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ORIGINAL ARTICLES
Economic Evaluation

Public Health Impact and Cost-Effectiveness of Hepatitis A Vaccination in the United States: A Disease Transmission Dynamic Modeling Approach

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ABSTRACT

Objective: To assess the population-level impact and cost-effectiveness of hepatitis A vaccination programs in the United States. **Methods:** We developed an age-structured population model of hepatitis A transmission dynamics to evaluate two policies of administering a two-dose hepatitis A vaccine to children aged 12 to 18 months: 1) universal routine vaccination as recommended by the Advisory Committee on Immunization Practices in 2006 and 2) Advisory Committee on Immunization Practices's previous regional policy of routine vaccination of children living in states with high hepatitis A incidence. Inputs were obtained from the published literature, public sources, and clinical trial data. The model was fitted to hepatitis A seroprevalence (National Health and Nutrition Examination Survey II and III) and reported incidence from the National Notifiable Diseases Surveillance System (1980–1995). We used a societal perspective and projected costs (in 2013 US $), quality-adjusted life-years, incremental cost-effectiveness ratio, and other outcomes over the period 2006 to 2106. **Results:** On average, universal routine hepatitis A vaccination prevented 259,776 additional infections, 167,094 outpatient visits, 4781 hospitalizations, and 228 deaths annually. Compared with the regional vaccination policy, universal routine hepatitis A vaccination was cost saving. In scenario analysis, universal vaccination prevented 94,957 infections, 46,179 outpatient visits, 1286 hospitalizations, and 15 deaths annually and had an incremental cost-effectiveness ratio of $21,223/quality-adjusted life-year when herd protection was ignored. **Conclusions:** Our model predicted that universal childhood hepatitis A vaccination led to significant reductions in hepatitis A mortality and morbidity. Consequently, universal vaccination was cost saving compared with a regional vaccination policy. Herd protection effects of hepatitis A vaccination programs had a significant impact on hepatitis A mortality, morbidity, and cost-effectiveness ratios.

Keywords: cost-effectiveness analysis, hepatitis A vaccine, hepatitis A virus, herd protection/immunity, simulation.

Introduction

Transmitted from person to person primarily through the fecal-oral route, hepatitis A virus (HAV) is the principal etiological agent of acute viral hepatitis, causing significant morbidity worldwide [1]. In the United States, hepatitis A was the most frequently reported type of hepatitis during the 1980s and 1990s, with an average of 26,000 cases reported annually [2]. Because not all cases were symptomatic or reported, the actual number of infections that occurred during this period was several times higher than the reported number of cases (estimated at 270,000 infections per year after correction for asymptomatic illness and underreporting) [3]. Although hepatitis A is usually a self-limiting disease, it can lead to several serious complications including fulminant liver failure and death [4]. The HAV infection can also result in significant direct medical costs (from possible hospitalization), lost productivity (from absenteeism from work or school for possibly several weeks or months), and additional costs associated with community outbreaks (including infection control costs) [5–7].

There is no specific curative therapy for hepatitis A disease. Management generally involves supportive care and medical treatment of serious complications. Vaccines against HAV infection became available in the United States in 1995 and have been recommended for use incrementally since then [8]. In 1996, the Advisory Committee on Immunization Practices (ACIP) recommended vaccinating persons at high risk of infection and children

Conflict of interest: All authors are either current or former employees of Merck. All current employees hold stocks and/or stock options.

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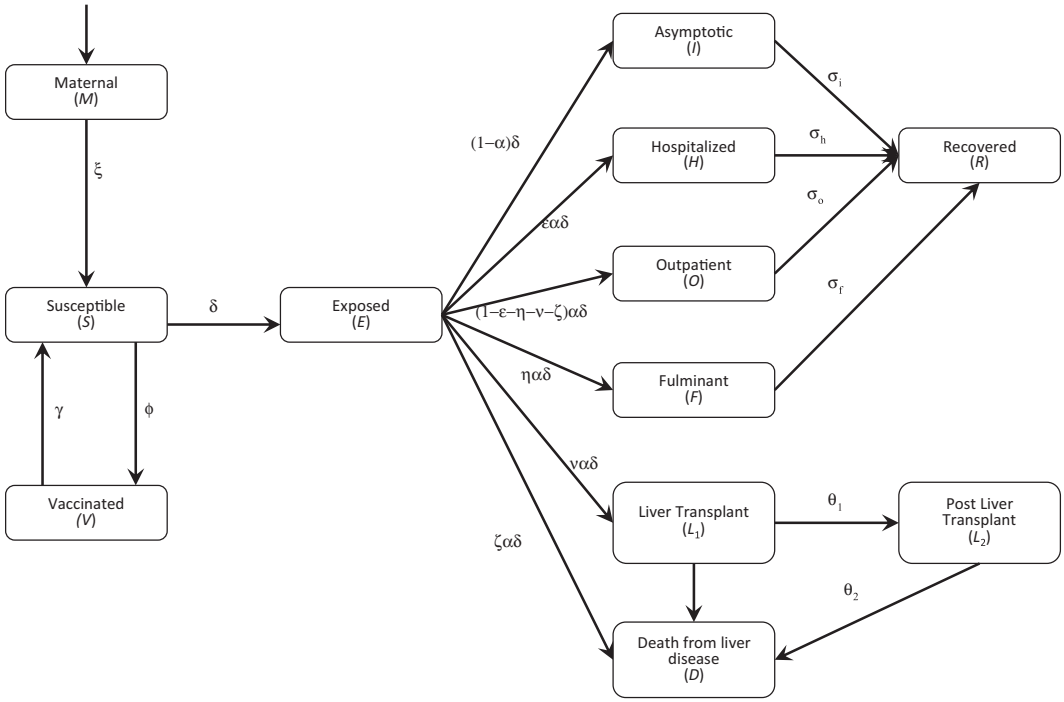

Fig. 1 – Flow diagram of hepatitis A virus transmission and vaccination model: newborns enter age group $a = 0$, and are assumed to be protected by maternal antibodies (*M*), and the protection is lost over time so the children become susceptible (*S*). Upon infection, a person moves to the exposed compartment (*E*) and becomes infectious after a latent period. The model distinguishes between several categories of infection and disease: Asymptomatic (*I*); symptomatic infections are treated as outpatient (*O*), hospitalized (*H*), with fulminant disease (*F*), requiring a liver transplant (*L*), or die from hepatitis A virus infection (*D*). Infected persons can clear their infection and move to the recovered compartment (*R*) with lifelong immunity. The model also applied age-specific all-cause mortality (not shown) to all persons in all epidemiologic classes.

living in communities at high risk [8]. In 1999, the recommendations were expanded to include children living in states, counties, and communities with HAV rates higher than the national average [8]. In 2006, the ACIP recommended routine vaccination for all children aged 12 to 23 months in the United States [8]. Although routine vaccination for all children is recommended, the uptake of the two-dose hepatitis A vaccine is well below the coverage rates of other pediatric and adolescent vaccines [9].

The low uptake of hepatitis A vaccine could be the main reason for a significant number of cases of HAV disease still occurring in the United States. For example, 1670 cases of HAV disease were reported in the United States. When adjusted for underreporting and asymptomatic cases, an estimated 17,000 cases occurred in 2009 [10].

A number of studies assessed the cost-effectiveness of routine or targeted hepatitis A vaccination in children or other risk groups [11]. Using a cohort model, Rein et al. [12] showed that universal hepatitis A vaccination of children in the United States is a cost-effective strategy. Cohort models, however, do not incorporate herd protection effects of vaccination. Using an empirical approach relating hepatitis A vaccination coverage to declines in hepatitis A incidence, one study showed that the inclusion of herd protection effects due to vaccination has a significant impact on the estimates of disease outcomes and the cost-effectiveness of hepatitis A vaccination [13].

It is well recognized that a more appropriate approach to estimate the impact of herd protection and vaccination is to use a dynamic model [14,15]. The aim of this study was to estimate the public health and economic impact of a two-dose universal hepatitis A vaccination program of children in the United States for the period 2006 to 2106 using a dynamic disease transmission model.

Methods

Modeling Approach

We developed a deterministic, age-structured, epidemiologic model to study the transmission of and vaccination against HAV infection in the United States. The population was divided into several distinct classes: maternal antibodies, susceptible, exposed, asymptomatic infection, outpatient, hospitalized, fulminant, patients with recent liver transplant, patients with past liver transplant, recovered, and vaccinated (Fig. 1). Each compartment was further categorized into 110 age groups (0 to <1, 1, …, and 109 years or older).

We chose a simple demographic model with an equilibrium age distribution and a stationary population, where the number of births is equal to the number of non–HAV-related deaths [16]. In the model, persons enter the population in the less-than-1-year age group, and persons move between successive age groups at an age-specific transfer rate per year. The transfer rate depends on the mortality rate and the number of years spent within an age group. Persons exit the model on death at an age-specific death rate per year [16].

All infants are born with maternal antibodies. After immunity derived from maternal antibodies wanes, infants move to the susceptible class and remain there until they are vaccinated, infected, or dead from causes other than HAV infection. A fraction of susceptible persons are exposed to infection at an age-specific and time-dependent rate (per capita force of infection) and enter the exposed compartment. The rate at which persons of a given age class at a given time are exposed to infection depends on the number of contacts, the fraction of

infected contacts, the transmission probability per contact, and the nature of mixing between different age groups. The contact pattern is governed by a conditional probability mixing matrix. Each cell in the mixing matrix represents the probability of a person of a given age class having contact with a person in another age class.

After a latent period, exposed persons can become infectious. Infection can be either asymptomatic or symptomatic. Patients with symptoms are treated as outpatient or hospitalized, can become fulminant, may require a liver transplant, or die from HAV infection. To account for differential mortality, costs, and quality of life during the period immediately after transplantation, we subdivided this health state into two: first year and subsequent years. Infected persons can clear their infection and move to the recovered compartment with lifelong immunity. Vaccinated persons leave the susceptible compartment at a given vaccination rate and enter the vaccinated compartment and remain there until they die or their immunity wanes.

The model used in the simulations consists of 1650 differential equations corresponding to the 15 epidemiologic classes within each of the 110 age groups. All differential equations and details of the epidemiologic model are given in the Appendix in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2015.02.004.

Vaccination Strategies

Vaccination of persons aged 1 year or older against HAV infection became available in the United States in 1995-1996. Before 2006, the ACIP adopted an incremental vaccination strategy, focusing primarily on vaccinating high-risk groups or children residing in geographical locations with persistently high hepatitis A incidence (termed regional vaccination policy in this study). In 2006, the ACIP expanded the recommendations to include the routine vaccination of children aged 1 year or more in the United States (termed universal vaccination strategy in this study) [8].

In the model, the vaccination at age 1 year is incorporated by moving a fraction of infants from the susceptible class to the vaccination class before they are 2 years old. We compared hepatitis A vaccination of children aged 1 year or older following a regional strategy with routine vaccination using a universal strategy.

Model Parameters and Data Sources

We identified baseline values for demographic, epidemiologic, vaccine, and economic inputs of the model through an extensive search of the published literature (Table 1). The following describes in brief the values and sources for key parameters.

Demographic Parameters

Death rates were obtained from US Decennial Life Tables for 1999 to 2001 for age-specific mortality rates across both sexes and all races [17]. Other demographic data were obtained from the US Census Bureau. For example, the US population in 2006 was assumed to be 298,379,912 [18].

Transmission Rates and Force of Infection

Persons in the model could be infected either from foreign travel or from coming in contact with an infected person living in the United States. Analyses of data for the period before 1995 indicated that international travel accounted for only 4% of the infections with a known source [19]. Recent estimates put hepatitis A infections from travel to hepatitis A–endemic countries to be more than 45% of total infections [20]. To estimate the force of infection for local transmission, we adjusted total infection downward using estimates of age-specific contribution of international travel to total transmission [21].

The epidemiologic data on HAV infection suggest a behavior of a dynamic system in transition [3]. To estimate the forces of infection before vaccination programs were initiated, we used least square methods to fit the model to data on age-specific seroprevalence from the National Health and Nutrition Examination Survey II and III and reported incidence from the National Notifiable Diseases Surveillance System (1980–1995) [22–24]. Because a high proportion of hepatitis A infections are anicteric (i.e., are not recognized) or reported, we divided the reported disease incidence by the age-specific probability of developing jaundice and an estimate of underreporting factor [3]. Our approach does not assume that the endemic disease has reached an equilibrium state before vaccination. Thus, the forces of infection continue to change with time during the prevaccination period (Table 1). Assuming proportionate mixing, we used the estimated age-specific force of infection to calculate activity levels in the contact-mixing matrix (see Appendix in Supplemental Materials). Other parameters of the natural history of HAV infection are summarized in Table 1.

Hepatitis A Disease

We modeled several health outcomes associated with HAV infection including outpatient visits, hospitalizations, fulminant disease, liver transplant, and death (Fig. 1). The conditional probabilities given symptomatic HAV infection were based on previous studies (Table 1). We assumed that anicteric cases do not require health care and that only the management of icteric hepatitis A cases entails the use of health care resources. Furthermore, we assumed that all hospitalizations including fulminant cases were reported to the public health authorities. Thus, the conditional probabilities given in Table 1 were divided by the underreporting factor to arrive at the probability of hospitalization and fulminant disease given an icteric case [12]. Outpatient rates were estimated as a residual after accounting for all other health outcomes among symptomatic patients.

Vaccine Parameters

Vaccine efficacy for one or two doses was assumed to be 100% [25]. Current data suggest that the duration of immunity conferred by vaccination is long [26]. We assumed that the median duration of protection of a completed one-dose and two-dose hepatitis A vaccination in the base case was 21 and 32 years, respectively, and examined alternative assumptions in sensitivity analyses [27]. We also assumed that one-dose vaccine coverage under the regional vaccination strategy stayed constant at 10% throughout the simulation period [28]. In the universal vaccination strategy, we assumed that receipt of at least one dose increased linearly from 60.4% in 2006 to 81.2% in 2011 and then remained at 81.2% thereafter [29]. For both vaccination strategies, we assumed that only 64.4% of the infants receiving the first dose will complete the two-dose vaccine series [29].

Costs

We adopted a societal perspective that requires the inclusion of both direct and indirect costs. The direct costs included treatment costs of HAV health outcomes and vaccination. Treatment costs included costs for outpatient visits, hospitalizations, fulminant disease, and liver transplantations [12,30,31]. For patients with liver transplant, we included a recurring annual cost for the rest of the patients' lives in addition to the health care cost during the year of the liver transplant. The vaccine costs included both the public acquisition cost and the private market price [32]. In particular, we used an average price, weighted by the market share of public and private vaccine for hepatitis A [33]. Vaccine administration cost was assumed to be $14 per dose [34]. We subtracted a $0.75 per dose Federal Excise Tax from total vaccine cost and did not include costs associated with any potential adverse events.

Table 1 – Base-case estimates and corresponding distributions for deterministic and probabilistic sensitivity analyses.

Parameter	Base case	Range	Distribution	Reference
Demography				
Population in 2006 (thousands)	298,380			[17]
Age-specific all-cause mortality	Varies			[17]
Infection				
Force of infection*				
Scale parameter, b_0	0.1021	Fixed		Estimated
Shape parameter, b_1	0.0001	Fixed		Estimated
Shape parameter, b_2	53.7928	Fixed		Estimated
Shift parameter for last period before vaccination, Δ	0.4773	Fixed		Estimated
Age-specific rate of exposure due to travel to endemic countries (per year)				[21]
0–4 y	1.90×10^{-3}	Fixed		
5–9 y	8.06×10^{-4}	Fixed		
10–19 y	1.42×10^{-4}	Fixed		
20–29 y	8.89×10^{-5}	Fixed		
30–39 y	5.94×10^{-5}	Fixed		
40–59 y	1.76×10^{-5}	Fixed		
60+ y	1.80×10^{-5}	Fixed		
Duration of maternal immunity (mo)	6.5	Fixed		[44]
Latency period (d)	14	Fixed		[8,45]
Age-specific mean duration of infectiousness (wk)				[21,46]
0–4 y	3.5	Fixed		
5–9 y	3.0	Fixed		
10+ y	2.5	Fixed		
Vaccine				
Vaccine efficacy, one dose only (%)	100	87.3–100	Derived distribution†	[25]
Vaccine efficacy, two doses (%)	100	87.3–100	Derived distribution†	Assumed
Median duration of vaccine-derived immunity, one dose only (y)	21	20.3–21.9	Gamma (2647.1, 0.0079)	Assumed
Median duration of vaccine-derived immunity, two doses (y)	32	30.9–33.4	Gamma (2517.63, 0.0127)	[27]
Vaccine uptake in 1995 and after, regional strategy, first dose (%)‡	10.0	1.8–17.0	Beta (5.88, 52.97)	[47]
Vaccine uptake in 2006, universal strategy, first dose (%)‡	63.4	60.9–64.5	Beta (1743.69, 1006.61)	[29]
Vaccine uptake in 2011 and after, universal strategy, first dose (%)	81.2	80.2–82.2	Beta (4761.11, 1102.33)	[29]
Vaccine adherence, probability of second dose given first dose (%)	64.3	61.8–66.8	Beta (906.60, 503.35)	[29]
Clinical outcomes				
Underreporting factor	7.2870	Fixed		Estimated
Probability an infection is icteric§	Varies			[3]
Scale parameter, α_0	0.852	Fixed		
Shape parameter, α_1	0.012	Fixed		
Shape parameter, α_2	1.903	Fixed		
Probability of hospitalization of an icteric infection (%)				[12]
≤4 y	0.638		Dirichlet (D1)‖	
5–14 y	2.333		Dirichlet (D2)	
15–39 y	3.088		Dirichlet (D3)	
40–59 y	2.539		Dirichlet (D4)	
60+ y	2.745		Dirichlet (D5)	
Probability of fulminant hepatitis A from an icteric infection (%)				[12]
≤4 y	0.052		Dirichlet (D1)	
5–14 y	0.007		Dirichlet (D2)	
15–39 y	0.093		Dirichlet (D3)	
40–59 y	0.755		Dirichlet (D4)	
60+ y	1.098		Dirichlet (D5)	
Probability of liver transplant from an icteric infection (%)				[12]
≤4 y	0.010		Dirichlet (D1)	
5–14 y	0.001		Dirichlet (D2)	
15–39 y	0.017		Dirichlet (D3)	

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Table 1 – *continued*

Parameter	Base case	Range	Distribution	Reference
40–59 y	0.142		Dirichlet (D4)	
60+ y	0.027		Dirichlet (D5)	
Probability of death from an icteric infection (%)				[12]
≤4 y	0.008		Dirichlet (D1)	
5–14 y	0.001		Dirichlet (D2)	
15–39 y	0.014		Dirichlet (D3)	
40–59 y	0.109		Dirichlet (D4)	
60+ y	0.736		Dirichlet (D5)	
Probability of death during first year of liver transplantation (%)	11.6	6.0–42.0	Beta (29.92, 228.02)	[48]
Probability of death from year 2 and beyond after liver transplantation (%)	4.4	2.4–11.0	Beta (4.63, 100.59)	[48]
Duration of hepatitis A symptoms (d)				[31]
Duration of outpatient icteric infection (d)	34.4	17–40	Gamma (34.37, 1.00)	
Duration of inpatient icteric infection (d)	67.8	27–78	Gamma (27.16, 2.50)	
Cost of one-dose vaccine (2013 $)				
Public sector	15.25			[32]
Private market	30.369			[32]
Proportion purchased by public sector	0.56			[33]
Cost of vaccine administration (2013 $)	14	11–17	Gamma (83.66, 0.16)	[34]
Medical costs (2013 $)				
Outpatient cost	1,130	809–1,355	Gamma (66.05, 17.11)	[12]
Hospitalization cost	11,165	6,360–22,841	Gamma (7.05, 1583.25)	[12]
Fulminant cost	33,227	16,613– 49,840	Gamma (15.37, 2162.31)	[12]
Annual cost of patients with liver transplant (first year)	191,661	175,345–208,693	Gamma (507.37, 377.76)	[30]
Annual cost of patients with liver transplant (subsequent years)	43,203	35,161– 52,062	Gamma (100.24, 431.02)	[30]
Public health cost of a reported infection (2013 $)	918	459–1,377	Gamma (15.37, 59.75)	[12]
Productivity losses				
Work loss, outpatient (d)	15.5	7–18	Gamma (1.95, 7.93)	[31]
Work loss, inpatient (d)	33.2	10–25	Gamma (1.04, 31.70)	[31]
Work loss, fulminant patient (d)	33.2	10–25	Gamma (1.04, 31.70)	[31]
Work loss, year of transplant (d)				
0–17 y	153.2	145–160	Gamma (1579.8, 0.09)	[12]
18–40 y	245	238–253	Gamma (4064, 0.06)	[49]
41–55 y	271	268–274	Gamma (36282, 0.007)	[49]
56–62 y	288	284–291	Gamma (23050.5, 0.012)	[49]
63+ y	314	306–321	Gamma (7389.12, 0.042)	[49]
Labor force participation rate (%)				[50]
16–19 y	34.3	33.5–35.0	Beta (5822.66, 11160.3)	
20–24 y	70.9	70.3–71.5	Beta (15461.3, 6336.7)	
25–34 y	81.7	81.3– 82.0	Beta (33464.2, 7509.8)	
35–44 y	82.6	82.2– 82.9	Beta (32733.2, 6907.8)	
45–54 y	80.2	79.8–80.6	Beta (35053.2, 8642.8)	
55–64 y	64.5	64.0– 65.0	Beta (24709.4, 13606.6)	
65+ y	18.5	18.0–18.8	Beta (7726.82, 34141.2)	
Median weekly earnings (2013 $)				[51,52]
16–24 y	452	6–1,230	Gamma (0.48, 931.86)	
25–34 y	706	99–1,559	Gamma (1.18, 596.60)	
35–44 y	868	206–1,733	Gamma (1.78, 485.25)	
45–54 y	892	224–1,758	Gamma (1.89, 472.20)	
55–64 y	907	235–1,773	Gamma (1.95, 464.39)	
65+ y	825	175–1,688	Gamma (0.61, 510.54)	
Discount rate per year (%)	3	0–5		
Utilities				
Average US population norms				[39]
20–29 y	0.920	0.913–0.927	Beta (5307.70, 461.54)	
30–39 y	0.905	0.898–0.912	Beta (6099.19, 640.25)	
40–49 y	0.874	0.867–0.882	Beta (6572.42, 947.51)	
50–59 y	0.848	0.840–0.857	Beta (5810.94, 1041.58)	
60–69 y	0.824	0.812–0.836	Beta (3187.16, 680.75)	
70–79 y	0.785	0.771–0.798	Beta (2791.9, 764.66)	

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Table 1 – *continued*

Parameter	Base case	Range	Distribution	Reference
80+ y	0.744	0.720–0.768	Beta (944.35, 324.94)	
Persons with anicteric hepatitis A	0.830	0.789–0.867	Beta (291.95,59.79)	[12]
Persons with icteric hepatitis A	0.642	0.607–0.682	Beta (410.13, 228.31)	[37]
Persons with liver transplant	0.730	0.630–0.840	Beta (49.40, 18.27)	[38]
Discount rate per year (%)	3	0–5		

* The force of infection at age group j is given by $\lambda^*_j = \Delta b_0 j^{b_1} e^{(-j/b_2)}$

† The distribution is given by $\frac{497}{249} - \frac{248}{249}\,\text{inversebetaregularized}[1,-\text{Uniform}(0,1),25,1]$.

‡ We assumed that vaccine uptake followed a linear trend between 2006 and 2011. We calculated the constant and the slope of the line using data from 2008 and 2011.

§ The probability of icteric infection among age group j is given by $\alpha_0[1-\exp(-\alpha_1 j^{\alpha_2})]$.

‖ The parameters of the Dirichlet distribution are as follows: D1 = (780.58043, 5.01309, 0.00617, 0.00017, 0.00014), D2 = (2960.87504, 70.72485, 0.00011, 0.00000, 0.00000), D3 = (5625.35118, 179.22808, 0.01977, 0.00054, 0.00044), D4 = (2792.46660, 72.77631, 1.29335, 0.03516, 0.02857), D5 = (880.83558, 24.93756, 2.73634, 0.04583, 0.04469).

Indirect costs included the costs associated with the work loss due to different health outcomes. These were estimated by multiplying the days of work loss from an HAV disease outcome by the labor force participation rate and daily wages of the patients' age group (Table 1).

Public health disease control costs are major components of the economic burden of a hepatitis A outbreak that include surveillance costs, immune globulin coordination and administration costs, and public notification costs [12,35]. We assumed that the total cost of an outbreak scales up linearly with its size and included a cost of $667 per reported symptomatic case of hepatitis A [12]. All costs were converted to 2013 dollars using the relevant component (medical care for direct costs and all items for indirect costs) of the consumer price index [36]. Future costs were discounted at a rate of 3% per year.

Utilities

We calculated quality-adjusted life-years (QALYs) by applying utility weights to time spent in each health state. We assumed a weight of 0.6819 for all outcomes related to hepatitis A, except liver transplant [37]. For patients with liver transplant, we assumed a weight of 0.73 for the remaining years of their lives [38]. We assumed that quality-of-life weight for persons in all other health states, including anicteric hepatitis A, is 1. To account for variation in background quality of life by age, all utility weights were multiplied by the age-specific US population norm [39]. Future QALYs were discounted at 3% per year.

Implementation

The model was programmed in Mathematica 9.0 (Wolfram Research, Inc., Champaign, IL). We used the built-in function NDSolve to find numerical solutions of the system of ordinary differential equations. NDSolve solves differential equations by using adaptive algorithms that include almost all the known integration methods such as the fourth-order Runge-Kutta method. The built-in function NMinimize was used for model fitting. We used Mathematica for all simulations, analysis, and production of figures.

Analyses

Base Case

We estimated expected health outcomes (total HAV infections, symptomatic HAV infections, outpatient visits, hospitalizations, fulminant cases, number of liver transplants, deaths, QALYs) and costs over a time horizon of 100 years.

Sensitivity Analyses

One-way sensitivity of the results was examined by changing the base-case values of the following parameters: vaccination parameters (efficacy, duration of protection, cost, coverage, and adherence), cost parameters, quality-of-life weights, and discount rate.

In addition, we performed probabilistic sensitivity analysis (PSA) using only a subset of parameters. We kept demographic parameters, force of infection parameters, and some other natural history parameters at their base-case values. Inputs related to vaccine properties and uptake, clinical outcomes, cost, and quality-of-life weights were included in a PSA (Table 1). The justification for the selection of the probability distribution function for each parameter included in the PSA is provided in the Appendix in Supplemental Materials. We used Latin hypercube sampling techniques to generate 1000 random samples for use as inputs in the simulations [40]. The results of PSA were summarized using the mean of outcomes and presented using a scatter plot in the incremental cost-effectiveness plane [41]. The plane summarizes uncertainty in the results of the cost-effectiveness analysis by showing the number of simulations for which a strategy is cost-effective for a range of maximum monetary values that a decision maker might be willing to pay for each QALY gained.

To further test the sensitivity of results to some inputs taking extreme values, we conducted several scenario analyses for which we made the following assumptions. First, we examined a scenario in which herd protection/immunity effects are ignored. This entails allowing the force of infection to change according to the prediction of the model without vaccination. Thus, only the direct benefits of vaccination are conferred on persons receiving the vaccine. Second, we assumed that adherence to the two-dose series is perfect. This implies a high effective coverage with two-dose series among 1-year-olds. Finally, we evaluated the cost-effectiveness of vaccination from the narrower health care perspective considering only direct medical costs and excluding indirect costs.

Model Transparency and Validation

To facilitate independent review of the model as well as replication of our results, the model's structure, all equations, inputs, and outputs were made available in the Supplemental Technical Report (see Supplementary Material found at http://dx.doi.org/10.1016/j.jval.2015.02.004) [42]. We assessed the face validity of the model by comparing its assumptions regarding the natural history of HAV infection and disease with previously published

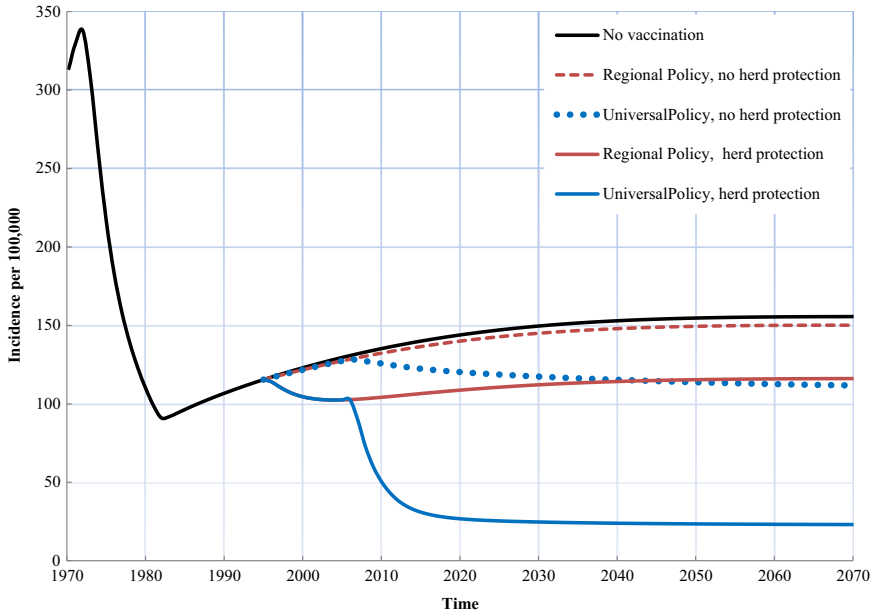

Fig. 2 – Impact of universal vaccination and regional vaccination on the incidence of hepatitis A disease. (Color version of figure appears online.)

studies [21,43]. To ensure internal validity, several tests were conducted (e.g., total outflow and inflow between compartments are balanced and adding the number of persons in each compartment is equivalent to the total population size). The predictive validity of the model was evaluated by comparing model results with epidemiologic data reported in the literature (see Appendix in Supplemental Materials).

Results

Base Case

Epidemiology results

The model predicted that universal childhood vaccination led to a significant reduction in the incidence of hepatitis A (Fig. 2). In particular, the incidence of any hepatitis A infection under regional vaccination declined from 103 per 100,000 in 2006 to 27 per 100,000 in 2020 under universal vaccination. Significant improvements in cumulative hepatitis A health outcomes in the long run were predicted after the introduction of universal vaccination (Table 2). For example, over a 100-year period, there would be 33.9 million cases of hepatitis A infection under the regional vaccination strategy and 7.9 million cases under the universal vaccination strategy. Thus, switching from a policy of regional vaccination to universal vaccination prevented 26.0 million cases of hepatitis A. Universal vaccination led to a significant reduction in all the disease outcome measures included in the model: outpatient visits, hospitalizations, fulminant hepatitis A, liver transplants, and deaths (Table 2). Also, the cumulative incremental benefits of universal vaccination increased over time. For example, relative to regional vaccination, universal vaccination prevented 28,152 hospitalizations over a 10-year period compared with 478,122 hospitalizations over a 100-year period.

Cost-effectiveness results

The economic impact of the two strategies is presented in Table 3. The results for costs and QALYs are presented on a per-person basis. For example, vaccinating children under a regional policy would cost $1.55 per person over 100 years compared with $12.39 per person under a universal vaccination strategy. Even though vaccination costs are higher under the universal vaccination strategy, the total cost of universal vaccination is lower due to lower direct and indirect medical costs compared with regional policy. In particular, universal vaccination costs $33.48 per person over 100 years compared with a total

Table 2 – Cumulative cases of hepatitis A disease in the US population with regional and universal vaccination of 1-y-olds over time (years after 2006).

Cumulative outcomes	Regional vaccination through			Universal vaccination through		
	10 y	50 y	100 y	10 y	50 y	100 y
Any infection (millions)	3.12	16.59	33.91	1.55	4.50	7.93
Anicteric infections (millions)	1.10	5.70	11.56	0.54	1.60	2.87
Icteric infections (millions)	2.03	10.89	22.35	1.01	2.90	5.06
Outpatient visits (millions)	1.96	10.53	21.61	0.98	2.80	4.90
Hospitalizations	56,195	301,348	617,936	28,043	80,205	139,814
Fulminant cases	6,567	39,059	82,481	3,199	10,569	19,464
Liver transplants	871	4,821	9,904	427	1,311	2,306
Deaths	2,115	13,748	29,926	1,024	3,700	7,163

Table 3 – Cost-effectiveness analysis of a universal vaccination program of 1-y-olds over time compared with a regional vaccination program.

Cumulative outcomes (per person)	Regional vaccination through			Universal vaccination through		
	10 y	50 y	100 y	10 y	50 y	100 y
Vaccination costs ($)	0.419	1.263	1.551	3.194	10.048	12.387
Disease costs ($)	10.905	34.762	43.294	6.303	12.287	13.933
Indirect costs ($)	6.178	19.730	24.505	3.164	6.242	7.159
Total costs ($)	17.502	55.754	69.350	12.661	28.577	33.480
QALYs (y)	7.498	22.617	27.776	7.498	22.618	27.777
ICER ($ per QALY)	–	–	–	Cost saving	Cost saving	Cost saving

ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years.

cost of $69.35 per person under a regional vaccination policy. Also, universal vaccination generates higher discounted QALYs per person than does a regional vaccination policy (Table 3). Thus, universal vaccination is cost saving over a 100-year period, with every $1 spent vaccinating a person through a universal vaccination strategy as compared with a regional one resulting in the society saving $2.7 in avoided disease costs and $1.6 in avoided productivity losses and disease control costs. In fact, universal vaccination was cost saving even when the time horizon was assumed to be 10 years.

Deterministic Sensitivity Analysis

The incremental cost of universal vaccination compared with a regional vaccination policy was sensitive to variations in the discount rate, vaccine uptake rate for the regional strategy, outpatient days lost to work, outpatient cost, median weekly earnings, hospitalization cost, public health cost of a reported infection, cost of vaccine administration, cost of treating a fulminant case, and vaccine efficacy (see Appendix Table S4 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2015.02.004). Nonetheless, universal vaccination compared with a regional vaccination policy remained cost saving over all the ranges of parameter values considered. Universal vaccination was also cost saving when we assumed that the adherence to the two-dose series is perfect (see Appendix Table S5 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2015.02.004). Because direct costs (vaccination + disease costs) were lower, universal vaccination compared with a regional vaccination strategy was also cost saving from the health care perspective (Table 3).

Herd protection

The exclusion of herd protection/immunity in the model had a significant effect on results (Table 4). For example, by ignoring herd protection 9.50 million cases of hepatitis A were avoided using a universal vaccination policy instead of following a regional policy for 100 years. In contrast, 25.98 million cases were avoided if herd protection/immunity is taken into account. Also, herd protection/immunity accounted for a significant share of the reduction in all the hepatitis A outcomes associated with vaccination. For example, including herd protection in the analysis led to a more than threefold increase in avoided outpatient visits, hospitalizations, and fulminant cases (Table 4). These public health benefits of herd protection/immunity led to significant cost reduction and QALY gains. For example, ignoring herd protection/immunity, when comparing universal vaccination with regional vaccination, there is an additional $3.487 in cost and 0.0002 in QALYs per person, for an incremental cost-effectiveness ratio of $21,223 per QALY. With inclusion of herd protection, however, universal vaccination was cost saving compared with regional vaccination.

Probabilistic Sensitivity Analysis

We performed a PSA using 1000 Monte Carlo simulations. The results showed that the mean incremental total cost per person of universal vaccination compared with a regional vaccination policy was –$45.09 (95% confidence interval –121.97 to –11.21). The corresponding values for QALYs were 0.00061 (95% confidence interval 0.00053–0.00069). The median incremental cost and QALY was –$37.23 and 0.00061 years, respectively. The incremental cost-effectiveness plane showed that all incremental cost-QALY pairs fall in the southeast quadrant, indicating that the universal vaccination policy is less costly and more effective than the regional vaccination policy in all the 1000 simulations (Fig. 3).

Table 4 – Impact of herd protection effects of a universal vaccination program of 1-y-olds in the US population compared with a regional vaccination program over 100 y.*

Incremental outcome measures	Without herd protection/ immunity	With herd protection/ immunity
Cases prevented		
Any infection (millions)	9.50	25.98
Icteric infections (millions)	4.76	17.28
Outpatient visits (millions)	4.62	16.71
Hospitalizations	128,634	478,122
Fulminant cases	6,943	63,017
Liver transplantations	1,140	7,598
Deaths	1,531	22,763
Additional costs ($ per person)		
Vaccination costs	10.836	10.836
Disease costs	–5.202	–29.361
Indirect costs	–2.147	–17.346
Total costs	3.487	–35.870
Additional QALY (years per person)	0.0002	0.0009
ICER ($ per QALY)*	21,223	Cost saving

ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years.

* ICER is not equal to total additional cost divided by total additional QALYs because of rounding errors.

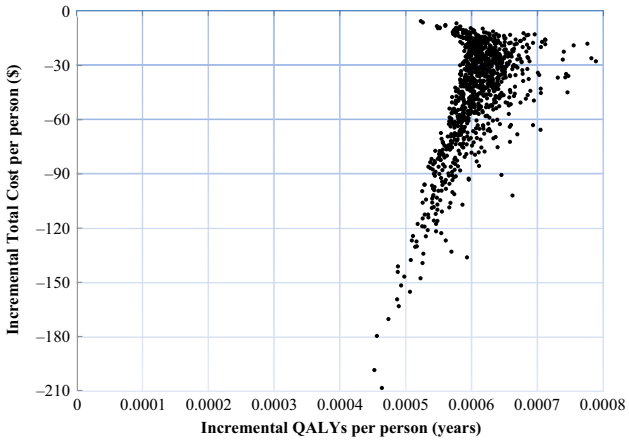

Fig. 3 – Scatter plot of estimated joint density of incremental total costs and QALYs per person of universal compared with regional vaccination. QALY, quality-adjusted life-year.

Discussion

We developed a dynamic model to evaluate the cost-effectiveness of universal hepatitis A vaccination of children in the United States. Previous cost-effectiveness models of hepatitis A vaccine in the United States used a cohort model. Although cohort models showed the HAV vaccine to be cost-effective, they do not estimate herd protection effects of vaccination on the disease costs and health outcomes. To our knowledge, this is the first cost-effectiveness evaluation of hepatitis A vaccination in the United States that used a dynamic modeling approach with herd protection effects. In the base case, universal vaccination was cost saving compared with a regional vaccination program. Universal vaccination also led to significant reductions in HAV cases and associated morbidity and mortality. The model also showed that herd protection effects played an important role in reducing HAV disease incidence and associated costs. In particular, the impact of herd protection on the cost-effectiveness ratio was profound. When we excluded herd protection effects, the incremental cost-effectiveness ratio changed from cost saving to $21,223 per QALY.

Some previous studies modeled changes in HAV incidence over time during prevaccination as exogenous exponential decay functions in time [3,12]. For example, Rein et al. [12] assumed that the incidence of hepatitis A would decline at a constant annual rate of 1.4% after 1990. To our knowledge, this is the first study that predicted endogenous changes in the incidence of hepatitis A during the prevaccine era in response to external effects on the force of infection (e.g., improvement in public infrastructure and sanitation). One other key difference between the model in this study and previous models is the inclusion of maternal antibodies. Several studies estimated seroprevalence at birth at 100% in many developed and developing countries [44,53,54]. A recent modeling study using data on infants from Nicaragua found the median time when antibodies would fall below the level of seroprotection (assumed 10 mIU/ml) was 11.1 months [54]. Because maternally derived antibodies persist for a relatively extended period of time in a significant proportion of infants, it is important to capture their influence on population-level immunity when assessing the impact of hepatitis A vaccination.

This study has several limitations. First, our findings were based on a modeling exercise, rather than real-world data. Because models are simplifications of reality, they have inherent limitations (e.g., may not accurately represent a very important real-world event). Second, because of lack of data to inform model's parameters (e.g., infectivity and contact patterns), we made several simplifying assumptions regarding disease transmission (e.g., proportionate mixing) and inferred the values of some of these parameters by fitting the model to historical data. We also assumed that several parameter values will stay constant during the simulation period. This may be a reasonable assumption for some, but unrealistic for others. For example, vaccine coverage, compliance with the two-dose vaccine series, and contribution of international travel to infection may change in the future. Third, because not all cases of HAV infection are reported to public health authorities, we adjusted the reported incidence data upward to account for underreporting. Fourth, values of parameters were obtained through a synthesis of the literature with some uncertainties around the values of some parameters. Finally, we did not include the cost or disutility of any adverse events. Because there are no serious adverse events associated with the administration of the vaccine, and most commonly reported adverse events (e.g., injection site pain, erythema, or swelling) are generally mild and self-limited, it is unlikely that the inclusion of adverse events will have any material effects on the results.

Although the ACIP recommended routine hepatitis A vaccination for all children in the United States in 2006, the uptake of the two-dose hepatitis A vaccine is well below the coverage rates of other pediatric and adolescent vaccines [9]. Even though the HAV disease burden in the United States is at its all-time low, there still remains a substantial burden of disease from hepatitis A. The results from the analysis presented here show that it may be a sound economic strategy to increase hepatitis A vaccine coverage given that the universal vaccination is cost saving from both a payer and a societal perspective.

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Supplemental Materials

Supplemental material accompanying this article can be found in the online version as a hyperlink at http://dx.doi.org/10.1016/j.jval.2015.02.004 or, if a hard copy of article, at www.valueinhealthjournal.com/issues (select volume, issue, and article).

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