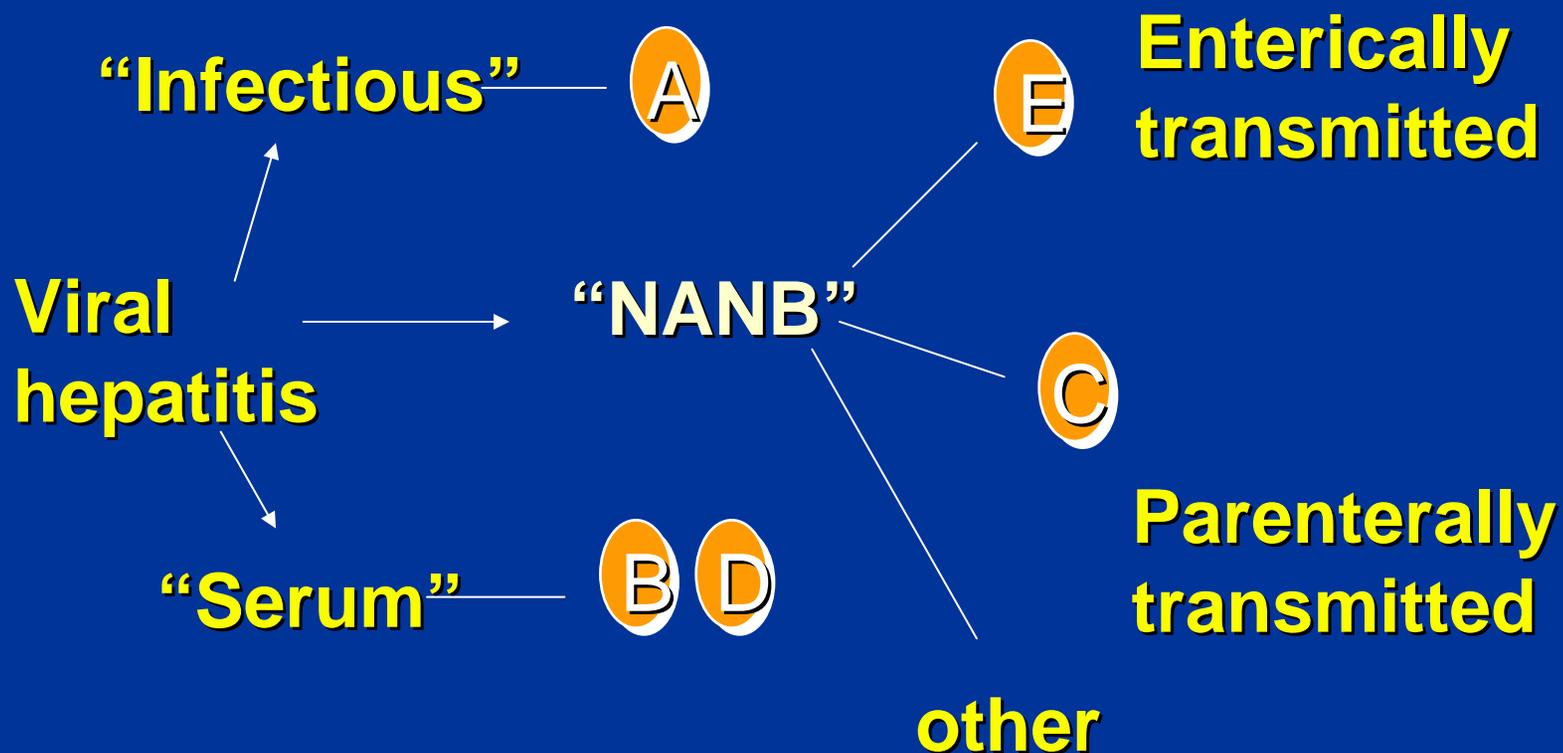


VIRAL HEPATITIS

HISTORICAL PERSPECTIVE



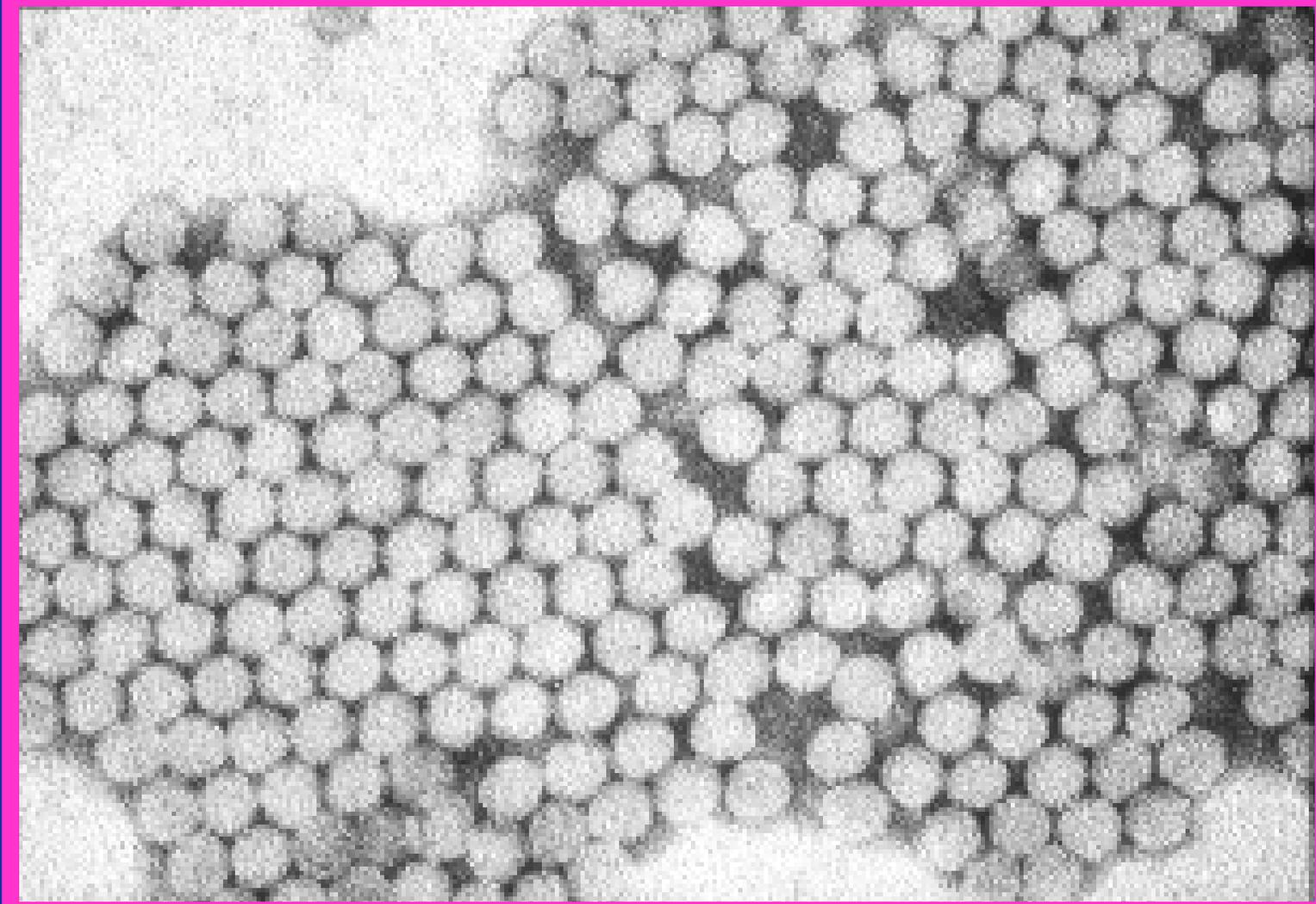
REPORTED CASES OF SELECTED NOTIFIABLE DISEASES PREVENTABLE BY VACCINATION, UNITED STATES, 2001

Hepatitis A	10,609
Hepatitis B	7,843
Pertussis	7,580
Meningococcal disease	2,333
H. influenzae, invasive	1,597
Mumps	266
Measles	116

Source: NNDSS, CDC



HEPATITIS A VIRUS



HEPATITIS A VIRUS

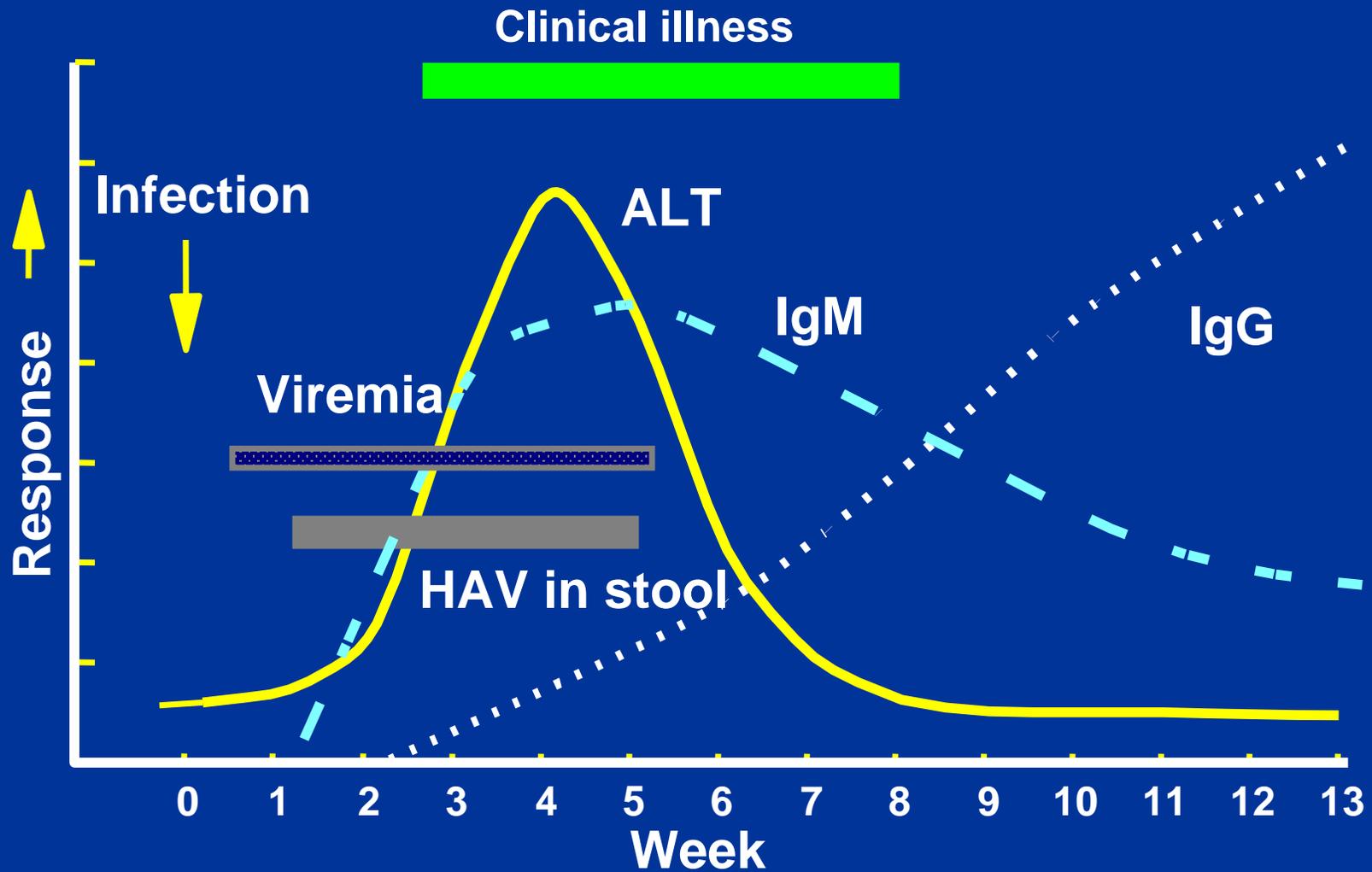
- RNA Picornavirus
 - Single serotype worldwide
 - Acute disease and asymptomatic infection
- No chronic infection
 - Protective antibodies develop in response to infection - confers lifelong immunity

HEPATITIS A - CLINICAL FEATURES

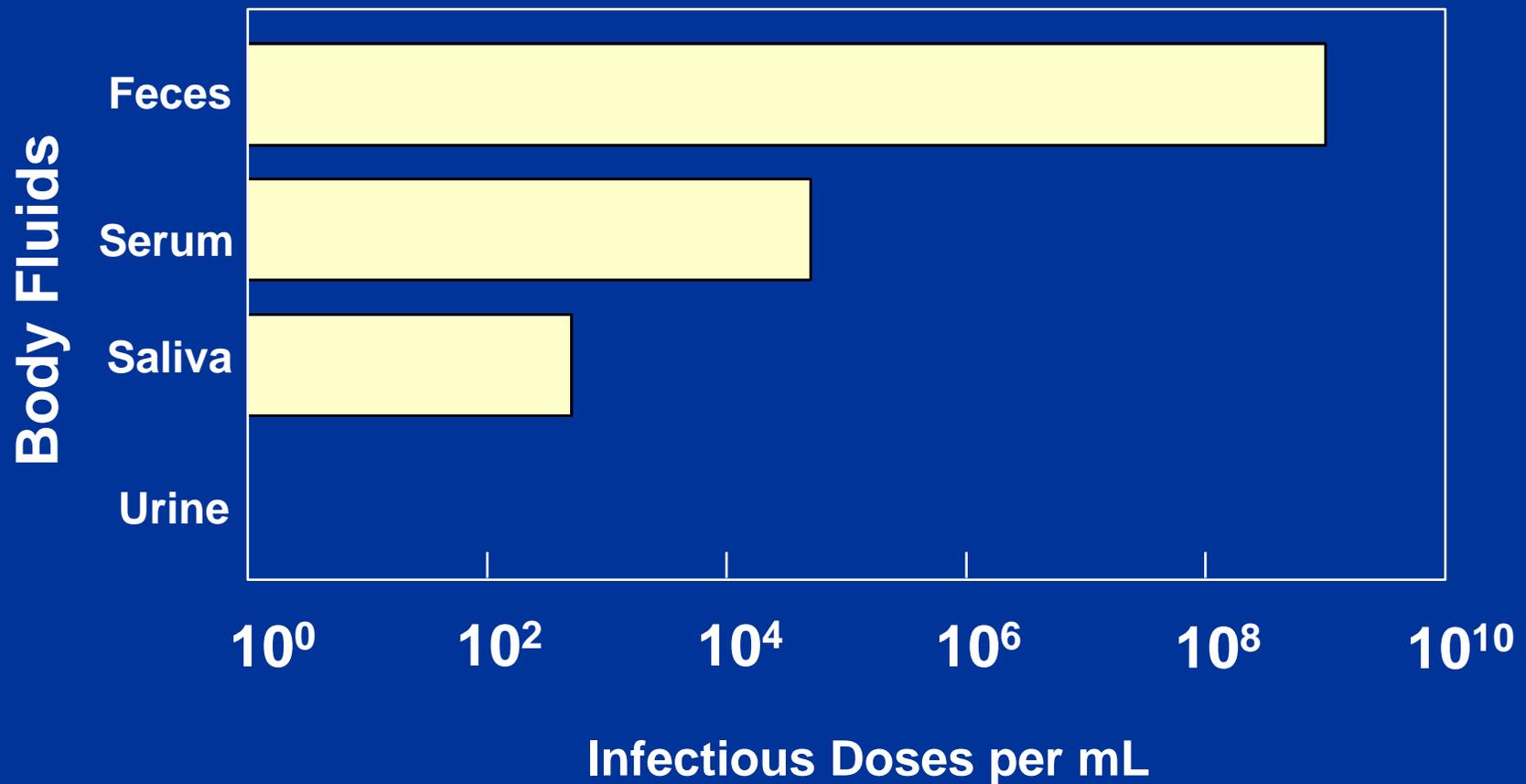
- Jaundice by age group:

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

EVENTS IN HEPATITIS A VIRUS INFECTION



CONCENTRATION OF HEPATITIS A VIRUS IN VARIOUS BODY FLUIDS

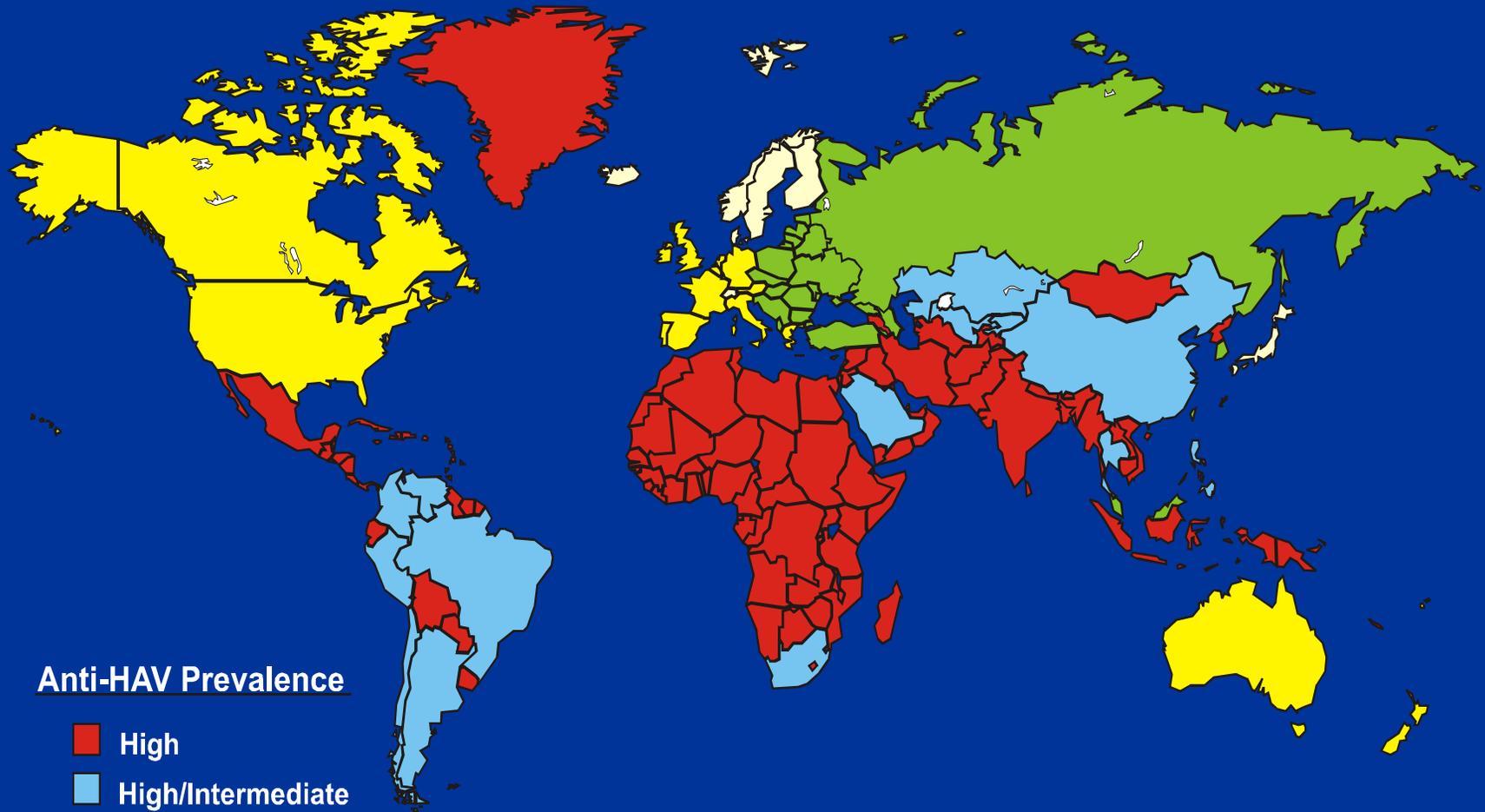


Source: Viral Hepatitis and Liver Disease 1984;9-22
J Infect Dis 1989;160:887-890

GLOBAL PATTERNS OF HEPATITIS A VIRUS TRANSMISSION

Endemicity	Disease Rate	Peak Age of Infection	Transmission Patterns
High	Low to high	Early childhood	Person to person; outbreaks uncommon
Moderate	High	Late childhood/young adults	Person to person; food and waterborne outbreaks
Low	Low	Young adults	Person to person; food and waterborne outbreaks
Very low	Very low	Adults	Travelers; outbreaks uncommon

GEOGRAPHIC DISTRIBUTION OF HEPATITIS A VIRUS INFECTION



Anti-HAV Prevalence

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

HEPATITIS A, UNITED STATES

- **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**
- **Some groups at increased risk**
 - **specific factor varies**
 - **do not account for majority of cases**
- **No risk factor identified for 40%-50% of cases**

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

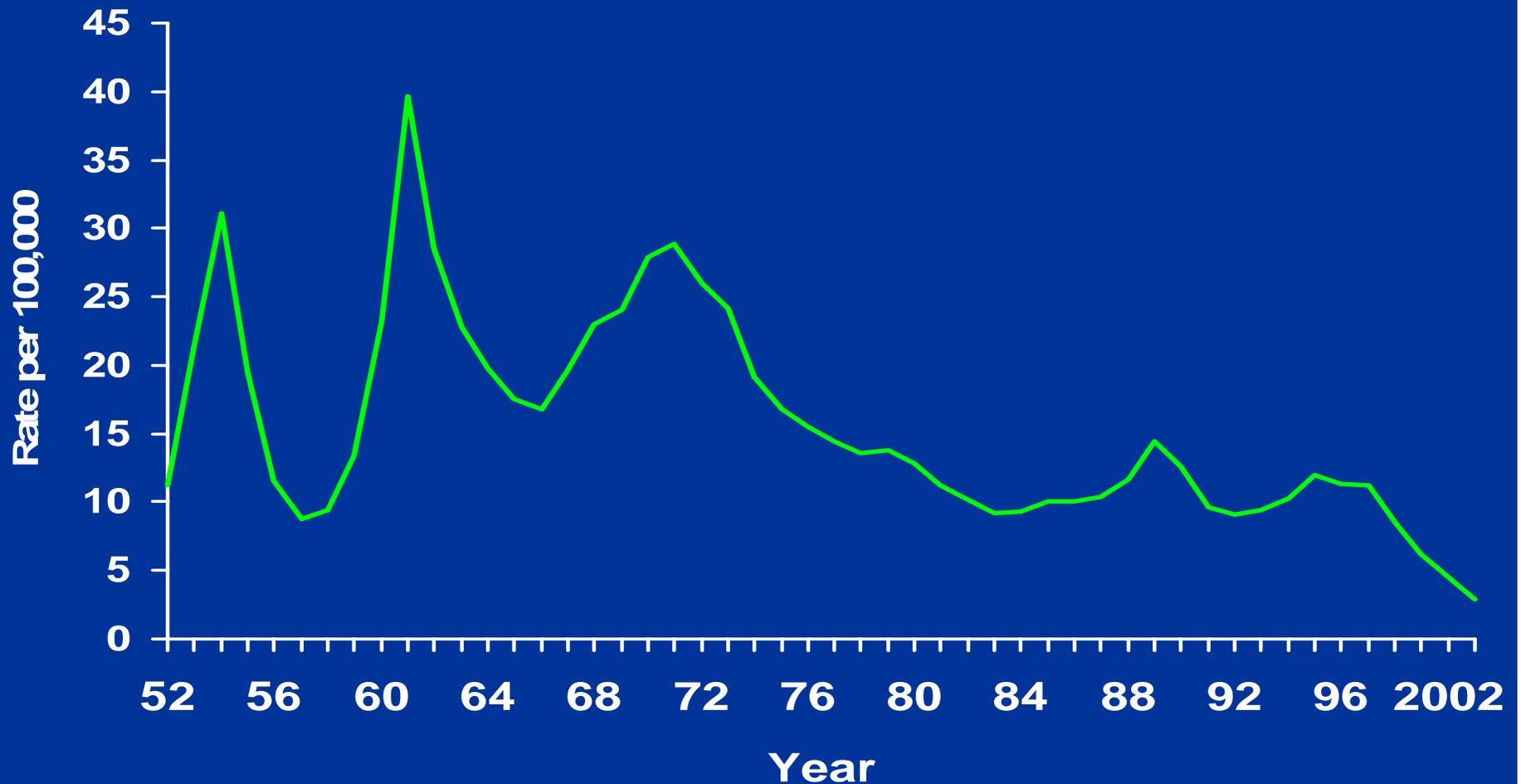
◆ Laboratory criteria

- 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).

REPORTED CASES OF HEPATITIS A, UNITED STATES, 1952-2002



Source: NNDSS, CDC



DISEASE BURDEN FROM HEPATITIS A UNITED STATES, 2001

**Number of acute clinical
cases reported** 10,609

**Estimated number of acute
clinical cases** 45,000

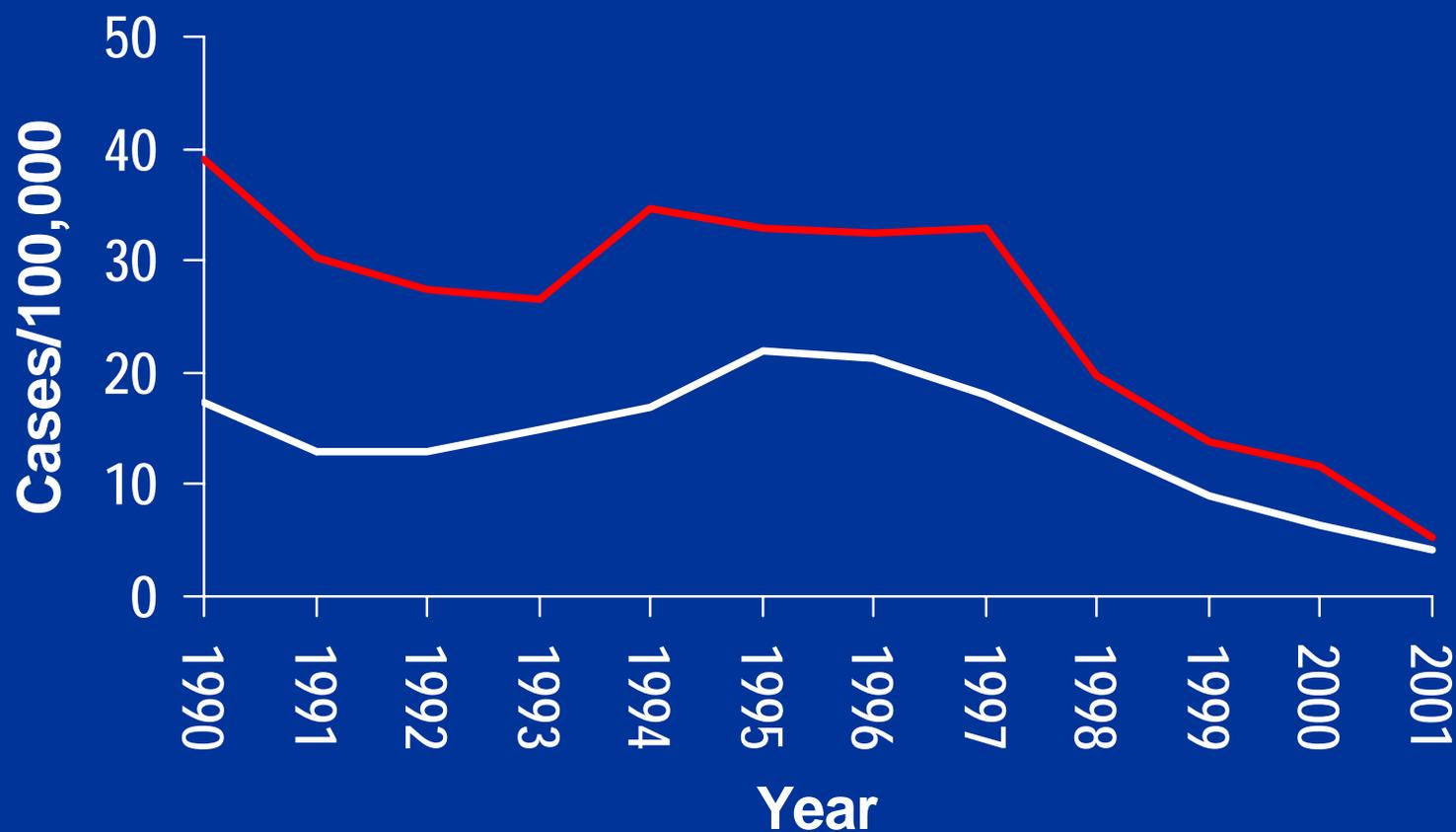
**Estimated number of
new infections** 93,000

Percent ever infected 31.3%

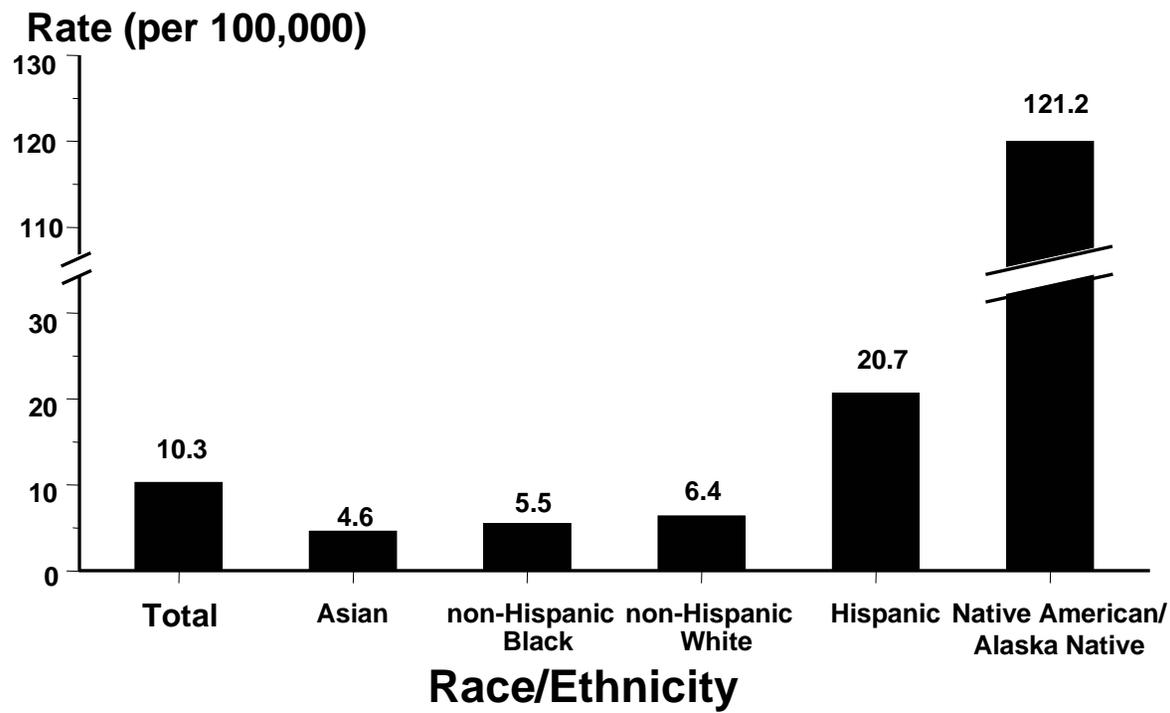


INCIDENCE OF HEPATITIS A BY AGE GROUP IN STATES WHERE VACCINATION IS RECOMMENDED & CONSIDERED, 1990-2001

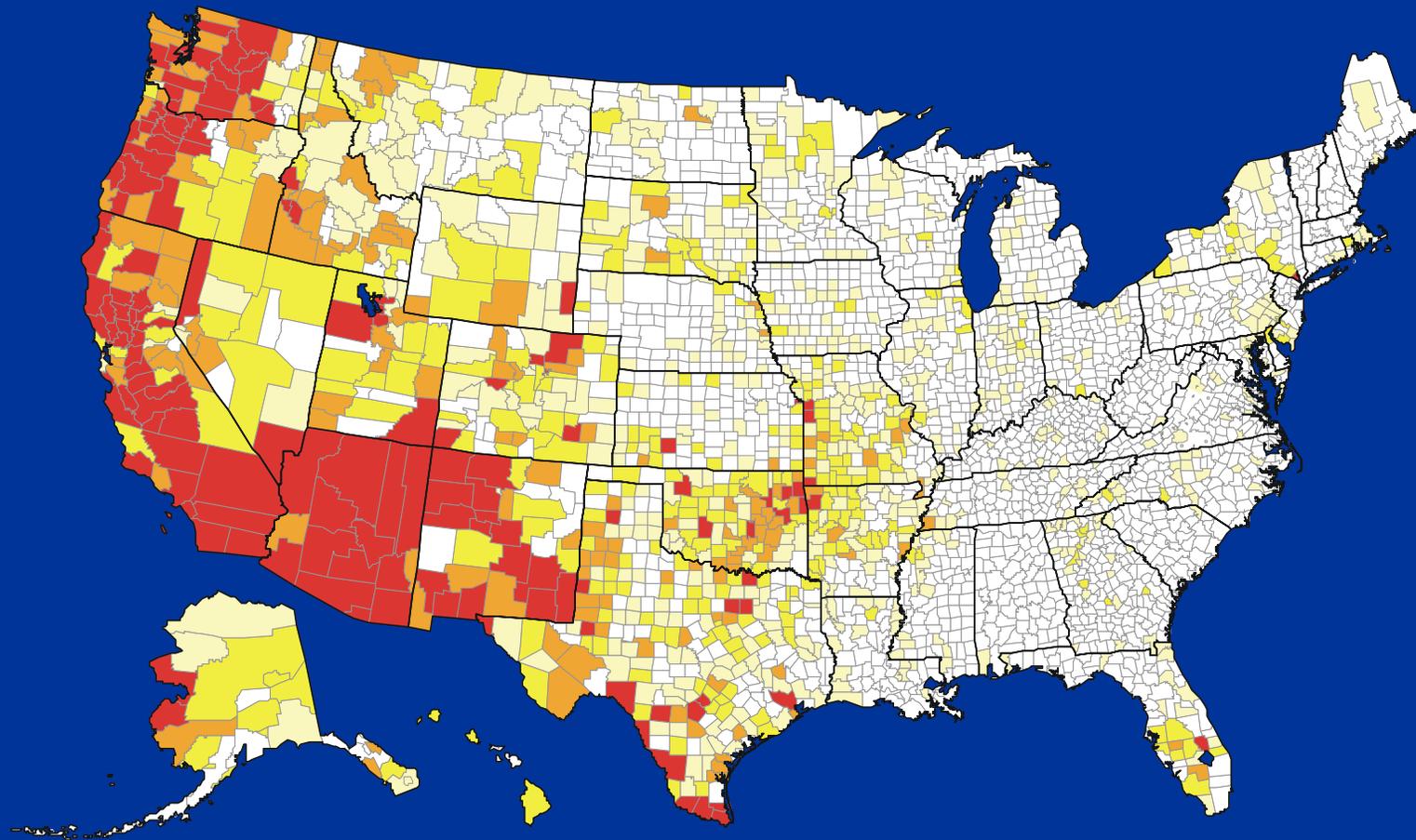
— 2-18 Year Olds — >18 Year Olds



HEPATITIS A RATES, BY RACE/ETHNICITY; 1994



NUMBER OF YEARS REPORTED INCIDENCE OF HEPATITIS A EXCEEDED 10 CASES PER 100,000, BY COUNTY, 1987-1997



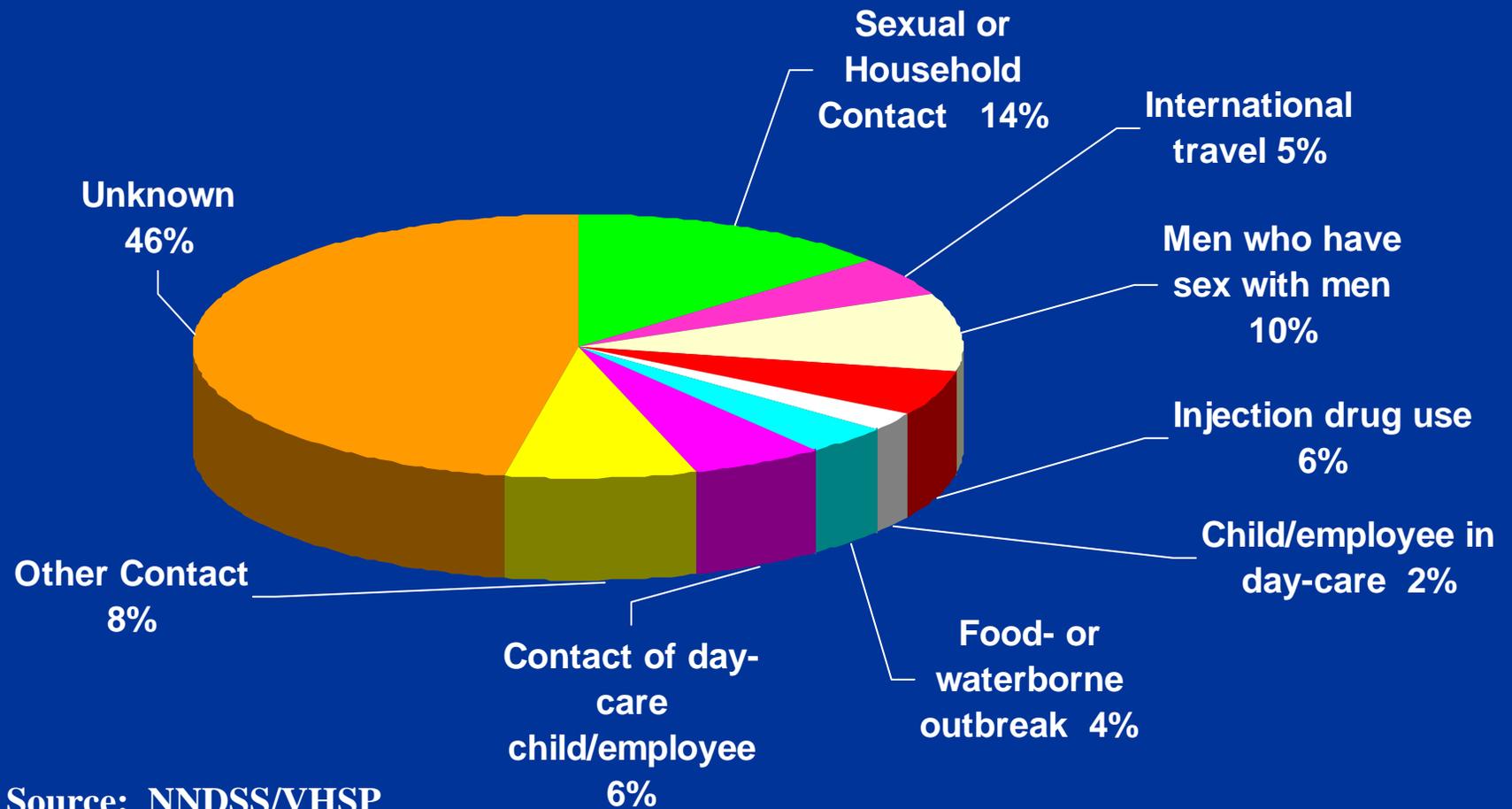
0-1 2-3 4-5 6-7 8-11



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)

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



Source: NNDSS/VHSP



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)

PREPARATION OF INACTIVATED HEPATITIS A VACCINES

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

HEPATITIS A VACCINES

- **Highly immunogenic**
 - **97%-100% of children, adolescents, and adults have protective levels of antibody within 1 month of receiving first dose; essentially 100% have protective levels after second dose**
- **Highly efficacious**
 - **In published studies, 94%-100% of children protected against clinical hepatitis A after equivalent of one dose**

HEPATITIS A VACCINE EFFICACY STUDIES

Vaccine	Site/ Age Group	N	Vaccine Efficacy (95 % CI)
HAVRIX[®]* (GSK) 2 doses 360 EL.U.	Thailand 1-16 yrs	38,157	94% (79%-99%)
VAQTA[®]** (Merck) 1 dose 25 units	New York 2-16 yrs	1,037	100% (85%-100%)

JAMA 1994;271:1363-4; N Engl J Med 1992;327:453-7



HEPATITIS A VACCINES

Recommended Dosages of Hepatitis A Vaccines

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



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**



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**

FACTORS ASSOCIATED WITH DECREASED IMMUNOGENICITY TO HEPATITIS A VACCINE

- **Decreased antibody concentration:**
 - **Concurrent administration of IG**
 - **Presence of passively-transferred maternal antibody**
 - **Age**
 - **Chronic liver disease**
- **Decreased seroconversion rate:**
 - **HIV infection**
 - **May be related to degree of immunosuppression**
 - **Liver transplantation**

USE OF HEPATITIS A VACCINE FOR INFANTS

- Safe and immunogenic for infants without maternal antibody
- Presence of passively-acquired maternal antibody blunts immune response
 - all respond, but with lower final antibody concentrations
- Age by which maternal antibody disappears is unclear
 - still present in some infants at one year
 - probably gone in vast majority by 15 months

COMBINED HEPATITIS A HEPATITIS B VACCINE

- Approved by the FDA in United States for persons ≥ 18 years old
- Contains 720 EL.U. hepatitis A antigen and 20 μg . HBsAg
- Vaccination schedule: 0,1,6 months
- Immunogenicity similar to single-antigen vaccines given separately
- Can be used in persons ≥ 18 years old who need vaccination against both hepatitis A and B
- Formulation for children available in many other countries

PRE-VACCINATION TESTING

- **Considerations:**
 - ◆ **cost of vaccine**
 - ◆ **cost of serologic testing (including visit)**
 - ◆ **prevalence of 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:

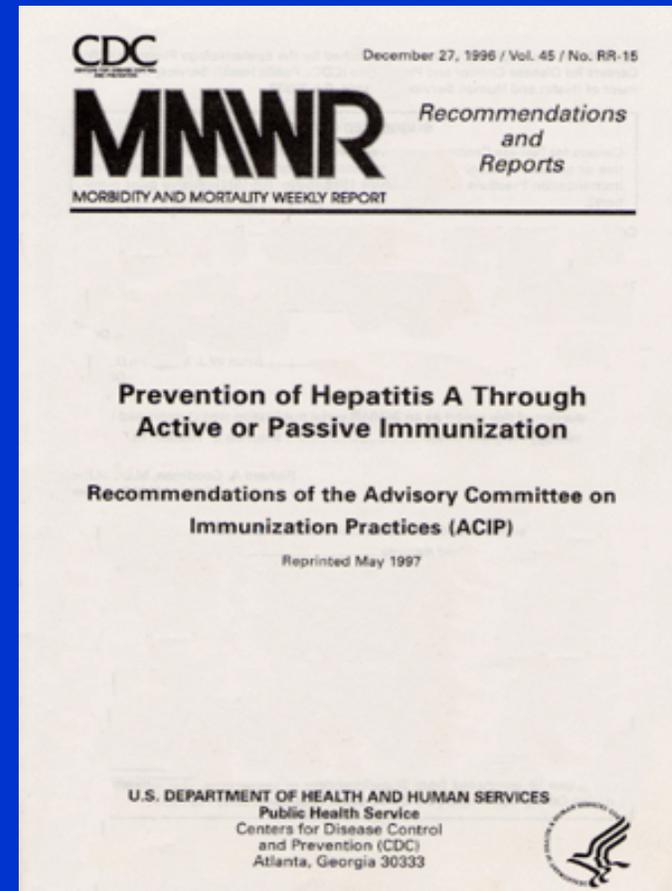
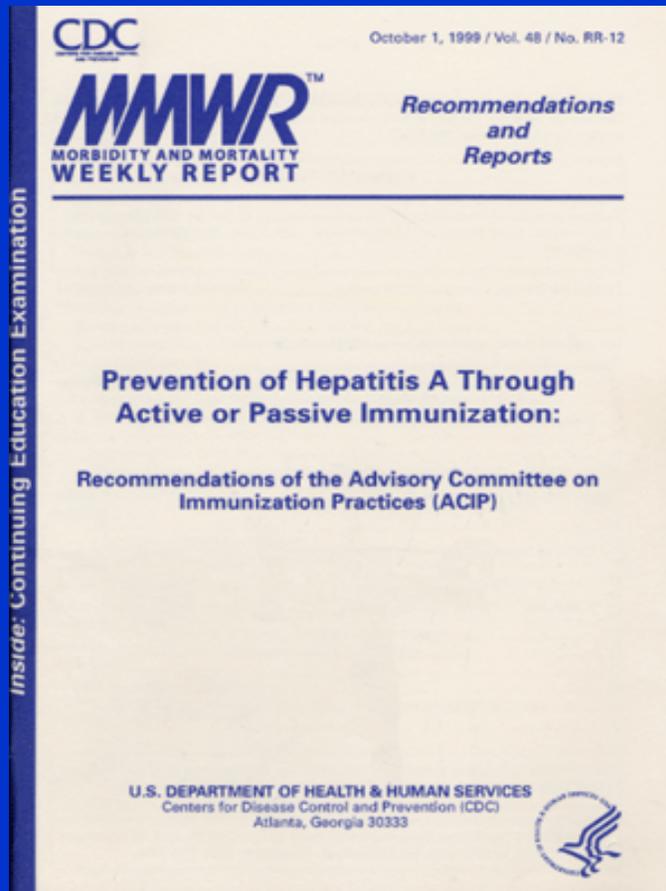
- High response rate among vaccinees
- Commercially available assay not sensitive enough to detect lower (protective) levels of vaccine-induced antibody

HEPATITIS A PREVENTION

IMMUNE GLOBULIN

- Pre-exposure
 - ◆ travelers to intermediate and high HAV-endemic regions
- Post-exposure (within 14 days)
 - Routine**
 - ◆ household and other intimate contacts
 - Selected situations**
 - ◆ institutions (e.g., day-care centers)
 - ◆ common source exposure (e.g., food prepared by infected food handler)

ACIP RECOMMENDATIONS FOR PREVENTION OF HEPATITIS A USING HEPATITIS A VACCINE



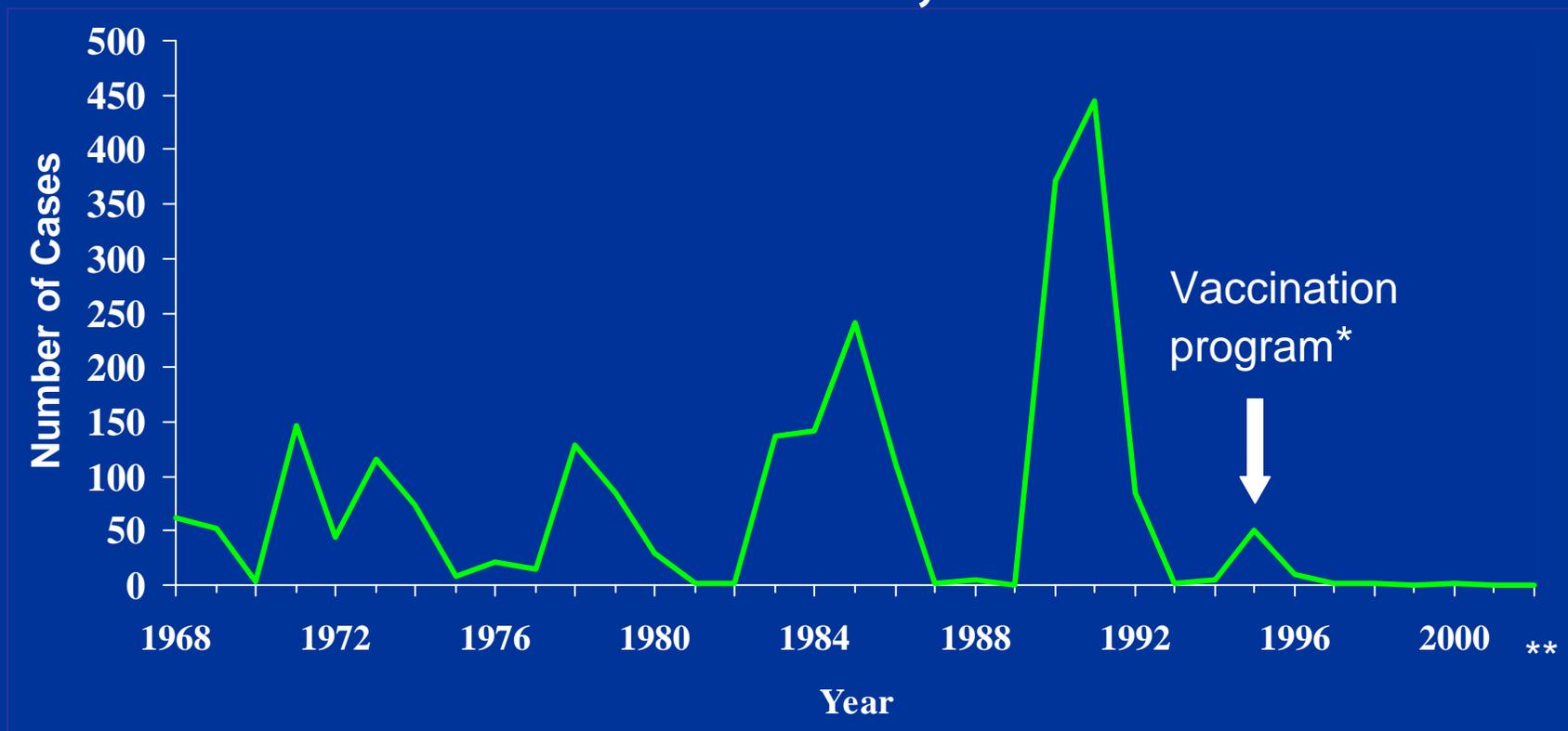
HEPATITIS A VACCINATION RECOMMENDATIONS: GUIDING PRINCIPLES

- **Need comprehensive strategy to reduce overall rates**
 - ◆ **Routine vaccination of children likely to be most effective**
- **Need creative approaches**
 - ◆ **Formulation not available that would allow integration into infant schedule**

INCREMENTAL IMPLEMENTATION OF ROUTINE HEPATITIS A VACCINATION OF CHILDREN

- 1996 - Children living in communities with the highest rates
- 1999- Children living in states/communities with consistently elevated rates during “baseline period”
- All children nationwide

Reported Hepatitis A Cases, By Year Northern Plains Indian Reservation† South Dakota, 1968-2002



* Estimated first dose coverage (children 2-12 years) = 71%

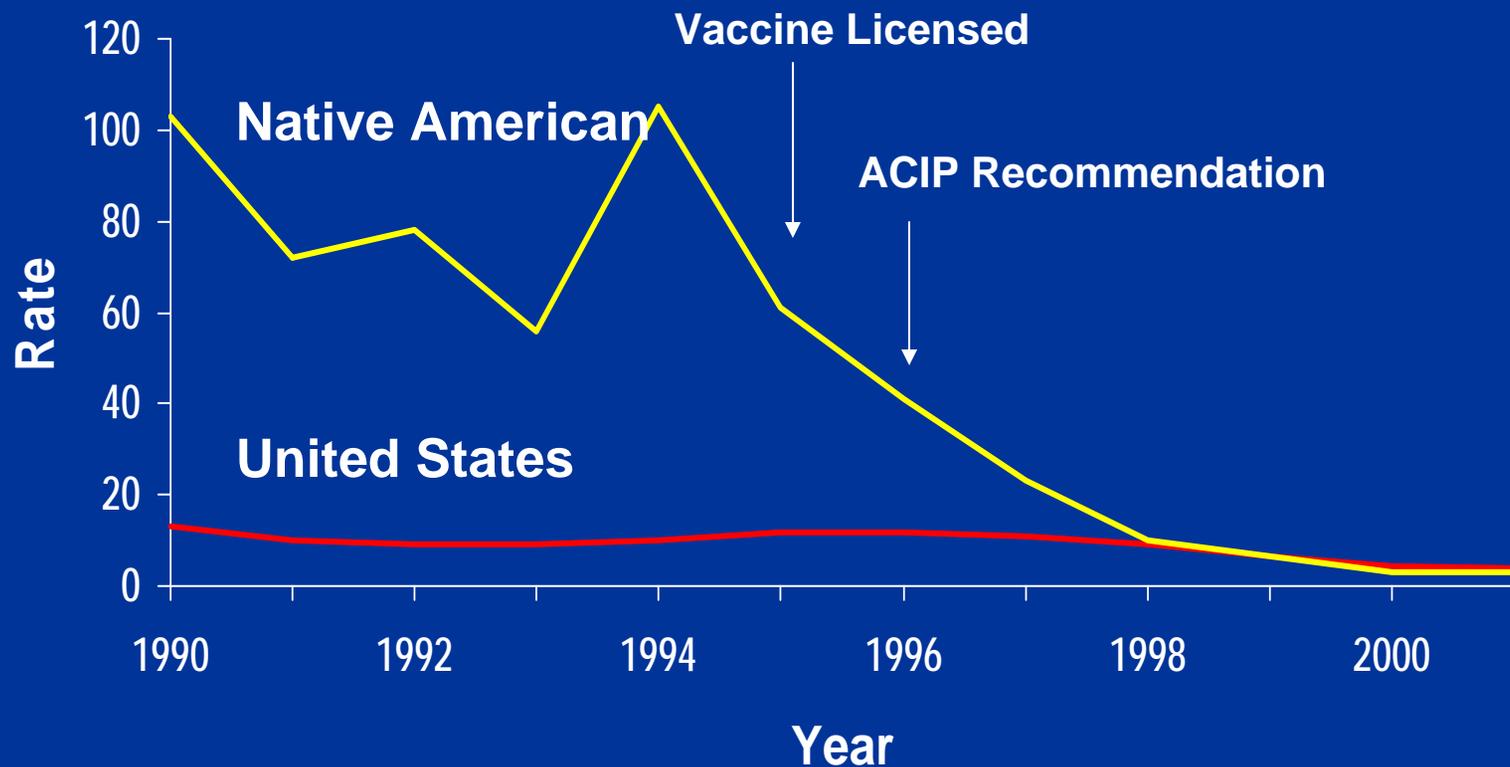
** 2002 Preliminary data

† Counties: Bennett, Corson, Dewey, Jackson, Roberts, Shannon, Todd, Ziebach

* † Source: South Dakota Department of Health



HEPATITIS A INCIDENCE UNITED STATES AND NATIVE AMERICANS 1990-2001



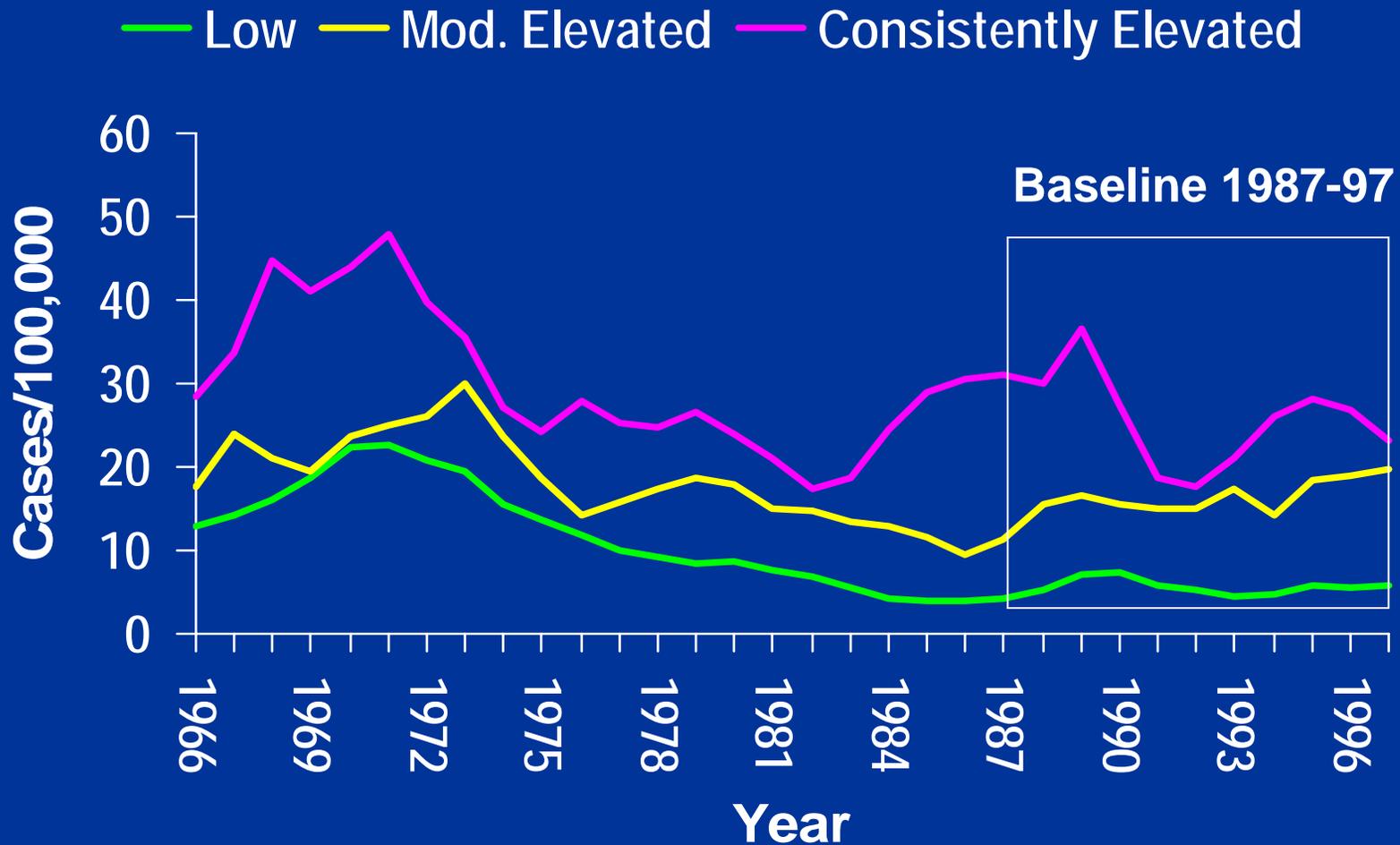
Source: NNDSS, CDC



1999 RECOMMENDATIONS FOR HEPATITIS A VACCINATION OF CHILDREN STRATEGY

- Further incremental step
- Not the same everywhere in the country
 - ◆ Regional recommendations using rate-based criteria during a “baseline period”
- Flexible implementation strategies
 - ◆ Children or adolescents
 - ◆ One or more single age cohorts
 - ◆ Selected settings, e.g., day-care

INCIDENCE OF HEPATITIS A BY REGION, UNITED STATES, 1966-1997



1999 ACIP RECOMMENDATIONS FOR ROUTINE HEPATITIS A VACCINATION OF CHILDREN

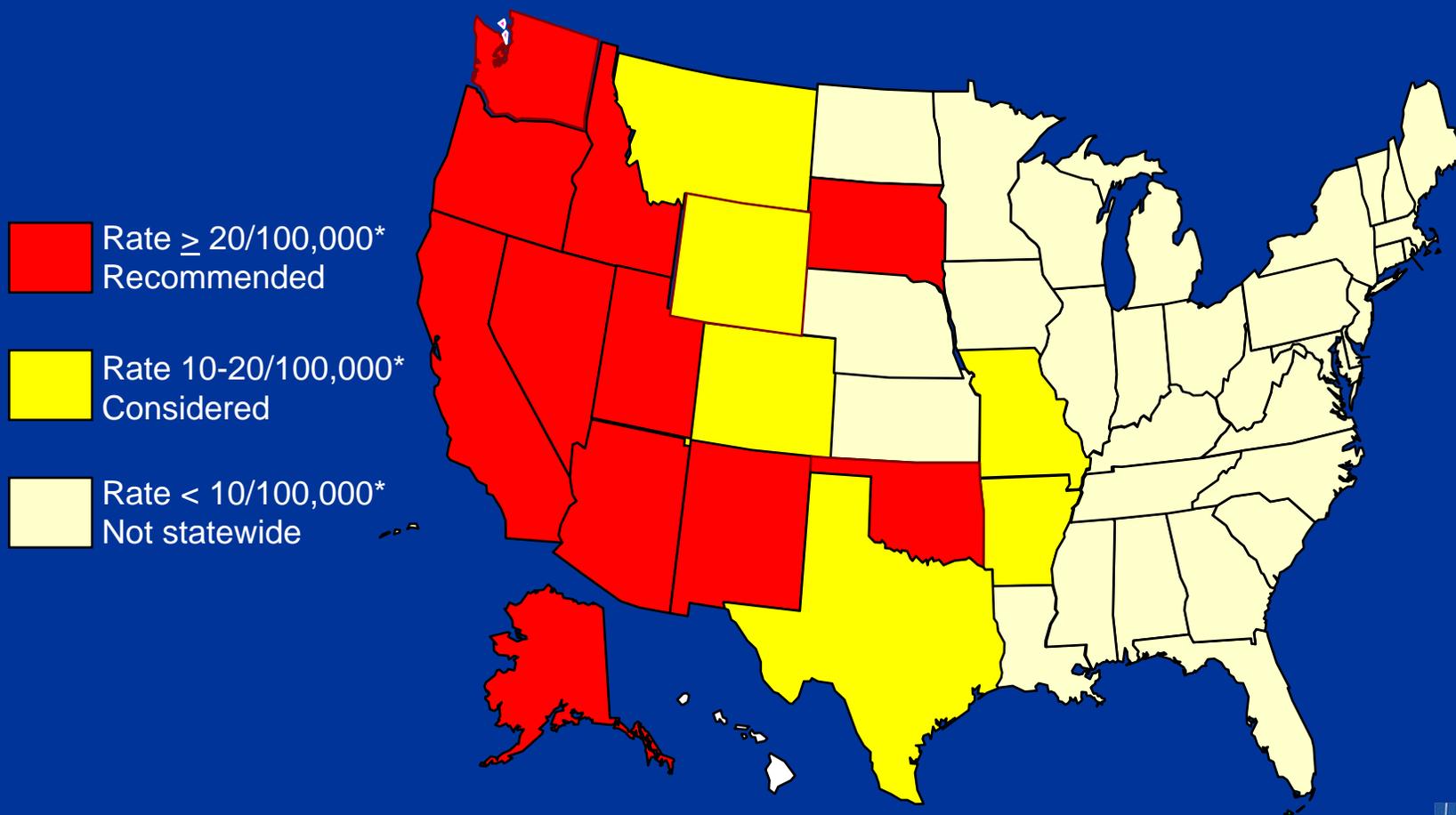
Children Who Should be Routinely Vaccinated

- living in states, counties, and communities where the average hepatitis A rate was ≥ 20 cases/100,000 during baseline period.

Children Who Should be Considered for Routine Vaccination

- living in states, counties, and communities where the average hepatitis A rate was <20 but ≥ 10 cases/100,000 during the baseline period.

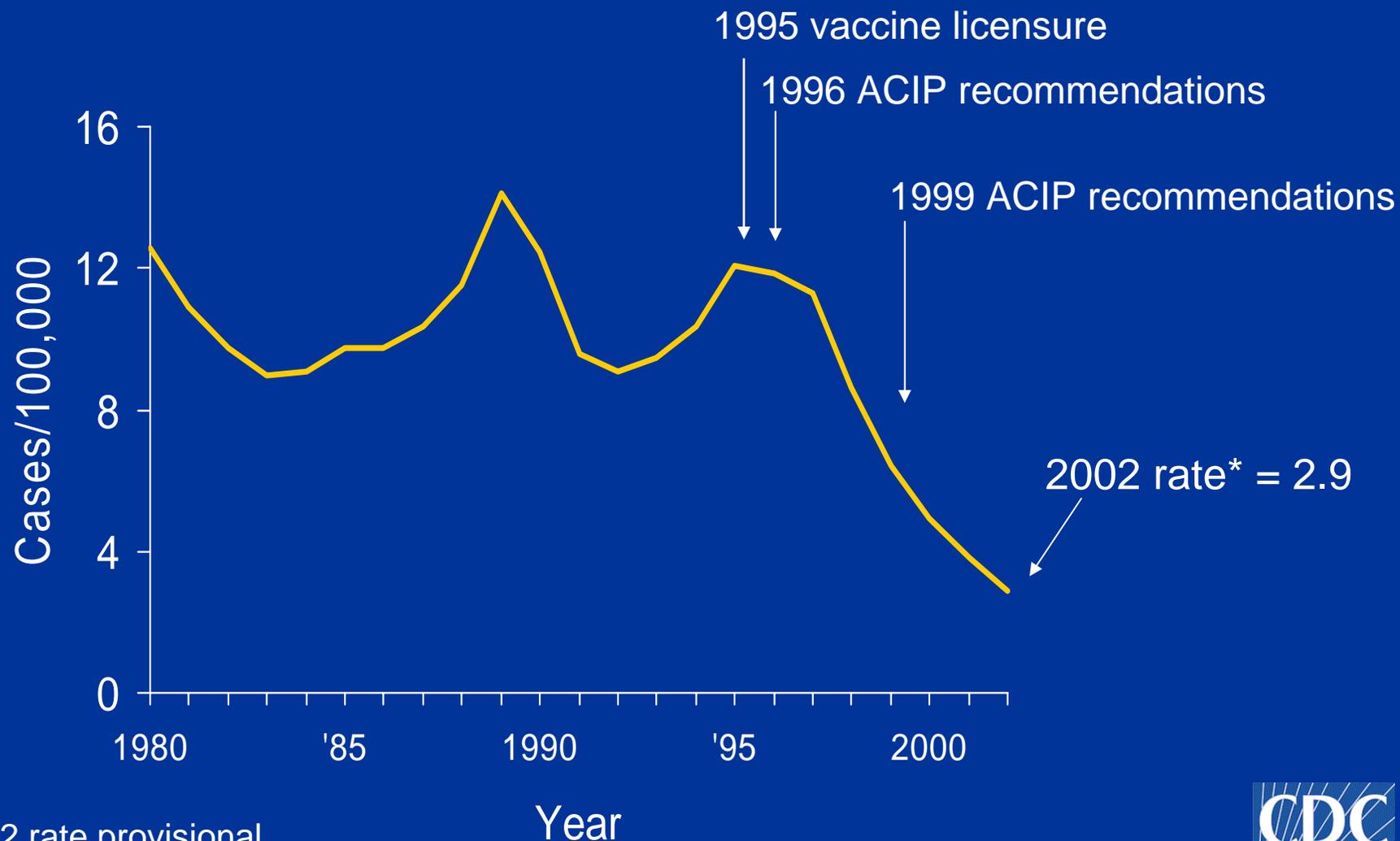
1999 ACIP RECOMMENDATIONS FOR STATEWIDE ROUTINE HEPATITIS A VACCINATION OF CHILDREN



* Based on average incidence rate during baseline period (1987- 97)



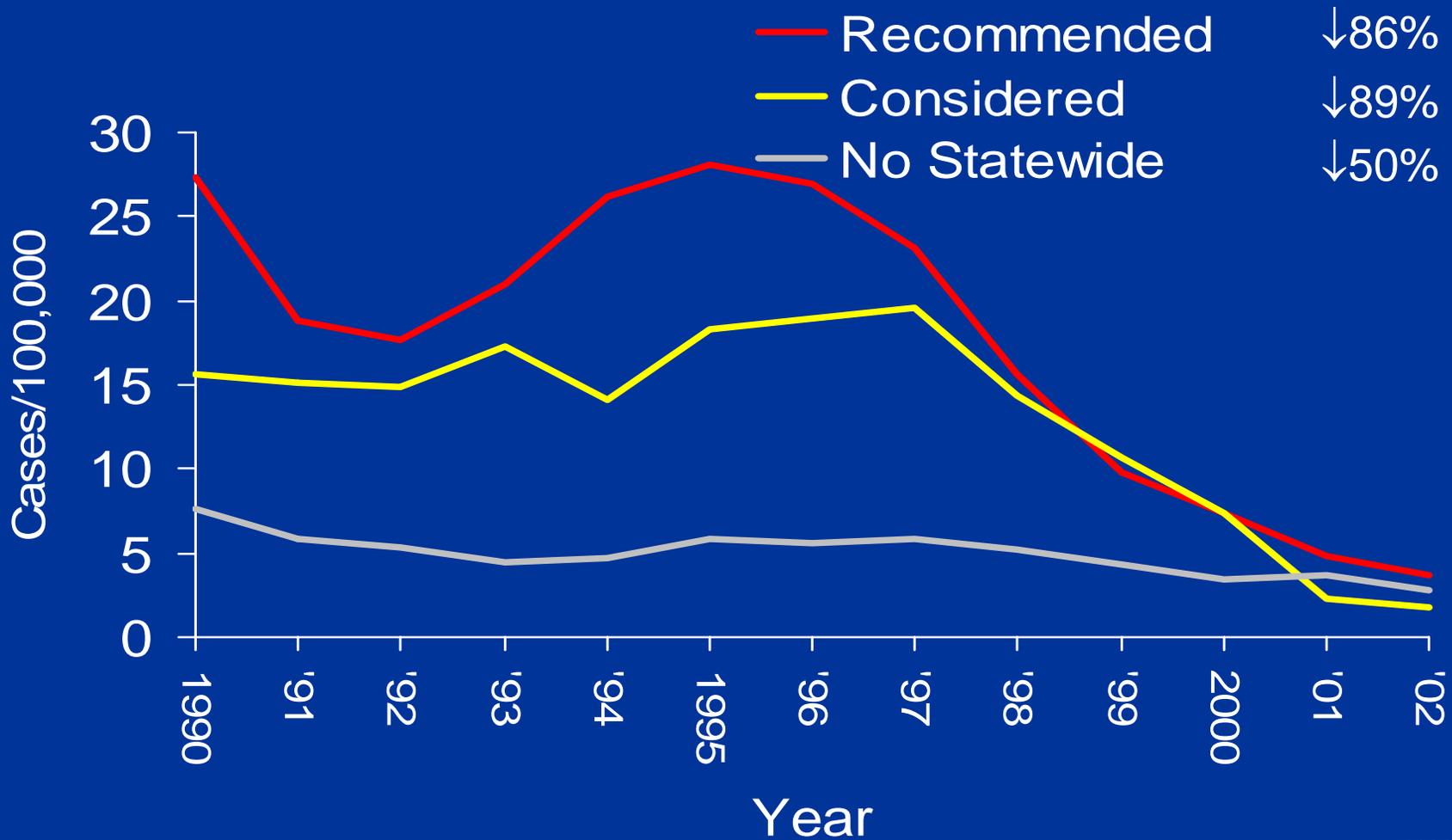
Hepatitis A Incidence, United States, 1980-2002*



*2002 rate provisional



Incidence of Hepatitis A by U.S. Region, 1990-2002*

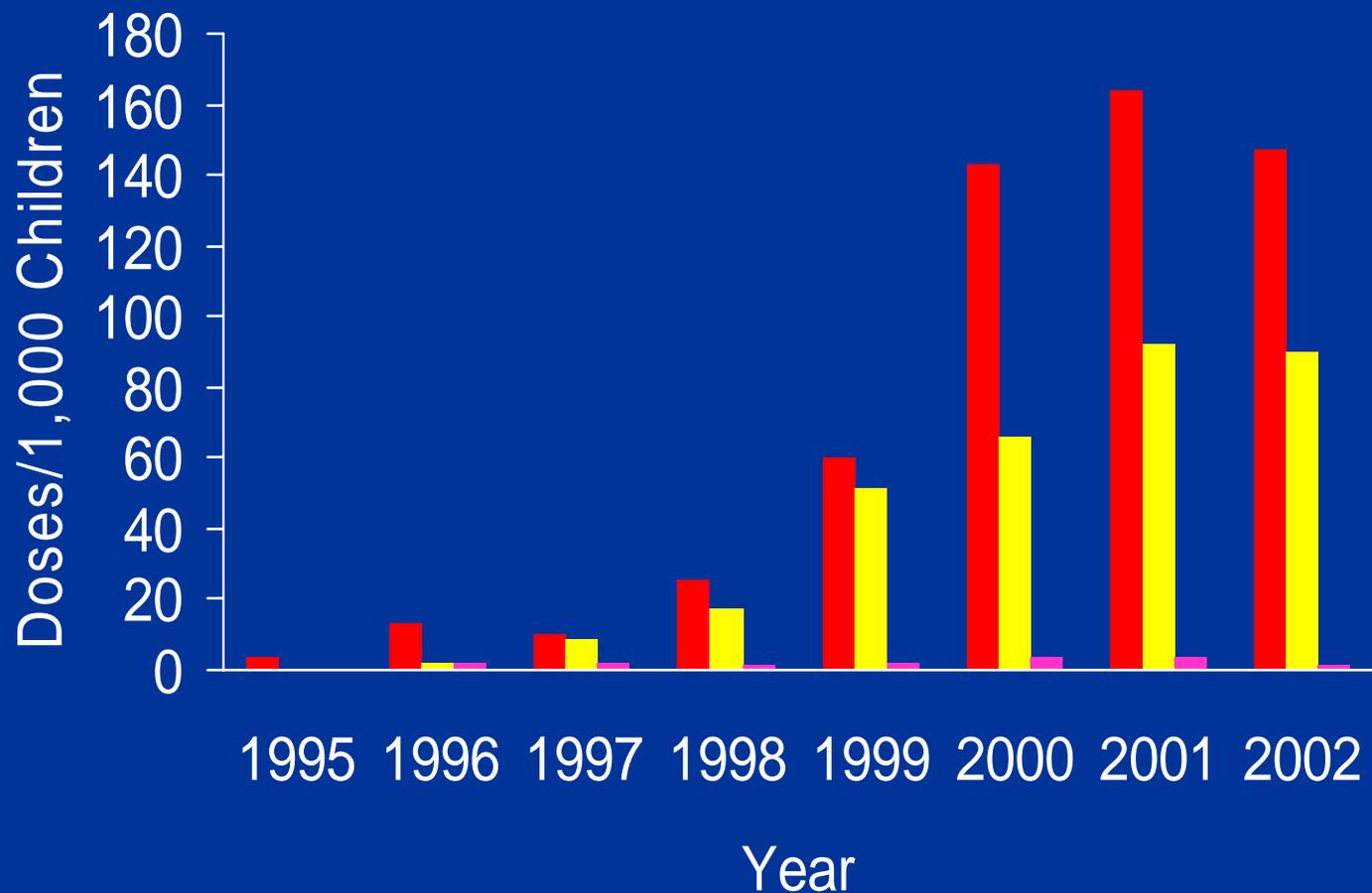


*2002 rate provisional



DOSES OF PEDIATRIC HEPATITIS A VACCINE PURCHASED BY PUBLIC SECTOR BY U.S. REGION, 1995-2002

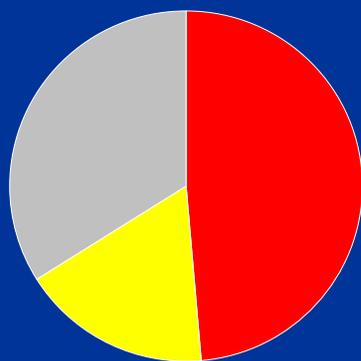
■ Recommended ■ Considered ■ No Statewide



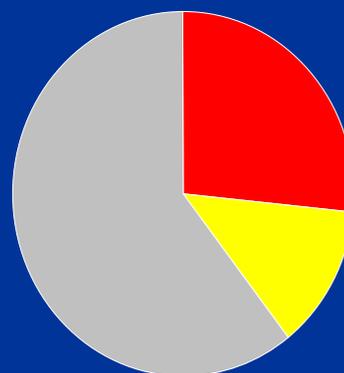
Summary of Hepatitis A Incidence by Region: Baseline, 2001, and 2002

	Rate/100,000		
	Baseline	2001	2002*
Recommended	25.9	4.5	3.6
Considered	16.1	3.8	1.8
No statewide	5.6	3.4	2.8

% Baseline Cases

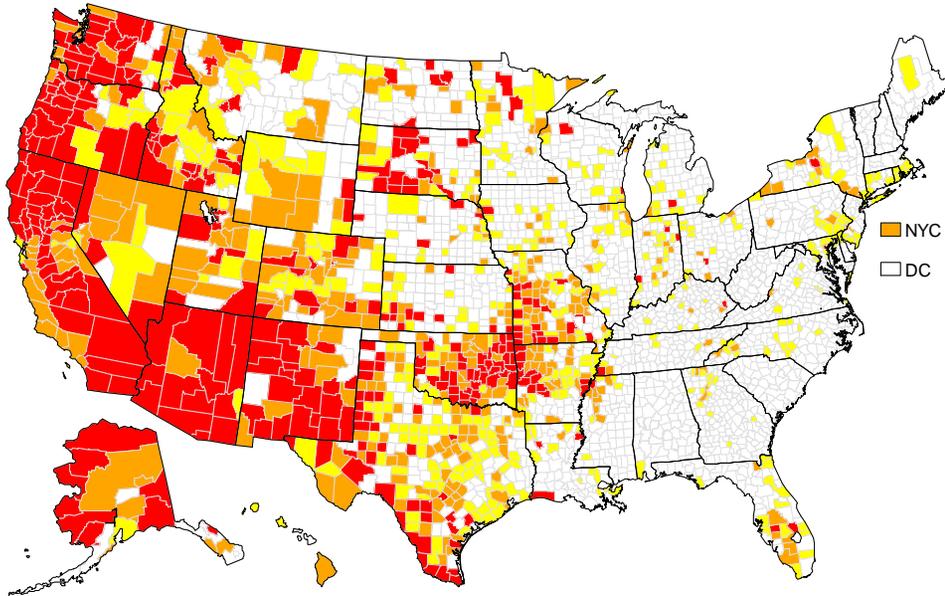


% Cases 2001

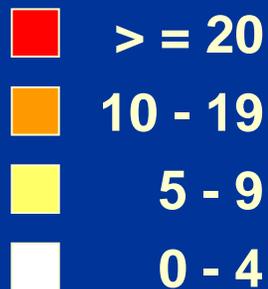


*2002 rate provisional

1987-97 average incidence

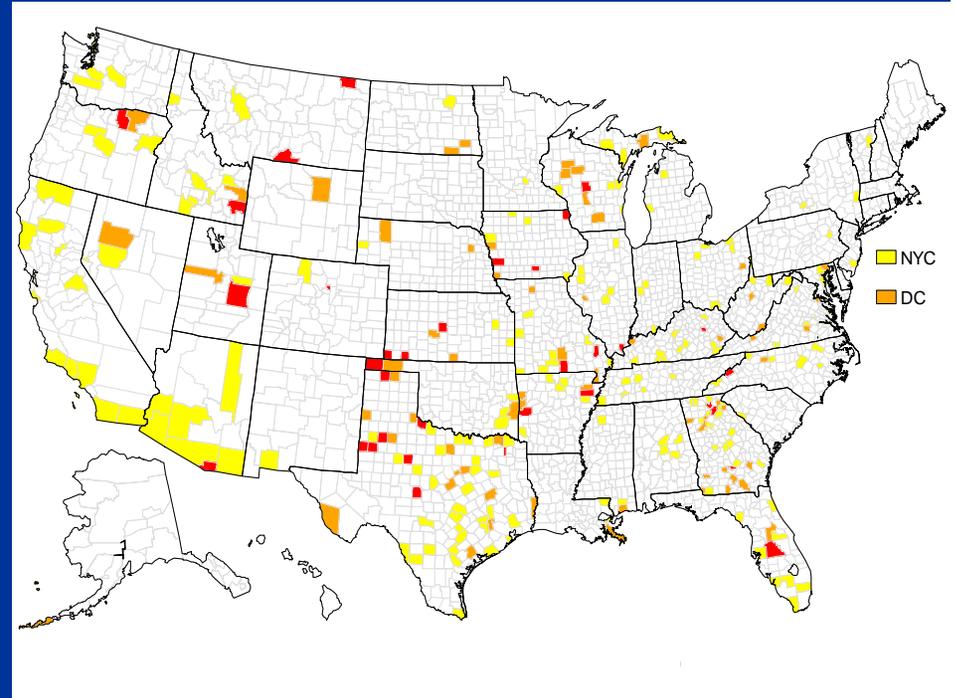


Rate per 100,000

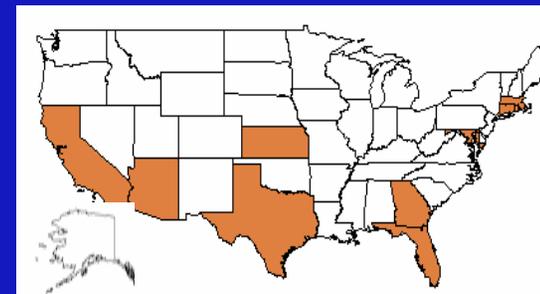
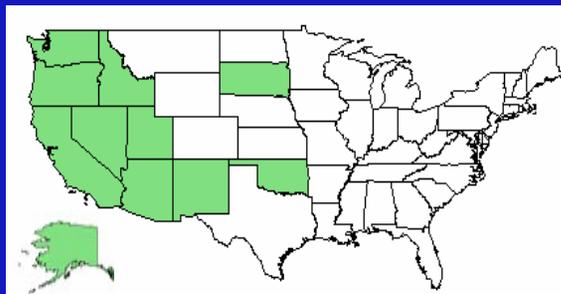


Hepatitis A Incidence

2002 incidence



TOP 10 STATES WITH THE HIGHEST HEPATITIS A RATES



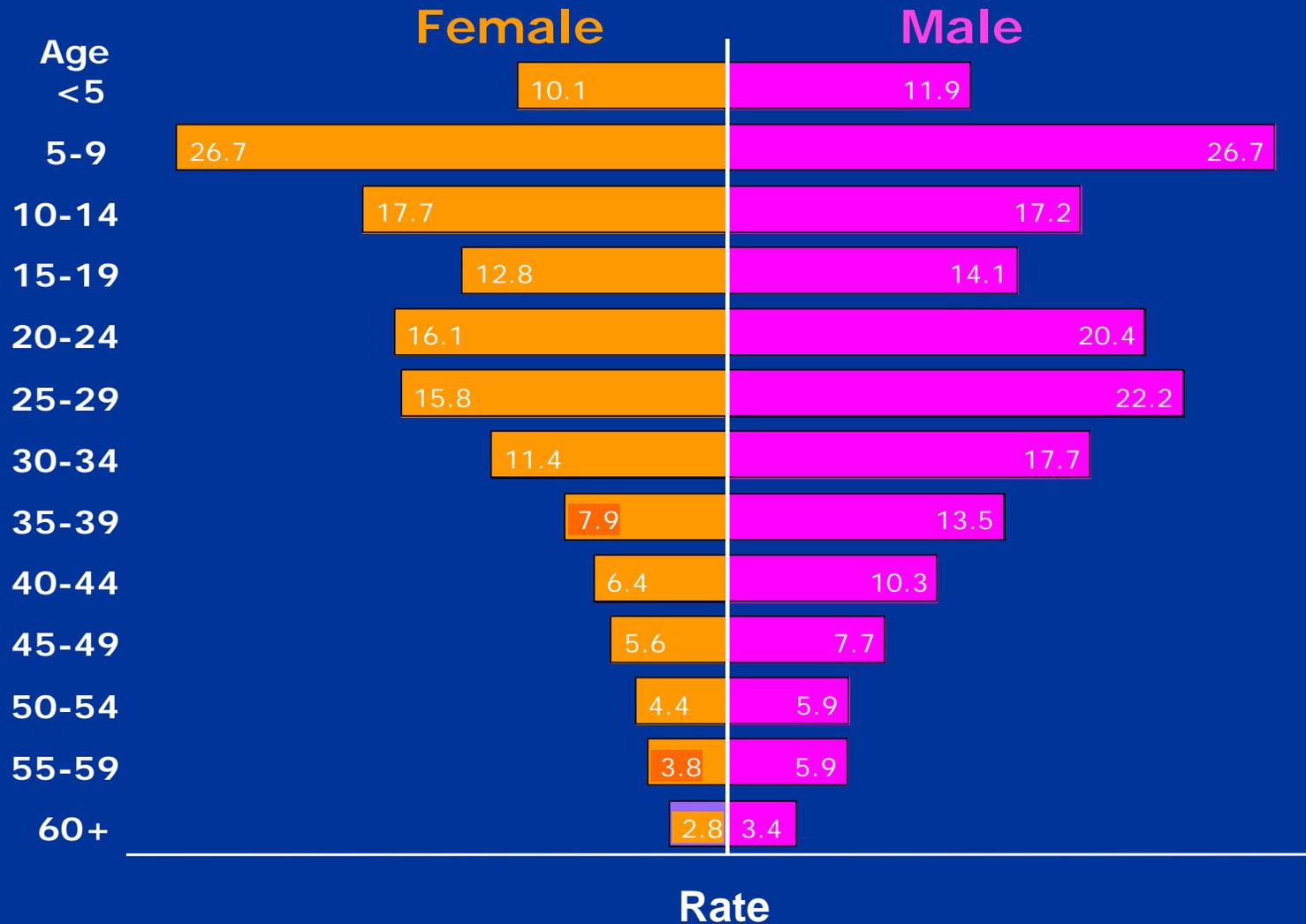
THEN
1987-1997

	Avg. rate		Rate
Arizona	48	D.C.	14
Alaska	45	Georgia	12
Oregon	40	Arizona	8
New Mexico	40	Rhode Island	7
Utah	33	Connecticut	7
Washington	30	Kansas	7
Oklahoma	24	Maryland	6
South Dakota	24	Massachusetts	6
Idaho	21	Texas	6
Nevada	21	Florida	5
California	20	California	5

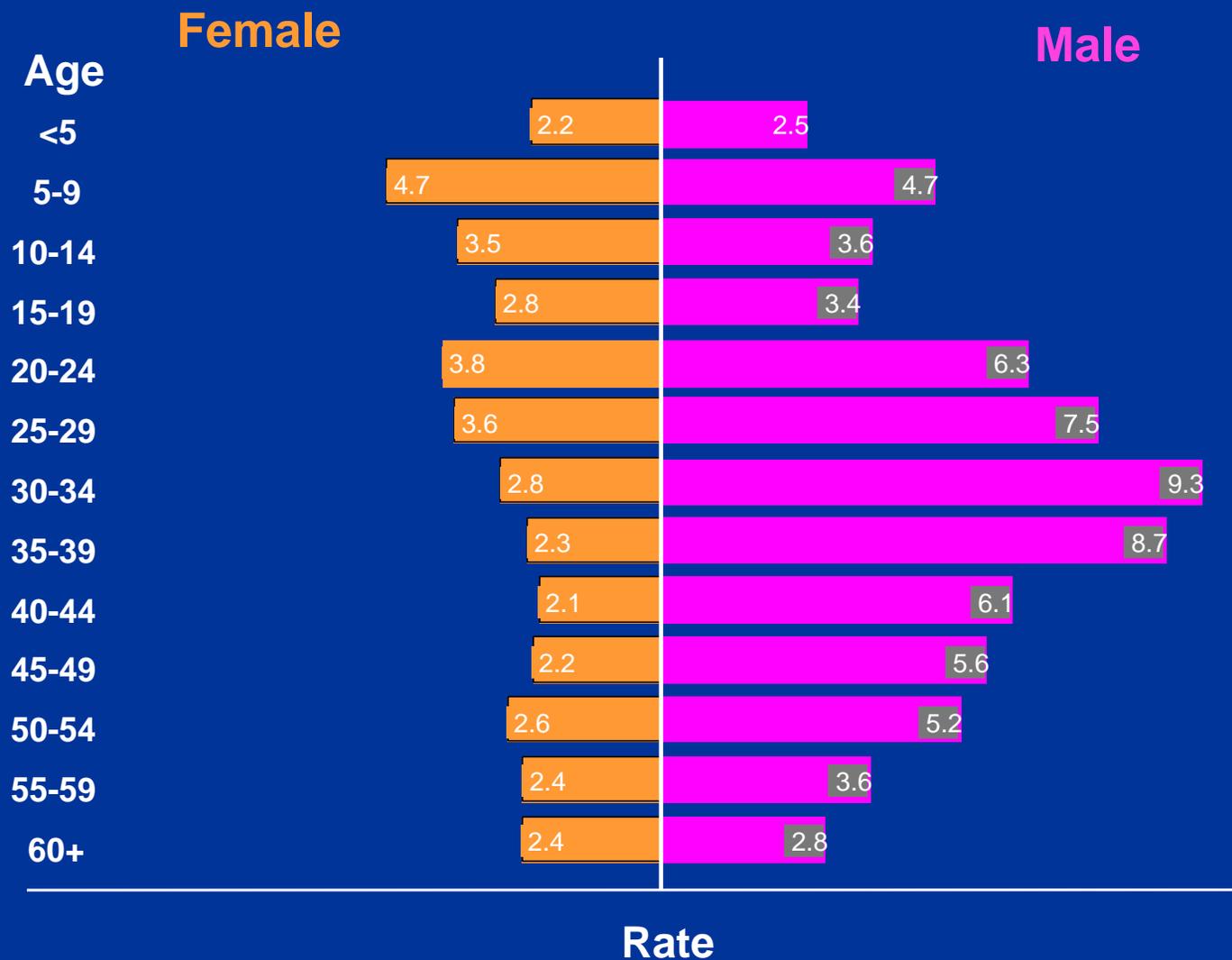
NOW
2001



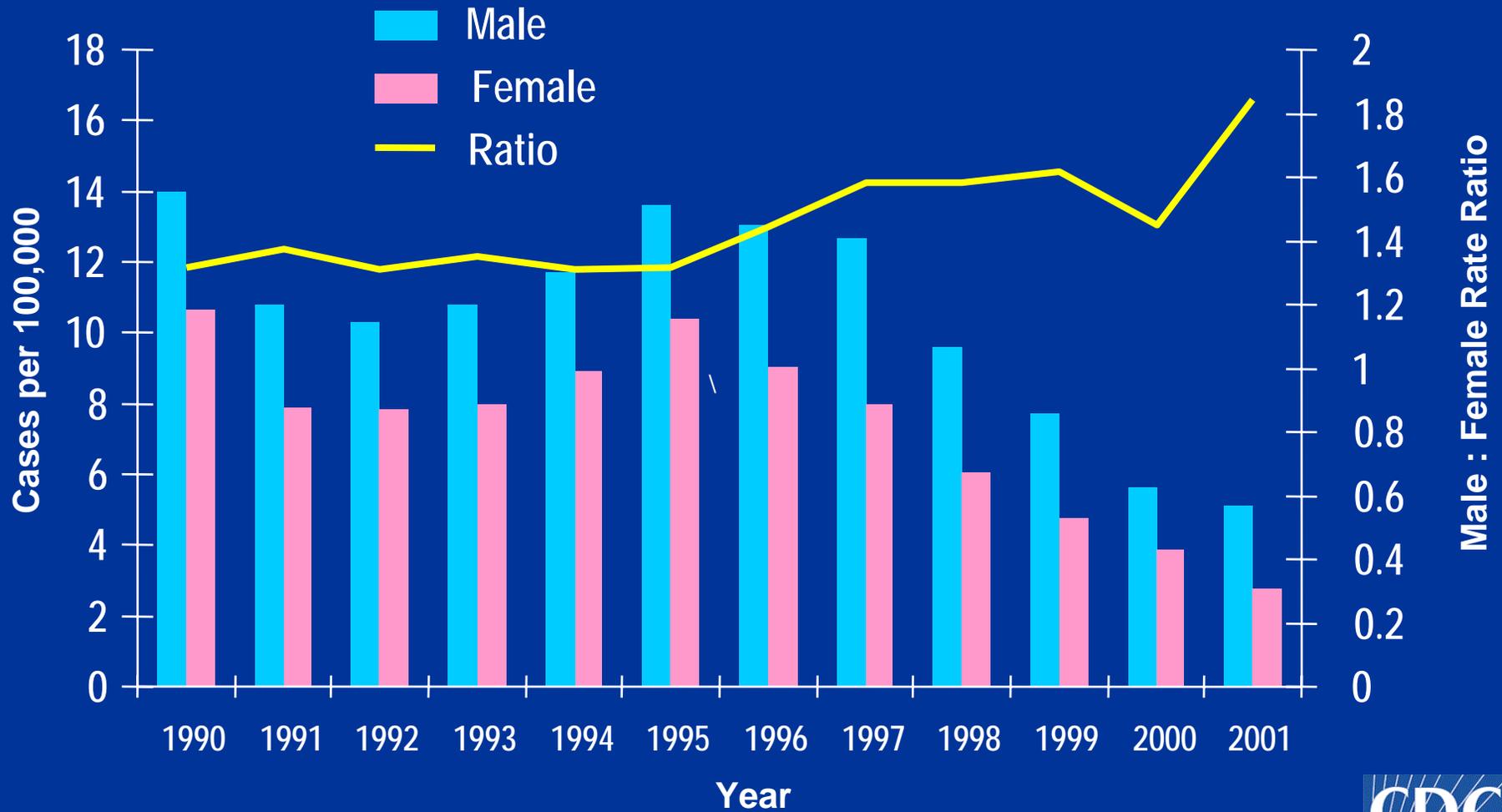
HEPATITIS A RATE, BY AGE AND GENDER UNITED STATES, 1990



HEPATITIS A RATE, BY AGE AND GENDER UNITED STATES, 2001



HEPATITIS A INCIDENCE BY GENDER, UNITED STATES, 1990-2001



ACIP RECOMMENDATIONS PERSONS AT INCREASED RISK OF INFECTION, 1996

- Men who have sex with men
- Illegal drug users
- International travelers
- Persons who have clotting factor disorders
- Persons with chronic liver disease

STD Treatment Guidelines

MMWR May 10, 2002 51(RR06)

“Vaccination against hepatitis is the most effective means of preventing sexual transmission of hepatitis A and B.”

Integration of services for high-risk adults

- Reports of converging epidemics (STD, HIV, hepatitis) impacting MSM, IDU, and others at risk
- Integration of services that target MSM, IDU, and others at risk saves \$\$\$ and improves services

Lack of integrated prevention activities leads to...

- **Individuals infected with HIV, hepatitis and other STDs remain undiagnosed, untreated and uninformed**
- **Infected and uninformed have higher levels of risky behavior and continue to transmit**
- **Counseling is mistakenly based on limited diagnosis and individuals at risk for HAV and HBV don't get immunized**

HEPATITIS A IN THE UNITED STATES -2002

- National rate lowest yet recorded
 - ◆ Continued monitoring needed to determine if low rates sustained and due to vaccination
 - ◆ Evaluation of age-specific rates to assess impact of vaccination strategy
- Rates increasing in some states
 - ◆ Occurring among adults in high risk groups (e.g. MSM, drug users)

HEPATITIS A VACCINATION IN THE UNITED STATES CHALLENGES FOR THE FUTURE

- **Continue implementation of the current recommendations for vaccination of children**
 - ◆ **Sustain vaccination in face of falling rates**
- **Further reduce incidence**
 - ◆ **Vaccination of high-risk adults**
 - ◆ **Vaccination of children nationwide**