Cost-Effectiveness Analysis of Catch-Up Hepatitis A Vaccination

Among Unvaccinated/Partially-Vaccinated Children

Supplementary Methods:

1. Economic Model

1-1. Transition Between States

With each annual time step of the model, the cohort is further divided between the model states based on transition probabilities. To demonstrate this concept, we can observe what happens to the portion of the cohort in the *Susceptible, not immunized* state (Figure 1-1).

Each year, a certain percentage of that group will be vaccinated and distributed between the 95 *Immune states (1, 2,…, 95 years to immunity loss)* and the *Susceptible, immunized* state.

Of those not vaccinated (in the *Susceptible, not immunized* state), a portion will be infected with HAV. Non-infected individuals will remain *Susceptible, not immunized* for the following cohort-year, while infected persons will transition into one of four states based on the probabilities of progression: *Immune (due to disease), immunity unknown*; *Immune (due to disease), immunity known*; *0 years since transplant*; or *Death*. Individuals who develop fulminant Hepatitis and survive the year of a liver transplant progress to *0 years since transplant*. All other who have icteric HAV that is identified and reported are moved to *Immune (due to disease), immunity known*. The rest of infected cases, which all have unreported anicteric or icteric HAV progress to *Immune (due to disease), immunity unknown*.

After all of the above transitions have occurred, a percentage of the cohort in all states transitions to *Death* to account for non-HAV related deaths. This process is repeated in following years with the portion of individuals that remain *Susceptible, not immunized*. In the case of intervention models, the proportion of the birth cohort that received zero or one dose of HAV vaccination prior to age two, will be eligible to receive one or two additional doses of HAV vaccine in years 3 of 17 of the simulation.

1-2: Health Outcomes
The model estimates multiple outcomes of HAV including the number of:

1) Cases of icteric and anicteric acute infections, HAV-related hospitalizations, acute liver failures, liver transplants and deaths.

2) Childhood and adult immunizations

3) Mild and severe adverse effects resulting from HAV immunizations

4) Days of work loss and productivity losses due to: care-giving or self-care for HAV-related illness, HAV-related death, getting a HAV vaccination, and care-giving or self-care for adverse effects resulting from HAV vaccination

5) Costs of medical care of HAV-related illness, including outpatient visits and hospitalizations

6) Childhood and adult HAV immunization costs

7) Public health response costs

8) Life years and QALYs: QALYs are calculated by weighting time spent in each health state by the state's utility value and summing over an individual's lifetime. In line with standard health economic practice, QALY values assume that individual healthy state background QALYs decline with age due to the increasing prevalence of other health conditions

2: Model Inputs: Data and Assumptions

2.1: Inclusion of Epidemiologic Methods

The health outcomes of interest were estimated using a rate-based multiplicative model of reported incidence rates for acute Hepatitis A infections, adjustments for under-reporting of acute cases, previous Hepatitis A vaccination rates among children <2 years of age, adolescents, and adults, transition probabilities between health states, and the effectiveness of HAV vaccination. The epidemiology of HAV incidence has changed dramatically since routine vaccination was recommended by ACIP in 2006, shifting from predominantly person-to-person transmission prior to the recommendation to infection from a contaminated source (such as imported food products). To reflect this shift, unlike previous uses of the same model, incidence was assumed to be uniform across age groups.

2.2: HAV Infection Clinical Characteristics and Disease Progression:

The model assumes that infections can only occur among those in the cohort in the *Susceptible, not immunized* state who were not vaccinated in the current year or anyone in the *Susceptible, immunized* state who lost immunity before the current year. In the model, the probability of probability of icteric (symptomatic jaundice) disease given infection increased with age based on a previously published equation describing this relationship.[19]

HAV disease development stages

New infections are divided into icteric and anicteric (asymptomatic or mildly symptomatic without jaundice) cases as based on a published age-related function.[19] By assumption, the model classifies 50% of anicteric cases as asymptomatic, 25% as mildly symptomatic resulting in minor QALY losses but no health care utilization, and 25% as mildly symptomatic resulting in mild QALY losses and one outpatient visit. Icteric cases are categorized as cases of moderate severity that utilize outpatient care, and high severity which require hospitalization. Hospitalized cases have an age-specific probability of developing fulminant liver failure (FLF). Those with FLF might resolve their infection and recover, die from their infection, or receive a transplant. Those with transplants experience an annual probability of death from transplantation that declined by year following transplant. Liver transplant recipients who die as a result of transplant-related causes in any year are considered to be deaths from HAV.

HAV-related disease outcomes

The model assumes that within each of the anicteric and icteric stages, patients require different degrees of healthcare. The rationale underlying these assumptions are described in previous model documentation and publications.[13,19] Asymptomatic anicteric cases do not require healthcare and are all unreported. Symptomatic anicteric cases are assumed to be relatively mild; only 50% of symptomatic anicteric HAV cases necessitate outpatient visits; of those, only 1 patient visit per person is assumed. All symptomatic anicteric cases are unreported. Icteric cases are either reported or unreported; the number of reported cases is calculated as the number of icteric cases divided by 2.95, which is the estimated number of total icteric cases per reported case.[15] The model assumes 95% of all icteric cases require outpatient visits. All reported cases, by definition, are assumed to require healthcare, either outpatient visits or hospitalizations.

All fulminant cases are assumed to require hospitalization. Not all fulminant cases receive a liver transplant; of those that do not, some die with a specified probability and the remaining recover. All fulminant cases receiving a transplant have a probability of death during and shortly after surgery, and one to 18 years after receiving the transplant.

Supplemental Table S-1. Hepatitis A model transition states

State	Description
Susceptible, not immunized	Never immunized and susceptible to infection
Immune:1-95 years to immunity loss	Immunized; vaccine immunity not (yet) lost. There are 95 states, one for each possible number of remaining years of immunity loss
Susceptible, immunized	Immunized; vaccine-induced immunity is lost and individual is susceptible to infection
Immune (due to disease), immunity unknown	Immune due to past disease. Disease was not identified, therefore immunity is not known and individual may seek vaccination
Immune (due to disease), immunity known	Immune due to past disease. Disease was identified and individual will not seek vaccination
Immune (due to disease), also vaccinated	Immune due to past disease. Disease was not identified and individual sought and received vaccination
0-20+ years since liver transplant	History of fulminant Hepatitis A which resulted in liver transplantation and subsequently in a reduced quality of life and increased risk of death. There are 21 states, one for each number of possible years since transplant (20 or more years are grouped together)
Death	Death due to Hepatitis A or non-Hepatitis A related cases. Productivity losses accumulated throughout lifetime.

Supplemental Table S-2. Reported cases and incidence of acute Hepatitis A by age and region in the United States, 2008-2012

	Total		2008		2009		2010		2011		20	
	Cases	Incidence*	Cases	Incidence*	Cases	Incidence*	Cases	Incidence*	Cases	Incidence*	Cases	In
Total	9,202	0.58	2,585	0.85	1,987	0.65	1,670	0.54	1,398	0.45	1,562	
Age-group												
0 - 9	599	0.29	210	0.51	130	0.31	125	0.31	72	0.18	62	
10-19	1107	0.53	322	0.78	236	0.57	209	0.49	172	0.41	168	
20 - 29	1777	0.83	436	1.03	413	0.96	347	0.81	279	0.64	302	
30 - 39	1340	0.66	382	0.94	311	0.77	234	0.58	206	0.51	207	
40 - 49	1223	0.56	380	0.86	273	0.62	201	0.46	168	0.39	201	
50 - 59	1185	0.57	344	0.86	223	0.55	196	0.47	181	0.42	241	
60+	1863	0.66	496	0.92	375	0.68	335	0.59	298	0.5	359	
Missing	108	---	15	---	26	---	23	---	22	---	22	
Region												
New England	491	0.68	128	0.89	108	0.75	95	0.66	77	0.53	83	
Mid. Atlantic	1369	0.67	333	0.82	275	0.67	276	0.68	252	0.61	233	
E.N. Central	1271	0.55	335	0.72	284	0.61	203	0.44	214	0.46	235	
W. N. Central	631	0.62	255	1.26	126	0.62	102	0.50	59	0.29	89	
S. Atlantic	1662	0.56	393	0.68	429	0.72	351	0.59	222	0.37	267	
E. S. Central	301	0.33	81	0.45	46	0.25	48	0.26	48	0.26	78	
W. S. Central	979	0.54	294	0.83	209	0.58	158	0.43	157	0.42	161	

Mountain	818	0.74	219	1.01	163	0.74	144	0.65	129	0.58	163	
Pacific	1680	0.68	547	1.11	347	0.70	293	0.59	240	0.48	253	

*Rate per 100,000

Table S-3 Parameters of Hepatitis A-disease progression

Parameter	Value	Source
Clinical characteristics and symptoms		
Probability of Icteric Infection by age		[19]
0-4 years of age	0.072	
5-9 years of age	0.371	
10-17 years of age	0.707	
≥18 years of age	0.852	
Probability of symptoms | anicteric HAV infection	0.50	Assumption
Total number of icteric cases per reported case	1.95	[15]
Progression of disease and healthcare		
Probability of outpatient visit and work loss |symptomatic anicteric infection	0.50	Assumption
Probability of receiving any level of medical care | icteric HAV infection	0.95	[25]
Probability of hospitalization | reported icteric HAV infection		[16]
All ages	0.427	
<18 years of age	0.243	
18-39 years of age	0.450	
40-64 years of age	0.662	
≥65 years of age	0.625	
Probability of fulminant HAV | reported icteric HAV infection		[39]
0-9 years of age	0.0038	
5-14 years of age	0.0005	
15-39 years of age	0.0068	
40-59 years of age	0.055	
60-95 years of age	0.08	
Probability of receiving liver transplant | Fulminant	0.65	[20]
Probability of death from Fulminant | no liver transplant	0.14	[20]
Annual Probability of death | liver transplant		
0-1 year	0.184	[40]
1-3 years	0.03	[40]
4-18 years	0.015	

Supplemental Table S-4. HAV vaccination adverse events, and costs*

Parameter	Value	Source
Adverse Events		
Probability of mild adverse event (all ages)	0.0051	41
Probability of severe adverse event (all ages)	0.000001	42
Severe adverse event (medical care costs - all ages)	$56,046.38	43
Direct Costs		
Proportion of vaccines purchased at public price		
ages 0-17 years	0.55	Personal Communication, GSK
ages 18-95 years	0.05	
Acquisition cost		
Public		
ages 0-17 years	$17.01	44,45
ages 18-95 years	$25.73	
Private		
ages 0-17 years	$28.74	
ages 18-95 years	$63.72	
Administration cost ages 2-11, 13-64	$14.00	46
Administration cost age 12†	$7.00	
Indirect costs		
Productivity		
Work days lost		
HAV vaccination		
age 0-12 years	0	13
age 13-95 years	0.125	
Mild adverse event (all ages)	0.875	
Severe adverse event (all ages)	5	

*All costs reflect 2015 $U.S. value
†At age 12, administration costs are $7.00 due to shared administration costs with other routine vaccines.

Supplemental Table S-5. Direct and indirect costs of Hepatitis A infection

	Value	Source
Direct costs		
Medical		
Number of outpatient visits for symptomatic anicteric HAV infection	1	Assumption
Outpatient cost for symptomatic anicteric HAV infection	$104.12	[24]
Number of outpatient visits for symptomatic icteric HAV infection	3	[26]
Outpatient costs of non-fulminant reported icteric HAV infection	$1,016	[25,26,28]
Inpatient costs of non-fulminant reported icteric HAV infection	$10,035	
Inpatient Cost of fulminant HAV with liver transplant		
Year of transplant	$353,715	[29]
Years after transplant (1-18 years)	$31,670	[26]
Inpatient Cost of fulminant HAV without liver transplant	$29,864	[26]
Percent reduction in medical costs for unreported versus reported icteric HAV infection	0.333	[13]
Indirect costs		
Productivity		
Probability of work loss and no medical care | symptomatic anicteric HAV infection	0.5	Assumption
Work days lost		
Symptomatic anicteric infection	3	Assumption
Non-hospitalized icteric infection		
Reported		
Ages 0-12 years	3.7	[47]
Ages 13-95 years	10	
Unreported	3	Assumption
Hospitalization - icteric infection	33.2	[26]
Hospitalization - fulminant Hepatitis / no liver transplant	33.2	
Liver transplant - per year	153.2	
Costs of productivity loss		
Daily cost of work loss		
Ages 0-15 years	$120.20	[30]
Ages 16-19 years	$63.42	Assumption
Ages 20-24 years	$83.40	
Ages 25-34 years	$121.53	
Ages 35-44 years	$143.15	[30]
Ages 45-54 years	$146.41	
Ages 55-64 years	$146.61	
Ages 65-95 years	$105.02	
Labor force participation rate		
Ages 0-15 years	0.815*	[48]
Ages 16-19 years	0.343	
Ages 20-24 years	0.709	
Ages 25-34 years	0.817	

Ages 35-44 years	0.826	
Ages 45-54 years	0.802	
Ages 55-64 years	0.645	
Ages 65-74 years	0.268	
Ages 75 and older	0.076	
*Labor participation rate, daily earnings of parent or caregiver (calculated as a weighted average of 20 to 44-year-olds).		

Supplement Table S-6. Public health response costs per Hepatitis A infection

Parameter	Value	Source
Public health response		
General		
Mean hourly wage for licensed practical or licensed vocational nurse	$21.3	49
Proportion of reported cases with follow-up by PHA	0.55	
Surveillance		
Probability of phone call by PHA to the infected patient's physician	1	
Length of time (hours), phone all by PHA to the infected patient's physician	1	13
Probability of phone call by PHA to the infected patient | physician phone call	0.8	
Length of time (hours), phone all by PHA to the infected patient	1	
Probability of visit by PHA to the infected patient | physician and patient phone	0.25	
Length of time (hours), visit by PHA to the infected patient	4	
IG coordination and administration		
IG cost per dose	$23.52	
Proportion of cases with follow-up for whom IG shots for contacts are coordinated by PHA	1	
Proportion of reported cases, FSW	0.06	
No. phone calls to contacts, FSW cases with follow-up	73	
No. phone calls to contacts, all other cases with follow-up	25	13
Length (hours) of phone calls to contacts	1	
No. IG shots to contacts, FSW cases with follow-up	29	
No. IG shots to contacts, all other cases with follow-up	10	
Length (hours) for coordination of IG shots for contacts	4	
Public notification		
Proportion of reported cases for whom visit made to employer (FSW cases only)	0.02	
Length (hours) employer visit (FSW cases only)	8	13
Proportion of reported cases for whom a public notification is made	0.002	
Length (hours) for PHS to make public notification	160	
IG: immunoglobulin; PHA: public health authority; FSW: food service workers		

Supplemental Table S-7. Quality Adjusted Life Years associated with HAV infection

Parameter	Value	Source
Duration of sickness (days)		
Symptomatic anicteric HAV infection	3	Assumption
Non-hospitalized icteric HAV infection	34.4	[26]
Hospitalization*	67.8	
QALY value		
Healthy		
ages 0-4 years	0.94	[49]
ages 5-17 years	0.93	
ages 18-34 years	0.915	
ages 35-44 years	0.895	
ages 45-54 years	0.865	
ages 55-64 years	0.805	
ages 65-74 years	0.77	
ages 75-95 years	0.695	
Annual QALY decrement		
Symptomatic anicteric HAV infection		[31]
*Jacobs, et al (2002)	0.007	
GBD (Model Baseline)	0.005	
Non-hospitalized icteric HAV infection		
*Jacobs, et al (2002)	0.039	
GBD (Model Baseline)	0.053	
Hospitalization**		
*Jacobs, et al (2002)	0.076	
GBD (Model Baseline)	0.21	

* Provided for comparison purposes only
**Includes fulminant, and pre- and post-transplant Hepatitis A infection
GBD: global burden of disease

Supplemental Table S-8: Variables and Values Used in Univariate Sensitivity Analyses Threshold Analyses

Category	Variable	Baseline	Low	High	Comments
Coverage	Catchup, 1st dose | Never Vaccinated	0.500	0.375	0.625	±25%
Costs	Child Vaccine Purchase Cost - Public	$16.18	$12.14	$20.23	±25%
	Child Vaccine Purchase Cost - Private	$31.49	$23.62	$39.36	±25%

	Percentage of Child Vaccine Purchased at the Public Price	0.550	0.413	0.688	±25%
	Annual Rate of Adult Vaccination	0.005	0.0038	0.0063	±25%
Risk	Incidence	1 per 100,000	n/a	Threshold analysis From 1.5 to 12.0 per 100,000	Model could not calculate incidence lower than 1 per 100,000
Health Impacts	QALY Decrements				Low combines the lowest values published across Jacobs, et al (2007) and the Salomon, et al (2012), high combines the highest.
	Mild	0.005	0.005	0.007	
	Moderate	0.053	0.039	0.053	
	Severe	0.210	0.076	0.210	
Effectiveness	Rate of Decline in Antibody Titers				Low combines the lowest values published across Rein, et al (2007) and the new analysis conducted for this study. High combines the highest values.
	Years 1-4	0.166	0.166	0.200	
	Years 5-9	0.650	0.050	0.650	
	Years 10+	0.054	0.050	0.540	
Value of Future Benefits	Discount Rate	0.030	0.000	0.050	Standard range

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