

Hepatitis A Vaccine Background

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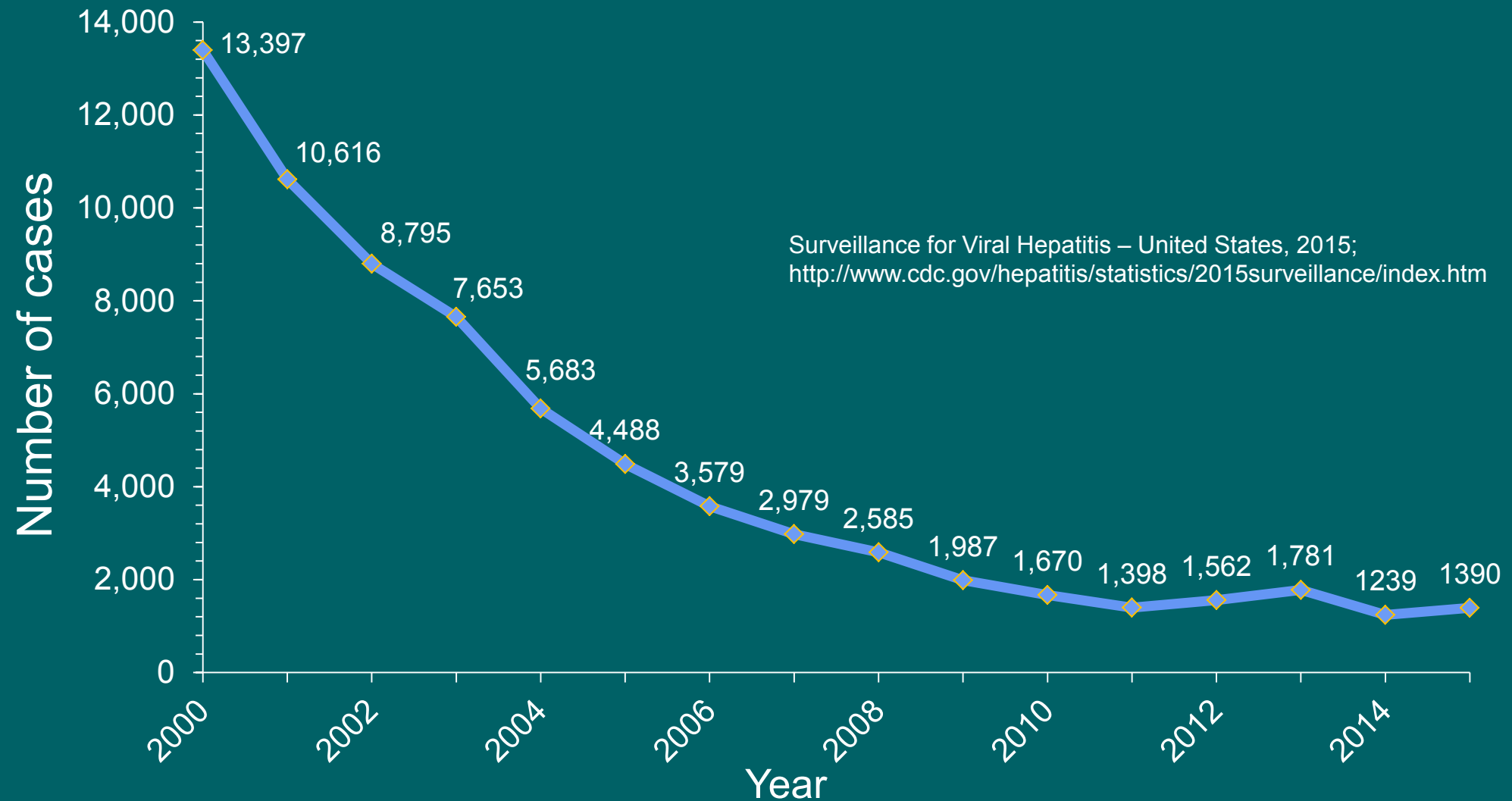
June 21, 2017

Outline

- Epidemiology
- Vaccine background
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- Vaccine coverage
- Alaska example
- Outbreaks
- Summary

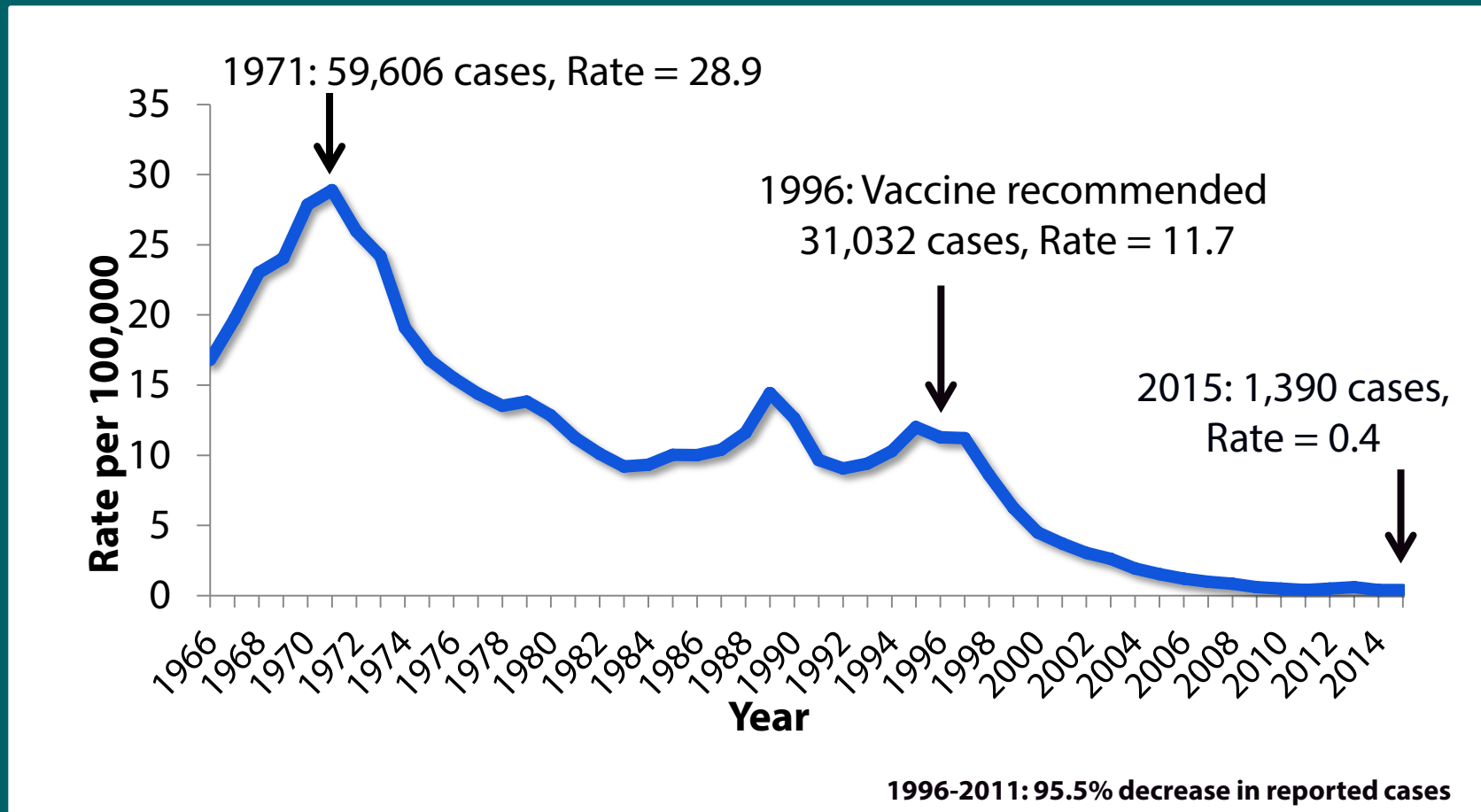
Hepatitis A Epidemiology

Reported Number of Acute Hepatitis A Cases United States, 2000-2015



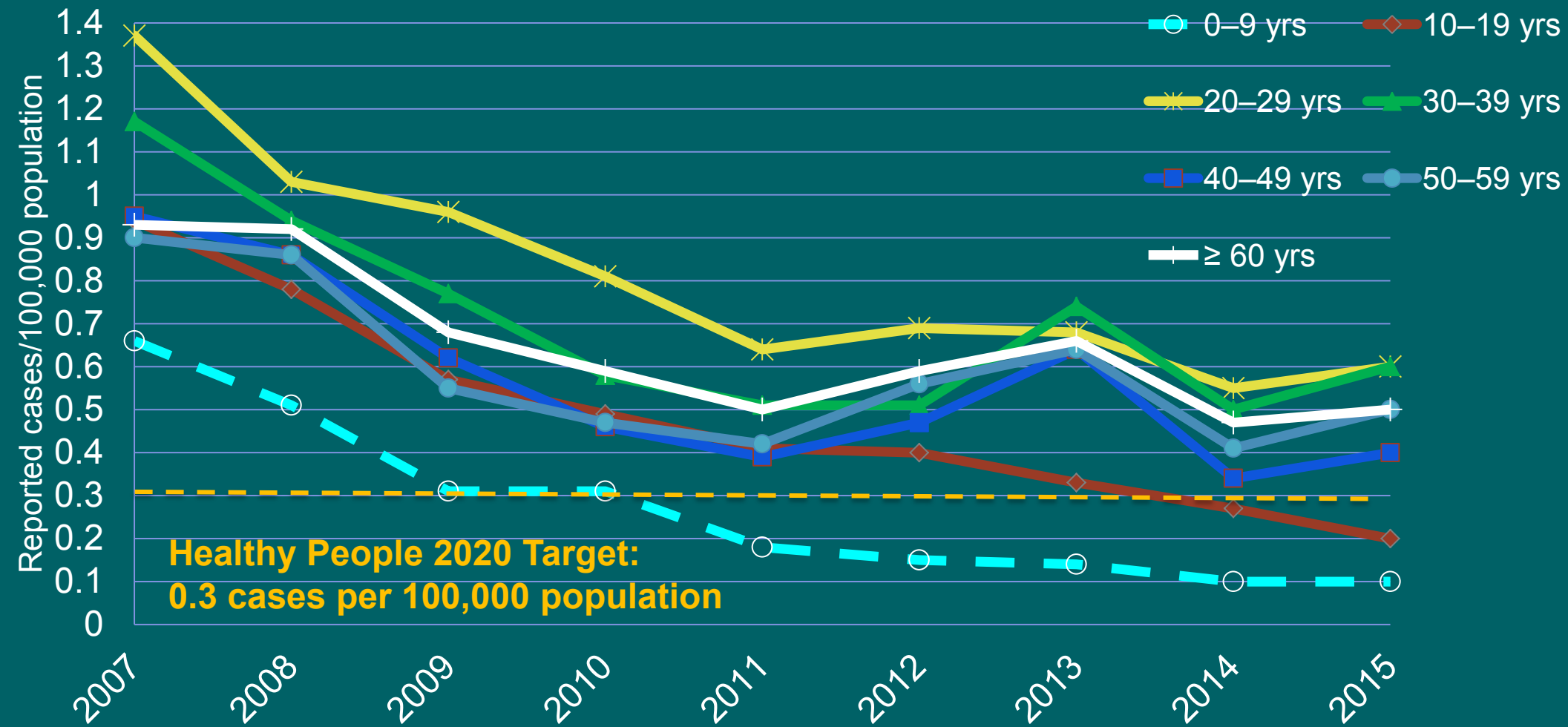
Source: CDC, National Notifiable Diseases Surveillance System (NNDSS)

Rates of Reported Acute Hepatitis A Cases United States, 1966-2015

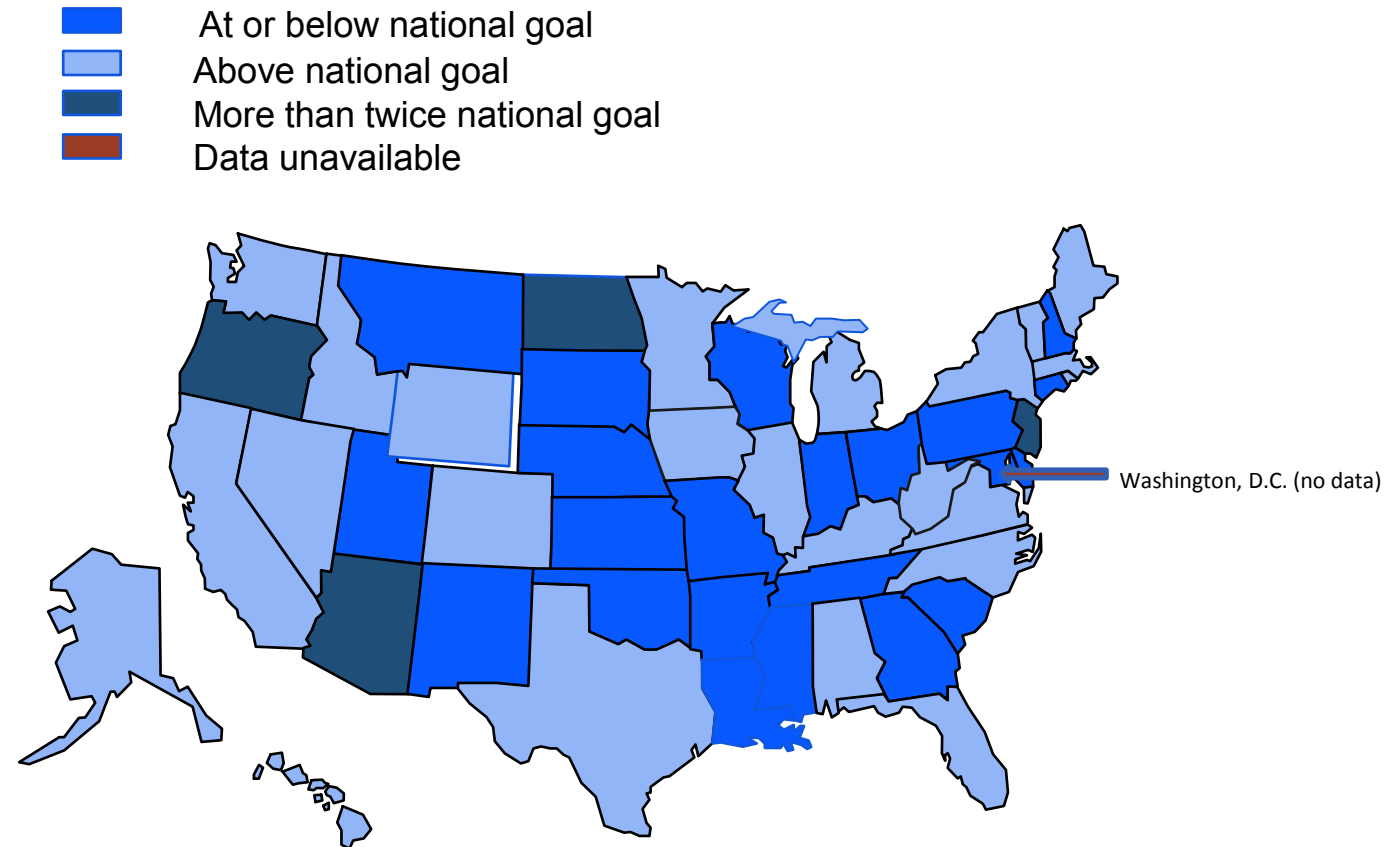


•National Notifiable Diseases Surveillance System (NNDSS); Armstrong GL. Pediatrics 2007;119:e22-9

Rates of Reported Acute Hepatitis A United States, 2007-2015



2015 State Acute Hepatitis A Incidence Compared to Healthy People 2020 National Goal*



Source: CDC, National Notifiable Diseases Surveillance System (NNDSS)

*National goal: 0.3 cases/100,000 population

Hospitalizations in Reported Cases of Hepatitis A — United States, 2009-2015

Year	Hepatitis A cases reported	Availability of valid data† for hospitalization		Cases hospitalized§	
	No.	No.	%	No.	%
2009	1,987	1,182	59.5	464	39.3
2010	1,670	1,020	61.1	433	42.5
2011	1,398	798	57.1	343	43.0
2012	1,562	1,022	65.4	468	45.8
2013	1,781	1,081	60.7	519	48.0
2014	1,239	757	61.1	344	45.4
2015	1,390	870	62.6	411	47.2

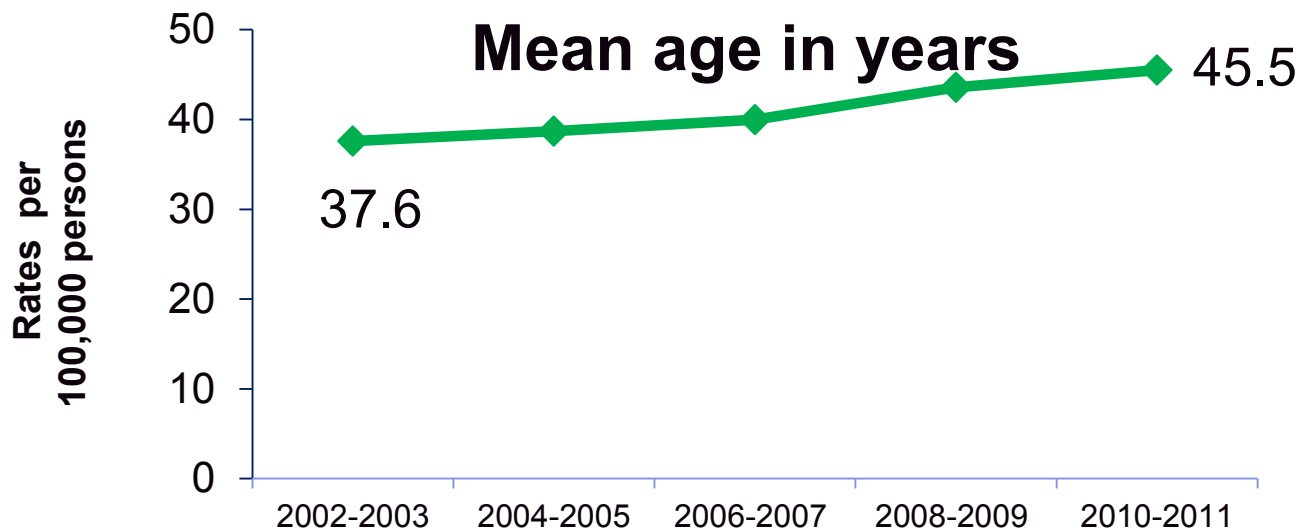
†Case reports for which questions regarding hospitalization were answered with “yes” or “no.”

§Numbers and percentages represent only cases with data regarding hospitalization; numbers likely are underestimates

National Notifiable Diseases Surveillance System (NNDSS); Division of Viral Hepatitis Surveillance Report (2009-2014)

Hepatitis A hospitalization trends, 2002-2011

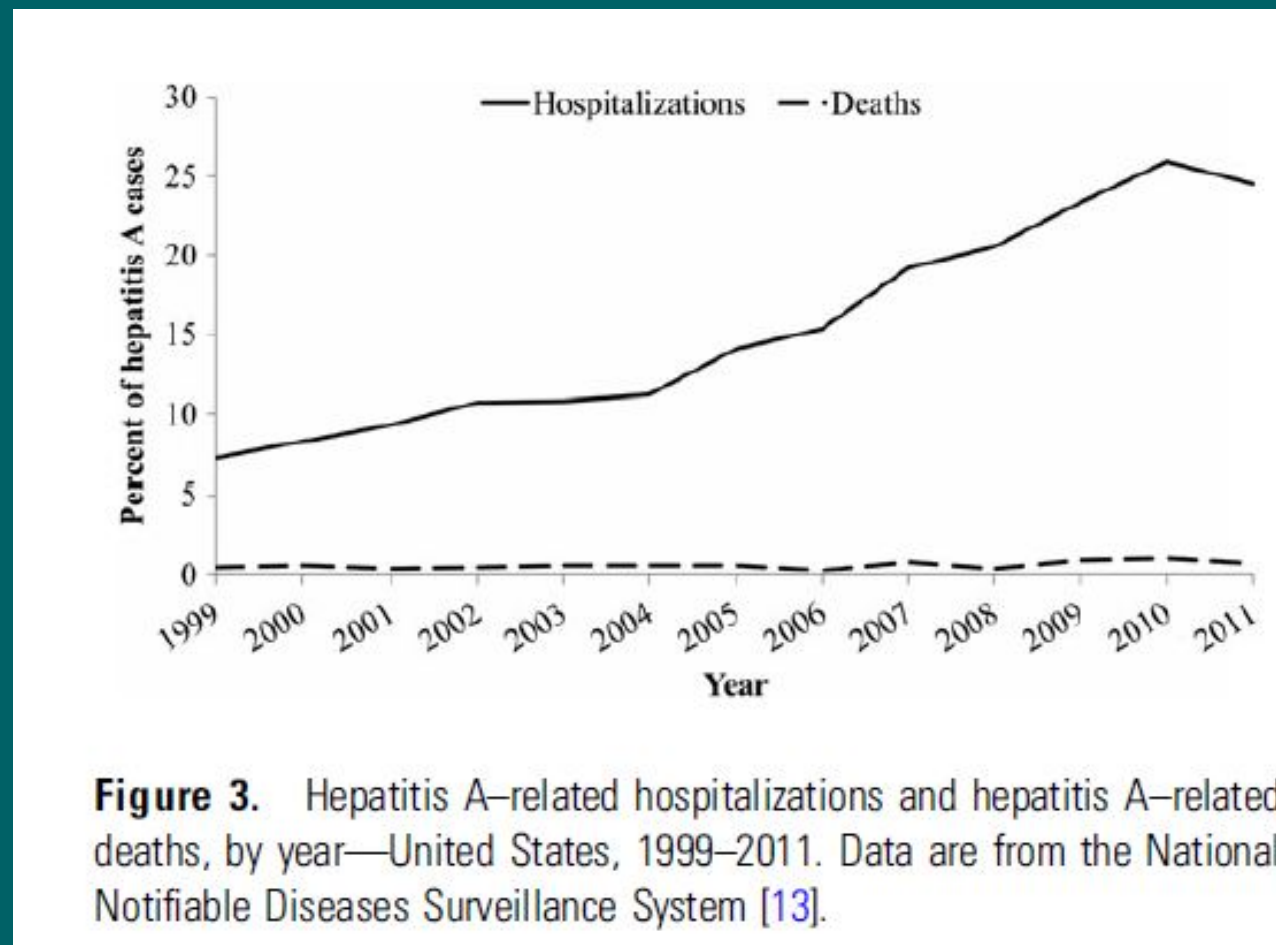
- **National Inpatient Sample (Healthcare Utilization Project or HCUP)**
 - Primary discharge diagnosis of hepatitis A
- **Mean age of persons hospitalized for hepatitis A has increased significantly over the study time period (mean age 37.6 years in 2002-2003 compared to 45.5 years in 2010-2011, $P < 0.0001$)**



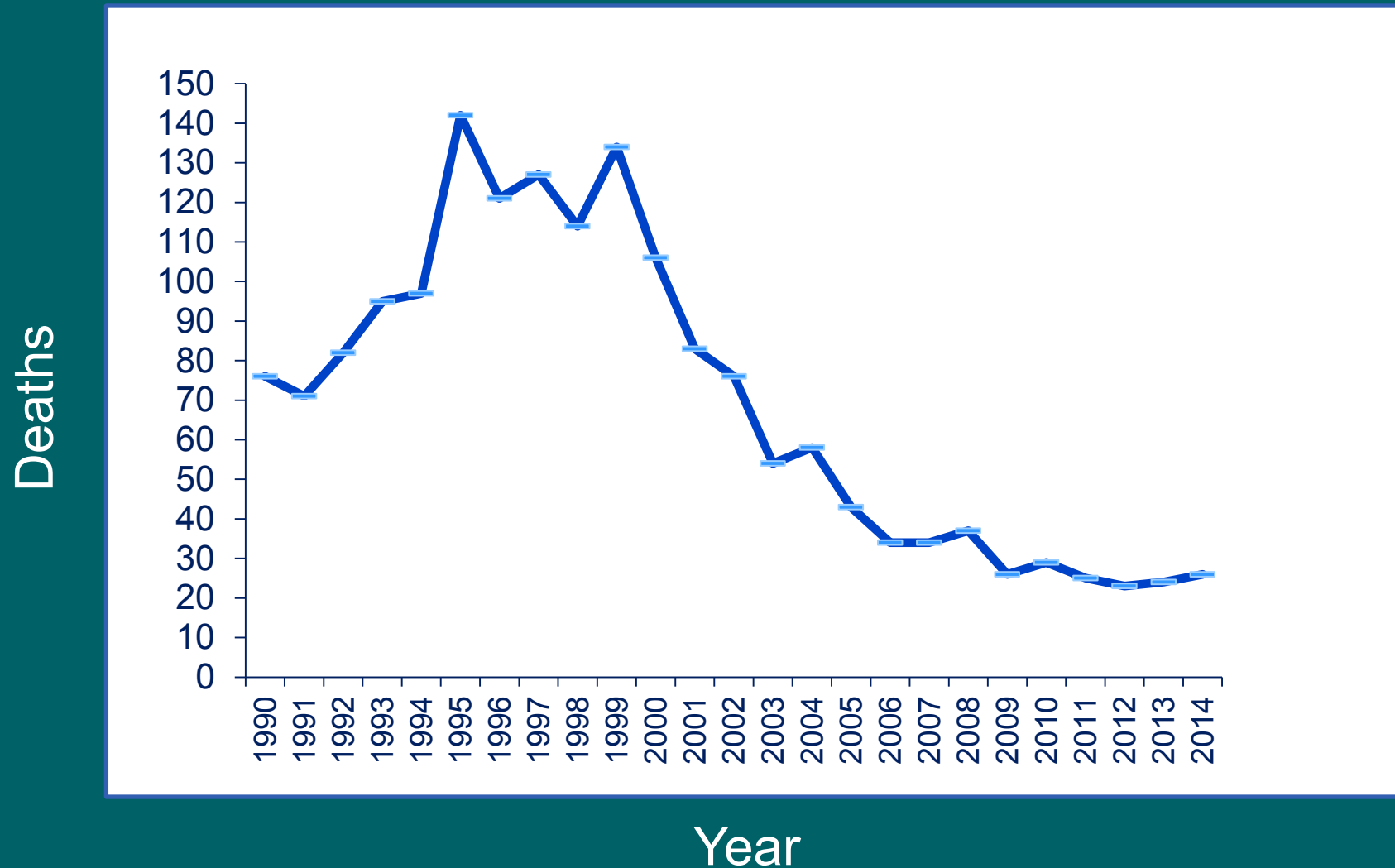
Hepatitis A hospitalization trends, 2002-2011

- Proportion with Medicare coverage increased in 2010 – 2011 (22.7%) compared to 2002 – 2003 (12.4%)
- Comorbid liver disease diagnosis increased in 2010 – 2011 (38.3%) compared to 2002 – 2003 (25.1%)
- Comorbid medical conditions increased in 2010 – 2011 (38.5%) compared to 2002 – 2003 (26.8%)
- No changes in mean length of stay or in-hospital deaths identified over the study period

Trends in Disease and Complications of Hepatitis A Virus Infection in the United States, 1999-2011

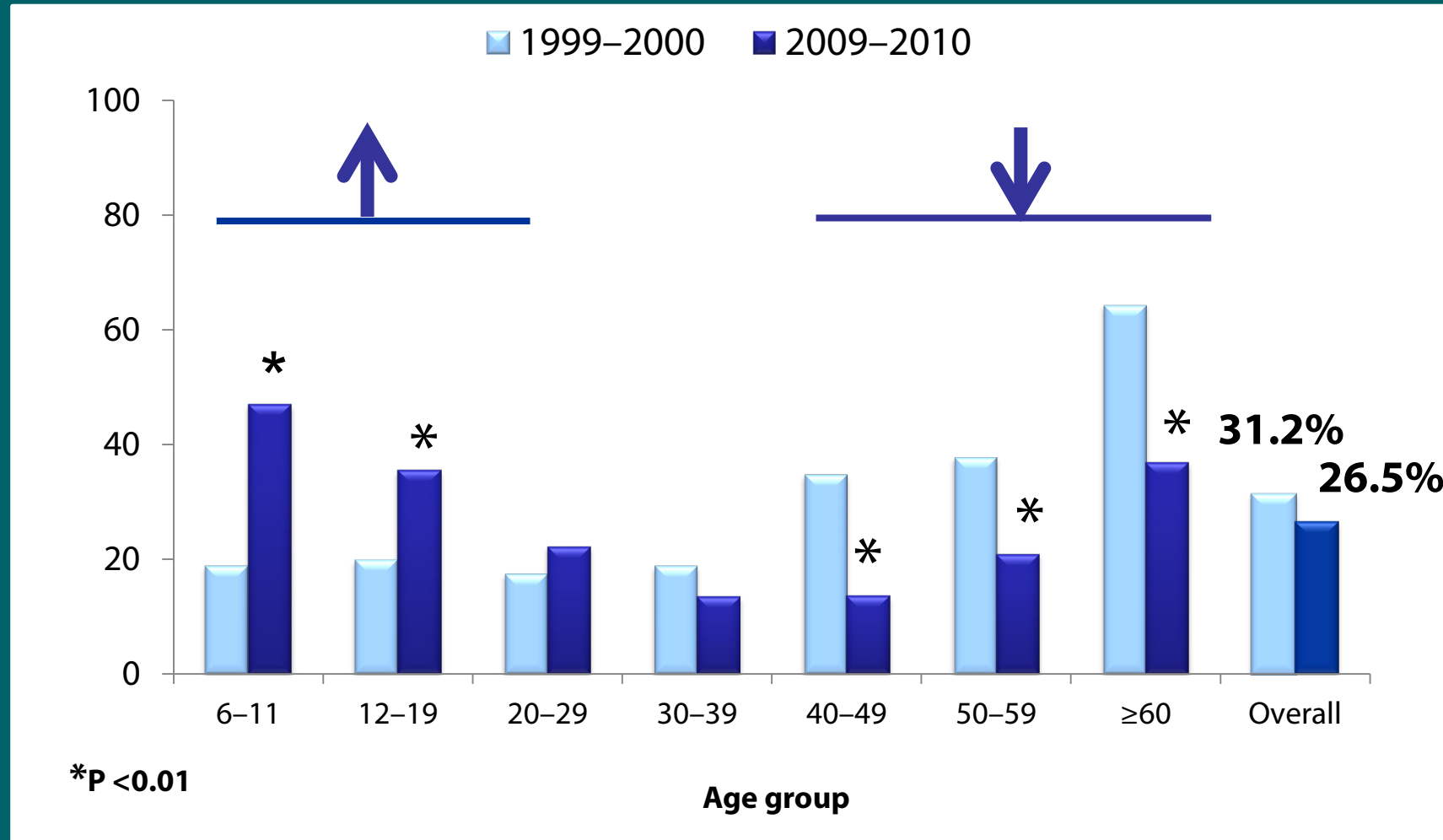


Hepatitis A Deaths in the United States, 1990-2014



Source: CDC, National Notifiable Diseases Surveillance System (NNDSS)

Prevalence of anti-HAV by age group NHANES, United States 1999–2000 and 2009–2010



Risk Factors

- International Travel
- Food/waterborne outbreak
- Men who have sex with men
- Injection Drug Use
- Sexual/household contact with hepatitis A-infected person
- Child/employee in a daycare center
- Contact with a daycare child or employee
- Other contact with hepatitis A patient

Hepatitis A Vaccine Background

Hepatitis A Vaccines in the United States

- All inactivated (killed virus)
- Monovalent, Merck CR326F strain, VAQTA™
- Monovalent, GSK HM175 strain, HAVRIX™
- Combination, GSK HM175 strain and recombinant hepatitis B surface antigen, TWINRIX™

Hepatitis A Vaccines in 1995 and 1996

Efficacy of 2-Dose Schedules

Vaccine*	Site and Age Group	Number in Trial	Vaccine Efficacy (95 % CI)
VAQTA®, Merck, Sharpe, and Dohme (MSD) ¹	New York 2-16 years	1,037	100% (85-100%) [§]
HAVRIX®, SmithKline Beecham (SKB) ²	Thailand 1-16 years	38,157	94% (74-98%)

*Pediatric formulation

§Determined 6–18 months after dose 1

(1) Werzberger, A et al. New Engl J Medicine. 1992;327:453–7

(2) Innis BL, et al. JAMA 1994;271:1328–34

Hepatitis A Vaccine Schedules

TABLE 2. Licensed dosages of VAQTA®*

Vaccine recipient's age	Dose (U) [†]	Vol. (mL)	No. doses	Schedule (mos) [§]
12 mos–18 yrs	25	0.5	2	0, 6–18
≥19 yrs	50	1.0	2	0, 6–18

* Hepatitis A vaccine, inactivated, Merck & Co., Inc. (Whitehouse Station, New Jersey).

[†] Units.

[§] 0 months represents timing of initial dose; subsequent numbers represent months after the initial dose.

TABLE 3. Licensed dosages of HAVRIX®*

Vaccine recipient's age	Dose (EL.U.) [†]	Vol. (mL)	No. doses	Schedule (mos) [§]
12 mos–18 yrs	720	0.5	2	0, 6–12
≥19 yrs	1,440	1.0	2	0, 6–12

* Hepatitis A vaccine, inactivated, GlaxoSmithKline (Rixensart, Belgium).

[†] Enzyme-linked immunosorbent assay units.

[§] 0 months represents timing of initial dose; subsequent numbers represent months after the initial dose.

Hepatitis A Vaccine Schedules

TABLE 4. Licensed dosages of TWINRIX®*

Vaccine recipient's age	Dose (hepatitis A/ hepatitis B)	Vol. (mL)	No. doses	Schedule (mos) [†]
≥18 yrs	720 EL.U. [§] /20 µg	1.0	3	0, 1, 6

* Combined hepatitis A and hepatitis B vaccine, GlaxoSmithKline (Rixensart, Belgium).

[†]0 months represents timing of initial dose; subsequent numbers represent months after the initial dose.

[§]Enzyme-linked immunosorbent assay units.

Accelerated Dosing: A series of 4 doses (1 mL each) given on days 0, 7, and 21 to 30 followed by a booster dose at month 12

Hepatitis A Vaccine Safety

- In pre-licensure trials, adverse reactions to HAVRIX, VAQTA and TWINRIX were **mostly injection site reactions and mild systemic reactions**
 - Most frequent side effects are soreness or erythema at injection site, fever, headache, and malaise
 - Multiple studies demonstrate no serious adverse event definitively attributed to inactivated vaccine
- **Postmarketing surveillance for adverse events following receipt of HepA vaccines has been performed primarily by two systems in the United States: the Vaccine Adverse Event Reporting System (VAERS) and the Vaccine Safety Datalink (VSD).**
 - No unusual or unexpected safety patterns were observed for any HepA vaccines
- **VAERS pregnancy reports following HepA were reviewed and no patterns of concern were observed**
 - Currently VSD is conducting an ongoing safety study of HepA and HepB vaccines in pregnant women

MMWR 2006;55(RR-7)

IOM 2011.

Moro PL, et al. Am J Obstet Gynecol. 2014 Jun;210(6):561.e1-6

Contraindications U.S.-Licensed HepA Vaccines

- History of severe allergic reaction to previous dose of HepA vaccine or vaccine component
- Precaution: Vaccination of persons with moderate or severe acute illness, with or without fever, should be deferred until illness resolves (as with other vaccines)

Long-term Protection

- The duration of protection after vaccination is unknown
- Anti-HAV has been shown to persist in vaccine recipients for at least 20 years in adults administered inactivated vaccine as children with a three dose schedule
- Detectable antibodies are estimated to persist for 40 years or longer based on mathematical modeling and anti-HAV kinetic studies
- Protection following natural infection is lifelong and may also be following vaccination

Theeten H, et al. Vaccine. 2015 Oct 13;33(42):5723-7.

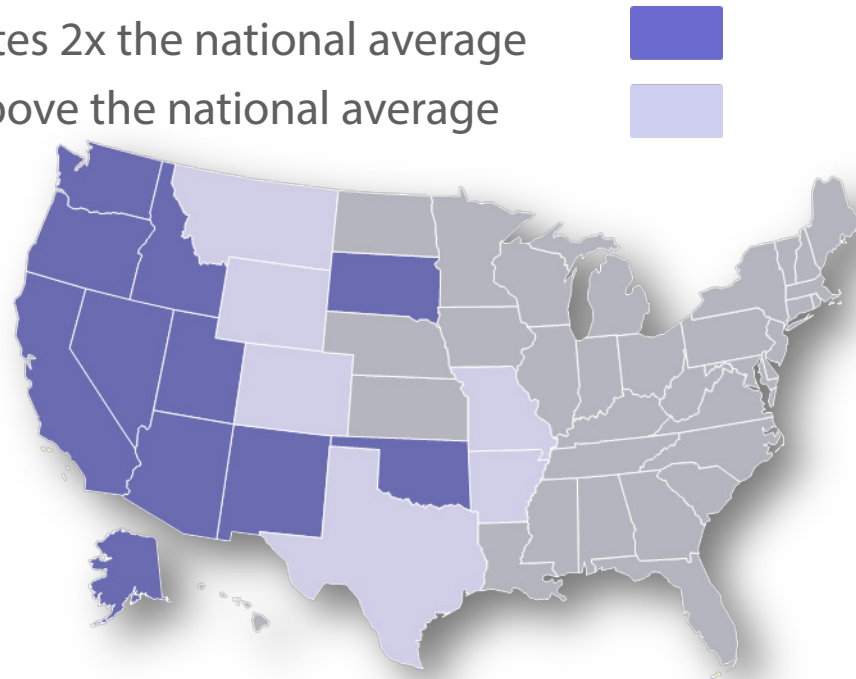
Plumb ID, et al. Viral Hepat. 2017;00:1–5.

Hepatitis A Vaccine Recommendations

ACIP hepatitis A vaccine recommendations

■ Targeted vaccination, 1996-1999

- 1996
 - Children at age 2 years in communities with high rates of disease
 - Children through teen years in outbreaks
- 1999
 - Recommended in 11 states with rates 2x the national average
 - Considered in 6 states with rates above the national average



ACIP hepatitis A vaccine recommendations

- **Universal childhood vaccination, 2006**
 - Recommended for use at age 12-23 months in all states
 - Continue existing vaccination programs for ages 2-18 years
 - Consider catch-up vaccination in outbreaks and areas with increasing disease rates
 - Any person wishing to obtain immunity

Note: No routine catch-up recommendation for children ages >23 months

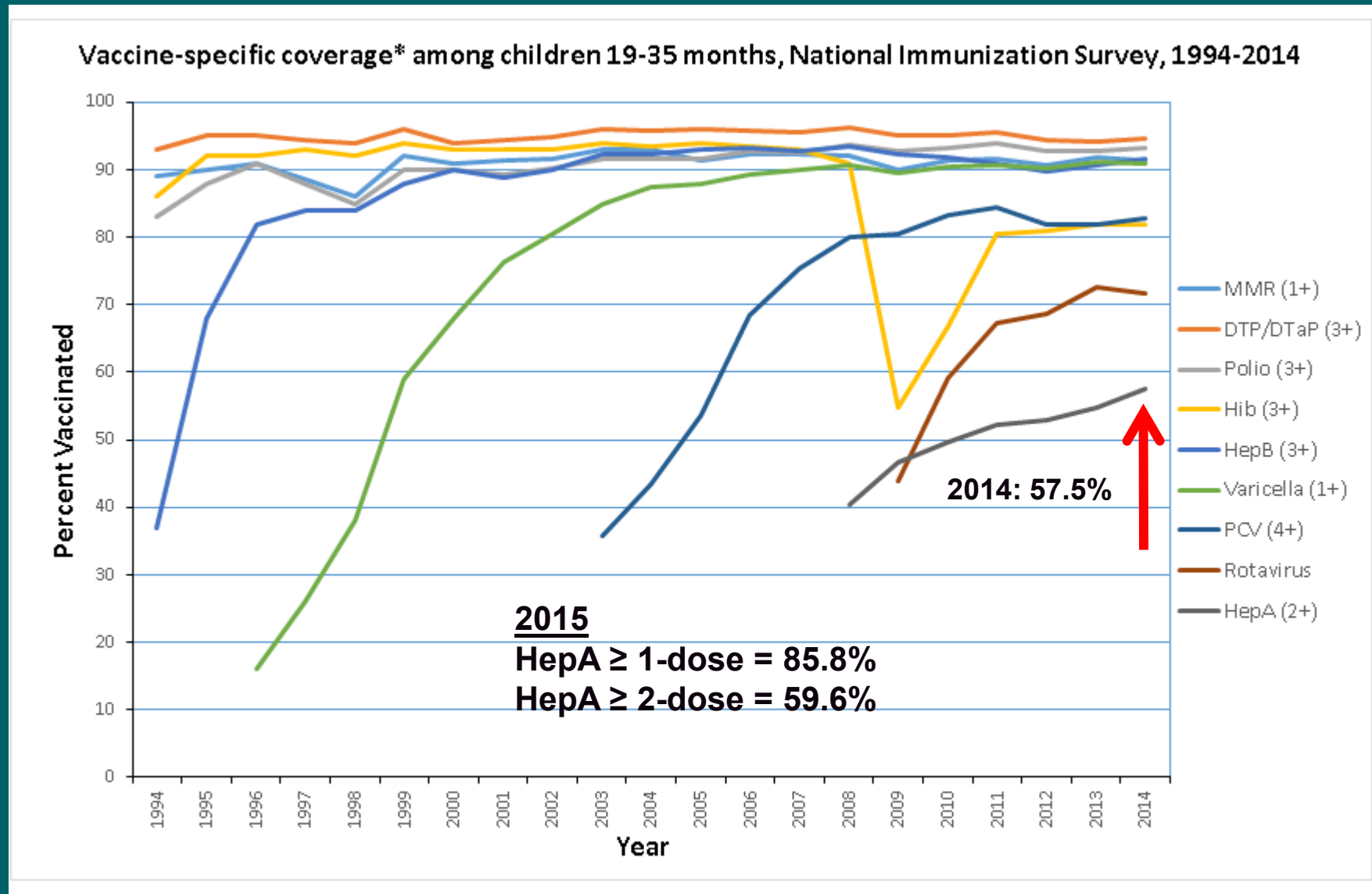
ACIP hepatitis A vaccine recommendations

Groups at increased risk of HAV or severe HAV disease

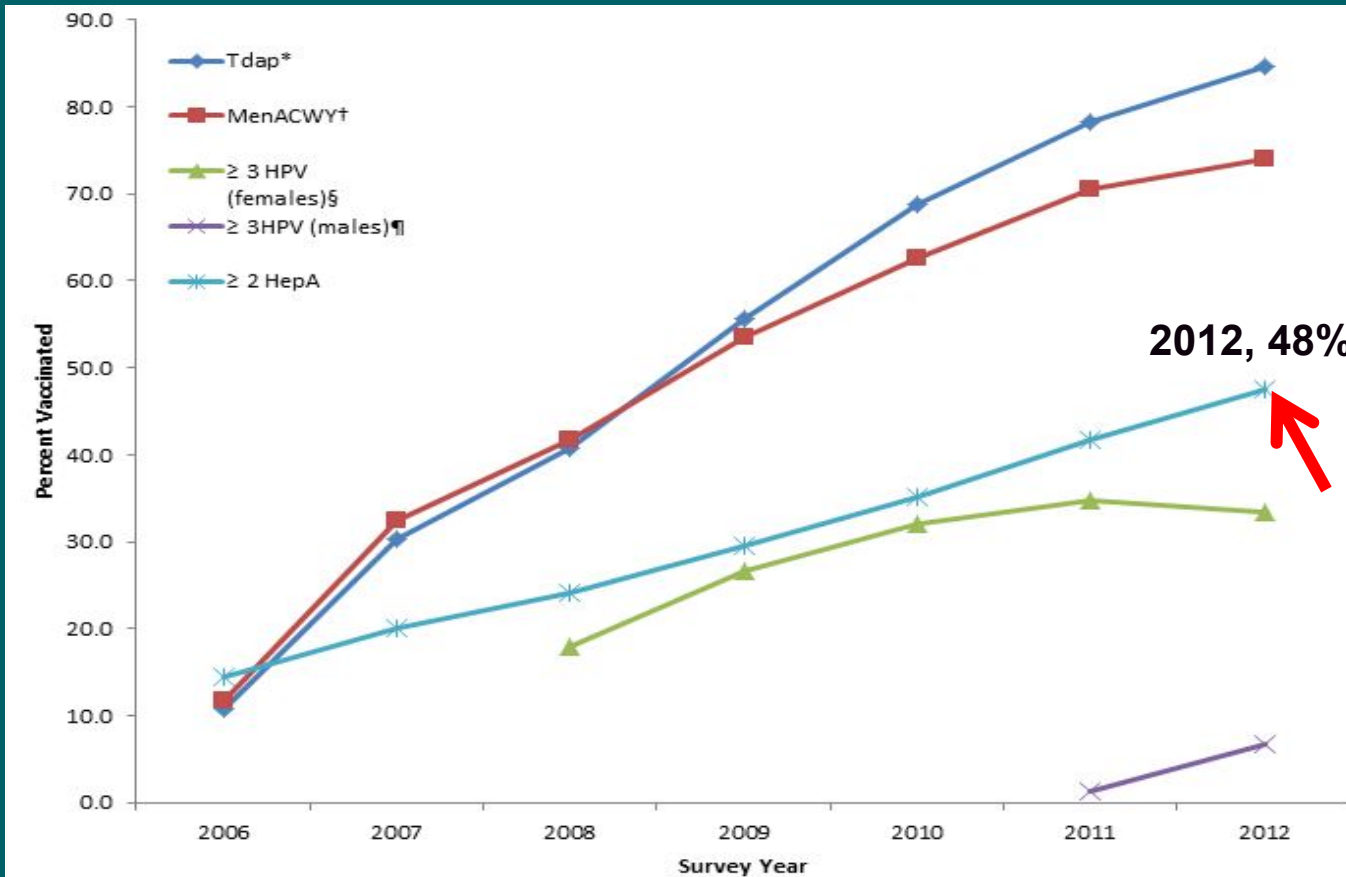
- Travelers
- Men who have sex with men
- Users of injection and non-injection drugs
- Persons with clotting-factor disorders
- Persons who work with nonhuman primates
- Persons who anticipate close personal contact with an international adoptee
- Persons with chronic liver disease
- Post-exposure prophylaxis for healthy persons aged 12 months-40 years

Hepatitis A Vaccine Coverage

Vaccine-specific Coverage among Children aged 19-35 months, National Immunization Survey, 1994-2014



Hepatitis A Vaccination Coverage, NIS-Teen, Age 13-17



* ≥1 dose Tdap vaccine on or after age 10 years.

† ≥1 dose MenACWY vaccine.

§ HPV vaccine, either bivalent or quadrivalent, among females.

ACIP recommends either bivalent or quadrivalent vaccine for females.

¶ HPV vaccine quadrivalent, among males. ACIP recommends the quadrivalent vaccine for males; however, some males might have received bivalent vaccine

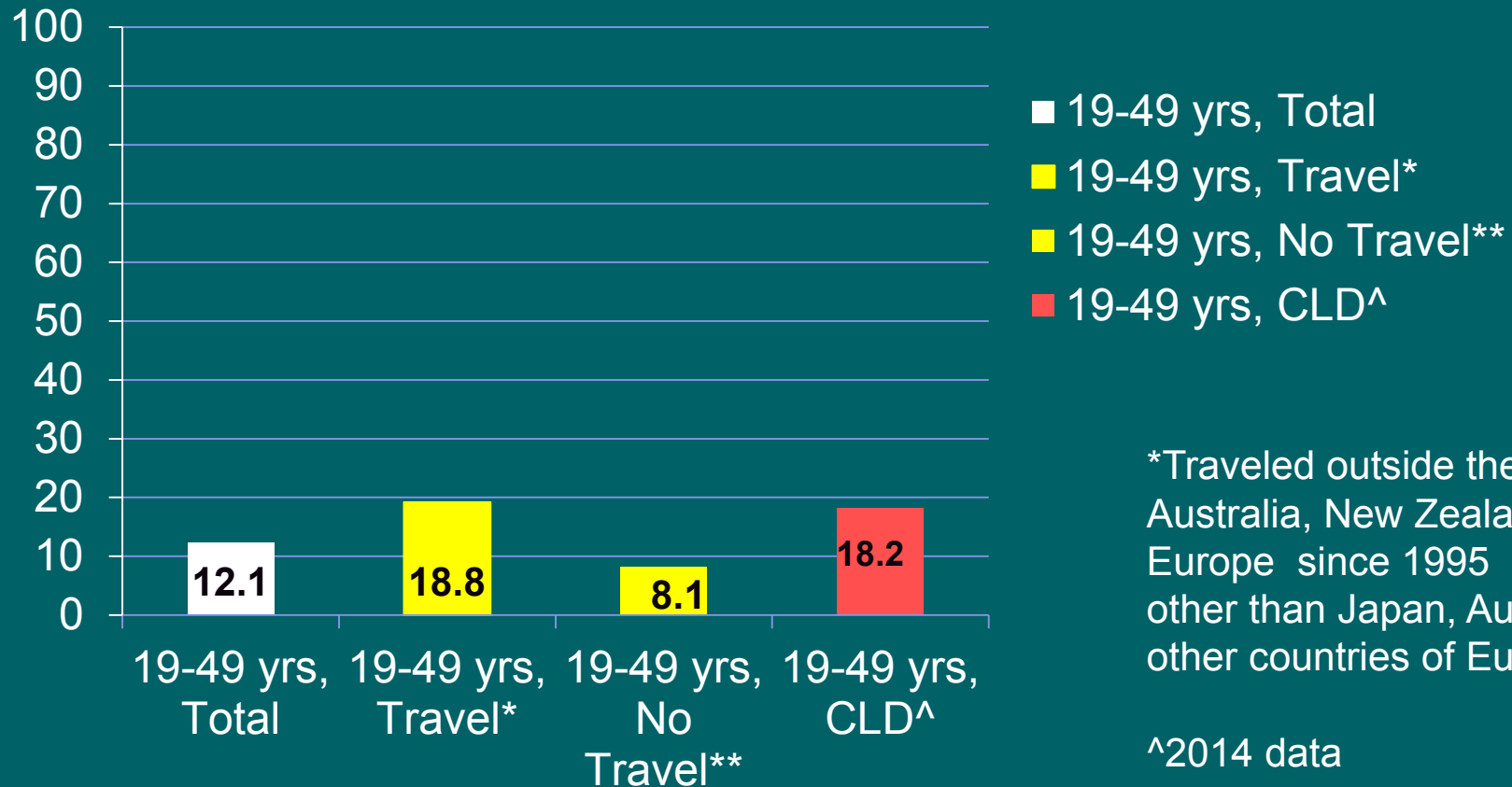
2012

HepA ≥ 1-dose = ~60%

HepA ≥ 2-dose = ~48%

In 2013, national vaccination coverage for 1 and ≥2 doses of HepA vaccine among adolescents was 62.5% and 51.0%, respectively. [Unpublished]

Hepatitis A Vaccine ≥ 2 -dose Coverage for ages 19-49 years, National Health Interview Survey (NHIS), 2015, Overall and Two Risk Groups



Williams WW, Lu PJ, O'Halloran A, Kim DK, Grohskopf LA, Pilishvili T, Skoff TH, Nelson NP, Harpaz R, Markowitz LE, Rodriguez-Lainz A, Fiebelkorn AP. Surveillance of Vaccination Coverage among Adult Populations - United States, 2015. MMWR Surveill Summ. 2017 May 5;66(11):1-28.

Alaska

Hepatitis A among Alaska Natives

- **1950-1990 – Cyclic HAV epidemics every 10-15 years**
 - 85% of Alaska Natives (AN) born before 1945, anti-HAV positive
- **Hepatitis A Vaccination**
 - 1996 – Universal vaccination, ages 2-14 years
 - 1997 – Age expanded, 2-18 years
 - 2001 – Daycare and school attendance requirement
 - 2006 – Age expanded, 1-18 years

Hepatitis A among Alaska Natives

- **Alaska HAV case assessment, 1972-2007**
 - 2002-2007, estimate 2052 symptomatic cases prevented with vaccine
 - 2006, 65% ≥ 1 dose vaccine coverage, AN children 2-18 years
 - 2008, 94% 2 dose coverage, AN children 11-17 years
 - 99.9% reduction in cases among AN people, 0.3/100,000 persons
- **Transmission halted: high vaccination coverage, routine childhood vaccination and mandatory school vaccination**

Outbreaks

Food Associated Outbreaks – 2013

- **Multi-state outbreak associated with frozen pomegranate arils imported from Turkey**
 - 165 cases
 - 7% aged <18 years
 - 93% aged ≥18 years
 - Complications
 - Overall 42% hospitalized
 - 2 cases fulminant hepatitis
 - 1 case liver transplant



Collier MG, et. al. Outbreak of hepatitis A in the USA associated with frozen pomegranate arils imported from Turkey: an epidemiological case study. Lancet Infect Dis. 2014 Oct;14(10):976-81.

Food Associated Outbreaks 2016 - Hawaii

- **On August 15, 2016, HDOH identified raw scallops served at Chain A restaurants on Oahu and Kauai as a likely source of the ongoing outbreak.**
 - Product: Sea Port Bay Scallops (Wild Harvest, Raw Frozen)
 - Origin: Philippines
 - Distributor: Koha Oriental Foods and True World Foods
 - Product embargoed and temporary closure of all Chain A restaurants on Oahu and Kauai
- **As of January 11, 2017**
 - Confirmed cases: 292
 - Hospitalized: 74
 - Onset of illness has ranged between 6/12/16 – 10/9/16



2016 – Multistate outbreak of hepatitis A linked to frozen strawberries

- 9 states
- **Source:** frozen strawberries imported from Egypt are the likely source of this outbreak
- **Location:** Smoothie Restaurant A Cafés
 - Product removed August 8, 2016
- **As of September 28, 2016:**
- **143 people with hepatitis A have been reported from nine states**
 - 129 of these cases reported eating a smoothie from Smoothie Restaurant A Café
 - 14 cases had no direct exposure to Tropical smoothie café
 - 12% were <18 years
 - 88% were ≥18 years
 - Age range of cases: 12-70
 - 56 cases hospitalized; no deaths

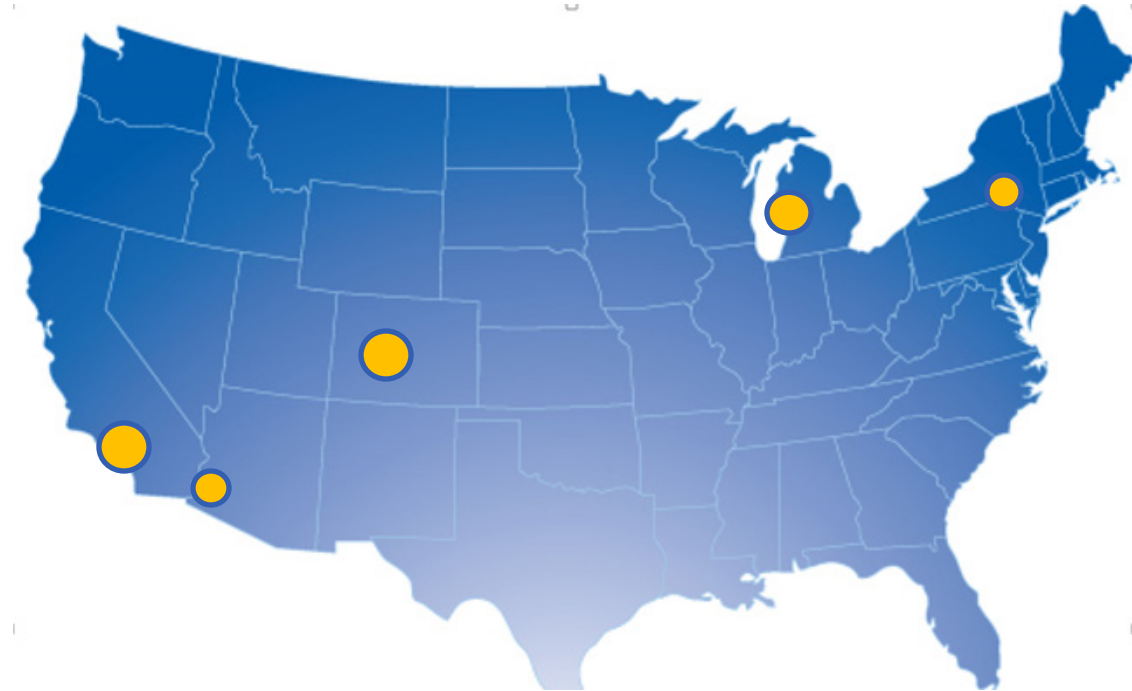


<http://www.vdh.virginia.gov/blog/2016/09/10/hepatitis-a-investigation>

<http://www.cdc.gov/hepatitis/outbreaks/2016/hav-strawberries.htm>

2017 Hepatitis A Outbreaks

- **San Diego**
 - 160 total confirmed or probable outbreak-associated cases
 - Hospitalizations: 120 (75%)
 - Deaths: 4 (2.5%)
 - Primarily in homeless individuals and/or illicit drug users
 - Secondary infections in inmates
- **Southeast Michigan**
 - 144 total confirmed, probable, or secondary outbreak associated cases
 - Hospitalizations: 121 (84%)
 - Deaths: 9 (6%)
 - Primarily in homeless individuals and IDU
- **Colorado**
 - 26 cases
 - Gender: 72% are male
 - Age: median 52 years
 - Primarily in MSM, second cluster in females who consumed smoothies
- **New York City**
 - 16 cases
 - Primarily in MSM
 - Linked to HAV strains circulating in Europe



Summary

Summary - I

- **Hepatitis A vaccine is largely responsible for the marked reduction in hepatitis A cases**
- **Increasing proportion of adults in United States are susceptible to hepatitis A**
 - Reduced exposure to HAV early in life
 - Significant decreases in anti-HAV seroprevalence in older adults (≥ 40 years)
 - Low 2-dose vaccination coverage exists in adults, including high risk adults (e.g., travelers -18.8%, chronic liver disease -18.2%)
 - Morbidity and mortality increases with age
 - Mean age of persons hospitalized for hepatitis A has increased significantly from 2002-2003 to 2010-2011
 - Hospitalization rates for reported hepatitis A cases increased from 2005 to 2011

Summary - II

- **Suboptimal hepatitis A vaccination 1 and 2-dose coverage among young children**
- **No routine hepatitis A vaccine recommendation for adolescents or adults**
- **HAV remains endemic in many areas of the world**
 - Risk for travelers to intermediate, high endemic countries
 - Risk for consumption of imported HAV contaminated food from global sources
 - Herd immunity does not protect against foodborne exposure

For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

