

Technical Documentation: The Cost-Effectiveness of Routine Childhood Vaccination for
Hepatitis A in the United States

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This report has been compiled to provide supporting documentation and information for the manuscript “The Cost-Effectiveness of Routine Childhood Vaccination for Hepatitis A in the United States.” The technical report consists primarily of reference tables and information, with text added in some instances to clarify or interpret the information contained in the tables. This report can also be used to understand how to modify and apply this model to other contexts. The report is divided into 13 sections.

I. Overall model functionality

The Hepatitis A (HepA) vaccine cost-effectiveness analysis tool uses a Markov model to simulate how a birth cohort progresses through states and transitions between states with respect to HepA. Figure 1.1 describes the basic structure for the model. A cohort progresses between the states on an annual basis to simulate a 95-year lifetime starting at birth. Progression is based on probabilities of relevant events, such as HepA infection or vaccination, and other transitions between states, such as those caused by passing time or death, encountered by the portion of the cohort in each state. Each state and event is associated with costs for medical care, gains for productivity and gains in life years and quality-adjusted life years (QALYs), as relevant; the model collects these values over the course of the cohort’s lifetime. On each model run, the cohort’s outcomes from both a baseline scenario (i.e. no vaccine or a more conservative vaccine policy) and then a scenario that includes the vaccination policy of interest are observed, recorded, and compared to calculate cost-effectiveness measures.

States. The model states are the following:

- *Susceptible, not immunized* – never been immunized; eligible for infection
- *Immune: 1, 2, ...95 years to immunity loss* – immunized; vaccine-induced immunity not (yet) lost
 - 95 states: 1 for each possible number of remaining years of immunity loss
- *Susceptible, immunized* – immunized; vaccine-induced immunity lost, therefore eligible for infection
- *Immune (due to disease), immunity unknown* – immune due to past disease exposure; disease was not identified, therefore immunity is not known and individual may seek vaccination
- *Immune (due to disease), also vaccinated* – immune due to past disease exposure; disease was not identified, therefore individual sought and received vaccination
- *Immune (due to disease), immunity known* – immune due to past disease exposure; disease was identified
- *0, 1, ...18+ years since transplant* – history of liver transplant due to HepA; immune due to past disease exposure; disease was identified; increased risk of death; reduced quality of life
 - 19 states: 1 for each possible number of years since transplant; 18 years after and later are grouped
- *Dead* – dead due to HepA or non-HepA-related causes; accumulating productivity losses

Transitions 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.

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

Of those not vaccinated (in the *Susceptible, not immunized* state), a certain portion will be infected with HepA. Infected persons will end up distributed between *Immune (due to disease), immunity unknown; Immune (due to disease), immunity known; 0 years since transplant; or Dead* based on their particular disease progression paths. Those who develop fulminant HepA and die either before or after a transplant are moved to the *Dead* state. Those who develop fulminant HepA then get and survive the year of a liver transplant end up in *0 years since transplant*. All others who have icteric HepA that is identified and reported are moved into *Immune (due to disease), immunity known*. The rest of infected cases, which all have anicteric or icteric HepA that never goes reported, end up in *Immune (due to disease), immunity unknown*.

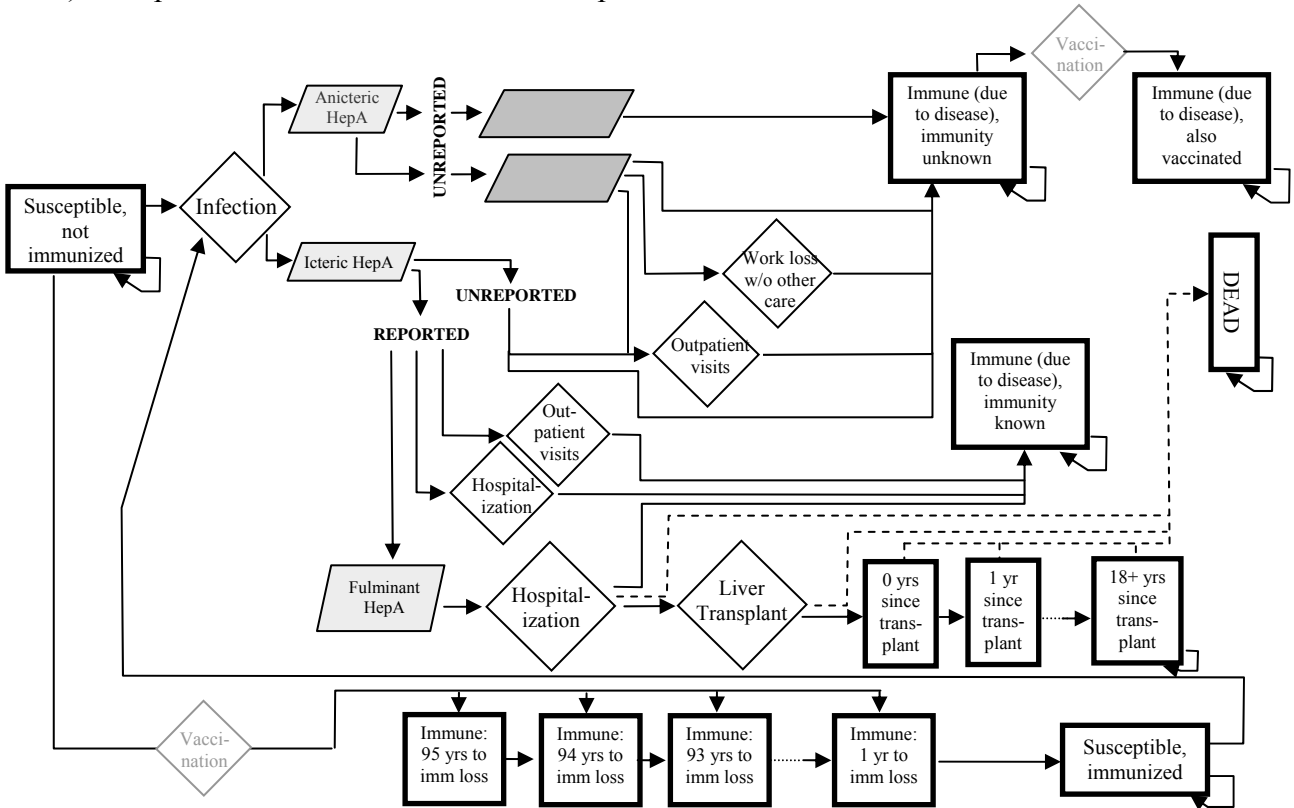
The portion of the cohort that is not vaccinated or infected stays in *Susceptible, not immunized* for the following year.

Finally, after all of the above transitions have occurred, a percentage of the cohort in all states transitions to the *Dead* state to account for non-HepA-related deaths.

This process is repeated in following years with whatever portion of the cohort is in the *Susceptible, not immunized* state at the time.

Figure 1.1 Model structure diagram

In this diagram, rectangular boxes represent “states” between which the cohort is distributed at the end of every year based on the transitions and events that occur. Diamonds represent events that affect costs and the end-of-year state. Disease development stages are represented by shaded parallelograms. Dotted lines indicate death from HepA-related causes. Death from non-HepA-related causes occurs at the same rate between all states (arrows for this transition not drawn). Hospitalization includes additional outpatient visits.



Outcomes. The model calculates cumulative outcomes, as well as incremental costs and outcomes associated with the vaccination policy of interest relative to baseline. It then compares these outcomes of the cohorts under both scenarios to assess the impact of the vaccination policy as compared to the baseline group using cost-effectiveness, cost-utility and cost-benefit analysis measures. Costs and QALYs are discounted using a user-defined. We collect the following outcomes:

- Cases of each level of HepA
- HepA-related outpatient visits, hospitalizations, liver transplants
- HepA-related deaths
- Childhood and adult immunizations
- Mild and severe adverse events from HepA immunizations
- Days of work loss due to:
 - Care-giving or self-care for HepA-related illness
 - HepA-related death
 - Getting HepA vaccinations
 - Care-giving or self-care for adverse events from HepA vaccinations
- Life years
- QALYs

- Costs for medical care of HepA-related illness
- Childhood and adult HepA immunization costs
- Productivity losses due to:
 - Care-giving or self-care for HepA-related illness
 - HepA-related death
 - Getting HepA vaccinations
 - Care-giving or self-care for adverse events from HepA vaccinations
- Public health response costs

Analyses. With a few exceptions, values of all parameters can be varied between model runs, however analyses typically vary by the following factors:

- Age of mass childhood vaccination (Age one for the analysis in the manuscript, this can be set to any age)
- Regions considered (in the manuscript these are specified to the three regions established by the 1999 ACIP recommendations, but the population of these regions can be specified to divide any area into at least three groups – with additional programming, the model could be modified to add additional regions)
- Policy scenario comparison

Policy change of interest	Baseline policy (comparator)	Policy of interest
Implementing a recommendation for childhood vaccination rather than no childhood vaccination	No vaccination	Recommend vaccination in high-incidence regions only
		Recommend vaccination nationwide
Expanding existing recommendation from high-incidence only to also include low-incidence regions	90% first dose coverage in high-incidence regions only	Recommend vaccination nationwide
Expanding recommendations in a way that increases coverage nationwide.	Partial vaccination coverage based on partial implementation in each of the three regions.	90% first dose coverage in each region of the country.

II. Incidence of Infection.

Incidence in the the Hepatitis A (HepA) vaccine cost-effectiveness analysis tool is defined as the annual probability of infection with Hepatitis A virus, given that a patient was not immune from previous infection. This probability depends on patient age and region of the country. The actual U.S. Hepatitis A incidence trends are characterized by approximately 5- to 15-year cycles and by a long-term decline. We modeled incidence based on the average incidence over the 5-year time frame of 1990 to 1995. These years were chosen because they immediately preceded the introduction of the hepatitis A vaccine in 1996, and the introduction of the vaccine was thought to alter U.S. patterns of incidence. Intuitively, we tried to model the level of incidence that should be expected in each region if a vaccine had never been invented. In the model, the introduction of vaccine would then protect patients from this underlying risk of infection.

To do this, we estimated an actual mean reported starting incidence value based on the average incidence from 1990 to 1995, and then an average annual rate of decline expected in subsequent years. To do this, we used a linear regression of the logarithm of reported hepatitis A rates against year. In this regression the intercept was allowed to vary across the 3 regions while the rates of decline were assumed to be equal.^{1,2,3} From the regression we estimated a starting (i.e. 1990) reported mean incidence of acute hepatitis A of 22.6 cases per 100,000 patients in the region 1, 14.1 cases per 100,000 patients in region 2, and 6.7 cases per 100,000 patients in region 3. We then estimated applied an estimated annual rate of decline of 1.4% to each intercept for each year after 1990 in the analysis. The model assumed that *without* immunization this rate of decline would have continued from 1990 indefinitely into the future.

Actual incidence varies widely by age from the mean population incidence. Age-specific incidence was estimated by multiplying the estimated average incidence for each region by the ratio of age-specific incidence to overall incidence during 1990 to 1995, the years immediately preceding the licensing of the HA vaccine.²

Reported cases represent only a portion of total incidence. Based on previous estimations, for each reported case of hepatitis we assumed there were 3.28 unreported cases.⁴ All reported cases were assumed to be icteric (symptomatic with jaundice). The number of additional anicteric cases (asymptomatic or mildly symptomatic without jaundice) was estimated by applying an age-specific ratio, also determined by regression.⁴

III. Loss of vaccine-acquire immunity

The level of immunity in a vaccinated person is measured by *geometric mean titre* (GMT) level; higher GMT levels equate to immunity to contracting HepA. In this model, people lose vaccine-acquired immunity if their GMT level falls below a certain threshold value; all those with a GMT above that level have immunity. The model assumes that after immunization GMT levels reach an initial peak followed by a decline over time based on an annual percentage loss. Among those within the cohort that are vaccinated, some are vaccinated with 1 dose and others 2; those who receive 2 doses generally have higher initial GMT levels. Then, among people receiving the same number of doses, the initial GMT levels after immunization vary based on a specified lognormal distribution. Therefore time to immunity loss also varies. Table 3.1 lists the parameters and corresponding default values that determine vaccine-acquired immunity.

When a portion of the cohort is immunized, that portion is assigned initial GMT levels and then, based on those levels, distributed into one of 96 states corresponding with 0 to 95 years until immunity loss. Those with 0 years until immunity loss never had a high enough GMT level to be immune and go directly to *Susceptible, immunized*; those with more years until immunity loss progress to one of the 95 *Immune* (after vaccination) states. Each year individuals who are newly immunized are introduced to these 96 states.

Those who were immunized in years prior and are still immune progress to the state corresponding with 1 less year until immunity loss, with the exception that after *Immune: 1 year to immunity loss* they progress to *Susceptible, immunized*.

Table 3.1. Parameters related to vaccine-induced immunity

Parameter	Default value	Source
Average GMT level immediately after receiving vaccine	1 dose: 141 2 doses: 1120	Van Herck K, Van Damme P (2001)
Lower bound of 95% CI of GMT levels immediately after receiving vaccine	1 dose: 112 2 doses: 912	Van Herck K, Van Damme P (2001)
Upper bound of 95% CI of GMT levels immediately after receiving vaccine	1 dose: 177 2 doses: 1374	Van Herck K, Van Damme P (2001)
Annual rate of loss of GMT in years following vaccination (0-1)	0 yrs since vac: 0 1-4 yrs since vac: 0.2 5-95 yrs since vac: 0.05	Van Damme P (personal communication)
GMT level at which immunity is lost	20	Delem A et al (1993)

CI = confidence interval

GMT = geometric mean titre level

yrs since vac = years since vaccination

The model conducts this process using the following 3 steps: determine the number of years of immunity from vaccination associated with the different initial post-vaccination GMT levels;

calculate the shape of the distribution of GMT levels among newly vaccinated people; and assign newly vaccinated to states.

Associated GMT levels with years of immunity. The model first determines the GMT levels that are associated with each year of remaining immunity by using the GMT at which immunity is lost and the annual rate of loss of GMT after vaccination. Table 3.2 presents selected GMT levels associated with each year of remaining immunity given the default values presented above in Table 3.1.

Table 3.2. Relationship between GMT level and years of immunity from vaccination.

If your GMT level after immunization is at least...*	Then you have this many remaining years of immunity...
20	1
25	2
31	3
63	10
82	15
105	20
176	30
294	40
820	60
2288	80
4938	95

Calculate standard deviation of distribution of GMT levels among newly vaccinated. The distribution of initial levels is assumed to have a lognormal distribution; the user specifies the distributional shape by an average value and 95% confidence interval bounds (first 3 parameters in Table 3.1 above). The default values are based on findings by the Belgian researchers Van Herck and Van Damme (2001), who observed GMT levels after hepatitis A vaccinations.

Decay rates are assumed to vary based on time since immunization; default values for that parameter are unpublished, but based on data collected by Van Damme.

The model uses the mean, confidence interval bounds, and sample size of GMT level data points in Equation 3.1 to calculate the standard deviation of the initial GMT levels observed. We applied Van Herck and Van Damme’s study sample size of 77 in our calculations.

$$\text{Standard deviation of GMT levels} = \frac{(CI \text{ upper bound} - CI \text{ lower bound})\sqrt{n}}{2 \cdot 1.96} \quad (3.1)$$

Assign newly vaccinated to states. Once the shape of the lognormal distribution is established, the model must then allocate the newly vaccinated portion of the population between the 96 post-vaccination states. It does this by determining the percentage of the

population that has GMT levels within the range associated with each number of years of immunity and, in turn, each state. In order to make this determination, the model makes use of the fact that the natural log of a lognormally distributed variable is normally distributed and follows the following process for both 1 and 2 doses:

1. Calculate the mean and standard deviation of the normally distributed natural log of GMT levels using Equations 3.2 and 3.3.

$$\text{Mean of } \ln(\text{GMT}) = \ln\left(\frac{\text{mean GMT}^2}{\sqrt{\text{std dev of GMT}^2 + \text{mean GMT}^2}}\right) \quad (3.2)$$

$$\text{Standard deviation of } \ln(\text{GMT}) = \sqrt{\ln\left(\frac{\text{std dev of GMT}}{\text{mean GMT}}\right)^2 + 1} \quad (3.3)$$

Based on the default values, the mean of $\ln(\text{GMT})$ is 4.33 for one dose and 6.71 for two doses; the standard deviation of $\ln(\text{GMT})$ is 1.11 for one dose and 0.79 for two doses.

2. Calculate the natural log of the GMT level defining the upper boundary of each post-vaccination state (20, 25, 31, etc.).
3. Standardize the natural log of each GMT level by subtracting the mean of $\ln(\text{GMT})$ and dividing the difference by the standard deviation of $\ln(\text{GMT})$. Plotting these standardized values forms a standard normal distribution.
4. The model has a stored table of values specifying the percent of the area under the curve within each 0.01-width bin of a standard normal distribution. The model uses these percent-under-the-curve values to calculate the percent of the newly vaccinated population falling within the range of GMT values corresponding to each year of immunity remaining (0-95). Table 3.3 reports

Table 3.3. Standardized GMT level and percent of newly vaccinated people with different years of remaining immunity.

Years of immunity*	GMT Level	One dose		Two doses	
		Standardized GMT level	% of newly vaccinated	Standardized GMT level	% of newly vaccinated
0	0	n/a	11	n/a	0
1	20	-1.2	5	-4.7	0
2	25	-1.0	5	-4.4	0
3-10	63	-0.2	24	-3.3	0
11-15	82	0.1	9	-2.9	0
16-20	105	0.3	9	-2.6	0
21-30	176	0.8	16	-1.9	3
31-40	294	1.2	11	-1.3	7
41-50	491	1.7	6	-0.7	18

Years of immunity*	GMT Level	One dose		Two doses	
		Standardized GMT level	% of newly vaccinated	Standardized GMT level	% of newly vaccinated
51-60	820	2.1	3	-0.4	24
61-70	1370	2.6	1	0.6	24
71-80	2288	3.1	0	1.3	15
81-90	3821	3.5	0	2.0	7
91-95	4938	3.8	0	2.3	2

*Only selected years of immunity presented

5. The newly vaccination portion of the population is distributed accordingly to the 96 post-vaccination states based on the determined years of immunity.

IV. Vaccine Costs

Vaccination cost include the costs associated with vaccine acquisition (including both public and private prices for pediatric and adult doses) and the costs of vaccine administration (Table 4.1). The vaccine acquisition costs for pediatric and adult doses were taken from the Vaccines for Children vaccine price list, which provide both private sector and CDC-contract public costs per dose.⁵

Based on vaccine purchase data we estimated the proportion of the pediatric (0-17 years) and adult (18+) population each would receive the public price for the vaccine. The proportion of children and adults receiving the public price was determined by net pediatric Hepatitis A vaccine sales from the Biologics Surveillance data (CDC-contract purchases during the time period of 1995 to 2003) and proprietary vaccine sales data, respectively.⁶

Finally, all vaccine prices were adjusted to reflect vaccine wastage of five percent and do not include federal excise taxes of \$0.75 per dose.

Administration costs per dose were calculated using the outpatient claims for 8,327 privately insured individuals found in the 2002 MarketScan[®] Commercial Claims and Encounters Research Database⁷. The sample was restricted to patients aged 12 years and younger not enrolled in a Health Maintenance Organization (HMO) with claims for which Hepatitis A pediatric vaccination was the primary procedure. To determine the administration cost, we deducted the private sector vaccine acquisition cost (\$26.66 per dose)⁵ from the mean cost per claim found in the sample (\$38.65) to produce a per dose cost of \$12.

We assumed the administration cost would be shared equally (\$6) when the Hepatitis A vaccine was administered concurrently with previously other existing routine vaccinations at the relevant ages (i.e. Hepatitis A vaccination during an office visit at age 1 may be shared with Measles Mumps Rubella (MMR) vaccination)

Table 4.1 summarizes the vaccination acquisition and administration input costs used in the base case analysis.

Table 4.1. Vaccination, Costs and Probabilities

Parameter			Parameter Value Base Case Analysis	Source
Proportion vaccines purchased at public price		Ages 0-17	0.59	⁶
		18-95	0.1	Assumption
Acquisition cost	Public	Ages 0-17	\$11.15	⁵
		18-95	\$18.77	⁵
	Private	Ages 0-17	\$27.75	⁵
		18-95	\$59.57	⁵
Administration cost	First dose	Ages 1	\$6	⁷ , Assumption
		2-11	\$12	⁷
		12	\$6	⁷ , Assumption
		13-95	\$12	⁷
	Second dose	Ages 1	\$6	⁷ , Assumption
		2-95	\$12	⁷

V. Adult Vaccination

We assumed a proportion of the non-aged adult population (aged 18 to 64 years) would receive Hepatitis A vaccination in the absence of a childhood recommendation due to international travel, military personnel requirements and participation in other high risk activities (i.e. illegal drug users, men who have sex with men etc) ⁸.

We estimated region-specific (regions determined according to the 1999 ACIP recommendations) probabilities of one dose adult coverage using proprietary vaccine purchase data as reported in Samandari T et al (2004) and unpublished dosage information taken from the Defense Military Surveillance System.⁹ The number of doses purchased privately and the number of military personnel vaccinated per state per year (during the time period of 1996 to 2001) was averaged (assuming one-dose coverage and applying a vaccine wastage rate of five percent to the vaccine purchase estimates) to create an overall probability of adult vaccination. We assumed the probability of receiving a second dose given one-dose coverage to be zero. Table 5.1 summarizes the coverage rates by region used in the base case analysis.

Table 5.1 Adult Vaccination, Probabilities

Parameter			Parameter Value Base Case Analysis	Source
Probability adult immunization first dose	High region	Ages 18-64	0.0133	⁹ 1
	Intermediate region	Ages 18-64	0.0131	⁹ 1
	Low region	Ages 18-64	0.0084	⁹ 1
Probability adult immunization second dose first dose	All regions	Ages 18-64	0	Assumption

VI. Adverse events

Adverse events resulting from vaccination were classified according to severity – mild or severe (Table 6.1). The probability of a mild adverse event – defined as fever 38°C or higher which interferes with daily activities – was calculated by multiplying the proportion of those vaccinated who reported fever (0.057)¹⁰ by the proportion of all vaccine complications determined to interfere with daily activities (0.089)¹¹. We assumed an associated work loss of 0.875 days and no additional medical care costs.

The probability (0.000001) and associated medical care costs (\$957) of a severe adverse event – defined as onset of Guillain–Barre’ syndrome – was taken from expert panel estimates reported by Meltzer MI et al (2001). We assumed an associated work loss of five days.

Table 6.1 Adverse Events Costs and Probabilities

Parameter		Parameter Value Base Case Analysis	Source
Probability mild adverse event	Ages 0-95	0.0051	¹⁰ ¹¹
Probability severe adverse event	Ages 0-95	0.000001	¹²
Severe adverse event (medical care costs)	Ages 0-95	\$957	¹²

VII. Herd immunity

Incident infection stems from a reservoir in children. Vaccination of children has led to disproportionate declines in incidence among unvaccinated children and adults. Model estimates the herd immunity benefits that accrue to the unvaccinated members of the child cohort.

Herd immunity is based on the proportion of children 0-18 with vaccination coverage. For each 1% increase in vaccination in this cohort, incidence attributed to children declines 3.9% in children (1% for those vaccinated and an additional 2.9% among the unvaccinated) and 1% among adults.

For children, 90% of incident infections were attributed to other children. For adults 25% of incident infections were attributed to children.

To account for herd immunity, the probability of infection applied to those with no vaccination coverage was estimated as;

$I * \text{Proportion of children 0 to 18 with vaccination coverage} * \text{Herd Immunity Adjuster} * \text{Proportion of incident infections from children} + I * \text{Proportion of infections not from children}$

With a vaccination strategy at age 2, for children aged 0 to 18 this is;

$$(I * ((16/18) * .729 * .90 * -.029) + (I * .10))$$

For adults 19 to 95 this is;

$$(I * ((16/18) * .729 * .25 * -.01) + (I * .75))$$

VIII. Productivity losses

Productivity losses were calculated by combining the age-specific labor participation rate¹³ and daily earnings¹⁴ with the duration of work loss attributable to Hepatitis A stages of infection, vaccine administration and adverse events (Equation 1).

Equation 1.

$$\text{Productivity Losses (before discounting)} = (\text{ProbWork}) * (\text{TimeWorkLoss}) * (\text{Wage})$$

Where ProbWork = Labor participation rate, by age

TimeWorkLoss = Duration of work loss, by infection state

Wage = Daily earnings, by age

For children aged 0 to 15 years, we applied the labor participation rate and daily earnings of a parent or caregiver (calculated as a weighted average of 20 to 44-year-olds). In addition, a labor participation rate of 0 was assumed for individuals aged 65 years and older.

In the case of death attributable to Hepatitis A infection, we assumed an annual work loss of 250 days (5 days per week for 50 weeks). Table 8.1 presents the parameter values used in the model and their respective sources for duration of work loss, labor force participation and daily earnings.

Table 8.1. Productivity Losses

Parameter	Parameter Value		Source		
	Base Case Analysis				
Work Days Lost	Symptomatic anicteric infection		3	Assumption	
	Non-hospitalized icteric infection	Reported	Ages 0-12	3.7	15
				13-95	10
		Unreported	Ages 0-95	3	Assumption
	Hospitalization, Icteric Infection		Ages 0-95	33.2	17
	Hospitalization, Fulminant, no transplant		Ages 0-95	33.2	17
	Liver transplant, Year of transplant		Ages 0-95	153.2	
	Vaccination	First dose	0-12	0	
			13-95	0.125	
		Second dose	0-2	0	
3-95			0.125		
Mild adverse event		Ages 0-95	0.875	Assumption	
Severe adverse event		Ages 0-95	5	Assumption	
Costs, Participation	Daily cost of work loss	Ages 0-15	\$120.2*	Assumption	
		16-19	\$63.42	14	
		20-24	\$83.4	14	
		25-34	\$121.53	14	
		35-44	\$143.15	14	
		45-54	\$146.41	14	
		55-64	\$146.61	14	
		65-95	\$105.02	14	
	Labor force participation rate	Ages 0-15	0.815*	13	
16-19		0.437	13		

	20-24	0.749	13
	25-34	0.8263	13
	35-44	0.836	13
	45-54	0.8197	13
	55-64	0.6217	13
	65-95	0	13

* Note: Labor participation rate, daily earnings of parent or caregiver (calculated as a weighted average of 20 to 44-year-olds).

IX. Order in which the Model Considers Simulated Events

For the model to proceed, the order of simulated events must be specified. We specified the order of simulated model states as follows:

1. **Immunity loss.** Those in immune-due-to-vaccination states progress to one less year remaining of immunity. Those who had only one year of immunity remaining lose immunity and progress to the *Susceptible, immunized* state.
2. **Vaccination.** Vaccination of a portion of cohort in *Susceptible, not immunized* and *Immune due to disease, immunity unknown*. Some of those vaccinated receive only one dose, others two. Based on resulting GMT levels, these newly vaccinated are distributed among the states *Immune: 1, 2, ...95 years to immunity loss* or *Susceptible, immunized*.
3. **HepA infection.** The model assumes that infections can only occur among those in the cohort in the *Susceptible, not immunized* state who are not just vaccinated in the current year or anyone in the *Susceptible, immunized* state who did not just lose immunity. By default, the risk of infection is the same among both groups, however the risk in the latter group can be reduced by a multiplicative factor (“Reduction in risk of infection | susceptible, immunized”) as compared to the risk among the former, although this feature was not used in the manuscript. The number of infections is therefore calculated using the following formula:

$$\begin{aligned}
 \text{Number of infections} &= [\text{Infections from } \textit{Susceptible, not immunized}] + & (9.1) \\
 &[\text{Infections from } \textit{Susceptible, immunized}] \\
 &= [(\% \text{ of cohort susceptible, not immunized} - \\
 &\quad \% \text{ of cohort just immunized}) \cdot \\
 &\quad P(\text{infection} \mid \text{susceptible, not immunized})] + \\
 &[(\% \text{ of cohort susceptible, immunized} + \\
 &\quad \% \text{ of cohort that just lost immunity}) \cdot \\
 &\quad P(\text{infection} \mid \text{susceptible, immunized})]
 \end{aligned}$$

4. **HepA disease development stages.** The degree of severity of hepatitis A varies between infected persons. In Figure 1.1 HepA disease development stages are represented by shaded parallelograms.

Table 9.1 Parameters that determine HepA disease development in infected cases

Parameter	Default value	Source
P(acute icteric HepA HepA infection) (0-1)	Varies from 0 at age 0 to 0.95 at age 95	Armstrong GL, Bell BP (2002)
P(symptomatic anicteric) (0-1)	0.5	Assumption by GL Armstrong

Total number of icteric cases per reported case	4.28	Armstrong GL, Bell BP (2002)
P(fulminant reported acute icteric HepA) (0-1)	Ages 0-4: 0.0038 Ages 5-14: 0.0005 Ages 15-39: 0.0068 Ages 40-59: 0.055 Ages 60-95: 0.08	Calculated from NNDSS (1990-2004)

Anicteric HepA (including symptomatic and asymptomatic). All cases that are not icteric are classified as *anicteric*. The model assumes that the number of symptomatic anicteric cases is equal to a percentage, 50% by default, of all anicteric cases.

Icteric HepA. The number of icteric cases is calculated as a percentage of infected cases. All icteric cases are, by definition, symptomatic.

Fulminant HepA. The number of fulminant cases is calculated as a percentage of reported icteric cases.

- HepA disease-related health outcomes.** The model assumes that within each of these stages, patients require different degrees of healthcare. Reporting of cases to the public health system also varies between stages, as well as within icteric. Costs for health care and work loss, either due to illness within the cohort or caretakers of those ill within the cohort, may be incurred.

Asymptomatic anicteric. Asymptomatic cases do not require healthcare and are all unreported.

Symptomatic anicteric. The model assumes that symptomatic cases are relatively mild and therefore do not require extensive healthcare. Only 50% of symptomatic anicteric HepA cases necessitate outpatient visits; of those, only 1 patient visit per person is assumed. All symptomatic anicteric cases are unreported.

Icteric. Icteric cases are either reported or unreported; the number of reported cases is calculated as the number of icteric cases divided by the number of icteric cases per reported case (4.28, by default, as estimated by Armstrong and Bell, 2003).

The model assumes 95% of all icteric cases require at least outpatient visits; the calculation of what percent require only outpatient visits (all among unreported cases) is derived based on this assumption and the probabilities of needing other healthcare. All reported cases, however, are assumed to require healthcare, either outpatient visits or hospitalizations. We make this assumption on the basis that, in order for a case to be reported, the patient must have sought healthcare for disease diagnosis.

In order to capture the phenomena that reported cases are more likely to have a higher severity of disease, the model assumes that, among those cases that require outpatient

visits only, reported cases require 3 outpatient visits, while unreported cases require 33% less, or 2.

Fulminant. 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.

Those that receive a transplant encounter a risk of death (i.e. a transition probability of death is applied) twice in the year of their transplant – once to represent the risk of death immediately after surgery and a second time to represent the remaining months of the year following surgery ($P(\text{death} \mid \text{transplant}), \text{yr of trans}$ in Table 9.2). The model then assumes that those patients with a history of a transplant are at increased risk of death due to transplant-related issues for the rest of their lives. The model calculates the percent of the cohort with history of a liver transplant as a sum of those who had a history of a liver transplant in the previous year and didn't die from transplant-related issues and those infections from the current year that resulted in a non-fatal transplant.

The number of outpatient visits, therefore, is determined by Equation 9.2.

$$\begin{aligned}
 \text{Number of OP visits} &= [\text{OP visits among reported icteric}] + & (9.2) \\
 & [\text{OP visits among nonreported icteric}] + \\
 & [\text{OP visits among anicteric}] \\
 &= [\text{Reported infections} \cdot \text{OP visits per reported icteric}] + \\
 & [\text{Nonreported icteric infections} \cdot \\
 & P(\text{OP visit} \mid \text{nonreported icteric}) \cdot \\
 & \text{OP visits per reported icteric} \cdot \\
 & (1 - \% \text{ reduction OP visits unrep'd vs. rep'd icteric})] \\
 & + [\text{Anicteric infections} \cdot \\
 & P(\text{symptomatic} \mid \text{anicteric}) \cdot \\
 & P(\text{OP visit} \mid \text{anicteric}) \cdot \\
 & \text{OP visits per anicteric}]
 \end{aligned}$$

The number of hospitalizations is calculated as the product of the number of reported infections and the sum of the probabilities of hospitalization given a reported infection and fulminant given a reported infection.

Table 9.2 Parameters that determine HepA disease-related health outcomes and costs in infected cases

Parameter	Default Value	Source
P(outpatient visit & work loss symptomatic anicteric infection) (0-1)	0.5	Assumption
P(any level of medical care icteric HepA) (0-1)	0.95	Bownds L et al (2003)
P(hospitalization, OP visit & work loss from non-fulminant HepA reported	Ages 0-4: 0.0465 Ages 5-14: 0.17	NNDSS (2000-2001)

Parameter	Default Value	Source
acute icteric HepA) (0-1)	Ages 15-39: 0.225 Ages 40-59: 0.185 Ages 60-95: 0.2	
Number of outpatient visits anicteric HepA requiring OP visits	1	Assumption
Number of outpatient visits reported icteric HepA requiring OP visits, but not hospitalization	3	Berge JJ et al (2000)
Percent reduction in number of OP visits for unreported vs. reported icteric HepA (0-1)	0.333	Assumption
P(death w/o transplant fulminant HepA) (0-1)	Ages 0-59: 0.145 Ages 60-95: 0.67	Schiodt FV et al (2003)
P(transplant fulminant HepA) (0-1)	Ages 0-59: 0.1875 Ages 60-95: 0.025	Schiodt FV et al (2003)
P(death immediately after transplant) (0-1)	0.0648	UNOS
P(death transplant) (0-1)	Yr of trans: 0.2419 1-2 yrs since trans: 0.0299 3-4 yrs since trans: 0.0236 5-9 yrs since trans: 0.0242 10-15 yrs since trans: 0.0262 16+ yrs since trans: 0.0136	UNOS Jain A et al (2000)

6. HepA disease-related healthcare costs.

Table 9.3 presents the parameters that determine costs once the model determines the cohort's outcomes.

Table 9.3 Parameters that determine HepA disease-related health outcomes and costs in infected cases

Parameter	Default Value	Source
Cost for health care fulminant acute icteric HepA w/ transplant	Yr of trans: \$285,900 Yrs after trans: \$25,598	Hauboldt RA (1999) Berge JJ et al (2000)
Cost for health care fulminant acute icteric HepA w/o transplant	\$24,138	Berge JJ et al (2000)
Cost for health care hospitalization and OP visits for non-fulminant acute icteric HepA	\$8,111	Dalton CB et al (1996); Berge JJ et al (2000)
Cost for health care OP visits only for non-fulminant acute icteric HepA	\$821	Dalton CB et al (1996); Berge JJ et al (2000)

Parameter	Default Value	Source
Percent reduction in medical costs for unreported vs. reported icteric HepA (0-1)	0.333	Assumption

7. **HepA disease-related productivity losses.** The model assumes that within each of the stages, costs for health care and work loss, either due to illness within the cohort or caretakers of those ill within the cohort, may be incurred.

The number of days of work loss incurred by each type of patient is calculated as follows:

Anicteric HepA. The number of anicteric cases for which work loss is experienced is equal to the number of symptomatic anicteric cases times the probability of employment times the probability of having to seek outpatient care or experiencing work loss without other care. The total amount of work loss is equal to the number of those cases times the number of days of work loss associated with an anicteric case.

Non-fulminant icteric HepA. The number of days of work loss among non-fulminant icteric cases differs by the severity of the icteric case; those unreported incur less work loss than those seeking outpatient care only who, in turn, incur less than those who are hospitalized. The total amount of work loss from this group is equal to the number of each of those types of cases times the probability of employment times the number of days of work loss associated with each.

Fulminant HepA. The number of days of work loss among fulminant cases also differs depending on whether a transplant is performed; those that receive transplants require significantly more days. The total amount of work loss from this group is equal to the number of each of those types of cases times the probability of employment times the number of days of work loss associated with each.

Costs for these lost work days depend on the patient's age. If a patient is younger than the starting age for work, the productivity losses are assumed to be for a caregiver; otherwise they are assumed to be incurred by the afflicted patient.

Table 9.3 Parameters determining productivity losses due to sickness associated with HepA

Parameter	Default value	Source
P(work loss, but no medical care symptomatic anicteric infection) (0-1)	0.5	Assumption
Number of work days lost symptomatic anicteric infection	3	Assumption
Number of work days lost unreported icteric HepA	3	Assumption

Number of work days lost OP visits only for reported non-fulminant HepA	Ages 0-12: 3.7 Age 13-95: 10	0-12: Jacobs RJ, Meyerhoff AS (2001) 13-95: O'Connor JB et al (1999)
Number of work days lost hospitalization for non-fulminant HepA	33.2	Berge JJ et al (2000)
Number of work days lost fulminant acute icteric HepA w/ transplant	153.2	Transplant Patient Partnering Pgm
Number of work days lost fulminant acute icteric HepA w/o transplant	33.2	Berge JJ et al (2000)
Age at which people start working (0-95; age public notifications & prod. losses from self begin)	16	Assumption

X. Table of all medical care costs and their sources

We applied medical care costs taken from multiple studies in the literature for each of the following Hepatitis A stages of infection:

- Symptomatic anicteric infection
- Non-hospitalized icteric infection(outpatient case)
 - Reported
 - Unreported
- Hospitalized icteric infection (inpatient case)
- Hospitalized fulminant liver disease (without a liver transplant)
- Hospitalized fulminant liver disease (with a transplant)

For symptomatic anicteric infections, we assumed a healthcare cost (\$84.16) equivalent to one office visit to the patient's primary care physician¹⁸.

Outpatient and inpatient healthcare costs (and ranges) associated with icteric infections were calculated using the results reported across four case studies of Hepatitis A outbreaks in the United States^{17,19-21}. Specifically, we took a weighted average of results reported by the two studies^{17,19} which used medical and chart data to determine the base case estimate of healthcare costs incurred by outpatient and inpatient cases. The remaining two studies which used patient self-report for cost and utilization information provided the upper and lower bounds. Finally, we assumed a 0.333 reduction in healthcare costs for unreported non-hospitalized (outpatient) icteric infection.

Table 10.1 presents the observed number of cases and associated medical care costs reported in each of the four studies considered.

Table 10.1 Medical Costs (non-fulminant reported icteric infections)^a

Study	Outpatient		Inpatient	
	No. Cases	Cost (2004 USD)	No. Cases	Cost (2004 USD)
Dalton et al (1996)	41	\$984	2	\$9,719
Berge JJ et al (2000)	217	\$790	37	\$8,024
Bownds et al (2003)	139	\$615	8	\$16,593
Sansom et al (2003)	73	\$588	16	\$4,620
Average (Range) ^b		\$821 (\$588-\$984)		\$8,111 (\$4,620-\$16,593)

^a All findings converted to 2004 United States dollars (USD) using the annual Consumer Price Index for all urban consumers.

^b Base cost determined by a weighted average of estimates reported in Dalton (1996) and Berge (2000); Preference for medical and chart data over self-report.

We assumed separate inpatient medical care costs – taken from case studies in the literature – for fulminant liver disease both with and without subsequent liver transplantation surgery^{17,22}. For those patients receiving a liver transplant, we applied a recurring annual cost in addition to

healthcare costs incurred during the transplant year for up to 18 years post-transplant. Table 10.2 summarizes all medical care cost estimates and their respective sources used in the base case analysis.

Table 10.2 Medical Care Costs

Parameter		Parameter Value Base Case Analysis	Source
Percent cost reduction, Unreported cases	Ages 0-95	0.333	Assumption
Symptomatic anicteric infection	Ages 0-95	\$84.16	¹⁸
Non-hospitalized icteric infection, Reported	Ages 0-95	\$821	¹⁹ ¹⁷
Hospitalized icteric infection	Ages 0-95	\$8,111	¹⁹ ¹⁷
Hospitalized fulminant, no transplant	Ages 0-95	\$24,138	¹⁷
Liver transplant	Year of transplant	Ages 0-95	²²
	Subsequent years (0-18 years)	Ages 0-95	¹⁷

XI. Calculation of public health cost per case

Public health response costs were classified into three major activities – Surveillance, Immune globulin (IG) coordination and administration, and Public Notification based on discussions with CDC public health experts with state and local health department experience. The costs associated with each activity per reported case were calculated separately and then added together using the following formulas (Equations 2 – 5) and inputs (Table 11.1).

Equation 2.

Public health costs =
 surveillance per reported case +
 Immune globulin (IG) coordination and administration +
 public notification

Equation 3.

Surveillance per reported case =
 $(1 / (1 + \text{Discount rate}) ^ (t - \text{Age of cohort at model start} - 1)) *$
 (No. cases reported *
 (Prob. follow-up by PHA *
 (Hourly wage PHA *
 (PMDCall * TimeMDCall + PInfCall * TimeInfCall + PInfVisit * TimeInfVisit)))

Where PHA = public health advisor
 PMDCall = Probability of phone call by PHA to the infected patient’s physician
 TimeMDCall = Length of time (hours), phone call by PHA to the infected patient’s physician
 PInfCall = Probability of phone call by PHA to the infected patient | physician phone call
 TimeInfCall = Length of time (hours), phone call by PHA to the infected patient
 PInfVisit = Probability of visit by PHA to the infected patient | physician and patient phone call
 TimeInfVisit = Length of time (hours), visit by PHA to the infected patient

$$\begin{aligned} &\text{Immune globulin (IG) coordination and administration} = \\ &(1 / (1 + \text{Discount rate}) ^ (t - \text{Age of cohort at model start} - 1))^* \\ &[(\text{No. cases reported} * \\ &(\text{Prob. follow-up by PHA} * \\ &(\text{Hourly wage PHA} * \\ &(\text{PIGCoord} * \text{TimeIGCoord} + \text{TimeIGCall} * \\ &(\text{PFSW} * \text{NumIGCallsFSW} + (1 - \text{PFSW}) * \text{NumIGCallsNonFSW}))) + \\ &\text{IGCost} * (\text{PFSW} * \text{NumIGFSW} + (1 - \text{PFSW}) * \text{NumIGNonFSW}))))] \end{aligned}$$

Where PHA = public health advisor
 PIGCoord = Proportion of cases with follow-up for whom IG shots for contacts are coordinated by PHA
 TimeIGCoord = Length of time (hours), coordination of IG shots for contacts
 TimeIGCall = Length of time (hours), phone call to contact
 PFSW = Proportion of reported cases, Food service workers (FSW)
 NumIGCallsFSW = No. phone calls to contacts, FSW cases with follow-up
 NumIGCallsNonFSW = No. phone calls to contacts, all other cases with follow-up
 IGCost = IG cost per dose
 NumIGFSW = No. IG shots to contacts, FSW cases with follow-up
 NumIGNonFSW = No. IG shots to contacts, all other cases with follow-up

$$\begin{aligned} &\text{Public Notification} = \\ &(1 / (1 + \text{Discount rate}) ^ (t - \text{Age of cohort at model start} - 1))^* \\ &\text{No. cases reported} * \text{Hourly wage PHA} * \\ &(\text{PFoodVisit} * \text{TimeFoodVisit} + (\text{PPublicNotif} * \text{TimePublicNotif})) \end{aligned}$$

Where PHA = public health advisor
 PFoodVisit = Proportion of reported cases for whom visit made to employer (FSW cases only) by PHA
 TimeFoodVisit = Length of time (hours), employer visit (FSW cases only)
 PPublicNotif = Proportion of reported cases for whom a public notification is made
 TimePublicNotif = Length of time (hours), public notification

Table 11.1 Public Health Response

Parameter		Parameter Value	
		Base Case Analysis	Source
General	Loaded mean hourly wage for licensed practical or licensed vocational nurse	\$21.3	23
	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 call by PHA to the infected patient's physician	1	
	Probability of phone call by PHA to the infected patient Physician phone call	0.8	
	Length of time (hours), phone call 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 & 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, Food service workers (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	
	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	
	Proportion of reported cases for whom a public notification is made	0.002	
	Length (hours) for PHS to make public notification	160	

XII. QALY calculations

Background health utilities were specified by age such that the number of QALYs annually accrued for those with no Hepatitis A infection were 0.94 for those 0-4; 0.93 for those 5-17; 0.915 for those 18-34; 0.895 for those 35-44; 0.805 for those 45-54; 0.805 for those 55-64; 0.770 for those 65-74; and 0.695 for those 75 and older²⁴. Relative utility values for infection states were set to 0.83 for symptomatic anicteric infection, 0.41 for non-fulminant icteric, 0.42 for fulminant pre-transplant, and 0.79 for fulminant post-transplant²⁵⁻²⁷.

To calculate an infected individual’s health utility, the relative value of their state was multiplied by their background utility. The QALY input values are then converted to annualized values based on the duration of sickness experienced in a given year (Equation 6).

Equation 6.

$$\text{Annual loss (before discounting)} = (\text{HealthyU} - (\text{HealthyU} * \text{SickU})) * (\text{TimeSick} / 365.25)$$

Where HealthyU = Utility value without Hepatitis A infection, by age
 SickU = Utility value for infection states
 TimeSick = Duration of sickness (days)

Table 12.1 summarizes the health utility values and their respective sources used in the model.

Table 12.1 Quality of Life

Parameter	Parameter Value		Source	
	Base Case	Analysis		
Duration of sickness	Symptomatic anicteric infection	Ages 0-95	3	Assumption

(days)	Non-hospitalized icteric infection	Ages 0-95	34.4	17
	Hospitalization	Ages 0-95	67.8	17
QALY value	Healthy	Ages 0-4	0.94	24
		5-17	0.93	24
		18-34	0.915	24
		35-44	0.895	24
		45-54	0.865	24
		55-64	0.805	24
		65-74	0.77	24
		75-95	0.695	24
	Symptomatic anicteric infection	Ages 0-95	0.83	18
	Non-fulminant icteric infection	Ages 0-95	0.41	17
Fulminant pre-transplant	Ages 0-95	0.42	27	
Fulminant post-transplant	Ages 0-95	0.79	27	

XIII. Probabilistic Sensitivity Analysis

The probabilistic sensitivity analysis (PSA) is an analysis in which the model is run repeatedly (each run is called an “iteration”), each time with different parameter values. Each parameter has an associated statistical distribution with an expected value equal to the base value and specified measures of variance. The model uses Excel’s random number generator to conduct random sampling from those distributions; those sample values are used as parameter values for each iteration. Section 14a describes the statistical distribution shapes that are available in the PSA. Section 14b describes the protocols that the model uses to generate random values from each type of distribution.

In order to simplify the PSA specifications, the model has PSA categories for specifying distributions for groups of parameters rather than specifying those for each parameter individually. Each parameter is assigned to a category; each parameter’s associated distribution is determined by its base value and its category’s specifications. Those categories are described in Section 14c.

13a. Statistical distribution shapes. The following distribution shapes can be applied to vary parameter values in the PSA: logistic normal, normal, triangular, or uniform. Table 14.1 lists the required and other parameters (referred to as “distribution parameters” hereafter to distinguish from the parameters that determine model progression) that must or can, respectively, be specified for each model parameter.

Table 13.1 Statistical distributions and associated parameters

Distribution	Required distribution parameters	Other distribution parameters
Logistic normal	<ul style="list-style-type: none"> • Mean (automatically set to base value) • Implicit lower or upper bound (% less or % more than base, respectively) • Minimum sample value limit (% less than base) • Maximum sample value limit (% more than base or absolute value) 	<ul style="list-style-type: none"> • None

Normal	<ul style="list-style-type: none"> • Mean (automatically set to base value) • 95% confidence interval lower bound (% less than base) • 95% confidence interval upper bound (% more than base) 	<ul style="list-style-type: none"> • Minimum sample value limit (% less than base) • Maximum sample value limit (% less than base or absolute)
Triangular	<ul style="list-style-type: none"> • Mode (automatically calculated so that the mean equals base value) • Minimum (% less than base) • Maximum (% more than base) 	<ul style="list-style-type: none"> • Minimum sample value limit (% less than base) • Maximum sample value limit (% more than base or absolute)
Uniform	<ul style="list-style-type: none"> • Mean (automatically set to base value) • Minimum (% less than base) • Maximum (% more than base) 	<ul style="list-style-type: none"> • Minimum sample value limit (% less than base) • Maximum sample value limit (% more than base or absolute)

The distribution parameters listed in Table 13.1 include the following:

Mean – expected value of the distribution; not set by user, but automatically set to the base value used in standard model runs

Implicit lower or upper bound (logistic normal only) – the bound of the 95% confidence interval around the mean of a value with a logistic normal distribution; based either on subjective estimates or objective data; specified as a percentage difference from the base value

Minimum or maximum sample value limit – lower or upper bound of the range of possible values that this model parameter can take; values derived from random sampling that fall outside this range are discarded and distribution is resampled; specified as a percentage difference from the base value for minimum or maximum or as an absolute maximum (e.g., probabilities can range from 0 to 1, which would be set as minimum = 100% less than the base value and absolute maximum = 1)

Minimum or maximum (triangular or uniform) – lower / upper bound of distribution; specified as a percentage difference from the base value

Mode (triangular only) – value of the variable at the peak of the distribution; not set by user, but automatically generated so that the mean of the distribution is equal to the base value used in standard model runs; calculated using the equation $Mode = 3 * Mean - (Minimum + Maximum)$

13b. Sampling from distributions

The methods for sampling from a distribution vary by the distribution shape. Each method applied in the model are described below.

13b.1 Normal

Values are randomly selected from a normal distribution defined by a mean and variance using the Polar Method, as outlined by Rich Timpone, adapted from Sheldon Ross' and Donald Knuth's books (http://psweb.sbs.ohio-state.edu/faculty/rtimpone/computer_resources/polar_vb5.htm).²⁹ Minimum and maximum sample value limits may also be applied.

1. If variance is equal to zero, randomly generated value ($RandNorm$) = *mean*.
Otherwise...

2. Generate 2 random numbers, *Rand1* and *Rand2*, between 0 and 1.
3. Calculate variables *V1*, *V2* and *S* using the following formulas:

$$V1 = 2 * Rand1 - 1$$

$$V2 = 2 * Rand2 - 1$$

$$S = V1^2 + V2^2$$

4. If $S \geq 1$ return to step 2 to get new values for *Rand1* and *Rand2*.

Otherwise...

5. If $S < 1$, calculate randomly generated value using the following formulas:

Z = randomly generated value from standard normal distribution

$$= (((-2 * \text{Log}(S)) / S)^{(1/2)}) * V1$$

$$\text{Standard deviation} = \text{variance}^{(1/2)}$$

$$\text{RandNorm} = \text{mean} + Z * \text{Standard deviation}$$

6. If *RandNorm* is below a specified minimum or above a specified maximum sample value limit, then return to to step 2 to get new values for *Rand1* and *Rand2*.

13b.2 Logistic normal

Values are randomly selected from a logistic normal distribution defined by a mean (*m*), lower or upper confidence interval bound, and minimum and maximum sample value limits (*min* and *max*, respectively) using the following method, as outlined by Doubilet and coauthors (1985).²⁸ Minimum and maximum sample value limits may also be applied.

1. If upper and lower bounds given, assign lower as bound (*b*)
2. Check if $m = b$ or $b = \text{min}$ or $b = \text{max}$ or $m = 0$. If any of those conditions are true, then parameter will not be varied in sensitivity analysis (user will be notified of error).

Otherwise...

3. Calculate mean of associated normal distribution (μ)

- 3a. Calculate logit transforms of the mean (*LogitM*) and bound (*LogitB*)

$$\text{LogitM} = \text{Log}((m - \text{min}) / (\text{max} - m))$$

$$\text{LogitB} = \text{Log}((b - \text{min}) / (\text{max} - b))$$

- 3b. Assign value of μ if certain special conditions hold:

If $(m / \text{max}) = 0.5$ Then

$$\mu = 0$$

Otherwise if $(m / \text{max}) = 0.025$ Or $m / \text{max} = 0.975$ Then

$$\mu = (\text{LogitM}^2 + \text{LogitB}^2) / (2 * \text{LogitB})$$

Otherwise...

- 3c. Calculate μ using the following formulas:

$E = 1.96 / \Phi^{-1}(m / \text{max})$ (Φ^{-1} represents the inverse of the normal distribution function)

$$\mu = (\text{LogitB} - E * \text{Sqr}(\text{LogitB}^2 - \text{LogitM}^2 + \text{LogitM}^2 * E^2)) / (1 - E^2)$$

4. Calculate standard deviation of associated normal distribution (*s*) using the following formula:

$$s = |\mu - \text{LogitB}| / 1.96$$

6. Generate a random variable (*RandNorm*) from the normal distribution defined by μ and *s* using the **Normal** protocol outlined above.
7. Calculate randomly generated value from logistic-normal distribution (*RandLgcnorm*) using the following formula:

$$RandLgcnorm = (min + max * \text{Exp}(RandNorm)) / (1 + \text{Exp}(RandNorm))$$

8. If *RandLgcnorm* is below a specified minimum or above a specified maximum sample value limit, then return to to step 6 to get a new value for *RandNorm*.

13b.3 Triangular

Values are randomly selected from a triangular distribution defined by a mean, minimum (*min*) and a maximum (*max*) using an inverse cumulate distribution function, as described at <http://www.brighton-webs.co.uk/distributions/triangular.asp>.³⁰ Minimum and maximum sample value limits may also be applied.

1. Calculate the mode of the distribution using the following formula:

$$mode = 3 * mean - (min + max)$$

2. Generate a random number (*Rand*) between 0 and 1.

3. If $Rand = (mode - min) / (max - mode)$ then assign the value from triangular distribution (*RandTriang*) to *mode*.

Otherwise...

4. If $Rand < (mode - min) / (max - mode)$ then calculate *RandTriang* using the following formula:

$$RandTriang = min + (Rand * (max - min) * (mode - min))^{(1/2)}$$

Otherwise...

5. Calculate *RandTriang* using the following formula:

$$RandTriang = max - ((1 - Rand) * (max - min) * (max - mode))^{(1/2)}$$

6. If *RandTriang* is below a specified minimum or above a specified maximum sample value limit, then return to to step 2 to get a new value for *Rand*.

13b.4 Uniform

Values are randomly selected from a uniform distribution defined by a minimum (*min*) and maximum (*max*) using the following protocol. Minimum and maximum sample value limits may also be applied.

1. Generate a random number (*Rand*) between 0 and 1.

2. Calculate a value from the uniform distribution (*RandUnif*) using the following formula:

$$RandUnif = min + Rand * (max - min)$$

3. If *RandUnif* is below a specified minimum or above a specified maximum sample value limit, then return to to step 1 to get a new value for *Rand*.

13c. PSA categories. In order to simplify the PSA specifications, the model has PSA categories for specifying relative and absolute characteristics of distributions for groups of parameters rather than specifying those for each parameter individually. Each parameter is assigned to a category; therefore each parameter's associated distribution is determined by its base value and category's specification. Table 14.2 lists the categories applied in the analysis. Users can add categories and re-assign categories as desired.

Table 13.2. PSA parameter categories

Category	Distributi on shape	CI lower bound	CI upper bound	Minimum limit on sampled	Maximum limit on sampled value:
----------	------------------------	-------------------	-------------------	--------------------------------	------------------------------------

					% more than base	absolute
Discounts	Triangular	33.3%	33%	100%	--	1
Do not vary	Do not vary	--	--	--	--	--
Known confidence interval (CI)	Triangular	10%	10%	100%	--	--
(Applied only if confidence interval bounds not actually specified)						
Large healthcare cost	Logistic normal	50%	--	100%	200%	--
Other	Logistic normal	10%	--	100%	100%	--
Probability	Logistic normal	10%	--	100%	--	1
Quality of life	Uniform	10%	10%	100%	--	1
Small healthcare cost	Logistic normal	50%	--	100%	100%	--
Wages	Logistic normal	20%	20%	100%	100%	--

Each category is defined by up to 6 specifications, as shown in Table 14.2. Those specifications are defined as follows:

Distribution shape – Defines the shape of the distribution. The following distribution shapes can be applied: logistic normal, normal, triangular, or uniform (as described in Section 14b.1). Categories can also be specified here to not be varied (by using “Do not vary”).

CI lower bound (Logistic normal or normal) or Minimum (Triangular or Uniform) – States a defining lower bound, either of a confidence interval (in the case of logistic normal or normal) or the distribution itself (triangular or uniform), relative to the base value. For example, we estimate that the lower bounds of the 95% confidence intervals around small healthcare costs are about 50% less than the small healthcare costs used in the model. If a cost was \$50, then the lower bound of the confidence interval around that cost would be \$25.

CI upper bound (Logistic normal or normal) or Maximum (Triangular or Uniform) – Similarly to the CI lower bound, the CI upper bound states a defining upper bound, either of a confidence interval (in the case of logistic normal or normal) or the distribution itself (triangular or uniform).

Minimum limit on sampled value – Defines the lower limit of the range of values that a parameter can reasonably be assigned, relative to the base value. If the random selection process chooses a value less than this minimum limit, then the random selection process is repeated until a value within the reasonable range is selected. This limit prevents the model from using negative or other nonsensical values from being applied to costs and other parameters.

Maximum limit on sampled value – Defines the upper limit of the range of values that a parameter can reasonably be assigned, either on an absolute scale or relative to the base value. If the random selection process chooses a value more than this maximum limit, then the random selection process is repeated until a value within the reasonable range is selected. This limit prevents the model from using nonsensical values from being applied to costs and other parameters, such as quality-of-life and probability values greater than 1.

Reference List

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