



Hepatitis A Vaccines

Noele Nelson, MD, PhD, MPH

CDC Lead, ACIP Hepatitis Vaccines Work Group

Advisory Committee on Immunization Practices

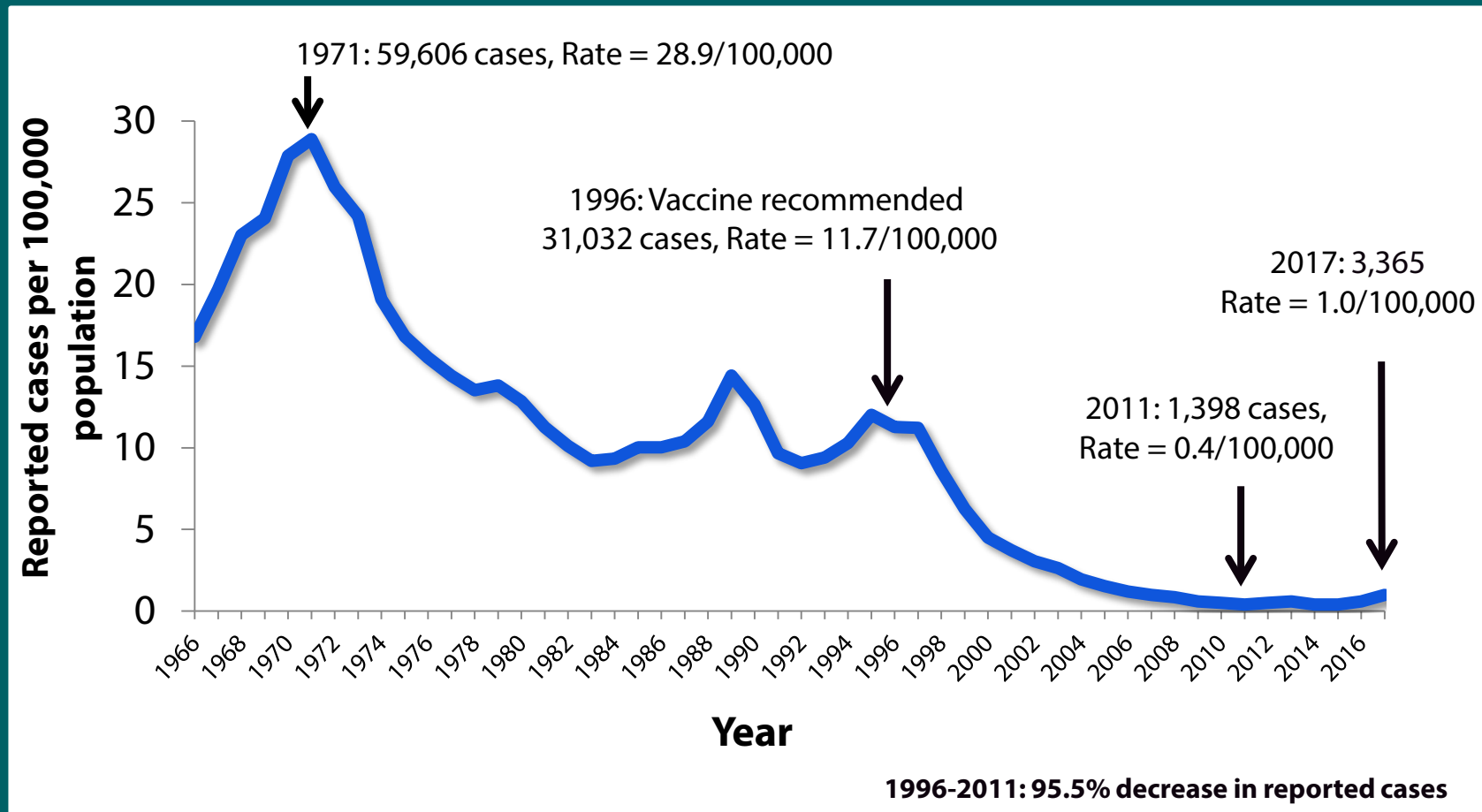
June 27, 2019

Outline

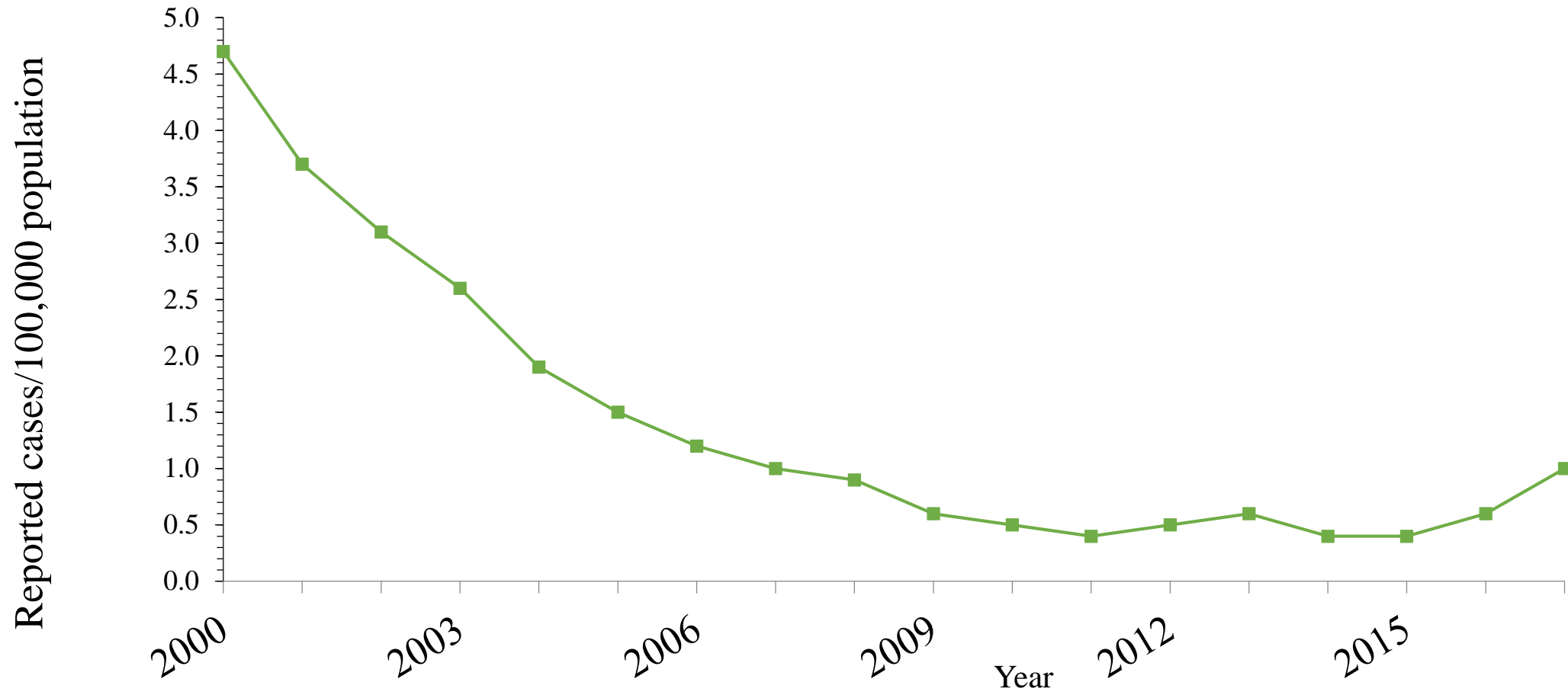
- Hepatitis A virus epidemiology
- Hepatitis A (HepA) vaccines
- Evidence to Recommendation Framework for catch-up HepA vaccination
- Evidence to Recommendation Framework for persons with HIV as a risk group for severe hepatitis A virus (HAV) infection (Review)
- Pregnancy
- Clotting Factor Disorders
- Proposed HepA vaccine recommendations

Epidemiology

Rates of Reported Acute Hepatitis A Cases — United States, 1966-2017

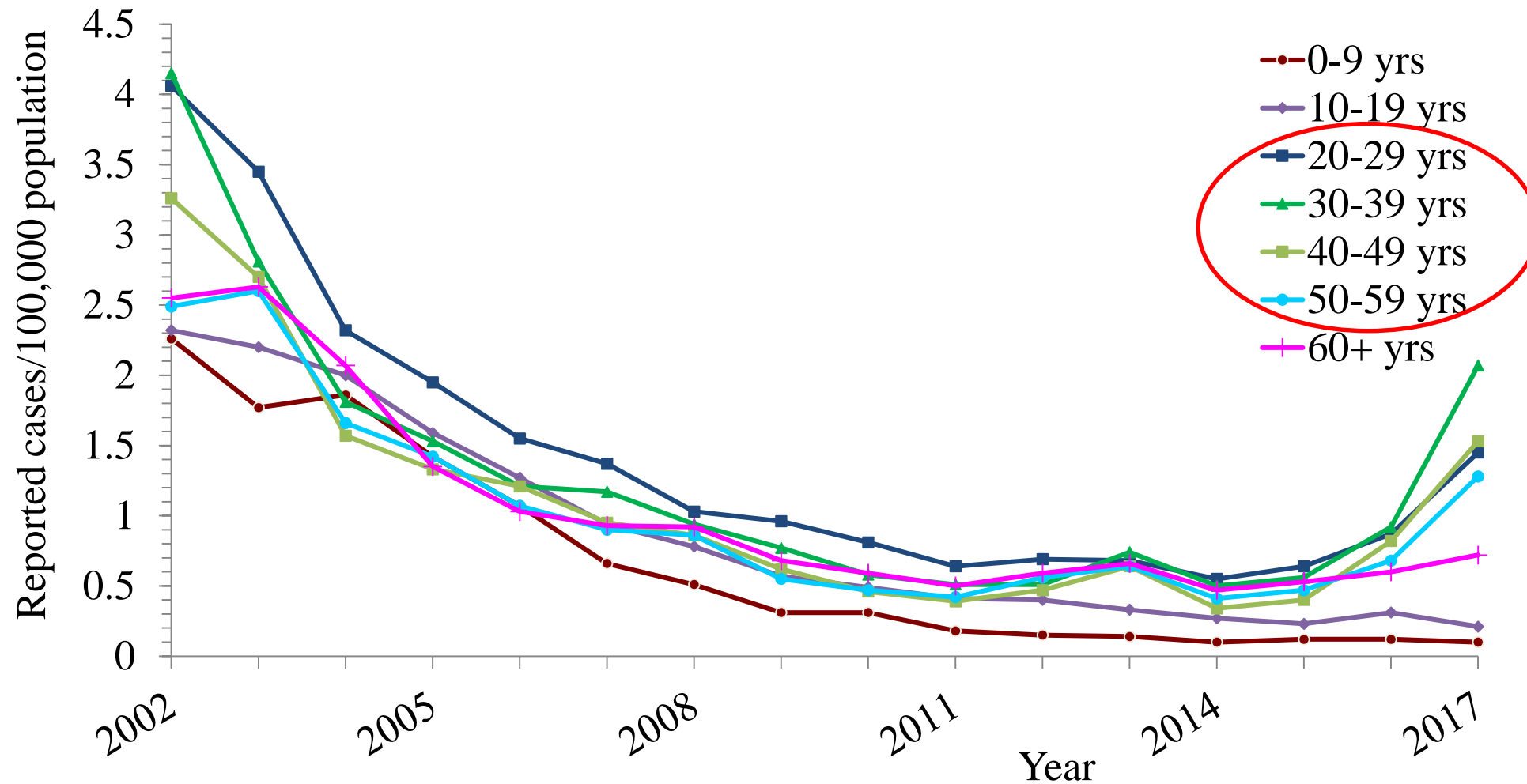


Rates of Reported Acute Hepatitis A Cases — United States, 2000-2017



Source: CDC, National Notifiable Diseases Surveillance System; Pre-Decisional: for federal use only; not for distribution.

Rates of Reported Acute Hepatitis A, by Age Group — United States, 2002-2017

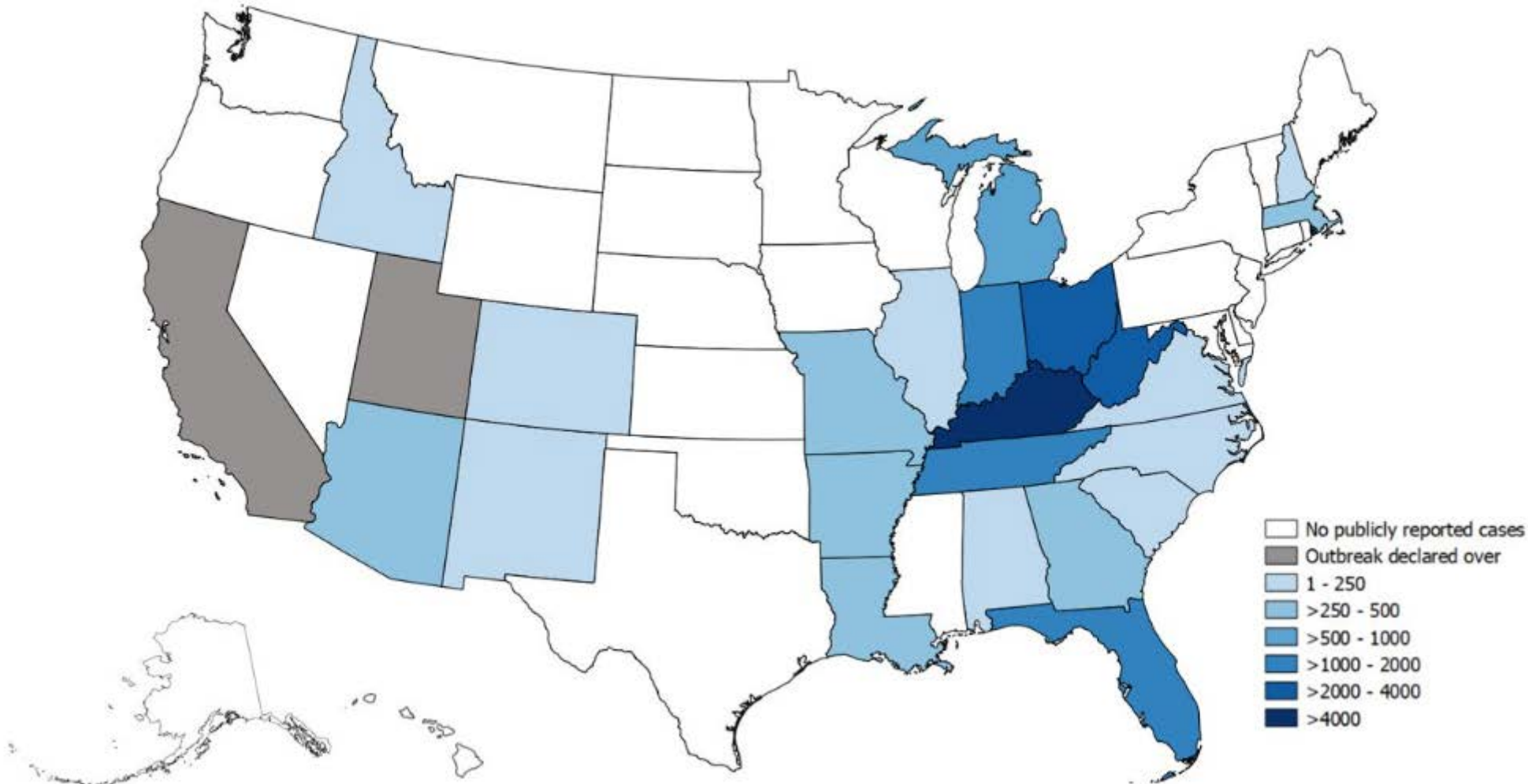


Source: CDC, National Notifiable Diseases Surveillance System.

Pre-Decisional; for federal use only; not for distribution.

Widespread Outbreaks of Hepatitis A across the United States: 2016-Present

State-Reported Hepatitis A Outbreak Cases as of June 21, 2019



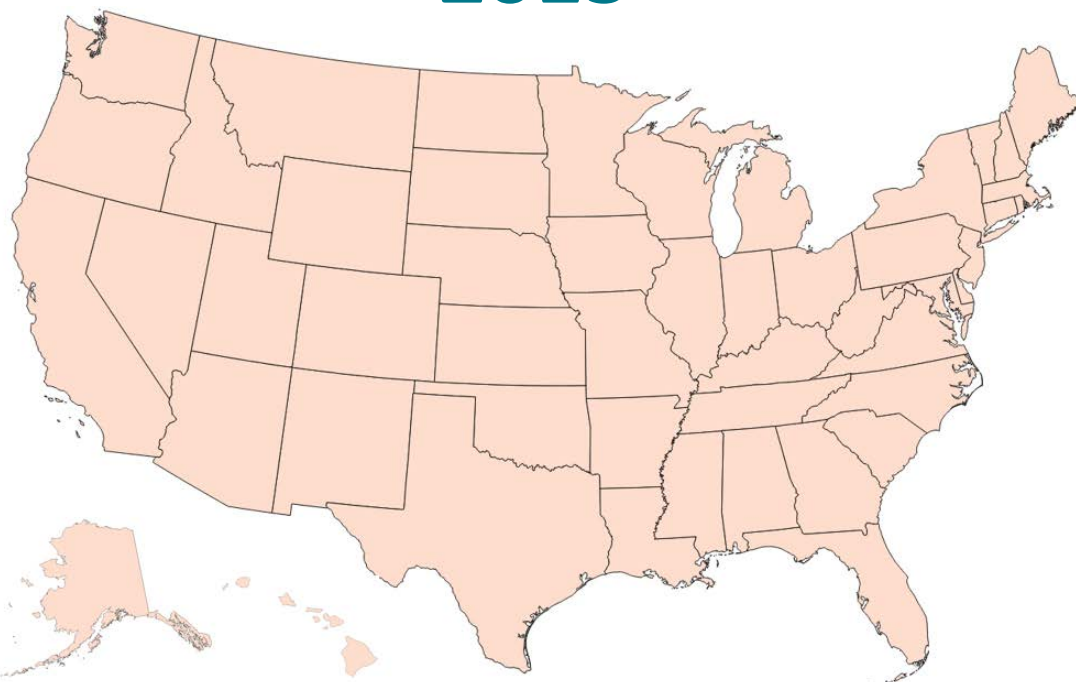
At A Glance

Since the outbreaks were first identified in 2016, 24 states have publicly reported the following as of June 21, 2019

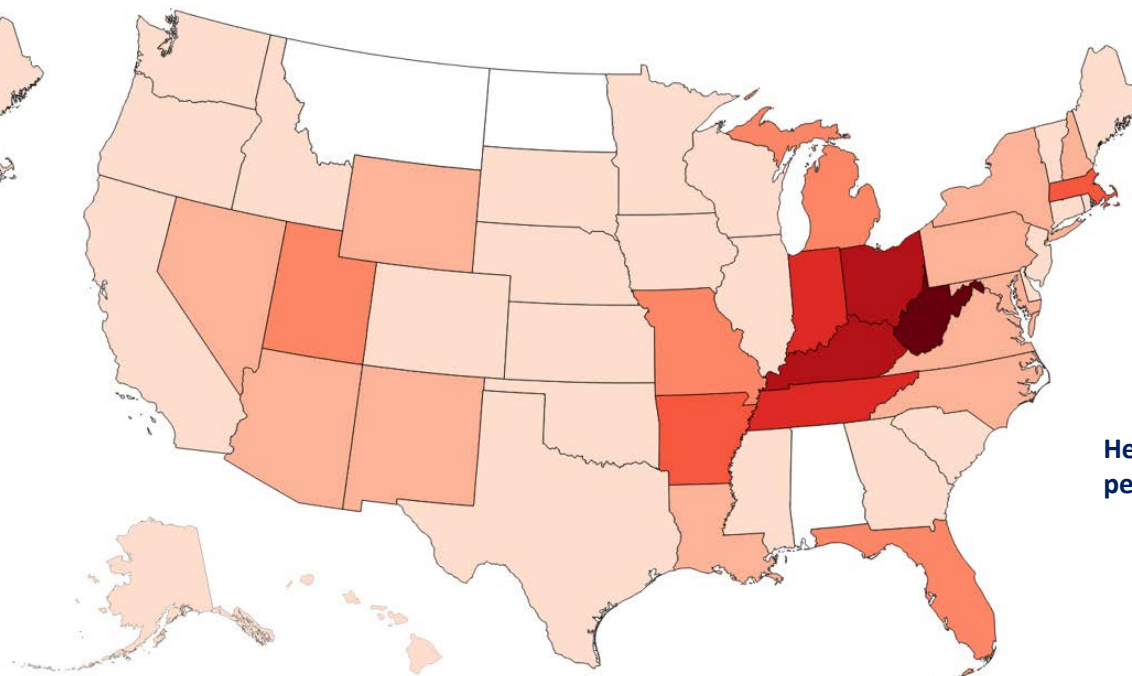
- Cases: 20,512
- Hospitalizations: 11,776 (57%)
- Deaths: 194

Hepatitis A Incidence – United States

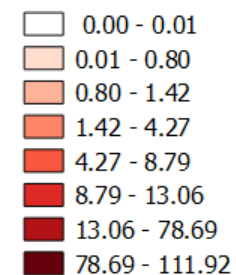
2015



2018*



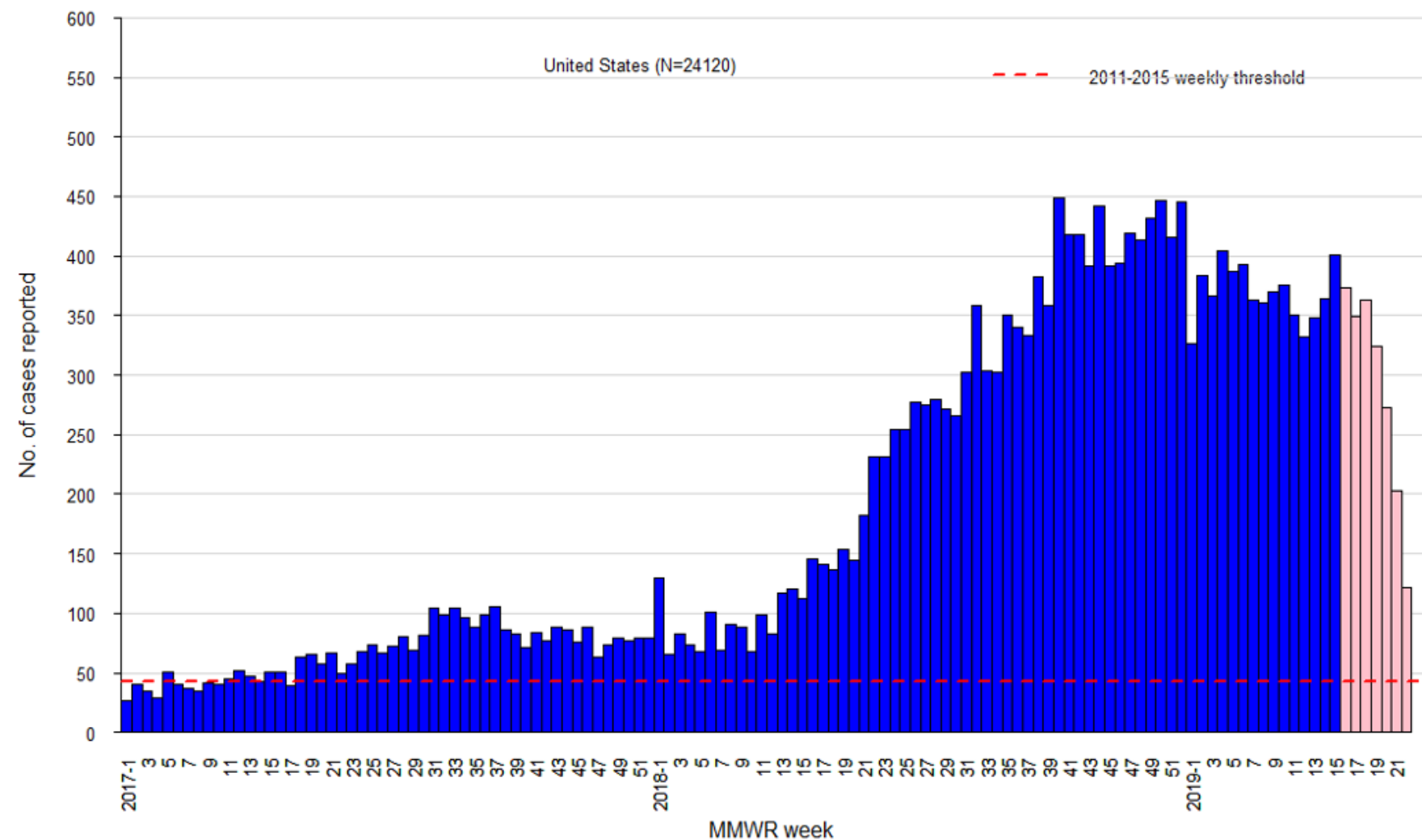
Hepatitis A incidence rate
per 100,000 population



Data Sources: National Notifiable Diseases Surveillance (NNDSS), US Census Bureau

*2018 Data are preliminary

Reported Incident Hepatitis A Cases by MMWR Week, NNDSS — United States, 2017–Present



(LIGHT PINK BARS IN THIS AND SUBSEQUENT FIGURES INDICATES 7-WEEK PERIOD OF POTENTIAL SURVEILLANCE REPORTING LAG)

Epidemiology of Hepatitis A Infections

- **Asymptomatic children were associated with HAV transmission in past outbreaks**
- **Recent outbreaks now primarily affect adults, causing severe disease**
 - Hepatitis B, hepatitis C co-infection
 - Many cases among persons who use drugs or persons experiencing homelessness
 - Person-to-person contact
 - Crowding, poor hygiene
 - Estimated tens of millions of dollars in healthcare costs
 - Men who have sex with men (MSM)
- **Person-to-person spread is now the predominant mode of HAV transmission**
- **Sporadic foodborne outbreaks continue to occur**

Hepatitis A Vaccines

Vaccines Used to Prevent Hepatitis A Virus (HAV) Infection

Vaccine	Trade name		Age (yrs)	Dosage	Route	Schedule	Booster
	(manufacturer)						
Hepatitis A vaccine, inactivated	HAVRIX		1–18	0.5 mL (720 ELU)	IM	0, 6–12 mo	None
	(GlaxoSmithKline)		≥19	1 mL (1,440 ELU)	IM	0, 6–12 mo	None
Hepatitis A vaccine, inactivated	VAQTA		1–18	0.5 mL (25 U)	IM	0, 6–18 mo	None
	(Merck & Co., Inc.)		≥19	1 mL (50 U)	IM	0, 6–18 mo	None
Combined hepatitis A - hepatitis B vaccine	TWINRIX		≥18 (primary)	1 mL (720 ELU HAV + 20 µg HBsAg)	IM	0, 1, 6 mo	None
	(GlaxoSmithKline)		≥18 (accelerated)	1 mL (720 ELU HAV + 20 µg HBsAg)	IM	0, 7, 21–30 d	12 mo

Abbreviations: ELU = ELISA units of inactivated HAV; HBsAg = hepatitis B surface antigen; IM = intramuscular; U = units of HAV antigen.

Hepatitis A Vaccines in 1995 and 1996

Efficacy of Hepatitis A Vaccines*

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

Immunogenicity of Hepatitis A Vaccines

- **All licensed vaccines are highly immunogenic when administered to children and adolescents according to multiple schedules**
 - 97%–100% of persons aged 2–18 years had protective levels of antibody 1 month after receiving the first dose
 - 100% had protective levels 1 month after the second dose, with high geometric mean titers (GMTs)
- **All licensed vaccines are highly immunogenic in persons aged >18 years when administered according to the recommended schedules**
 - Protective antibody levels were identified in 94%–100% of immunocompetent adults one month after the first dose
 - After the second dose, all persons had protective levels of antibody, with high GMTs

Clemens R et al. J Infect Dis 1995;171(Suppl 1):S44–9.

McMahon BJ, et al. J Infect Dis 1995;171:676–9.

Van Herck et al. Expert Review of Vaccines 2005; 4(4): 459-471.

Nalin DR. VAQTA™; Drugs of the Future 1995;20:24–9.

Sharapov et al. Hepatology, 2012; 56: 516–522.

Immunogenicity – Long-term Protection

- Anti-HAV has been shown to persist in vaccine recipients for at least 22 years in adults administered inactivated vaccine as children with a three-dose schedule¹
- At least 20 year anti-HAV persistence was demonstrated among adults vaccinated with a two-dose schedule as adults²
- Detectable antibodies are estimated to persist for 40 years or longer based on mathematical modeling and anti-HAV kinetic studies^{2,3}
- Protection following natural infection is lifelong and may also be following vaccination

1. Mosites, E, et al. *J Med Virol*. 2018; 90: 1418– 1422.; 2. Theeten H, et al. *Vaccine*. 2015 Oct 13;33(42):5723-7.

3. Hens N, et al. *Vaccine*. 2014;32(13):1507-1513.

Hepatitis A Vaccine Safety

- In pre-licensure trials, adverse reactions to HAVRIX, VAQTA and TWINRIX were mostly injection site reactions and mild systemic reactions
- Postmarketing surveillance for adverse events following receipt of HepA vaccines performed primarily by two systems in the U.S.: the Vaccine Adverse Event Reporting System (VAERS) and the Vaccine Safety Datalink (VSD)
 - No unusual or unexpected safety patterns observed for any HepA vaccines licensed in the U.S.

ACIP Hepatitis A Vaccine Recommendations

■ Targeted vaccination, 1996-1999

— 1996

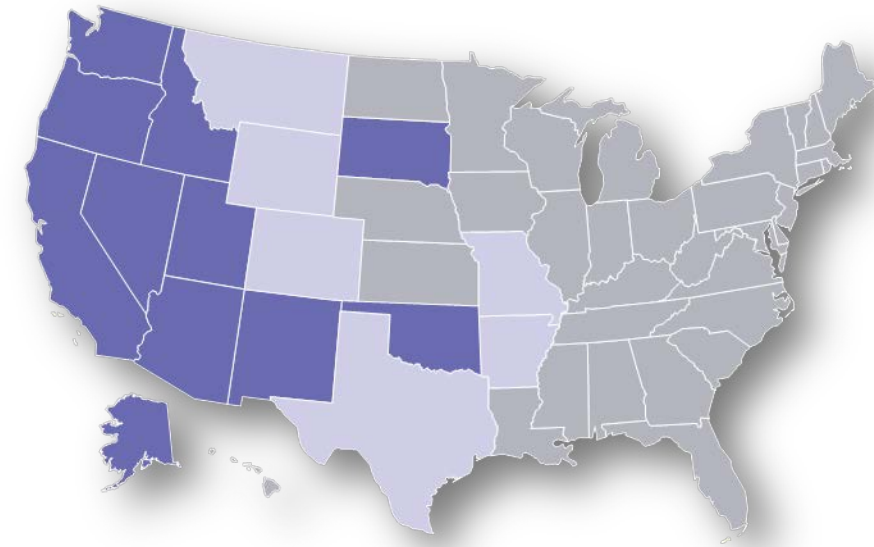
- Children at age 2 years in communities with high rates of disease
- Children at age 2 years and older children in outbreaks

— 1999

- Recommended in 11 states with rates 2x the national average
- Considered in 6 states with rates above the national average

■ Routine vaccination, 2006

- Universal early childhood vaccination
 - 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



ACIP Hepatitis A Vaccine Recommendations

Groups at increased risk of HAV or severe HAV disease

- Persons traveling
- Men who have sex with men
- Persons who use injection and non-injection drugs
- ~~Persons with clotting factor disorders~~
- Persons with occupational risk for infection
- Persons who anticipate close personal contact with an international adoptee
- Persons experiencing homelessness
- Persons with chronic liver disease
- **Persons with HIV**

Hepatitis A Vaccine Coverage, United States, 2017

■ Children¹

- 59.7% for children age 19-35 months, ≥ 2 doses
- 86.0% for children age 19-35 months, ≥ 1 dose

■ Adolescents²

- 68.4% for adolescents age 13-17 years, ≥ 2 doses
- 77.2% for adolescents age 13-17 years, 1 dose

■ Adults³

- 10.9% for adults ≥ 19 years, ≥ 2 doses; Travelers, 17.7%; Chronic liver disease, 20.8%
- 15.7% for adults 19-49 years, ≥ 2 doses; Travelers, 22.2%; Chronic liver disease, 25.1%
- 6.1% for adults ≥ 50 years, ≥ 2 doses

1. Hill HA, et al. MMWR 2018;66:1171–1177.

2. Unpublished data from Assessment Branch/ISD/NCIRD/CDC – Not for Distribution

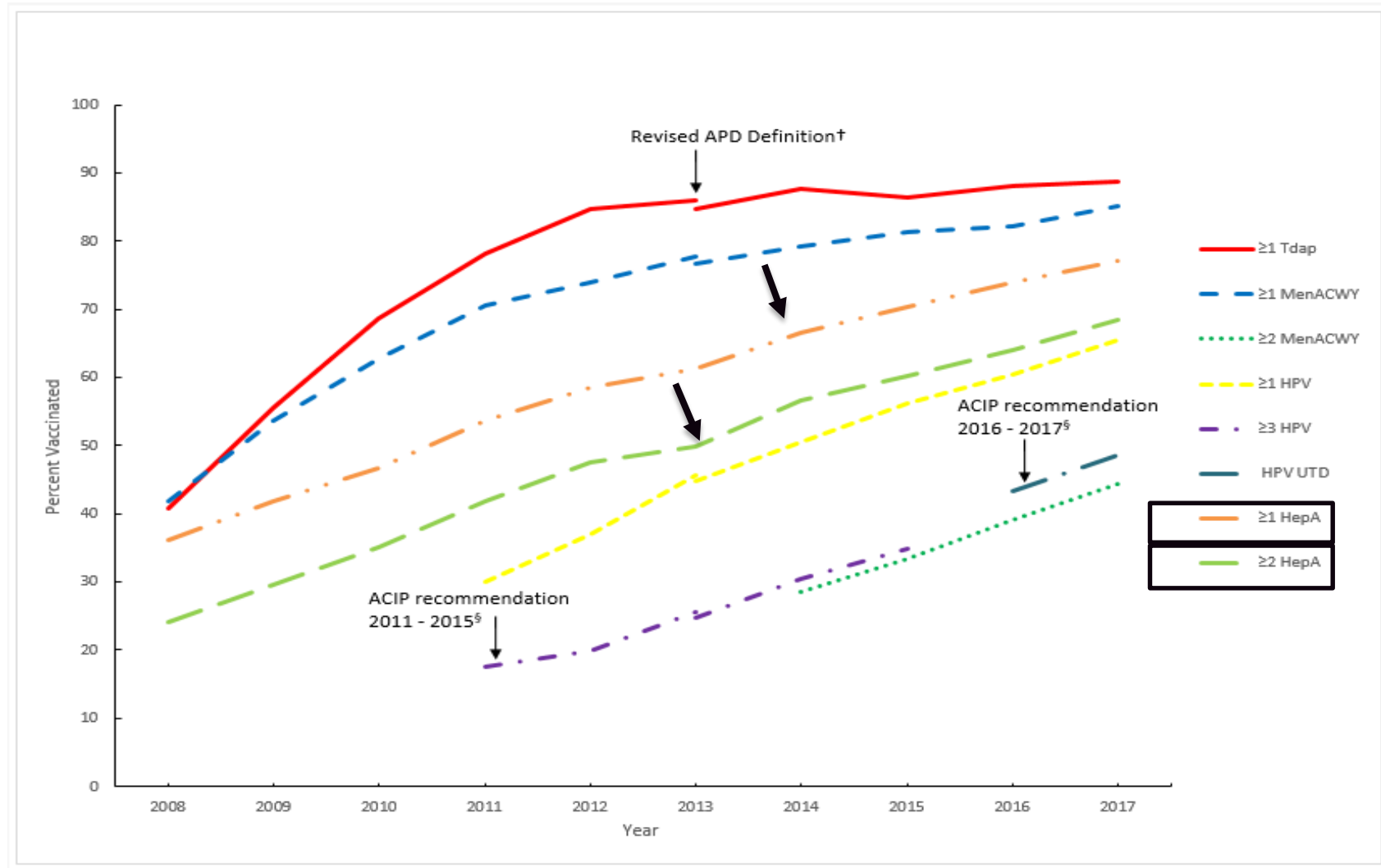
3. Vaccination Coverage Among Adults in the United States, National Health Interview Survey, 2017.

<https://www.cdc.gov/vaccines/imz-managers/coverage/adultvaxview/pubs-resources/NHIS-2017.html#box2>

Estimated Vaccination Coverage with Selected Vaccines and Doses* among Adolescents Aged 13-17 Years, by Survey Year — National Immunization Survey-Teen, United States, 2008-2017[†]

Abbreviations:

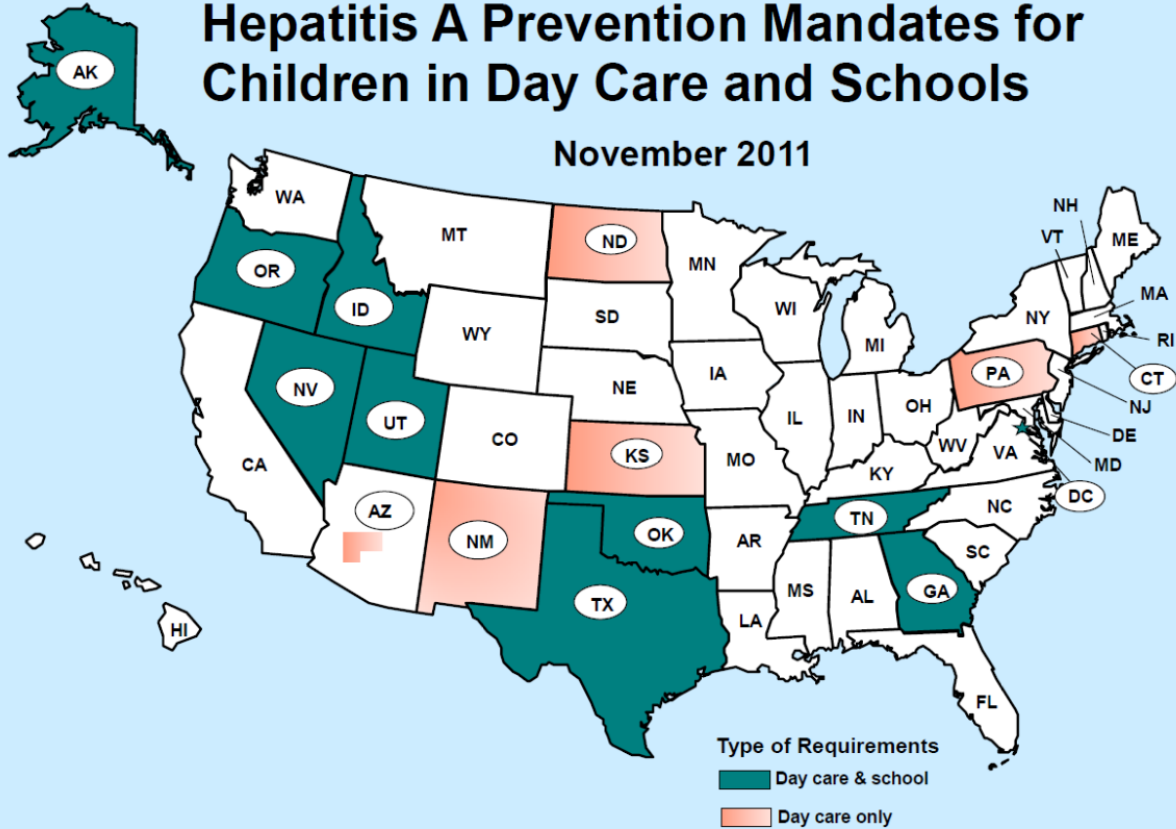
Tdap = tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine;
MenACWY = quadrivalent meningococcal conjugate vaccine;
HPV = human papillomavirus; APD = adequate provider data.



State Requirements for Hepatitis A Vaccine

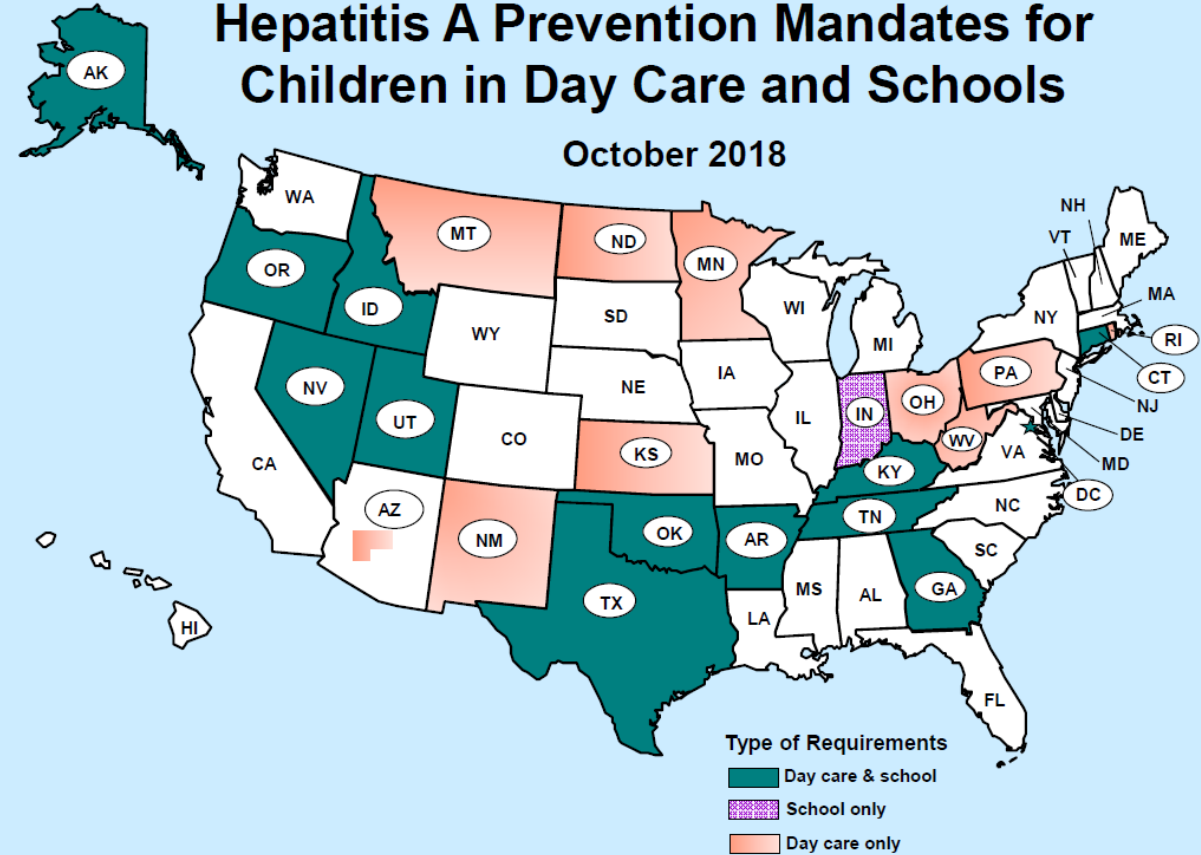
Hepatitis A Prevention Mandates for Children in Day Care and Schools

November 2011



Hepatitis A Prevention Mandates for Children in Day Care and Schools

October 2018



Catch-up Hepatitis A Vaccination

Proposed Routine Recommendations for Children

- **ACIP recommends hepatitis A vaccination for all children aged 12-23 months [Current]**
- **ACIP recommends that all children and adolescents aged 2 through 18 years who have not previously received hepatitis A vaccine be vaccinated at any age (i.e., children and adolescents are recommended for catch-up vaccination) [Proposed]**

Policy question:

Should hepatitis A catch-up vaccination be recommended for children aged 2-18 years?

Population	Children aged 2-18 years
Intervention	Hepatitis A vaccination (HepA vaccine series)
Comparison	Hepatitis A vaccination based on clinical decision making
Outcomes of interest	<ul style="list-style-type: none">• Hepatitis A infection• Adverse events

Criteria 1: Is the problem of public health importance?

WORK GROUP JUDGEMENTS

☐ No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☒ Yes | ☐ Varies

EVIDENCE

- **Incidence:** The rate of reported acute hepatitis A cases in 2017 was 1.0 case/100,000 population (Unpublished, CDC)
 - 1.45 cases/100,000 population among young adults aged 20-30 years (unpublished, CDC)
 - 0.87 cases/ 100,000 population in 2016 (NNDSS)
 - 2.07 cases/100,000 population among adults aged 30-39 years (unpublished, CDC)
 - 0.92 cases/ 100,000 population in 2016 (NNDSS)
 - Highest rate and more than double the 2016 rate for this age group
- **HepA vaccine coverage:** In 2017, national hepatitis A vaccine ≥ 2 dose coverage was 68.4% for adolescents age 13-17 years; 1 dose coverage was 77.2% (Unpublished, CDC)
 - Among adolescents age 13-17 living in states where routine vaccination at 12-23 months was first recommended in 2006, coverage is only slightly lower than the total cohort, 61% for ≥ 2 doses and 71% with ≥ 1 dose, despite catch-up vaccination being based on shared clinical decision making.

Criteria 1: Is the problem of public health importance?

WORK GROUP JUDGEMENTS

☐ No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☒ Yes | ☐ Varies

Additional Information

- **HAV outbreaks:** Since the outbreaks were first identified in 2016, as of June 21, 2019, 24 states have publicly reported the following: Cases: 20,512; Hospitalizations: 11,776 (57%); Deaths: 194
<https://www.cdc.gov/hepatitis/outbreaks/2017March-HepatitisA.htm>
 - Among states with publically available case information by age group, the median age of HAV cases is in the 30s, with a substantial percentage of cases aged in their 20s and 40s
- **HepA vaccine coverage:**
 - Vaccinating adolescents who could be at risk for HAV infection at present or in the future (e.g., persons who use drugs, persons experiencing homelessness, travelers) can have an impact on improving coverage among young adults

Criteria 2: How substantial are the desirable anticipated effects?

WORK GROUP JUDGEMENTS

☐ Minimal ☐ Small ☐ Moderate ☒ Large ☐ Don't know | ☐ Varies

EVIDENCE

- HAVRIX and VAQTA are highly immunogenic when administered to children and adolescents
 - 97%–100% of persons aged 2–18 years had protective levels of antibody 1 month after receiving the first dose, and 100% had protective levels 1 month after the second dose, with high GMTs (Clemens 1995, Nalin 1995, McMahon Williams 1995, Asher 1999, Balcarek 1995, Horng 1993, Findor 1996, Sharapov 2012, Van Herck 2005)
 - Anti-HAV has been shown to persist for at least 22 years in adults administered inactivated vaccine as children (aged 3-6 years) (Plumb 2017, Mosites 2018)
- Mathematical modelling based on persons vaccinated as adults predicted that seropositive anti-HAV levels would persist in $\geq 95\%$ vaccinees at year 30 and $\geq 90\%$ at year 40 (Theeten 2015)
- Cellular immunity has been shown to promote HAV-specific cellular immunity similar to that induced by natural infection (Melgaco 2015)

Criteria 2: How substantial are the desirable anticipated effects?

WORK GROUP JUDGEMENTS

☐ Minimal ☐ Small ☐ Moderate ☒ Large ☐ Don't know | ☐ Varies

■ Additional Information:

- Catch-up vaccination is a way to increase herd immunity and ensure the percentage of children/adolescents who miss vaccination as scheduled or who were born outside of the routine vaccination cohort are protected
- Since the implementation of risk-based vaccination in adults has been poor, catch-up vaccination will more rapidly increase the proportion of adults with risk factors who are protected
- HepA vaccination in childhood has demonstrated long-term protection

Criteria 3: How substantial are the undesirable anticipated effects?

WORK GROUP JUDGEMENTS

☒ **Minimal** ☐ Small ☐ Moderate ☐ Large ☐ Don't know | ☐ Varies

EVIDENCE:

- Rates of adverse events following HAVRIX, VAQTA and TWINRIX vaccination were similar to those seen with separately administered vaccines
- No unusual or unexpected safety patterns were observed in VAERS for any HepA vaccines (unpublished, CDC 2016)

Additional Information:

- Limited data from studies conducted among adults indicate that simultaneous administration of hepatitis A vaccine with diphtheria, poliovirus (oral and inactivated), tetanus, typhoid (both oral and IM), cholera, Japanese encephalitis, rabies, or yellow fever vaccines does not decrease the immune response to either vaccine or increase the frequency of reported adverse events (Bienzle 2002, Jong 2002, Gil 1996)

Criteria 4: Do the desirable effects outweigh the undesirable effects?

WORK GROUP JUDGEMENTS

☒ **Favors intervention** ☐ Favors comparison ☐ Favors both ☐ Favors neither | ☐ Unclear

EVIDENCE

- HepA vaccination affords long-term protection against HAV infection
- Disease severity increases in older persons and persons who are immunocompromised, have chronic liver disease or other underlying health conditions
- Over 20 years of safety monitoring have shown no known safety concerns
- Earlier HepA vaccination among healthy children/adolescents provides protection against HAV infection before persons develop increased risk for HAV infection or HAV-associated complications

Criteria 5: What is the overall certainty of this evidence for the critical outcomes?

WORK GROUP JUDGEMENTS

Effectiveness of the intervention

☒ No included studies | ☐ Very low ☐ Low ☐ Moderate ☐ High

WORK GROUP JUDGEMENTS

Safety of the intervention

☒ No included studies | ☐ Very low ☐ Low ☐ Moderate ☐ High

Additional Information

- GRADE was not used to evaluate the evidence
 - HepA vaccine has been recommended for administration to children since 1996
 - HepA vaccine has been recommended for catch-up vaccination based on shared clinical decision-making since 2006
 - The efficacy and safety of HepA vaccines has been evaluated and well-documented
 - There are no known safety concerns with HepA vaccines

Criteria 6: Does the target population feel that the desirable effects are large relative to undesirable effects?

WORK GROUP JUDGEMENTS

☐ No ☐ Probably No ☐ Uncertain ☒ **Probably Yes** ☐ Yes | ☐ Varies

EVIDENCE

- Substantial catch-up implementation and acceptance despite a recommendation based on shared clinical decision-making
 - In 2017, HepA coverage among adolescents aged 13-17 years nationally was 68.4% (≥ 2 doses), and 77.2% (1-dose), compared to 2008 coverage of 25.3% (≥ 2 doses) and 36.2% (1-dose); (Unpublished CDC, Nelson 2018)
- Clear demand and preference for protection against hepatitis A
 - Although specific studies of desirability among older children or parents for hepatitis A vaccine have not been conducted, almost 80% of adolescents had initiated the hepatitis A vaccine series by 2017 (even without a recommendation for routine catch-up vaccination)

Additional Information

- The HepA vaccine adolescent 2-dose coverage is comparable or greater than other vaccines with a routine catch-up schedule which provides evidence of acceptability by the target population

Criteria 7: Is there important uncertainty about or variability in how much people value the main outcomes?

WORK GROUP JUDGEMENTS

- ☐ Important uncertainty or variability ☐ Possible important uncertainty or variability
- ☒ **Probably no important uncertainty or variability** ☐ no important uncertainty or variability |
- ☐ No known undesirable outcomes

EVIDENCE

- The high coverage rate, despite this recommendation being based on shared clinical decision making, provides strong and consistent evidence that most parents/patients believe that it is important (as important as some routinely recommended vaccines)

Criteria 8: Is the intervention acceptable to key stakeholders?

WORK GROUP JUDGEMENTS

☐ No ☐ Probably No ☐ Uncertain ☒ **Probably Yes** ☐ Yes | ☐ Varies

EVIDENCE

- CDC currently does not have a routine catch up recommendation for children age 2-18 years, yet ~44% of states have introduced mandates for daycare or daycare plus school or school alone (Immunize.org)
 - These states independently choose to achieve higher rates of vaccine coverage for children
 - Increase in states with mandates from 28% in 2011 to 44% in 2018
- HAV multistate outbreak response has led to growing level of awareness among all clinicians, states, and the general public about the value of a vaccine that provides lifelong protection
<https://www.cdc.gov/hepatitis/outbreaks/2017March-HepatitisA.htm>
 - Educational communications and two Health Alert Network advisories have been disseminated and accepted among these groups

Additional Information

- The HepA adolescent 2-dose coverage is comparable or greater than other vaccines with a routine catch-up schedule which provides evidence of acceptability by key stakeholders population

Criteria 9: Is the intervention a reasonable and efficient allocation of resources?

WORK GROUP JUDGEMENTS

☐ No ☐ Probably No ☐ Uncertain ☒ **Probably Yes** ☐ Yes

EVIDENCE

- Cost-effectiveness model used to assess nationwide routine hepatitis A vaccination was adapted to assess the cost-effectiveness of catch-up HepA vaccination among unvaccinated and partially vaccinated children compared with unvaccinated children (Hankin-Wei 2016)
- **Findings:** Over the lifetime of the cohort, catch-up vaccination would reduce the total number of infections relative to the baseline by 741 while increasing doses of vaccine by 556,989
- Across age-cohorts, the cost-effectiveness of catch-up vaccination was most favorable at age 12 years, due to splitting administration costs with other vaccines, resulting in an incremental cost-effectiveness ratio (ICER) of \$189,000 per QALY gained
- Catch-up was more cost-effective when it is assumed to replace more adult vaccination
 - Targeting children in late adolescence: higher probability of symptomatic disease among older children, less discounting of future costs of disease and less delay in averting adult vaccination costs
- The impact of vaccination on the incremental cost-effectiveness ratio (ICER) was most sensitive to the discount rate (3%), followed by the rate of adult vaccination

Criteria 9: Is the intervention a reasonable and efficient allocation of resources?

WORK GROUP JUDGEMENTS

☐ No ☐ Probably No ☐ Uncertain ☒ **Probably Yes** ☐ Yes

Additional Information

- **Limitations:** model output is based on hepatitis A incidence from 2008-2012; conclusions are strongly tied to factors such as vaccine uptake and disease transmission patterns which may change over time, altering future cost; model excluded herd immunity effects of vaccination
 - The incremental costs of catch-up now would be more favorable, because adolescent vaccination coverage rates are much higher than when this study was conducted
 - 2009, 1 dose: 42%, 2-dose: 29.5%
 - 2017, 1 dose: 77.2%, 2-dose 68.5%
 - Higher HAV incidence overall today due to ongoing multistate outbreaks
 - 2012, 0.5 cases/100,000 population
 - 2017, 1.0 case/100,000 population

Criteria 9: Is the intervention a reasonable and efficient allocation of resources?

WORK GROUP JUDGEMENTS

☐ No ☐ Probably No ☐ Uncertain ☒ **Probably Yes** ☐ Yes

Additional Information

Cost Example:

Targets: 80% completion, 90% initiation

Assumptions:

- 1) 2017 coverage rates apply to all (younger adolescents have higher coverage)
- 2) 100% of 1-dose recipients complete series when calculating cost of 80% completion
- 3) Assumed 50% of vaccination cost is at the private price and 50% at the CDC price
- 4) Vaccine cost: \$32.89 Private; \$20.52 CDC

Adolescent population aged 12-17 years, 2017: 25,062,399

HepA Vaccination Coverage	2017	To reach target
1 dose, age 13-17y	77.2%	12.8% need 1 dose to reach 90%
2 dose, age 13-17y	68.4%	8.8% need one more dose; 2.8% need two doses to reach 80%

Coverage (using total 12-17 population and 2017 coverage)	Additional 1-dose vaccinees	Additional 2-dose vaccinees	Cost - Private (50%)	Cost - CDC (50%)
90% 1 dose age 12-17	3,207,987	0	\$52,755,347	\$32,913,947
80% 2 dose age 12-17	2,205,491	701,747	\$59,349,766	\$37,028,191

Criteria 10: Is the intervention feasible to implement?

WORK GROUP JUDGEMENTS

☐ No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☒ Yes | ☐ Varies

EVIDENCE

- Of the 30 registries American Immunization Registry Association (AIRA) were able to query to test forecasting algorithms, 27 already routinely forecast hepatitis A vaccine as being due for an 18 year old who has never been vaccinated
 - All 30 algorithms forecast the 2nd dose in any 18 year old who has had one dose
 - Therefore, 27 of 30 tested registries would not have to change to implement routine catch-up

Additional Information

- Routine HepA vaccine catch-up already exists in states with school mandates
- In New York City, all children and adolescents not previously vaccinated should receive the two-dose hepatitis A vaccine series by their 19th birthday for lifetime protection (NYC Bureau of Health)
- Opportunities to administer HepA vaccine to adolescents concurrently with vaccines protecting against other infections, such as HPV and meningitis

Criteria 10: Is the intervention feasible to implement?

WORK GROUP JUDGEMENTS

☐ No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☒ Yes | ☐ Varies

Additional Information:

- A 2014 survey found that if ACIP made a recommendation for catch-up HepA vaccination at health maintenance visits for all children 2 to 18 years of age, 96% of pediatricians and 79% of family medicine physicians reported it would be very feasible to routinely assess HepA vaccination status and vaccinate children/adolescents who were not fully vaccinated; an additional 4% and 19%, respectively, indicated it would be moderately feasible (Nelson 2017)
 - Since then, increased education and awareness among providers and the public due to the ongoing HAV outbreaks, have likely decreased barriers to vaccination

Balance of consequences

WORK GROUP JUDGEMENTS

- ☐ Undesirable consequences *clearly outweigh* desirable consequences in most settings
- ☐ Undesirable consequences *probably outweigh* desirable consequences in most settings
- ☐ The balance between desirable and undesirable consequences *is closely balanced or uncertain*
- ☒ **Desirable consequences *probably outweigh* undesirable consequences in most settings**
- ☐ Desirable consequences *clearly outweigh* undesirable consequences in most settings
- ☐ There is insufficient evidence to determine the balance of consequences

Is there sufficient information to move forward with a recommendation?

☒ Yes

☐ No

Policy Options for ACIP Consideration

- ☐ ACIP does not recommend the intervention
- ☐ ACIP recommends the intervention for individuals based on shared clinical decision-making
- ☒ ACIP recommends the intervention

Proposed Routine Recommendations for Children

- **ACIP recommends hepatitis A vaccination for all children aged 12-23 months [Current]**
- **ACIP recommends that all children and adolescents aged 2 through 18 years who have not previously received hepatitis A vaccine be vaccinated at any age (i.e., children and adolescents are recommended for catch-up vaccination) [Proposed]**

References

- 37th Annual Meeting of the European Society for Paediatric Infectious Diseases; May 6-11, 2019; Ljubljana, Slovenia.
- Ashur Y, Adler R, Rowe M, Shouval D. Comparison of immunogenicity of two hepatitis A vaccines—VAQTA® and HAVRIX®—in young adults. *Vaccine* 1999;17:2290–6.
- Balcarek KB, Bagley MR, Pass RF, Schiff ER, Krause DS. Safety and immunogenicity of an inactivated hepatitis A vaccine in preschool children. *J Infect Dis* 1995;171(Suppl 1):S70–2.
- Clemens R, Safary A, Hepburn A, Roche C, Stanbury WJ, André FE. Clinical experience with an inactivated hepatitis A vaccine. *J Infect Dis* 1995;171(Suppl 1):S44–9.
- Dhankhar P, Nwankwo C, Pillsbury M, Lauschke A, Goveia MG, Acosta CJ, Elbasha EH. Public Health Impact and Cost-Effectiveness of Hepatitis A Vaccination in the United States: A Disease Transmission Dynamic Modeling Approach. *Value Health*. 2015 Jun;18(4):358-67. doi: 10.1016/j.jval.2015.02.004. Epub 2015 Apr 4. PubMed PMID:26091589
- Hepatitis A Vaccine Mandates for Children in Daycare Facilities, Elementary, and Secondary Schools.
<http://www.immunize.org/laws/hepa.asp>
- Horng YC, Chang MH, Lee CY, Safary A, Andre FE, Chen DS. Safety and immunogenicity of hepatitis A vaccine in healthy children. *Pediatr Infect Dis J* 1993;12:359–62.
- McMahon BJ, Williams J, Bulkow L, et al. Immunogenicity of an inactivated hepatitis A vaccine in Alaska Native children and Native and non-Native adults. *J Infect Dis* 1995;171:676–9.
- Melgaço JG, Morgado LN, Santiago MA, Oliveira JM, Lewis-Ximenez LL, Hasselmann B, Cruz OG, Pinto MA, Vitral CL. A single dose of inactivated hepatitis A vaccine promotes HAV-specific memory cellular response similar to that induced by a natural infection. *Vaccine*. 2015 Jul 31;33(32):3813-20. doi: 10.1016/j.vaccine.2015.06.099. Epub 2015 Jul 2. PubMed PMID:26144899.

References

- Mosites E, Gounder P, Snowball M, Morris J, Spradling P, Nelson N, Bulkow L, Bruce M, McMahon B. Hepatitis A vaccine immune response 22 years after vaccination. *J Med Virol*. 2018 Aug;90(8):1418-1422. doi: 10.1002/jmv.25197. Epub 2018 May 1. PubMed PMID:29663458.
- Nalin DR. VAQTA™: hepatitis A vaccine, purified inactivated. *Drugs of the Future* 1995;20:24–9.
- Nelson NP, Allison MA, Lindley MC, Brtnikova M, Crane LA, Beaty BL, Hurley LP, Kempe A. Physician Knowledge and Attitudes About Hepatitis A and Current Practices Regarding Hepatitis A Vaccination Delivery. *Acad Pediatr*. 2017 Jul;17(5):562-570.
- Nelson NP, Yankey D, Singleton JA, Elam-Evans LD. Hepatitis A vaccination coverage among adolescents (13-17 years) in the United States, 2008-2016. *Vaccine*. 2018 Mar 14;36(12):1650-1659. doi: 10.1016/j.vaccine.2018.01.090. Epub 2018 Feb 12. PubMed PMID:29449100; PubMed Central PMCID:PMC5895091.
- New York City Bureau of Immunization. <https://www1.nyc.gov/site/doh/health/health-topics/hepatitis-a.page>
- Plumb ID, Bulkow LR, Bruce MG, Hennessy TW, Morris J, Rudolph K, Spradling P, Snowball M, McMahon BJ. Persistence of antibody to Hepatitis A virus 20 years after receipt of Hepatitis A vaccine in Alaska. *J Viral Hepat*. 2017 Jul;24(7):608-612. doi: 10.1111/jvh.12676. Epub 2017 Feb 2. PubMed PMID:28092416.
- Sharapov UM, Bulkow LR, Negus SE, Spradling PR, Homan C, Drobeniuc J, Bruce M, Kamili S, Hu DJ, McMahon BJ. Persistence of hepatitis A vaccine induced seropositivity in infants and young children by maternal antibody status: 10-year follow-up. *Hepatology*. 2012 Aug;56(2):516-22. doi: 10.1002/hep.25687. Epub 2012 Jun 11. PubMed PMID:22371069.
- Theeten H, Van Herck K, Van Der Meeren O, Crasta P, Van Damme P, Hens N. Long-term antibody persistence after vaccination with a 2-dose Havrix (inactivated hepatitis A vaccine): 20 years of observed data, and long-term model-based predictions. *Vaccine*. 2015 Oct 13;33(42):5723-5727. doi: 10.1016/j.vaccine.2015.07.008. Epub 2015 Jul 16. PubMed PMID:26190091.
- Widespread outbreaks of hepatitis A across the United States. <https://www.cdc.gov/hepatitis/outbreaks/2017March-HepatitisA.htm>

Persons With HIV

Proposed Recommendation for Persons With HIV (PWHIV)

- **ACIP recommends that all persons with HIV aged ≥ 1 year be vaccinated with hepatitis A vaccine [Proposed]**

Policy Question

Should routine two-dose* vaccination to prevent hepatitis A virus infection be given to HIV-positive persons?

*Or three-dose when combination vaccine is used

Population	Adult HIV-positive persons regardless of another indication for vaccination
Intervention	Routine two-dose hepatitis A vaccination
Comparison	No routine two-dose hepatitis A vaccination
Outcomes of interest	<ul style="list-style-type: none">▪ Hepatitis A Infection▪ Mild Adverse Events▪ Serious Adverse Events

Background: Persons With HIV

- At the end of 2016, an estimated 1.1 million people aged 13 years and older had HIV infection in the United States¹
- When PWHIV are co-infected with HAV infection, they experience higher HAV viral loads and a prolonged duration of hepatitis A viremia than persons without HIV infection^{2,3}
 - HAV infection has the potential to increase HIV viral loads and HIV transmission
- PWHIV respond to HepA vaccine with a seroconversion rate of 48.5%-93.9% following a 2-dose monovalent vaccine schedule, and factors associated with a protective antibody response in PWHIV include a CD4 cell count >200 cells/mm³ and a low HIV RNA viral load^{4,5}

1) CDC. HIV Surveillance Supplemental Report 2019;24(1).

2) Puoti, M., et al. Semin Liver Dis (2012) 32(02): 103-113.

3) Gallego, M., et al. Journal of the International Association of Physicians in AIDS Care, vol. 10, no. 1, Jan. 2011, pp. 40–42.

4) Weissman, S. , Feucht, C. and Moore, B. A. (2006), Journal of Viral Hepatitis, 13: 81-86.

5) Mena, G et al. Human vaccines & immunotherapeutics vol. 11,11 (2015): 2582-98.

Diagnoses of HIV Infection, by Age, 2017, U.S. and 6 Dependent Areas

- In 2017, the number of new HIV diagnoses in the U.S. and 6 dependent areas was 38,739

Age (Years)	Number of Diagnoses of HIV Infection, 2017
13-14	25
15-19	1,723
20-24	6,416
25-29	7,755
30-34	5,678
35-39	4,365
40-44	3,032
45-49	3,006
50-54	2,729
55-59	1,918
60-64	1,108
65 and older	885

Diagnoses of HIV Infection by Transmission Category

- CDC classifies HIV diagnoses into transmission categories to which transmission may be attributed

Transmission Category	Adult and Adolescent Males	Adult and Adolescent Females	Total (%)
Male-to-male sexual contact	25,748	NA	25,748 (66.6)
Injection drug use	1,373	1,016	2,389 (6.2)
Male-to-male sexual contact and injection drug use ^a	1,252	NA	1,252 (3.2)
Heterosexual contact ^b	2,829	6,341	9,170 (23.7)
Other ^c	37	44	81 (0.2)

- 76% of ALL persons currently newly diagnosed with HIV have a risk factor for which HepA vaccine is already recommended (shown in red font)

^a Includes infections attributed to male-to-male sexual contact *and* injection drug use (men who reported both risk factors).

^b Heterosexual contact with a person known to have, or to be at high risk for, HIV infection.

^c Includes hemophilia, blood transfusion, perinatal exposure, and risk factor not reported or not identified.

What percentage of PWHIV do not have an existing risk factor for which HepA vaccine is recommended?



**MEDICAL
MONITORING
PROJECT**

Risk Factors for which HepA Vaccination is Recommended Among PWHIV, MMP, 2016

Risk Factor	Number	Weighted Percent	95% CI
MSM in past 12 months	1202	32.5	(30.3 - 34.6)
Non-injection drug use in past 12 months	1156	28.7	(26.0 - 31.5)
Injection drug use in past 12 months	114	2.4	(1.7 - 3.2)
Homeless in past 12 months	332	8.4	(7.3 - 9.5)
Chronic liver disease	601	15.0	(13.4 - 16.6)
Clotting factor disorder*	8	0.2*	(0.05 - 0.3)
Any of the above	2313	59.9	(57.3 - 62.4)
None of the above	1529	40.1	(37.6 - 42.7)

*CV>.3, estimate is unstable

Denominator is all records containing a diagnosis dataset

GRADE Summary

GRADE SUMMARY |

Outcome	Design (# studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Evidence type
BENEFIT						
Hepatitis A Infection	RCT (3)	No serious	No serious	Serious ¹	No serious	2
	Observational (19)	Serious	No serious	Serious ²	No serious	4
HARMS						
Mild Adverse Events	RCT (2)	No serious	No serious	No serious	No serious	1
	Observational (1)	No serious	No serious	No serious	No serious	3
Serious Adverse Events	RCT (2)	No serious	No serious	No serious	Very Serious ³	3
	Observational (1)	No serious	No serious	No serious	Serious ⁴	4

¹ Inconsistent seroconversion thresholds for hepatitis A antibodies used, including ≥ 33 mIU/mL, ≥ 20 mIU/mL, ≥ 10 mIU/mL.

² Few studies compared the intervention to no vaccine in the comparison group.

³ One study has small population (n = 26)

⁴ One study has small population (n = 22)

Evidence to Recommendation Framework

Balance of consequences	Undesirable consequences <i>clearly outweigh</i> desirable consequences in most settings <input type="checkbox"/>	Undesirable consequences <i>probably outweigh</i> desirable consequences in most settings <input type="checkbox"/>	The balance between desirable and undesirable consequences <i>is closely balanced or uncertain</i> <input type="checkbox"/>	Desirable consequences <i>probably outweigh</i> undesirable consequences in most settings <input checked="" type="checkbox"/>	Desirable consequences <i>clearly outweigh</i> undesirable consequences in most settings <input type="checkbox"/>	There is insufficient evidence to determine the balance of consequences <input type="checkbox"/>
-------------------------	--	---	--	--	--	---

Policy Options for ACIP Consideration	ACIP does not recommend the intervention <input type="checkbox"/>	ACIP recommends the intervention for individuals based on shared clinical decision-making <input type="checkbox"/>	ACIP recommends the intervention <input checked="" type="checkbox"/>
---------------------------------------	--	---	---

HAV infection among PWHIV

- Among people with a diagnosis of HIV who received outpatient HIV medical care during 2014-2017, the prevalence of a diagnosis of hepatitis A recorded in the medical record at the primary HIV care site during a 2-year period was 0.48% (95% CI=0.26-0.70)
 - The weighted frequency (population estimate) of hepatitis A infection was 4404 (+/- 1105)
 - The population estimate of persons receiving HIV care was 917,942
 - This does not include undiagnosed hepatitis A infection and cases diagnosed elsewhere and not recorded in the medical record of the primary HIV care site

HAV Outbreaks and PWHIV

- **HIV co-infection outbreak data is available for a limited number of states:**
 - Among 249 reported cases of HAV in Tennessee, 11 (4%) patients were PWHIV (September 20, 2018)
 - Among 359 reported cases of HAV in Massachusetts, 14 (4%) were PWHIV (June 5, 2019)
 - Among 85 reported cases of HAV in Illinois, 7 (8.2%) were PWHIV (June 5, 2019)
- **Clear excess HAV infection risk among PWHIV**
 - U.S. population estimate of 327 million
 - PWHIV are less than 0.34% of the general U.S. population

<https://www.census.gov/quickfacts/fact/table/US/PST045218>

Brennan J, Moore K, Sizemore L, et al. MMWR Morb Mortal Wkly Rep 2019;68:328–329.

<http://www.dph.illinois.gov/hepatitisA> (accessed 6/12/2019).

<https://www.mass.gov/info-details/current-hepatitis-a-outbreak> (accessed 6/12/2019)

ACIP Committee Questions from February 2019

- Is there value in knowing laboratory criteria before administering the vaccine? Should anti-HAV titers be checked periodically after vaccine administration? Will CD4 count thresholds be utilized for the recommendation of HepA vaccination among PWHIV?
- What are the costs of vaccinating PWHIV?

Laboratory Postvaccination Testing

- Since response to vaccine might be reduced in PWHIV who are immunosuppressed (lower CD4 counts), postvaccination testing is proposed to be recommended for all PWHIV at least 1 month after vaccination
- Although patients with lower CD4 counts may respond less well to the vaccine, in order to avoid missed opportunities to immunize, immunization against hepatitis A should not be delayed until the CD4 count exceeds a particular threshold
- PWHIV who do not respond to vaccine should be considered susceptible to HAV infection and counseled about precautions to prevent HAV infection and the need to obtain IG post-exposure prophylaxis for any known or likely exposure to an HAV infected person

Costs of Vaccination – Adult Vaccination Price List

Vaccine	Brandname/ Tradename	NDC	Packaging	CDC Cost/ Dose	Private Sector Cost/ Dose
Hepatitis A- Adult [a]	Vaqta® Merck	00006- 4096-02	10 pack – 1 dose syringe	\$28.28	\$68.23
		00006- 4841-41	10 pack – 1 dose vial	\$26.29	\$68.23
Hepatitis A Adult [a]	Havrix® GlaxoSmithKline	58160- 0826-52	10 pack – 1 dose syringe	\$28.28	\$67.55
Hepatitis A- Hepatitis B Adult [b]	Twinrix® GlaxoSmithKline	58160- 0815-52	10 pack – 1 dose syringe	\$56.76	\$104.00

Footnotes

a. Vaccine cost includes \$0.75 per dose Federal Excise Tax

b. Vaccine cost includes \$1.50 per dose Federal Excise Tax

How much would it cost to vaccinate PWHIV?

- A formal cost effectiveness analysis was not done for PWHIV as a risk group for HepA vaccination
- Consider ~400,000 PWHIV, potentially unvaccinated for HepA (assume 50% vaccine uptake)
 - $200,000 \times \$68 = \$13,600,000$ (1-dose)
 - $200,000 \times \$136 = \$27,200,000$ (2-doses)
 - Vaccine administration fees range from a few dollars up to twenty dollars (best available data)
- Other considerations:
 - Not all PWHIV will be vaccinated at the same time; cost would be spread out over time
 - Herd protection - vaccination in this high risk population would help disrupt outbreaks
- In an outbreak response the costs associated including health care expenses and deferred activities is substantial

Proposed Recommendation for Persons With HIV (PWHIV)

- **ACIP recommends that all persons with HIV aged ≥ 1 year be vaccinated with hepatitis A vaccine [Proposed]**

Pregnancy - Update

Recommended Adult Immunization Schedule by Medical Condition and Other Indications, United States, 2019

Table 2 Recommended Adult Immunization Schedule by Medical Condition and Other Indications
United States, 2019

Vaccine	Pregnancy	Immuno-compromised (excluding HIV Infection)	HIV Infection CD4 count		Asplenia, complement deficiencies	End-stage renal disease, on hemodialysis	Heart or lung disease, alcoholism ¹	Chronic liver disease	Diabetes	Health care personnel ²	Men who have sex with men
IIV or RIV or LAIV	1 dose annually										
	CONTRAINDICATED					PRECAUTION				1 dose annually	
Tdap or Td	1 dose Tdap each pregnancy	1 dose Tdap, then Td booster every 10 yrs									
MMR	CONTRAINDICATED			1 or 2 doses depending on Indication							
VAR	CONTRAINDICATED			2 doses							
RZV (preferred) or ZVL	DELAY				2 doses at age ≥50 yrs or 1 dose at age ≥60 yrs						
HPV Female	DELAY	3 doses through age 26 yrs			2 or 3 doses through age 26 yrs						
HPV Male		3 doses through age 26 yrs			2 or 3 doses through age 21 yrs						2 or 3 doses through age 26 yrs
PCV13		1 dose									
PPSV23		1, 2, or 3 doses depending on age and Indication									
HepA	2 or 3 doses depending on vaccine										
HepB						2 or 3 doses depending on vaccine					
MenACWY	1 or 2 doses depending on Indication, then booster every 5 yrs if risk remains										
MenB	PRECAUTION	2 or 3 doses depending on vaccine and Indication									
Hib		3 doses HSCT ³ recipient only			1 dose						

Yellow Recommended vaccination for adults who meet age requirement, lack documentation of vaccination, or lack evidence of past infection
Purple Recommended vaccination for adults with an additional risk factor or another indication
Orange Precaution—vaccine might be indicated if benefit of protection outweighs risk of adverse reaction
Pink Delay vaccination until after pregnancy if vaccine is indicated
Red Contraindicated—vaccine should not be administered because of risk for serious adverse reaction
Gray No recommendation

1. Precaution for LAIV does not apply to alcoholism. 2. See notes for influenza; hepatitis; measles, mumps, and rubella; and varicella vaccinations. 3. Hematopoietic stem cell transplant.

02/19/19

Centers for Disease Control and Prevention | Recommended Adult Immunization Schedule, United States, 2019 | Page 3

Hepatitis A Virus Infection - Pregnancy and Infancy

- **Review published data on hepatitis A during pregnancy¹**
 - Associated with gestational complications (e.g. preterm labor, placental abruption, premature rupture of membranes)²
 - Infants born to mothers with HAV infection are healthy (rare exceptions)
 - No increased risk of maternal or infant mortality after HepA vaccination in pregnancy

¹Chaudhry SA, Koren G. Hepatitis A infection during pregnancy. Can Fam Physician 2015;61:963-964.

²Elinav E, Ben-Dov IZ, Shapira Y, Daudi N, Adler R, Shouval D, Ackerman Z. Acute hepatitis A infection in pregnancy is associated with high rates of gestational complications and preterm labor. Gastroenterology. 2006 Apr;130(4):1129-34

VAERS Study 2014 – HepA Vaccination in Pregnancy

- Searched VAERS for adverse event (AE) reports in pregnant women who received HepA or HepAB vaccine from Jan. 1, 1996 – April 5, 2013
- VAERS received 139 reports of AEs in pregnant women; 7 (5.0%) were classified as serious; Sixty-five (46.8%) did not describe any AEs; no maternal or infant deaths were identified
 - No unusual clustering of birth defects were observed in this review
- **Conclusion: This review of VAERS reports did not identify any concerning pattern of AEs in pregnant women or their infants following maternal HepA or HepAB immunizations during pregnancy**

Vaccine Safety Datalink (VSD)

- Preliminary results of a large, ongoing retrospective cohort study in the Vaccine Safety Datalink (VSD) were presented to the work group
- Among pregnancies ending in live births, HepA vaccine was not associated with common maternal and infant adverse events, but a potential signal for small for gestational age (SGA) births was identified
 - The observed effect size for SGA was an absolute difference of 4% (12.3 vs. 8.3%)
 - General US prevalence estimates for SGA are approximately 10%, and up to 14% among women of Asian race (who comprised 30% of the vaccine exposed group in the study)
- The investigators and the work group considered that this SGA finding was likely due to unmeasured confounding, and unlikely to be clinically meaningful
- This study is expected to be published later this year

Proposed Hepatitis A Vaccine Recommendation for Pregnant Women

■ ACIP recommends that:

- Pregnant women who are identified as being at risk for HAV infection during pregnancy or for having a severe outcome from HAV infection (e.g., travelers, persons who use injection and non-injection drugs, persons who have occupational risk for infection, persons who anticipate close personal contact with an international adoptee, persons experiencing homelessness, persons with chronic liver disease, PWHIV) should be vaccinated during pregnancy if not previously vaccinated [Proposed]
- Pregnant women who are not vaccinated against HAV infection during pregnancy should be counseled concerning other methods to prevent HAV infection [Proposed]

Clotting Factor Disorders

Clotting Factor Disorders – Proposed Removal of Recommendation

- **Persons who have clotting-factor disorders have been recommended to receive the HepA vaccination since 1996¹**
- **However, the risk of HAV infection has decreased over time, and the risk for viral transmission for persons with clotting factor disorders is considered the same as that for the general population²**
 - In the U.S., >80% of persons with hemophilia are treated with recombinant clotting factor concentrates, which are sterilized (e.g., pasteurization, heat inactivation, filtration) enabling these factors to be safe²
 - Previously, some processes focused only on treatment with solvents/detergents which inactivated lipid-enveloped viruses (3), but not non-enveloped viruses, such as HAV, resulting in a risk for HAV infection⁴
 - Secondary virus reduction steps are now common^{2,5,6}

(1) Fiore AE, Wasley A, Bell BP. MMWR Recomm Rep 2006;55:1-23 (2) Klamroth, R. , Gröner, A. and Simon, T. L. (2014), Transfusion, 54: 1406-1417.

(3) Tabor, E. (1999), Transfusion, 39: 1160-1168. (4) Mannucci PM, Gdovin S, Gringeri A, et al. Ann Intern Med 1994;120:1–7.

(5) GRÖNER, A. (2008), Haemophilia, 14: 54-71.

(6) US Food and Drug Administration. Guide to inspections of viral clearance process for plasma derivatives. 2009. [cited 2013 Jan 25]. Available from:

<https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/PB98137144.xhtml>

1996 ACIP Hepatitis A Vaccine Recommendation - Background

■ Persons Who Have Clotting-Factor Disorders

- During 1992–1993, several outbreaks of hepatitis A were reported in Europe among persons who had clotting-factor disorders who had been administered solvent detergent–treated factor VIII concentrates that presumably had been contaminated from plasma donors incubating HAV¹
- In the United States, data from one serologic study suggested that hemophilic patients may be at increased risk for HAV infection²
- During 1995–1996, several patients who had clotting-factor disorders reportedly developed hepatitis A after having been administered solvent-detergent–treated factor VIII and factor IX concentrates³

(1) Mannucci PM, Gdovin S, Gringeri A, et al. Ann Intern Med 1994;120:1–7.

(2) Mah MW, Royce RA, Rathouz PJ, et al. Vox Sang 1994;67(suppl 1): 21–2.

(3) CDC. MMWR 1996;45:29–32.

2006 ACIP Hepatitis A Vaccine Recommendations

■ **Persons with Clotting-Factor Disorders**

- (same as 1996) Susceptible persons who are administered clotting-factor concentrates, especially solvent-detergent–treated preparations, should receive HepA vaccine
- (added) Changes in clotting factor preparation practices and donor screening have greatly reduced the risk for hepatitis A for recipients of clotting factors

Case Studies of Hepatitis A among Persons who Have Clotting Factor Disorders

- No case studies of hepatitis A infections among U.S. persons with clotting factor disorders were found in the literature in the last 20 years

Soucie JM, Robertson BH, Bell BP, et al. Hepatitis A virus infections associated with clotting factor concentrate in the United States. Transfusion 1998;38:573-9.

Clotting Factor Disorders

■ Work Group Considerations:

- Persons who have clotting-factor disorders has been a risk group for HepA vaccination since 1996
- Risk of HAV has decreased over time, and persons with clotting factors are currently at an extremely low risk for infection with HAV
- No case study reported for any person in the U.S. infected with HAV after exposure to clotting factor in 20 years (1)
- Secondary virus reduction steps are now common instead of solvent-detergent treated
- Many of the clotting factors now in use are recombinant factors
- Source plasma is now screened for HAV (2)
- No longer a specific risk of HAV infection associated with clotting factor disorders; therefore this group may be removed from consideration as part of a high risk population for whom HepA vaccination is specifically recommended

(1) Soucie JM, Robertson BH, Bell BP, et al. Transfusion 1998;38:573-9.

(2) Gröner, A. (2008). Haemophilia, 14: 54-71.

Proposed Recommendations

Proposed Routine Recommendations for Children

- ACIP recommends hepatitis A vaccination for all children aged 12-23 months [Current]
- **ACIP recommends that all children and adolescents aged 2 through 18 years who have not previously received hepatitis A vaccine be vaccinated at any age (i.e., children and adolescents are recommended for catch-up vaccination) [Proposed]**

Recommended Risk Groups for HepA Vaccination

Persons At Increased Risk for HAV Infection

- Persons traveling to or working in countries that have high or intermediate endemicity of Infection.
- Men who have sex with men (MSM)
- Persons who use injection or non-injection drugs
- Persons who have occupational risk for infection
- Persons who anticipate close contact with an international adoptee
- Persons experiencing homelessness
- ~~Persons with clotting factor disorders~~

Persons At Increased Risk For HAV Associated Complications

- Persons with HIV [Vote 2]
- Persons with chronic liver disease (update)

Any person wishing to obtain immunity

Persons With HIV (PWHIV)

- **ACIP recommends that all persons with HIV aged ≥ 1 year be vaccinated with hepatitis A vaccine [Proposed]**
- **Clinical guidance**
 - Since response to vaccine might be reduced in PWHIV who are immunosuppressed, post-vaccination testing is recommended for all PWHIV at least 1 month after vaccination
 - Although PWHIV with lower CD4 cell counts or percentages may have reduced response to the vaccine, in order to avoid missed opportunities to immunize, immunization against hepatitis A should not be delayed until the CD4 cell count exceeds a particular threshold
 - PWHIV who do not respond to vaccine should be considered susceptible to HAV infection and counseled about precautions to prevent HAV infection and the need to obtain IG post-exposure prophylaxis for any known or likely exposure to HAV
 - PWHIV who received hepatitis A vaccine should be counseled that the vaccination against hepatitis A infection may not provide long term protection and they may need to obtain IG after a high risk HAV exposure (e.g., sexual or household contact)

Persons with Chronic Liver Disease [Update]

- **ACIP recommends that:**
 - Persons with chronic liver disease (including, but not limited to, persons with hepatitis B virus infection, hepatitis C virus infection, 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) should be routinely immunized against hepatitis A.
[Proposed]

Proposed Hepatitis A Vaccine Recommendation for Pregnant Women

- **ACIP recommends that:**

- Pregnant women who are identified as being at risk for HAV infection during pregnancy or for having a severe outcome from HAV infection (e.g., travelers, persons who use injection and non-injection drugs, persons who have occupational risk for infection, persons who anticipate close personal contact with an international adoptee, persons experiencing homelessness, persons with chronic liver disease, PWHIV) should be vaccinated during pregnancy if not previously vaccinated [Proposed]
- Pregnant women who are not vaccinated against HAV infection during pregnancy should be counseled concerning other methods to prevent HAV infection [Proposed]

Implementation Strategies

■ Settings Providing Services to Adults (NEW)

- Settings in which a high proportion of persons have risk factors for HAV infection (e.g., health care settings targeting services to people who use injection or non-injection drugs, group homes and nonresidential day care facilities for developmentally disabled persons). A health care provider (HCP) may assume that unvaccinated adults age ≥ 19 years are at risk for HAV infection and offer hepatitis A vaccination without individual risk-factor screening if they have not previously completed vaccination
- Hepatitis A vaccination may be offered in outreach and other settings in which services are provided to persons at risk for HAV infection (e.g., homeless shelters, syringe service programs)
- HCP should consider implementing standing orders to identify adults recommended for hepatitis A vaccination and administer vaccination as part of routine services
- Vaccination of staff should be considered in facilities where hygiene is difficult to maintain (e.g., group homes for developmentally disabled)

Recommendations for Hepatitis A Vaccination During an Outbreak (Update)

- **ACIP recommends that:**

- All unvaccinated children aged ≥ 1 year and adults age ≥ 19 years who are at risk for HAV infection (e.g., persons who use injection or non-injection drugs, persons experiencing homelessness) should receive one dose of hepatitis A vaccine during a hepatitis A outbreak [Proposed]
- In the event of a community outbreak propagated by person-to-person transmission, public health officials should consider recommending administration of pre-exposure hepatitis A vaccination in close congregate settings providing services to high risk persons in the vicinity of the outbreak (e.g., persons incarcerated in correctional facilities, health care settings targeting services to people who use injection or non-injection drugs, homeless shelters, syringe service programs) due to the risk of an outbreak in these settings and increased risk of HAV infection among persons in these settings [Proposed]

Prevaccination Serologic Testing (Update)

- Prevaccination serologic testing for hepatitis A immunity prior to vaccination is not recommended, but may be considered in specific settings as a way to reduce costs by not vaccinating persons who are already immune
- Prevaccination serologic testing should not be a barrier to vaccination of susceptible persons, especially in populations that are difficult to access
- If prevaccination serologic testing is performed, commercially available tests for total anti-HAV or IgG anti-HAV should be used
- Antibody production in response to HAV infection results in lifelong immunity to hepatitis A and, presumably, to HAV infection
- Prevaccination serologic testing of children is not indicated because of their expected low prevalence of infection

Prevaccination Serologic Testing (Update)

- Persons for whom prevaccination testing will likely be most cost-effective include adults who were either born in or lived for extensive periods in geographic areas that have a high or intermediate endemicity of HAV; and adults in certain population groups; American Indians, Alaska Natives, and Hispanics
- **In populations that are expected to have high rates of previous HAV infection, vaccination history should be obtained where feasible prior to testing or vaccination**
- **Vaccinations should not be postponed if vaccination history cannot be obtained, if records are unavailable or if prevaccination testing is not feasible**
- Vaccination of a person who is immune because of previous infection does not increase the risk for adverse events from vaccination

Postvaccination Serologic Testing (Update)

- Testing for the presence of anti-HAV antibody after vaccination is recommended for the persons whose subsequent clinical management depends on knowledge of their immune status: PWHIV, and other immunocompromised persons (e.g., hematopoietic stem-cell transplant recipients, persons receiving chemotherapy)
- Testing should be performed at least one month after administration of the final dose of the vaccine series with total anti-HAV or IgG anti-HAV assays
- Postvaccination testing is not indicated for other persons because of the high rate of hepatitis A vaccine response among children and adults
- Persons who do not respond immunogenically to vaccination should be considered susceptible to HAV infection and counseled about precautions to prevent HAV infection and the need to obtain IG post-exposure prophylaxis for any known or likely exposure to a HAV infection

Revaccination (New)

- Revaccination (i.e., booster dose, challenge dose, or revaccination with a complete series) is not generally recommended for persons with a normal immune status who were vaccinated as infants, children or adults (Theeten 2015, Spradling 2016, Mosites 2018)
- Anti-HAV long-term persistence studies do not indicate a need for additional hepatitis A vaccine doses beyond the 2-dose primary vaccine series or 3-dose series if combination Hepatitis A-Hepatitis B vaccine was administered
- For other immunocompromised persons (e.g., PWHIV, hematopoietic stem-cell transplant recipients, persons receiving chemotherapy), the ACIP has no specific guidance because limited data are available to determine the need for booster doses or revaccination with a complete series

Other Guidance

- **Interrupted Schedules and Minimum Dosing Intervals**
- **Other Immunization Management Issues and Considerations**

Acknowledgements

- **NCHHSTP/Division of Viral Hepatitis**
 - Incident Management Team
- **NCHHSTP/Division of HIV/AIDS Prevention**
- **NCIRD/Immunization Services Division**
- **Doug Campos-Outcalt**
 - GRADE and Evidence to Recommendation Framework
- **American Immunization Registry Association**
- **Food and Drug Administration**

- **ACIP Hepatitis Work Group**

Maria Cano	Alaya Koneru
Mona Doshani	Jeff Nemhauser
Penina Haber	Tina Objio
Aaron Harris	Sarah Schillie
Beth Hibbs	Phil Spradling
Megan Hofmeister	Tureka Watson
Andrew Kroger	John Weiser
David Kim	Mark Weng

Proposed VOTE #1

- ACIP recommends that all children and adolescents aged 2 through 18 years who have not previously received hepatitis A vaccine be vaccinated at any age (i.e., children and adolescents are recommended for catch-up vaccination)

Proposed VOTE #2

- ACIP recommends that all persons with HIV aged ≥ 1 year be vaccinated with hepatitis A vaccine

Proposed VOTE #3

- ACIP affirms the updated statement “Prevention of Hepatitis A Virus Infection in the United States: Recommendations of the Advisory Committee on Immunization Practices”

Thank you

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.

