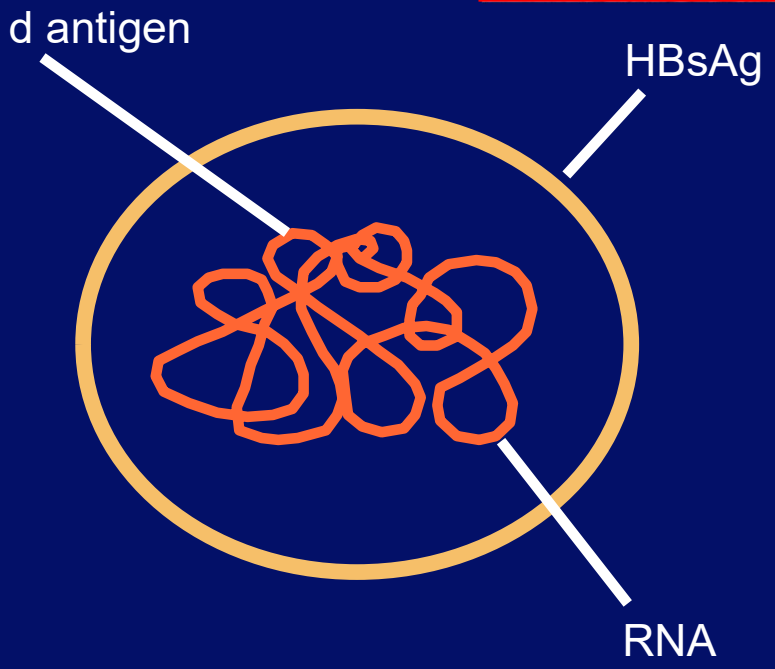
Abbreviations: AASLD-IDSA = American Association for the Study of Liver Diseases and the Infectious Diseases Society of America; HCP = health care personnel; HCV = hepatitis C virus; NAT = nucleic acid test.

ACIP 2020: https://www.cdc.gov/mmwr/volumes/69/rr/pdfs/rr6906a1-H.pdf

Hepatitis Delta Virus

- Referred to as “defective” virus
  - HDV RNA
  - surrounded by coat of HBsAg
- HDV dependent on presence of HBV to establish infection
  - requires a protein coat of HBsAg to be released from infected hepatocytes
  - HBsAg mfg by HBV





Infection with HDV

HBV-HDV Coinfection

- Simultaneous infection with HBV and HDV in a person susceptible to HBV
- Low risk of death from chronic liver disease

HBV-HDV Superinfection

- Infection with HDV in a person with chronic HBV
- High risk of severe chronic liver disease and death

Persons immune from HBV infection – either through vaccination or resolved infection – cannot become infected with HDV

Epidemiologic Features of HDV

- Transmission similar to HBV
  - Percutaneous – highly efficient
  - Sexual
  - Perinatal

  } Much less efficient than HBV
- Uncommon in U.S. - seen mainly in IDU's
- Worldwide, endemic in Amazon, Mediterranean, Central Asia, Africa

Prevention of HDV

HBV-HDV coinfection

- Hepatitis B vaccination

HBV-HDV superinfection

- Prevent exposure to HBV
  - screen blood for HBV (need HBV for HDV)
- Reduce high-risk behaviors
  - safer sex practices
  - safer injection practices

Current and Future Issues

- Identification of infected persons
  - Screening and testing not routinely performed
  - Lack effective methods for reaching those whose risk was in the remote past
    - Risk factor ascertainment in routine healthcare visits is rare
- Therapy regimens less than ideal, especially those with genotype 1
  - In US, treatment offered to low % of HCV-positives
- Implications of multiple co-factors on liver disease progression and response to therapies not well understood
  - Impact likely to grow creating an even greater challenge
- Need to be alert to changes in epidemiology

Viral Hepatitis - Overview

- Primary infection of the liver caused by at least five unrelated viruses: A, B, C, D, E
- HAV and HEV
  - Fecal-oral route
  - Acute self-limited disease; no chronic infection
- HBV, HCV, HDV
  - Percutaneous or mucosal exposures to blood
  - Chronic infection – major causes of cirrhosis and hepatocellular carcinoma worldwide

Viral Hepatitis in US: Trends

HHS.gov

- ~2M living with HCV in US
- ~1M Living with HBV in US
- More than half of persons with hepatitis do not know they have the virus
  - 67% of persons with HBV
  - 51% of persons with HCV
- Baby boomers (mid-50s to early 70s) made up 36.3% chronic HCV
- HCV increasing in the US
- Viral hepatitis is leading cause of liver cancer

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Geographic Differences in HCV Transmission Patterns

Exposures among prevalent infections	Contribution of exposures to disease burden by HCV prevalence		
	Low	Moderate	High
Injecting drug use	++++	++	+
Transfusions (before testing)	+++	+++	+++
Unsafe therapeutic injections	+	++++	++++
Occupational	+	+	+
Perinatal	+	+	+
High-risk sex	++	+	+/-