Hepatitis A Vaccine Background

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Advisory Committee on Immunization Practices

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Outline

- Epidemiology
- Vaccine background
- Vaccine recommendations
- 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)

Number of cases

Year


13,397 10,616 8,795 7,653 5,683 4,488 3,579 2,979 2,585 1,987 1,670 1,398 1,562 1,781 1,239 1,390

Surveillance for Viral Hepatitis – United States, 2015;

Source: CDC, National Notifiable Diseases Surveillance System (NNDSS)
Rates of Reported Acute Hepatitis A Cases United States, 1966-2015

1971: 59,606 cases, Rate = 28.9
1996: Vaccine recommended
31,032 cases, Rate = 11.7
2015: 1,390 cases,
Rate = 0.4

1996-2011: 95.5% decrease in reported cases

*National Notifiable Diseases Surveillance System (NNDSS); Armstrong GL. Pediatrics 2007;119:e22-9*
Rates of Reported Acute Hepatitis A United States, 2007-2015

Healthy People 2020 Target:
0.3 cases per 100,000 population
2015 State Acute Hepatitis A Incidence Compared to Healthy People 2020 National Goal*

- At or below national goal
- Above national goal
- More than twice national goal
- Data unavailable

*National goal: 0.3 cases/100,000 population

Source: CDC, National Notifiable Diseases Surveillance System (NNDSS)
## Hospitalizations in Reported Cases of Hepatitis A — United States, 2009-2015

<table>
<thead>
<tr>
<th>Year</th>
<th>Hepatitis A cases reported</th>
<th>Availability of valid data† for hospitalization</th>
<th>Cases hospitalized§</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>2009</td>
<td>1,987</td>
<td>1,182</td>
<td>59.5</td>
</tr>
<tr>
<td>2010</td>
<td>1,670</td>
<td>1,020</td>
<td>61.1</td>
</tr>
<tr>
<td>2011</td>
<td>1,398</td>
<td>798</td>
<td>57.1</td>
</tr>
<tr>
<td>2012</td>
<td>1,562</td>
<td>1,022</td>
<td>65.4</td>
</tr>
<tr>
<td>2013</td>
<td>1,781</td>
<td>1,081</td>
<td>60.7</td>
</tr>
<tr>
<td>2014</td>
<td>1,239</td>
<td>757</td>
<td>61.1</td>
</tr>
<tr>
<td>2015</td>
<td>1,390</td>
<td>870</td>
<td>62.6</td>
</tr>
</tbody>
</table>

†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

Figure 3. Hepatitis A–related hospitalizations and hepatitis A–related deaths, by year—United States, 1999–2011. Data are from the National Notifiable Diseases Surveillance System [13].
Hepatitis A Deaths in the United States, 1990-2014

![Graph showing hepatitis A deaths from 1990 to 2014](image)

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

NHANES, National Health and Nutrition Examination Survey
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

<table>
<thead>
<tr>
<th>Vaccine*</th>
<th>Site and Age Group</th>
<th>Number in Trial</th>
<th>Vaccine Efficacy (95 % CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAQTA®, Merck, Sharpe, and Dohme (MSD)¹</td>
<td>New York 2-16 years</td>
<td>1,037</td>
<td>100% (85-100%)§</td>
</tr>
<tr>
<td>HAVRIX®, SmithKline Beecham (SKB)²</td>
<td>Thailand 1-16 years</td>
<td>38,157</td>
<td>94% (74-98%)</td>
</tr>
</tbody>
</table>

*Pediatric formulation
§Determined 6–18 months after dose 1

# Hepatitis A Vaccine Schedules

## TABLE 2. Licensed dosages of VAQTA®*

<table>
<thead>
<tr>
<th>Vaccine recipient's age</th>
<th>Dose (U)†</th>
<th>Vol. (mL)</th>
<th>No. doses</th>
<th>Schedule (mos)§</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 mos–18 yrs</td>
<td>25</td>
<td>0.5</td>
<td>2</td>
<td>0, 6–18</td>
</tr>
<tr>
<td>&gt;19 yrs</td>
<td>50</td>
<td>1.0</td>
<td>2</td>
<td>0, 6–18</td>
</tr>
</tbody>
</table>

*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®*

<table>
<thead>
<tr>
<th>Vaccine recipient's age</th>
<th>Dose (EL.U.)†</th>
<th>Vol. (mL)</th>
<th>No. doses</th>
<th>Schedule (mos)§</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 mos–18 yrs</td>
<td>720</td>
<td>0.5</td>
<td>2</td>
<td>0, 6–12</td>
</tr>
<tr>
<td>&gt;19 yrs</td>
<td>1,440</td>
<td>1.0</td>
<td>2</td>
<td>0, 6–12</td>
</tr>
</tbody>
</table>

*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

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


TABLE 4. Licensed dosages of TWINRIX®

<table>
<thead>
<tr>
<th>Vaccine recipient’s age</th>
<th>Dose (hepatitis A/ hepatitis B)</th>
<th>Vol. (mL)</th>
<th>No. doses</th>
<th>Schedule (mos)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥18 yrs</td>
<td>720 EL.U.$/20 µg</td>
<td>1.0</td>
<td>3</td>
<td>0, 1, 6</td>
</tr>
</tbody>
</table>

*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.
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.
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.

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

MMWR 2006;55(RR-7)
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

MMWR 1996;45(RR-15); MMWR 1999;48(RR-12); MMWR 2006;55(RR-7)
Hepatitis A Vaccine Coverage

2014: 57.5%

2015
HepA ≥ 1-dose = 85.8%
HepA ≥ 2-dose = 59.6%

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

- 19-49 yrs, Total
- 19-49 yrs, Travel*
- 19-49 yrs, No Travel**
- 19-49 yrs, CLD^*

*Traveled outside the U.S. to countries other than Japan, Australia, New Zealand, Canada or the other countries of Europe since 1995
**No travel outside the U.S. to countries other than Japan, Australia, New Zealand, Canada or the other countries of Europe since 1995
^2014 data

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

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

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)

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.