SUPPLEMENTARY DATA

**Calculation of Selected Input Variables.** Incidence of Acute Hepatitis B Infection in Persons with Diagnosed Diabetes

The estimated incidence of acute hepatitis B infection in persons with diabetes is shown in column 7 of Table 1. The reported incidence in the general population is multiplied to reflect higher incidence rates in persons with diabetes and is adjusted to reflect underreporting of symptomatic cases and the fact that some acute infections are asymptomatic. Specifically, the incidence is calculated as follows:

(Incidence of hepatitis B infection per 100,000 persons in the general population, by age group)
X
(Hepatitis B incidence ratio among adults with vs. without diagnosed diabetes)
X
(Underreporting multiplier)
/
(Probability of jaundice)

**Supplementary Table 1.** Incidence of Acute Hepatitis B Infection per 100,000 Persons with Diagnosed Diabetes, by Age Group, 2007

| (1) Age Group | (2) Reported Incidence (per 100,000 general population) | (3) Hepatitis B Incidence Ratio among Adults with vs. without Diagnosed Diabetes | (4) Reported Incidence (per 100,000 persons with diagnosed diabetes) = (2)*(3) | (5) Under-Reporting Multiplier | (6) Probability of Jaundice | (7) Incidence (per 100,000 persons with diagnosed diabetes) = (4)*(5)/(6) |
|---|---|---|---|---|---|---|
| 20–24 | 1.46 | 2.1 | 3.06 | 2.79 | 0.25 | 34.10 |
| 25–29 | 2.61 | 2.1 | 5.48 | 2.79 | 0.3 | 50.93 |
| 30–34 | 3.01 | 2.1 | 6.32 | 2.79 | 0.3 | 58.79 |
| 35–39 | 3.05 | 2.1 | 6.41 | 2.79 | 0.3 | 59.64 |
| 40–44 | 2.95 | 2.1 | 6.19 | 2.79 | 0.3 | 57.57 |
| 45–49 | 2.49 | 2.1 | 5.24 | 2.79 | 0.3 | 48.69 |
| 50–54 | 1.94 | 2.1 | 4.07 | 2.79 | 0.3 | 37.87 |
| 55–59 | 1.54 | 2.1 | 3.23 | 2.79 | 0.3 | 30.02 |
| 60+ | 0.76 | 1.5 | 1.14 | 2.79 | 0.3 | 10.63 |

Notes: Centers for Disease Control and Prevention, Division of Viral Hepatitis (2009, May 22). Incidence of hepatitis B infection per 100,000 persons in the general population in 2007, by age group. *Morbidity and Mortality Weekly Report*, *58*(SS-3), 24. Rates were estimated as weighted average of sex-specific rates, with weights based on 2007 U.S. population by age and sex. Varied in univariate and probabilistic sensitivity analyses, using 95% confidence intervals and beta distributions for each age group.

Hepatitis B incidence ratio among adults with vs. without diagnosed diabetes. Data from Emerging Infections Program, 2009–2010. Schillie S, Smith E, Reilly M, Murphy TV. Odds of acute hepatitis B among persons with diabetes at eight Emerging Infection Program sites. Presentation to Advisory Committee on Immunization Practices, October 25, 2011. 95% confidence intervals: 1.5–3.0 for ages 20–59; 0.8–2.7 for ages 60+. Varied in univariate and probabilistic sensitivity analyses.

Underreporting multiplier: Centers for Disease Control and Prevention Surveillance System for Hepatitis. Varied from 2.5 to 3.2 in univariate sensitivity analyses (Centers for Disease Control and Prevention expert opinion, personal communication from Sarah Schillie, June 8, 2011). Not varied in probabilistic sensitivity analyses (columns [2] and [3] were varied).

Probability of jaundice: McMahon et al. (26). Varied from 0.2 to 0.4 in univariate sensitivity (10). Not varied in probabilistic sensitivity analyses (columns [2] and [3] were varied).

Incidence Rates for Susceptible Persons with Diagnosed Diabetes

Table 1 shows incidence rates for all persons with diagnosed diabetes. However, incident acute infections occur in individuals who are susceptible to infection; persons who have had previous infections or have achieved seroprotection through previous vaccination are not susceptible. Table 2 shows infection rates for persons with diagnosed diabetes who are susceptible to hepatitis B. Components of the calculation are described below.

**Supplementary Table 2.** Hepatitis B Incidence Rates for Susceptible Persons with Diagnosed Diabetes

| Age Group | Incidence of HBV (per 100,000 persons with diagnosed diabetes) | Prevalence of Previous HBV Infection (per 100,000 persons with diagnosed diabetes) | Existing Vaccine Coverage | Efficacy of Prior Vaccination | Incidence Rates for Susceptible Persons with Diagnosed Diabetes (per 100,000) |
|---|---|---|---|---|---|
| 20–24 | 34.10 | 1.78 | 73.0% | 84.5% | 91 |
| 25–29 | 50.93 | 4.5 | 53.8% | 84.5% | 98 |
| 30–34 | 58.79 | 4.5 | 45.6% | 84.5% | 100 |
| 35–39 | 59.64 | 4.5 | 44.9% | 84.5% | 101 |
| 40–44 | 57.57 | 4.5 | 39.1% | 84.5% | 90 |
| 45–49 | 48.69 | 8.9 | 34.8% | 84.5% | 76 |
| 50–54 | 37.87 | 8.9 | 30.2% | 84.5% | 56 |
| 55–59 | 30.02 | 8.9 | 26.8% | 84.5% | 43 |
| 60–64 | 10.63 | 8.9 | 23.2% | 84.5% | 15 |
| 65–69 | 10.63 | 8.06 | 17.0% | 84.5% | 14 |
| ≥70 | 10.63 | 8.06 | 10.1% | 84.5% | 13 |

Notes: Incidence of HBV (per 100,000 with diabetes): From Table 1above.

Prevalence of previous HBV infection (per 100,000 with diabetes): National Health and Nutrition Examination Survey, 2007–2008.

Existing vaccine coverage: 2007 Behavioral Risk Factor Surveillance System; see Table 3.

Efficacy of prior vaccination: 2007 Behavioral Risk Factor Surveillance System, 2009 National Health Interview Survey, and Kim et al. (10); see Table 4.

Incidence rates for susceptible persons with diagnosed diabetes (per 100,000) = Incidence / (1 – (prevalence / 100) – (Existing Coverage * Efficacy of Prior Vaccination) + (Prevalence / 100) * (Existing Coverage * Efficacy of Prior Vaccination)).

SUPPLEMENTARY DATA

**Previous Vaccination Coverage Rates.**

Estimates were based on the 2007 Behavioral Risk Factor Surveillance System data on the percentage of adults with diagnosed diabetes who reported having received at least 1 dose of hepatitis B vaccine. The resulting coverage rates are given in Table 3.

**Supplementary Table 3.** Previous Vaccination Coverage Rates

| Age Group | Previous Coverage (%) |
|---|---|
| 20–24 | 73.0 |
| 25–29 | 53.8 |
| 30–34 | 45.6 |
| 35–39 | 44.9 |
| 40–44 | 39.1 |
| 45–49 | 34.8 |
| 50–54 | 30.2 |
| 55–59 | 26.8 |
| 60–64 | 23.2 |
| 65–69 | 17.0 |
| ≥70 | 10.1 |

**Efficacy of Previous Vaccination**

Efficacy of previous vaccination was calculated as a function of previous vaccination rates from the 2007 Behavioral Risk Factor Surveillance System; 2009 National Health Interview Survey estimates of the share of adults with diagnosed diabetes who received ≥ 1 and ≥ 3 doses of hepatitis B vaccine; and assumptions about the efficacy of previous vaccination with 1, 2, and 3 doses of the hepatitis B vaccine. Coverage in the Behavioral Risk Factor Surveillance System was based on the question, "Have you ever received ≥ 1 dose of the hepatitis B vaccine?" NHIS asked the question for both ≥ 1 and ≥ 3 doses. We applied the relevant National Health Interview Survey values for the entire population (19.6% and 16.7%) to the Behavioral Risk Factor Surveillance System data. Of those who received more than 1 and less than 3 doses (i.e., 19.6% − 6.7%), we assumed that half received 1 dose with efficacy 30% and half received 2 doses with efficacy 75%. These efficacy rates were based on estimates in Kim et al. (10) that were based on the general population. Efficacy was assumed to be 90% for persons who received 3 or more doses. Based on these assumptions, the weighted efficacy of previous coverage was calculated as 84.5%.

**Diabetes Mortality Rates**

Diabetes mortality rates by age group were estimated using general population mortality rates for 2006 (27), the relative risk of death for persons with diabetes, and the prevalence of diabetes in 2005–2006 (28). The formula for the calculation is as follows:

The diabetes mortality rate = c * General population mortality * (1/(1 + Prevalence of diabetes*(c-1)))

where c is the relative risk of death for persons with diabetes. The last term in the equation accounts for the fact that the general mortality rate is a weighted sum of the mortality rates for persons with diabetes and persons without diabetes. The relative risk of death for persons with diabetes is approximately 2 for most age groups (29-31), but it is lower for age groups 75 or older (32). This may be important because many deaths occur in these age groups. The calculated mortality rates are listed in Table 4. For sensitivity analyses, we varied the relative risk of death for persons with diabetes by a multiplicative factor between 0.75 and 1.25.

SUPPLEMENTARY DATA

**Supplementary Table 4.** Diabetes Mortality Rates

| Age | General Mortality Rate | Diabetes Relative Risk | Diabetes Prevalence | Diabetes Mortality Rate |
|---|---|---|---|---|
| 15–19 years | 64.4 | 2.0 | 2.10% | 126.2 |
| 20–24 years | 100.2 | 2.0 | 2.10% | 196.3 |
| 25–29 years | 100.9 | 2.0 | 2.10% | 197.6 |
| 30–34 years | 111.9 | 2.0 | 2.10% | 219.2 |
| 35–39 years | 148.7 | 2.0 | 7.90% | 275.6 |
| 40–44 years | 229.3 | 2.0 | 7.90% | 425.0 |
| 45–49 years | 347.7 | 2.0 | 7.90% | 644.5 |
| 50–54 years | 516.4 | 2.0 | 7.90% | 957.2 |
| 55–59 years | 730.1 | 2.0 | 17.50% | 1242.7 |
| 60–64 years | 1,110.2 | 2.0 | 17.50% | 1889.7 |
| 65–69 years | 1,656.6 | 2.0 | 17.50% | 2819.7 |
| 70–74 years | 2,554.8 | 2.0 | 14.80% | 4450.9 |
| 75–79 years | 4,033.4 | 1.8 | 14.80% | 6491.5 |
| 80–84 years | 6,524.0 | 1.6 | 14.80% | 9587.1 |
| 85 years or older | 13,253.1 | 1.3 | 14.80% | 16496.6 |

**Vaccine Uptake Rate**

It is uncertain how many persons with diabetes age 20 to 59 will seek hepatitis B vaccination if such vaccination is recommended. Our main analysis assumes that vaccination will be offered to all adults age 20 to 59 with diagnosed diabetes and that 10% of adults with diagnosed diabetes who are susceptible to hepatitis B and who report no previous vaccination will accept the vaccination.

The 10% assumption is based on the following indirect evidence:

- Uptake of the hepatitis B vaccine is 5.5 percentage points higher (22.2% vs. 16.7%) among persons with diagnosed diabetes and chronic liver disease, chronic kidney disease, or high-risk behavior (all groups who are recommended for vaccination) than it is for all adults with diagnosed diabetes (analysis of National Health Interview Survey data, personal communication, Kathy Byrd, Centers for Disease Control and Prevention, April 15, 2011).
- Average projected increase in demand from hepatitis B vaccine manufacturers if the vaccine is recommended for adults with diagnosed diabetes is <5% (personal communication, Sarah Schillie, Centers for Disease Control and Prevention, May 5, 2011, based on presentations to the Advisory Committee on Immunization Practices Hepatitis Working Group, 2010; used with permission).
- In 2005, the Advisory Committee on Immunization Practices recommended that adults needing a tetanus booster vaccine receive it as part of the tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap). In 2007, 2.1% of adults received Tdap in the last 2 years, or about 1% per year (33). Because tetanus boosters should be received every 10 years, the recommended rate for Tdap is 10% per year. Therefore, the actual uptake rate of 1% is approximately 10% of the recommended rate.

Individually, none of the pieces of indirect evidence is conclusive, but collectively they provide support for a 10% (or lower) assumption. We chose the 10% uptake rate to match the largest of the three pieces of evidence and to reflect that the Advisory Committee on Immunization Practices recommendation may have a significant effect on uptake. In sensitivity analyses, we consider alternative uptake rates ranging from 5% to 40%.

**Seroprotection Rates for Hepatitis B Vaccination**

Efficacy of vaccination (Table 5) is based on a Centers for Disease Control and Prevention review (personal communication from Sarah Schillie, Trudy Murphy, and Brittney Baack, April 15,

2011) of vaccine studies in adults (19 studies with sample sizes ranging from 56 to 1,580 persons) and persons with diagnosed diabetes (10 studies with sample sizes ranging from 9 to 99). The studies in adults were generally much larger than the studies in persons with diabetes. Some of the diabetes studies represent retrospective subanalyses of small numbers of persons with diagnosed diabetes in trials that were not intended for such analyses. Four of the diabetes studies focus on special subsets of the diabetes population (persons with end-stage renal disease, chronic renal disease, or dialysis), and four others focus on type 1 diabetes and include children.

**Supplementary Table 5.** Efficacy of Hepatitis B Vaccination in Adults with Diagnosed Diabetes

| Age Group | Efficacy | Lower Limit (approx) | Upper Limit (approx) |
|---|---|---|---|
| 15–19 | 95% | 90% | 100% |
| 20–24 | 95% | 90% | 100% |
| 25–29 | 95% | 85% | 100% |
| 30–34 | 90% | 85% | 95% |
| 35–39 | 90% | 70% | 95% |
| 40–44 | 85% | 70% | 95% |
| 45–49 | 80% | 65% | 95% |
| 50–54 | 80% | 60% | 95% |
| 55–59 | 70% | 55% | 90% |
| 60–64 | 70% | 50% | 90% |
| 65–69 | 60% | 45% | 85% |
| ≥70 | 40% | 35% | 65% |

The following studies were included in the report:

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3. Chow KM, Law MC, Leung CB, Szeto CC, Li PK. Antibody response to hepatitis B vaccine in end-stage renal disease patients. Nephron Clin Pract. 2006;103(3):c89-93.
4. Cumberland NS, Sloss JM, Green AD, Masterton RG, Sims MM. Immunisation of armed service medical personnel against hepatitis B infection. J R Army Med Corps. 1995;141(2):78-81.
5. de Rave S, Heijtink RA, Bakker-Bendik M, Boot J, Schalm SW. Immunogenicity of standard and low dose vaccination using yeast-derived recombinant hepatitis B surface antigen in elderly volunteers. Vaccine. 1994;12(6):532-4.
6. Douvin C, Simon D, Charles MA, Deforges L, Bierling P, Lehner V, et al. Hepatitis B vaccination in diabetic patients. Randomized trial comparing recombinant vaccines containing and not containing pre-S2 antigen. Diabetes Care. 1997;20(2):148-51.
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8. Gold MR, Siegel JE, Russell LB, Weinstein MC. Cost-effectiveness in health and medicine. New York: Oxford University Press; 1996.
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14. Ocak S, Eskiocak AF. The evaluation of immune responses to hepatitis B vaccination in diabetic and non-diabetic haemodialysis patients and the use of tetanus toxoid. Nephrology (Carlton). 2008;13(6):487-91.
15. Pozzilli P, Arduini P, Visalli N, Sutherland J, Pezzella M, Galli C, et al. Reduced protection against hepatitis B virus following vaccination in patients with type 1 (insulin-dependent) diabetes. Diabetologia. 1987;30(10):817-9.
16. Rendi-Wagner P, Kundi M, Stemberger H, Wiedermann G, Holzmann H, Hofer M, et al. Antibody-response to three recombinant hepatitis B vaccines: comparative evaluation of multicenter travel-clinic based experience. Vaccine. 2001;19(15-16):2055-60.
17. Roome AJ, Walsh SJ, Cartter ML, Hadler JL. Hepatitis B vaccine responsiveness in Connecticut public safety personnel. JAMA. 1993;270(24):2931-4.
18. Stoffel M, Lievens M, Dieussaert I, Martin I, Andre F. Immunogenicity of Twinrix in older adults: a critical analysis. Expert Rev Vaccines. 2003;2(1):9-14.
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21. Treadwell TL, Keeffe EB, Lake J, Read A, Friedman LS, Goldman IS, et al. Immunogenicity of two recombinant hepatitis B vaccines in older individuals. Am J Med. 1993;95(6):584-8.
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SUPPLEMENTARY DATA

## Alternative Uptake Rates

As uptake rates increase, net costs and QALYs saved increase as more persons are vaccinated (Table 6). The cost-effectiveness ratio does not change because its numerator and denominator increase proportionately.

**Supplementary Table 6.** Alternative Uptake Rates of Hepatitis B Vaccination for Persons with Diagnosed Diabetes, Age 20 to 59 years

| Uptake Rate | Cost of the Program | Medical Costs Saved | Net Costs | QALYs Saved | Cost-Effectiveness Ratio ($/QALY) |
|---|---|---|---|---|---|
| 5% | $55,086,198 | $9,372,570 | $45,713,628 | 609 | $75,094 |
| 10% | $110,172,395 | $18,745,140 | $91,427,255 | 1,218 | $75,094 |
| 15% | $165,258,593 | $28,117,710 | $137,140,883 | 1,826 | $75,094 |
| 20% | $220,344,790 | $37,490,279 | $182,854,511 | 2,435 | $75,094 |
| 25% | $275,430,988 | $46,862,849 | $228,568,138 | 3,044 | $75,094 |
| 30% | $330,517,185 | $56,235,419 | $274,281,766 | 3,653 | $75,094 |
| 35% | $385,603,383 | $65,607,989 | $319,995,394 | 4,261 | $75,094 |
| 40% | $440,689,580 | $74,980,559 | $365,709,022 | 4,870 | $75,094 |

QALY = quality-adjusted life year

## Vaccine Available at the CDC Price

The main analysis assumes that the hepatitis B vaccine will be obtained at the private patient price ($52.50 per dose). The CDC price ($28.00 per dose) cost reflects contract prices for CDC vaccine contracts that are established for the purchase of vaccines by immunization programs that receive CDC immunization grant funds (i.e., state health departments, certain large city immunization projects, and certain current and former U.S. territories). Private providers and private citizens cannot directly purchase vaccines through CDC contracts. At the lower CDC vaccine price, the cost-effectiveness ratio falls to $41,622 per QALY (Table 7). It is not known how many adults receive the hepatitis B vaccine at the CDC price.

**Supplementary Table 7.** Estimated Outcomes and Cost-Effectiveness Ratio, Ages 20-59, CDC Vaccine Price.

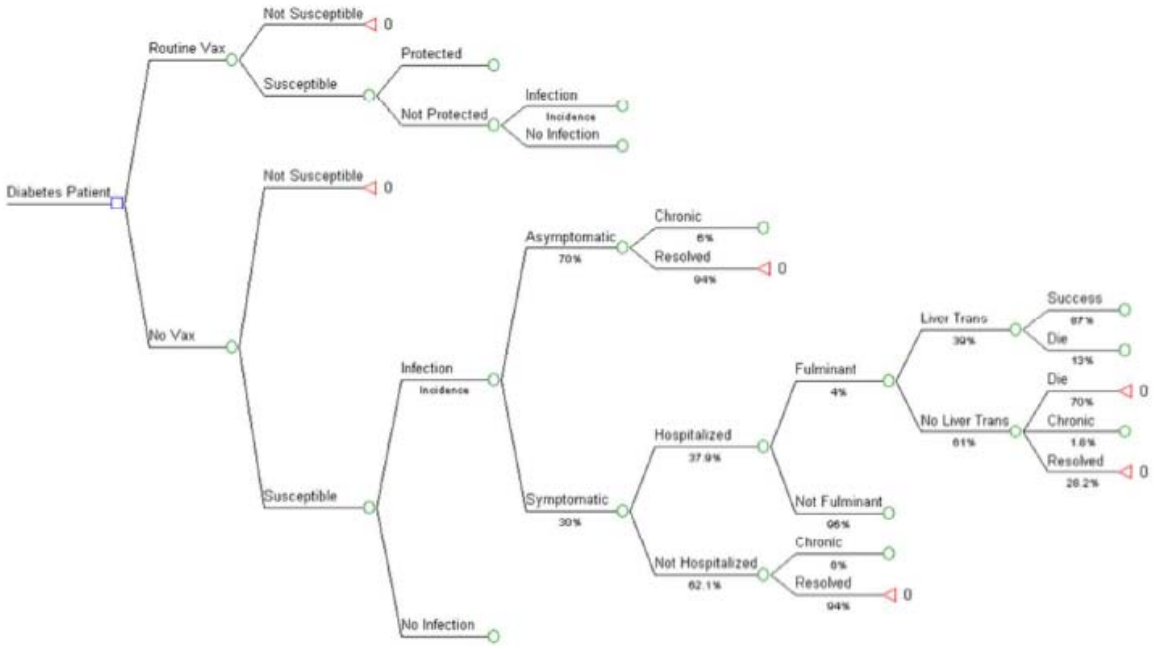
| Age | Number Vaccinated with 10% Uptake | Program Cost | Medical Costs Saved | Net Costs | QALYs Saved | Cost per QALY Saved |
|---|---|---|---|---|---|---|
| 20–59 | 528,047 | $69,420,391 | $18,745,140 | $50,675,251 | 1,218 | $41,622 |

QALY = quality-adjusted life year

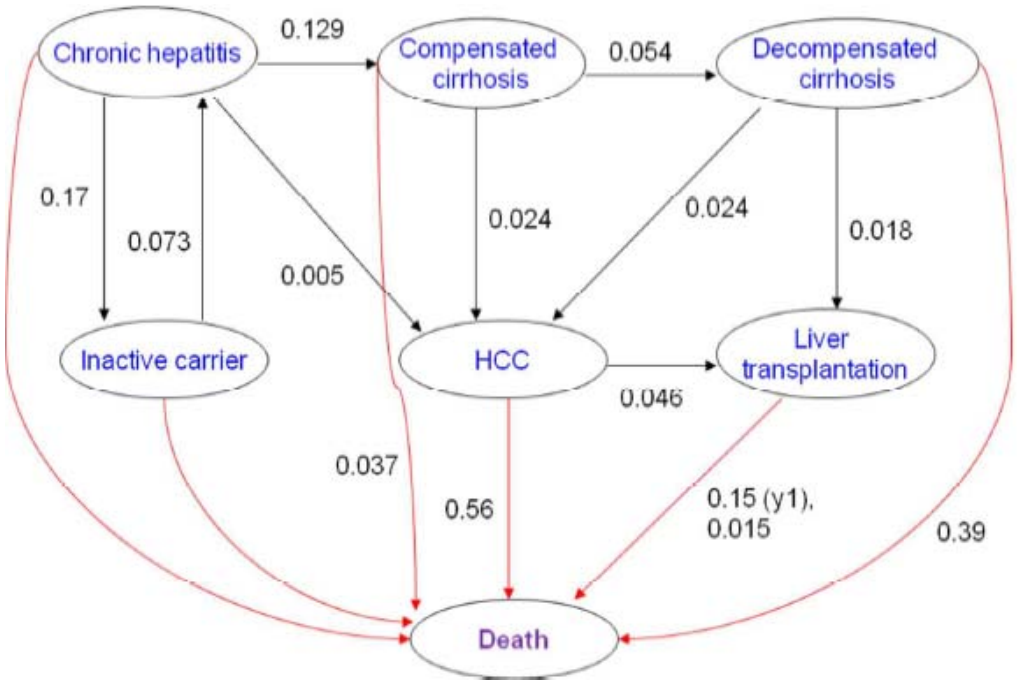
SUPPLEMENTARY DATA

**Supplementary Figure 1.**

a. Acute Hepatitis B




b. Chronic Hepatitis B



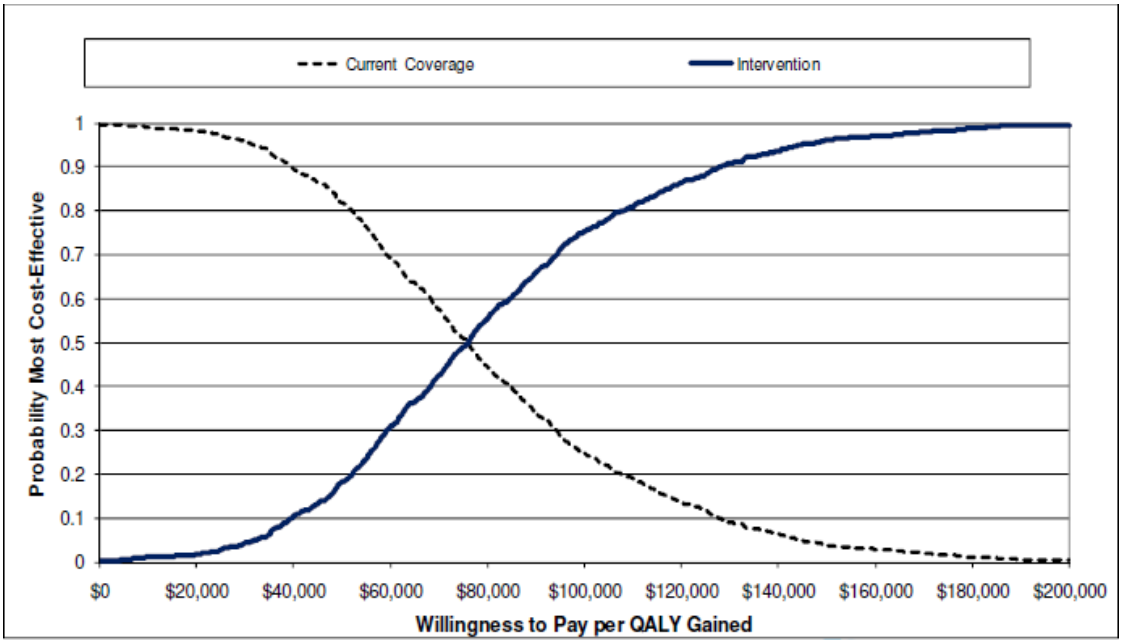

HCC = hepatocellular carcinoma

SUPPLEMENTARY DATA

**Probabilistic Sensitivity Analyses**

The cost-effectiveness ratio based on the probabilistic sensitivity analysis results is $74,478 per QALY gained, slightly lower than the results using baseline values. The bootstrapped 95% credible interval for the cost-effectiveness ratio ranges from $69,000 to $80,400 per QALY gained. The cost-effectiveness acceptability curve based on the probabilistic sensitivity analysis is shown in Figure 2. A cost-effectiveness acceptability curve shows the probability that an intervention is more cost-effective than its alternative, given a specified societal willingness-to-pay per QALY gained. The figure shows that the vaccination strategy is less likely to be cost-effective than no vaccination for willingness-to-pay up to $74,478 per QALY and more likely to be cost-effective for willingness-to-pay that is higher than that value.

**Supplementary Figure 2.** Probabilistic Sensitivity Analysis: Cost-Effectiveness Acceptability Curve, Ages 20 to 59




Note: QALY = quality-adjusted life year