

Alternative Vaccine Strategies for Hepatitis B in Cambodia:
A Cost-Effectiveness Analysis of Pre-filled Disposable Syringes
(Uniject) Compared to One-Dose Vials and Ten-Dose Vials

by

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Submitted to the Public Policy Program
in Partial Fulfillment of the
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ABSTRACT

Given the high endemicity of Hepatitis B virus (HBV) infections in Cambodia caused by high rates of mother to child transmission, I performed a cost-effectiveness analysis of alternative vaccine strategies to increase delivery of a birth dose within seven days of a newborn's life. I developed a Markov disease model using decision analysis software to evaluate the costs and effectiveness gained in expanding the status quo vaccine policy. Presently the Ministry of Health uses ten-dose vials coupled with auto-disable (AD) syringes to administer vaccines in health centers and outreach visits. I analyze the cost-effectiveness of permitting midwives to administer the vaccine with one-dose vials coupled with AD syringes or Uniject devices, a pre-filled disposable syringe. Being freeze sensitive and heat stable, Hepatitis B vaccines can be stored out of the cold chain in the homes of midwives until they visit a client's home. I conclude from my analysis that one-dose vials delivered by midwives is the most cost-effective strategy at an incremental cost of \$31.08 per quality-adjusted life years (QALYs) gained compared to the status quo policy of no midwife strategy. Uniject use by midwives has an incremental cost of \$31.26 per QALY gained. According to my one-way sensitivity analyses, Uniject would only be more cost-effective if it cost less than \$0.90, one-dose vials cost more than \$0.84 per vial, or the wastage rate of ten-dose vials exceeded 46%. The model adopts the time horizon of a Cambodian newborn's lifetime from age zero to death and is performed from the perspective of the Cambodian Ministry of Health and National Immunization Program. I evaluate all vaccine policies at a 3% annual discount rate on both utilities and costs.

KEYWORDS: Hepatitis B, Cambodia, vaccine, autodisposable syringe, Uniject, freeze sensitivity, wastage, outreach immunization, developing countries, cost-effectiveness

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Assistant Professor of Medicine and, by courtesy, of Economics

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1. Introduction

There are over 350 million Hepatitis B (Hep B) carriers worldwide, and 25-30% of these carriers will die from scarring of the liver (cirrhosis) and/or hepatocellular carcinoma (HCC or liver cancer) (Joshi et al. 2004, p. 472). A decade later, DNA technology led to a more effective genetically engineered or recombinant Hep B vaccine and made vaccinating millions possible. In 1980, the Hep B vaccine became the first “cancer vaccine” to prevent liver cancer by protecting people against chronic infection of the Hep B virus (HBV) (Blumberg 2002, p. 134). Though the Hep B vaccine is widely available, it is more expensive than the traditional vaccines in the Expanded Program on Immunizations (EPI),¹ making it difficult for low-income countries with high HBV carrier rates to implement into their national immunization programs (WHO 2001). Countries like Cambodia have adopted Hep B vaccines into their vaccination schedules, but financing dilemmas and an absence of formal country-specific cost studies have contributed to poor national coverage of birth doses that prevent further transmission.

I evaluate the uncertainties and constraints affecting effective implementation of infant Hep B vaccines by calculating the incremental dollars per quality-adjusted life years (QALYs) gained with alternative vaccine policies. I analyze three different vaccine presentations – ten-dose vials, one-dose vials, or Uniject – administered in health centers, outreach visits, or at home by midwives. As seen in **Figure 1**, the syringe and vial are integrated in the Uniject device as opposed to the AD syringes needed with ten-dose vials and one-dose vials (**Figure 2**).

Differences in costs and effectiveness are also attributed to threats of vaccine potency due to freeze sensitivities, heat instabilities, and a newly adopted ten-dose vial policy implemented in

¹ Many countries adopt an Expanded Program on Immunization or EPI program to provide the following vaccine preventable diseases for free: polio (OPV), tuberculosis (BCG), measles, mumps, and rubella (MMR), diphtheria, pertussis, and tetanus (DPT), and Hep B (HBV). The HBV vaccine is considered the newest and costliest addition to the EPI program, which is run by each of the country’s Ministry of Health (MoH) in close cooperation with WHO, UNICEF, and other partners.

June 2005. Other variables include wastage rates, storage volume, and prices per dose. I perform sensitivity analyses on variables like wastage rates, pricing, and expected timeliness of rural coverage to determine critical thresholds where different vaccine strategies lose or gain dominance. After calculating the cost in U.S. dollars per effectively immunized child for each vaccine strategy, I will rank the cost-effectiveness of each vaccine strategy in preventing chronic HBV infection among newborns in Cambodia. Additionally, I assess the feasibility of implementing changes in Cambodia's public health system regarding the Hep B birth dose vaccine strategies. Although previous studies have compared one-dose vaccines to ten-dose vaccines and Indonesia successfully incorporated Uniject in their immunization program, my study is the first to compare ten-dose vaccines to one-dose vaccines and Uniject in Cambodia. By employing a formal cost-effectiveness analysis, I provide a quantitative argument for the use or disuse of various vaccine strategies at the policy level and contribute to Cambodia's strategic planning for its Hep B immunization program.

Figure 1. Demonstration of size and use of Uniject device



Source. Children's Vaccine Program. <http://www.childrensvaccine.org/>

Figure 2. Auto-disable (AD) syringes and Traditional Vaccine Vial



Source. Becton, Dickinson, and Company. <http://www.bd.com>

1.1 Background on the Hep B Virus

With an asymptomatic period ranging from 30 to 40 years, HBV detrimentally affects middle-aged adults when they are needed by those around them. William Muraskin, author of *The War Against Hep B: A History of the International Task Force on Hep B Immunization*, described the phenomenon as follows, “Couples can and do rapidly replace their young children, but children cannot readily replace their parents, or society its most economically productive members” (1995, p. 2). Though Hep B afflicts adults, the disease is contracted in childhood and manifests itself as cancer or cirrhosis of the liver as they age. There are about 350 million Hep B carriers and 170 million Hep C carriers worldwide, and approximately 2,000 to 5,000 people throughout the world die each day from cancer or cirrhosis of the liver because of a HBV infection they contracted in childhood (Muraskin 1995, p. 10).

With 85 percent of cases of liver cancer or hepatocellular carcinoma caused by HBV, an estimated 1.5 million annual deaths result from HBV and other outcomes of HBV infection (Blumberg 2002, p. 150). This figure is comparable to the annual number of deaths attributed to HIV, yet HBV does not receive the same amount of media coverage. The major difference between HBV and HIV, however, is that HBV is vaccine preventable, leading many to consider it the first cancer vaccine since it prevents liver cancer by protecting people against chronic HBV infection – the leading cause of liver cancer. Worldwide, HCC is the third most common cause of death from cancer in men and the seventh most common cause in women, but this statistic probably underestimates true figures because cancer registries do not exist in areas where it is most prevalent, such as Asian and sub-Saharan Africa nations (Blumberg 2002, p. 150).

Statistics on HBV prevalence and its cause of liver cancer are overwhelming, but understanding the disease’s ease in transmission partially explains its prevalence. There are two

modes of transmitting the disease – horizontal transmission and vertical transmission. In the developed world, the former mode often occurs during adulthood through sexual intercourse, sharing needles, or personal care items like razors and toothbrushes. Infection with HBV later in life is not as serious as early infection, which allows a longer time for the disease to adversely affect its host. Vertical transmission where a mother infects her child during delivery, however, is the more common route in developing countries. If not transmitted at birth, the probabilities of HBV infection increase if mothers and siblings are carriers through breast-feeding, skin lesions, and sharing implements. Earlier infection increases the likelihood of becoming a chronic carrier and ultimately a victim of liver cancer. The risk of HCC in the offspring of HBV carrier mothers is about five to twelve-fold, which is in the same range as the risk for cancer of the lung in cigarette smokers (Blumberg 2002, p. 161).

Interestingly, mother-to-child transmission in Africa occurs months or years after birth, while in Asia, transmission may occur before, at the moment of, or shortly after birth (Blumberg 2002, p. 162). In the late 1970s and early 1980s, studies in the African countries of Senegal and Mali sampled blood from umbilical cords of 1500 women to assess the HBV status of the child at and before birth. None of the children became infected before five months of age, whereas in Asia, children became chronically infected within the first few weeks of birth. The differences in genetic responses to HBV infection at birth allow a more flexible vaccination period for children in African nations than in Asia where the birth dose within seven days becomes more critical. Horizontal transmission could also explain this difference since infected family members and children often interact with one another while suffering from abrasions or skin lesions. Because HBV is found in body fluids like blood, semen, vaginal fluid, and breast milk, it can be easily

transmitted if hands are not washed, personal hygiene items like toothbrushes are shared, or open sores and cuts are not properly covered with a bandage.

The physical indications of weight loss, abdominal pain, a mass in the right upper part of the abdomen, and unexplained deterioration in the general condition usually occur when diagnosis and treatment are too late. Liver cancer has one of the lowest survival rate after clinical diagnosis at about five percent for the subsequent five years (Blumberg 2002, p. 149). In explaining the evolution of the virus, the geneticist Blumberg wrote, “HBV has managed to insinuate itself into the main functions that allow humans to perpetuate themselves: childbirth, sexual union, and family interaction. It doesn’t kill its host until the later decades of life when the possibilities of transmission are greatly decreased” (p. 167). Treatment of liver cancer also continues to be unsatisfactory, and survival after treatment does not greatly exceed the survival rate for untreated cases. Fortunately, development of the Hep B vaccine means transmission between generations and amongst peers can be stopped.

1.2 Study Significance

In spite of the widespread availability of the vaccine, there are many low-income countries that continue to have high endemicity rates of HBV. The World Health Organization recommends universal immunization with the Hep B vaccine, but developing countries like Cambodia often lack domestic resources to implement such a program. Partnered with the Program for Appropriate Technologies in Health (PATH), the Children’s Vaccine Program, and the Australian International Health Institute of the University of Melbourne, the Cambodian government is attempting to fulfill its commitment to the Bill Gates-backed Global Alliance for Vaccines and Immunization (GAVI) and the Vaccine Fund. Assisting countries establish a self-

supporting public health system, GAVI requires that every participating country vaccinate at least 80 percent of its children within five years and requires poor countries like Cambodia to take over funding of vaccination services by conducting yearly financial sustainability analyses.

Child immunization programs have been in place since 2003 to reduce vertical, or mother-to-child, transmission of this preventable disease. By vaccinating newborns within the WHO-recommended 24 hours of delivery, the country prevents death from liver cancer in chronic Hep B carriers. It is difficult, however, to vaccinate newborns, 90% of whom are delivered at home in rural provinces of the country (PATH 2002, p. 9). The difficulties in delivering a birth dose within 24 hours have led countries to accept birth dose vaccinations within seven days, which has an acceptably reduced efficacy in preventing transmission. The PATH program has made efforts to quantify its successes through assistance in serological surveys and monetary assistance, but Cambodia currently lacks a cost-effectiveness analysis of Hep B vaccination using country-specific data on prevalence rates and resource constraints.

The Cambodian government has a goal of reducing the number of HBV carriers but acknowledges high vaccine wastage rates as a key weakness in their current program. The UNICEF recommended budget price for a ten-dose vial of Hep B vaccine in 2006 is \$2.40, but if more than half are wasted during outreach visits, the cost per dose doubles from \$0.24 ($\2.40 divided by 10 doses) to \$0.48 ($\2.40 divided by 5 doses). A one-dose vial of Hep B vaccine, however, costs \$0.41 but takes up more storage space during refrigeration and transportation. Unless wastage rates are decreased, the cost-savings associated with purchasing ten-dose vials like ten-dose formats will not be realized. The 2002 government issued report states, “The financial impact of vaccine wastage will be magnified once DTP/Hep B is introduced nationally since it is a much more expensive vaccine relatively. Wastage rates over the last five years for

each of the antigens indicate a low chance of declining in following years” (Huot and Chhon 2002, p. 13).

The Ministry of Health in Cambodia has implemented outreach immunization visits to reach home delivered newborns in rural areas. Health care workers associated with one of the more than 900 health centers in the country conduct outreach programs to surrounding villages (8-12) once a month. Many children will not receive a birth dose within seven days if their parents rely on these outreach sessions. Presently children must be brought to the nearest public health center if they are to receive their first dose in a timely manner. The difficulty is that transportation to health centers is costly and difficult for villagers and their newborns, especially during the rainy seasons.

Prior to having refrigerators in every health center, the government required that health care workers discard unused doses of a ten-dose vials even if they used only one dose at an outreach session. This discard policy resulted in an estimated wastage rate of 50 percent a ten-dose vial of Hep B vaccine because enough children are not always present at outreach sessions (PATH 2003). The alternative is for health workers to turn away children because they are reluctant to open a new vial.

In an effort to reduce wastage and not miss a vaccine opportunity, Cambodia used its Immunization Services Support funds to invest in refrigerators and adopted a new open vial policy. In April 2005, 95% of the country’s health centers received gas powered refrigerators while health centers located in or near health centers at the operational district (OD) level shared refrigerators. The Central Medical Store is responsible for nationwide distribution of medical supplies and vaccine equipment to health centers at the provincial, OD, and local town level on a quarterly basis or every three months. Prior to refrigeration capacity, local health centers

frequented the OD health centers every week to transport vaccines in a 24 liter cool box (Vichet Personal Interview 8/26/05). As of April 2005, health centers have decreased weekly visits to OD health centers to monthly visits to procure additional vaccines. This reduced frequency results in lowered transportation costs associated with traveling between health centers and ODs.

Refrigeration capacity has allowed the government to adopt an open vial policy also known as a ten-dose vial policy (MDVP) in June of 2005. Instead of discarding unused doses from an outreach visit, vaccines can be used at subsequent immunization sessions for up to four weeks provided that health care workers ensure the following: 1) the expiration date has not passed; 2) vaccines are stored in the cold chain, which is between 2 and 8°C; 3) aseptic or sanitary techniques have been used to withdraw all doses; 4) the vaccine vial monitor (VVM) has not changed color indicating over heat exposure; and 5) the punctured vial septum, or rubber seal on top the vial, has not been submerged in non-sterile water (NIP/MOH Handbook 2005, p. 18). As of early September 2005, however, there is inconsistent implementation of the MDVP policy at the health center level with some health centers continuing to discard opened vials during outreach visits. For example the province of Kampong Cham has been implementing Hep B vaccines since 2002 and its health centers were aware of the MDVP policy. In Kampong Chhnang, however, the Hep B vaccine was introduced in 2004, and health care workers at the Oreung Ov health center were not aware of the national open vial policy. The effect of refrigerators and the MDVP policy on wastage rates continue to vary among health centers.

Given the difficulties of previous re-useable and sterilizeable syringes and the associated increased risk of transmitting other diseases, the creators of Uniject, an international nonprofit organization called Program for Appropriate Technologies in Health (PATH), designed a pre-filled, one-dose device to prevent reuse. This is similarly accomplished with one-dose vials used

with auto-disable (AD) syringes. The device costs more than previous injection methods, but in Indonesia its 1% wastage rate has been proven to be more cost-effective than ten-dose vials with disposable syringes (Levin et al. 2002). The Indonesian government partnered with trained midwives who deliver babies at home and are able to administer the first dose of Hep B vaccine within 24 hours. Given the dilemmas of wastage and coverage rates with ten-dose vials, a study on the cost-effectiveness of switching to one-dose vials or Uniject devices is warranted in Cambodia where midwives are considered government health care workers trained to give injections but are not allowed to administer them outside the health center.

1.3 Problem Statement

I analyze which vaccine presentation – ten-dose vials, one-dose vials, or Uniject – is the most cost-effective in delivering the first Hep B vaccine at birth given resource constraints. Additionally, I will address why small, low-income countries with high carrier rates of HBV, such as Cambodia, have been unable to implement Uniject in their national immunization programs. Studies on the cost-savings of Uniject devices with Hep B vaccines (HB-Uniject) have been conducted in Indonesia (Sutanto et al. 1999; Levin et al. 2002) and India (Joshi et al. 2004). In contrast, I use a theoretical model based on country specific data to compare multiple vaccine strategies among three available vaccine formats. By conducting a cost-effectiveness analysis of Uniject compared to one-dose and ten-dose vials, I evaluate how prices and wastage rates affect which Hep B birth dose vaccine strategy is most cost-effective.

While Cambodia appears similar to these countries at first glance, its population of 13.4 million people pales in comparison to Indonesia's 214.5 million and India's 1.1 billion (World Bank 2003). This smaller Cambodian population results in lower economies of scale since

existing infrastructures like multiple health centers, trained health care workers, and effective vaccine distribution systems are large capital expenditures. Additionally, Cambodia has an equally high 10% rate of HBV infection, but as of 2000, it is a poorer country with a GDP per capita of \$282 that is much lower than Indonesia's \$684 and India's \$523. This makes the fight against Hep B and its associated liver cancer much more difficult for a small population, low income, and highly endemic country like Cambodia. Unable to manufacture its own vaccines and injection equipment like Indonesia, Cambodia must import its immunization equipment from outside, which further increases costs.

My cost-effectiveness analysis contributes to the literature needed by the National Immunization Program to evaluate the impact of "new vaccine presentations to lower wastage" (Huot and Chhon 2002, p. 21). The 2002 Financial Sustainability Report submitted to the Global Alliance for Vaccine Initiatives (GAVI) suggests switching to one-dose or five-dose vaccines from the present ten-dose strategy, but the report does not mention pre-filled AD syringes like Uniject. The importance of a cost-analysis, however, is clearly stated in the report, "The financial impact is particularly important for DTP/Hep B vaccine, since it is relatively more expensive" (Huot and Chhon 2002, p. 21). I quantitatively compare the country's current ten-dose vaccine format and compare it to a one-dose vial and Uniject option by calculating the incremental cost per quality-adjusted life (QALY) years averted by effectively immunizing a Cambodian child with each vaccine strategy.

2. Literature Review

2.1 Hepatitis B Child Immunization Programs: Global Overview

Scholarly articles detailing the child immunization efforts in Cambodia come as generalized status reports conducted and issued by the Cambodian Ministry of Health (MOH), the World Health Organization (WHO), the United Nations Institute for Children's Education Fund (UNICEF), the Program for Advanced Technology Health (PATH), and the Global Alliance Vaccine Initiative (GAVI). These reports contribute a global perspective on immunization coverage goals and the financial backing for vaccination programs. Unfortunately, no published cost-effectiveness studies on Hep B in Cambodia are available, but economic analyses on Hep B disease burden and vaccination programs are available for countries like the Gambia, India, Taiwan, and Indonesia.

Recognizing country-specific differences, Aggarwal, Ghoshal, and Naik (2003) assessed the cost-effectiveness of introducing Hep B vaccines in countries currently lacking effective immunization programs. Since 1992, the World Health Assembly recommended all countries introduce the Hep B vaccine by 1997. Over 100 countries with high national incomes or with high Hep B endemicity rates like the Gambia have accomplished this task. In reality, many more countries will not reach an 80% coverage target until after 2010 (GAVI 2003, p. 8). These countries contribute to the 350 million Hep B carriers worldwide, a quarter of whom will develop serious liver disease and one million of whom will die annually (Aggarwal et al. 2003, p. 215).

Realizing health administrators in low-income countries are unconvinced of the cost-effectiveness of universal childhood Hep B immunization, the authors used data on India to conduct a cost analysis. The authors define a low-income country as having a GNP below

US\$745 and a country with intermediate infection as having carrier rates between 2-8%. India has a GNP of \$530 (2003) and a 4% Hep B carrier rate (World Bank 2004). The country lacks a universal Hep B immunization program and contributes nearly one million new carriers every year with its 25 million births annually (Aggarwal et al. 2003, p. 215). Given these figures, the authors focus on India because it is representative of the countries unable to reduce rates of HBV.

In addition to the country's demographics, India's availability of data has made the country ideal for studies on Hep B cost calculations (Sahni 2004) and effective use of Uniject for Hep B vaccines (Joshi et al. 2004). Before extrapolating conclusions from studies in India, differences between these two low-income countries highlight the need to perform a country-specific study on Cambodia. First, Cambodia's GNP of \$310 (2003) is much lower than India's GNP of \$530 (2003) (World Bank 2004). Second, Cambodia's high Hep B carrier rate of 10-12% greatly exceeds India's intermediate Hep B carrier rate of 4% (CVP 2004, p. 3; Aggarwal 2003, p. 216). The two countries differ in other respects like health care infrastructure, population, economic growth, and political stability.

2.2 Lack of Formal Cost Study in Cambodia

Previous studies confirmed the efficacy of national vaccination programs in reducing infection rates of HBV (Aggarwal et al. 2003) and decreasing the prevalence of hepatocellular carcinoma (HCC or liver cancer) in children (Chang et al. 1997), while others contested the widely adopted universal immunization over selective immunization programs (Sahni et al. 2004). The importance of delivering the critical Hep B birth dose led to another field research study on the optimal timing needed to prevent mother-to-child transmission of HBV (Boot et al.

2004). Additionally, reports analyzed the use of vaccines out of the WHO recommended cold chain (Sutanto et al. 1999), the use of traditional birth attendants (Levin et al. 2002), the differences in one-dose versus ten-dose vaccine vials, and the applications of the novel Uniject device (Joshi et al. 2004; Fleming 2003; Nelson et al. 2002; Sutanto et al. 1999). The varied perspectives on this common issue highlight the complexities of Hep B birth doses in Cambodia's immunization program.

To my current knowledge, there has been no comparative cost studies performed specifically on AD syringes and Uniject devices for birth doses of Hep B vaccines in Cambodia. The most recent studies have focused specifically on the safety and effectiveness of administering Hep B vaccines in Uniject devices in India (Joshi et al. 2004). However, Cambodia is representative of a low-income country (GNP below US\$745) with high HBV endemicity (carrier rate greater than 8 percent). India, in contrast, is a low-income country with intermediate HBV endemicity, defined as a carrier rate between 2 and 8 percent. Previous clinical studies in the medicine field have confirmed that Uniject devices increase the rate of immunogenicity, or the ability to stimulate an immune response, as effectively as ten-dose vials and syringes (Nelson et al. 2002). My analysis contributes to literature in this field by building upon earlier studies of pre-filled syringes in Indonesia to smaller and less-developed countries like Cambodia.

2.3 Cost-Effectiveness Studies: Theoretical Model

Aggarwal, Ghoshal, and Naik (2003) acknowledge that previous cost-effectiveness studies conducted in the 20th century focused on high-income countries like the United Kingdom (Edmunds 1998), Spain (Garuz et al. 1997), and Poland (Wiewiora-Pilecka 2000), or high

endemicity countries like Gambia (Hall et al. 1998). Studies on low-income, intermediate endemicity countries, in contrast, limit their analysis to a global perspective (Miller and McCann 2000). The authors, however, contribute to the literature on medical econometric analyses on Hep B programs in India, and they conclude that universal Hep B immunization is highly cost-effective in low-income countries with intermediate endemicity rates like India.

The authors used a decision analysis software (TreeAge) to construct a Markov model² used to find the marginal cost of every life-year and quality-adjusted life-year (QALY) gained with universal Hep B vaccination. Sonnenberg and Beck (1993) presented the Markov model as a method suitable for medical decision making. This model estimated health outcomes and costs for two hypothetical cohorts of newborns in India: one that received the three doses of Hep B vaccine and one that did not receive the vaccine. Each simulation followed a hypothetical cohort over time, which is known as a Markov transitional probability model. Portions of cohort members transitioned between different health states over each unit of time period, or one year in this case. The authors included five states of health: healthy persons, Hep B carrier state, compensated cirrhosis, decompensated cirrhosis, liver cancer, and death.

The average number of years lived, QALY lived, and costs incurred per newborn allowed the authors to calculate the marginal cost-effectiveness and marginal cost-utility of Hep B vaccination. A lower value is favored because it means less money is spent to gain each extra life-year and QALY. They also performed two analyses: one excluding medical expenses related to treatment for long-term Hep B complications and one including these costs at a discounted

² Markov models represent decision problems that continuously incur probabilities over time by assuming a person transitions between discrete health states, called Markov states. Matrix algebra, cohort simulation, Monte Carlo simulation, or Markov-cycle trees can be used to solve Markov models. In clinical settings, Markov models allow for more accurate representations of repetitive events and the time dependence of both probabilities and utilities.

annual rate of 3%. Sensitivity analysis and a Monte-Carlo simulation³ further verified the robustness of their results.

They obtained probability estimates used in their model from published medical literature that generally favored the “no-immunization” policy. Their assumptions included a carrier rate of 4.0%, Hep B vaccine efficacy rate of 95%, a wastage rate of 20% for supplied vaccine in any immunization program, Hep B vaccine costs of US\$1.60-2.00 per pediatric dose (or US\$0.50 when purchased in bulk quantities); and vaccine administration costs at US\$0.19-0.50 per dose (Aggarwal et al. 2003, p. 216).

In order to derive their rates of disease progression from one state of health to another, the authors rely on previously published reports that range from 1989 to 1995 in order to choose a fairly high 27.5% rate that carriers would die, which they believe is similar to the “widely quoted” 20-27% estimate (Aggarwal et al. 2003, p. 216). They also obtained Quality of Life (QOL) data from estimates of clinicians caring for patients with liver disease. QOL took on the values of 1.00 for perfect health and 0 for death.

Overall, universal immunization led to reduction in Hep B carrier rate in a birth-cohort from 4 to 1.5%. Hep B carrier rate decreased by 71%, the number of years lived by a birth-cohort increased by 0.173 years (61.072 vs. 60.899), and the number of QALY by a birth-cohort increased by 0.213 years (61.056 vs 60.843). Marginal costs of US\$16.27 per life-year gained and US\$13.22 per QALY gained did not exceed the annual per capita income. These values, they conclude, are 27.1-fold and 33.3-fold lower than India’s per capita GNP (Aggarwal et al. 2003, p. 217). Analyses on excluding and including health-care costs of long-term complications of Hep B led to similar conclusions and inclusion of such costs actually made the immunization

³ A Monte-Carlo simulation calculates multiple scenarios of a model by randomly generating values for uncertain variables from a specified probability distribution for sensitive variables.

strategy more cost-effective.

In spite of these impressive statistics, the authors made several unrealistic assumptions in order to simplify the Markov model. For example, they assume all chronic Hep B infection occurred within an infant's first year of life and ignore indirect costs of reduced productivity, direct non-medical costs like time spent to receive treatment and cost of traveling, and intangible costs such as pain and suffering due to illness. Their exclusion of reduced productivity and pain and suffering is reasonable since it is difficult to quantify, but their omission of non-medical costs like time for traveling is a serious concern.

The authors acknowledge that "indirect costs of time and money spent by parents to bring the child for immunization were not included, since Hep B immunization does not require any additional visits to healthcare facility," but their assumed total cost of three doses of vaccination at US\$3.00 per infant is inaccurate (Aggarwal et al. 2003, p. 216). They fail to account for the predominance of outreach programs for initial child birth doses in low-income countries. In Cambodia, outreach is an important mode of service delivery that requires health workers to travel to remote areas (Huot and Chhon 2002, p. 10). Transportation costs and per diem wages would increase the total cost of vaccination per child. Many children are not immunized because they are difficult to access (CVP 2004, p. 5). The largely theoretical nature of this study fails to incorporate the realistic cost barriers facing immunization programs. Field research conducted by Sahni, Kapil, Nalini, Kumudha, and Puliyeel (2004) better accounts for the true costs of vaccination. This is particularly relevant in calculating the cost of administering the critical birth dose within seven days, or when possible, within 24 hours (CVP 2004, p. 4).

In spite of this oversight, the authors' one-way sensitivity analyses and probabilistic sensitivity analyses using a Monte-Carlo simulation on 1,000 hypothetical newborns provide

interesting results. A low Hep B carrier rate of 1% gave marginal costs of each life-year to be US\$64.52 and QALY to be US\$52.88, which are 6.8- and 8.3-fold lower than India's annual per capita GNP (Aggarwal et al. 2003, p. 218). The authors varied the cost of immunizing one child against Hep B in three doses from a total cost of US\$1.50 to US\$6.00, and the rise in cost increased the marginal cost of every life-year and QALY gained yet remained below India's per capita GNP. The resulting information supports a universal immunization program in all low-income countries with intermediate Hep B endemicity.

2.4 Cost-Effectiveness Studies: Field Study Model

One year later, Sahni, Kapil, Nalini, Kumudha, and Puliyeel (2004) reached a different conclusion on the cost-effectiveness of similar Hep B vaccination efforts in India. Instead of a theoretical approach, the authors conducted a field study that incorporated associated costs of administering the critical birth dose. In order to prevent vertical transmission from mother to child, newborns must be vaccinated with the first dose of Hep B vaccine within 48 hours (Sahni et al. 2004, p. 1). This project evaluated the cost of such a program by obtaining data from a community health project in Sangam Vihar, which is located on the outskirts of Delhi with a population of 65,000. The authors recognize that the WHO recommends universal immunization with Hep B vaccine, but they conclude that this recommendation is not cost-beneficial in India. According to their calculations, the cost of every life-year gained with the vaccination is greater than India's per capita GNP.

The authors rely upon formulas from several papers in order to compute statistics for their analysis. For example, they calculated the true prevalence of HBsAG (Hep B surface antigen) among pregnant women who delivered during the one-year study period using a formula

found in a 1992 paper written by Tu, Litvak, and Pagan (1992). They also used a technique described by Tyagi, Saroj, Sawhney, Vikas, and Puliyeel (2003) to justify comparing the cost per QALY gained to India's per capita gross national product (GNP). A module devised by Tandon, Irshad, Mathur, and Rao (1991) assisted the authors in calculating the cost of universal immunization compared to selective vaccination based on the cost of a three-dose series of the Hep B vaccine and the cost of testing.

In line with other medical papers, the authors drew upon previous findings to supplement their own data and analysis in evaluating the cost-effectiveness of Hep B vaccinations in the studied community. This study provided a cost benefit analysis of universal immunization and selective immunization for Hep B. From December 1, 2001 to November 30, 2002, the study identified 252 primiparous women, or first time mothers, infected with Hep B. This is out of the 1100 mothers who had a delivery in the study area in this one year time period. Given the difficulty of vaccinating all babies at birth, or universal immunization, the project team vaccinated babies born to identified HBsAg-positive mothers at the seventh month of pregnancy. This selective vaccination strategy reduced the cost of manpower needed in a universal immunization program (Sahni et al. 2004, p. 3). For example, one health worker working half-time could service the community area for the newborns' first vaccination at home. In contrast, one full-time worker and a half-time worker would be needed to implement a universal vaccination in the authors' study population. The authors factored the cost in wages and travel of health workers, the cost of three doses of the vaccine, and the cost of one-dose vials of the vaccine in their community-based study to project a national cost for universal and selective immunization. Additionally, they performed sensitivity analyses on the declining cost of vaccines due to economy of scale.

For data, the authors relied on UNICEF (1999) for the fertility rate in India to compute the number of mothers who need HBsAg testing in the study population. In calculating national cost of vaccination, they used statistics from a paper by Dhir and Mohandas (1998). For example, approximately 5,000 people in India will die from liver cancer due to Hep B. The authors referred to Miller and Kane (2000) for figures predicting life expectancy in 2040 in India, which will be 66 years. At this time, benefits of vaccination are realized since the liver cancer develops in adults around the age of 45 years. They find that for each case of liver cancer avoided, 21 years are saved (Sahni et al. 2004, p. 3). Figures from Miller and Kane (2000) are again used to conclude that 20.6 QALY are saved for each case of liver cancer averted, given utility estimates of liver cancer at 0.2 QALYs and probability of death occurs within six months of diagnosis (Sahni et al. 2004, p. 3). Drawing upon data from other papers and their own community-based study, the authors suggested that 20.6 QALY are saved for each case of liver cancer averted with the undiscounted cost per QALY saved at 45,540 Rupees (Rs), or US\$910.80 given $\text{INR}50 = \text{US}\1 (Sahni et al. 2004, p. 3). This cost, they concluded, is double the per capita GNP of India, which is Rs 20,250, or US\$405. If discounting at a rate of 3% for 45 years to account for the opportunity cost of money, the discounted cost per QALY rises to Rs 259,610, or US\$5,192.20. In both cases, the cost per QALY saved with universal vaccination greatly exceeds the country's GNP.

The cost-to-benefit ratio of universal immunization in India was high due to the relatively small benefit of lives saved and the low mortality rate among Hep B carriers in India. Late accrual of benefits (nearly 45 years later) also discounted the benefits and made today's costs of vaccines and costs of administering vaccines more unfavorable. The analysis concludes that universal Hep B immunization is not cost-beneficial yet fails to offer alternative measures of

cost-effectiveness in a program. Furthermore, projecting findings and numbers from the community-based study to national statistics could be inaccurate if the sample population is not representative of the true national population.

Conclusions made by Sahni, Kapil, Nalini, Kumudha, and Puliyeel (2004) conflict with those of Aggarwal, Ghoshal, and Naik (2003) because they differ in methodologies and statistics used for calculations. The community-based study focused on a specified study area and allows the authors to account for finer details. In this case, those details included associated costs of delivering a child's first Hep B birth dose within a constrained time period. The dilemma, however, occurs when the authors project findings from this site-specific study to estimate national figures. The authors do not compare the health project area in Sangam Vihar to other communities in the large country. Lastly, timely delivery of the first dose of Hep B vaccine prevents downstream costs and decrements in utilities from resulting HBV complications. Efforts to reduce this cost, however, are not explored.

2.5 Home Delivery Births: Costs of HB-Uniject Compared to Wastage Rates

Another controversial aspect of the study conducted by Aggarwal, Ghoshal, and Naik (2003) concerns the statement, "Changes in vaccine wastage rate and vaccine efficacy rate had only minor effect on marginal cost-effectiveness." (Aggarwal et al. 2003, p. 218). The authors, though, ignore the significance of high wastage rates resulting from ten-dose vials. When health care workers administer the first Hep B birth dose for a newborn, they must open a vial that contains enough doses for ten shots. The low probability that nine other children will be born in proximity of one another means the opened ten-dose vial will go to waste. The second issue concerns safety since more than 80% of health workers have had at least one needle-stick

accident during re-capping of a standard disposable syringe. Standard syringes differ from autodisposable (AD) syringes that block the plunger after a single use. For these reasons, Drain, Nelson, and Lloyd (2003) compared ten-dose vaccine vials to one-dose vials on a programmatic and economic basis.

As of 2000, ten-dose vials comprise an estimated 80% of vaccines administered throughout the world (Drain et al. 2003, p. 726). Rising wastage rates have offset the lower per-dose price advantage of ten-dose vials. The WHO estimated 60% of vaccines were wasted in 1992, while 45% were wasted in 1994 after a switch from twenty-dose vials to ten-dose and five-dose vials (Drain et al. 2003, p. 728). Price advantages of ten-dose vials diminish with even moderate wastage rates. For example, a one-dose vial is preferred to ten-dose vials when wastage exceeds 44% (Drain et al. 2003, p. 728). A study by Levin Nelson, Widjaya, Moniaga, and Anwar (2002) found that one-dose devices like Uniject were cost saving when wastage rates exceeded 33% (Levin et al. 2002, p. 10).

Unfortunately, the increased volume of one-dose vials and its higher manufacturing costs may outweigh the increase in immunization coverage, increase in safety, and decrease in wastage. The one-dose format evaluated is similar to the Uniject device since syringe and vaccine are integrated into one unit. Overall, the manufacturing costs of one-dose formats are about 2.5 times greater than the manufacturing costs of ten-dose vials (Drain et al. 2003, p. 727). This estimate does not include the vaccine price, which varies with the type of vaccine used. Manufacturing costs of filling costs, vaccine overfill, and packaging costs represent a large portion of the price component of inexpensive vaccines. After comparing the two formats, the paper concluded that cheaper vaccines and limitations in cold-chain storage capacity make ten-dose vials more appropriate in certain settings.

Nevertheless, one-dose formats simplify inventory logistics, such as vaccine tracking and estimating wastage rates associated with ten-dose vials. A drawback of one-dose vials concerns their packed volume per dose, which is six times greater than ten-dose vials (Drain et al. 2003, p. 727). The authors note that pre-filled AD devices occupy 30% more volume in cold chain storage than one-dose vials. This concern is extremely important in countries with poor health infrastructures and poorly equipped health centers. In Cambodia, for example, refrigerators were only recently installed in health centers in April 2005 to maintain vaccines in the cold chain without freezing (Huot and Chhon 2002, p. 7). The number of unimmunized children in rural areas further complicates the issue of administering vaccines out of the cold chain for extended periods.

These concerns about taking Hep B vaccines out of the cold chain have led to studies on the heat stable properties and efficacy of vaccines when taken out of the recommended two to eight degrees Celsius of storage. Beginning in 1995, a pilot program innovatively employed midwives to keep HB-Uniject in their homes and out of the cold chain. Each device contained a vaccine vial monitor that changed colors when it should be discarded because of excess heat exposure. An earlier study conducted by Sutanto, Suarnawaw, Nelson, Stewart, and Soewarso (1999) confirm that Hep B vaccines, as well as tetanus toxoid (TT) vaccines, are heat stable and can be stored for two to six months at 37 degrees Celsius (Sutanto et al. 1999, p. 119). This property makes HB-Uniject ideal for outreach projects in tropical climates like India, Indonesia, Vietnam, China, and of course, Cambodia. Furthermore, a field study on the Indonesian islands of Lombok and Bali conducted between July 1995 and April 1996 confirmed that vaccines retain their potency after storage in midwives' homes for up to one month. Hep B vaccines suffered a

small 1% drop in potency, but this did not affect an infants ability to build immunity against HBV (Sutanto et al. 1999, p. 120).

In addition to the authors' field study, they conducted a cost-effectiveness study comparing two models of immunization programs explored in Indonesia at the time. The first model administered the birth dose at 6 weeks of age, and completed the three doses of Hep B during monthly sessions held at health centers. They based their second model on their field study, which immunized children within a week of birth and required the second and third doses to be administered in health centers as well. After ten months, the authors estimate the total cost per child immunized was US\$6.57 using a Uniject device for first dose at home. This method was more cost saving than the US\$7.19 for administering the dose to a six-week infant with a standard disposable syringe at health centers (Sutanto et al. 1999, p. 122).

The authors favor the use of Uniject devices because the Indonesian Expanded Program on Immunization discarded 36% or 1.6 million doses per year in 1995-96 (Sutanto et al. 1999, p. 122). The retained potency of Hep B vaccines out of the cold chain, the cost savings of administering birth doses at home, the reduction in vaccine wastage rates, improvement in safety issues, and the acceptability among mothers and midwives influenced the Indonesian Ministry of Health to expand the program to target all of its five million annual birth by 2003 (Levin et al. 2002 p. 3). In spite of the optimistic results in Indonesia, the authors warn that "the introduction of Uniject device into routine immunization practice would require site specific analysis" (Sutanto et al. 1999, p. 123). Once again, the importance of country-specific differences support a field study incorporating cost-effective analysis in Cambodia to better evaluate the use of HB-Uniject for birth doses.

A paper by Levin, Nelson, Widjaya, Moniaga, and Anwar (2002) updated and built upon the efficacy and cost-savings of the field study conducted by Sutanto, Suarnawaw, Nelson, Stewart, and Soewarso (1999). The authors use sensitivity analyses to individually vary three variables: vaccine wastage rates, immunization coverage rates, and prices for vaccines and injection devices. The 2002 study confirm that HB-Uniject is economically worthwhile when wastage rates exceed 33% (Levin et al. 2002, p. 10). In this study, the pre-filled, one-dose format replaced five-dose vials and disposable syringes for all three doses of Hep B vaccines. The two Indonesian studies differ because the 1999 study only analyzed the cost savings of HB-Uniject for the single critical birth dose and used ten-dose vials in comparing costs. The more recent study also uses data obtained from the provinces of East Java, West Nusa Tenggara, and Yogyakarta, as opposed to two islands in the older study. Both studies used existing midwives and village health care workers to immunize children born within seven days using HB-Uniject. The successful use of HB-Uniject in Indonesia inspires other countries to consider this innovative strategy. The combination of traditional birth attendants with a technologically advanced pre-filled injection device demonstrates the possibility of immunizing children in rural areas against HBV. Levin, Nelson, Widjaya, Moniaga, and Anwar (2002) acknowledge the success of Uniject for the heat stable vaccine tetanus toxoid (TT) in Afghanistan and Mali, but they caution that “countries without community-level vaccinators face a greater challenge” (Levin et al. 2002, p. 10). The opportunity for programmatic innovations, however, increases with the availability of Uniject devices pre-filled with heat stable vaccines like Hep B and TT.

2.6 Evaluating the Appropriateness of Cost-Effectiveness Analyses (CEA)

Economic evaluations prove useful in determining the most effective health care intervention given a constraint on resources through systematic analyses. Drummond, O'Brien, Stoddart, and Torrance (1997) frame the usefulness of economic evaluations in terms of efficacy, effectiveness, and availability. Not only must the health procedure, service, or program work and provide more good than harm, but it must also be accessible to those who need it. New health interventions must be compared to existing activities as alternative programs. Additionally, it is important to establish the analytic viewpoint since the real cost of the program is calculated in terms of its opportunity cost, or foregone health outcomes in another intervention. If a societal viewpoint as opposed to a patient perspective is adopted, productivity changes in either costs or consequences will affect the analysis. Furthermore, Drummond, O'Brien, Stoddart, and Torrance clearly distinguish between cost-minimization analyses, cost-effectiveness analyses, cost-benefit analyses, and cost-utility analyses that prove useful in defining my study as a cost-effectiveness analysis.

Policymakers may find cost-benefit analyses (CBA) more useful since it provides dollar estimates for costs and benefits derived by the health program, but CEAs are also practical in that they give outcomes in natural units like cost per infection prevented or cost per child immunized. This allows readers or policymakers to individually interpret the ratio and translate it to costs, if they prefer. The use of willingness-to-pay is particularly subjective while health improvement in health effects allows for broader comparisons among interventions. Cost-utility analysis (CUA) is also inappropriate since use of either injection device does not affect the quality of life, such as a cancer therapy treatment with side effects.

My study appears similar to a cost-minimization analysis because I am searching for the least cost alternative. The difference, however, is that the three injection methods do not achieve the same degree of effectiveness, as measured by coverage rates. Instead, a cost-effectiveness analysis is more appropriate because ten-dose vials, one-dose vials, and Uniject have differential successes and costs in achieving the same outcome of interest – national coverage. Cost-minimization would compare alternatives on the basis of cost per immunization, whereas cost-effectiveness compares the ratio of costs and benefits for each device. Without a difference in benefits or consequences, the denominator of a CE ratio would not exist and the analysis would be solely based on costs. I use the following basic formula to calculate the incremental cost-effectiveness ratio (ICER) between each strategy:

$$\text{ICER} = [\Delta (\text{Costs} - \text{Savings}) / \Delta \text{Effectiveness}] \quad (1)$$

2.7 CEA Applied to Different Injection Methods

In performing an economic evaluation on Hep B infant immunization programs in Cambodia, I have identified alternative injection equipments with different costs and consequences. I compare the current use of ten-dose vials to the potential use of one-dose vials and Uniject devices to effectively deliver the first birth dose of Hep B vaccine within Cambodia's seven-day policy. Implementing each alternative, however, differs in terms of device costs, training costs, transportation costs, storage costs, and wastage rates. Shared common overhead services will not be included in the calculations. The consequences or outputs of each injection device mainly differ in the number of children vaccinated due to reduced costs, increased timeliness, and reliability. Withstanding tropical temperatures for up to three months, the Hep B vaccine can be stored in the homes of health vaccinators and traditional birth

attendants until they are called for service at a home delivered birth (Levin et al. 2005; Nelson et al. 2004). In the form of either Uniject devices or one-dose vials, Hep B vaccines have the potential to reach children in more rural areas of the country since it does not require stringent cold chain storage and eliminates wastage of unused doses. Both Uniject devices and one-dose vials would require more storage capacity in health centers or more frequent distributions prior to allocation among midwives and TBAs.

My hypothesis is that the number of infants immunized within the critical seven-day time period will be greater with Uniject and logistically simpler than one-dose vials and ten-dose vials. Other differential benefits include reducing the prevalence of needle reuse that is associated with standard disposable syringes. Auto-disposable syringes mechanically prevent reuse by retracting needle upon use, but standard disposable syringes are reused in spite of warnings. In Cambodia, vaccinators use auto-disposable (AD) syringes. In addition to increased coverage, the benefits of a one-time use device like Uniject includes preventing transmission of blood-borne diseases.

2.8 Debates in the Field of CEA

If a health prevention program extends the life of a person, should future costs related to prolonged living be included in calculations? This question served as the basis of a debate between Allen Garber and Charles Phelps (1995) and David Meltzer (1997), all of whom are leading cost-effectiveness analysts in the field. Meltzer argued that all future medical and non-medical expenditures must be included for CEA to be consistent with lifetime utility maximization. This contradicted previous recommendations by Garber and Phelps (1995) who concluded that consistently including or excluding future costs is irrelevant because relative

rankings are preserved. Garber and Phelps (1995) conclude that previous studies not accounting for future costs of medical care can be used to rank interventions.

Meltzer, however, found Garber and Phelps used a more restrictive formula for lifetime resource allocation. Instead Meltzer proposes a more general formula for lifetime expected utility maximization. This debate is particularly relevant in the field of geriatric health care since current CEA bias interventions that extend life over those that improve the quality of life. Additionally, it is uncommon practice to include these costs in medical CEA because of unreliable estimates of future costs. Meltzer's arguments pose a challenge to the existing theoretical debate on whether or not to include costs incurred with prolonged living.

Gold, Russell, Siegel, and Weinstein (1996) also address this dispute over future costs. They argue that costs related to the intervention should be included while unrelated health and non-health costs are excluded because their measurement may induce error (p. 47). The troublesome category, however, is related to costs that occur in years of life added or subtracted by the intervention. The authors ultimately concluded, "The comprehensive exclusion of future 'unrelated' costs would therefore be difficult, if not impossible, in practice" since there are practical and conceptual difficulties with separating "related" and "unrelated" components of costs (p. 48).

In their 1997 article, Garber and Phelps formally justified CEA as a technique on the basis of first principles of microeconomics, unlike previous analyses that simply assumed CEA was a tool for utility maximization. The authors also recognized, "The handling of 'unrelated future medical costs' is important because they can be large enough to raise the CE ratio substantially. The impact is greatest when the intervention primarily extends life, such as vaccines against potentially fatal contagious diseases" (p. 4). Nevertheless, their final

recommendation depends on consistency and availability of data. If future costs are measurable, they should be included as a default since it is unknown if such costs are actually unrelated. Through a series of first order analyses, they conclude that CE ratios are consistent with or without inclusion of future costs.

Relevant to my study, Garber and Phelps wrote, “The positive effects of vaccines also diminish with time. They prevent infectious diseases by stimulating the production of specific antibodies, whose levels gradually decline after the initial response to the vaccine” (p. 19). My model, however, does not account for the diminishing return to effectiveness over time for vaccinations like Hep B because the U.S. Center for Disease Control does not recommend booster shots.

2.9 Conclusion

Upon reviewing the literature to date, it is reasonable to conclude that previous researchers have not calculated the cost savings of switching from AD syringes to Uniject devices, specifically for delivering birth doses of the Hep B vaccine to Cambodian infants. Given the relatively recent introduction of Hep B vaccination in the country, I analyze the cost-effectiveness of currently used AD syringes in conjunction with ten-dose vials. As of April 2006, economic analyses on the use of Uniject for Hep B vaccines in Cambodia to reduce wastage rates and vaccination costs do not exist. Recognizing the importance of country-specific attributes, I update earlier studies of Uniject with Hep B vaccines in Indonesia and India with respect to Cambodia by performing a cost-effectiveness analysis of alternative vaccine policies the Ministry of Health is considering. I compare presently used ten-dose vials and AD syringes to one-dose vials and Uniject devices and determine the most cost-effective injection method.

3. Methodology

3.1 Data Gathered on Current Vaccine Coverage and Strategies

During my field research in September of 2005, Dr. Chea Kim Ly, a deputy manager of the National Immunization Program (NIP), provided me with 2006 population estimates used in vaccine procurement requests to UNICEF. Cambodia's total population is expected to be 14,080,653 for the year 2006. Of this number, he estimated that 376,467 will be newborns given the annual number of pregnant women per year. Ideally there would be 100% coverage of newborns for all three complete doses of Hep B at birth, 6 weeks, and 14 weeks.

The NIP, however, has paced its ultimate goal of 90% coverage by 2010 – as set by the WHO – by starting with a 2006 coverage target of 35% for the Hep B birth dose to prevent vertical transmission and 85% coverage of the combined vaccine of Hep B with diphtheria, pertussis, and tetanus (HepB-DPT) to prevent horizontal transmission. The HepB-DPT vaccine can not be used to administer the first dose of Hep B at birth. As described in **Table 2**, the combined vaccine is used only for a newborn's second and third dose. **Table 1** summarizes the 2005 coverage target for Hep B in the context of Cambodia's national immunization goals. From my observations in September 2005, the government will need to heighten its efforts in expanding coverage of the Hep B birth dose, which is currently lagging.

As of the First Semester of 2005, the country achieved 9% coverage for Hep B and 41% for HepB-DPT. In contrast to more established and cheaper vaccines in the country's Expanded Program on Immunization (EPI) schedule, the First Semester of 2005 coverage rate was 43% for BCG to prevent tuberculosis and 41% for OPV to prevent polio (MidYear Review Workshop 2005). The drop out rates or percentage of children not receiving all three doses of DTP-HepB

were 5% and OPV at 9%. **Table 1** depicts the large variances between operational districts⁴ noted in parentheses. To simplify my model, however, I assume that infants receiving a birth dose will complete their vaccination series as they follow their immunization schedules.

Table 1. Summary of Rates in First Semester of 2005

	Coverage Target for 2006	1 st Semester Coverage 2005	1 st Semester Drop Out	1 st Semester Wastage Rate
Hep B (birth)	35%	9%	N/A	30 % (6–59)
Hep B-DPT	85%	41%	5 % (1–26)	39 % (17–52)
BCG (b irth)	95 % (2005)	43%	N/A	87 % (20 doses)
OPV	88 % (2005)	41%	9 % (1–44)	48%
Measles (9 months)	82 % (2005)	39%	N/A	76%

“Mid Term Review Workshop: On National Immunization Activities for the 1st Semester.” 22-24 August, 2005 at NMCHC, Phnom Penh, Cambodia.

Wastage rates are another important variable in the vaccination program. They were as high as 56% in January of 2004, but they dramatically dropped to 39% for DPT-HepB vaccines by June 2005. The national wastage rate for DPT-HepB was 39%, with Phnom Penh being the lowest at 17% and Takeo being the highest at 52%. The wastage rate for Hep B vaccines was 30% in the First Semester with a low 6% in the operation district of Kampong Chhnang, above average 40% in Kampong Cham, and high 59% rate in the remote area of Pursat. In contrast to the wastage of other EPI vaccines, the twenty-dose vials of BCG had the highest wastage rate at 87%, ten-dose vials of measles at 76%, and ten-dose vials of OPV at 48%. There are two main reasons for the high wastage in BCG vaccines. It is supplied as a freeze-dried product that is reconstituted or mixed with the accompanying solution for diluting (diluent). Once the vaccine is reconstituted, it must be discarded within 8 hours, and this often results in high wastage rates since there are 20 doses in one vial of BCG. The cost of BCG, however, is quite low at around US\$ 0.05 per dose. In contrast, the cost of Hep B is quite high and increases the importance of reducing wastage rates.

⁴ The Ministry of Health in Cambodia has divided the country’s primary health care sector into 73 Operational Districts (ODs), which oversee the approximately 600 Health Centers located throughout the country. Each health center serves a local population of at least 10,000 Cambodians.

As the seventh and last vaccine to be added to the EPI schedule, the Hep B vaccine remains the most expensive at a price of US\$ 0.29 to US\$ 0.41 compared to the price of DTP, measles, and polio vaccines that range from US\$ 0.06 to US\$ 0.10 per dose according to the product guide for vaccines supplied by UNICEF for the Global Alliance for Vaccines and Immunization (GAVI). As of November 8, 2005, GAVI and UNICEF have shipped a total of 1,661,500 DTP-Hep B vaccines (first half in February and second half in August) along with 854,000 auto-disable syringes with 0.5 mL needles and 8,4500 safety boxes.

The proposed strategy for 2006 would miss nearly 245,000 newborns that have a 90% chance of contracting HBV infection at birth if their mothers are chronic carriers – as measured by a positive Hep B surface antigen (HBsAg) test and a positive Hep B e-antigen (HBeAg) test for infectivity. As concluded by a 2000 seroprevalence survey⁵ in the province of Kampong Cham in Cambodia, 10.3% of women of child bearing age are positive for HBsAg and 32.4% of these women are also positive HBeAg.

3.2 Alternative Vaccine Formats

Table 2. Current Immunization Scheduling Options for Hep B

		Option 1	Option 2	Option 3	Option 4
Age	Visit	No Birth Dose	No Birth Dose	With Birth Dose	With Birth Dose
Birth	0			HepB1	HepB1
6 weeks	1	HepB1	DTP-HepB1		DTP-HepB1
10 weeks	2	HepB2	DTP-HepB2	HepB2	DTP-HepB2
14 weeks	3	HepB3	DTP-HepB3	HepB3	DTP-HepB3

Handbook on Vaccine Preventable and Other Communicable Diseases in Cambodia. 2005. 1st ed. National Immunization Program (NIP). Ministry of Health. Kingdom of Cambodia.

⁵ Seroprevalence surveys establish the number of persons in a population testing positive for a specific disease based on blood tests.

As of September 2005, the Cambodian Ministry of Health has adopted Option 4 as depicted in **Table 2**. This strategy recognizes the limitations of administering a birth dose to the 90% of children born at home in a rural setting that comprises 80% of the country. Children that receive the birth dose are scheduled to receive an excessive fourth Hep B birth dose when they receive their last Hep B-DTP dose in the three-dose series. Option 4 also simplifies logistics since the three dose polio vaccine follows the DTP schedule whereas Option 3 requires the second Hep B dose be given at 10 weeks as opposed to week two. Instead of administering the DTP and Hep B shots separately and risk inducing fevers in infants from a monovalent dose of DTP, the combined DTP-Hep B vaccine reduces the chances of an infant having a fever and eliminates the need for multiple shots and syringes. This advantage occurs at a huge cost of \$1.29 per dose compared to the lowest ten-dose vial price of US\$ 0.25 per dose of Hep B. For this reason, Cambodia receives its supply of DTP-Hep B vaccines through a grant from GAVI that began in 2002.

Given the scheduled reductions in GAVI/Vaccine Fund sources by 2010, I explore three other vaccine strategies based on Option 3 to assist Cambodia in phasing out its reliance on the expensive DTP-Hep B vaccine. There are three possible locations for a newborn to be vaccinated depending on the place of delivery – at home, at a private clinic, or at a health center/hospital. A fifth location – outreach sessions – is possible for the second and third dose. There are also four possible vaccine presentations that could be used – Uniject, one-dose, ten-dose with a discarding policy, or ten-dose with an open vial policy (MDVP). This analysis will calculate the current and potential costs associated with fully vaccinating one child with three complete doses of the Hep B vaccines. Given the success of midwives administering Uniject at home for the first birth dose

and use of ten-dose vaccines for the second and third doses at health centers, this will be considered Strategy 1 in **Table 3**.

Table 3. Summary of Strategies based on Option 3 Variations

		Strategy 1	Strategy 2	Strategy 3	Strategy 4
Age	Visit			Discard	Open Vial Policy
Birth	0	Uniject at home	1 dose at home	10-dose	10-dose
6 weeks	1				
10 weeks	2	10-dose	10-dose	10-dose	10-dose
14 weeks	3	10-dose	10-dose	10-dose	10-dose

Alternatively, a one-dose format with a syringe could be used at home by midwives with the second and third doses administered at the health center or outreach sessions (Strategy 2). The unprecedented use of one-dose vials outside of health centers, however, means Strategy 3 will be more likely with ten-dose vaccines used for all three doses in either health centers/hospitals or outreach sessions. The last strategy, Strategy 4, is similar to Strategy 3 but reinforces the use of an open vial policy where vaccines are reused once they are opened. The Advanced Immunization Management (AIM) program recommends countries “consider the best mix of vial sizes” dependent on the different regions – urban versus rural – of their country. AIM continues by saying, “For example, in many newly independent states, countries buy some 80% of their Hep B vaccine doses in ten-dose vials to use in populated areas that hold large immunization sessions. To reduce wastage, they buy the remaining 20% of doses in one-dose vials for use in rural areas where few people come to each immunization session” (AIM e-learning site, 2005). I address this advice during later calculations of which vaccine format to purchase given the geographic makeup of Cambodia.

3.3 Vaccine Policy Decision Model

Using decision analysis software (TreeAge Pro Suite 2006, release 0.1), I develop a theoretical decision tree model of nine vaccine policy decisions branches, each containing nine Markov states that predict the clinical outcomes and costs of vaccinating one newborn over its lifetime depending on the vaccine format used. The infant enters the HBV Markov disease model from one of nine competing policies chosen by the government. The vaccine policy chosen results in different coverage rates and alters the number of vaccinated and unvaccinated newborns entering the Hep B disease progression model. I summarize the nine Hep B birth dose vaccine policies in **Table 4**.

Table 4. Summary of Competing Vaccine Policies Considered in Analysis

Strategies	Health Center	Outreach	Midwives
<i>Note</i>	<i>In the Cold Chain</i>	<i>In the Cold Chain</i>	<i>Out of Cold Chain</i>
Policy A	10-dose vials	10-dose vials	
Policy B	10-dose vials	10-dose vials	One-Dose
Policy C	10-dose vials	10-dose vials	Uniject
Policy D	10-dose vials	One-Dose	
Policy E	10-dose vials	One-Dose	One-Dose
Policy F	10-dose vials	One-Dose	Uniject
Policy G	10-dose vials	Uniject	
Policy H	10-dose vials	Uniject	One-Dose
Policy I	10-dose vials	Uniject	Uniject

Initial costs associated with each vaccine strategy and incremental costs associated with annual health care for healthy and HBV carriers serve as the numerator for the cost-effectiveness ratio. These costs vary according to the coverage rates achieved with the use of ten-dose vials, one-dose vials, and Uniject devices in health centers, outreach visits, or homes. Given the large number of births that occur in hospitals, I do not include them as a possible location in my analysis since the use of ten-dose vials has been successful with minimal wastage rates.

I base my model of chronic Hep B disease progression on the Hep Disease Burden Model (Version 1.2) developed by Susan Goldstein, Fangjun Zhou, Stephen Hadler, Beth Bell, Eric Mast, and Harold Margolis of the Division of Viral Hep and National Immunization Program at the Centers for Disease Control and Prevention (CDC) in Atlanta, USA. I develop my own model because the CDC model estimates the HBV-related disease burden and potential reduction in morbidity and mortality with Hep B vaccination in terms of total number of infections (resolved and chronic), number of chronic infections, number of acute symptomatic infections (acute Hep), total number of HBV-related deaths, number of deaths from acute Hep B, number of deaths from cirrhosis, and number of deaths from hepatocellular carcinoma (liver cancer). Similarly my model follows a Cambodian newborn over its lifetime and uses age-specific risk of acquiring HBV infection, progressing from chronic HBV to cirrhosis, progressing from chronic HBV to liver cancer, dying from cirrhosis, and dying from liver cancer.

The major difference is that I adopt quality-adjusted life years (QALYs) as my measurement of effectiveness, and I assume full linear scaleability to translate costs and QALYs gained per Cambodian newborn to the entire birth cohort population. The incremental cost-effectiveness ratio for a vaccine strategy is computed in reference to the next most cost-effective option and is most relevant in deciding which Hep B vaccine strategy to adopt since the Hep B vaccine already exists in the national immunization schedule. This means I will include incremental costs associated with introducing different vaccine formats while excluding all costs occurring independently of a change in vaccine strategy. To calculate the incremental cost-effectiveness ratio ICER between two competing vaccine policies (Status Quo Policy A and Proposed Policy B), I would use the following equation:

$$\text{ICER} = (\text{Costs of A} - \text{Costs of B}) / (\text{Effectiveness of A} - \text{Effectiveness of B}) \quad (2)$$

Depending on the vaccine strategy chosen by the government, different costs are incurred and the number of unvaccinated newborns entering my Markov model varies. Ultimately the total cost of each vaccine strategy depends on the coverage rates achieved with each vaccine format. I base probabilities of receiving the Hep B birth doses on First Semester 2005 coverage rates released at the Mid-Year Review Workshop held in August. I adopt the perspective of the Cambodian Ministry of Health, which attempts to immunize the country's 2006 birth cohort of 376,467 newborns to prevent future occurrences of HBV-related complications and deaths. I follow this cohort over a lifetime horizon determined by the expected average life expectancy of 59 years (CIA Factbook 2006). I discount all costs and utilities by 3.0% since costs incurred now are valued more in the future, particularly in preventive interventions like vaccination programs. The importance of discounting is evidenced in the sensitivity analyses found in my results.

3.4 Vaccine Policy Assumptions

In all vaccine policies I consider, health centers continue present use of ten-dose vials in the cold chain since they can safely adopt and maintain an open vial policy with refrigerators. Outreach sessions similarly have equipment to keep vaccines in the cold chain by wrapping vials in paper or cotton and placing them uprights in vaccine carriers lined with ice packs. Literature on current open vial policy, also known as ten-dose vial policy, varies from no detectable contamination (Christensen, Mordhorst, and Jepsen 1992) to a 23% contamination rate (Bothe 1973). In Cambodia, auto-disable syringes are used and do not allow for needle reuse. Adopting an open vial policy continues to be a careful balance between cost minimization and the patient's well being since the vaccine could be compromised if not stored and refrigerated properly after opening.

At a CDC conference in 2000, attendees were strongly recommended to use pre-filled syringes or one-dose vials for inexpensive but widely used substances. Reuse of an open vial for a single patient carries little risk of cross contamination, but multiple entries into a vial for several patients poses more risk if the vial is transported between vaccinations, as practiced in outreach sessions. Given my concern surrounding open vial policy with outreach sessions, I have analyzed current use of ten-dose vials in outreach sessions (Policies A, B, and C), as well as potential use of one-dose vials (Policies D, E, and F) and Uniject devices (Policies G, H, and I).

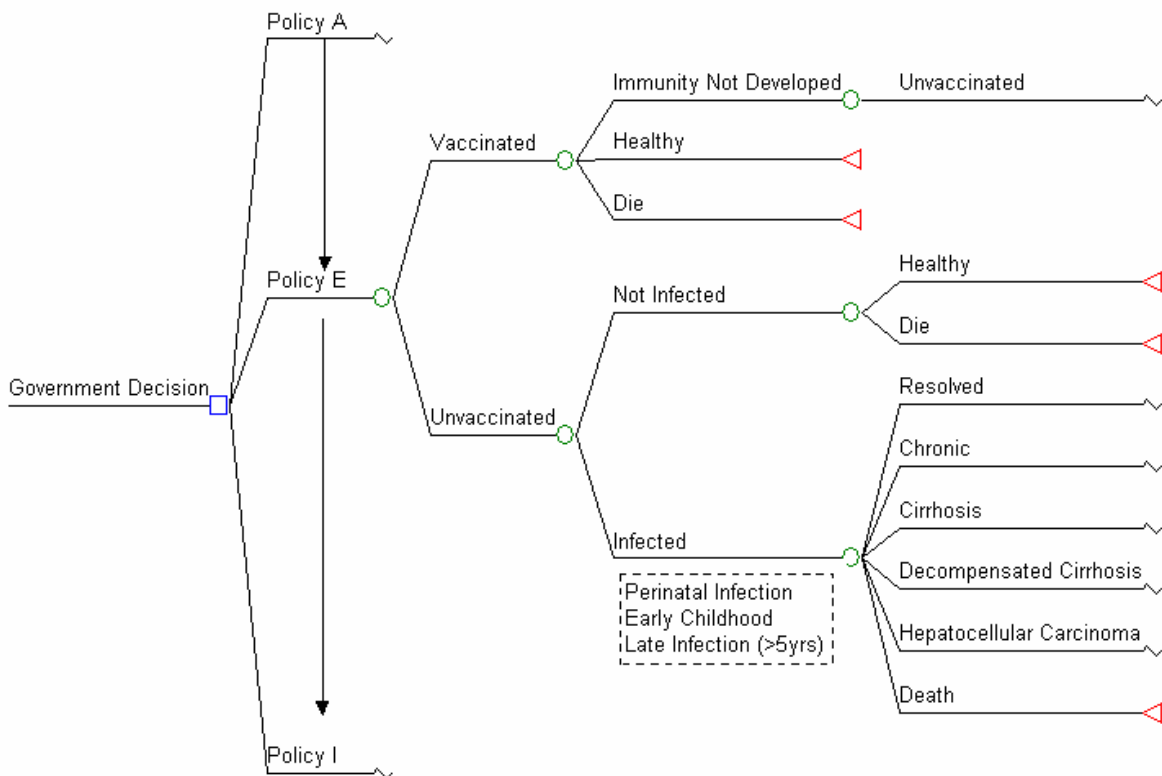
Lastly I consider the National Immunization Program's possible authorization of midwives, or government trained traditional birth attendants, to administer Hep B birth dose vaccines to babies delivered at the home of their clients. Unlike the health center and outreach approach, the midwife option would require midwives to administer the vaccine out of the cold chain. Studies like Nelson, Wibisono, Purwanto, Mansyur, Moniaga, and Widjaya (2004) have demonstrated the heat stability properties of the Hep B vaccine and efficacy of Hep B vaccines delivered out of the cold chain when stored in ambient temperatures for up to 60 days. I model this option after the Indonesian case study by Levin, Nelson, Widjaya, Moniaga, and Anwar (2005) where midwives administered Hep B vaccines in Uniject out of the cold chain. Midwives would retrieve monthly supplies of the Hep B vaccine from the nearest health center and store them un-refrigerated in their homes until they visit a client to deliver her baby and administer the first birth dose within seven days. My analysis does not allow midwives to administer ten-dose vials because attending ten deliveries in one day is uncommon. Additionally, the rarity of refrigerators in midwives' homes means they would be unable to maintain an opened vial policy where refrigeration is required after opening a ten-dose vial. Midwives, however, have the potential to be trained to administer vaccines using a one-dose vial or Uniject device. Given the prevalence of home delivered births in rural Cambodia, midwives are often the first health care workers to come in contact with a newborn within the recommended seven days of the Hep B birth dose vaccines. Traditional birth attendants (TBAs) are more prevalent than midwives, of

which there are 28.8 per 100,000 people in Cambodia (Mohan 2002, p. 12). The Ministry of Health, however, does not treat TBAs as health workers because they lack formalized training. I therefore do not include potential use of TBAs in my vaccine strategies.

3.5 Detailing the Markov Model

Markov Transitioning for the Vaccinated Population

Figure 3. Simplified Overview of Decision Tree Model

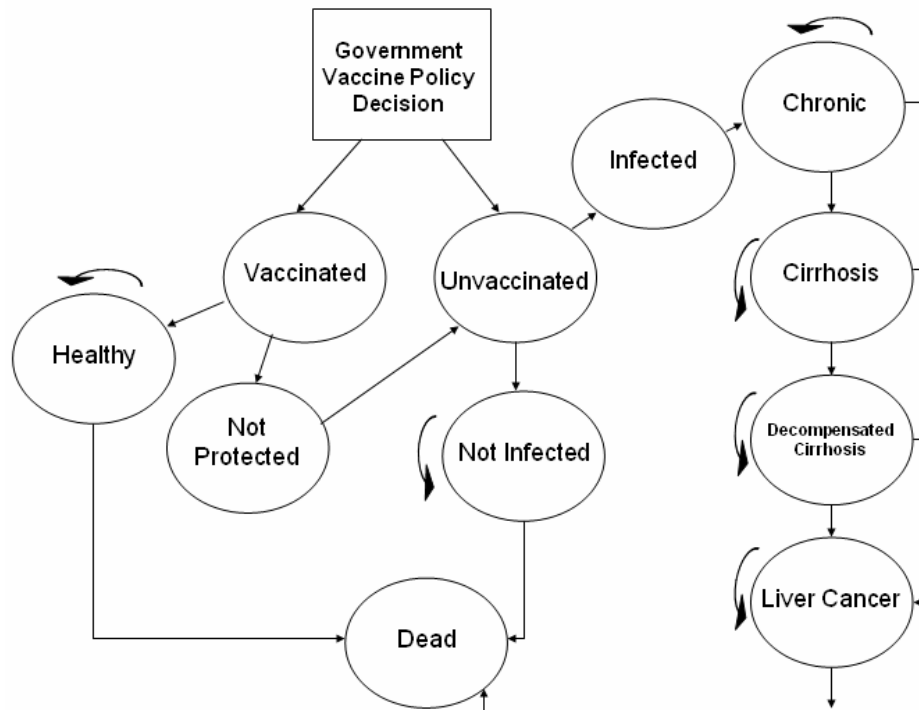


As seen in **Figure 3**, the government decides between the nine vaccine policies listed in **Table 4**, which have different costs depending on the vaccine format used and the number of infants vaccinated through coverage rates at health centers, outreach sessions, or at home. Policies A, D, and G have the same base coverage rate of 40%, Policies, B, E, and H have the same base coverage rate of 60%, and Policies, C, F, and I have the same base coverage rate of

70%. Total coverage rates affect the number of vaccinated newborns incurring effectiveness for immunological protection and costs of annual health care for a longer lifetime. The vaccinated cohort follows natural mortality rates throughout the infants' lifetime horizons, which is determined by Cambodia's average lifetime expectancy. A percentage of infants will receive the vaccine but fail to develop immunity to Hep B because of natural failure in immune response or because the vaccine has been compromised due to freezing or excessive heat exposure. This probability of vaccine efficacy is included in the model. Death is an absorbing state based on the 1999 WHO life table for Cambodia (WHO-SEA 2000, p. 19). Because natural mortality transition probabilities vary with time, I reference a table of stage-dependent values where stage equals the average lifetime expectancy. Age-specific natural mortality estimates used in the model are included in the Appendix.

Markov Transitioning for the Unvaccinated Population

Unvaccinated newborns that did not receive the vaccine or failed to develop an immunological response will either stay uninfected throughout their lifetimes to die a natural death as depicted in **Figure 4** or develop HBV infection perinatally at birth, in early childhood before the age of five, or later in life. People can remain in their health state, denoted by a curved arrow, or transition to a new health state, denoted by a straight arrow. Depending on age of infection, the infant faces different probabilities of developing symptoms and becoming a chronic HBV carrier. A person infected early in life faces a greater risk of dying from HBV. Additionally chronic carriers face an annual risk of progressing into a health state of cirrhosis, decompensated cirrhosis, liver cancer, or death. Upon progression into advanced stages of Hep B complications, the person suffers a decrement in quality-adjusted life years (QALYs).

Figure 4. Markov State Diagram of HBV Infection

Source: Adapted from Kanwal et al. 2005

Immediate Risk of Perinatal Infection

In evaluating the risk of vertical transmission from mother to child, I assume that 10.3% of childbearing age mothers have positive Hep B surface antigen (HBsAg), which indicates a person is infected with HBV. This statistic is based on a 2000 seroprevalence survey in the province of Kampong Cham. Of the women who were HBsAg positive, 32.4% also tested positive for the Hep B e-antigen (HBeAg), which indicates active viral replication and greater infectivity. According to the CDC model by Goldstein, Zhou, Hadler, Bell, Mast, and Margolis (2005), a woman both HBsAg positive and HBeAg positive poses a 90% chance of transmitting HBV to her child through perinatal infection. A woman HBsAg positive but HBeAg negative poses a 10% chance of perinatal transmission. A woman HBsAg negative has a 100% chance of

not transmitting HBV to her child. Further details of the complications and probabilities associated with perinatal transmission are included in the Appendix.

Continued Risk of Subsequent HBV Infection

If newborns do not acquire HBV perinatally from their mothers, they continue to be at risk for contracting HBV in early childhood infection or late infection. While a mother's HBsAg and HBeAg status determines rates of perinatal transmission, the prevalence of antibodies to Hep B core antigen (anti-HBc) serves as a marker of infection since it can persist in the blood for 15-20 years. In the 2001 seroprevalance survey conducted in Kampong Cham, the prevalence of anti-HBc in children at age 5 years of age is estimated at 12.6% while adults greater than or equal to 30 years old have a 52.4% prevalence of anti-HBc. I use these statistics in my model to estimate the probabilities of early childhood infection and late infection. The age at which a child acquires infection alters the natural history of HBV infection, and the child faces different probabilities of developing complications. I include further details on how I model time and age dependent probabilities in the Appendix.

Progression of Hep B Complications

The risk of dying from cirrhosis and hepatocellular carcinoma deaths varies according to age, generally increasing from age 40 onwards. I model subsequent transitions from a state of chronic carrier to cirrhosis and HCC using age-specific probabilities. A table of the baseline values and ranges for the variables used in the model are included in the Appendix.

3.8 Model Assumptions

Current and Expected Coverage Rate Estimates

As previously stated, infants enter the HBV Markov disease model from one of nine competing policies chosen by the government. I assume Policies A, D, and G have the same total base coverage rate since each of these choices relies only on Hep B birth doses administered in health centers and outreach visits. Based on 2005 First Semester estimates, I adopt a base Hep B birth dose coverage rate of 28% at health centers (varied between 10.5% and 42%) and a rate of 12% coverage through outreach sessions (varied between 4.5% and 18%).

Similarly, I assume Policies B, E, and H have the same coverage rates in health centers and outreach visits as the first set of policies (A, D, and G), but I assume midwives with one-dose vials could attain a coverage rate of 20% (varied between 10% and 30%) (Cambodia Demographic and Health Survey 2000, p. 29). Policies, C, F, and I are similar to the second set of policies (B, E, and H), but I assume midwives using Uniject could achieve a slightly higher coverage rate of 25% (varied between 20% and 35%) since one-dose vials are not as easy to administer as Uniject devices. According to a 2003 status report by Programs for Appropriate Technologies in Health, individuals not trained to deliver injections successfully administered Uniject with minimal training. The portability and compactness of the device could also increase the coverage rate by midwives compared to one-dose vials.

Health Care Costs

Calculating the Initial Costs of Competing Vaccine Strategies

I calculate the cost of fully vaccinating one newborn with three doses of the Hep B vaccine using ten-dose vials, one-dose vials, or Uniject in either a health center, outreach, or

midwife setting. To calculate the total expected initial cost in 2006 US dollars of each of the nine competing vaccine policies, I multiplied the total cost of administering one vaccine to a newborn using each of the vaccine formats by the probability of receiving all three doses of Hep B and the number of doses – three – needed for full protection from HBV. I assume this probability is 100% in the base-case analysis but vary it in subsequent sensitivity analyses. According to 2005 First Semester immunization coverage estimates in Cambodia, the probability of Hep B vaccine completion is closer to 64%. This is the estimated proportion of children who have completed the three-dose HepB-DTP series, which follows a similar vaccine schedule as HepB.

The total cost of using alternative vaccine formats in different settings depends on the cost of the vaccine and its associated freight cost and wastage rate. The cost of safety boxes and their associated freight cost depends on the boxes' capacity for storing used AD syringes, as well as the wastage associated with AD syringes from mishandling. My model includes the cost of transporting the disposal of AD syringes and the cost of personnel to administer one vaccine. Training costs of introducing one-dose vials into outreach visits are not included because health care workers are accustomed to using a syringe to administer a dose from a vaccine vial. Midwives, however, will need to be trained in how to use one-dose vials and Uniject devices during home delivery visits. The training needed to learn how to use Uniject devices is minimal because the device is manufactured with a pre-filled amount of Hep B vaccine and integrated syringe. I assume health care workers using Uniject in outreach visits also incur an initial training cost. **Table 5** lists the base-case costs associated with the alternative vaccine formats in different settings. Detailed equations of total costs of each vaccine strategy are included in the Appendix.

Table 5. Total Cost of Vaccine Strategies per Newborn in Base Case Analysis

Alternative Vaccine Strategy	Cost of 3 doses per newborn
Ten-Dose in Health Center	\$ 0.51
Ten-Dose in Outreach	\$ 0.52
One Dose in Outreach	\$ 0.57
One Dose by Midwives	\$ 0.59
Uniject by Outreach	\$ 1.71
Uniject by Midwives	\$ 1.73

I assume infants vaccinated at home by midwives will rely on outreach sessions to receive the subsequent two doses during outreach sessions. Midwives only administer the first birth dose to infants within the recommended seven days to prevent potential perinatal transmission. The total cost of the midwife strategy equals the first dose by midwife plus the second and third doses by health care workers visiting villages once a week in routine outreach visits. Mothers of infants vaccinated with the Hep B birth dose in health centers, however, are assumed to proactively seek childhood immunizations and will return for their child's second and third dose at this fixed site.

Calculating the Initial Cost of Unvaccinated Newborns

Unvaccinated newborns do not incur initial health care costs, but vaccinated newborns in whom the vaccine failed to protect have the same probabilities of developing HBV as the unvaccinated population. In the Markov model, I multiply the total cost of the vaccine strategy by one minus the probability of vaccine efficacy to account for the cost of vaccinated but unprotected newborns.

Calculating the Incremental Costs of Vaccinated and Unvaccinated Newborns

Upon entering one of nine competing vaccine policies, a Cambodian newborn who has effectively received all three doses of the Hep B vaccine is assumed to remain virus-free for the remainder of their lives. The child is therefore not at risk of developing cirrhosis or its

complications. The vaccinated newborn incurs incremental costs for annual health care expenses incurred from age zero to death. I base my estimate of the incremental annual health care cost (cInchC) to be USD\$36 on the annual per-capita health care amount spent by the Cambodian Ministry of Health in 2000 (SEAM 2003, p. 18).

The unvaccinated cohort incurs the same incremental annual health care cost of USD\$36 as the vaccinated cohort, but newborns that progress to states of chronic HBV, cirrhosis, decompensated cirrhosis, and liver cancer (HCC) incur additional health care costs associated with each state in the disease progression of HBV. My model also accounts for the newborn that receives three doses of the Hep B vaccine but fails to achieve immunological protection.

Though I include health care costs associated with disease progression, treatment-specific costs related to HBV infection like antiretroviral treatment and routine physician visits are largely unavailable to the rural population most affected by the disease. The Ministry of Health Statistics states that 16% of the Cambodian population live in urban areas while 84% live in rural areas. In urban areas, infants are born in private or public hospitals and clinics that routinely provide Hep B vaccines along with other childhood immunizations. I vary my base estimates for health care costs associated with these HBV infection complications in sensitivity analyses.

Quality Adjusted Life Years

The effectiveness outcome is measured in terms of incremental costs per quality-adjusted life years (QALYs) gained. The WHO measures outcomes in terms of disability adjusted life years (DALYs) averted, which is equivalent to $DALY = 1 - QALY$, but I employ QALYs in accordance with the National Panel on Cost-Effectiveness in Health and Medicine (Gold 1996). I refer to the article by Kanwal, Gralnek, Martin, Dulai, Farid, and Spiegel (2005) on “Treatment Alternatives for Chronic Hep B Virus Infection: A Cost-Effectiveness Analysis” for

my health state utility base estimates as measured in QALYs for different quality of life years HBV carriers undergo. I adopted the authors' patient health preferences, or utilities, for chronic Hep B and related complications like compensated cirrhosis, decompensated cirrhosis, and hepatocellular carcinoma. All utility estimates are included in **Table 5** of the Appendix, which were discounted at a standard rate of 3% per year and varied between 0% and 5% in the sensitivity analysis to account for different net present values.

Timeliness of Birth Dose Vaccines

The model also assumes a lifelong protection from HBV infection after receiving a birth dose within seven days along followed by two doses. Experts like Dr. Samuel So at the Asian Liver Center, however, recommend that the first dose of vaccine be administered within the first 24 hours to prevent perinatal infection. Infants receiving the first dose of vaccine after 24 hours of birth are considered susceptible to perinatal infection but protected from early childhood and late infection. In Cambodia, the National Immunization Program allows the birth dose to occur within seven days. Research has shown, however, that after 24 hours, the first dose's effectiveness in preventing vertical transmission precipitously decreases.

Though the WHO says, "There is no evidence of protection against perinatal transmission if the first dose of vaccine is given more than seven days after birth," I have had difficulty finding the degradation in efficacy past 24 hours (WHO 2001, p. 9). In 1991, the CDC also emphasizes the importance in early vaccination of infants when they stated, "In populations in which screening pregnant women for HBsAg is not feasible, all infants should receive their first dose of Hep B vaccine within 12 hours of birth" (WHO 1991, p. 3). Given limited data on differences and present difficulty of delivering timely vaccines in Cambodia, in this model I

assume the efficacy of a Hep B birth dose vaccine delivered within 24 hours is equivalent to the efficacy of a vaccine delivered within seven days. The WHO states, “Infants of HBsAg-positive carrier mothers respond less well to the vaccine since it is often delivered after infection has occurred. The vaccine efficacy in preventing chronic HBV carriage in these infants ranges from 75% to 95%. Adding one-dose of Hep B immune globulin⁶ (HBIG) at birth to the vaccine schedule may improve efficacy somewhat, but use of HBIG is not feasible in most developing countries” (Carr et al. 2000 p. 17). I therefore vary the probability of vaccine efficacy between 75% and 95% in the sensitivity analysis.

Concerns about Freezing Sensitivity

I do not explicitly include the uncertainty of freezing because I assume all vaccine formats – Uniject, one-dose, and ten-dose – face similar probabilities of freezing. They are centrally distributed by Cambodia Medical Supplies and face equal chances of reaching below zero degrees Celsius during transportation. The importance of accidental freezing of Hep B vaccines, however, should not be dismissed. My model variable measuring probability of vaccine efficacy is varied in the sensitivity analysis.

According to the WHO Vaccine Transportation guidelines, the Hep B vaccine’s efficacy is compromised when frozen inside the cold box used to transport vaccines between vaccine locations, primarily from province to districts. The guidelines emphasize a need to condition the ice packs used to maintain proper cold chain storage in the cold box. When taken immediately

⁶ Hep B immune globulin (HBIG) provides immediate and effective short-term passive immunity to people who have been recently exposed to HBV via perinatal infection or as an adult in contact with HBV patients. HBIG is costly because it is prepared from pooled human plasma from selected donors with a high level of anti-HBs who are seronegative for bloodborne infections. In developed countries, HBIG is administered concurrently with the Hep B vaccine to provide long term protection against the virus.

out of the freezer, icepacks are at a temperature of about -20°C and must be “conditioned” by keeping them at room temperature until it reaches a temperature of 0°C and beads of water cover the surface. Experiments have shown, however, that proper conditioning can still cause Hep B vaccines to accidentally freeze inside the cold box. Nelson, Wibisono, Purwanto, Mansyur, Moniaga, and Widjaya (2004) used data loggers in Indonesia to document that nearly 75% of baseline shipments are inadvertently frozen during transport and storage of freeze-sensitive Hep B vaccines. The authors propose policy changes to limit storage of Hep B vaccines in the cold chain, or at temperatures >2 to 8°C , to reduce the likelihood of freezing, which destroys the potency of the vaccine. Storing Hep B vaccines out of the cold chain, therefore, reduces the likelihood of freezing and increases potential coverage rates when given to midwives to store in their homes.

Sensitivity Analyses

The table of base-case estimates in the Appendix lists my probability estimates with ranges for my sensitivity analyses. Where available, I derived range estimates from the literature; otherwise, I varied estimates $\pm 25\%$. TreeAge allows users to perform a Tornado analysis of one-way sensitivity analyses on multiple variables. The Tornado results identified the most sensitive variables that cause the highest variation in my results. I conducted additional one-way sensitivity analyses to evaluate results to changes in parameters. I varied estimates of wastage rate, coverage rate, price of vaccines, cost of training, and discount rates.

4. Results

4.1 Base-Case Analysis

Table 6. Summary of Base-Case Results of Vaccine Policies

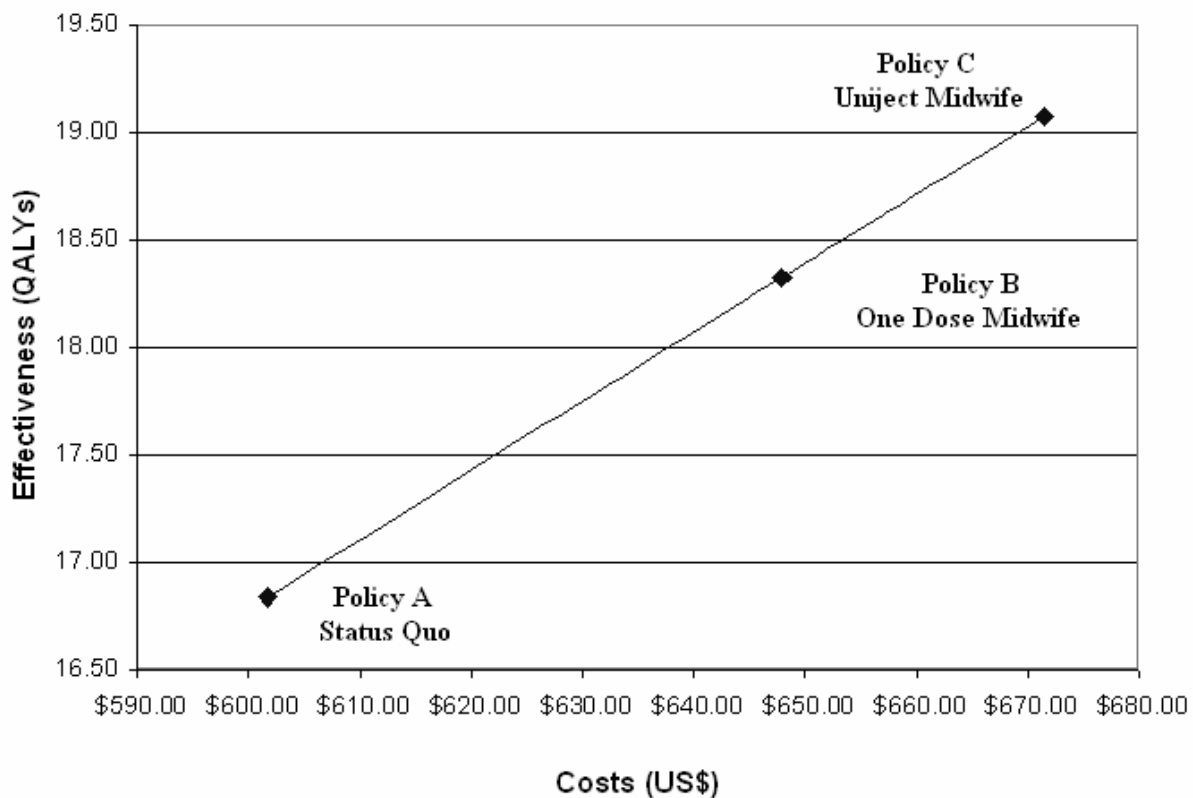
Strategy	Notes	Cost	Incr Cost	Eff QALY	Incr Eff	Incr C/E (ICER)
Policy A	Status Quo	\$ 601.65		16.84		
Policy B	One-dose Midwife	\$ 647.92	\$ 46.26	18.32	1.49	\$ 31.08
Policy C	Uniject Midwife	\$ 671.46	\$ 69.81	19.07	2.23	\$ 31.26
Policy D	One-dose Outreach	\$ 601.71		16.84		(Dominated)
Policy E	One-dose Midwife	\$ 648.06	\$ 46.35	18.32	1.49	\$ 31.17
Policy F	Uniject Midwife	\$ 671.63	\$ 69.91	19.07	2.23	\$ 31.33
Policy G	Uniject Outreach	\$ 603.15		16.84		(Dominated)
Policy H	One-dose Midwife	\$ 651.21	\$ 48.06	18.32	1.49	\$ 33.29
Policy I	Uniject Midwife	\$ 675.25	\$ 72.10	19.07	2.23	\$ 32.96

As seen in **Table 6**, Policy A is the status quo vaccine strategy with ten-dose vials being used in health centers and outreach sessions. As expected, the status quo results in the least cost at \$601.65 per person vaccinated. In conjunction with ten-dose vials used in health centers, Policy D uses one-dose vials in outreach sessions and costs an additional \$0.06 per person while Policy E uses Uniject devices in outreach sessions and costs an additional \$1.50 per person compared to the status quo. This incremental cost reflects the base \$0.24 per dose cost for a ten-dose vial compared to \$0.41 for a single-dose vial and \$1.46 cost for a Uniject device without taking wastage rates into account. **Table 6** lists the ICER for each policy in reference to the status quo of Policy A. For example, I compute the incremental costs per QALY gained for Policy B of using one-dose vials by midwives in reference to Policy A using the following calculation:

$$\begin{aligned}
 & \text{ICER of Policy B} && (3) \\
 & = (\$647.92 - \$601.65) / (18.32 \text{ QALYs} - 16.84 \text{ QALYs}) \\
 & = \$31.08/\text{QALY}
 \end{aligned}$$

With a low incremental cost of \$31.08 per QALY gained, allowing midwives to use one-dose vials in Policy B is the most cost-effective strategy. Using one-dose vials in outreach sessions and in homes by midwives in Policy E is the next preferred strategy with an ICER of \$31.17. Policy C allowing midwives to use Uniject devices is the third most dominating strategy with an incremental cost of \$31.26 per QALY gained. As seen in **Figure 5**, Policy B and Policy C dominate the status quo vaccine strategy. Policy E would be plotted just to the right of Policy B because they incur the same QALYs but Policy E costs \$0.14 more per person.

Figure 5. Cost-Effectiveness of Policy A, Policy B, and Policy C

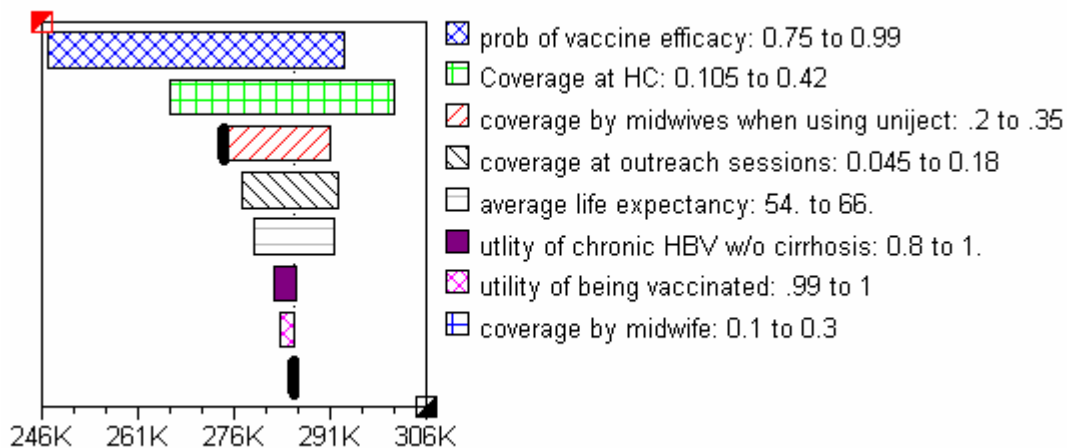


Policy A, Policy D, and Policy G result in 16.84 QALYs gained because I assumed a constant base total coverage rate of 40% for health centers and outreach visits. This first set of policies ranges in cost from \$601.65 to \$603.15 per person. Similarly Policy B, Policy E, and

Policy H incur 18.32 QALYs with an assumed base coverage rate of 60% when midwives use one-dose vials. This second set of policies ranges in cost from \$647.92 to \$651.21. Policy C, Policy F, and Policy I result in the greatest utility with 19.07 QALYs gained because the base coverage rate is projected to equal 70% if midwives use Uniject devices to administer vaccines at home. This last set of policies ranges in cost from \$671.46 to \$675.25. Policy A, Policy B, and Policy C are the most dominant vaccine strategies because they achieve the same number of QALYs gained as policies with identical coverage rate but a lower cost.

4. 2 Sensitivity Analysis

Figure 6. Results of Tornado Diagram



In **Figure 6**, I present a Tornado diagram used to determine the most sensitive variables in my model. By varying my estimated parameters in one-way sensitivity analyses over plausible estimates, I found that my model is most sensitive to the following in order from greatest to least: discount rate, probability of vaccine efficacy, coverage rate at health centers, coverage rate at outreach sessions, coverage by midwives using one-dose vials, coverage by midwives using Uniject, average life expectancy, utility of being a chronic carrier, and utility of being

vaccinated. I do not include the discount rate in **Figure 6**, because the magnitude of its impact on the results skews the spread of the other variables. I perform further one-way sensitivity analyses on the top three sensitive variables, and I determine the critical thresholds at which Policy B or the use of one-dose vials loses dominance to Uniject use by midwives in Policy C.

Table 7. One-way Sensitivity Analysis on the Discount Rate of Costs and Utilities

Discount Rate	Strategy	Cost	Eff	Incr C/E (ICER)
0%	Policy A	\$ 1,133.60	31.3	
	Policy B	\$ 1,255.20	35	\$ 33.10
	Policy C	\$ 1,316.30	36.8	\$ 33.32
3%	Policy A	\$ 601.70	16.8	
	Policy B	\$ 647.90	18.3	\$ 31.08
	Policy C	\$ 671.50	19.1	\$ 31.63
5%	Policy A	\$ 440.80	12.4	
	Policy B	\$ 467.90	13.4	\$ 29.08
	Policy C	\$ 481.90	13.8	\$ 29.96

In **Table 7**, I vary the base discount rate of 3% between 10% and 5% to calculate the costs, effectiveness, and ICERs with respect to the next best alternative. Discounted costs and QALYs are valued more in the present than in the future. The fact that the discount rate is an important and sensitive variable reflects the nature of Hep B as a slowly progressive and delayed disease affecting adults in their forties. For example, Policy B incurs an undiscounted cost of \$1,255.20 per person with a gain in 35 QALYs. At a 5% discount rate, however, Policy B costs \$467.90 per person for a gain in 13.4 QALYs. There is an inverse relationship between the discount rate and the vaccine strategies ICERs. As costs and utilities are increasingly discounted, the incremental costs per QALY gained and strategies become more cost-effective in the future. Independent of the discount rate, Policy B remains the most cost-effective strategy because it incurs the lowest incremental cost per QALY gained.

After varying the second most sensitive variable in my model – the probability of vaccine efficacy – I found a positive relationship with the ICERs of each vaccine policy. As the probability of vaccine efficacy varies from 75% to 99%, the cost-effectiveness of each strategy increases from an incremental cost of \$7.07 per QALY gained to \$31.76 per QALY gained. In addition to a failure in immunological protection or receiving a birth dose after seven days, compromised vaccines from freezing, contamination, or excessive heat exposure could reduce the probability of vaccine efficacy and the incremental costs per QALY gained.

Table 8. One-way Sensitivity Analysis on the Probability of Vaccine Efficacy

pVaxnEfx	Strategy	Cost	Eff	Incr C/E (ICER)
75%	Policy A	\$ 580.40	16.2 QALYs	
	Policy B	\$ 581.90	16.4 QALYs	\$ 7.07
	Policy C	\$ 583.00	16.5 QALYs	\$ 9.79
89%	Policy A	\$ 595.70	16.6 QALYs	
	Policy B	\$ 629.40	17.8 QALYs	\$ 29.79
	Policy C	\$ 646.70	18.3 QALYs	\$ 30.46
99%	Policy A	\$ 605.90	17.0 QALYs	
	Policy B	\$ 661.10	18.7 QALYs	\$ 31.67
	Policy C	\$ 689.20	19.6 QALYs	\$ 32.17

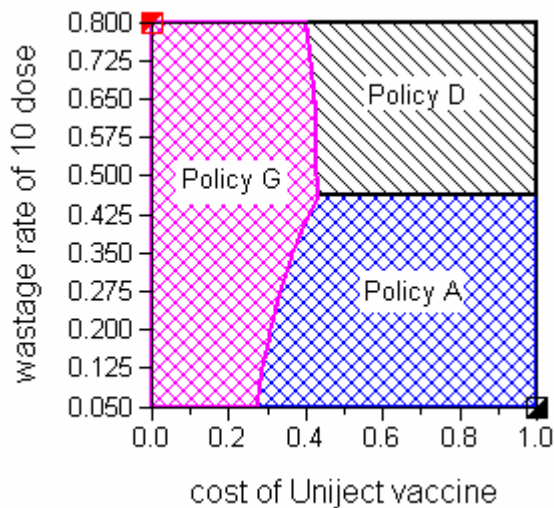
Table 9. One-Way Sensitivity Analysis on Coverage Rates at Health Centers

CovqHC	Strategy	Cost	Eff	Incr C/E (ICER)
11%	Policy A	\$562.00	15.5 QALYs	
	Policy B	\$608.00	17.0 QALYs	\$ 30.92
	Policy C	\$631.40	17.8 QALYs	\$ 31.41
23%	Policy A	\$590.50	16.5 QALYs	
	Policy B	\$636.70	18.0 QALYs	\$ 31.03
	Policy C	\$660.20	18.7 QALYs	\$ 31.57
42%	Policy A	\$633.40	17.9 QALYs	
	Policy B	\$679.90	19.4 QALYs	\$ 31.20
	Policy C	\$703.50	20.1 QALYs	\$ 31.81

Given the importance of coverage rate at health centers in my model, I varied the parameter base estimate of 28%. As the coverage rate at health centers increases, both Policy B and Policy C incur additional incremental costs per QALY gained since more children are being vaccinated. From a coverage rate of 11% to 42%, the ICER of Policy B increases by \$0.28 and remains the most cost-effective strategy.

Arguments in support of Uniject and one-dose vials depend on the cost of the equipment and wastage rates. In a one-way sensitivity analysis on the cost of Uniject, I calculated the pre-filled device would have to cost less than \$0.90 before it became more cost-effective than one-dose vials. The cost of one-dose vials would have to exceed \$0.84 for Uniject devices to be a preferred strategy for midwives. Similarly I determined that Policy B would lose dominance when the wastage rate for ten-dose vials reached 46%. When nearly half of ten-dose vials are being discarded or mishandled, Policy C or the use of Uniject by midwives becomes more cost-effective.

Figure 7. Two-Way Sensitivity Analysis on the Cost of Uniject and Wastage Rate of Ten-Dose Vials



Uncertainties surrounding the cost of Uniject and wastage rates of ten-dose vials warrant a two-way sensitivity analysis to examine the impact of simultaneously changing both variables. As seen in **Figure 7**, the boundaries between the different shaded regions represent the thresholds at which different policies become more cost-effective holding all other parameters constant. If the wastage rate of ten-dose vials exceeds approximately 45% and the cost of Uniject exceeds \$0.41 per device, Policy D of ten-dose vials at health centers and one-dose vials in outreach sessions becomes the optimal strategy, otherwise the status quo is preferred. The use of Uniject devices in outreach sessions and midwife visits in Policy G would only be optimal if the cost of the Uniject was less than \$0.28 per device.

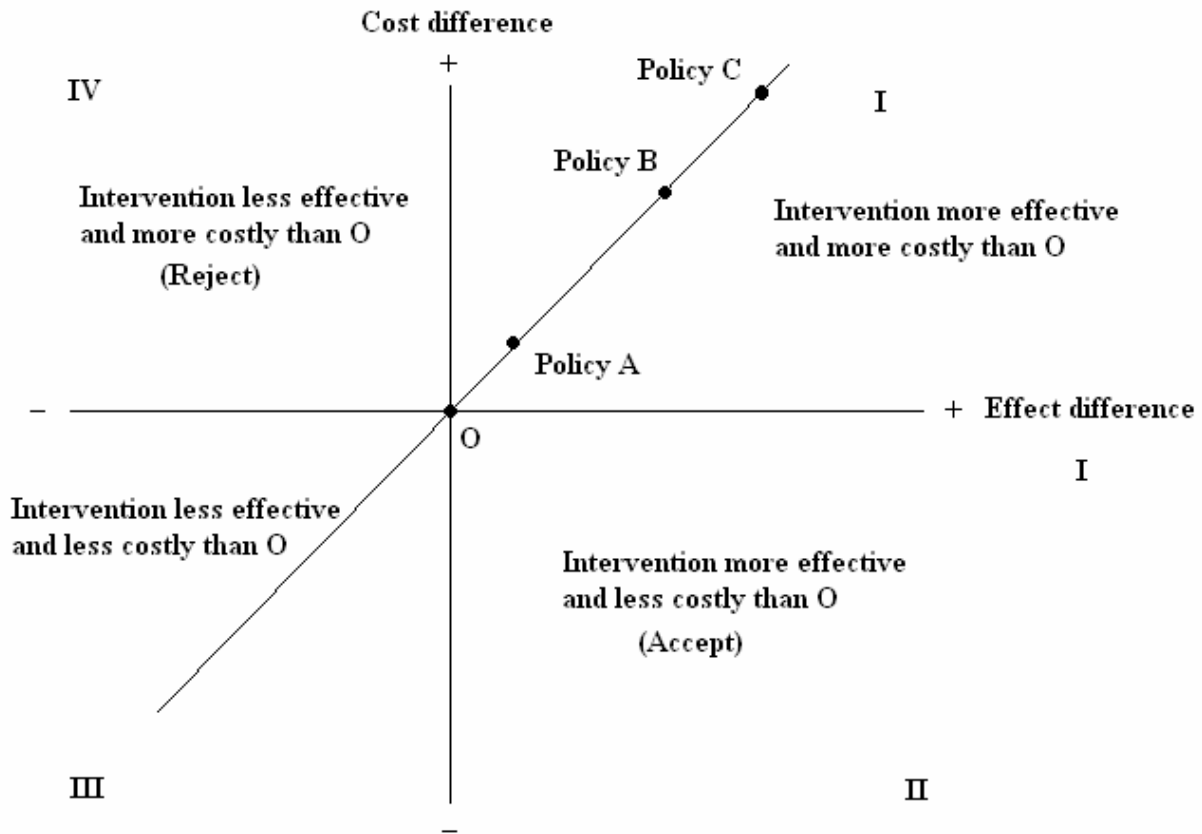
5. Discussion

Table 10. Table of Total Costs and QALYs of Vaccine Policies for 2006 Birth Cohort

Strategy	Notes	Cost	Incr Cost	Eff QALY	Incr Eff	Incr C/E
Policy A	Status Quo	\$ 226,503,078.91		6,338,120.80		
Policy B	One-dose Midwife	\$ 243,920,299.24	\$ 17,417,220.33	6,898,605.31	560,484.52	\$ 31.08
Policy C	Uniject Midwife	\$ 252,784,395.46	\$ 26,281,316.55	7,178,847.57	840,726.77	\$ 31.26

Assuming full linear scaleability, I calculated the total costs associated with each vaccine policy for the 2006 birth cohort of 376,467 found in **Table 9**. The status quo vaccine policy of ten-dose vials in health centers and outreach visits results in a total cost of \$226.5 million and 6.3 million QALYs. As vaccine coverage rates increase from 40% in Policy A to 60% and 70% in Policy B and C, the cost of vaccinations and number of vaccinated newborns increases while costs are saved from health care costs and QALYs accrued by the unvaccinated population. According to my analysis, the government of Cambodia would increase effectiveness by over 560,000 QALYs with the use of one-dose vials by midwives at an incremental cost of \$17.4 million.

Uniject devices administered by midwives leads to the greatest utility gained at almost 7.2 million QALYs. As with many preventive measures, the proposed midwife strategy falls in quadrant I or Northeast of the incremental cost-effectiveness place depicted in **Figure 8**. The midwife strategy using one-dose vials and Uniject results in positive costs in terms of vaccine expenses and positive effects in terms of QALYs. In this quadrant, trade-offs depend on the willingness-to-pay of the decision maker. While Policy B results in less incremental costs per QALY gained, the absolute costs of implementing the vaccine policy may deter the government of Cambodia, which already faces funding difficulties for its immunization programs.

Figure 8. Cost-Effectiveness Plane

Source: Adapted from Drummond, Sculpher, Torrance, O'Brien, Stoddart 2005

One important limitation of my model is the lack of costs and QALYs attributed to people who naturally resolved HBV infection. This form of natural immunity is more likely to occur during late infection rather than perinatal or early childhood infection. Additionally the estimates I use for coverage rates achieved by midwives using one-dose vials and Uniject devices is an estimate that needs to be verified by on the ground pilot studies. The greater availability of one-dose vials compared to Uniject devices also strengthens the argument for choosing Policy B over my proposed Policy C, but the ease of use and simplification (or complication) of logistics in the field are not explicitly factored in my model. My policy recommendation hinges on the government's approval of using Hep B vaccines out the cold chain and permitting midwives to administer them outside of an institutionalized setting.

6. Conclusion

In order to reach its Hep B first dose coverage of 90% by 2010, the Ministry of Health in Cambodia will need to implement a multi-prong vaccination strategy that tailors different vaccine formats and policies according to the rural or urban setting of its geographically diverse country. The results of my decision analysis demonstrate the cost-effectiveness of alternative vaccine formats and expanded coverage through midwives. Additionally, there is a need to develop private-public partnerships with the more widely available traditional birth attendants (TBAs) and private clinics since these are the preferred choices of many Cambodian women. Instead of viewing these currently used services as oppositions to progress in public health, the government should assist TBAs who work as private practitioners and private clinics in providing cleaner and safer deliveries and medical services.

While these TBAs do not have formal training, they are often respected within the community and serve as reliable sources of information on vital events like births, deaths, and illnesses. Currently, the “MOH does not discourage building strong links between the TBAs and the health facility midwives for obtaining current information regarding these vital events but emphasizes the importance of using trained midwives for maternity care and that infant immunization can only be carried out by official health staff” (Mohan 2002, p. 9). Officials may consider tailoring health services to the cultural norms and preferences of Cambodians to be perpetuating faulty services, but the predominance and popularity of such services warrants immediate redress in the short and mid-term.

6. 1 Discussion on the Pros, Cons, and Barriers to Uniject

The success of Uniject to administer Hep B vaccines in Indonesia, tetanus in Mexico, and Oxitoxin in Mexico, lead to the question, “Why do other developing countries not adopt this technology?” Studies like the 1999 outreach immunization in Indonesia point to the satisfaction level of both health care workers administering the vaccine, as well as clients or parents of clients receiving the vaccine. Many cite the ease in use and reduced preparation time involved.

The largest barrier to Uniject is sustainability in terms of government support, funding, and supply. The most cited example of Uniject use is in Indonesia where traditional birth attendants attended to births at home and provided HB-Uniject to newborns upon delivery. This required government support and training of Indonesian TBAs who were literate and more educated than their counterparts in Cambodia. This home context allows birth doses to be delivered within the recommended 24 hours, but requires public backing of TBAs and giving them government sanction to administer Hep B vaccines out of the cold chain. Currently, the Cambodian Ministry of Health strictly forbids the use of non-government health workers to administer vaccines since they are seen as being untrained and unable to assist in the country’s immunization efforts.

Funding is an additional barrier since Cambodia relies on vaccine supplies provided by UNICEF. This relationship means the country may only purchase immunization materials from WHO pre-qualified manufacturers. In June of 2005, BioFarma in Indonesia temporarily lost its WHO pre-qualification status, which would have halted a supply to countries like Cambodia attempting to use Uniject in their national campaigns. The inconsistency and lack of reliability in constantly supplying Uniject and using WHO funds to purchase the product are barriers to implementing the device in Cambodia. Interviews with policymakers like Dr. Toda of the WHO

in Cambodia additionally suggest that the element of sustainability is extremely important since beginning Uniject would make it logistically and culturally difficult to revert to the traditional method when supplies stopped.

Currently, there are only two manufacturers for Uniject, BioFarma in Indonesia and Beckton Dickinson in the US, and their supplies are limited to their host countries. Procuring an adequate supply of Uniject at a cost competitive to the traditional vial and syringe method will be difficult given the low demand and therefore high costs of this device.

6.2 Potential Partnerships

The preliminary findings of a survey on private sector immunization presented at the NIP workshop (First Semester 2005) indicated a continued reliance on private facilities. According to a Social Demographic Survey in 2004, more than two-thirds of the population turns first to the private sector for medical care, but recent EPI reviews provided evidence that these services are of poor quality standard. Additionally the private sector has a high prevalence of immunizations. For example, 92.9% (or 26 out of 27 private clinics) with inpatient services surveyed provide immunization surveys while 76% (or 63 out of 83 facilities) store vaccine. These private clinics provide a variety of vaccines, but TT and Hep B are the most common at 71% and 45% respectively. The study also extrapolates that 24,000 deliveries (or 6% of the infant cohort) occur in such private clinics, making a partnership with them a viable alternative. The researchers found that the mean private purchase cost of Hep B vaccine per dose is \$7.18 with a min of \$0 and a max of \$12. The mean cost of BCG, however, was at \$0.68 since it is subsidized by the government. The most expensive vaccine was the Hep A vaccine at a mean private sector per dose price of \$25.

Given the preference of some women for deliveries in private clinic, the government should pursue a similar subsidizing of Hep B to improve its birth dose coverage. Another surprising result of this survey was the lower than expected use of public vaccine in the private sector. For example, only 5% of Hep B vaccines administered in the private sector comes from the public sector (or 4 out of 70 facilities with publicly procured Hep B vaccines), whereas 33% of TT vaccines administered in the private sector comes from the public sector. Furthermore, of the 202 vaccine procurements at 83 facilities, 80% were sourced from the private sector while 20% were sourced from the public sector.

It is important to realize, however, that a majority of private sector staff supplement their wages by moonlighting or setting up private clinics as out of hours business that have been reported to interrupt their duties in the private setting. Another troubling aspect of private practitioners is their low knowledge of proper immunization schedules – only 8 of 71 facilities or 11% provided correction information on the Hep B vaccine scheduling. Poor immunization waste management practices and poor immunization practices were also observed since safety boxes were rarely used and waste was disposed in public garbage sites or simply disposed of in plastic bottles. Fortunately, the private sector did express a willingness to collaborate with the public sector.

Though 80% of birth deliveries occur at home with the assistance of a TBA and are the first to see a child within 24 hours of its lifetime, the Ministry of Health currently forbids non-government health care workers to administer vaccines. This policy is premised on the low literacy rates and low education of many TBAs who learn their trade orally and not through the government sponsored medical education system. There are foreign NGOs in Cambodia, however, that offer TBA kits and teach these traditional women to perform sanitary births,

practice clean hygiene, and inform mothers of the need to vaccinate their children. The progress and current collaboration between TBAs and NGOs does not exist with the health care officials.

Instead of viewing these services in a hostile or competitive manner, a more collaborative approach should be adopted to improve their services and practice medicine properly. Public assistance to private markets is rationale since Cambodians prefer these avenues since they are cited as more reliable in hours of opening, cleaner since they are in an enclosed environment with air conditioning, closer in proximity to their rural village, and more trusted since these individuals have a long standing reputation in the community. Based on my observations and interviews, I also found that many public health officials find the government salary inadequate and resort to private practice or moonlighting so they can supplement their low and delayed income from the Ministry of Health. Unless the Cambodian government can offer competitive salaries to public health care workers, it must learn to leverage the already preferred private sector by engaging strong participation and leadership among traditional birth attendants and private health clinics.

In interviews with private pharmacies and clinics offering vaccines, I learned that their business in the Hep B vaccine had significantly diminished as a result of the national expansion of the program. The previous widespread use and demand of Hep B indicates there is an existing knowledge base among Cambodians about the importance of this vaccine to prevent ascites, which is characterized by a swollen belly or *pboou!s toh!m* (□□□□□) and physically indicates advanced cirrhosis from advanced liver cancer. Cambodian folk stories place importance on the liver or *tiam* (□□□□□) as a source of courage and strength. The superstitions and beliefs on the importance of the liver, the organ most affected by HBV, serves a great example of how existing cultural notions and structures can be utilized to expand the Hep B birth dose coverage through education and appropriate use of TBAs, midwives, and private health clinics.

6.3 Cultural nuances and considerations: traditional practices

In the countryside, the lifestyles of Cambodian women prevent them from leaving their homes and taking their newborns to a health clinic within the recommended seven days for the Hep B birth dose. During my field research, I observed the Hep B birth dose vaccination of a handful of newborns brought to the health clinic by a close relative, usually a grandmother or aunt. According to a May 2004 evaluation of the birth dose of Hep B Vaccine in the pilot province of Kampong Chhnang, 38% of mothers interviewed relied on relatives to bring infants into health centers for vaccination (p. 15). Of those interviewed, outreach sessions are another successful avenue of immunization coverage since health workers traveling to villages provided another 28% of the birth dose vaccines. If she was like many Cambodian women in the countryside, she had an average of five children and stayed at home to take care of her other children. In addition to her maternal duties, the mothers who had just delivered her child would often follow the traditional practice of staying on a heated bed for seven days. Without access to modern technology associated with child deliveries, Cambodians have developed a natural remedy for purging the delivery material from their wombs. After talking to female government workers, a professor of Cambodian culture at Panasastra University, and my own family relatives in the country, I was told that a smoldering fire is lit under the new mother's bamboo or wooden beds while she drinks an alcoholic mixture. The heat and the alcohol open her blood vessels and "new" blood enters her system as a heated rock or stone is wrapped in a towel and placed on her abdomen to push out the excrement. If this practice is not followed, there is a belief that the "old" blood prior to giving birth will leave spots on her face or will continue to make her weak.

In urban areas, a growing number of women give birth in the hospitals and do not stay on a heated bed, but they do continue to place a heated stone on their abdomens. Modern practices

of suctioning remnants of the caul and placenta from a womb with a vacuum replace these traditional practices in urban areas. By learning about the intensive post-labor procedures and economic burden mothers in rural areas undergo, public health officials can better understand the burden placed on women to leave their homes and find transportation to a public health center for her newborn's first birth dose of Hep B and subsequent immunizations. Outreach sessions provide a monthly opportunity for mothers to continue their children's vaccine schedules, but these will miss providing newborns with the needed birth dose within seven days and more preferably 24 hours to prevent vertical transmission of HBV.

6.4. Debate between short term solutions (outreach) versus long term goals (fixed sites)

As of 2002, the Ministry of Health implemented outreach sessions in addition to the existing fixed site sessions held at health centers. Though outreach visits conducted by health center staff constitute nearly 80% of all vaccinations given, there is a debate amongst health care officials as to the long term effects of bringing health care to remote villages. Instead of instilling a culture where villagers turn to their local health centers for care, there is a concern that outreach sessions perpetuate a tradition that does not value preventive medicine. If this logic is extended further to vaccinations at home, public health officials like Dr. Kohei Toda at the WHO regional office in Cambodia fear that outreach sessions perpetuate a sub-optimal existing culture (Personal Interview 8/26/05). Instead of citizens that proactively seek medical care, outreach sessions could be seen as catering to a Cambodian who does not value preventative medicine and acknowledges that the public health care system must come to them. There is also a growing trend towards fixed site immunizations that could be indicative of reduced reliance on outreach visits to a certain extent. For example, the ratio of fixed to outreach vaccine sessions has

increased in favor of fixed sites from 100% outreach in January 2004 to 36.45% outreach in August 2004 and 80.14% fixed sites in June 2005 (Mid-term Review 2005). By continuing outreach sessions and even expanding health care to the home through TBAs and midwives, there is concern that Cambodians will continue to not rely on fixed sites (public health centers) since resources are being diverted to mobile health care. In contrast, Dr. John Grundy takes into account the poor infrastructure of the country and prefers an “every opportunity approach” that encompasses both long term and short term strategies (Personal Interview 8/23/05). While he agrees with Dr. Toda’s long term solution of reliance on public health clinics, he acknowledges the importance of short term solutions like outreach sessions, midwives, and TBAs even though it might slow down the building of a health care system around fixed sites. By increasing coverage of the Hep B birth dose through outreach and at home delivery, there is a possibility of increasing the likelihood of completing the series and other childhood immunizations since education occurs during at home visits. The importance of education is needed for community acceptability, especially with regards to interventions used on newborns since traditional beliefs are wary of exposing infants to the evil eye (Mohan 2002).

The McKinsey Report conducted for GAVI in 2003 remarks that “decentralized models typically require monitoring and strong second/third level management to ensure district performance” (GAVI 2003, p. 10). This remark is especially relevant to Cambodia, which has adopted a decentralized health infrastructure. Since 1996, the Health Coverage Plan created 24 provinces with Provincial Health Departments and 73 operational districts, which in turn offer a total of 940 health centers and 68 referral hospitals (Huot and Chhon 2002, p. 7). As the McKinsey Report states, the current status of the country’s health service delivery system means a longer time to transition from remote outreach programs to fixed delivery from a health center.

For this reason, Cambodia falls under GAVI's definition of a Turnaround segment since the country faces a broad set of barriers in its national health system (GAVI 2003, p. 9). The decentralized health service also results in unreliable and irregular funding. This inconsistent funding leads to a shortage in the first quarter of the year, which is ideal time for immunization outreach to remote areas because it is the dry season in Cambodia (Huot and Chhon 2002, p. 10)

In 2000, it was estimated that 55% of Cambodians had access to primary level health services, defined as living within 10 kilometers, or a two hour walk of a HC. Approximately 80% of the planned HCs are currently in place and functioning (Huot and Chhon 2002, p. 7). In the same year, Cambodia demonstrated its ability to immunize children against a vaccine preventable disease when it was certified polio-free (Huot and Chhon 2002, p.13). Efforts in the form of surveillance and periodic supplementary immunization activities (SIA) are positive indicators that the country will retain this status and contribute to the global eradication of polio. Additionally, investments in equipment and personnel training have the potential to positively spillover into Cambodia's Hep B immunization efforts (GAVI 2003, p. 4). The country's birth registry has only been in existence since 2002. The report also suggests health workers need to be better motivated and existing community structures should increasingly be mobilized. I focus on the latter suggestion, specifically with regards to traditional birth attendants who have the potential to play a similar role as midwives in Indonesia (Huot and Chhon 2002, p. 22). The report places a large emphasis on improving the efficiency and effectiveness of outreach services but does not place a similar emphasis on leveraging existing traditional health workers living in remote areas to increase outreach.

In my research on Hep B birth dose vaccine strategies in rural Cambodia, I have come to realize that successful programs rely on increased collaboration between the MOH and

community leaders on public health initiatives. In Cambodia, village chiefs who are respected in their community inform their neighbors about health programs and use their homes as common meeting grounds for immunization and family planning outreach visits by public health centers. Similarly, midwives and traditional birth attendants are both more prevalent and trusted amongst Cambodian women who prefer to deliver their newborns at home. Currently the government does not allow these women who are in most direct contact with newborns in need of immunizations to provide vaccines. Instead the MOH encourages more facility-based deliveries where birth doses could be easily administered.

The structure of the system can also be arranged to provide health care workers with incentives to encourage women to complete their children's three doses of Hep B vaccine. Dr. Samuel So, the director of the Asian Liver Center at Stanford, has been involved with Hep B immunization programs in China, particularly in their catch-up vaccination program. He suggested that vaccine providers be rewarded on a compensation scale that promotes completion of all three doses. The last dose, however, would receive the largest compensation. Accuracy of reporting and possibilities of corruption would need to be checked by independent parties.

6.5 Implementation

It is important to clarify if Cambodia's existing infrastructure, personnel, and training are equipped to handle a switch to Uniject. The case of Indonesia relied upon traditional birth attendants to administer the first dose, whereas in Cambodia, the use of midwives is common but perhaps not sufficiently well-structured to replicate Indonesia's success. While the case in Indonesia will be helpful, there are dilemmas and circumstances that differentiate it from Cambodia. In a phone conversation, Carol Levin explained how the Indonesian government

placed great importance on the health of the nation (Phone Interview 4/26/2005). The rise in public health care expenditure occurred in the 1980s and coincided with President Suharto's loss of a friend to liver cancer (Muraskin 1995). A similar story may exist in Cambodia, but the country's poor economy also means funding of nationwide initiatives is unreliable. Indonesia serves as a comparative point of reference to understand the challenges around outreach programs to rural areas and home delivered birth in a highly HBV endemic country.

I conclude from my cost-effectiveness analysis that a vaccine policy allowing midwives to administer Hep B birth doses out of the cold chain is cost-effective. Given the unstable and scarce supply of Uniject, I recommend the Cambodian Ministry of Health adopt Policy B and train midwives to administer one-dose vials out of the cold chain. Theoretically, Uniject device is logistically easier to administer, previous difficulties with WHO pre-qualification lead me to question its sustainability. One-dose vials, however, have similarly low wastage rates and permitting midwives to them will leverage the heat stability properties of Hep B vaccines while avoiding their freeze sensitive nature. I recommend the country's National Immunization Program verify my cost-effectiveness model by implementing a pilot study of Policy B to increase coverage of the birth dose within the recommended seven days.

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APPENDIX

Appendix 1. Calculating Total Subunit Cost of Vaccine Formats

Total Cost of Ten-dose vials in Health Centers

$$= ((cVaxn10vial*(1+Freight10))/((1-pWaste10)*nDose10) + (cSftyBox10*(1+FreightSftyBox))/(nTotSyringe*(1-pWasteAD)) + (cADsyringe*(1+FreightAD)*(1+pWasteAD))+cTranspDisposeAD+cPersonHC)$$

Total Cost of Ten-dose vials in Outreach Visits

$$= (cVaxn10vial*(1+Freight10))/((1-pWaste10)*nDose10) + (cSftyBox10*(1+FreightSftyBox))/(nTotSyringe*(1-pWasteAD)) + (cADsyringe*(1+FreightAD)*(1+pWasteAD))+cTranspDisposeAD+cPersonOR$$

Total Cost of One-dose vials used by Midwives

$$= (cVaxn1doseVial*(1+FreightOne))/((1-pWasteOne)*nDoseOne) + (cSftyBox10*(1+FreightSftyBox))/(nTotSyringe*(1-pWasteAD)) + (cADsyringe*(1+FreightAD)*(1+pWasteAD))+cTranspDisposeAD + cPersonMW+cHomeVisitBox+cVaxnCarrier+cTrainOneDoseMW$$

Total Cost of One-dose vials in Outreach Visits

$$= (cVaxn1doseVial*(1+FreightOne))/((1-pWasteOne)*nDoseOne) + (cSftyBox10*(1+FreightSftyBox))/(nTotSyringe*(1-pWasteAD)) + (cADsyringe*(1+FreightAD)*(1+pWasteAD))+cTranspDisposeAD+cPersonOR$$

Total Cost of Uniject devices used by Midwives

$$= ((cVaxnUniject*(1+FreightUniject))/((1-pWasteUniject)*nDoseUniject) + (cSftyBoxUniject*(1+FreightSftyBox))/(nTotSyringe*(1-pWasteUniject)) + cTranspDisposeUniject+cPersonMW+cHomeVisitBox+cVaxnCarrier+cTrainUniMW)$$

Total Cost of Uniject devices in Outreach Visits

$$= ((cVaxnUniject*(1+FreightUniject))/((1-pWasteUniject)*nDoseUniject) + (cSftyBoxUniject*(1+FreightSftyBox))/(nTotSyringe*(1-pWasteUniject)) + cTranspDisposeUniject+cPersonOR+cTrainUniOR)$$

I calculated the total subunit cost (TotCost) of delivering one dose of Hep B vaccine with each vaccine format by multiplying the cost of one dose (cVaxn10vial, cVaxn1dosevial, or cVaxnUniject) with the associated freight cost (Freight10, FreightOne, FreightUniject). This numerator is then divided by the denominator of number of doses in each vaccine format (nDose10, nDoseOne, nDoseUniject) multiplied with one minus the probability of wastage

(pWaste10, pWasteOne, pWasteUniject). In line (a) of Equation (6) and (7) included in this section, the resulting value is the cost of one dose of a vaccine format accounting for freight cost and wastage. For example, a ten-dose vial costs \$2.40 according to the UNICEF Supply Division's Forecast for the 2006 Recommended Budget Prices used in preliminary budget planning. At a 40% wastage rate, however, the cost per dose of Hep B would be \$0.40 per dose as opposed to \$0.24 per dose if there were zero wastage.

Line (b) of both equations calculates the cost of a 5 liter safety box (cSftyBox or cSftyBoxUniject) for proper disposal of a used auto-disable (AD) syringe. Associated costs of the safety box include freight cost (FreightSftyBox) and wastage associated with AD syringes (pWasteAD) from mishandling. The resulting value must be divided by the number of total syringes (nTotSyringe) that a safety box can store. Line (c) of Equation (6) calculates the cost of AD syringes, including the freight cost (FreightAD) and associated wastage of syringes, incurred when using ten-dose vials and one-dose vials. Line (c) does not exist in Equation (7) because the Uniject device integrates the syringe and vial component and costs are saved on AD syringes. Line (d) of both equations calculates both the cost of personnel to administer a Hep B vaccine (cPersonHC, cPersonOR, or cPersonMW) associated cost of transporting used syringes (cTransDisposeAD or cTransDisposeUniject) for disposal in incinerators to avoid needlestick injuries and the spread of other blood-borne pathogens. Based on Levin, Nelson, Widjaya, Moniaga, and Anwar (2005) study in Indonesia, I assume the cost of personnel for outreach visits and vaccination by midwives is greater than the cost of personnel at health centers because of fuel costs associated with traveling to remote villages. Additionally, I assume the disposal cost of AD syringes is greater than the cost of disposing the more compact Uniject. Lastly, using Uniject requires additional costs calculated in Line (e) of Equation (7). In the 2005 Indonesian

study, midwives incur costs from carrying a home visit box (cHomeVisit Box), costs from carrying a vaccine carrier transport box (cVaxnCarrier), and costs from additional training to use either the Uniject device or the one-dose vial (TrainUniMW or TrainMWOneDose). In Policies G, H, and I, Hep B vaccines administered in outreach visits with Uniject devices also incur costs for training to use Uniject (TrainUniOR).

cVaxn10vial = cost of a ten-dose vial of Hep B vaccine

cVaxn1doseVial = cost of a one-dose vial of Hep B vaccine

cVaxnUniject = cost of a Hep B vaccine in a Uniject device

Freight10 = percentage of a ten-dose vial freight cost

FreightOne = percentage of a one-dose vial freight cost

FreightUniject = percentage of a Uniject device freight cost

pWaste10 = probability of wasting a ten-dose vial

pWasteOne = probability of wasting a one-dose vial

pWasteUniject = probability of wasting a Uniject device

nDose10 = number of doses in a ten-dose vial

nDoseOne = number of doses in a one-dose vial

nDoseUniject = number of doses in a Uniject device

cSftyBox10 = cost of one 5L safety box for used syringes

FreightSftyBox = percentage of safety box freight cost

nTotSyringe = number of total syringes that can fit in a safety box

pWasteAD = probability of wasting auto-disable (AD) syringes

cADsyringe = cost of one AD syringe

FreightAD = percentage of one AD syringe freight cost

cTranspDisposeAD = cost of transporting the disposal of one AD syringe

cPersonHC = cost of personnel for health centers

Appendix 2. Immediate Risk of Perinatal Infection

Unvaccinated newborns either did not receive the vaccine or failed to develop an immunological response. This cohort enters the elaborate unvaccinated subtree simplified and decomposed in **Figures A.1 – A.6**. As illustrated in part one of the unvaccinated subtree (**Figure A.1**), the entire unvaccinated cohort enters the “Newborn Unvaccinated” branch because they are all at risk of developing perinatal infection and contracting HBV at birth from their potentially infected mothers. I adopt the CDC Hep B model’s assumption that HBV infection occurs in three age periods: 1) perinatal or at birth, 2) early childhood or after birth through five years old, and 3) late or more than five years old through adulthood.

A portion of the unvaccinated cohort will develop perinatal infection and continue into its associated subtree found in **Figure A.3**. Newborns not infected perinatally enter the “Not Infected” Markov state illustrated in part two of the unvaccinated subtree found in **Figure A.2**. If perinatal transmission occurs, there is a 99% chance that the child will display no symptoms of infection and be considered asymptomatic. He or she then has a 10% chance of naturally resolving the infection in their bodies and a 90% chance of becoming a chronic carrier of HBV. Only 1% of perinatal transmissions result in symptomatic infections that rarely cause acute liver failure or fulminant hepatitis. This is a rare but potentially fatal disease in developing countries where supportive management and/or liver transplantation are not available. It is estimated that 70% of patients with fulminant hepatitis will die, regardless of when they contract HBV. Infants that become chronic HBV carriers at birth from vertical transmission enter the “Chronic Perinatal Infection” Markov state and face annual rates of staying a chronic carrier for life, spontaneously clearing the disease (rare), developing cirrhosis, developing hepatocellular carcinoma (HCC or liver cancer), or naturally dying.

Appendix 3. Continued Risk of Subsequent HBV Infection

As seen in **Figure A.2**, the unvaccinated and not perinatally infected cohort face annual probabilities of becoming infected later, staying uninfected, or dying uninfected throughout their lifetimes. I employ a logic node and tunnel counter at the “Infected Later” branch to pose an annual risk of later infection. Each tunnel represents one year of an infants life. Between the ages (or tunnels) of zero through five, infants face a 13.8% annual probability of contracting HBV in early childhood and entering the Markov state “Early Childhood Infection” (K. Cham 2001, p. 5). After age five, the unvaccinated cohort faces a 2.66% annual probability of contracting HBV infection late in life.

I use a Tunnel Crossover variable to send infants into the appropriate Markov state if later infection occurs. This function of TreeAge software allows the tunnel counter to continue incrementing uninterrupted when transitioning from one state to a different state that also uses tunnels. Tunnel counters retain memory of time and transitions in a state since Markov models are considered “memoryless.” Transitions between Markov states are unidirectional, and the model maintains no memory of previous states unless the tunnel counter is used. I use this tunnel counter because the age at which a child acquires infection alters the natural history of HBV infection, and the child faces different probabilities of developing complications. As illustrated in **Figure A.5**, infants that become chronic HBV carriers later in life enter the “Chronic from Early Childhood” or “Chronic from Late Infection” Markov state and face annual rates of staying a chronic carrier for life, spontaneously clearing the disease (rare), developing cirrhosis, developing liver cancer (HCC), or naturally dying.

Figure A. 1. Simplified Decision Tree of Competing Vaccine Policies

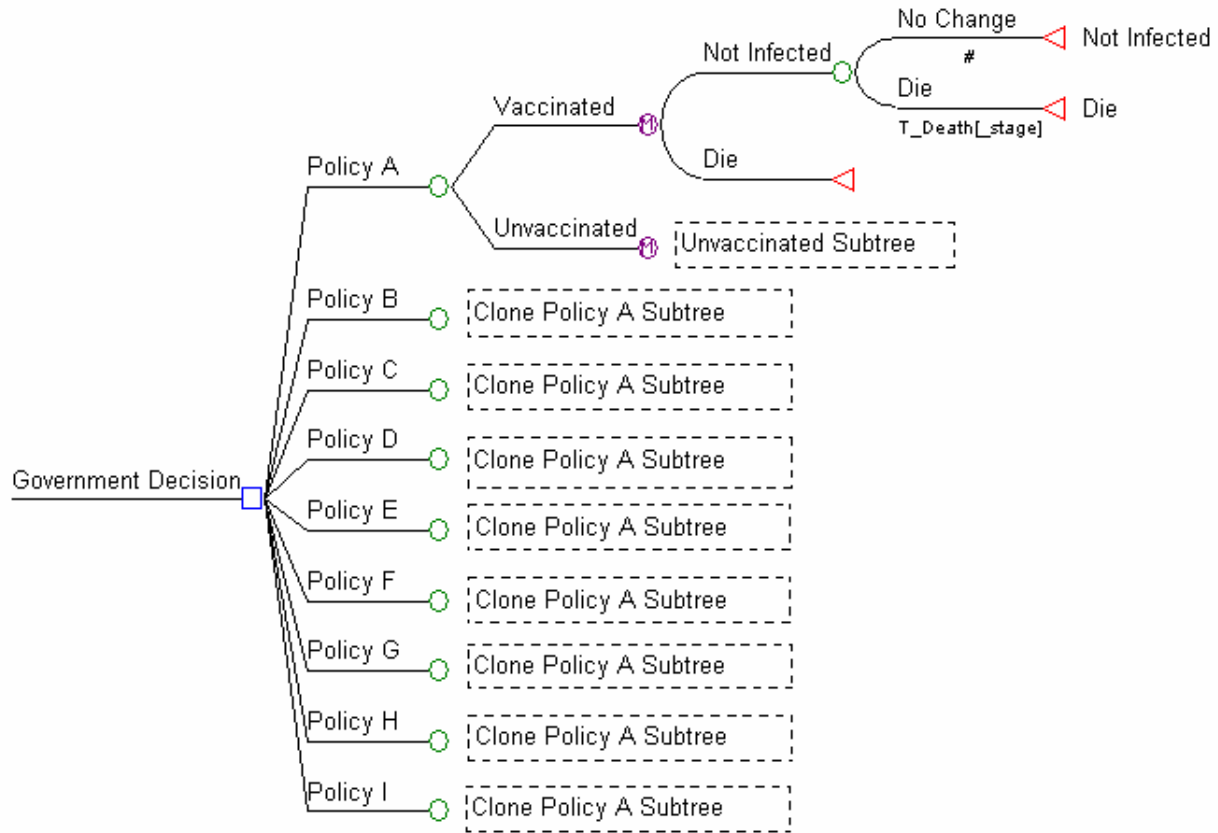


Figure A.2. Unvaccinated Subtree

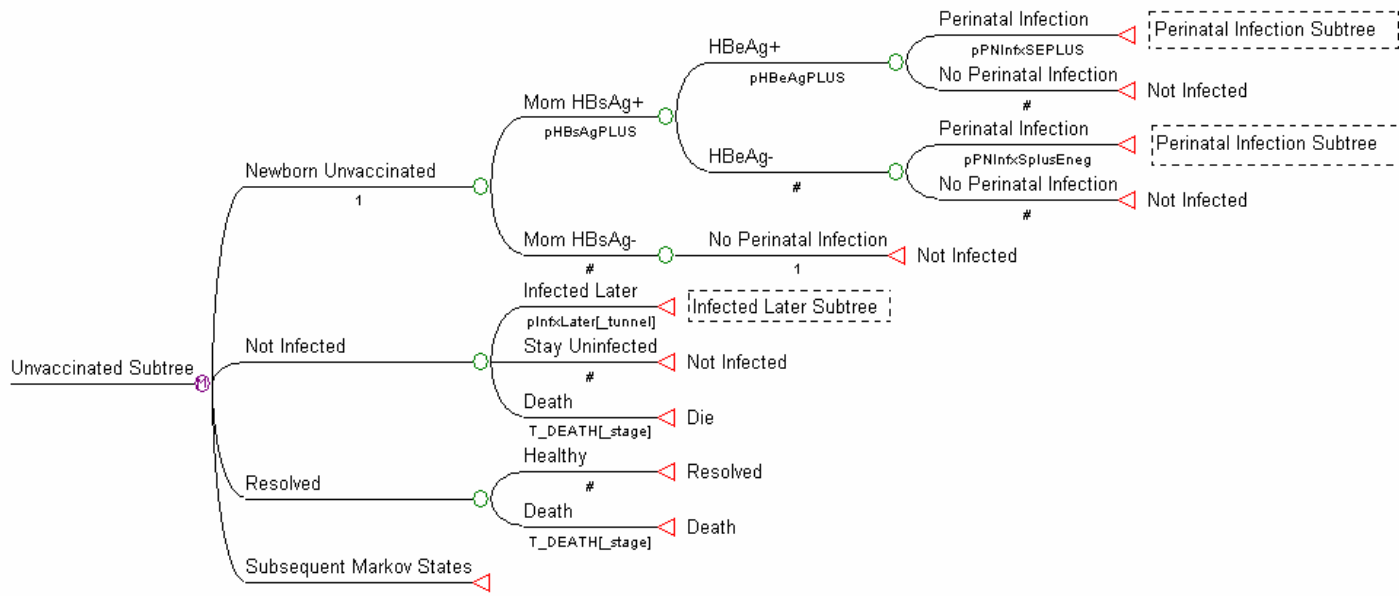


Figure A.3. Perinatal Infection Subtree

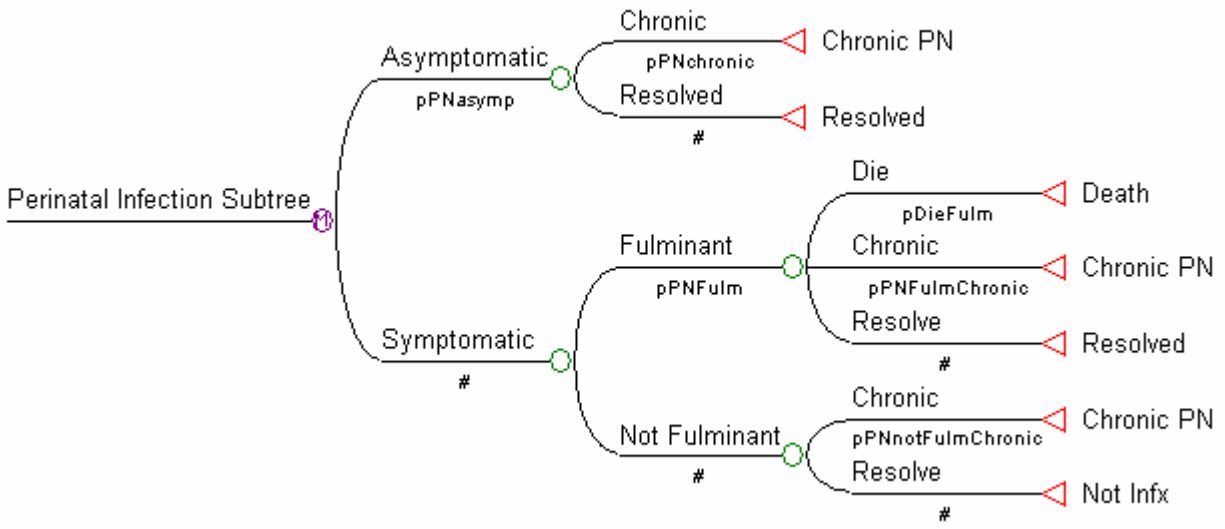


Figure A.4. Infected Later Subtree

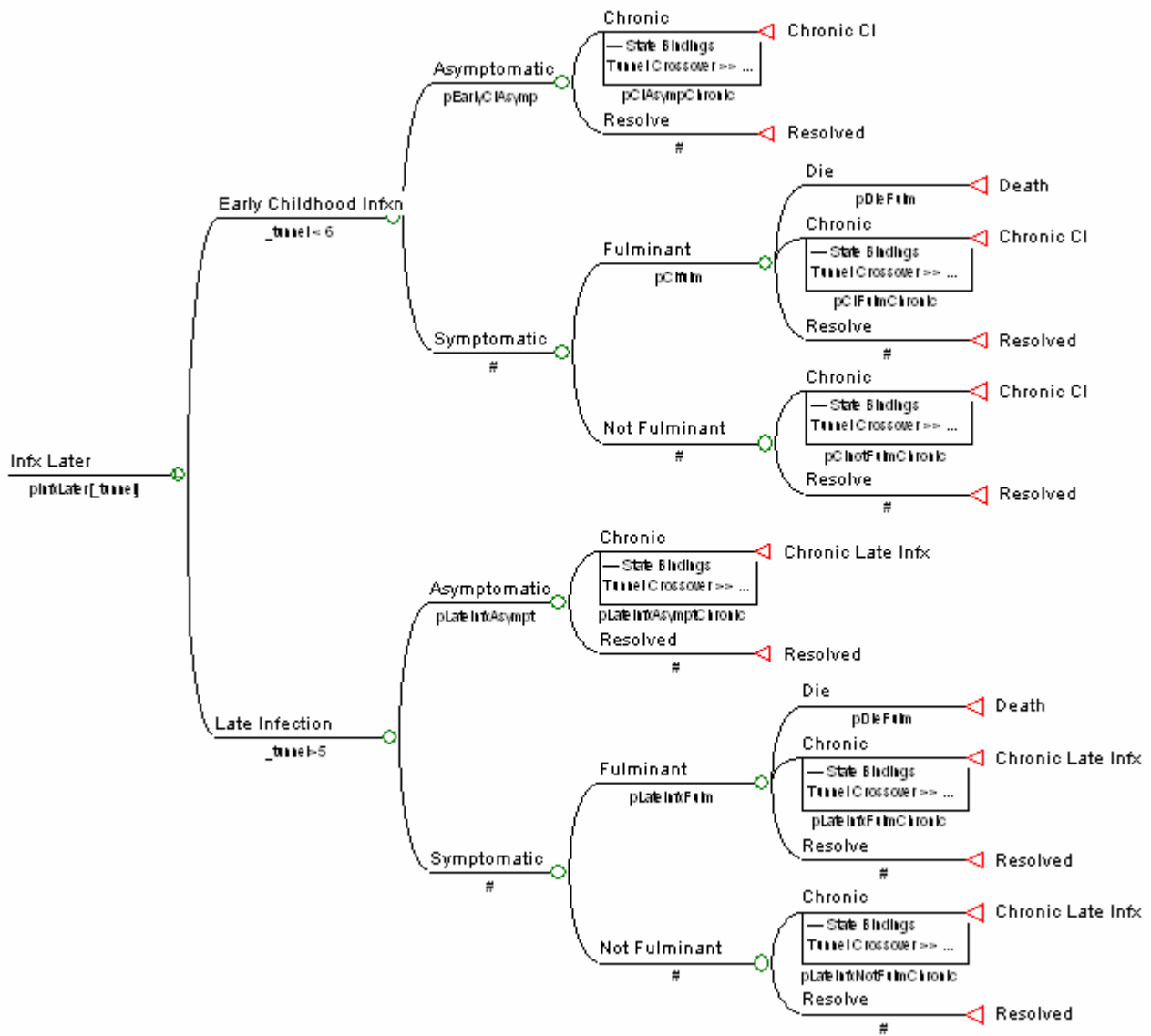


Figure A.5. Unvaccinated Subtree (Part Two)

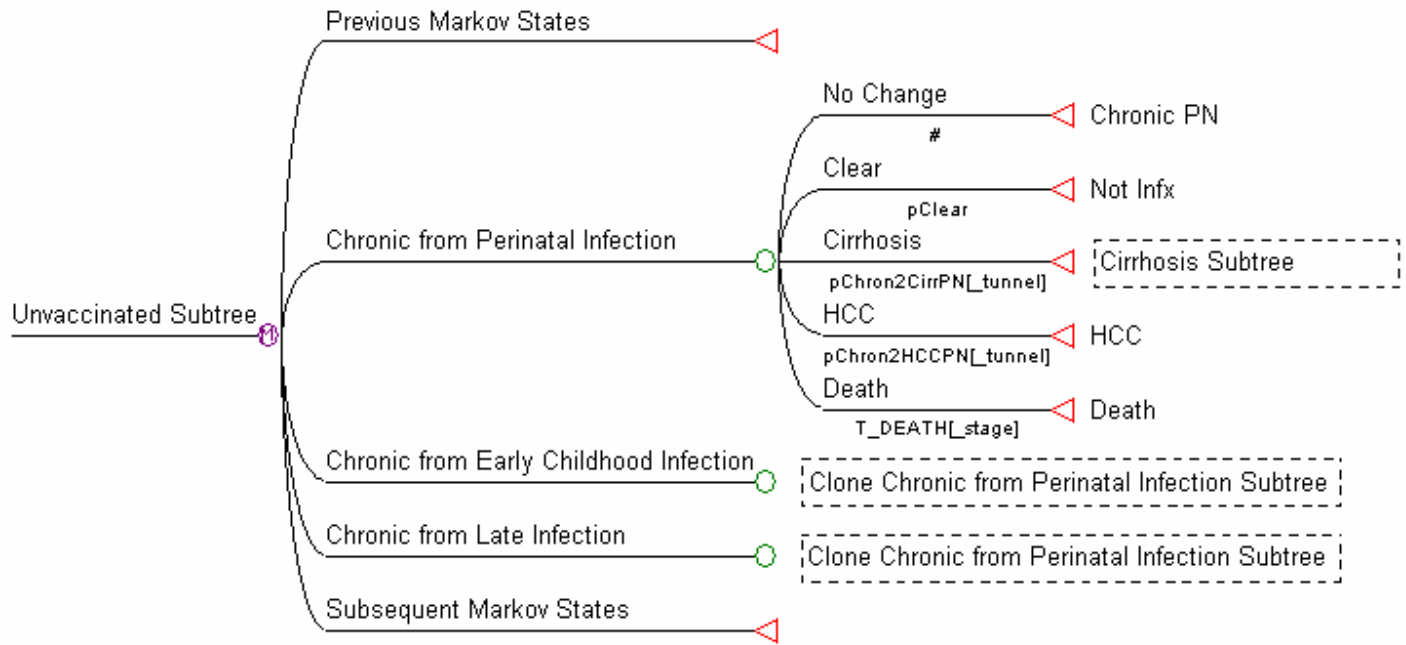


Figure A.6. Unvaccinated Subtree (Part Three)

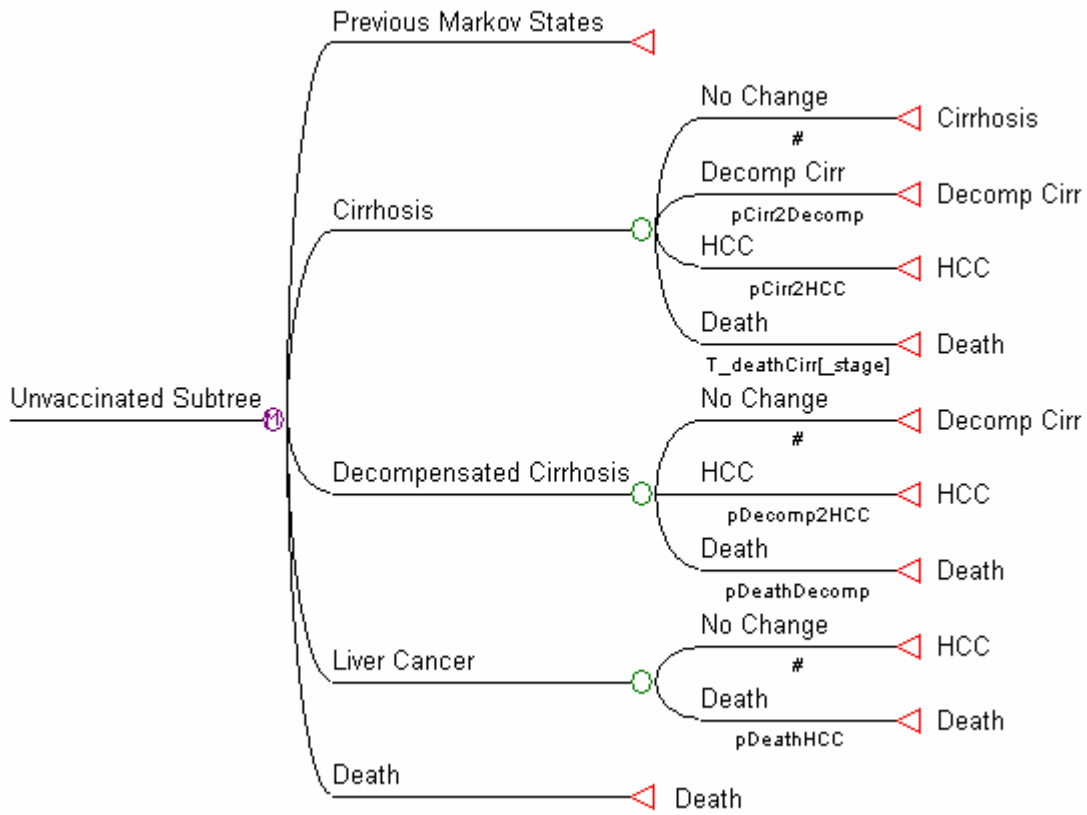


Table A. 1. Baseline Values and Ranges for Model Variables

Description	Baseline	Low	High	Sources
Coverage Related Estimates				
Population of 2006 birth cohort in Cambodia	376,467.00	300,000.00	400,000.00	Soeung 2006
Average life expectancy	59	54	66	WHO life table 1999
Coverage at health centers	0.28	0.105	0.42	MidTermReview 2005
Coverage by midwife using one-dose vials	0.20	0.10	0.30	Estimated
Coverage by midwives using uniject	0.30	0.15	0.35	Estimated
Coverage at outreach sessions	0.12	0.045	0.18	MidTermReview 2005
Discount rate	0.03	0.00	0.05	Estimated
Vaccine Related Costs, 2005 US\$				
Cost of ten-dose vial	\$ 2.40	\$ 1.50	\$ 4.70	MidTermReview 2005
Cost of Uniject vaccine	\$ 1.46	\$ 1.00	\$ 2.00	MidTermReview 2005
Cost of one-dose vial	\$ 0.41	\$ 0.30	\$ 0.50	MidTermReview 2005
Cost of safety box 5L for AD syringes	\$ 0.64	\$ 0.50	\$ 0.75	Levin et al. 2005
Cost of home visit carrier box	\$ 0.004	\$ 0.002	\$ 0.006	Levin et al. 2005
Cost of auto-disable (AD) syringe	\$ 0.058	\$ 0.030	\$ 0.080	UNICEF Prices 2006
Cost of Uniject safety box	\$ 0.004	\$ 0.002	\$ 0.007	Levin et al. 2005
Cost of vaccine carrier transport box	\$ 0.003	\$ 0.001	\$ 0.005	Levin et al. 2005
Cost of transporting AD syringes for disposal	\$ 0.004	\$ 0.002	\$ 0.006	Levin et al. 2005
Cost of transporting Uniject for disposal	\$ 0.007	\$ 0.004	\$ 0.009	Levin et al. 2005
Cost of personnel at health center	\$ 0.004	\$ 0.002	\$ 0.006	Levin et al. 2005
Cost of personnel for midwife visit	\$ 0.009	\$ 0.007	\$ 0.010	Levin et al. 2005
Cost of personnel at outreach	\$ 0.007	\$ 0.005	\$ 0.009	Levin et al. 2005
Cost of training midwives to use one-dose vials in home visits	\$ 0.015	\$ 0.009	\$ 0.100	Estimated
Cost training midwives to use Uniject in home visits	\$ 0.015	\$ 0.010	\$ 0.025	Estimated
Cost of training outreach workers to use Uniject	\$ 0.002	\$ 0.001	\$ 0.003	Levin et al. 2005
Unvaccinated Population Related Costs				
Cost of health care for chronic	\$ 1.00	\$ -	\$ 3.00	Estimated
Cost of health care for becoming symptomatic	\$ 2.00	\$ -	\$ 5.00	Estimated
Cost of health care for cirrhosis	\$ 2.00	\$ -	\$ 5.00	Estimated
Cost of health care for decompensated cirrhosis	\$ 3.00	\$ -	\$ 10.00	Estimated
Cost of health care for hepatocellular carcinoma (liver cancer)	\$ 5.00	\$ -	\$ 15.00	Estimated
Cost of incremental health care defined as annual per capita	\$ 36.00	\$ 25.00	\$ 40.00	SEAM 2003

Table A. 2. Baseline Ranges and Values for Model Variables (Cont'd)

Description	Baseline	Low	High	Sources
Vaccine Related Estimates				
Freight rate for 10-dose vials	0.06	0.05	0.07	UNICEF Prices 2006
Freight rate for AD syringes	0.15	0.145	0.15	UNICEF Prices 2006
Freight rate for One-dose vials	0.10	0.09	0.10	UNICEF Prices 2006
Freight rate for safety box	0.15	0.145	0.15	UNICEF Prices 2006
Freight rate for Uniject devices	0.15	0.10	0.20	Estimated
Number of total syringes that can fit into one 5L safety box	100	90	115	Levin et al. 2005
Probability of vaccine efficacy	0.95	0.75	0.99	WHO 1991
Wastage rate of 10-dose vials	0.40	0.05	0.6	MidTermReview 2005
Wastage rate of AD syringes	0.10	0.09	0.11	MidTermReview 2005
Wastage rate of One-dose vials	0.05	0.01	0.10	MidTermReview 2005
Wastage rate of Uniject devices	0.01	0.00	0.05	Levin et al. 2005
Utility Estimates				
Utility of chronic HBV w/o cirrhosis	0.99	0.80	1.00	Kanwal et al. 2005
Utility of becoming symptomatic	0.85	0.80	0.90	Kanwal et al. 2005
Utility of cirrhosis	0.80	0.70	0.90	Kanwal et al. 2005
Utility of decompensated cirrhosis	0.60	0.50	0.70	Kanwal et al. 2005
Utility of hepatocellular carcinoma (liver cancer)	0.73	0.50	0.80	Kanwal et al. 2005
Utility of not being infected	1.00	0.99	1.00	Estimated
Utility of being vaccinated	1.00	0.99	1.00	Estimated
Perinatal Infection Related Estimates				
Probability of Cambodian mother being HBsAg positive	0.103	0.09	0.1183	CVP-Path 2003
Probability of Cambodian mother being HBeAg positive	0.324	0.30	0.35	CVP-Path 2003
Probability of perinatal infection if HBsAg positive and HBeAg positive	0.90	0.85	0.95	CVP-Path 2003
Probability of perinatal infection if HBsAg positive and HBeAg negative	0.10	0.05	0.15	Goldstein et al. 2005
Probability of becoming asymptomatic if perinatally infected	0.99	0.95	0.999	Goldstein et al. 2005
Probability of becoming a chronic HBV carrier if perinatally infected	0.90	0.85	0.95	Goldstein et al. 2005
Probability of developing fulminant symptoms if perinatally infected	0.001	0.0005	0.0015	Goldstein et al. 2005
Probability of chronic HBV if perinatally infected with fulminant Hep B	0.27	0.22	0.32	Goldstein et al. 2005
Probability of becoming a chronic carrier if infected perinatally but not fulminant	0.90	0.85	0.95	Goldstein et al. 2005
Probability of dying from fulminant Hep B	0.70	0.65	0.75	Goldstein et al. 2005

Table A. 3. Baseline Ranges and Values for Model Variables (Cont'd)

Description	Baseline	Low	High	Sources
Early Childhood Infection Related Estimates				
Probability of Early Childhood Infection	0.126	0.10	0.25	CVP-Path 2003
Probability of being asymptomatic if infected early in childhood	0.99	0.90	0.999	Goldstein et al. 2005
Probability of being chronic if asymptomatic and contract in early childhood	0.30	0.25	0.35	Goldstein et al. 2005
Probability of fulminant hep b if infected in early childhood and symptomatic	0.006	0.004	0.01	Goldstein et al. 2005
Probability of becoming chronic if infected in early childhood with fulminant symptoms	0.09	0.085	0.10	Goldstein et al. 2005
Probability of becoming chronic if infected in early childhood and not fulminant	0.30	0.25	0.35	Goldstein et al. 2005
Late Infection Related Estimates				
Probability of Late Infection	0.524	0.45	0.775	CVP-Path 2003
Probability of becoming asymptomatic if infected in late infection	0.90	0.85	0.95	Goldstein et al. 2005
Probability of becoming a chronic carrier if asymptomatic when infected in late infection	0.06	0.055	0.065	Goldstein et al. 2005
Probability of developing Fulminant Hep B if infected in late infection	0.006	0.0055	0.0065	Goldstein et al. 2005
Probability of becoming a chronic carrier if late infx and fulminant	0.02	0.015	0.025	Goldstein et al. 2005
Probability of becoming a chronic carrier if late infxn but not fulminant	0.06	0.055	0.065	Goldstein et al. 2005
Natural History Estimates				
Annual Rate of spontaneously clearing Hep B	0.00065	0.0005	0.0008	Hsu et al. 1992
Annual Rate of transitioning from chronic Hep B to cirrhosis	0.03	0.02	0.04	Aggarwal et al. 2003
Annual Rate of transitioning from chronic Hep B to HCC	0.015	0.00	0.10	Kanwal et al. 2005
Annual Rate of transitioning from cirrhosis to decompensated cirrhosis	0.05	0.025	0.10	Aggarwal et al. 2003
Annual Rate of transitioning from cirrhosis to HCC	0.03	0.005	0.04	Aggarwal et al. 2003
Annual Rate of transitioning from cirrhosis to death	0.04	0.03	0.05	Kanwal et al. 2005
Annual Rate of transitioning from decompensated cirrhosis to HCC	0.03	0.005	0.04	Kanwal et al. 2005
Annual Rate of transitioning from decompensated cirrhosis to death	0.37	0.10	0.40	Aggarwal et al. 2003
Annual Rate of transitioning from HCC to death	0.40	0.20	0.60	Aggarwal et al. 2003

Table A. 4. Age-Specific Natural Mortality Estimates

Age	Probability	Age	Probability
0	0.06878	30	0.0051
1	0.009	31	0.0051
2	0.009	32	0.0051
3	0.009	33	0.0051
4	0.009	34	0.0051
5	0.00255	35	0.00595
6	0.00255	36	0.00595
7	0.00255	37	0.00595
8	0.00255	38	0.00595
9	0.00255	39	0.00595
10	0.002	40	0.00815
11	0.002	41	0.00815
12	0.002	42	0.00815
13	0.002	43	0.00815
14	0.002	44	0.00815
15	0.00335	45	0.01225
16	0.00335	46	0.01225
17	0.00335	47	0.01225
18	0.00335	48	0.01225
19	0.00335	49	0.01225
20	0.0043	50	0.0186
21	0.0043	51	0.0186
22	0.0043	52	0.0186
23	0.0043	53	0.0186
24	0.0043	54	0.0186
25	0.00405	55	0.02725
26	0.00405	56	0.02725
27	0.00405	57	0.02725
28	0.00405	58	0.02725
29	0.00405	59	0.02725

Table A. 5. Age-Specific Transitions from Chronic HBV to HCC

Age	Probability	Age	Probability
0	0	30	0.005
1	0	31	0.015
2	0	32	0.015
3	0	33	0.015
4	0	34	0.015
5	0	35	0.015
6	0	36	0.015
7	0	37	0.015
8	0	38	0.022
9	0	39	0.022
10	0	40	0.022
11	0	41	0.022
12	0	42	0.022
13	0	43	0.022
14	0	44	0.022
15	0	45	0.022
16	0	46	0.022
17	0	47	0.022
18	0	48	0.022
19	0	49	0.03
20	0	50	0.03
21	0.005	51	0.03
22	0.005	52	0.03
23	0.005	53	0.03
24	0.005	54	0.03
25	0.005	55	0.03
26	0.005	56	0.03
27	0.005	57	0.03
28	0.005	58	0.03
29	0.005	59	0.03

Table A. 6. Age-Specific Transitions from Chronic HBV to Cirrhosis

Age	Probability	Age	Probability
0	0	30	0.005
1	0	31	0.015
2	0	32	0.015
3	0	33	0.015
4	0	34	0.015
5	0	35	0.015
6	0	36	0.015
7	0	37	0.015
8	0	38	0.022
9	0	39	0.022
10	0	40	0.022
11	0	41	0.022
12	0	42	0.022
13	0	43	0.022
14	0	44	0.022
15	0.001	45	0.022
16	0.001	46	0.022
17	0.001	47	0.022
18	0.001	48	0.022
19	0.001	49	0.022
20	0.001	50	0.022
21	0.005	51	0.022
22	0.005	52	0.022
23	0.005	53	0.022
24	0.005	54	0.022
25	0.005	55	0.022
26	0.005	56	0.022
27	0.005	57	0.022
28	0.005	58	0.022
29	0.005	59	0.022