Cost-effectiveness analysis of catch-up hepatitis A vaccination among unvaccinated/partially-vaccinated children

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Overview

- Motivation
- Timeline
- Methods
- Results
- Limitations
- Conclusions

Motivation

- Large population of adolescents and young adults who remain unvaccinated against hepatitis A
- Due to lower rates of incident infection in childhood, lower rates of disease-acquired HAV immunity among the US adult population
  - Increased vulnerability to outbreaks
  - Several HAV outbreaks due to contaminated food observed
- Severity of HAV symptoms increases with age of infection
  - Decreased incidence → Older average age of infection → More severe outcomes when infection occurs
  - Catch-up vaccination may be necessary due to decreasing population anti-HAV seroprevalence

Motivation, cont.

- Hepatitis A vaccine is the only vaccine on the childhood vaccination schedule without a catch-up recommendation
- In order to contemplate a recommendation change regarding catch-up, the cost-effectiveness of catch up vaccination needed to be assessed
- This study assessed the cost-effectiveness of a one-time, age-cohort-based, catch-up vaccination campaign for US children aged 2–17 years

Timeline

- February - April 2015
  - ACIP Hepatitis Vaccines Work Group discussed HAV vaccination including the methods and results of this study
- July 2016
  - Results published*
- The ACIP Hepatitis Vaccines Work Group resumed discussing the findings in the context of Hepatitis A catch-up vaccination from March to May 2017

* Hankin-Wei A, Rein DB, Hernandez-Romieu A, Kennedy MJ, Bulkow L, Rosenberg E, Trigg M, Nelson NP. Cost-effectiveness analysis of catch-up hepatitis A vaccination among unvaccinated/partially-vaccinated children. Vaccine. 2016 Jul 29;34(35):4243-9.

Methods: Economic model

- Previously published Markov model of HAV vaccination*
  - Same model used for 2005 ACIP HAV vaccination discussions

- Tested the cost-effectiveness of a policy of catch-up HAV vaccination of unvaccinated and partially vaccinated children as compared to no catch-up, with catch-up defined as:
  - A probability and cost of two doses of HAV vaccine for children with no documentation of previous vaccination
  - A probability and cost of a second dose for children with documentation of only a single prior dose

*Rein DB, Hicks KA, Wirth KE, Billah K, Finelli L, Fiore AE, et al. Costeffectiveness of routine childhood vaccination for Hepatitis A in the United States. Pediatrics 2007;119:e12–21.

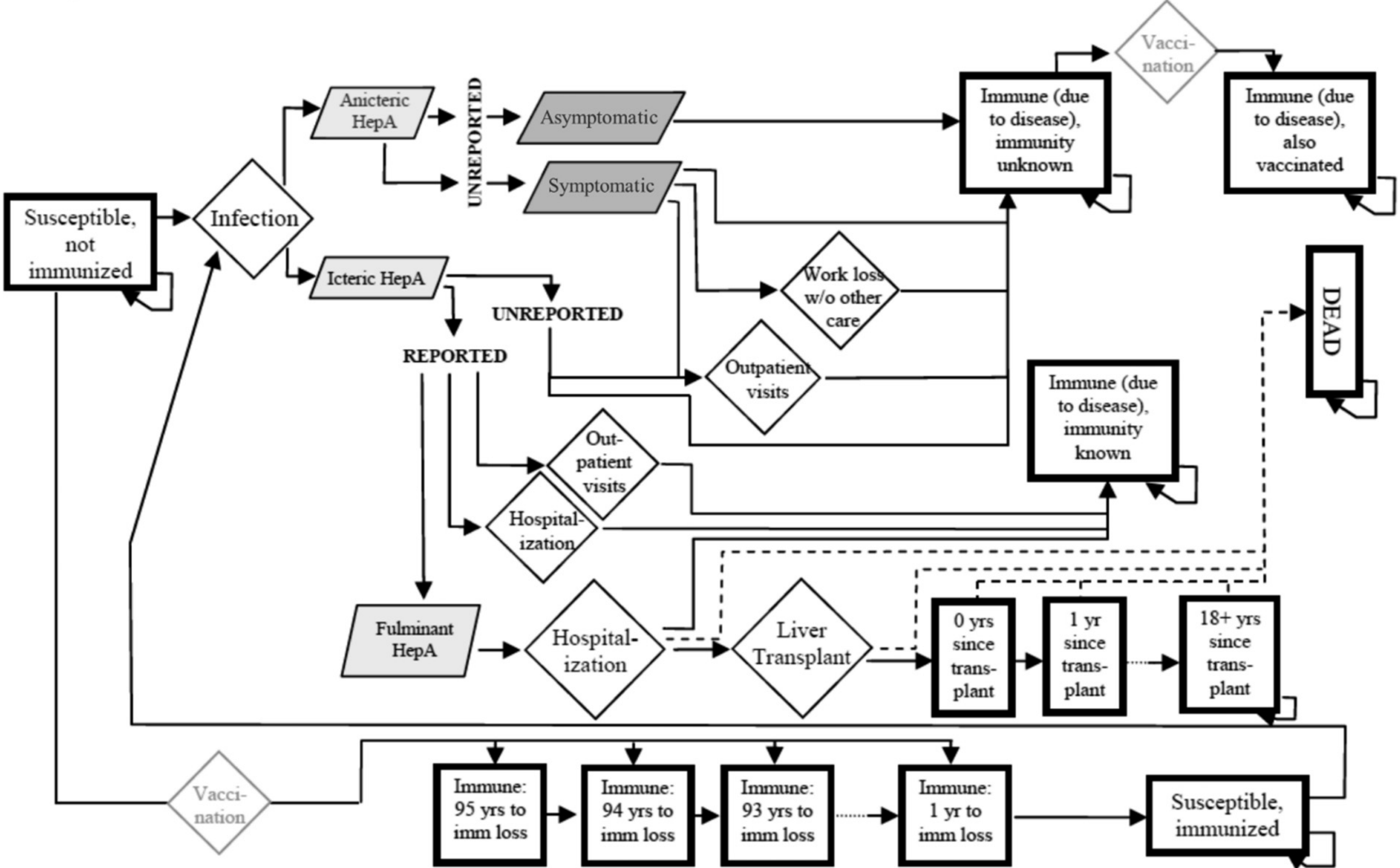
Methods: Economic model, cont.

- Simulated outcomes in succession for each age from 2 to 17 and summed outcomes and costs in excel to calculate final results

- The model simulates patient progression between eight possible HAV-related states based on the probability of vaccination, HAV infection, and health complications due to vaccination or infection

- Model parameters include
  - Vaccine costs
  - Rates of HAV infection
  - Probability of disease complications, and associated healthcare costs
  - Gradual loss of vaccine acquired immunity
  - Public health costs for an HAV-associated outbreak
  - Costs of productivity loss
  - All-cause probability of death due to non-HAV causes among the lifespan of the age cohort

- Costs and Quality-Adjusted Life Years (QALYs) assigned by state annually


Susceptible, not immunized
Infection
Anicteric HepA
Icteric HepA
UNREPORTED
Asymptomatic
Symptomatic
UNREPORTED
REPORTED
Work loss w/o other care
Outpatient visits
Out-patient visits
Hospital-ization
Fulminant HepA
Hospital-ization
Liver Transplant
Immune (due to disease), immunity unknown
Vacci-nation
Immune (due to disease), also vaccinated
DEAD
Immune (due to disease), immunity known
0 yrs since trans-plant
1 yr since trans-plant
18+ yrs since trans-plant
Vacci-nation
Immune: 95 yrs to imm loss
Immune: 94 yrs to imm loss
Immune: 93 yrs to imm loss
Immune: 1 yr to imm loss
Susceptible, immunized

Methods: Parameters

- Incidence: 1 case per 100,000 persons.
  - Average national incidence from 2008 to 2012
  - No evidence of regional variation; very different from earlier analyses
- Adjustment for under-reporting: 1:1.95 reported to unreported cases. Lower than previous analyses
- Probability of symptomatic disease increased with age according to published estimates
- Distribution of disease severity based on surveillance data
- Loss of vaccine acquired immunity by year estimated based on new data

Klevens RM, Liu S, Roberts H, Jiles RB, Holmberg SD. Estimating acute viral hepatitis infections from nationally reported cases. Am J Public Health 2014;104:482–7.
Van Herck K, Van Damme P. Inactivated hepatitis A vaccine-induced antibodies: follow-up and estimates of long-term persistence. J Med Virol 2001;63:1–7.
Armstrong GL, Bell BP. Hepatitis A virus infections in the United States: model based estimates and implications for childhood immunization. Pediatrics 2002;109:839–45.
Rein DB, Hicks KA, Wirth KE, Billah K, Finelli L, Fiore AE, et al. Costeffectiveness of routine childhood vaccination for Hepatitis A in the United States. Pediatrics 2007;119:e12–21.
Taylor RM, Davern T, Munoz S, Han S-H, McGuire B, Larson AM, et al. Fulminant hepatitis A virus infection in the United States: incidence, prognosis, and outcomes. Hepatol Baltim Md 2006;44:1589–97.
McMahon BJ, Williams J, Bulkow L, Snowball M, Wainwright R, Kennedy M, 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.

Methods: Parameters, cont.

- Existing Coverage: NIS for children age 19–35 months and 13–17 years
  - Age-specific coverage estimated linearly based on two estimates
- Catch-up adoption: Assumed rate
  - No comparable catch-up program to estimate vaccine uptake
  - 50% of those unvaccinated and unaware of prior infection would receive the first dose of vaccine
  - 50% of those who received the first dose would receive the second dose
- Adult vaccination: Adults aged 18–64 years vaccinated at a rate of 0.5% per year
  - Estimated from GlaxoSmithKline proprietary sales data

Centers for Disease Control and Prevention (CDC). Hepatitis A vaccination rate weighted estimates for 19–35 month old children in U.S. 50 States + DC, 2003
Centers for Disease Control and Prevention (CDC). Hepatitis A vaccination rate weighted estimates for 13–17 year old children in U.S. 50 States + DC, 2008
Trofa A, personal communication, 2 April 2015

Methods: Parameters, cont.

- QALYs, updated using Global Burden of Disease study values
- Updated costs using four case studies of U.S. hepatitis A outbreaks
  - Mild symptomatic disease
  - Unreported icteric infection
  - Reported icteric infection
  - Hospitalization
  - Fulminant liver failure
    - With Transplant
    - Without Transplant
- Productivity losses for parents/caregivers and death from HAV
- Lifetime time horizon using a 3% annual rate

2011 Health Care Cost and Utilization Report | HCCI n.d. http://www.healthcostinstitute.org/2011report (accessed August 31, 2015).
Bownds L, Lindekugel R, Stepak P. Economic impact of a hepatitis A epidemic in a mid-sized urban community: the case of Spokane, Washington. J Community Health 2003;28:233–46.
Berge JJ, Drennan DP, Jacobs RJ, Jakins A, Meyerhoff AS, Stubblefield W, et al. The cost of hepatitis A infections in American adolescents and adults in 1997. Hepatology 2000;31:469–73.
Dalton CB, Haddix A, Hoffman RE, Mast EE. The cost of a food-borne outbreak of hepatitis A in Denver, Colo. Arch Intern Med 1996;156:1013–6.
Rein DB, Hicks KA, Wirth KE, Billah K, Finelli L, Fiore AE, et al. Cost-Effectiveness of Routine Childhood Vaccination for Hepatitis A in the United States. Pediatrics 2007;119:e12–21. doi:10.1542/peds.2006-1573.

Methods: Summary measures

- Incremental difference in costs and QALYs
  - Intervention scenario (catch-up) minus the baseline scenario (no catch-up)
  - Difference in vaccine costs, vaccine administration costs, HAV infection and adverse event-related medical costs, productivity losses, and public health response costs
- Sensitivity analyses were performed for the 10 year-old cohort, the midpoint age for catch-up vaccination
- Threshold analyses were conducted for disease incidence

Incremental summary outcome measures per age cohort included in the analysis and for all age-cohorts pooled together.

Cohort			Incremental Results						
Age	Year of birth	Starting population	Infections	Discounted QALYs	Discounted life years	Discounted costs	$/person	QALY/person	ICER*
2	2012	3,952,841	−772	13	4	$9,172,919	$2.32	0.0000033	$694,240
3	2011	3,953,590	−679	13	3	$9,522,024	$2.41	0.0000033	$717,691
4	2010	3,999,386	−652	14	4	$9,896,821	$2.47	0.0000035	$724,814
5	2009	4,130,665	−665	17	6	$10,414,199	$2.52	0.0000041	$627,967
6	2008	4,247,694	−685	19	7	$10,775,540	$2.54	0.0000045	$569,416
7	2007	4,316,233	−710	21	9	$10,992,191	$2.55	0.0000049	$512,475
8	2006	4,265,555	−699	21	9	$10,834,800	$2.54	0.0000049	$511,802
9	2005	4,138,349	−721	22	11	$10,418,910	$2.52	0.0000053	$476,165
10	2004	4,112,052	−741	23	10	$10,199,218	$2.48	0.0000056	$452,239
11	2003	4,089,950	−762	23	11	$9,933,351	$2.43	0.0000056	$436,144
12	2002	4,021,726	−774	25	13	$4,679,302	$1.16	0.0000062	$189,782
13	2001	4,025,933	−802	24	12	$9,174,316	$2.28	0.0000060	$386,316
14	2000	4,058,814	−837	26	14	$8,884,981	$2.19	0.0000064	$338,425
15	1999	3,959,417	−852	27	14	$8,265,037	$2.09	0.0000068	$307,849
16	1998	3,941,553	−876	27	15	$7,618,023	$1.93	0.0000069	$294,083
17	1997	3,880,894	−889	27	15	$7,016,799	$1.81	0.0000070	$268,626
All years		61,141,811	−12,116	342	157	$147,798,431	$2.42	0.0000056	$432,159

* ICER is not exactly equal to discounted costs divided by discounted QALYs due to rounding.

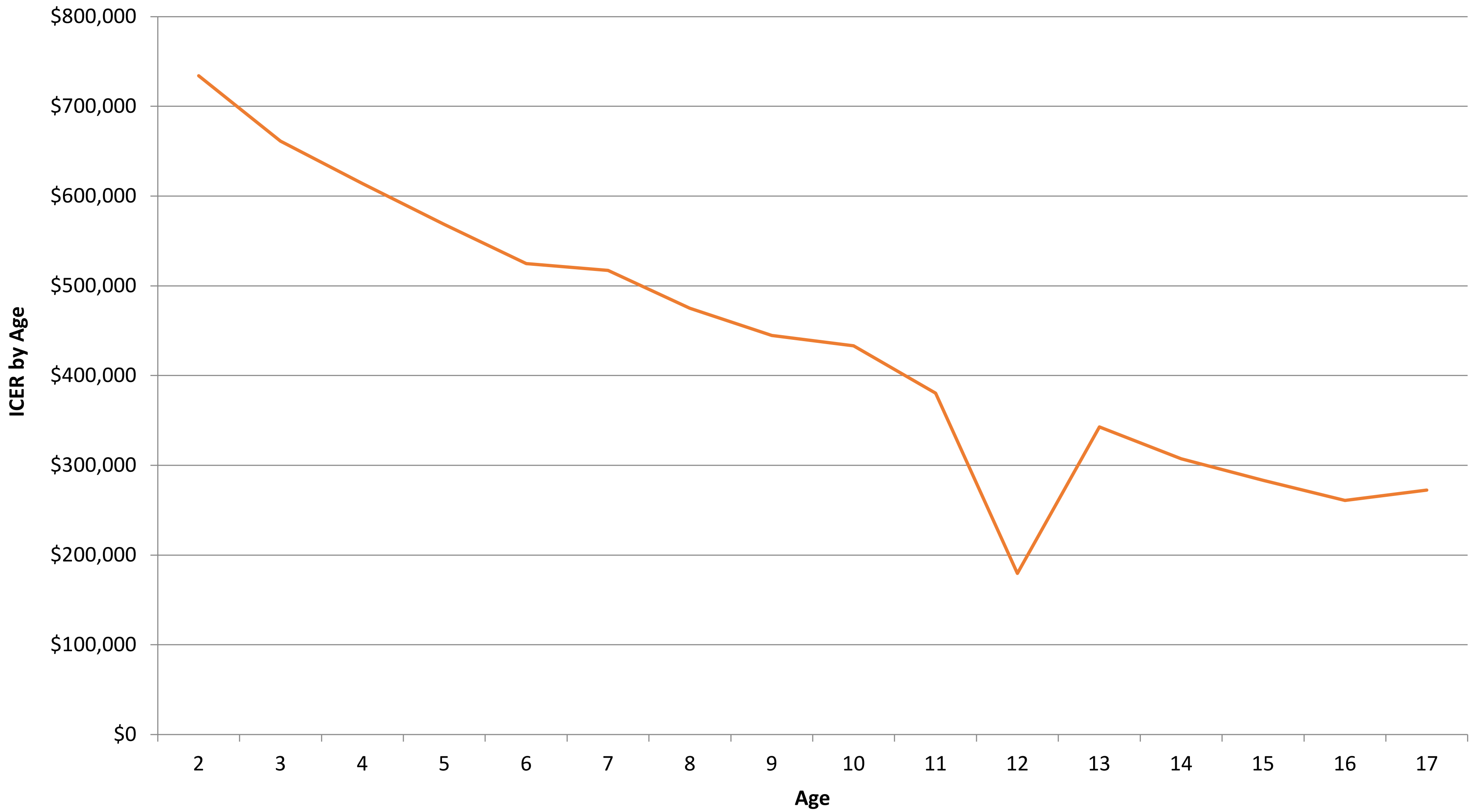
Hankin-Wei A, Rein DB, Hernandez-Romieu A, Kennedy MJ, Bulkow L, Rosenberg E, Trigg M, Nelson NP. Cost-effectiveness analysis of catch-up hepatitis A vaccination among unvaccinated/partially-vaccinated children. Vaccine. 2016 Jul 29;34(35):4243-9.

Comparison of Top-line Results (ages 2 to 17)

Variable	Result
Incremental Costs	$147 million
Incremental QALYs	342
Overall ICER	$432,159
ICER Range by age	$190,000-$724,000

Hankin-Wei A, et al. Vaccine. 2016 Jul 29;34(35):4243-9.

Results by Age Compared



Created from draft results.

Example Results for Age 10 Cohort

- Catch-up vaccination reduced total HAV infections by 741, with 556,989 additional vaccine doses administered

- For every 752 additional doses administered, one case of HAV infection would be averted

- Catch-up vaccination increased total discounted QALYs across the 10 year-old cohort by 23, or 0.000006 QALYs per person

- Catch-up vaccination increased net costs by $10.2 million or $2.38 per person

- The catch-up vaccination intervention increased vaccine and administration costs for children, but decreased these costs for adults, as individuals vaccinated by the catch-up campaign would not require HAV vaccination in adulthood

- The incremental cost of the HAV vaccine catch-up at age 10 years was $452,239 per QALY gained

Results All Cohorts, cont.

- Cost-effectiveness of catch-up vaccination decreased with the age of the cohort targeted for vaccination, with catch-up becoming more cost-effective when targeting children in late adolescence

- This effect was due to several factors:
  - Higher probability of symptomatic disease among older children
  - Less discounting of future costs of disease
  - Vaccination of older children averted the need for higher-cost adult vaccination with less delay in averting these costs

- The cost-effectiveness of catch-up vaccination was most favorable at age 12 years, resulting in an ICER of $190,000 per QALY gained
  - Model assumes that the administration costs of HAV vaccination were split with other vaccines routinely administered at age 12 years, thus lowering the cost of vaccination

Results, Sensitivity Analysis

- Results were most sensitive to
  - Discount rate. ICER = $24,000/QALY when the discount rate is 0%
  - Cost of child vaccine in the public and private market
  - Annual rate of adult vaccination. Catch-up more cost-effective when it is assumed to replace more adult vaccination
  - Incidence, Baseline = 1/100,000
    - ICER = $47,000 at an incidence of 5/100,000
    - Cost-saving at an incidence of 12/100,000

- Results were insensitive to rate of catch-up adoption, QALY decrements and rate of loss of vaccine acquired immunity

Limitations

- The values of certain parameters used in the model are uncertain; the most important among these are the rates of HAV vaccine catch-up uptake and adult vaccination
    - Sensitivity analyses indicate that the ICER of catch-up is insensitive to uptake, but is sensitive to adult vaccination rate
    - Since catch-up vaccination is assumed to replace adult vaccinations, as the annual rate of adult vaccination increases, the cost-savings associated with replacing more expensive adult vaccine with less expensive children's formulations increases
    - Our annual rate of adult vaccination might be underestimated because we were only able to obtain data from GlaxoSmithKlein at the time of the study

- The model output is based on hepatitis A incidence from 2008 to 2012 and the cost-effectiveness conclusions are tied to factors disease transmission patterns which may change over time, altering future cost

Limitations, cont.

- Utilized the current US ACIP two-dose recommendation only
  - World Health Organization Strategic Advisory Group of Experts have advised that national immunization programs may consider inclusion of single dose HAV vaccine in immunization schedules
- Herd immunity effects of vaccination were excluded from the model; however, previous analyses indicate that herd immunity associated with routine vaccination would result in even lower incidence and less favorable cost-effectiveness for catch-up

Conclusions

- Our findings suggest that, given the current US HAV disease incidence, a catch-up vaccination program would not be cost-effective at thresholds of $50,000, $100,000 or $200,000 per QALY saved.
- The ICER of vaccination falls below $50,000/QALY saved at an HAV incidence of 5.0 cases per 100,000 persons.
- The incremental cost per QALY given current US HAV disease incidence ranged from a low of $190,000 per QALY gained at age 12 years to a high of $725,000 per QALY gained at age 4 years

Conclusions, cont.

- Relative to the cost per QALY projected for hepatitis A catch-up vaccination, studies assessing the economic impact of catch-up interventions for other vaccinations show lower cost per QALY

- The improved cost-effectiveness of these catch-up vaccination interventions (e.g., HPV vaccine, meningococcal conjugate vaccine) relative to hepatitis A are driven by higher baseline disease incidence, higher case-fatality ratio, and higher costs of care for complications

- Because incidence is so low the cost-effectiveness of catch-up vaccination is poor; however, catch-up vaccination could be justified based on offsets to adult vaccination if such substitution occurs

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Thank You!

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