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Abstract

Objective: Three doses of monovalent Hepatitis B vaccinations that given for six months were the most effective as well as a safe way to prevent Hepatitis B viral infection. Ethiopia is one of the countries with high endemicity of Hepatitis B infection. Hence, examining cost-utility analysis of hepatitis B vaccination coverage among healthcare workers in Ethiopia was found the most essential work.

Method: Markov model for expanding vaccination coverage (3 doses of hepatitis B vaccine) was simulated based on the data obtained from black lion specialized hospitals and distinctive works of literature. In Ethiopia, the current vaccine coverage among health care workers accounts for around 14%. Most health workforce (241,250) of Ethiopia was first considered as susceptible with a probability of getting Hepatitis B Virus acutely and 5-10% chance of progressing to chronic Hepatitis B. This study was conducted from a healthcare payer perspective, with 3% discount rate of cost and health outcome as WHO recommendation. Primarily health outcome was measured by QALY gain and ICER. Deterministic analysis and tornado diagrams were employed to manage parameter uncertainty and show a plausible range of cost and effectiveness of variables obtained from published articles and black lion specialized hospitals.

Result: Current vaccination program is more expensive (US$29.99) with a positive incremental cost of US$ 1.32 and less effective that have negative incremental effectiveness of -0.08 and total life year gains of 28.54 than Expanded Hepatitis B vaccination strategy which costs US$ 28.67 and gives relatively high total life-year gain of 28.62. The resulting ICER was US$ 16.23 per QALY gained. Hence, ICER was a negative current vaccination strategy that was dominated which means that is a more expensive and less effective strategy. One-way sensitivity analysis provides that the current vaccine coverage was dominated for an increase in the risk of infection among unvaccinated individuals.

Conclusion: Increasing current vaccine coverage from 14% to 80% among all Ethiopian all healthcare workforces was the most cost-effective strategy.

Keywords: Cost-Utility; Hepatitis-B virus prevalence; Hepatitis B vaccination coverage; Healthcare Workforce; Ethiopia

Introduction

Hepatitis B Virus (HBV) is one of the serious global health burdens that affect the lives of more than two billion peoples. Recently it was estimated that around 350 million peoples all over the world live as chronic carriers of the virus with a prevalence of 3.5% [1]. However, the endemicity of HBV varies across the world with the highest prevalence occurring in Asia and Africa [2]. Particularly healthcare workers have 10 times more risk of acquiring HBV infection than the general population[3]. Annual incidences of hepatitis B infection in healthcare professionals reach 6% throughout the world. Hepatitis B (HepB) is primarily transmitted by percutaneous or mucosal contact of infected blood and body fluids, and occupationally exposure of healthcare workers during dental, medical and surgical procedures [4].

Hepatitis B Virus could be acute or chronic based on the persistence of HepB surface antigen (HBsAg) for less or more than six months. Most of the acute HepB infections were self-limiting that doesn't require specific treatment. However, 0.5-1% of individuals may develop fulminant hepatitis with a mortality rate of 70-80%. Meanwhile, 3-5% of adults with acute HepB have a chance of progressing into chronic HepB [5]. Chronic HepB could be treated by highly effective antiviral therapy like Tenofovir, lamivudine, etc. Despite that only 5% of CHB patients have access to treatment for various reasons[6]. Patients with chronic HepB may have a 40% risk of developing sequelae like cirrhosis, liver failure, and Hepatocellular Carcinoma. Consequently, 15-25% of peoples with chronic HepB infection die every year due to liver complications [6].

Currently, three doses of monovalent HepB vaccinations which are given for six months were the most effective and safe way to prevent HepB infection [7]. WHO (CDC) in collaboration with the Ethiopian FMOH recommends all health professionals to be vaccinated against HBV. Accordingly, HBV vaccination coverage among highly susceptible health professionals like midwifery, surgeons, dialysis workers, and laboratory reach 90% [8]. However, it's coverage among all healthcare workforce who directly or indirectly participate in the healthcare service delivery including health extension workers, medical waste handlers, janitors remain low (<20%)[9].

In Ethiopia, the reason for the low coverage of vaccination across health professionals such as lack of vaccine availability at healthcare centers, higher cost of vaccine at private health facilities, lack of knowledge about the severity of HBV infection, and low attitude towards risk factors and efficacy of the vaccine [10,11]. Hence, this cost-utility analysis will determine the cost

of increasing HepB vaccine coverage among all healthcare workforces such as nurses, laboratory, pharmacy, medical doctors, midwives, janitor workers, supportive staff and its effectiveness on disease prevention, QALY gained in comparison to current HepB vaccination coverage.

Method

Ethiopian Ministry of Health is the main public healthcare deliverer which is responsible for policy formulation, planning, development, and management of all health issues. The minster office has above 241,250 health workforces under various categories such as health extension workers (15%), paramedical professionals (35%), medical doctor professionals (3%), supportive and administrative staff (30%) and others. The average age of individuals was estimated at 32 years. All these health workforces are included in this study because these peoples have a relatively high occupational exposure to the HepB virus compared to the general population and in one way or another way they are involved in the Ethiopian healthcare service delivery. In Ethiopia, the risk of exposure is high among physicians, clinical nurses, midwives, laboratory technicians, and anesthetists consecutively[12]. Accordingly, this study would be implemented across all health facilities i.e. 16,243 health posts, 3,743 health centers, 220 primary hospitals, 64 general hospitals, 27 referral hospitals, and other administrative offices like the regional health bureau, district health offices, and minster of health[8].

Cost-utility analysis of expanding HepB vaccination was conducted in comparison to current Ethiopian HepB coverage among healthcare workers. This study was conducted from the healthcare payer perspective i.e., Ethiopian federal minister of health, though vaccines are financed by international donors. Finally, the cost of increasing vaccination coverage and its effect on the life year gains, quality of life, incremental cost-effectiveness ratio (ICER), and disease prevention was evaluated over the lifetime of healthcare workers i.e., 65 years since it was assumed that vaccines provide lifetime protection. The cost and QALY were adjusted to a 3% discount rate as of WHO recommendation. Synthesis based estimate of data was used accordingly, several studies conducted in China, USA, and Ethiopia were referred, and mean value was taken to overcome misleading data findings from a single study.

All necessary pharmaceuticals including the HepB vaccine were procured and supplied primarily by the Ethiopian pharmaceutical supply agency (EPSA). Antiviral drugs like Tenofovir 300mg, Lamivudine 150mg alone which are used for the treatment of chronic HepB

are not included in the pharmaceutical procurement list of Ethiopia [13]. However, they are assumed to be supplied by EPSA and currently available at a black lion specialized hospital. Cost related data were gathered by interviewing expertise from Black-lion hospital (nurses, physicians, and pharmacists), WHO HBV guideline and effectiveness related information were also gathered from distinctive pieces of literature review. All costs were expressed in USD at an exchange rate of 28 Ethiopian Birr to US$ l on June, 1 1, 2019.

Model structure

As the model of HepB virus disease progress depicted in (Fig 1) indicates any susceptible individual may stay at "susceptible state" without acquiring an infection. Otherwise, get infected by HBV first acutely with a 5-10% chance of progressing to chronic HepB and 0.5-1% case fatality rate. The other chance of susceptible individuals is either develop self-immunity or get vaccinated from prior infection. Any person who has immunity could stay an "immune" health state. The other health state is the "Chronic hepatitis" state. In this health state, an infected person may live as a chronic carrier or get treatment then progress to a healthy ("immune") state. On the other hand, when any abnormality following or resulting from a chronic HepB infection such as liver permanent damage (cirrhosis), the individual inters to "Sequelae" health state. Despite this, any health state has a probability of entering into an absorbing state i.e., death.

Assumptions

Hepatitis B vaccines are available in different formulations for an instant in combination with other vaccines, like diphtheria—tetanus—pertussis (DTP), Haemophilus influenzae type b (Hib), and inactivated poliovirus (IPV). However, in this economic evaluation, only the monovalent HepB vaccine was considered since it is presently implemented in Ethiopia [1,8]. The term immunized is considered as healthcare workers receive a complete series of 3 doses of HepB vaccine within a six-month duration. All Healthcare workers who didn't receive the vaccination before were assumed to be eligible for vaccination without being screened for HBV. Utility value for chronic HepB, sequelae, immune and susceptible was adopted from a study conducted in the USA. The transmission of HepB virus infection at health facilities and healthcare workers was not considered in our model. In this economic evaluation treatment cost of acute hepatitis is not included because it is essentially self-limiting infection. For patients with liver complications such as hepatocellular carcinoma and cirrhosis only supportive care like resuscitation, symptomatic treatment was taken into consideration. Vaccination results in life long (up to 65 ELY) immunization of healthcare workers.

Analytic Method

- ✓ Cost-Utility analysis

Model Input

Effectiveness Data

Data regarding chronic hepatitis B disease progression, the natural history of the disease, vaccine effectiveness in infection prevention, treatment effectiveness in reducing disease progression to sequelae, and health outcome was taken from various kinds of literature and guidelines including [5,6,14] (Table 1)

Cost Data

Cost of three series doses of HepB vaccine (Table 2) for every unvaccinated susceptible health workforce which accounts around 86% of the currently active healthcare workforce was determined and the price of one dose monovalent HepB vaccine is 17.8$ and costs related to vaccine administration was also considered (cost of the vaccine and its administration US$ 57). For HepB treatment generic TDF 300 mg tablet was given as once-daily dose also optionally Propranolol 1 Omg, Furosemide 20mg tablet may be given as prophylaxis to sequelae and its cost was estimated US$ 57 per length cycle (l year) [5].

Laboratory monitoring and investigation for a patient with chronic HepB was estimated to cost ~US$ 57. This cost covers most of necessary laboratory tests like liver function tests (ALT, AST), HBsAg, Albumin, BIR, and BUN except HBV DNA test which is the most expensive and inaccessible test. For patients who develop sequelae like cirrhosis, Ascites, portal hypertension, and hepatocellular carcinoma cost of hospitalization and symptomatic treatment (US$ 189) were also added to Lab cost and treatment cost. Liver transplant cost for patients with liver failure was not estimated since it is not applicable in Ethiopia. Most of the information regarding the cost of HepB vaccination and chronic HepB disease management was obtained from pharmacists, nurses, and physicians who actively work in black lion specialized hospitals at the department of Gastroenterology, pharmacy, and internal medicine. Indirect cost, transportation cost, capital item costs like cold chain storage, deep freezer vans or vehicles, and other operational costs related to logistics were not included. Finally, the upfront cost for (e.g., fryers/advertisement) to increase vaccine coverage was not considered due to a lack of data (Table 2).

Model Output

As an output of this economic evaluation incremental cost, incremental effectiveness, quality-adjusted Life years gains of expanding HepB vaccination among all health workforce, and finally its ICER per QALY was calculated.

Sensitivity Analysis

To manages some uncertainty relating to methodological assumption, time, cost, and effectiveness variation of distinctive parameters and heterogeneity of healthcare workforce deterministic sensitivity analysis was employed. additionally, tornado diagram was used to show the plausible ranges of parameters obtained from published literature and guidelines of the country.

Results

The current vaccination program is more expensive (US$29.99) with a positive incremental cost of US$1.32 and less effective that have negative incremental effectiveness of -0.08 and total life year gains of 28.54 than Expanded Hepatitis B vaccination strategy which costs US$ 28.67 and gives relatively high total life-year gain of 28.62. The resulting ICER was US$ 16.23 per QALY gained. Overall current vaccination strategy was dominated by increasing vaccination coverage (Table 4).

Since Ethiopia does not have a standardized cost-effectiveness threshold (CET), the World Bank report of Ethiopia's GDP per capita (US$ 783) was used to determine CET. Accordingly, GDP was multiplied by three to obtain an estimated CET of US$ 2349 per QALY gains. Despite that since ICER was negative current vaccination strategy was dominated which means increasing vaccination coverage on cost-effectiveness plane lies on quadrant two, which is a less expensive and more effective quadrant.

One-way sensitivity analysis provides that the current vaccine coverage was dominated for an increase in the risk of infection among unvaccinated individuals. For instance, when the probability of infection is increased among unvaccinated individuals; the outcome of ICER has increased from -0.9 to -0.81. Accordingly, the cost has increased from 1.54 to 2.04 while the effectiveness had decreased from -0.09 to -0.13 as the chance of infection is raised with the current vaccine coverage. The additional incurred cost was related to treatment costs after infection. Similarly, tornado result revealed that the probability of die due to sequelae, death due to hepatitis B infection, the progression of untreated chronic hepatitis B to sequelae, cost of lab investigation, probability of treating chronic hepatitis B is the main parameter which possibly affects the ICER value. Varying cost parameters in the allowable range could increase the ICER value and the rest of the parameters might reduce or increase the ICER value base on the range (Fig 3).

From the two-way sensitivity analysis (Fig 2), it was found that irrespective of probability of death occurrence in chronic hepatitis B and the probability of HBV infection in unvaccinated individuals increasing vaccine coverage improve total QALY gain.

Discussion

The foremost aim of this economic evaluation was to compare cost-utility analysis of increasing vaccination versus keeping current coverage by doing these costs required per every healthcare worker in either strategy was determined, welfare obtained in kind of life year gains, utility increment and infection prevention were also calculated. Several data used to conduct this analysis were obtained from published articles particularly effectiveness data, and estimated cost data for vaccination and chronic hepatitis B treatment was also used from black lion specialized hospital[4,6,15].

The new strategy reduces the cost by US$ 16.23 that was expended by the current vaccination program for every QALY gains in lifetime horizon. Besides this promoting vaccination coverage was necessary because it is a less expensive and highly effective strategy to combat hepatitis B infection among healthcare workers. Alongside in Ethiopian health care system economic evaluations was not common practice, hence conducting such analysis would help policymakers, public healthcare payers to invest scarce healthcare resource cost-effectively.

Deterministic sensitivity analyses showed that varying the probability of different variables of cost and effectiveness as the new strategy significantly dominates the current program. While tornado result indicates that some variables impact on ICER value. Cost-effectiveness threshold of US$ 2349 i.e. three times of Ethiopia GDP was used to check the affordability of the new strategy. Therefore, since the ICER has a negative value implementation of the new program was not affected by the cost of the program.

Increasing vaccination coverage among healthcare works is vital in Ethiopia. The prevalence has shown progress from 7.4% to 6% with the current vaccination coverage[16] in the country. However, a high prevalence of Hep B among healthcare works in Ethiopia was reported. For instance, the seroprevalence of Hepatitis-B viral infection among the sample healthcare workers was 4.52% (95% CI: 2.4, 6.5) and 2.6% at Gondar and Addis Ababa referral hospitals respectively[10,12]. Moreover, the pooled estimation of prevalence among healthcare work presented a 5% prevalence in Ethiopia. When compared with other studies from African countries, the burden of Hep B viral infection is somewhat lesser. Health works are at high risk for viral infection compared to other ordinary people. Predisposing factors such as contamination due to medical procedures, workover load, and other factors are claimed to be responsible[10,11,14,16]. Moreover, regarding the accessibility of vaccines for health work remind a

challenge particularly unavailability and cost are repotted[10,11,14]. This implies the burden of this viral infection is being an additional challenge for the health system of Ethiopia since the government is facing other diseases such as infectious and non-communicable diseases.

Study limitation

This economic evaluation has some limitations especially regarding costing variables. We did not include viral transmission rates among study participants, this might underestimate the benefit. Indirect cost related to increasing vaccination coverage such as vaccine transport and cold chain equipment cost was not included even though the expansion of vaccination coverage to around 80% over all the country health facility requires a high investment of capital items. This might cause an underestimation cost of the expanded vaccination program and might result in the absolute dominance of the current vaccination strategy. So, we recommend for future studies to include those costs.

On the other hand, the cost of a liver transplant for patients with liver failure and the cost of acute hepatitis B treatment was not explicitly determined. Also, direct non-medical cost like transport cost, loss of work due to the disease of every healthcare workforce was also not included. Although this study gives high emphasis to reduce healthcare worker occupational exposure to hepatitis B infection by providing vaccines, it does not determine the cost of screening before vaccination it uses a methodological assumption of all healthcare workers are susceptible and eligible to vaccination. Of Despite all these limitations efforts have been made to use reliability data by gathering cost data from active physicians and other health professionals in black lion hospital. In addition, a sensitivity analysis was conducted to test the robustness of the model to check whether it is consistent with the base-case analysis or not.

Conclusion

From this economic evaluation, it is possible to conclude that increasing current vaccine coverage from 14% to at least 80% among all Ethiopian all healthcare workforces was the most cost-effective strategy. As long as expanding hepatitis B vaccine coverage does not incur additional costs and in the meantime, it improves the healthy life of susceptible healthcare workers Ethiopian FMOH should work on its implementation.

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Figure legends

Figure 1: Model of Hepatitis B virus disease progress and consequence

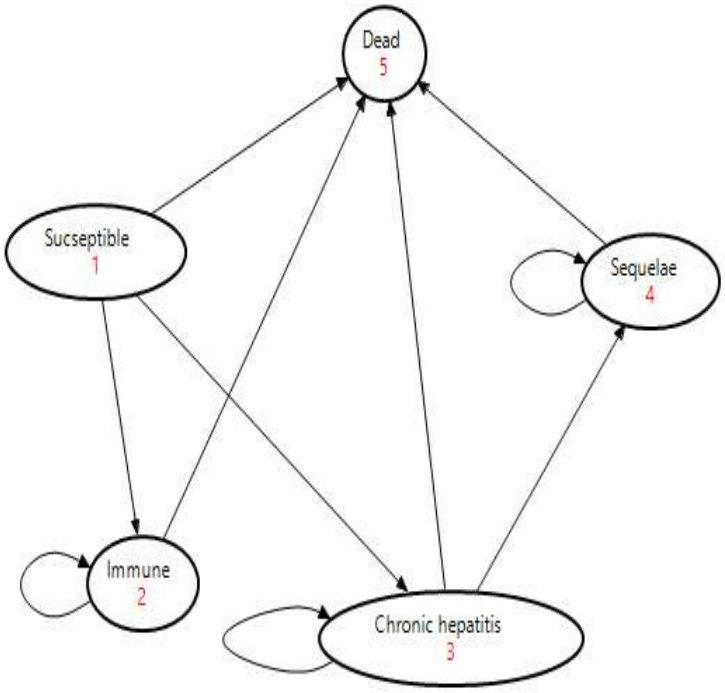


Figure 1Model of Hepatitis B virus disease progress and consequence

Figure 2: Cost-effectiveness increasing Hepatitis B vaccination coverage

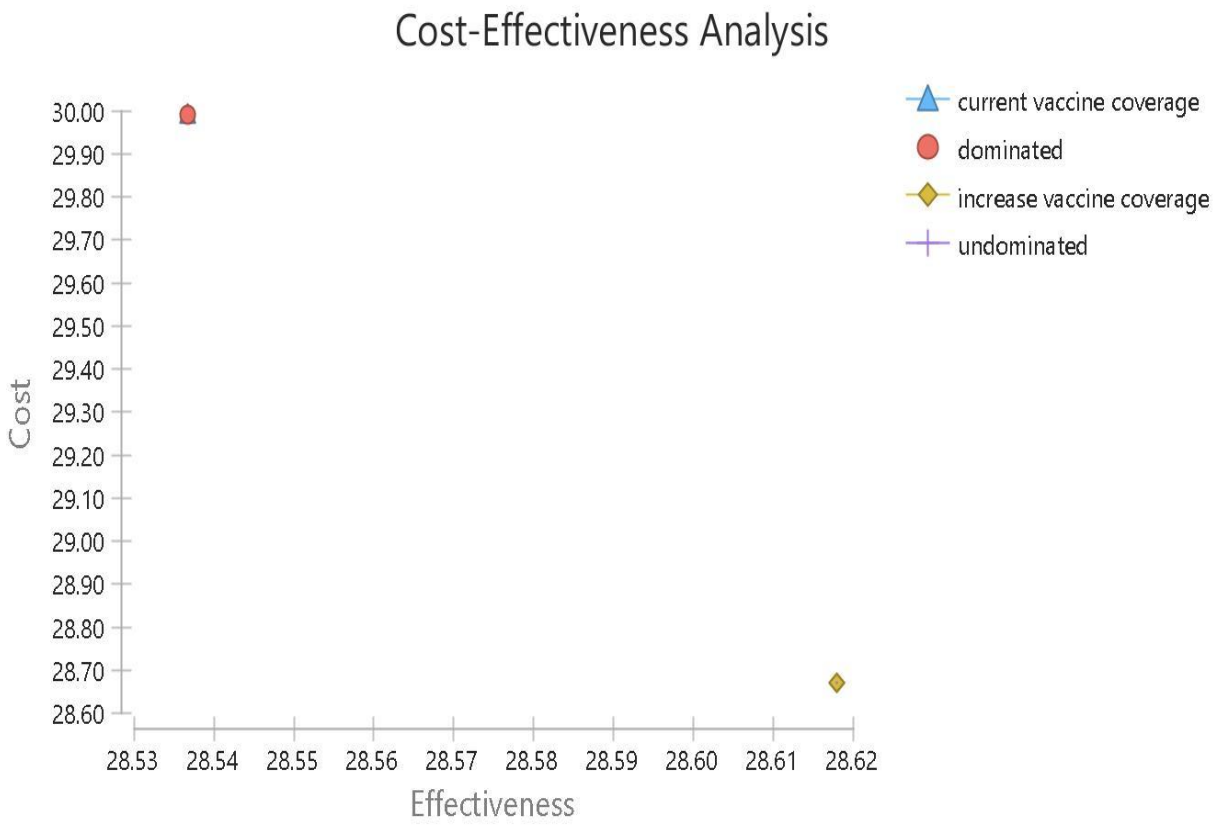


Figure: The two-way sensitivity analysis

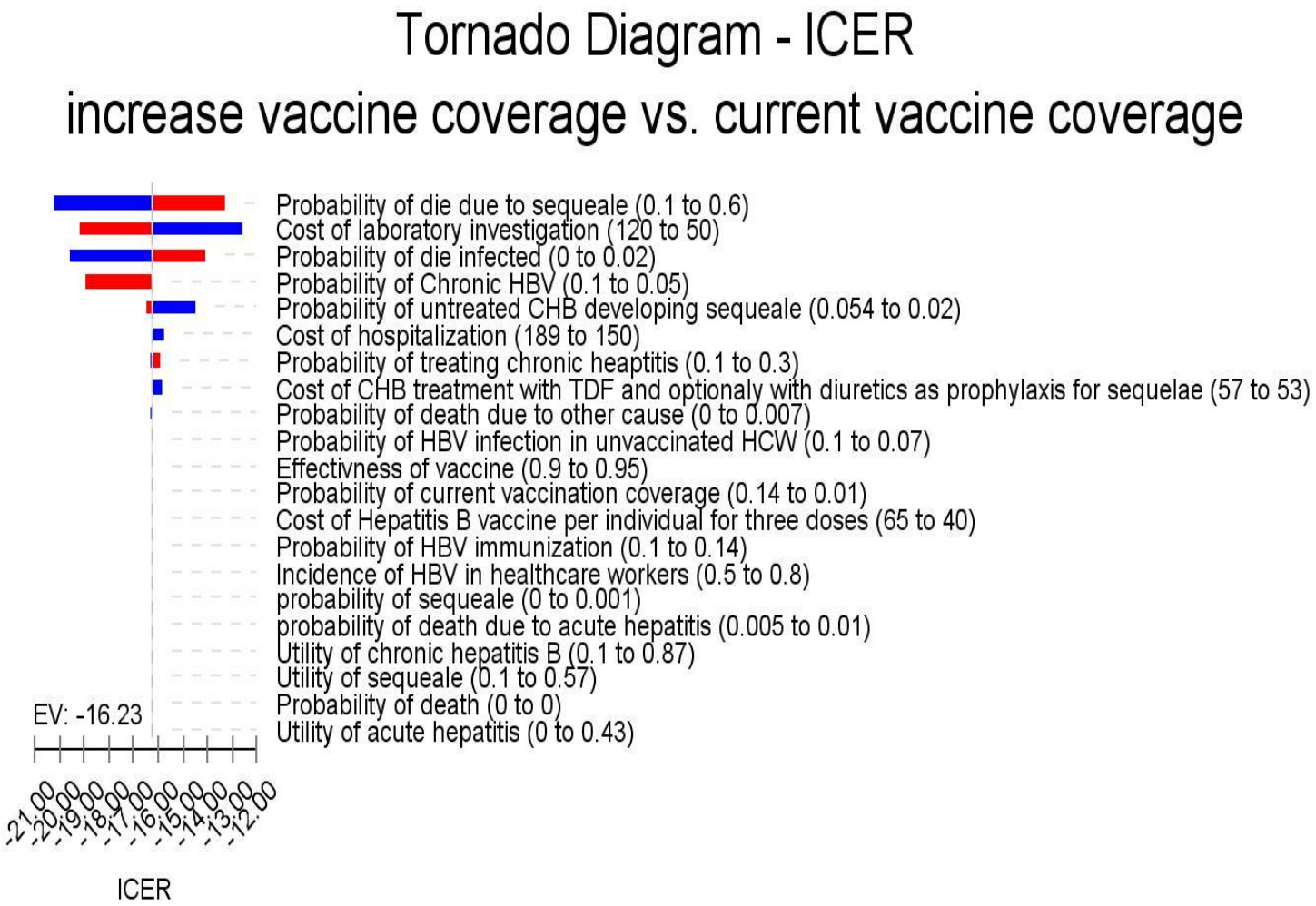
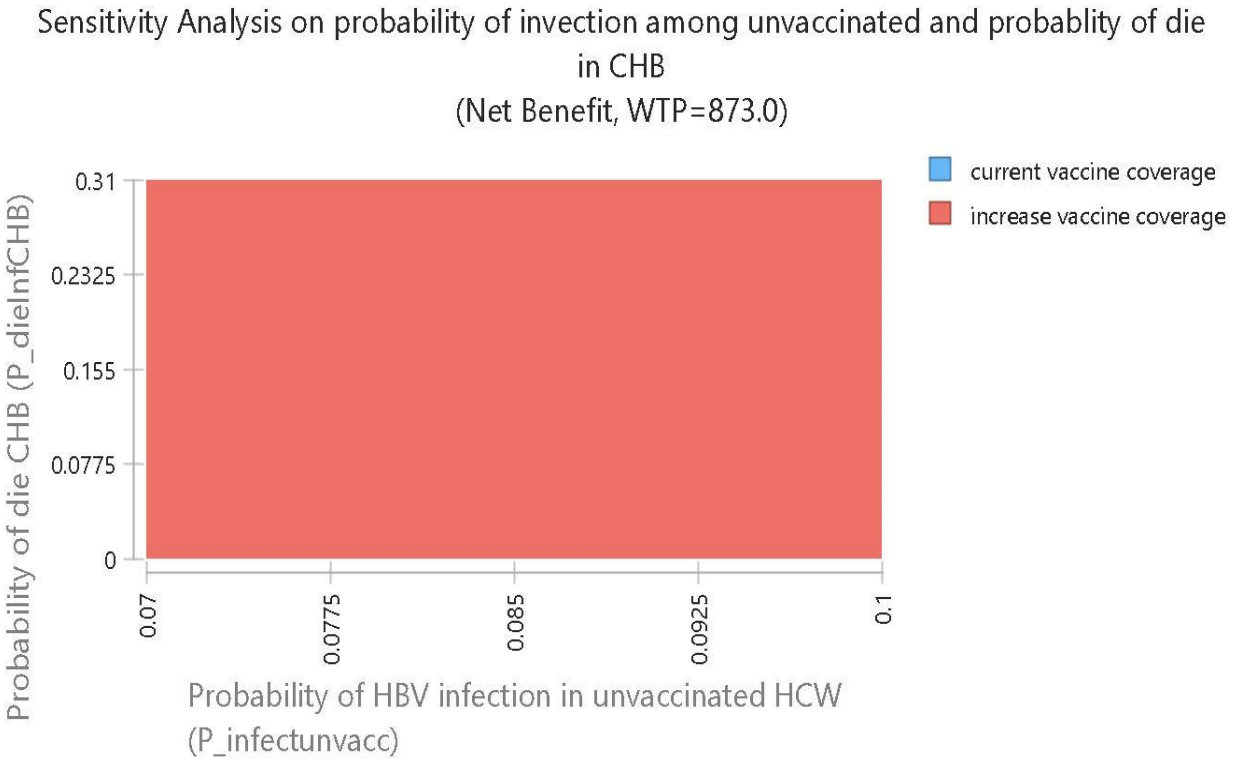


Figure 4: Two-way sensitivity analysis of death in CHB vs infection unvaccinated



Cost-Utility; Hepatitis B virus prevalence; Hepatitis B vaccination coverage; Healthcare Workforce; Ethiopia

Table legends

Table 1: Various probability estimation of Hepatitis B disease progression obtained from published follow-up studies.

Health event incidence/transition	Probability	Range	Data source
Incidence of hepatitis B infection without vaccination among healthcare workers	0.05	0.4-0.8	15
The transition of acute hepatitis B to chronic hepatitis B	0.05	0.05-0.1	5
Progression of Untreated hepatitis B to sequelae (cirrhosis, HCC)	0.05	0.02-0.054	4
Death due to hepatitis B infection	0.0106	0-0.0106	
Incidence of sequelae chronic following hepatitis B treatment	0.0175	0.017-0.022	1,5
Death due to Hepatitis B complication	0.2	0.15-0.25	16
Utility of chronic hepatitis B	0.87	--	14
Utility of sequalae hepatitis B	0.57	--	
Utility of acute hepatitis B	0.43	--	

Table 2: Estimated individual annual hepatitis B vaccination cost vs hepatitis B disease management cost

Service	List of items consumed/ service provided	Cost per each service delivery	Total cost per year
Vaccination	Hepatitis B, glove, syringe	US$ 19	US$ 57
Hepatitis B treatment	TDF 300mg daily +/- diuretics	US$ 0.147	US$ 57
Laboratory investigation	HBsAg ALT, AST, INR, BUN, Albumin, Creatinine	US$ 22.14	US$ 88.56
Hospitalization cost	Symptomatic treatment and bed admission	US$ 9	US$ 189

Table 3: Method summary

Disease	Hepatitis B
Population	Healthcare workforce
Intervention	Increasing vaccination
Comparators	Current vaccination
Outcome	Disease prevented, QALY gained, Cost
Perspective	Health care payer
Time horizon	Lifetime
Discounting	3%
Sensitivity analysis	Deterministic Sensitivity analysis
Type of model	Markov modeling

Table 4: Base case results from cost-effectiveness analysis of Expanding Hepatitis B vaccination coverage versus Current vaccination coverage (June 2019)

Strategy	Cost	Life Years	ICER	NMB	C/E
Expanding Hep B vaccination coverage	28.67	28.62	----	24,954.85	1
Current He B vaccination coverage	29.99	28.54	-16.23	24,882.53	1.05

Figures

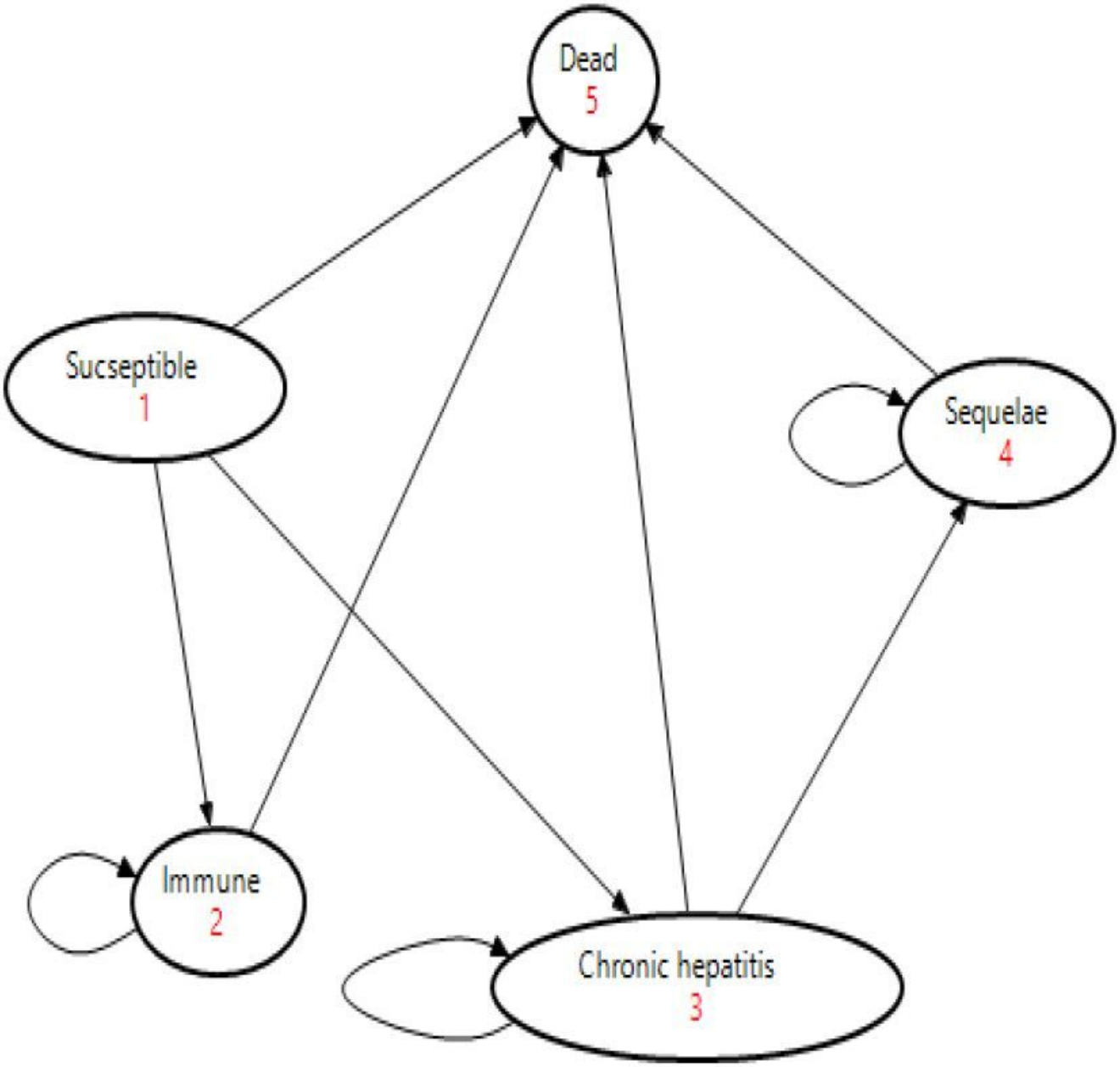


Figure 1

Model of Hepatitis B virus disease progress and consequence

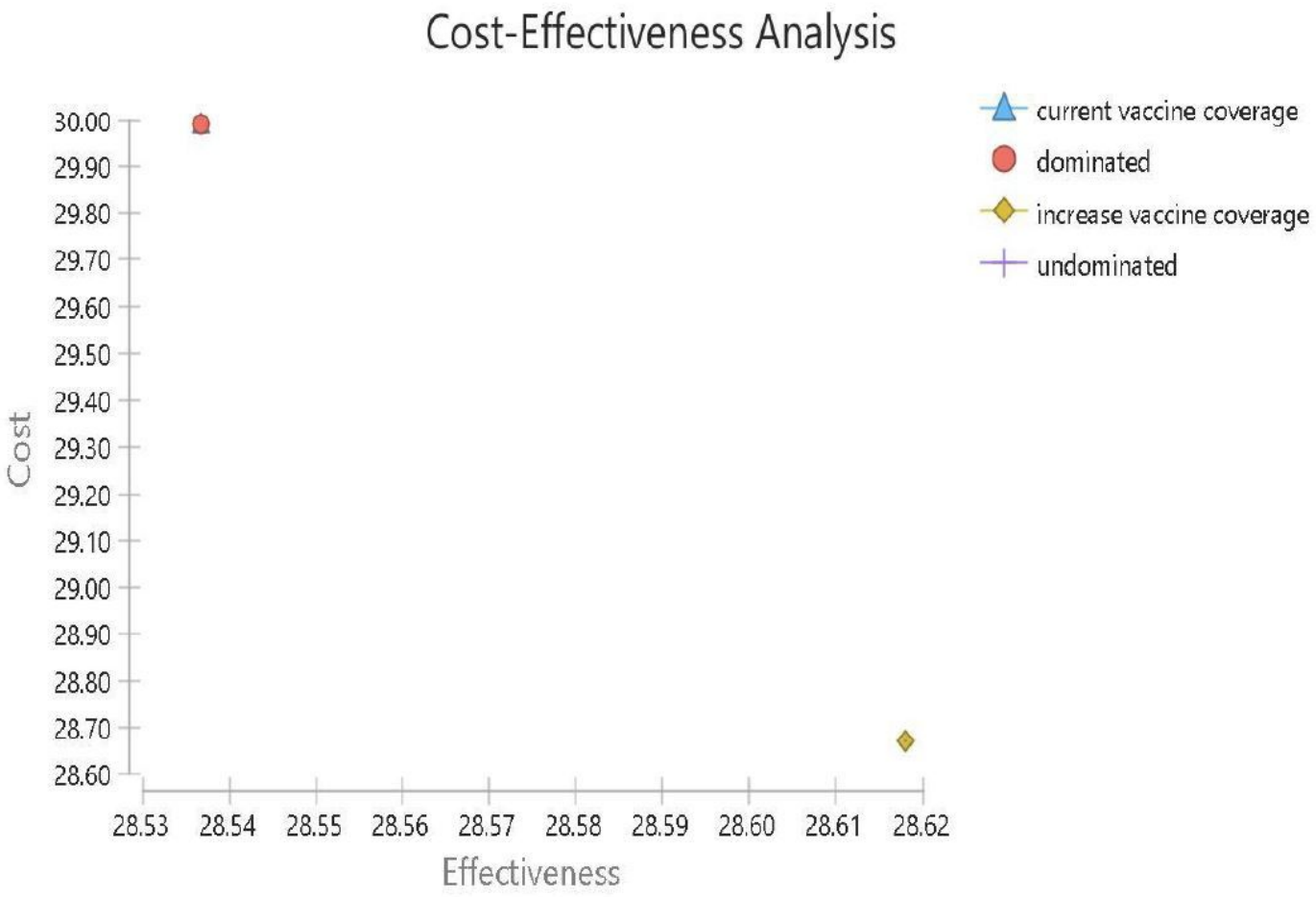


Figure 2

Cost-effectiveness increasing Hepatitis B vaccination coverage

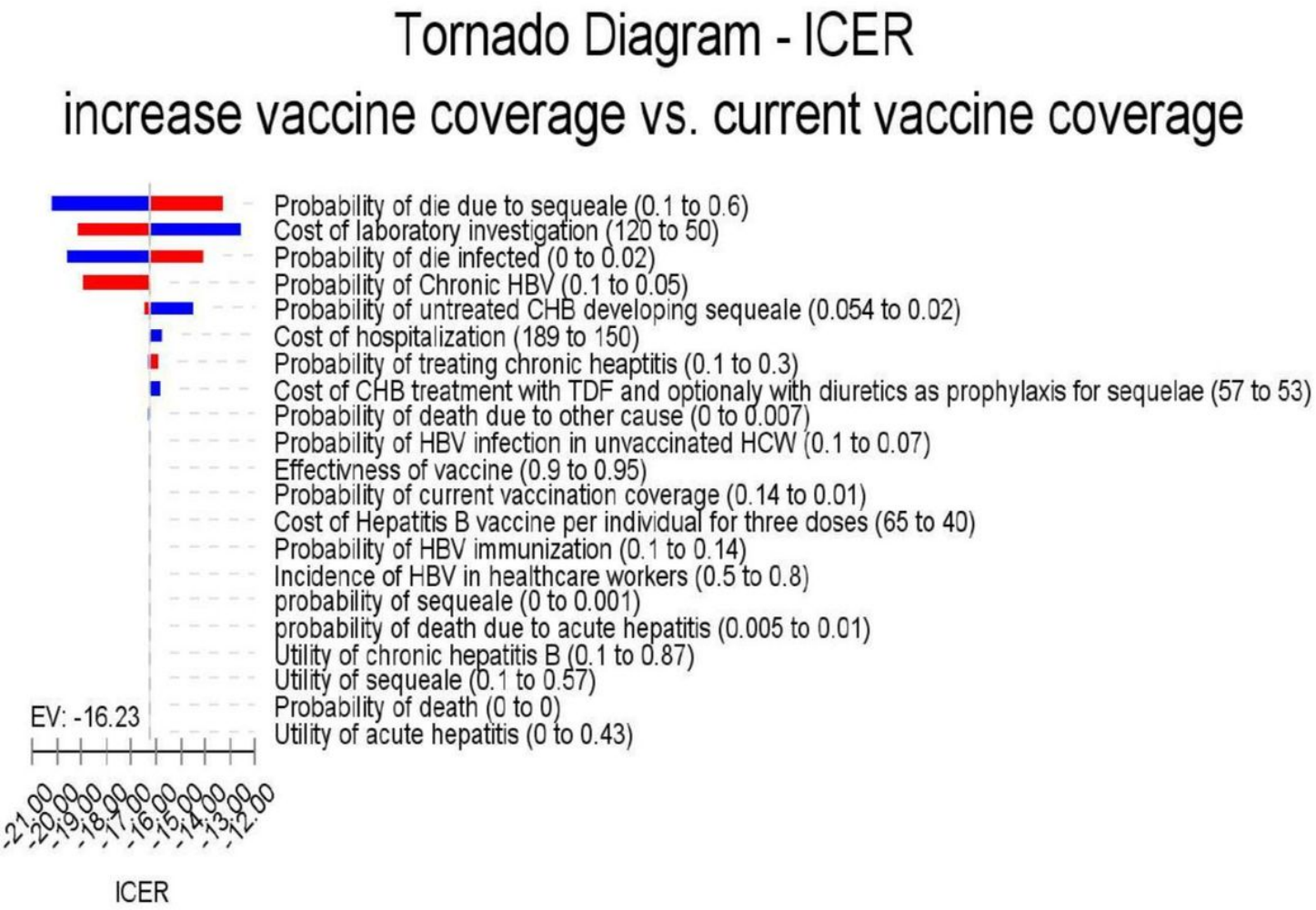
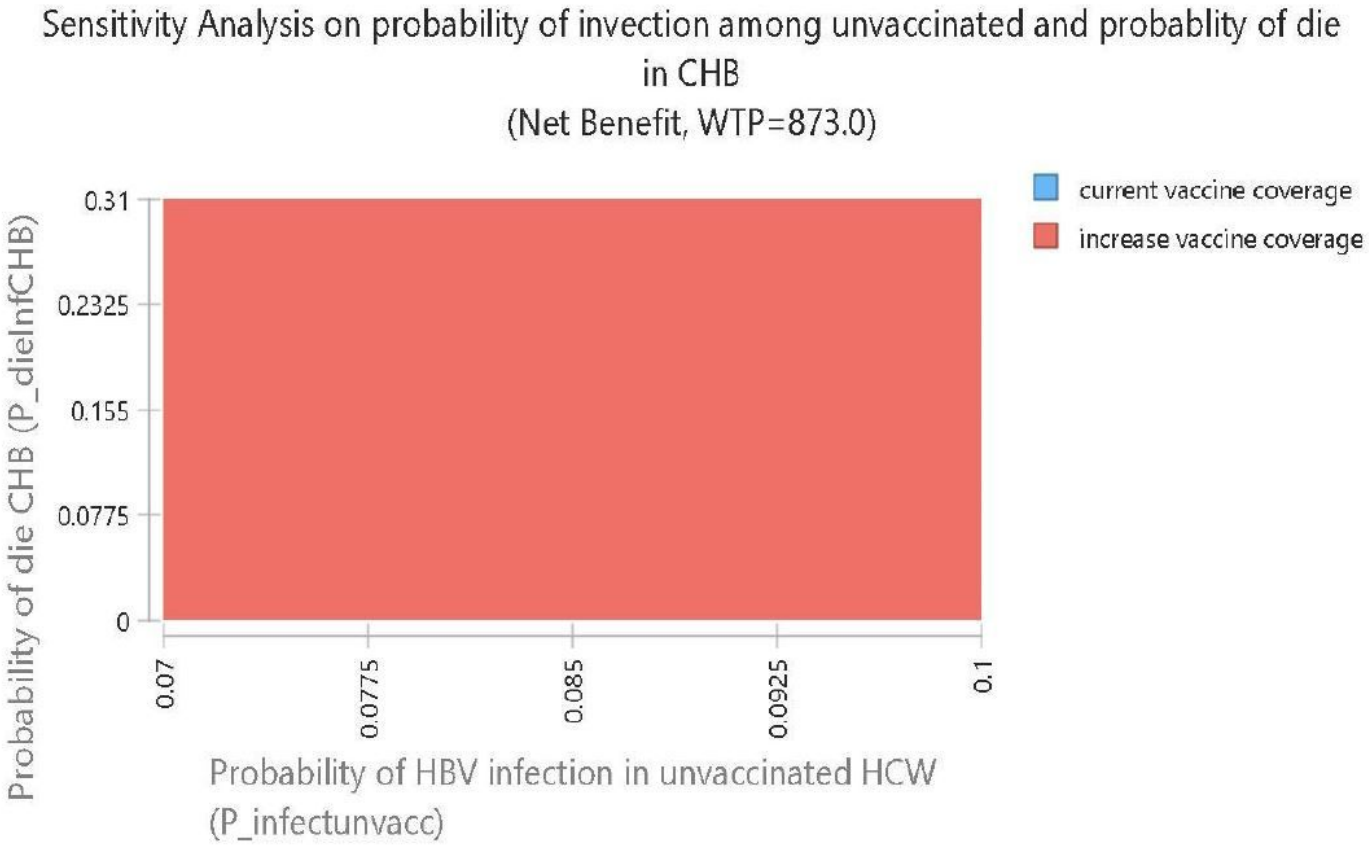


Figure 3

The two-way sensitivity analysis



Cost-Utility; Hepatitis B virus prevalence; Hepatitis B vaccination coverage; Healthcare Workforce; Ethiopia

Figure 4

Two-way sensitivity analysis of death in CHB vs infection unvaccinated