

Hepatitis A Virus Infections

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Objectives

- Discuss the pathogenesis and epidemiology of hepatitis A virus (HAV) infections
- Discuss clinical features of HAV infections
- Discuss the risk factors for HAV infections
- Discuss methods to prevent HAV infections

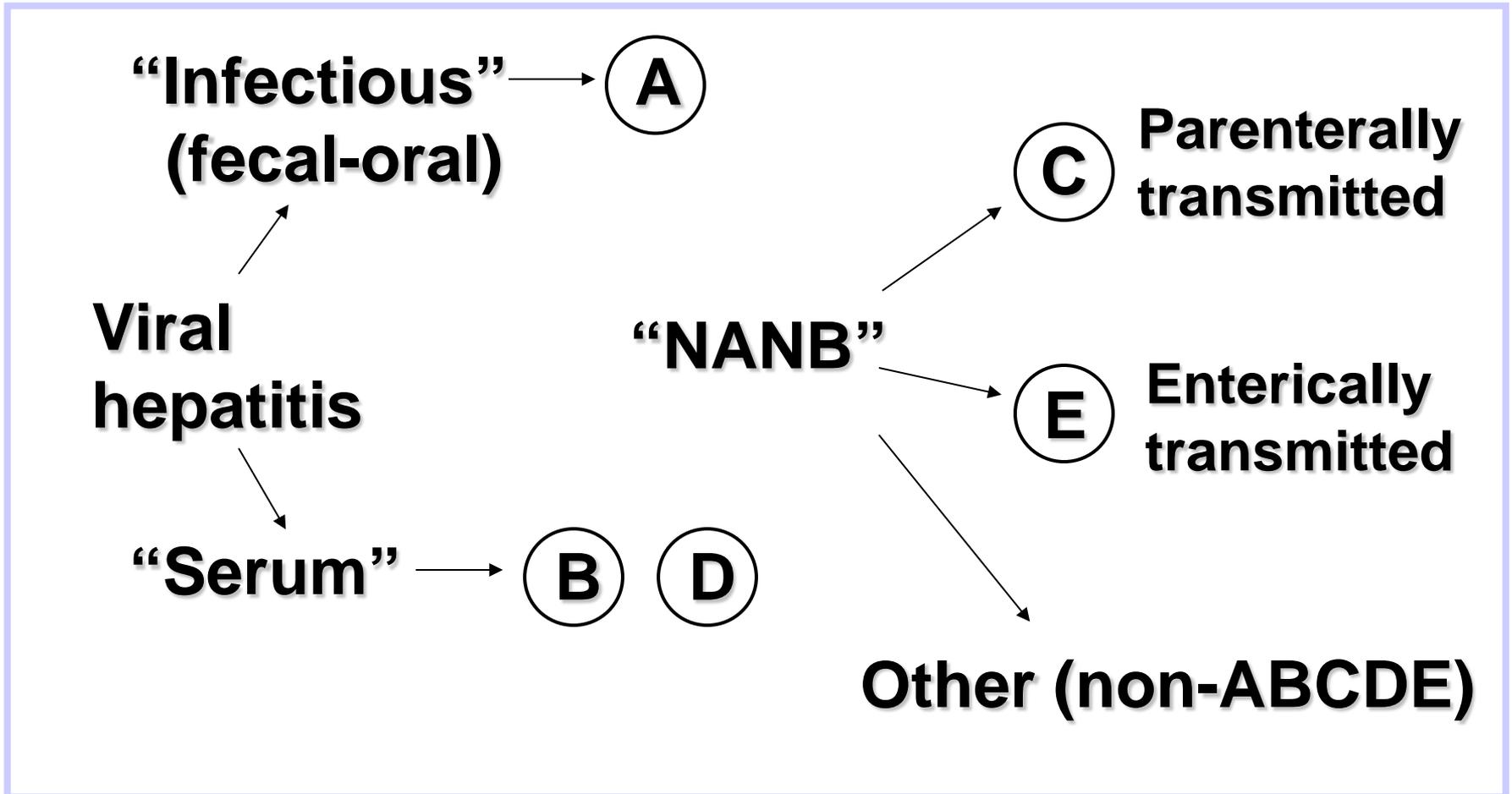


Hepatitis A – History Tidbits

- Epidemic jaundice described by Hippocrates, as early as 400 BC
- Further outbreaks of jaundice in 17th and 18th Century Europe, associated with conflicts
- Earliest recorded US outbreak, Norfolk, VA 1812
- HAV likely was one of the causes of “camp jaundice” or “field jaundice” in wartimes
- **Krugman differentiated “infectious” hepatitis from “serum” hepatitis in 1967**
- Serologic tests developed in 1970s
- Vaccines licensed in 1995 and 1996

Viral Hepatitis – Historical Epi Perspective

Before 1960s

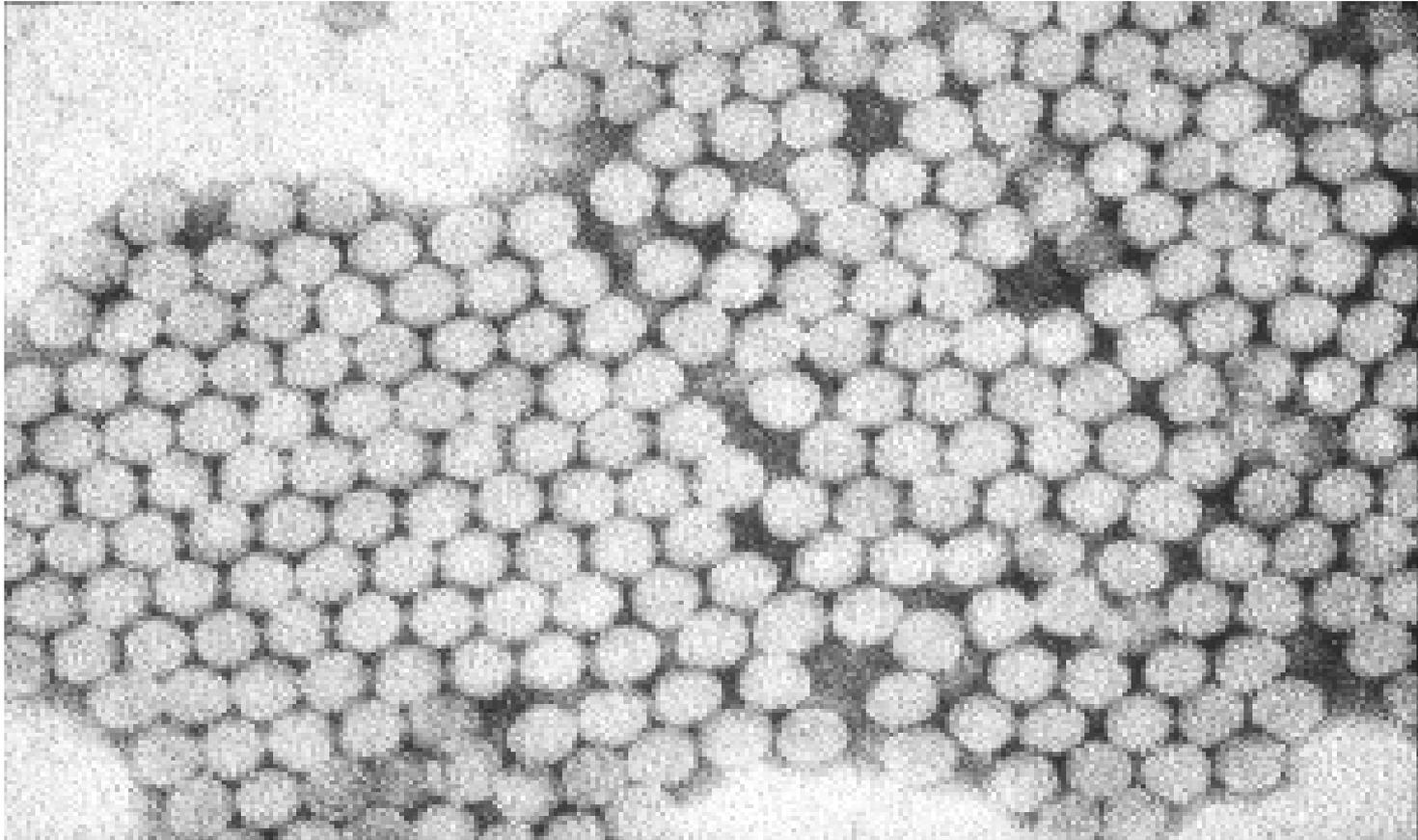




Hepatitis A Virus (HAV)

- Picornavirus (RNA), 27-32 nm in diameter
- Spherical with icosahedral symmetry
- 1 serotype and 6 genotypes. Genotypes I, II, and III, with subtypes A & B infect humans. Genotype IIIA may cause more severe disease.
- **Humans and non-human primates are natural hosts**
- Stable at low pH (pH 1 for 2 hours)
- Inactivated by high temperature ($\geq 185^{\circ}\text{F}$), formalin, chlorine, autoclaving (250°F – 30 min)
- **Complete inactivation in food, e.g., shellfish, requires heating to $\geq 185^{\circ}\text{F}$ for at least one minute**
- **May survive days to weeks in shellfish, soil, water, or marine sediment**

Hepatitis A Virus



Electron micrograph of Hepatitis A virus

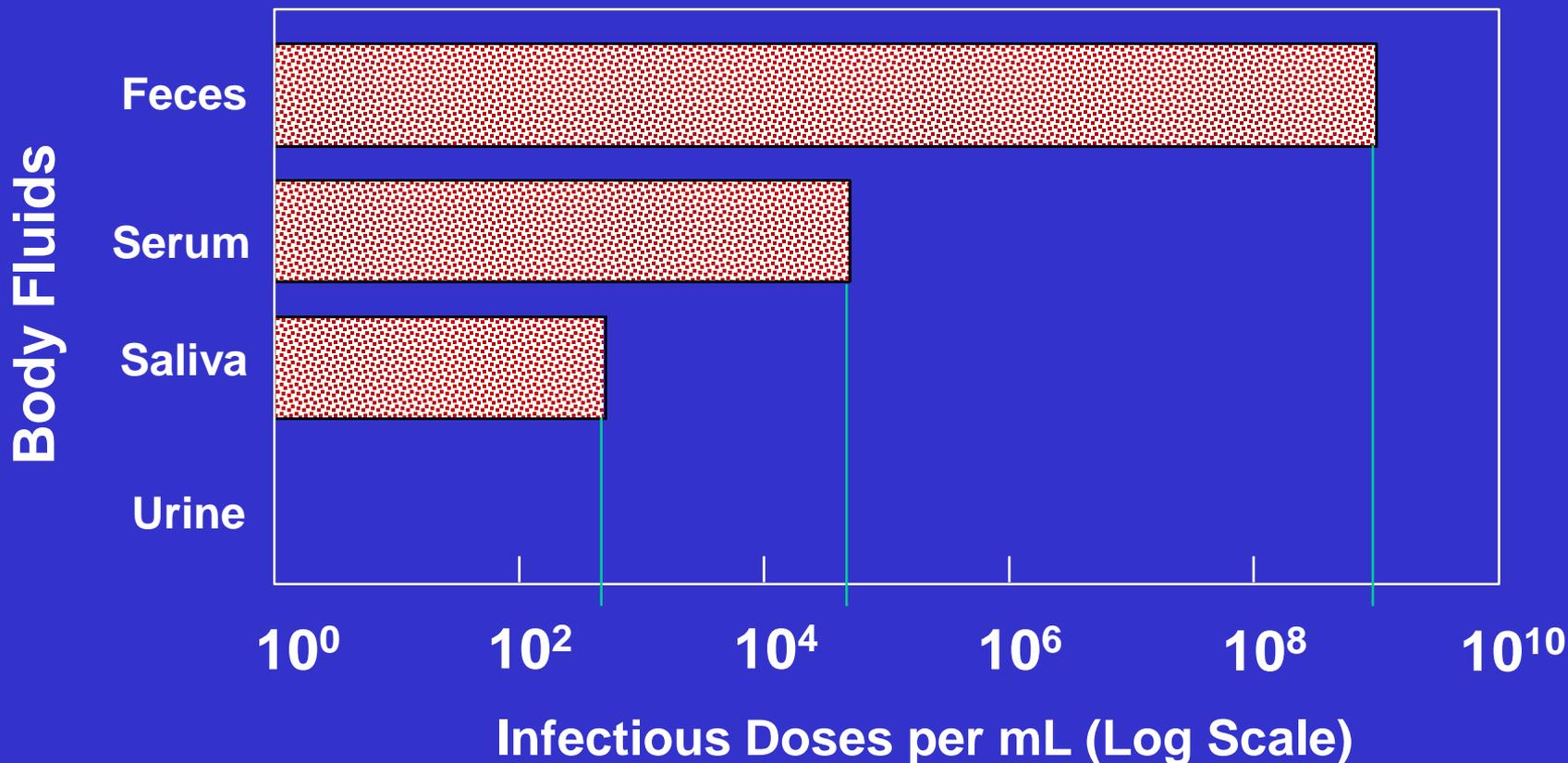


Hepatitis A Pathogenesis

- **Entry into the mouth (fecal-oral transmission is the most common mode of HAV transmission)**
- Acid resistant virus, passes through stomach to intestines
- Transport to liver, major site of viral replication
- Virus present in liver, bile, blood, and feces
10-12 days after infection
- Virus excretion may continue for up to 3 weeks after onset of symptoms. Virus excretion can extend up to six months in infected neonates.
- **Period of infectivity, e.g., one week after jaundice appears,** is shorter than duration of HAV RNA in stool



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

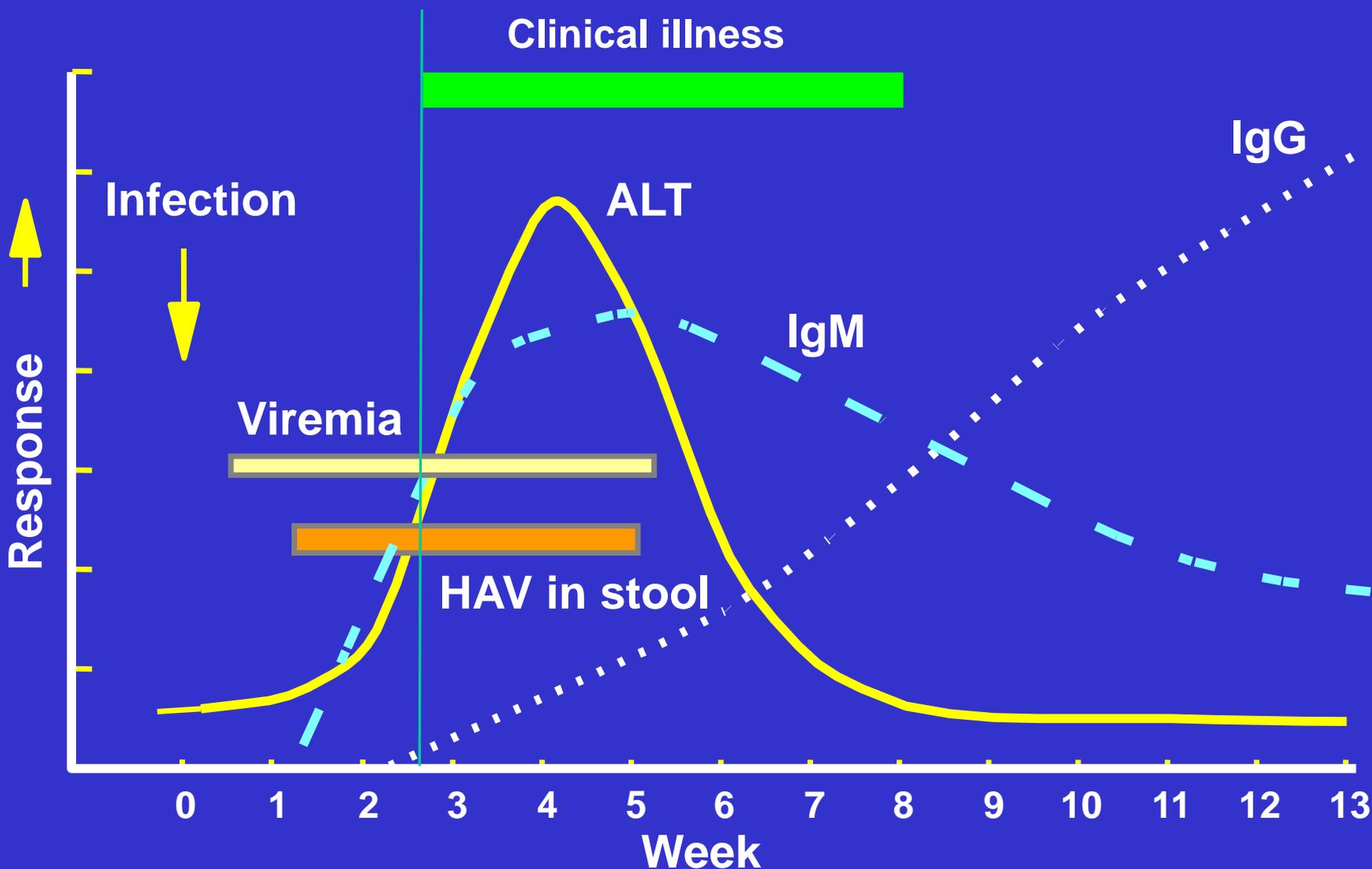


Acute Hepatitis A - Clinical Features

- **Incubation period averages 28 - 30 days (range 15 - 50 days)**
- Illness not specific for hepatitis A
- Hepatitis A virus excreted in feces for 1-2 weeks before onset and for at least one week after onset
- Likelihood of symptomatic illness and hospitalization directly related to age
 - Children generally asymptomatic, adults symptomatic
- **No chronic infection from HAV**
 - Protective antibodies develop in response to acute hepatitis A infection and confer lifelong immunity



Events In Hepatitis A Virus Infection





Acute Hepatitis – Clinical Symptoms

- Asymptomatic infections > Symptomatic diseases > Fulminant Liver Failure > Death
- Symptoms (if present) are similar, regardless of cause (e.g., A, B, C, other viruses, toxins)
 - Fever
 - Nausea, vomiting
 - Loss of appetite
 - Abdominal pain
 - Dark urine
 - Jaundice (yellowing of eyes, skin)
 - Light (clay) colored stools
 - Diarrhea (more common in children with hepatitis A)



Jaundice





Acute Hepatitis A

- Symptoms

- Jaundice 84%
- Weight loss 82%
- Malaise 80%
- Fever 76%
- Nausea 69%
- Vomiting 47%
- Abd pain 37%
- Arthralgias 6%

- Clinical Findings

- Hepatomegaly 87%
- Splenomegaly 9%
- Skin rashes 3%
- Mild edema 2%
- Petechiae 2%
- Cardiac arrhythmias <1%

1988 Shanghai epidemic, 8647 hospitalized patients



Acute Hepatitis A

- Symptoms

- Dark urine 68-94%
- Anorexia 71-85%
- Malaise 76-80%
- N / V 67-79%
- Headache 19-73%
- Pale stool 52-58%
- Fever 18-58%
- Abd pain 26-54%
- Arthralgias 6-19%

- Signs

- Jaundice 40-80%
- Hepatomegaly 14-78%
- Hep. tenderness 39-46%
- Bradycardia 17%
- Skin rash 14%
- Splenomegaly 3-13%
- Lymphadenopathy 4%

Epidemic and sporadic cases of acute hepatitis A



Acute Hepatitis A - Serology

- **Detection of specific IgM anti-HAV in single acute phase serum specimen**
- IgM anti-HAV remains positive for most patients for 6 to 12 months
- IgM anti-HAV remains positive for up to 12 months in up to 25% of patients and can last 2 years or longer
- **IgM anti-HAV has been detected 2--3 weeks after administration of one dose of HepA vaccine in 8%--20% of adults**
- Total anti-HAV antibody (IgM plus IgG) results are not clinically helpful unless reflex testing for IgM anti-HAV occurs



Hepatitis A Virus Transmission

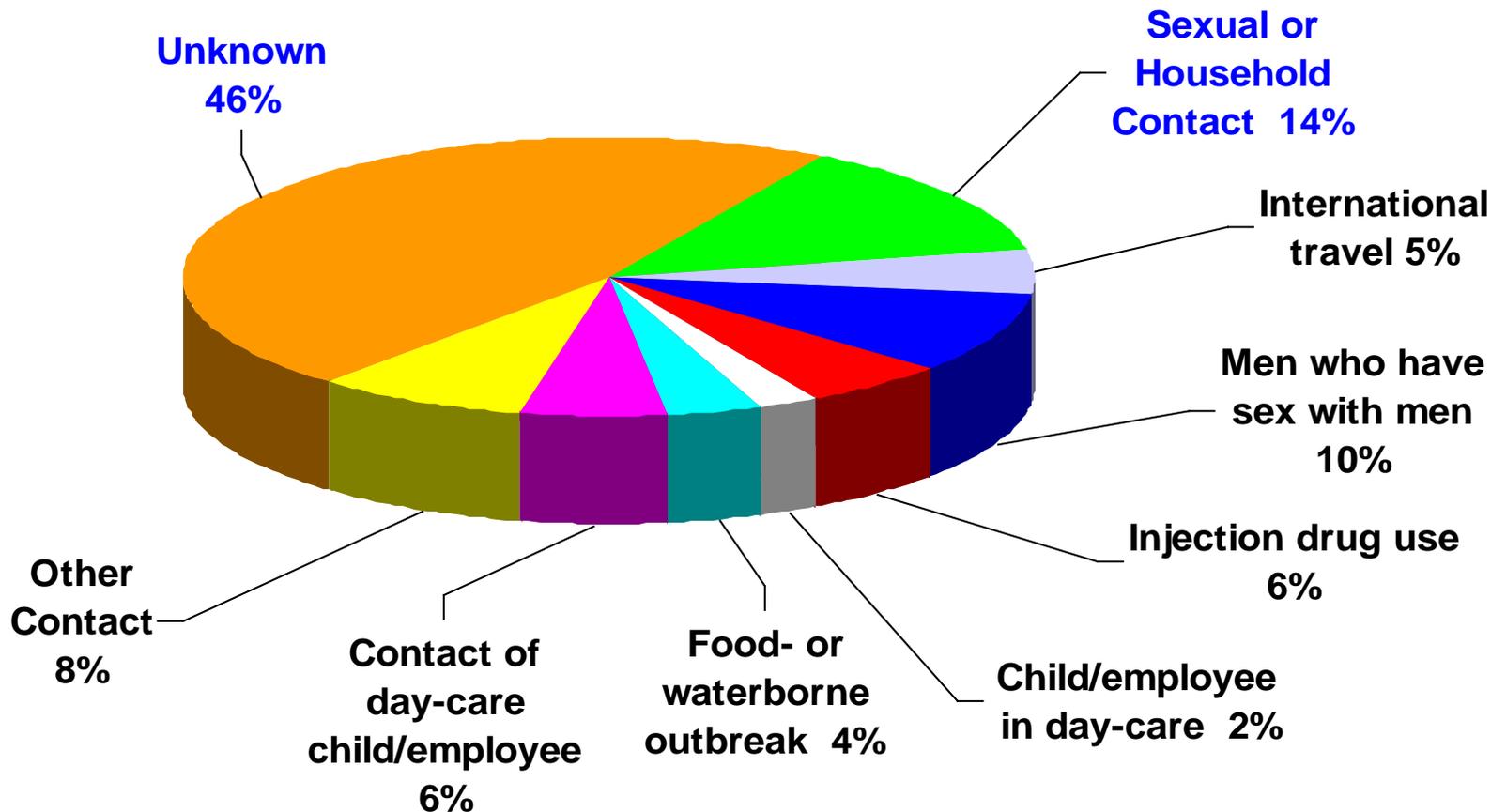
- **Fecal-oral** – Primary means worldwide
- **Close personal contact**
(e.g., household contact, sexual contact, child day care centers)
- **Contaminated food or water**
(e.g., infected food handlers, raw or undercooked mollusks harvested from contaminated water, contaminated produce [e.g., lettuce, strawberries, green onions, or pomegranate seeds])
- **Blood exposure (rare)**
(e.g., injecting drug use, rarely by transfusion and clotting factor concentrates)





Risk Factors Associated with Reported Hepatitis A

United States 1990 - 2000



Source: CDC (NNDSS/ VHSP)

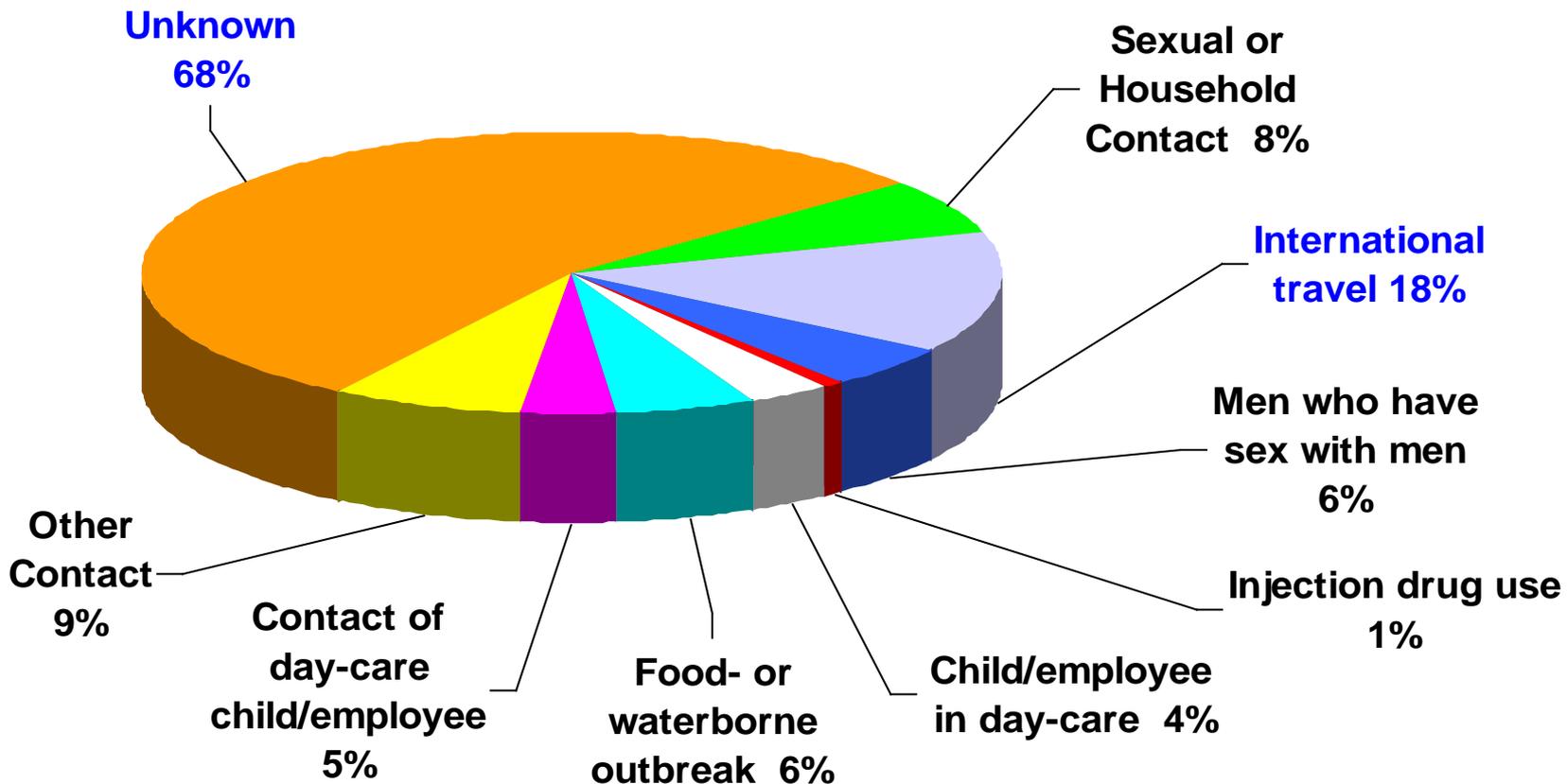
Cabinet for Health and Family Services





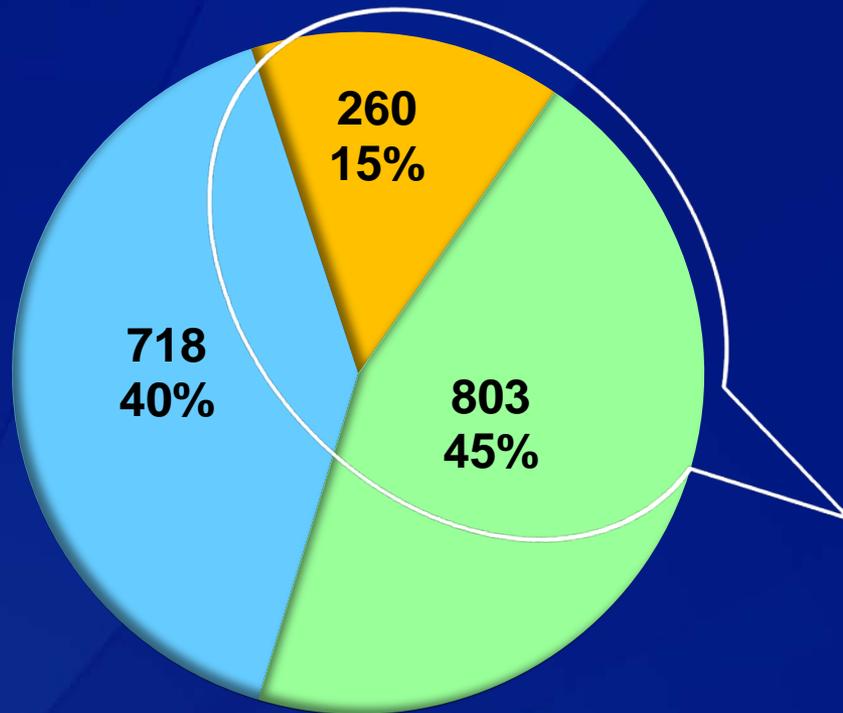
Risk Factors Associated with Reported Hepatitis A

United States 2007



Percentages based on total number of cases for which information about that risk factor was reported – may not total 100%

Availability of Risk Exposures / Behaviors Associated with Acute Hepatitis A — United States, 2013



2013 – 1,781 cases

- Risk identified*
- No risk identified
- Risk data missing

When risk factors were reported, about 25% of case reports had at least one risk exposures / behaviors in the 2 through 6 weeks prior to onset of illness (1,063 case reports).

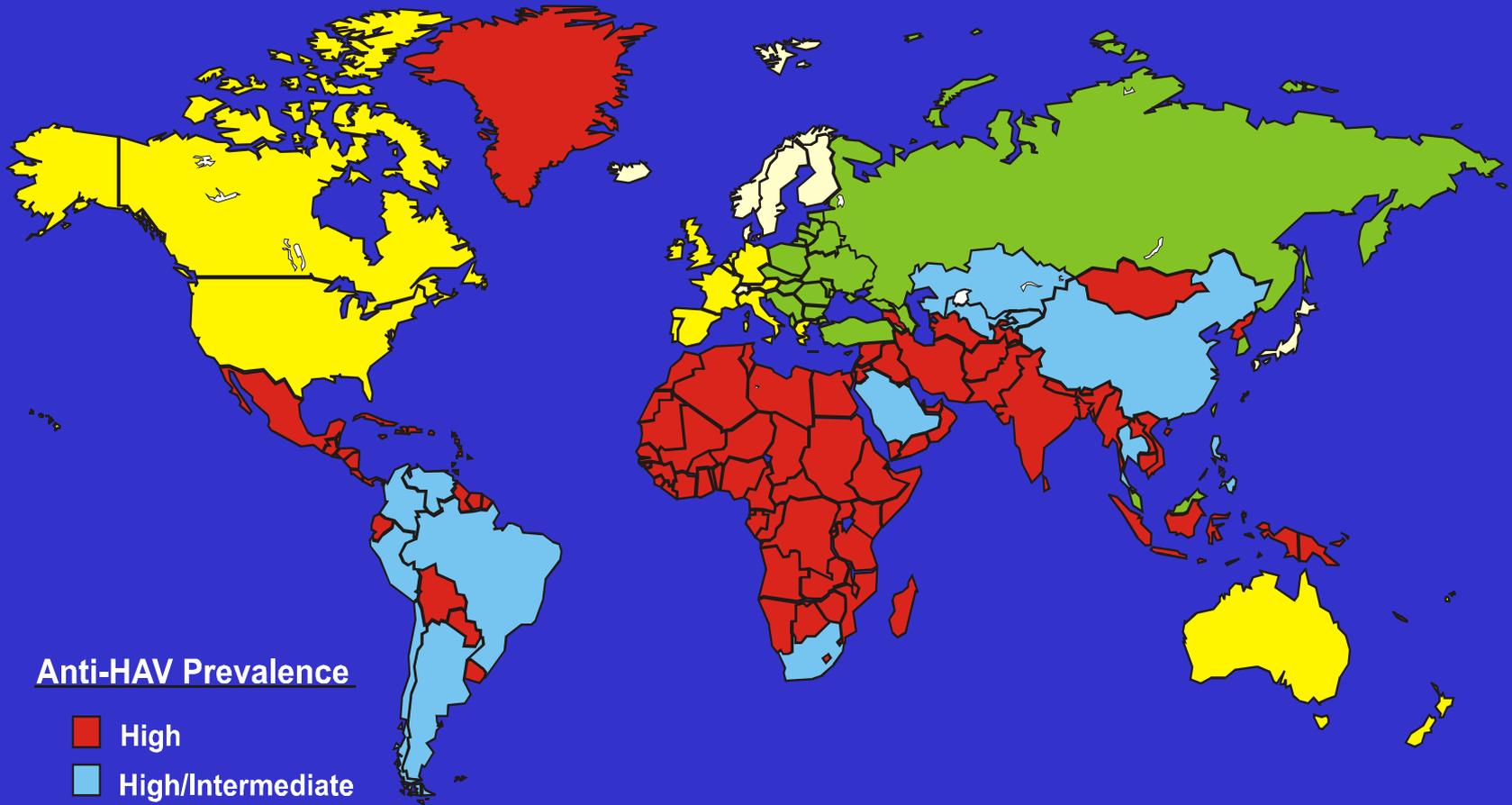
* Includes case reports indicating the presence of at least one of the following risks 2–6 weeks prior to onset of acute, symptomatic hepatitis A: 1) having traveled to hepatitis A-endemic regions of Mexico, South/Central America, Africa, Asia/South Pacific, or the Middle East; 2) having sexual / household or other contact with suspected / confirmed hepatitis A patient; 3) being a child / employee in day care center / nursery / preschool or having had contact with such persons; 4) being involved in a foodborne / waterborne outbreak; 5) being a man who has sex with men; and 6) using injection drugs.

Source: National Notifiable Diseases Surveillance System (NNDSS)





Geographic Distribution of HAV Infection, 2008



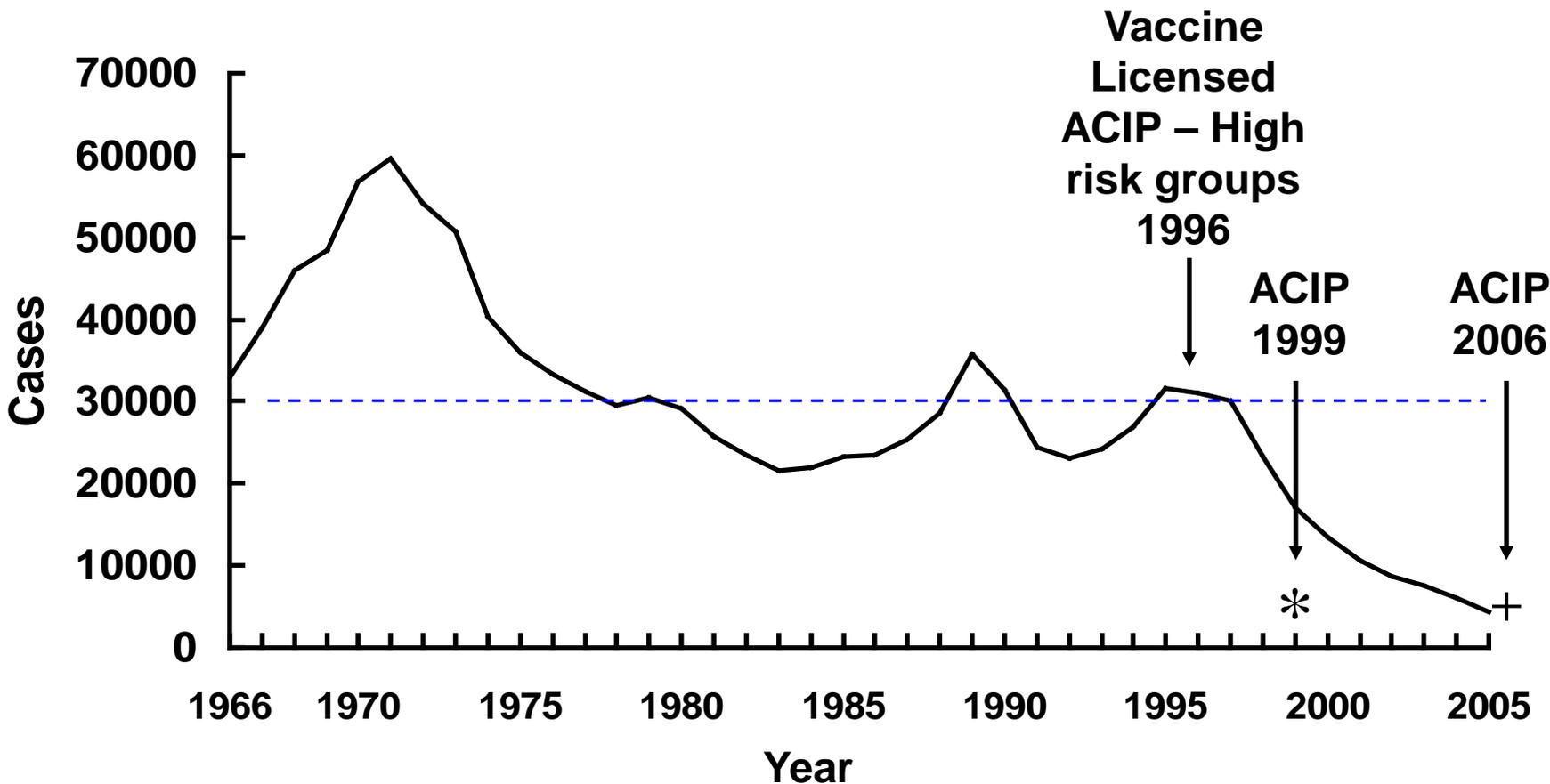
Anti-HAV Prevalence

- High
- High/Intermediate
- Intermediate
- Low
- Very Low

Countries outside the US other than Canada, Australia, New Zealand, Japan, and Western Europe should be considered to have high or intermediate endemicity for hepatitis A virus.



Hepatitis A - United States, 1966 - 2005*



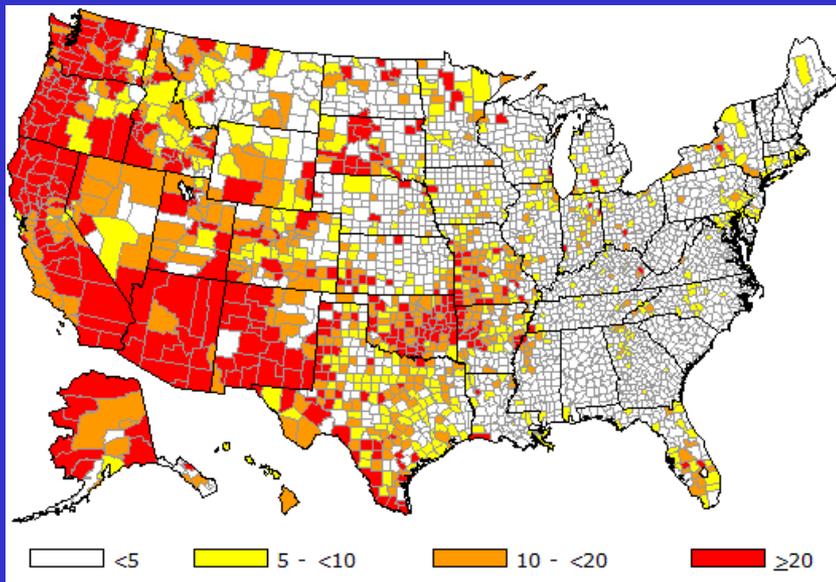
ACIP – Routine childhood schedule
 * 1999 Vaccine – 11 High risk western states
 + 2006 Vaccine – Routine ACIP schedule

*2005 provisional total
 2007 – 2,791 cases reported
 2010 – 1,670 cases reported

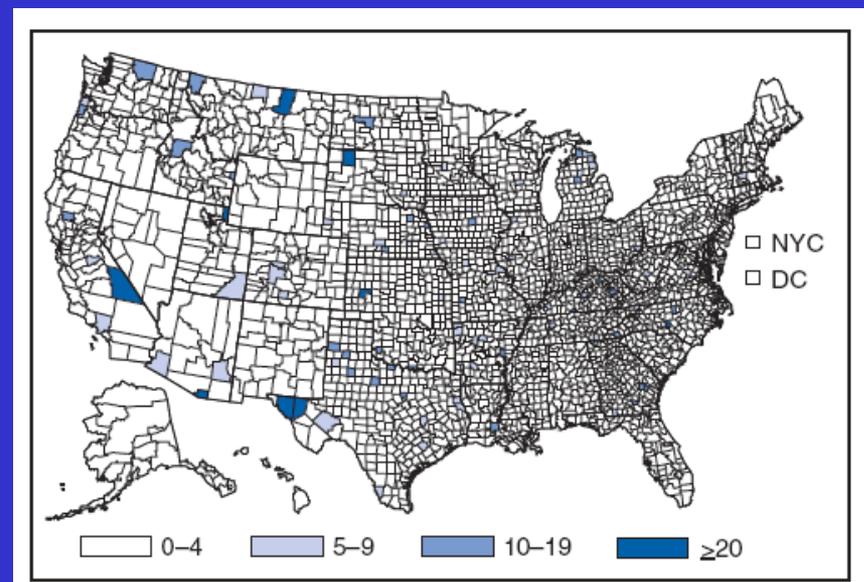


Map of Acute HAV Cases – United States

1987 – 1997*



2006



Average reported cases of Hepatitis A per 100,000 population

*11 western states – 50% of Hepatitis A cases but only 11% of US population

<http://www.cdc.gov/hepatitis/HAV/Historical-USMap.htm>

Reported cases of Hepatitis A per 100,000 population

Rates in the West were about the same as other US regions

<http://www.cdc.gov/mmwr/preview/mmwrhtml/ss5702a1.htm>

Reported Number of Acute Hepatitis A Cases United States, 2000–2013

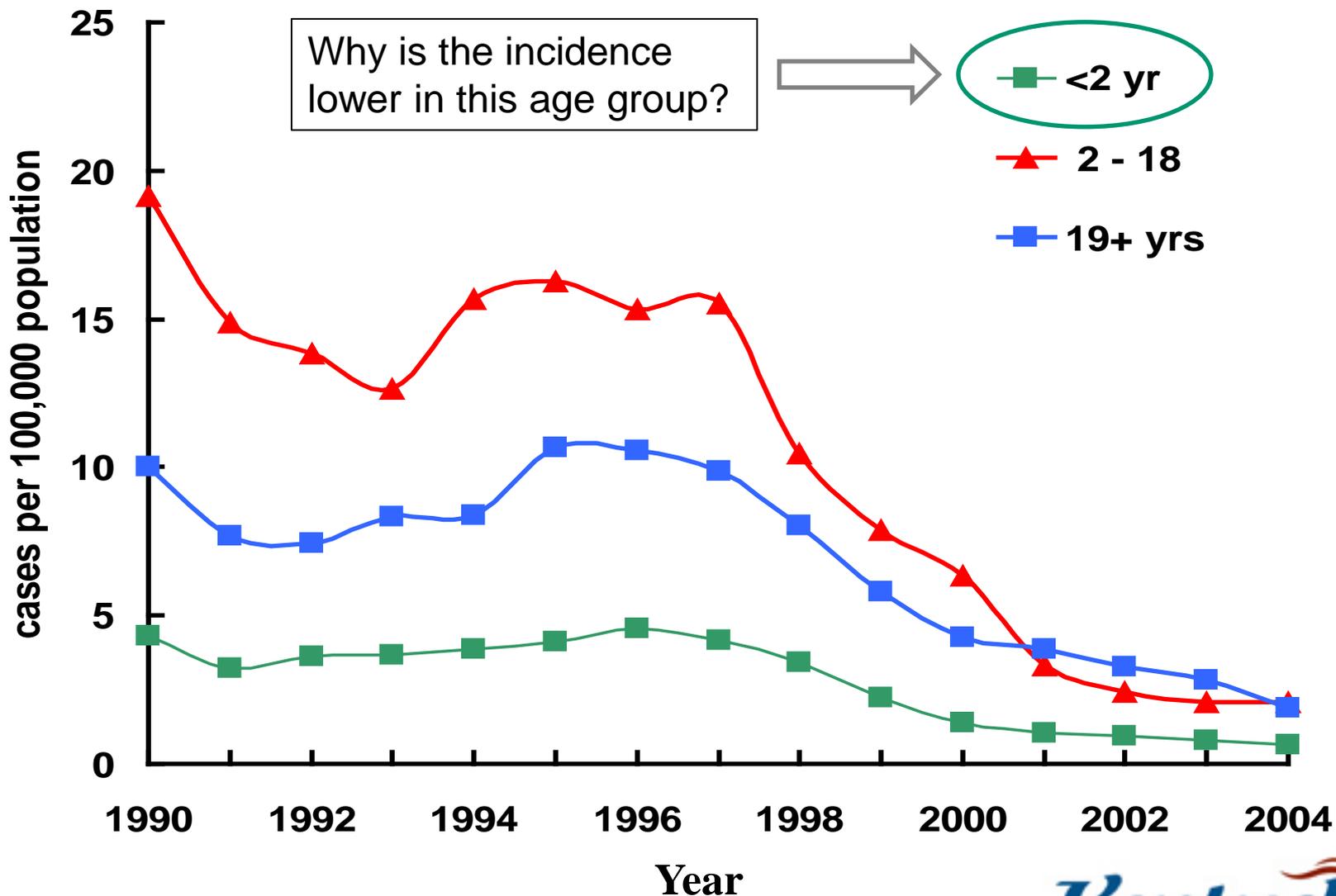
Case counts declined by 86.7% from 2000 to 2013



Source: National Notifiable Diseases Surveillance System (NNDSS)

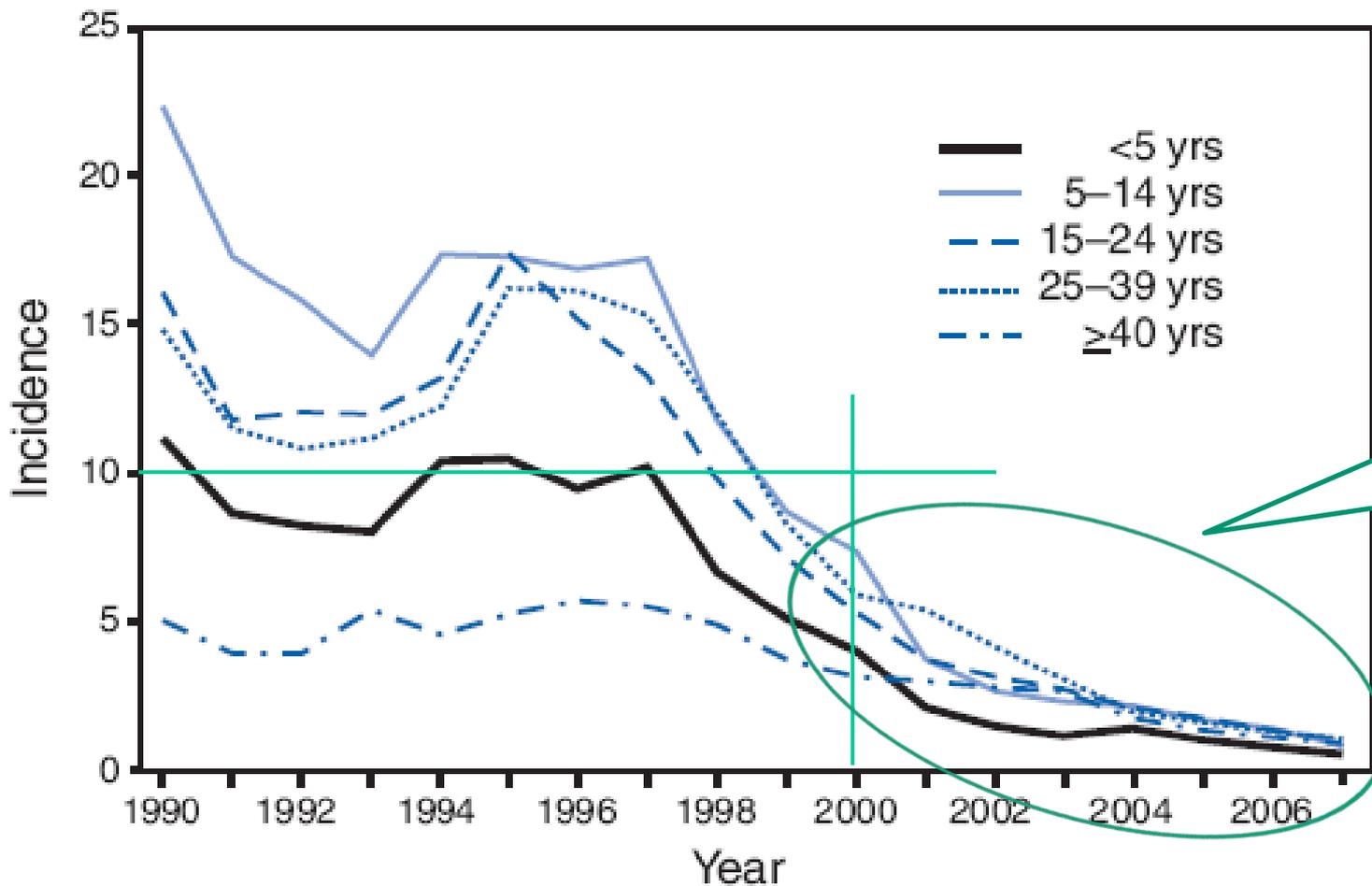


Hepatitis A Incidence By Age Group, 1990 - 2004





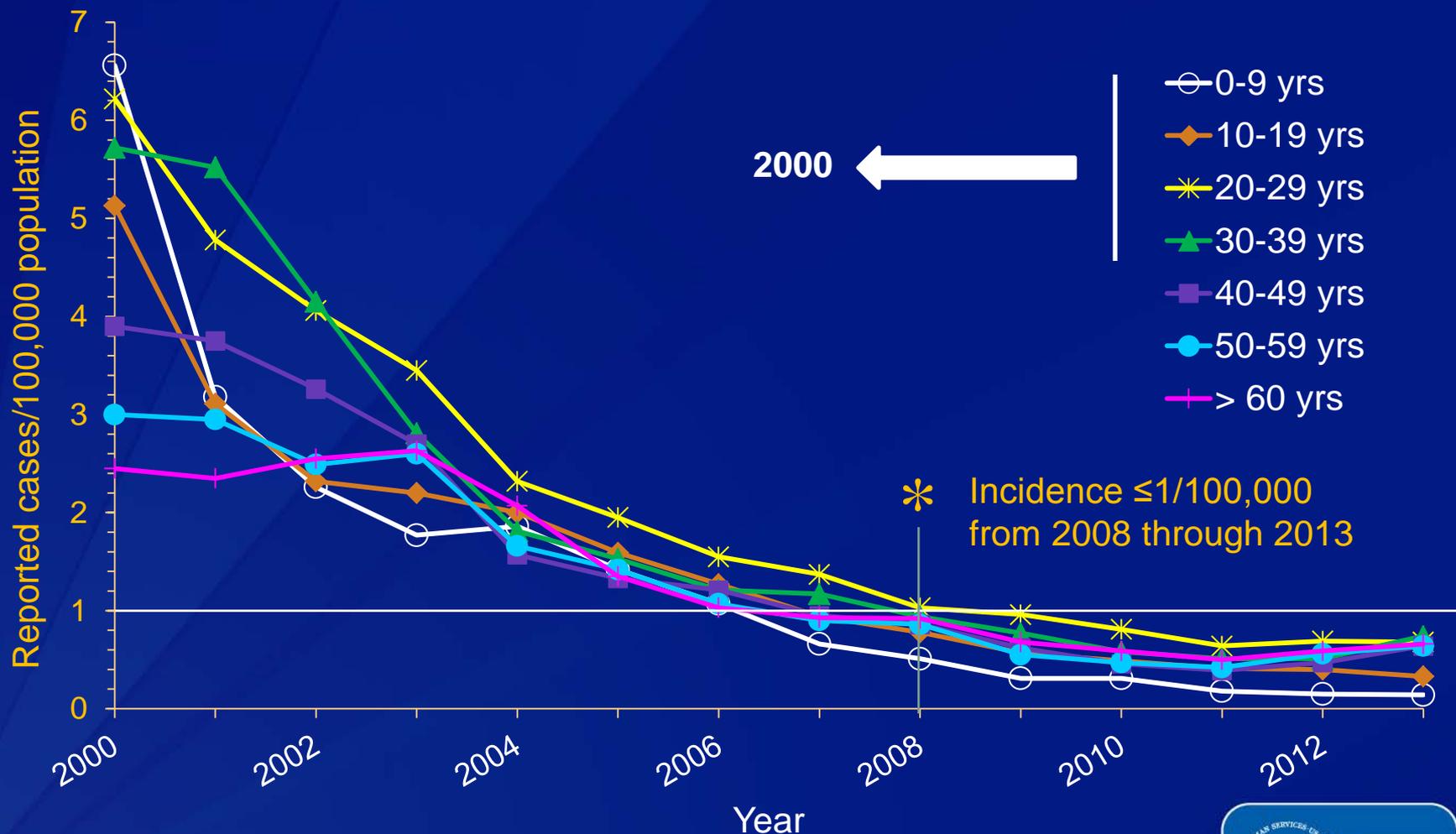
Hepatitis A Incidence By Age Group, 1990 - 2007



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Per 100,000 population

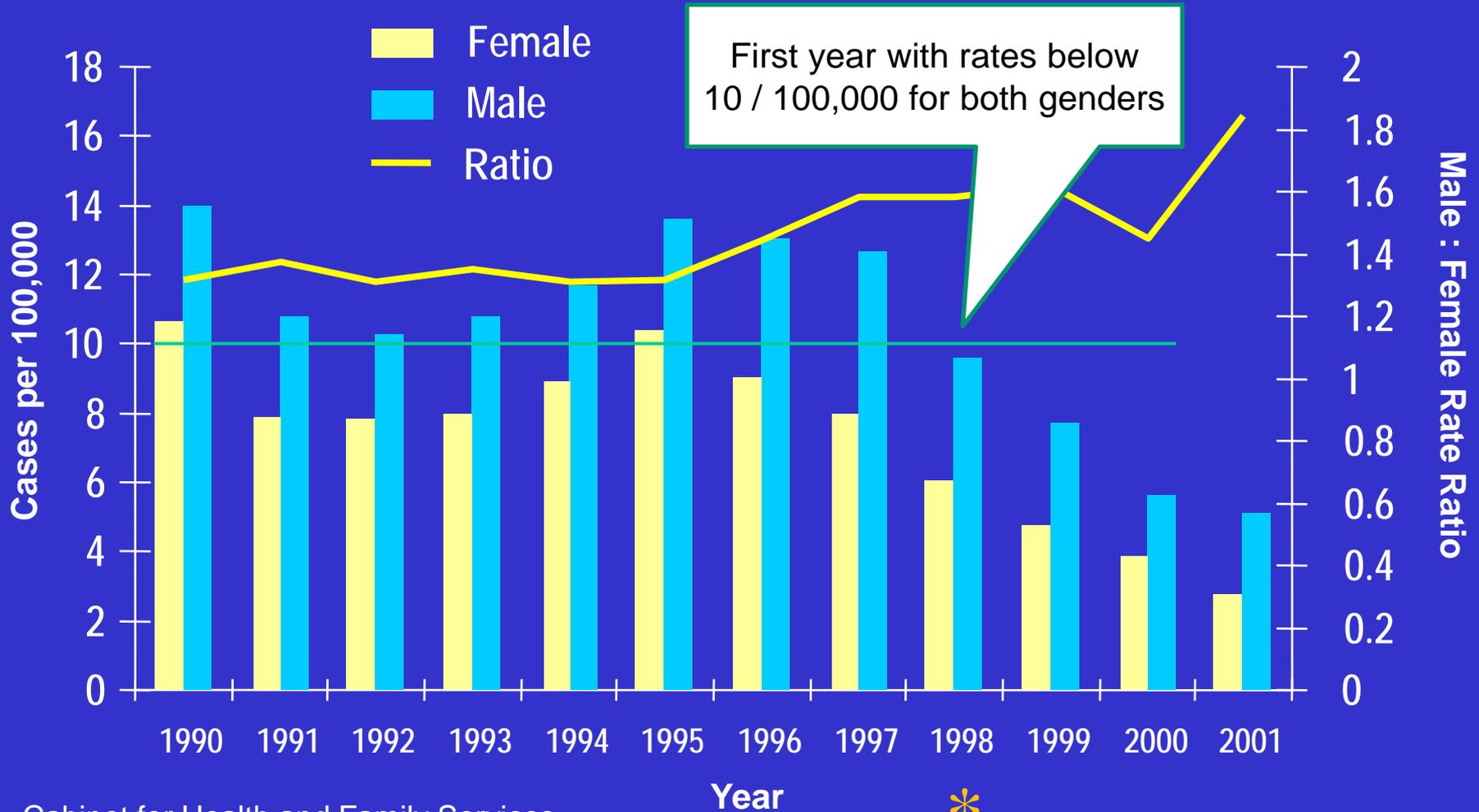
Incidence of Acute Hepatitis A, by Age Group United States, 2000–2013



Source: National Notifiable Diseases Surveillance System (NNDSS)

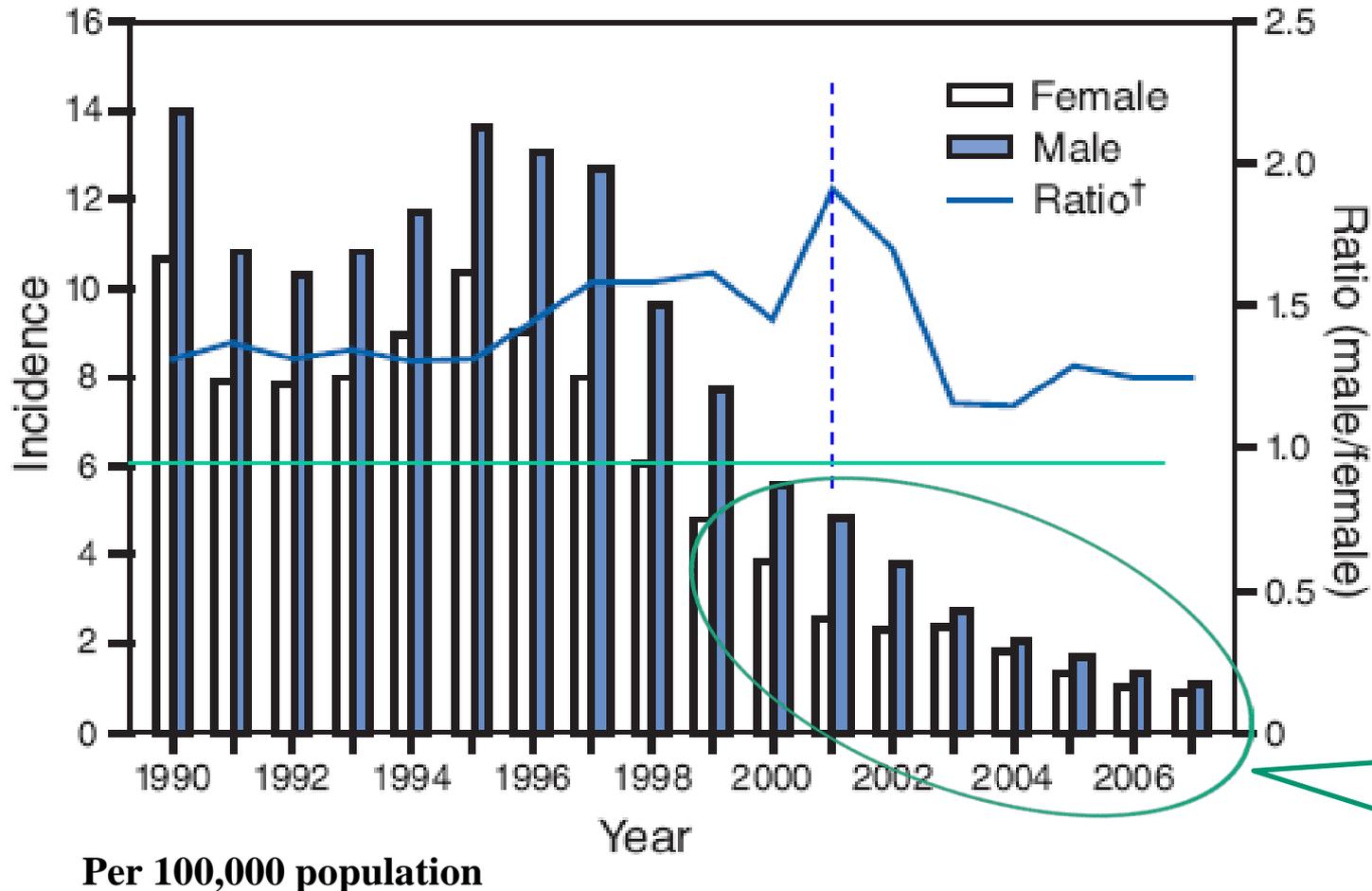


Hepatitis A Incidence by Gender, United States, 1990 - 2001



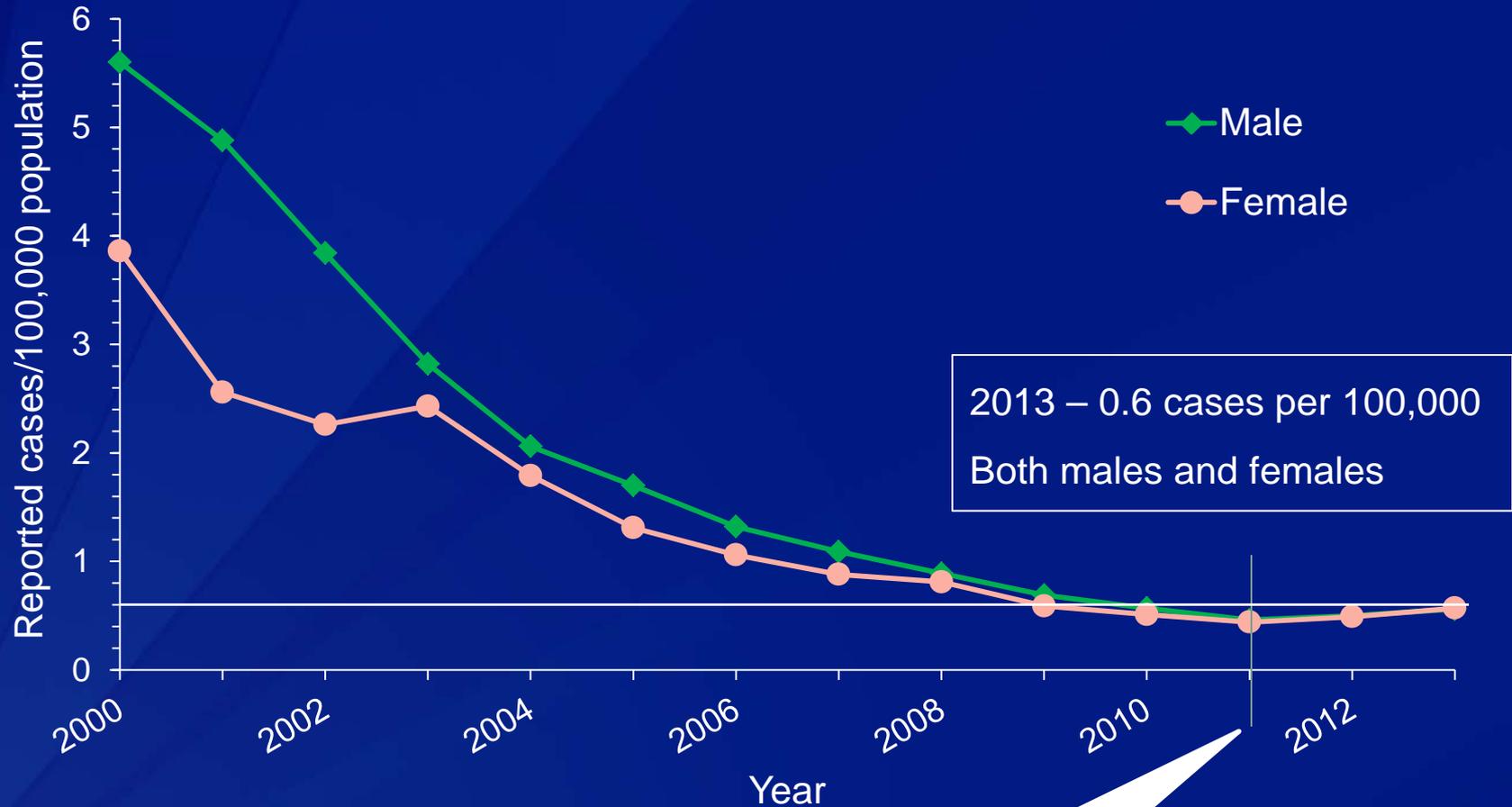
Hepatitis A Incidence by Gender,

United States, 1990 - 2007



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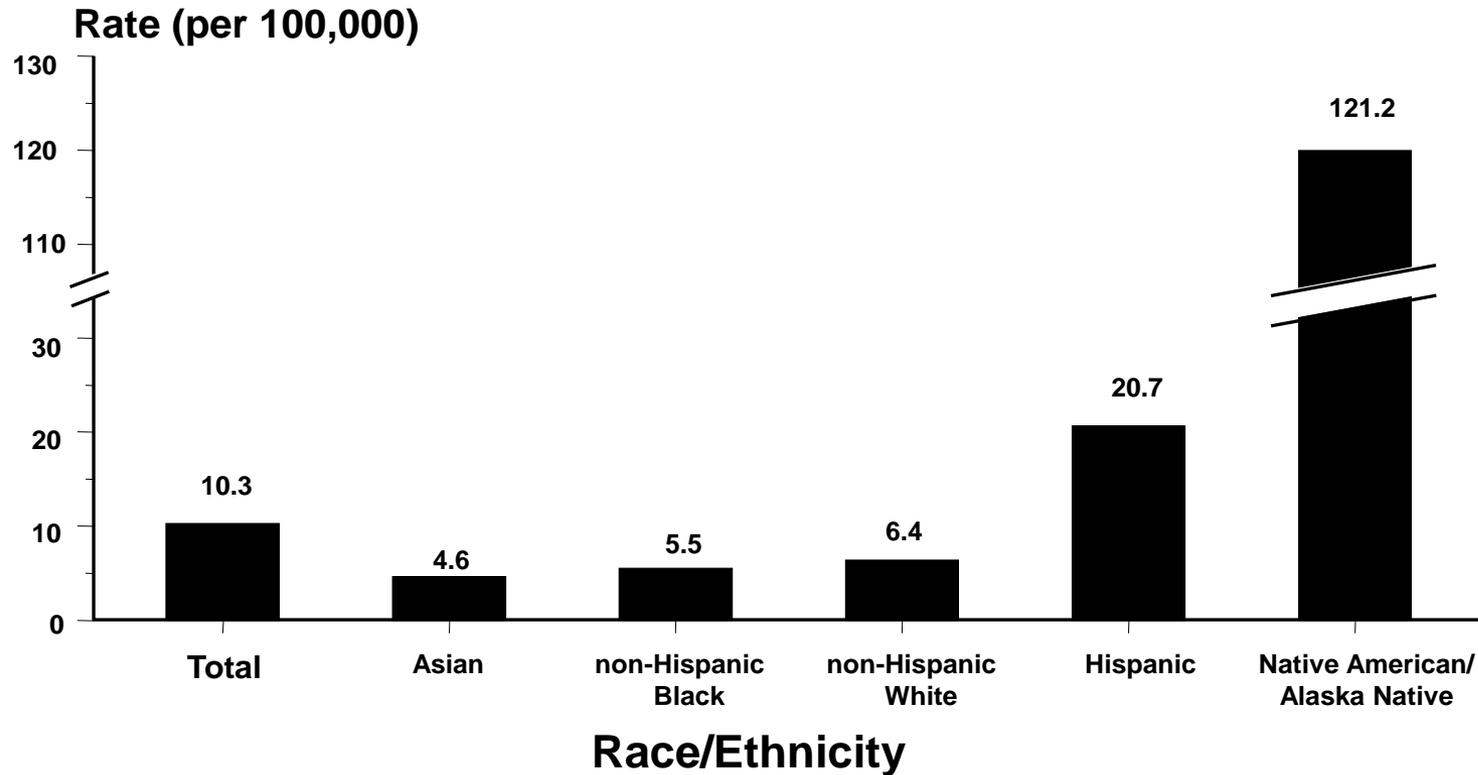
Incidence of Acute Hepatitis A, by Sex United States, 2000–2013



Source: National Notifiable Diseases Surveillance System (NNDSS)



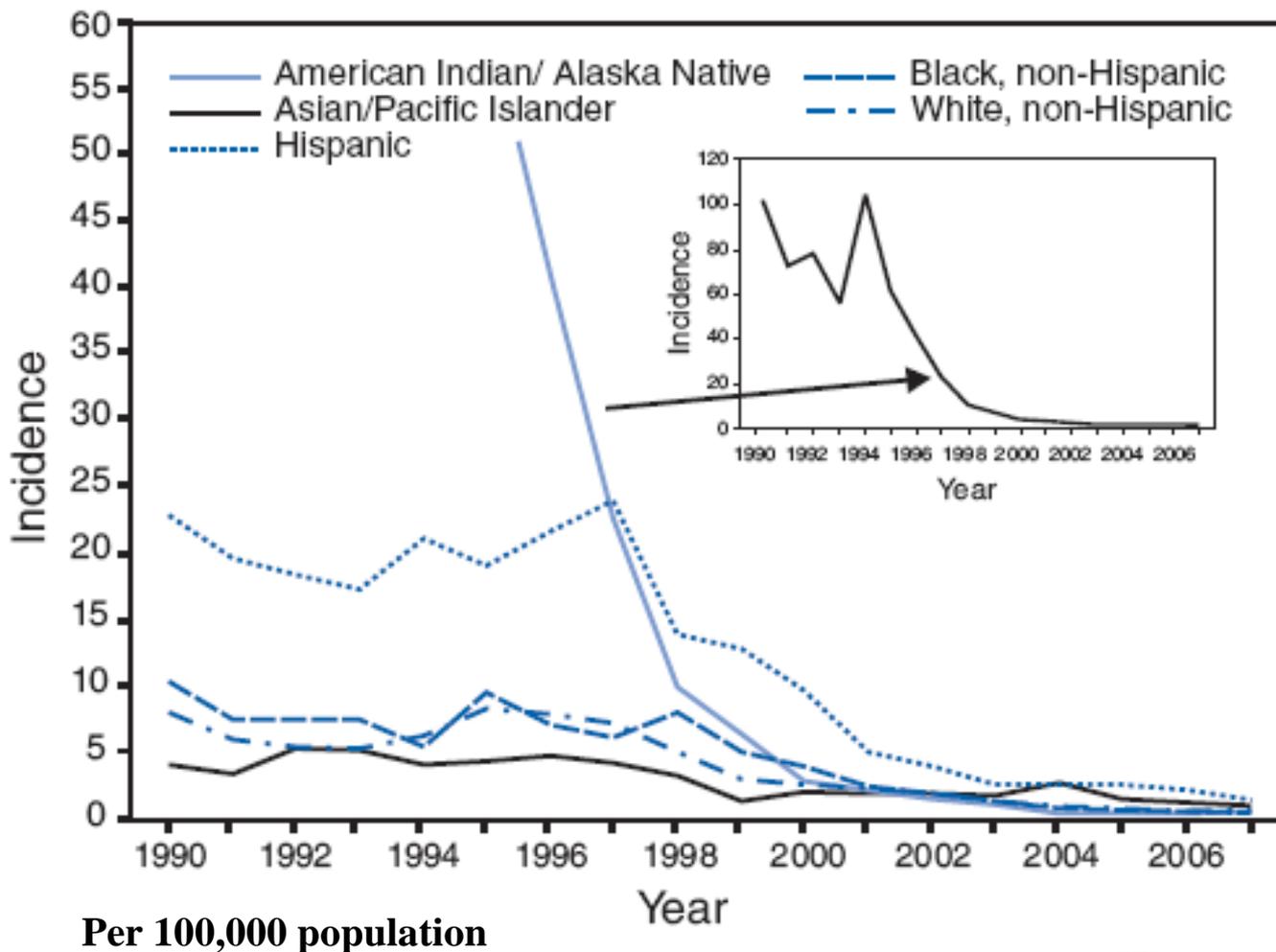
Hepatitis A Rates, by Race / Ethnicity; 1994



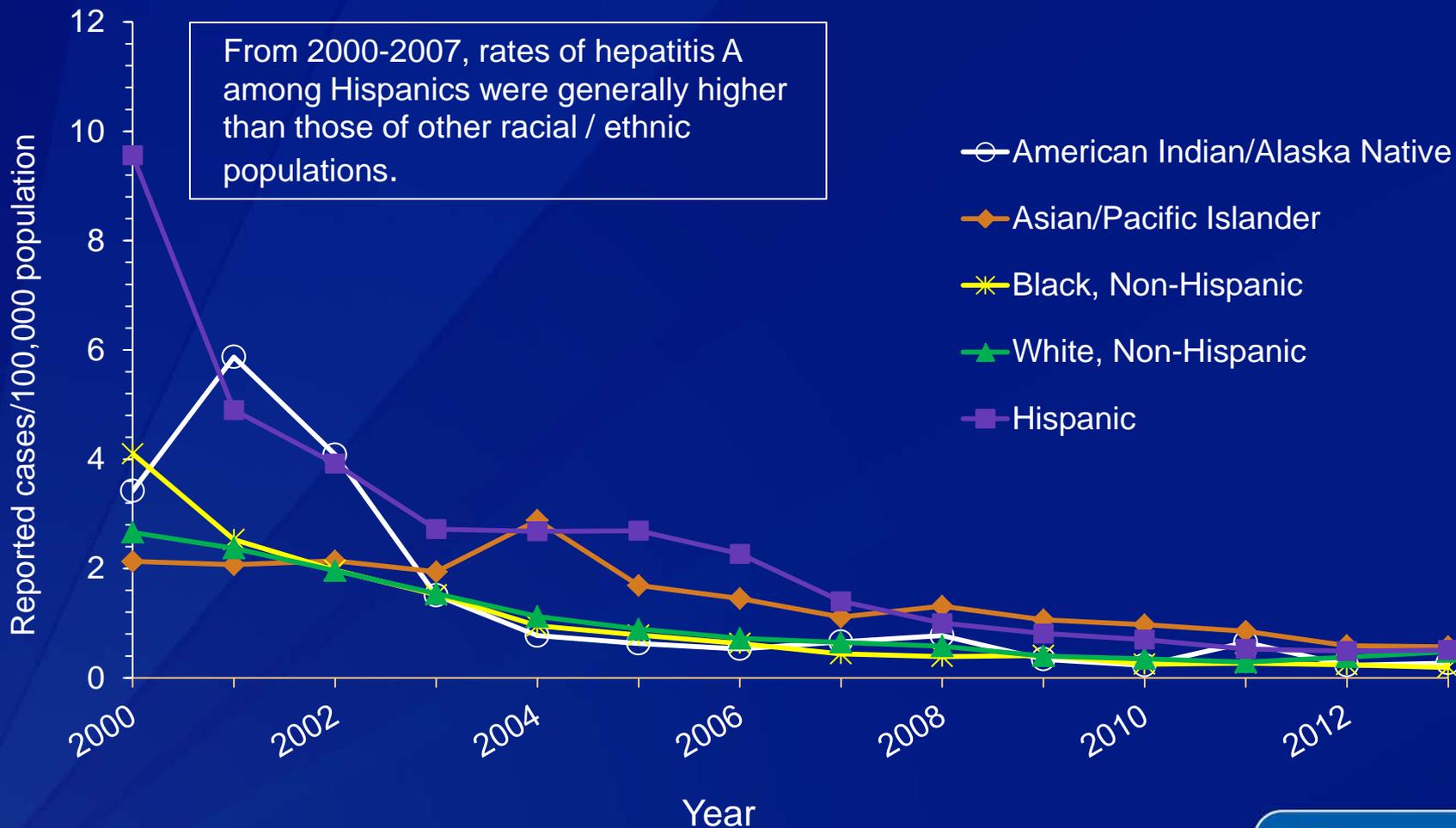


Hepatitis A Rates, United States,

by Race / Ethnicity; 1990 - 2007



Incidence of Acute Hepatitis A, by Race / Ethnicity United States, 2000–2013



Source: National Notifiable Diseases Surveillance System (NNDSS)





Prevention of Hepatitis A Infections

- Improved personal hygiene, particularly handwashing
- Provision of safe drinking water
- Proper sanitary waste disposal
- Preexposure immunization
- Postexposure immunization and / or administration of immune globulin

Hepatitis A chapter in Feigin and Cherry's Textbook of Pediatric Infectious Diseases, 7th Ed, 2014



Hepatitis A Vaccines

Single-antigen Vaccines

- Inactivated whole virus vaccines
- HAVRIX (GlaxoSmithKline)
- VAQTA (Merck)
- Pediatric and adult formulations
- Licensed for persons aged 12 months and older



Hepatitis A Vaccine Immunogenicity

Single-antigen Vaccines

Adults

- >95% seropositive after one dose
- 100% seropositive after two doses

Children (≥ 12 months) and Adolescents

- >97% seropositive after one dose
- 100% seropositive after 2 doses



Hepatitis A Vaccines

Schedule for Single-antigen Vaccines

Adults

- 1 dose
- Booster dose 6-18 months after first dose

Children and Adolescents

- 1 dose
- Booster dose 6-18 months after first dose

HEPATITIS A VACCINES

Recommended Dosages of Single-antigen Hepatitis A Vaccines

<u>Vaccine</u>	<u>Age (yrs)</u>	<u>Dose</u>	<u>Volume (mL)</u>	<u>2-Dose Schedule (mos)</u>
HAVRIX[®] #	1-18	720 (EL.U.*)	0.5	0, 6-12
	>18	1,440	1.0	0, 6-12
VAQTA[®] ##	1-18	25 (U**)	0.5	0, 6-18
	>18	50	1.0	0, 6-18

* EL.U. – Enzyme-linked immunosorbent assay (ELISA) units, ** Units

has 2-phenoxyethanol as a preservative, ## has no preservative



Hepatitis A Vaccination of Children

- All children should receive hepatitis A vaccine at age one year (i.e., 12 through 23 months of age)
- Vaccination should be integrated into the routine childhood vaccination schedule
- Children who are not vaccinated by 2 years of age can be vaccinated at subsequent visits (For the VFC Program, DPH recommends catch-up vaccinations through age 18 years)



Hepatitis A Vaccine Recommendations for

Pre-exposure Protection for High Risk Groups

- **International travelers**
- **Close contact with international adoptee from a country with high or intermediate endemicity**
- Men who have sex with men
- Persons who use illegal drugs
- Persons who have a clotting-factor disorder
- Persons with occupational risk
 - Persons who work with HAV-infected primates or with HAV in laboratory research
- Persons with chronic liver disease



Hepatitis A Prevention

Recommendations for Pre-exposure Protection for International Travelers (2007 ACIP)

- Susceptible persons traveling to or working in in high- or intermediate- risk countries (e.g., Mexico or South America)
- Give single-antigen hepatitis A vaccine or IG before departure. Single-antigen hepatitis A vaccine, at the age appropriate dose, is preferred over IG.
 - Healthy persons (aged 40 and younger) – one dose of single-antigen hepatitis A vaccine given at any time before departure should be protective
 - Older adults, immunocompromised persons, persons with chronic liver disease or other chronic medical conditions planning to depart to an at-risk area in less than two weeks: give first dose of single antigen hepatitis A vaccine **AND** give IG (0.02 mL/kg) at a separate site



Hepatitis A Prevention

Recommendations for Pre-exposure Protection for International Travelers (2007 ACIP) (continued)

- Travelers who refuse vaccine, are aged less than 12 months, or who have vaccine contraindications – give a single dose of IG (0.02 mL/kg) for up to 3 months of protection against hepatitis A infection
- For such travelers whose travel period is expected to be longer than two months, give IG (0.06 mL/kg); repeat the IG administration if the travel period is longer than five months.
- Completion of the hepatitis A vaccine series is necessary for long-term protection



Single-antigen Hepatitis A Vaccine

Recommendations for Selected Occupational Groups

- Healthcare workers: not routinely recommended
- Child care centers: not routinely recommended for staff
- Sewer workers or plumbers: not routinely recommended
- Food handlers: may be considered based on local circumstances

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

Pre-Vaccination Testing

- Considerations for cost vs. benefit:
 - Cost of vaccine
 - Cost of serologic testing (including visit)
 - Prevalence of hepatitis A infection
 - Impact on compliance with vaccination
- Likely to be cost-effective for:
 - Persons born in high endemic areas
 - Older U.S. born adults
 - Older adolescents and young adults in certain groups (e.g., Native Americans, Alaska Natives, Hispanics, IDUs)

POST-VACCINATION TESTING

Not Recommended for Single-antigen Hepatitis A Vaccines

- High response rate among vaccinees
- Commercially available assay not sensitive enough to detect lower (protective) levels of vaccine-induced antibody



Hepatitis A Vaccines

Combination Vaccines

- TWINRIX[®] (GlaxoSmithKline)
- Combination of inactivated whole HAV (pediatric HAVRIX[®], 720 EL.U.) and hepatitis B surface antigen (adult ENGERIX-B[®], 20 mcg HBsAg)
- Licensed for persons 18 years of age and older
- Licensed by FDA in 2001 for 3-dose schedule
- FDA approved 4-dose accelerated dosing schedule in 2007
- Indicated for persons at risk for exposure to both HAV and hepatitis B viruses (see PHSR Immunization chapter)
- **Should not be used in PEP for close contacts to acute hepatitis A infection**

HEPATITIS A VACCINES

Recommended Dosages of Hepatitis A / Hepatitis B Combination Vaccine

<u>Vaccine</u>	<u>Age (yrs)</u>	<u>Dose</u>	<u>Volume (mL)</u>	<u>3-Dose Schedule (mos)</u>	<u>4-Dose Schedule (days)</u>
TWINRIX [®] #	18	720 (EL.U.*)	1.0	0	0
	and	20 mcg HBsAg	1.0	1	7
	older		1.0	6	21 to 30
Booster, 4-dose schedule (only)			1.0		12 Months

* EL.U. – Enzyme-linked immunosorbent assay (ELISA) units, HAV

has no preservatives



Hepatitis A - Postexposure Prophylaxis (PEP)

- Persons exposed to HAV who have no prior history of hepatitis A vaccination: Give single dose of single-antigen hepatitis A vaccine or immune globulin (IG, 0.02-mL/kg IM) as soon as possible (2007 ACIP recommendation)
 - Healthy persons aged 12 months through 40 years, single-antigen hepatitis A vaccine, at the age appropriate dose, is preferred over IG
 - Children younger than 12 months – give IG
 - Adults older than 40 years, preferable give IG. Use single-antigen hepatitis A vaccine if IG is unavailable.
 - Immunocompromised persons, persons with chronic liver disease diagnosed, or persons for whom vaccine is contraindicated – give IG
- Persons given IG for whom vaccine is also recommended can be given a dose of vaccine simultaneously with IG
- Persons given vaccine should complete the series



Acute Hepatitis A – Surveillance Case Definition

- **2012, Clinical criteria of an acute illness with:**
 - Discrete onset of any sign and symptom consistent with acute viral hepatitis (e.g., fever, headache, malaise, fatigue, anorexia, nausea, vomiting, diarrhea, and abdominal pain), **AND**
 - Either jaundice or elevated serum aminotransferase levels
- **Laboratory criteria**
 - IgM antibody to hepatitis A virus (IgM 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).



Investigation of a case

- **Public health – urgent event**, team response
 - CONFIRM DIAGNOSIS IN INDEX CASE
 - Identify close contacts (e.g. household, sexual)
 - Limited timeline (i.e., 14 days of last exposure) to provide postexposure prophylaxis (PEP)
 - Secondary attack rates in households – 15% to 30%
 - No evidence on efficacy of PEP when given two weeks or more after last HAV exposure
 - Maintain surveillance for 50 days after last exposure
 - Infection control
 - Handwashing
 - Contact precautions for first two weeks of illness, but no more than one week after onset of jaundice

Investigation – Special circumstances

- **Food handler with acute hepatitis A infection**
 - Environmental inspection of establishment
 - Environmental cleaning – 1:100 dilution chlorine bleach for surfaces
 - PEP (i.e., single-antigen hepatitis A vaccine or IG) should be give to other food handlers in same establishment
 - Higher risk of HAV exposure to patrons in infectious period if:
 - Food handler had diarrhea
 - Food handler had deficiencies in personal hygiene
 - Food handler prepared foods that were not heated
 - Food handler directly handled cooked foods
 - Any response with single-antigen hepatitis A vaccine or IG has to be completed within 2 weeks of last exposure
 - Maintain surveillance for 50 days after last exposure

Investigation – Special circumstances

- **Day care centers; child care centers – Acute hepatitis A infections**
 - PEP (i.e., Hepatitis A vaccine or IG) is indicated for ALL PREVIOUSLY UNVACCINATED adult staff and attendees when:
 - One or more cases of hepatitis A are recognized in children or adult staff
 - Two or more households of attendees have cases
 - Only treat classroom contacts of index case in centers that have no children in diapers
 - Outbreak (three or more families have hepatitis A cases), treat members of households with attendees in diapers



Kentucky Public Health
Prevent. Promote. Protect.



Questions ?

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