Cost-effectiveness Background

Vaccination has long been understood as a potentially cost-effective (and often cost-saving) mechanism to increase the quality and quantity of life around the world.(1) In the area of viral hepatitis, reviews of model based estimates of cost-effectiveness found a range of possible values, with half the strategies estimated at a cost per quality adjusted life year (QALY) gained of below $20,000 (US) or below.(2) The same review found that the cost-effectiveness of targeted strategies against hepatitis A depended highly on the incidence of infection among the targeted population.(2) Studies of hepatitis B vaccination have strongly supported the cost-effectiveness of mass vaccination programs against that disease. For example, a model of immunizing infants in the Gambia against hepatitis B estimated that the strategy cost only $28 (US) per DALY averted.(3)

Studies of the cost-effectiveness of hepatitis A and B vaccines have found that cost-effectiveness is most sensitive to the incidence of the disease among the target population, the cost of the vaccines, and the number of doses required by an immunization program. Vaccination against hepatitis B has been found to be more cost-effective than vaccination against hepatitis A because of the existence of a chronic state in hepatitis B and the long term risk of liver disease, cancer, and death resulting from hepatitis B infection. In contrast, hepatitis A does not develop into chronic infection, and all morbidity and mortality associated with it is limited to acute infection.

The clinical presentation and consequences of hepatitis E virus resemble those of hepatitis A. Patients infected with the virus develop acute, self-limiting infections. These infections are often asymptomatic, with the risk of symptomatic infection likely increasing with age. Like hepatitis A, Symptomatic infections involve jaundice, fever, malaise, and in extreme cases fulminant liver failure which can lead to death.(4) Unlike hepatitis A, hepatitis E appears to result in high rate of severe disease and potentially fatal complications among pregnant women.(4) Several recent studies from the

developed world have presented evidence of chronic infection with hepatitis E which may cause complications for individuals with immune deficiencies or chronic liver disease.(5)

Cost-effectiveness of Hepatitis E Vaccination

The cost-effectiveness of hepatitis E vaccination programs in outbreak settings has not been studied. Although two vaccines against hepatitis E have been evaluated in human populations, with one (Hecolin®) licensed for commercial use, no cost-effectiveness studies have evaluated the use of the vaccine. New information on the types of implementation strategies anticipated for the new vaccine, the cost of the vaccine in public health settings, and the cost-effectiveness of these strategies based on simulation results would be helpful in understanding the appropriateness of expanding these strategies to different countries. Vaccination in outbreak circumstances could be beneficial and offer options in otherwise difficult circumstances. On the other hand, vaccination could be a poor use of resources if vaccination is of low effectiveness either because of low immune response or because it is implemented after the outbreak has peaked. As an exercise to inform the SAGE committee, we developed a simplified cost-effectiveness simulation of the use of hepatitis E vaccination in an outbreak situation.

Simplified Simulation

We built a highly simplified model of hepatitis E infection in an outbreak situation and its response to vaccination in Microsoft excel. The model was developed to assess the cost-effectiveness of mass vaccination of all individuals but did not account for the increased risk of death associated with infection in pregnancy. The model was specified to fit the characteristics of a single observed outbreak observed in Kitgum, Uganda and estimates from the model may not be applicable to other outbreak situations if they differ markedly from that context.(6)

Based on the findings from the Uganda study, the model estimated a probability of jaundice by age, and then assigned an overall probability of death given jaundice.(6) We distributed the starting population in the model by age according to World Bank estimates of the population distribution for sub-Saharan Africa (developing nations).(7) We assigned disability adjusted life year (DALY) losses to symptomatic illness and death assuming a constant background DALY value of 1.0 at all ages. We also assigned medical costs to each dose of vaccine administered, vaccine administration cost per dose of vaccine, and medical costs to symptomatic illness and deaths. The model assumed a vaccination age of 1 in the mass vaccination scenario and of 20 in the targeted pregnancy vaccination scenario, and assumed a life expectancy of 70, the global life expectancy at birth in 2011.(8) All benefits and costs were discounted to the year of vaccination. The model then summed costs associated with hepatitis E with and without vaccination, and used the differences in DALYs and costs to estimate the cost per DALY averted. We performed univariate sensitivity analyses to assess the sensitivity of the simplified model's results to changes in model parameters.

Parameters

Model parameters were selected from published sources using a non-systematic review (systematic reviews were beyond the scope of this committee) or from assumptions (Table 1). The model assigned the probability of jaundice during the outbreak based on the age-specific values published using data from the outbreak in Kitgum, Uganda, and assigned the probability of death given jaundice based on the total number of deaths observed during the outbreak (160), divided by the estimated total number of cases with jaundice (10,196).(6) For each case of jaundice, we assigned a DALY loss of 0.053, equivalent to the loss associated with a moderate acute episode of infectious disease estimated by the Global Burden of Disease Study.(9) We also assigned 1 DALY lost per year of life expectancy lost discounted to the base year of the outbreak.

Given the lack of information of global health expenditures per episode of disease, we assumed $100 of medical costs associated with each symptomatic infection and $1,000 of medical costs associated with each death. Based on published reports, we assumed a cost for the vaccine of $17.18 per dose (110 Renminbi), and that vaccination required a 3 dose series, and an additional $1 of expense per dose associated with vaccine administration..(10) As a baseline assumption, we used a vaccine efficacy of 50% to account for both possible weakness of the vaccine and delays in implementation.(11) We present cumulative costs and benefits for a population size of 19,098, the size of the camp population in Kitgum.

Baseline Results

Assuming all individuals in the Kitgum, Uganda area were vaccinated and a vaccine efficacy of 50%, we estimated a total cost of vaccination of $984,311, and an administration cost of $57,294. These invested costs of vaccination averted $353,904 in future health expenditures for a cumulative cost of the intervention of $687,701. Across the population, we estimated that a mass vaccination program would avert 786 DALYs, 0.04 per person. At the baseline parameter inputs, vaccination against hepatitis E cost $875 per DALY averted.

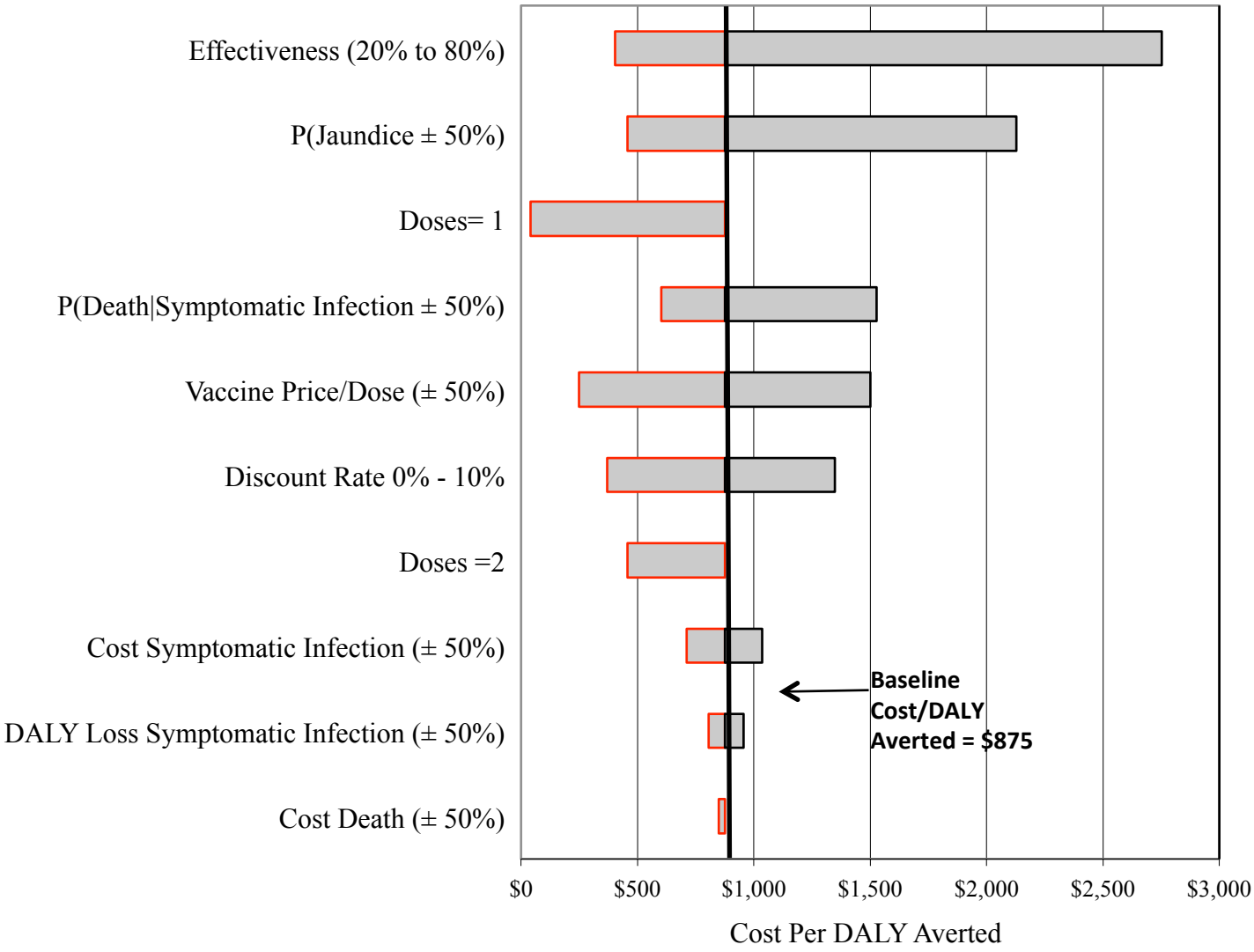
Sensitivity Analyses

The cost per DALY averted was sensitive to the effectiveness of the vaccine, the probability of jaundice, the ability to use 1 dose of vaccine, the probability of death given jaundice, the vaccine price, and the discount rate (Figure 1). The cost-effectiveness was less sensitive to the ability to use two doses, the costs assigned to caring for symptomatic infection or symptomatic infections that result in death, and DALY losses associated with symptomatic illness.

Table 1. Parameters Used in Simplified Simulation of Cost-effectiveness of Hepatitis E Vaccine when Used in a Specific Outbreak Context

Parameter #	Paramter		Source/Notes	Ref #
1	Total Population	19098	Teshale, et al (2010)	(6)
2	Number of annual Infections	12,299	Teshale, et al (2010)	(6)
3	Probability of Jaundice Ages <2	0.068	Teshale, et al (2010)	(6)
4	Probability of Jaundice Ages 2-4	0.167	Teshale, et al (2010)	(6)
5	Probability of Jaundice Ages 5-9	0.175	Teshale, et al (2010)	(6)
6	Probability of Jaundice Ages 10-14	0.187	Teshale, et al (2010)	(6)
7	Probability of Jaundice Ages 15-45	0.336	Teshale, et al (2010)	(6)
8	Probability of Jaundice Ages 45+	0.373	Teshale, et al (2010)	(6)
9	P(Death|Jaundice)	0.016	Teshale, et al (2010)	(6)
10	QALY Loss Symptoms	0.053	GBD (2012)	(9)
11	QALY Loss Death (Per Year)	1	Assumption	
12	Background QALY	1	Assumption	
13	effectiveness	0.5	Assumption, Zhu, et al (2010)	(11)
14	Discount Rate	0.05	Assumption	
15	Cost Per Dose	17.18	Park (2012)	(8)
16	Administration Cost/Dose	1	Assumption	
17	Doses	3	Park (2012)	(8)
18	Medical Cost Symptomatic Illness	100	Assumption	
19	Medical Cost Death	1000	Assumption	

Figure 1. Sensitivity of Cost per DALY Averted Estimate to Uncertainty in Parameter Estimates (Outbreak Vaccination Scenario)



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