Economic Evaluation of the WHO Elimination Strategy for Hepatitis B for the Philippines

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ABSTRACT

Background. The World Health Organization (WHO) estimates that in 2015, approximately 325 million or 4.4% of the global population were living with chronic hepatitis B or hepatitis C infection. In the same year, around 1.34 million died from this disease.

Objectives. This study aimed to estimate the burden of hepatitis B in the Philippines and to determine the cost-effectiveness of possible interventions.

Methods. This study utilized the Center for Disease Analysis Foundation's (CDAF's) mathematical disease burden model of hepatitis B. Model inputs were collected using literature review, key informant interviews, expert panel interviews, and records review, and were validated through a series of round table discussions with experts.

Results. Results show that in 2017, the prevalence of chronic hepatitis B infection in the Philippines was 9.7%, equivalent to 10 million infected individuals. Although the model projects a decreasing trend in chronic hepatitis B virus (HBV) infections, liver-related mortality and morbidity due to these viruses are expected to rise if the status quo is maintained. Results show that substantial increase in government subsidy for WHO elimination scenarios would be required to achieve cost-effective outcomes.

Conclusion. Hepatitis B remains a huge problem in the Philippines. The HBV modelling exercise reveal that it will be worthwhile and cost-effective to adhere to the WHO elimination targets. A substantial financial investment will be necessary to do so, specifically a significant scale up in the screening, diagnosis, treatment, and monitoring of patients with HBV. While this modelling exercise does not yield burden of disease as accurate as a prevalence survey, experts consulted in the round table discussions agreed with the modelling inputs.

Keywords: Hepatitis B, cost-effectiveness, Philippines, burden of disease

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INTRODUCTION

In 2015, approximately 325 million or 4.4% of the global population were living with chronic hepatitis B or hepatitis C infection and around 1.34 million died from this disease.[1] Currently, the burden of viral hepatitis (VH) infection worldwide is growing. From 1990 to 2013, VH infection mortality increased by 63% and disability adjusted life years (DALY) lost increased by 34%.[2]

Hepatitis B virus (HBV) and hepatitis C virus (HCV) account for 96% of all VH infection mortality, due to these viruses' ability to develop chronic infections resulting to cirrhosis and hepatocellular carcinoma (HCC).[2]

Geographically, the distribution of the burden of hepatitis B infection is unequal. Among World Health Organization (WHO) Member States, HBV infection prevalence is highest

in the Western Pacific Region with 115 million people living with the disease followed by Africa with 60 Million.[1]

Estimates showed 16.7% of adult Filipinos were chronically infected with HBV in 2003 – this rate was more than double the 8% average prevalence rate of HBV infection in the Western Pacific Region.[3] Furthermore, data from the Department of Health Philippine Integrated Disease Surveillance and Response (DOH PIDSR) from 2012-2015 estimated a case fatality rate (CFR) of 0.82% to 1.29% for hepatitis B infection.[4]

Acknowledging the growing problem of VH, the United Nations (UN) included combating hepatitis as one of the goals in the 2030 Agenda for Sustainable Development.[5] To meet this goal, the WHO established the Global Hepatitis Program. Through this, the Regional Action Plan for Viral Hepatitis in the Western Pacific (RAPVH) and the Global Health Sector Strategy for Viral Hepatitis (GHSSVH) were developed and the following concrete targets were set: 90% reduction in new cases of HBV infection by 2030 (20% reduction by 2020) compared with 2015; 65% reduction in liver-related deaths by 2030 (10% by 2020), and 90% of all chronic infections diagnosed by 2030 (50% by 2020).[1,6]

To inform policy makers in the crafting of its policies and guidelines to achieve this goal, a burden of disease study on VH is urgently needed. Unfortunately, Philippine HBV and HCV prevalence data have not been updated, and the populations of these studies were often isolated to certain risk groups, regions, and facilities. It is thus not a surprise, that the burden of VH in the Philippines remains largely unknown. Modeling will allow prediction of the long-term influence of detection rates, and anti-viral treatments on VH disease burden. Estimates from the model will allow policy makers to know the extent of the VH problem, design appropriate public health programs, and monitor and evaluate the program's accomplishment vis-à-vis the RAPVH and GHSSVH.

OBJECTIVES

The aim of this study was to estimate the burden of hepatitis B infection in the Philippines using modeling and to determine the cost-effectiveness of various intervention strategies to achieve the WHO 2030 GHSSVH Targets for HBV.

The specific objectives were:

1. To model the HBV disease burden in the Philippines using the Center for Disease Analysis Foundation HBV disease burden model using Philippine-specific data as inputs.
2. To identify intervention strategies that achieve the WHO 2030 GHSSVH Targets for HBV burden and their corresponding financing modes
3. To determine the Incremental Cost-Effectiveness Ratio (ICER) of the identified interventions from the public payer's and societal perspective
4. To validate the inputs and the model results
5. To identify how HBV patients acquire health service including medications from both the private and public sectors

METHODS

This study utilized the Markov-based disease burden model for hepatitis B developed by Center for Disease Analysis Foundation (CDAF). CDAF is a nonprofit public health research firm with expertise in epidemiology and disease burden modeling. CDAF is known for their work on complex and poorly understood diseases and is a leading source of epidemiological data for hepatitis B in the world.[7]

Model inputs were collected using literature review, records review from various government agencies, key informant interviews (KIIs), and consultation with experts through several round table discussions (RTDs). Model results were subjected to one-way sensitivity analysis (OSA) and probabilistic sensitivity analysis (PSA) to estimate the effect of uncertainty. Local epidemiologic and economic cost data were used to populate the model. In the absence of local data, analogue country data were used as substitute.

The prevalence of HBV infection, its morbidity and mortality, the costs and health outcomes of each scenario or strategy, and the cost per DALY of the assumed intervention strategies relative to the base case were calculated. Time horizon used was from 2015 until 2030.

This study obtained ethical clearance from the University of the Philippines Manila Research Ethics Board (UPMREB). The duration of the study was from June 2017 to October 2018.

Study Population and Study Sites

Purposively-selected HBV patients and their relatives were recruited for a KII to garner the inpatient, outpatient, and medication cost and patient co-payment using a uniform interview tool. They were asked to identify how they acquire health service (including medications) from both the private and public sectors. Assistance from known physicians who handle HBV patients (i.e., gastroenterologists, hepatologists) and the Yellow Warriors Society Philippines, Inc. (YWSP) – a nationwide, community-based, voluntary non-government organization (NGO) dedicated to VH advocacy, were sought for the recruitment of respondents.

Cost-of-care related parameters were gathered from secondary data sources such as hospitalization benefits claims from the Philippine Health Insurance Corporation (PhilHealth) for inpatient costs. The prices of diagnostics and medications were obtained through a mail survey of purposively-selected public and private health facilities from Luzon, NCR, Visayas, and Mindanao. Overall, the study team obtained responses from one public and three private health facilities in Luzon, two public and two private health facilities in NCR, two public and two private health facilities in Visayas, and one private health facility in Mindanao.

To validate model inputs and results, known experts (i.e., gastroenterologists, hepatologists) on hepatitis B were consulted through a series of RTDs. Experts from Luzon, NCR, Visayas, and Mindanao were invited through the assistance of the Hepatology Society of the Philippines (HSP). RTDs took place in Dagupan City, Quezon City, Cebu City, and Davao City during the month of April 2018.

Overall, the models for HBV were ran three times by CDAF. The first run was conducted before this study's protocol was developed by selected members of the study team who worked closely with the Department of Health – Epidemiology Bureau (DOH EB). The second run was done during this study's progress. Inputs and results of the second run were validated through the abovementioned RTDs with experts. Lastly, the third run incorporated all the applicable inputs from the expert RTDs.

Model Structure

CDAF's HBV compartmental, deterministic, and dynamic disease burden model quantifies the HBV-infected population by year, health state, sex, and age. The Markov-based progression model is built in Microsoft Excel and Microsoft Visual Basic.

The model follows the transmission of HBV both horizontally and vertically using mother-to-child transmission rates. The model tracks individuals in the susceptible population as they age and progress through the different stages of the disease. Each disease stage is further divided into treatment status (treated, untreated, or treatment non-responders), HBV DNA levels (high or low viral load based on a cut-off of 20,000 IU), and vaccination status (Figure 1).

Philippine Specific Epidemiological Input Parameters

HBsAg prevalence by age and sex was taken from Wong et al., which collected 2,150 serum samples from the 2003 National Nutrition and Health Survey (NNHeS) participants aged 20 and above giving a computed prevalence of hepatitis B surface antigen (HBsAg) positive adults in the Philippines of 16.7% (95%CI: 14.3%-19.1%)[3] (Table 1). The prevalence among the pediatric age group per sex was estimated from Malaysian analogue studies; while the prevalence of hepatitis B e antigen (HBeAg) positive (23.91%) and HBsAg positive (9.6%) among women of child bearing age were taken from Taguba et al.[8] In addition, Wiseman et al. computed the prevalence of HBeAg negative and HBeAg positive women of child bearing with high viral load to be at 13% and 90%, respectively.[9] Experts during the RTD agreed to apply these values to the Philippine setting. Epidemiological input parameters are summarized in Table 2.

The total number of patients assumed to have been previously diagnosed with HBV was estimated at 260,000 (16% of total infections) in 2015. This was based on average diagnosis rate in Southeast Asian countries and according to experts during the RTD.

The number of annually diagnosed patients through sentinel surveillance sites (either hospitals or laboratories) was 47,000.[10] However, experts consulted during the RTD commented that even the 47,000 might be an overestimate since there are no means of determining duplicate data set from the sentinel sites. Experts estimated an average of 21.25% of patients would have tests taken more than once either due to their attending physician's request or borne from their own

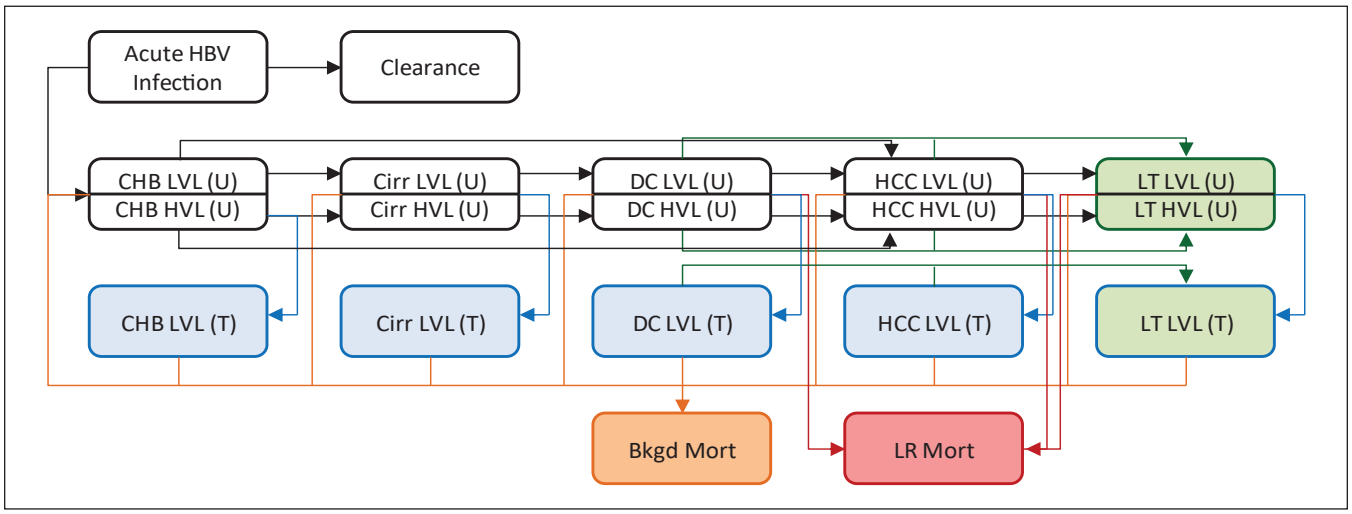

Figure 1. Flow of disease progression of HBV.

HBV – hepatitis B virus, CHB – chronic hepatitis B, Cirr – compensated cirrhosis, DC – decompensated cirrhosis, HCC – hepatocellular carcinoma, LT – liver transplant, LVL – low viral load, HVL – high viral load, U – untreated/non-responder, T – treatment responder, Bkgd Mort – background mortality, LR Mort – liver-related mortality.

black arrows – disease progression, orange arrows – background mortality, red arrows – liver-related mortality, blue arrows – treatment response, green arrows – transplantation.

Table 1. Hepatitis B Surface Antigen (HBsAg) Prevalence by Age and Sex

Age	Estimate (%)*	
	Male	Female
0-4	4.85	4.82
5-9	5.44	5.49
10-14	9.99	9.26
15-19	18.59	16.02
20-24	19.50	16.60
25-29	19.50	16.60
30-34	20.20	14.90
35-39	20.20	14.90
40-44	12.40	18.20
45-49	13.40	18.20
50-54	19.50	16.60
55-59	20.20	14.90
60-64	20.20	14.90
65-69	12.40	18.20
70-74	13.40	18.20
75-79	12.40	14.40
80-84	12.40	14.40
85+	12.40	14.40

**2003 National Nutrition and Health Survey (NNHeS)*

Table 2. Epidemiological Input Parameters

Parameter	Estimate	Source
Total patients diagnosed in 2015 (n)	260,000	RTD with experts
Annually diagnosed patients (n)	38,763	(10)
Total patients treated per year (n)		Pharmaceutical sales data, RTD with experts
2014	3,443	
2015	2,756	
2016	3,423	
2017	4,058	
Patients initiating treatment annually	1,200	RTD with experts
Total liver transplants per year (n)		Personal communication, RTD with experts
1988	1	
1989	0	
1990	1	
1991	2	
1992	2	
1993	0	
1994	0	
1995	0	
1996	0	
1997	0	
1998	0	
1999	0	
2000	2	
2001	1	
2002	3	
2003	1	
2004	1	
2005	2	
2006	1	
2007	2	
2008	1	
2009	2	
2010	0	
2011	2	
2012	2	
2013	0	
2014	7	
2015	3	
2016	5	
2017	4	
Liver transplants attributable to HBV n (%)	14 (41)	Philippine Network for Organ Sharing, RTD with experts *(Caveat: not all patients may have been operated on)*
Prevention of perinatal transmission (birth dose alone and Hep B3) (%)		Data from DOH, administrative data, surveys, RTD with experts
HepBB		
2016	56	
2015	59	
HepB3		
2015	60	
2016	91	
Women of child bearing age with high viral load of ≥20,000 IU/mL (%)		(9), RTD with experts
HBeAg-	13%	
HBeAg+	90%	

HBV – hepatitis B virus, HepBB – hepatitis B vaccine dose at birth, HepB3 – completed 3 doses of hepatitis B vaccine, HBeAg – Hepatitis B e Antigen

accord. The recomputed total annually diagnosed patients was at 38,763 after considering the estimated duplicate tests.

Total treated annually was computed based on the units of antiviral drugs sold from pharmaceutical sales data in the country from 2014 to 2017. The total number initiating treatment was estimated at 1,200 patients annually after experts decided that the best approximation would be to multiply the number of gastroenterologists in the country with the average number of patients initiated for HBV treatment by each gastroenterologist. Based on their approximations, 400 gastroenterologists in the country would initiate treatment for three patients.

The estimated total number of liver transplants per year was estimated based on personal communication with a local liver transplant expert which the experts agreed on during the RTD. Liver transplants attributable to HBV was estimated based on the number of patients and their diagnosis enlisted for a liver transplant from the Philippine Network for Organ Sharing of the DOH. However, the caveat of using this data is that the patient may not have proceeded to actual transplant, but nonetheless, this is the closest local data that the experts agreed upon.

The estimated value for the prevention of perinatal transmission (birth dose and Hep B3) were taken from the WHO – United Nations Children's Fund (UNICEF) estimates of national immunization coverage for the Philippines, defined as, "percentage of births which received a dose of hepatitis B vaccine within 24 hours of delivery."[11] Estimates were computed from data by the DOH, administrative data, and surveys if they exist (Table 3). The WHO and UNICEF estimates were used for the first model run. However, upon discussing the values for HepBB and HepB3 with members of the Department of Health, they suggested to use official government estimates. This was then utilized for the second application of the model and was presented to the experts during all the RTDs. The experts agreed to use the official values for the third run, 56% for 2015 and 59% for 2016 for birth dose alone, and 60% for 2015 and 91% for 2016 for HepB3.

Model Arms

The RTDs yielded four scenarios for modeling. These scenarios are treated as arms within the model structure so that they may be compared to each other. These scenarios are:

A. Base Case Scenario (Status Quo)
B. WHO elimination Strategy (which assumes 48% government subsidy)
C. WHO elimination Strategy with 90% government subsidy
D. WHO elimination Strategy with 90% government subsidy plus DNA testing using GeneXpert

Economic Parameters

Diagnostic costs were estimated from price data of 12 health facilities and one private diagnostic laboratory (Table 4). The mean values were computed after price outliers were excluded from the sole semi-private hospital for the cost of HBsAg, HBeAg, alanine transaminase (ALT), and HBV DNA. Results of the price survey were then presented in RTDs, and majority of the experts agreed that the mean prices collected were close to the prices of diagnostics of their respective hospitals.

The screening and initial evaluation costs were also estimated from price data of health facilities. The annual outpatient costs were computed based on the laboratory tests and professional fees during follow-up. The frequency of

Table 3. Hepatitis B Vaccine Birth Dose Estimates (2015 and 2016)

Data Sources	HepBB		HepB3	
	2015	2016	2015	2016
Estimate	56%	59%	60%	86%
[a]***Official***	56%	59%	60%	91%
[b]***Administrative***	51%	54%	55%	86%
[c]***Survey***	NA	NA	NA	NA

[a] *Estimated coverage reported by national authorities that reflects their assessment of the most likely coverage based on any combination of administrative coverage, survey-based estimates or other data sources or adjustments.*

[b] *Reported by national authorities and based on aggregated administrative reports from health service providers on the number of vaccinations administered during a given period (numerator data) and reported target population data (denominator data)*

[c] *Based on estimated coverage from population-based household surveys among children aged 12-23 months or 24-35 months following a review of survey methods and results. Information is based on the combination of vaccination history from documented evidence or caregiver recall.*

Table 4. Hepatitis B Diagnostic Costs (Mean Price in PhP of 12 Purposively-selected Health Facilities)

Diagnostic Costs	Public			Private		
	n	Mean	SD	n	Mean	SD
HBsAg	4	215.25	52.63	8	734.65	489.90
HBeAg	2	386.50	153.44	8	1,011.03	429.00
HBV DNA	1	4,950.00	–	4	5,337.50	776.07
ALT	5	176.00	96.07	8	347.93	224.77

tests and professional fees were estimated during the RTD with experts. The costs were computed based on type of health facility the patient is consulting (public versus private) and which practice guideline is being used by the attending physician (current practice consensus from experts versus WHO treatment guidelines).

The average HBV-specific medication costs were estimated during the RTD. Experts suggested to include only the medications that are recommended by the WHO as first line. Thus, sales data of Tenofovir and Entecavir were requested from distributors. Upon analyzing data from four brands available in the market, it was found that Tenofovir accounted for 54% of the treatment, while Entecavir accounted for the remaining 46%. This proportion multiplied with the market retail price of Tenofovir (PhP 50.00) and Entecavir (PhP 266.00) and considering the assumption that patients are expected to take one tablet daily for the whole year, results to a total HBV medication cost of PhP 54,516.40 annually per patient. Since the government does not procure nor provide free treatment to HBV patients, medication costs are equal for both patients seeking care in public and private health facilities.

Integrating diagnostic cost and professional fee incurred every follow-up visit, and HBV-specific medication cost, the total annual public treatment cost for HBV in the Philippines is PhP 67,973.96 while the total private treatment cost is PhP 73,909.14. Using the frequency of diagnostics and follow-up of WHO guidelines, and integrating the cost of treatment, the total annual public treatment cost for HBV in the Philippines is PhP 61,743.51 while the total private treatment cost is PhP 64,837.47.

Current annual health care costs (excluding HBV-specific medication costs) were estimated per stage of the disease and per type of health facility visited (Table 5). The estimates were based on KIIs with patients, PhilHealth data, hospital survey, and RTDs with experts. Inpatient costs were estimated from the PhilHealth database using International Classification of Diseases 10th edition (ICD-10) and Relative Value Scale (RVS) codes per disease stage. Medication costs were estimated based on the consensus of experts on the usual medications given to patients undergoing the three different disease stages. The list of medications and their usual dose per year were then multiplied by the average retail prices from four public pharmacies and the country's largest pharmacy chain.

The cost of prevention of perinatal transmission includes HBV Vaccine (1 dose), HBIG, and Antiviral Treatment for HBsAg positive pregnant women. Public sector cost of HBV Vaccine (1 dose) was based on the government procurement price of PhP 8.00. On the other hand, the private cost of the vaccine was assumed to be the mean value of the prices at which private practitioners procure vaccines from distributors which equals to PhP 593.67.

There is no price for hepatitis B immune globulin (HBIG) in the public sector since the government does not procure HBIG and is not regularly utilized in the public setting. For the private sector, HBIG cost is assumed equal to the price from the country's largest pharmacy chain amounting to PhP 1,050.00.

Usually, there is no antiviral treatment prescribed for mothers who are positive for HBV in the country. However, it has been the practice of several private physicians to prescribe Tenofovir to mothers with high viral load on the third trimester up to three months post-partum.[11] Given that treatment of Tenofovir (PhP 50.00) is given once daily from the first day of the third trimester up to the last day of three months post-partum (30 days/month), the cost of complete treatment for the private sector would amount to around PhP 9,000.00. On the other hand, there is no price applicable for public providers since the government currently does not procure Tenofovir for hepatitis B.

Ethical Considerations

While this study did not involve human subjects directly, ethical considerations related to data privacy and assumptions in modelling were taken into account. Data sources,

Table 5. Current Annual Health Care Costs (PhP)

Annual Cost per Diagnosed Patient	Public				Private			
	Outpatient Cost	Inpatient Cost	Medication Cost*	Patient Copay	Outpatient Cost	Inpatient Cost	Medication Cost*	Patient Copay
Chronic Hepatitis B	13,458	0	0	0	19,393	0	0	0
Chronic Hepatitis B (WHO Elimination Scenario)	7,227	0	0	0	10,321	0	0	0
Chronic Hepatitis B (WHO Elimination Scenario with GeneXpert)**	3,338	0	0	0	10,321	0	0	0
Compensated Cirrhosis	15,000	23,326	2,098	38%	50,000	47,823	2,236	70%
Decompensated Cirrhosis	30,000	39,449	40,013	52%	100,000	64,384	41,610	71%
Hepatocellular Carcinoma	40,000	48,367	45,351	67%	80,000	52,749	55,845	71%
Liver Transplant	104,000	2,000,000	27,447	97%	184,000	5,000,000	194,000	99%
Liver Transplant – Subsequent Years	60,600	0	360,000	0	194,400	0	600,000	0

**Excluding HBV-specific drugs (e.g., Tenofovir, Entecavir, etc.)*
***GeneXpert which costs much less PhP 1,061*

Table 6. Current Standard of Care Projected to beyond 2020

Year	2016	2017	2018	2019	>2020
Total Treated	3,423	3,423	3,423	3,423	3,423
Newly Diagnosed	38,700	38,700	38,700	38,700	38,700
Treated Age	20+	20+	20+	20+	20+
Treatment Eligible	All HVL	All HVL	All HVL	All HVL	All HVL

HVL – high viral load

including PhilHealth claims and administrative records, were anonymized to protect patient confidentiality. Additionally, ethical concerns regarding the assumptions made in the absence of real-world data were mitigated by validating key inputs with expert stakeholders.

RESULTS

The prevalence of HBV infection, its morbidity and mortality, the costs and health outcomes of each scenario or strategy, and the cost per DALY of the assumed intervention strategies relative to the base case were calculated. Time horizon is from 2015 until 2030.

Base Case Scenario: If there are no changes until 2030

The Base Case Scenario serves as the point of comparison to the intervention scenarios and utilized the assumptions detailed in Table 6. A total of 3,423 patients were treated with antiviral regimens in 2016 based on pharmaceutical sales data. Treatment eligibility was restricted to patients who were 20 years of age or older and were assessed to have high viral loads.

In 2017, it was estimated that the prevalence of chronic hepatitis B in the Philippines is 9.7%, representing 10 million Filipinos with chronic infections. Chronic HBV prevalence seem to peak among the adult population (Figure 2). More females than males have chronic HBV in the 50+ age group – consistent with the trend that women develop the chronic disease during the later years of their lives compared to men who probably have succumbed to the disease during their mid-adulthood.

Provided that the current practices are sustained until 2030, the prevalence of chronic hepatitis B in the Philippines is expected to drop to 7.0% or 8.7 million chronic infections by the year 2030 (Figure 3).

The 2017 perinatal prophylaxis coverage is equivalent to 59% of newborns getting a dose of HBV vaccine within 24 hours of delivery.[11] In addition, the three-dose HBV vaccine coverage for those surviving infants is 91%.[11] Assuming that these percentages remain constant, it is estimated that the prevalence of HBsAg will decrease among infants as well as among 5-year-olds. Hence, the prevalence among 5-year-olds will reach 0.5% by 2030.

Strategies to Reduce Mother to Child Transmission

The following two different scenarios representing strategies to reduce mother-to-child transmission as suggested by DOH informants were analysed:

Scenario 1 (Table 7): Building on the base case, birth dose coverage and the three-dose HBV vaccine coverage would remain at 59% and 91%, respectively, until year 2019. Beginning 2020 onwards, the coverage for both birth dose and the three-dose HBV vaccines would be 95%.

Scenario 2 (Table 8)**:** Holding all other things constant, birth dose coverage and the three-dose HBV vaccine coverage would remain at 59% and 91%, respectively, until year 2019. HBIG utilization would remain at 0% until 2019 but starting 2020, 90% of infants of HBV-infected mothers receiving the birth dose would receive HBIG. As with Scenario 1,

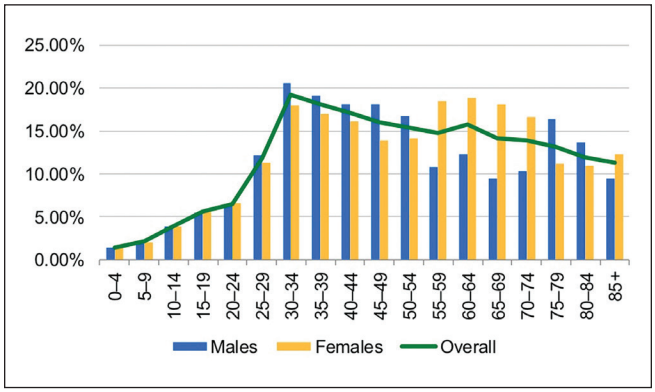

Figure 2. Projected prevalence of chronic HBV in the Philippines for 2017.

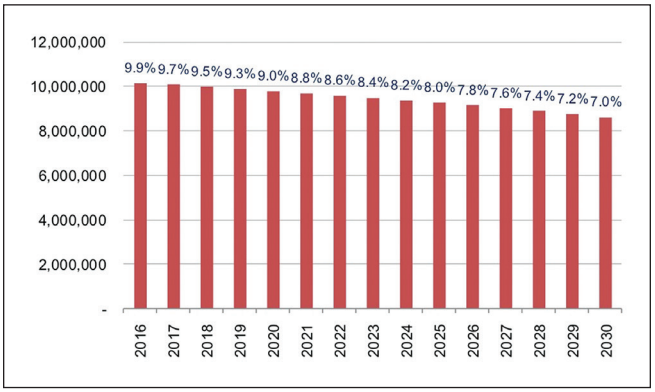

Figure 3. Projected prevalence of chronic HBV in the Philippines from 2016 to 2030 for base case scenario.

beginning 2020 onwards, the coverage for birth dose and the three-dose would be 95%.

Both scenarios would significantly reduce incidence and prevalence among 5-year-olds in 2030 where it would be 0.2% (95/95) and 0.1% (+HBIG) (Figure 4). However, the effect of vaccination programs on HBV morbidity and mortality will not be seen until several years later.

WHO Elimination Scenario

A third scenario wherein the final outcome is the achievement of the 2030 Global Health Sector Strategy (GHSS) HBV elimination targets set by the WHO. Under this scenario, the model was run to include Scenario 1 above, a treatment age of 15-year-old, and all high viral load patients were eligible for treatment. With this scenario, HBsAg prevalence will decrease by 15% (Figure 5A), and HBV-related morbidity and mortality are projected to decrease by

Table 7. Scenario 1 Parameters for Vaccination Coverage

Types of Vaccination	2017	2018	2019	2020	2022	2025
% Birthdose coverage	59%	59%	59%	95%	95%	95%
% HepB3	91%	91%	91%	95%	95%	95%

HepB3 – three doses of HBV vaccine

Table 8. Scenario 2 Parameters for Vaccination Coverage

Types of Vaccination	2017	2018	2019	2020	2022	2025
% Birthdose coverage	59%	59%	59%	95%	95%	95%
% HepB3	91%	91%	91%	95%	95%	95%
% Birthdose receiving HBIG	0%	0%	0%	90%	90%	90%

HepB3 – three doses of HBV vaccine, HBIG – hepatitis b immune globulin

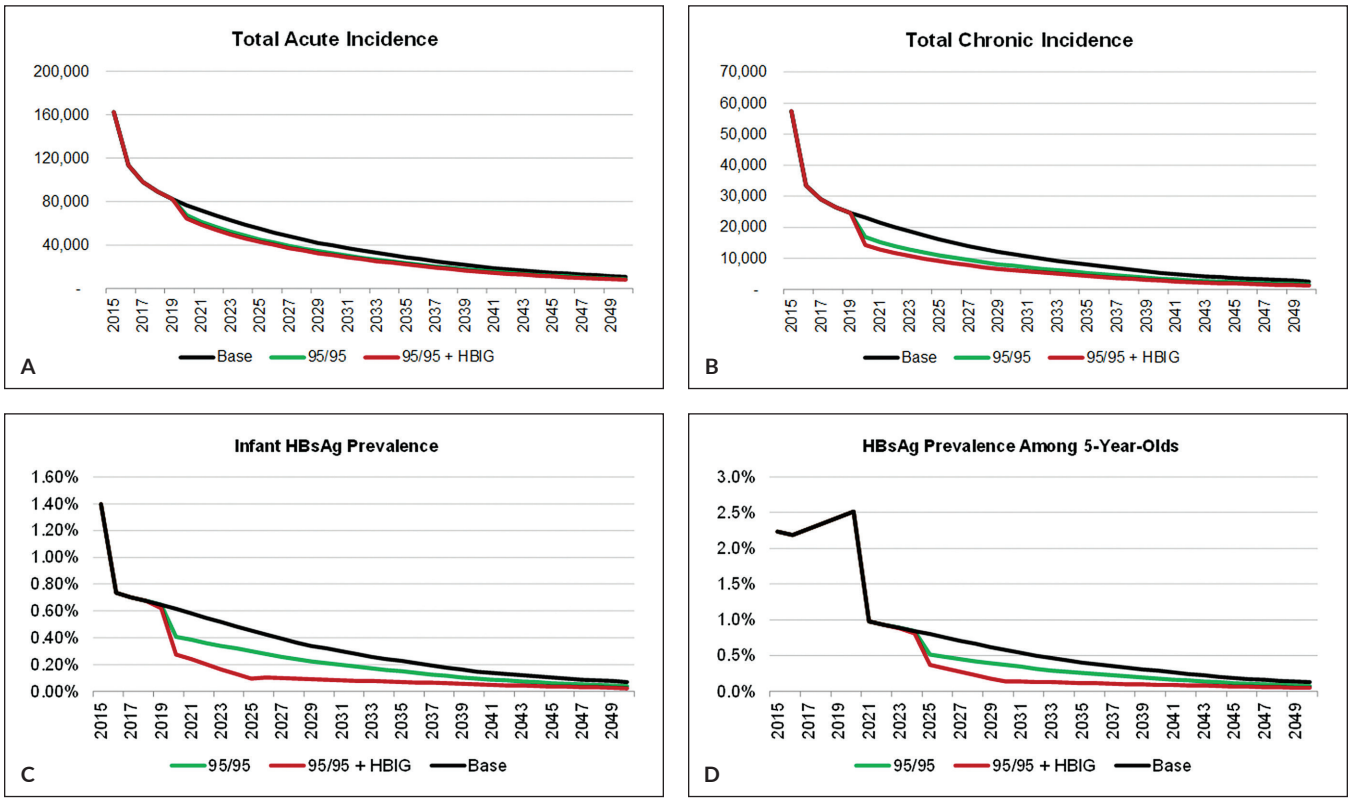

Figure 4. **(A)** Total acute incidence for the population. Base Case Scenario versus Scenario 1 versus Scenario 2. **(B)** Total chronic incidence for the population. Base Case Scenario versus Scenario 1 (95/95) versus Scenario 2 (95/95 + HBIG). **(C)** HBsAg prevalence for infants. Base Case Scenario versus Scenario 1 versus Scenario 2. **(D)** HBsAg prevalence among 5-year-olds. Base Case Scenario versus Scenario 1 versus Scenario 2.

Table 9. Total Treated and Newly Diagnosed Needed to Achieve WHO Elimination Scenario

WHO Elimination Scenario	2017	2018	2020	2021	2022	2026
Total Treated	4,058	100,000	200,000	350,000	750,000	2,800,000
Newly Diagnosed	38,700	80,000	200,000	600,000	1,400,000	1,995,000

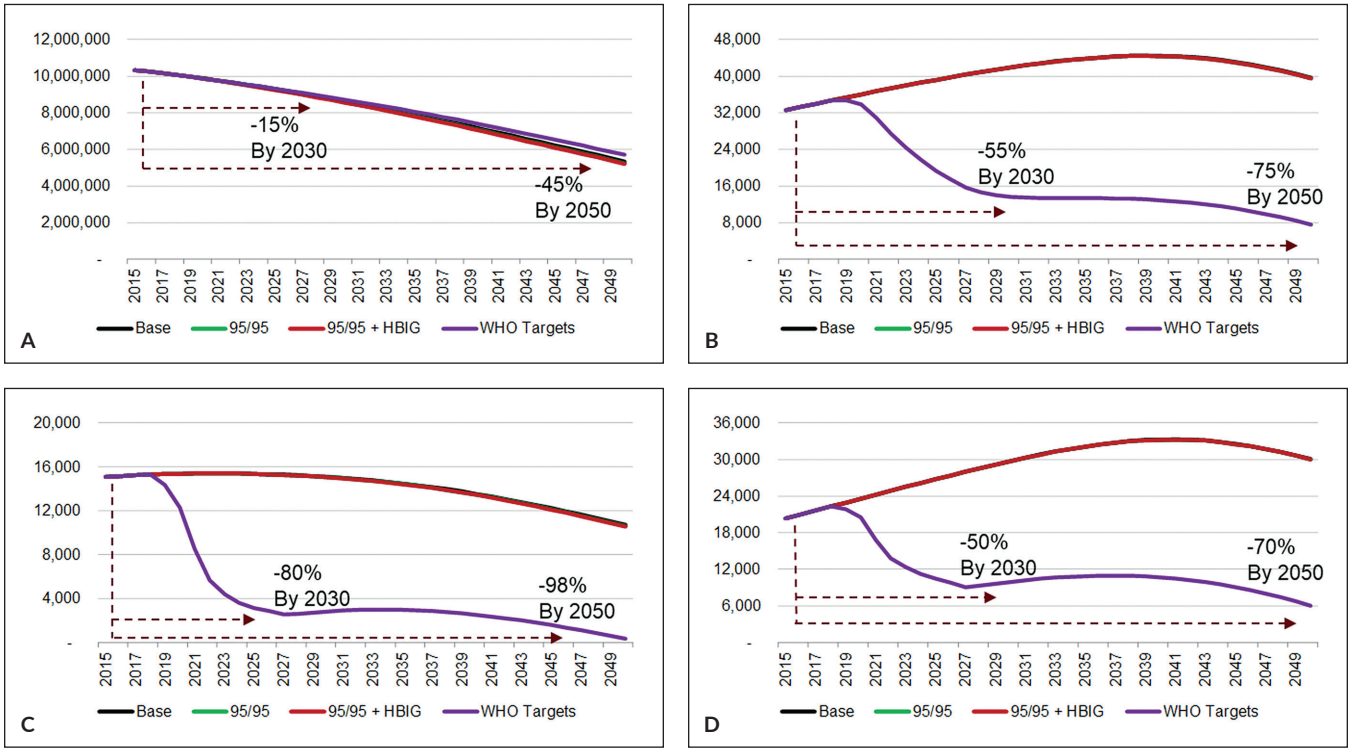

Figure 5. **(A)** Total infected with HBV. Base Case Scenario versus WHO Elimination Scenario. **(B)** Projected annual liver-related deaths. Base Case Scenario versus WHO Elimination Scenario. **(C)** Projected incidence of decompensated cirrhosis. Base Case Scenario versus WHO Elimination Scenario. **(D)** Projected incidence of HCC. Base Case Scenario versus WHO Elimination Scenario.

50% to 80% (Figures 5B to D). Patient costs differ from the base case since WHO recommended streamlined regimens. Cost of treatment using Tenofovir was assumed to cost USD 55 per annum.

To achieve these results, both the number of patients treated and the newly diagnosed must increase substantially between 2017 to 2026 (Table 9). From the 2017 value of 4,058, the total number of patients treated in 2018 should be 100,000 and thereafter increase to 2,800,000 by 2026. In addition, 38,700 of the newly diagnosed in 2017 would have to dramatically increased to 80,000 in 2019 and will eventually have to increase to 1,995,000 by 2026.

Economic Analysis

The costs to the society (meaning direct and indirect costs are combined) and health outcomes were computed for both the base case and WHO Elimination scenario. Indirect costs were measured using the DALY and the value of a statistical life year which is equal to the 2017 GDP per capita of PhP 150,654.[12] Since the WHO Elimination scenario requires more people to be diagnosed and enrolled in treatment, an investment in treatment and lab costs, and screening costs must be made relative to the base case. It is assumed that 48% of these costs are borne by the public sector - the ratio calculated based on the proportion of patients seeking treatment in public - versus private health facilities based on PhilHealth claims database.

Moreover, two other scenarios are presented: The first scenario is instead of having the public coverage assumed at 48%, the same WHO elimination scenario will have 90% of costs covered by public funds by 2024. This is called the WHO + 90% Public Scenario and represents ideal PhilHealth coverage. The second scenario is the WHO + 90% Public Scenario with a change in the price of HBV DNA testing. Since HBV DNA is a major cost for patients and with the possible availability of WHO-prequalified GeneXpert for HBV DNA in the community setting, we applied a fourth scenario wherein the GeneXpert is widely available and is used instead of HBV DNA. This is aptly referred to as WHO + 90% + GeneXpert Scenario.

Healthcare costs are expected to increase, despite savings from averted cases. Direct costs are expected to increase but will eventually decrease by 2026, while indirect costs and DALYs are expected to decrease immediately after the strategy implementation.

Under the WHO Targets scenario, cumulative costs would total to PhP 2.6 trillion by 2030 and PhP 3.9 trillion by 2050. When 90% of costs are covered by public funds, cumulative costs would total 2.1 trillion pesos by 2030 and PhP 3.6 trillion by 2050. With the use of the GeneXpert, cumulative costs would drop to PhP 1.8 trillion in 2030 and PhP 3.1 trillion in 2050. Hence, direct and indirect costs combined will generally be higher in the WHO Elimination scenario than the base case. However, when public funds are used to pay for 90% of the costs, and when GeneXpert is used, WHO Elimination scenarios yielded savings versus the base case.

The WHO Elimination scenario will be cost-effective in the societal perspective by 2027 and highly cost-effective by 2045 because cost per averted DALY is always less than 3x current GDP per capita of PhP 150,654.28 (Figure 6). When 90% of costs are covered by public funds, the WHO Targets scenarios will be cost-effective in 2021 (2020 with the use of the GeneXpert) and highly cost-effective in 2030 (2023 with GeneXpert). This implies that screening and treating more people is a worthwhile and a value-for-money investment the society must undertake.

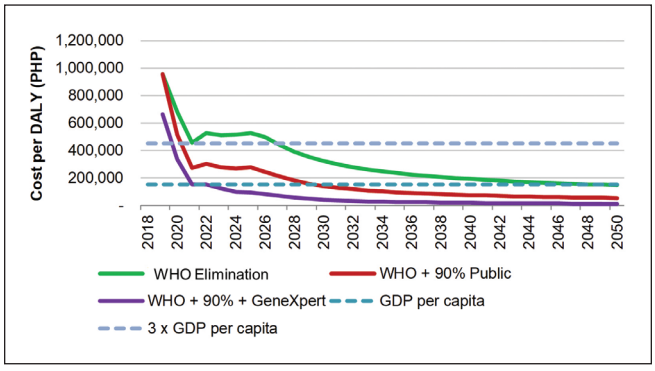

Figure 6. Cost per DALY averted (2015 to 2050) with different scenarios.

In terms of return on investment (ROI), the WHO scenario reaches a positive ROI after 2050. When 90% of costs are covered by public funds, the cumulative ROI will be positive starting in 2031. Lastly, when using the GeneXpert, cumulative ROI becomes positive in 2023.

Sensitivity Analysis

To address geographic variations in disease burden, healthcare costs, and other input parameters, one-way sensitivity analyses (OSA) using tornado diagrams and multivariate probabilistic sensitivity analyses (PSA) using scatterplots were done. This is to assess the reliability and robustness of the model and the results of the study. Tornado diagrams will identify the most influential variables by showing how changes in individual parameters will affect the outcome, while PSA examines relationships among key variables, revealing patterns and the extent of variability in the data. These analyses will provide a deeper understanding of the robustness of our results, ensuring that our conclusions remain valid across a range of plausible scenarios.

One-way sensitivity analyses results were cumulative from 2018-2030, 3.5% discount rate were applied following DOH recommendation, and were presented in tornado diagrams. For the multivariate PSA, 1,000 Monte Carlo iterations were made and results were presented in a scatter plot where the Y-axis was the medical costs, and the X-axis was the DALYs averted.

Table 10 summarizes the OSA and PSA parameters used, their respective downside and upsides, distribution, and source. All parameters were assumed to follow the Beta distribution in the PSA.

Prevalence seemed to have the highest influence on both total infected (Figure 7A) and healthcare costs (Figure 7B) when incidence factor was allowed to range from 773,299 to 1,021,099. The next parameter with the highest influence on the total infected (healthcare cost) is the progression rate

Table 10. One-way Sensitivity Analysis (OSA) and Probabilistic Sensitivity Analysis (PSA) Parameters and their Ranges

Input	Base Case	Downside	Upside	Source
Incidence factor	930,938	773,299	1,021,099	(13)
Progression rates				
CHB LVL to Cirrhosis LVL	1.00	0.00	2.00	
CHB LVL to Cirrhosis LVL	1.00	0.00	2.00	
CHB HVL to HCC HVL	1.00	0.00	2.00	
CHB LVL to HCC LVL	1.00	0.00	2.00	
Cirrhosis HVL to HCC HVL	1.00	0.00	2.00	
Decompensated Cirrhosis LVL	1.00	0.53	1.91	
Cirrhosis LVL to HCC LVL	1.00	0.00	2.00	
Mother to child transmission (HVL, no vaccination)	100.0%	95.6%	99.9%	(8,9)
Mother to child transmission (% of HBeAg- with HVL)	13%	14%	13%	

CHB – chronic hepatitis B, LVL – low viral load, HVL – high viral load, HCC – hepatocellular carcinoma, HBeAg- – Hepatitis B e Antigen negative

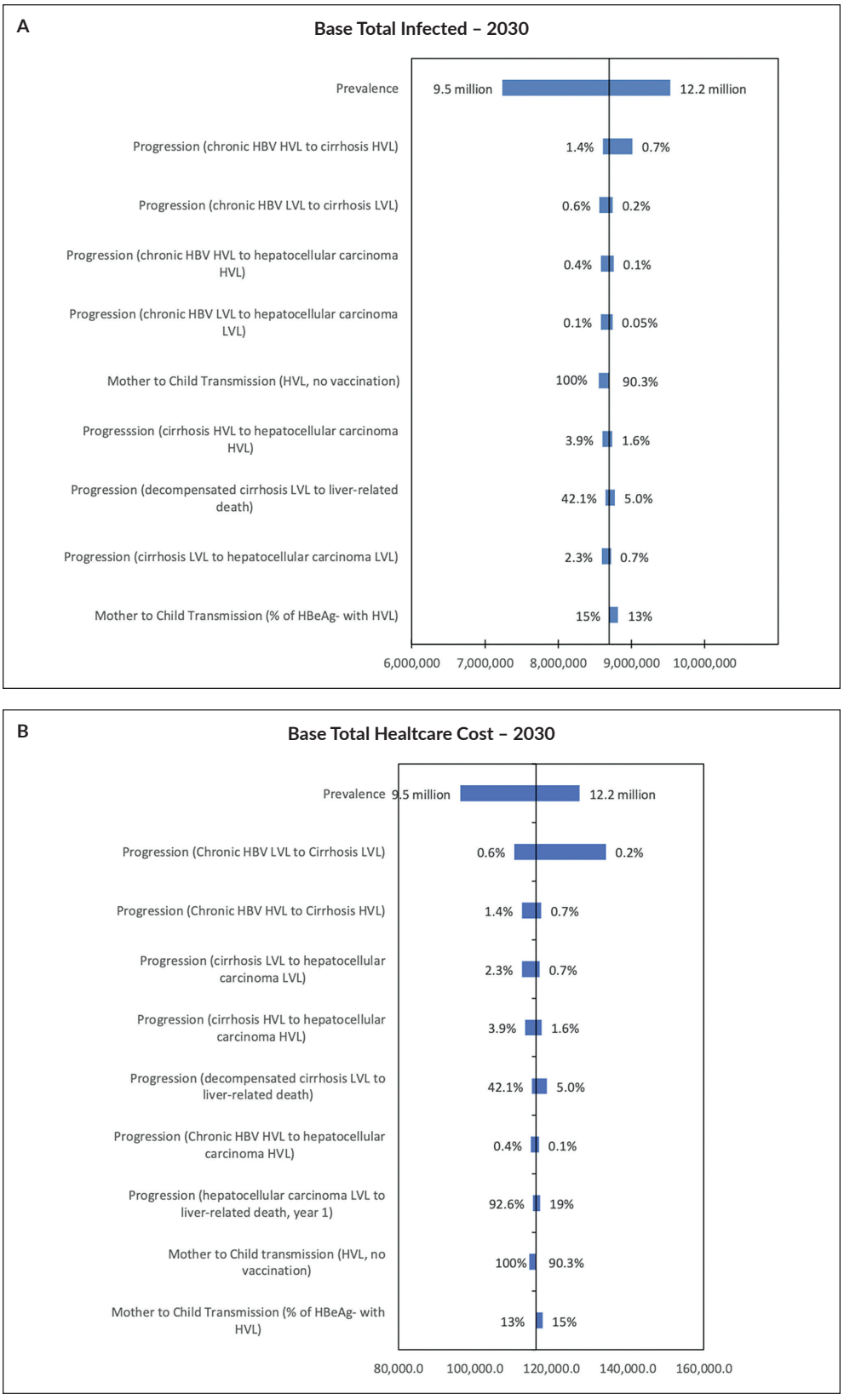

Figure 7. **(A)** Tornado diagram for the base case scenario for total infected from 2018 to 2030. **(B)** Tornado diagram for the base case scenario for healthcare cost from 2018 to 2030

HBV – hepatitis B virus, LVL – low viral load, HVL – high viral load, HBeAg- – hepatitis B e Antigen negative

from chronic hepatitis B high viral load (CHB HVL) to cirrhosis high viral load.

Following the base case, for the WHO Elimination Targets scenario, prevalence seemed to have the highest influence on both total infected and healthcare costs (Figures 8A and 8B) when incidence factor was allowed to range from 773,299 to 1,021,099. The next parameter with the highest influence on the total infected (healthcare cost) is the progression rate from CHB HVL to Cirrhosis HVL.

A multivariate probabilistic sensitivity analysis of the WHO Targets Elimination scenario shows that most iterations in the scatter plot fall under the first quadrant, which implies that while the intervention is effective in terms of DALY averted, medical cost savings will rise versus the base case (Figure 9A). A negligible number of iterations fall under the second quadrant.

In the WHO Targets Elimination scenario where the public payer pays 90% of medical costs, it is assumed 90% of all medical costs are borne by the public sector versus the previous scenario where only 48% is borne by the government. Like the previous scenario, most iterations in the scatter plot fall under the first quadrant, which implies that while the intervention is effective in terms of DALY averted, medical cost savings will rise versus the base case (Figure 9B). A negligible number of iterations fall under the second quadrant.

In another WHO Targets Elimination scenario where the public payer pays 90% of medical costs and GeneXpert is used for diagnosis, the GeneXpert is introduced to the scenario where the government shoulders 90% of the medical costs in implementing the WHO elimination targets. Like the two previous scenarios, most iterations in the scatter plot fall under the first quadrant (Figure 9C). Note that a sizeable number of iterations fall under the fourth quadrant, which is the cost-savings quadrant. However, like the previous two scenarios, a negligible number of iterations fall under the second quadrant.

DISCUSSION

The HBV modeling exercise revealed that it will be worthwhile to adhere to the WHO elimination strategies, wherein less than 3x GDP per capita threshold is considered cost-effective, and highly cost-effective if less than 1x GDP per capita as per WHO guidelines, while less than 1x GNP per capita in the Philippine guidelines.

The WHO elimination strategy (which assumes 48% government subsidy) was shown to be cost-effective beginning 2021 and highly cost-effective beginning 2046, as per WHO guidelines, and cost-effective starting 2046 as per Philippine guidelines.

The WHO elimination strategy with 90% government subsidy, and the WHO elimination strategy with 90% government subsidy plus DNA testing using GeneXpert would be considered highly cost-effective (as per WHO guidelines) and cost-effective (as per Philippine guidelines) earlier: 2030 for WHO elimination strategy with 90% government subsidy, and 2024 for WHO elimination strategy with 90% government subsidy and DNA testing using GeneXpert.

It is clear from the modeling exercise that in order to achieve the 2030 targets in the WHO elimination scenario, a substantial financial investment will be necessary. This will also entail a significant scale up in the screening, diagnosis, treatment, and monitoring of patients with HBV. A significant scale up in the coverage for the birth dose vaccine as well as the subsequent three doses in the first year of life is also needed. The costs can significantly be driven down by adhering closely to WHO treatment guidelines on screening, diagnosis, and treatment. Further simplification of treatment algorithms can further reduce costs. Providing access to cheaper and more accessible point of care tests can likewise reduce costs. Because a large part of the VH care in the country is handled in the private sector, strengthening the public health sector services for the care of patients with HBV can shift the public to private ratio of VH care to the public sector where diagnostic and treatment costs are lower. Hence, would lead to lower costs to society.

The limitations of the study lie in the innate challenges of using a modeling approach for studies. A modeling approach is not as accurate as a prevalence survey or a retrospective or prospective cohort study, due to the need to make assumptions regarding certain parameters and future projections. However, it must also be acknowledged that modeling is a useful tool that can generate information for health policy in a more expeditious manner that is at the same time less costly. Moreover, the model used in this study has been utilized in many previous studies in other countries and has been published by the developers - the Center for Disease Analysis Foundation – and their collaborators in high-impact journals. Another limitation is the quality of the data used for the inputs in the models. Because of the dearth of published data on VH in the country, majority of the data used in the assumptions were obtained through estimates from informal surveys, secondary data analyses. To address this limitation, the proponents validated the estimates through RTD with experts that were convened in the country's capital and three major islands. Additionally, real-world patient behaviors, such as adherence to treatment and healthcare-seeking patterns, may differ from model assumptions, affecting applicability to policy decisions. These limitations were addressed by using sensitivity analyses in order to assess the reliability of the results despite multiple uncertainties and assumptions.

Another potential limitation of the study is the change of the prices of goods and services since the time of data collection and analysis. Some assumptions, such as coverage rates beyond 2020, may introduce uncertainty in projecting future trends and may limit external validity of the findings. However, the results of the study remain valid because these are based on threshold analyses, which are robust against inflationary changes that may affect point estimations.

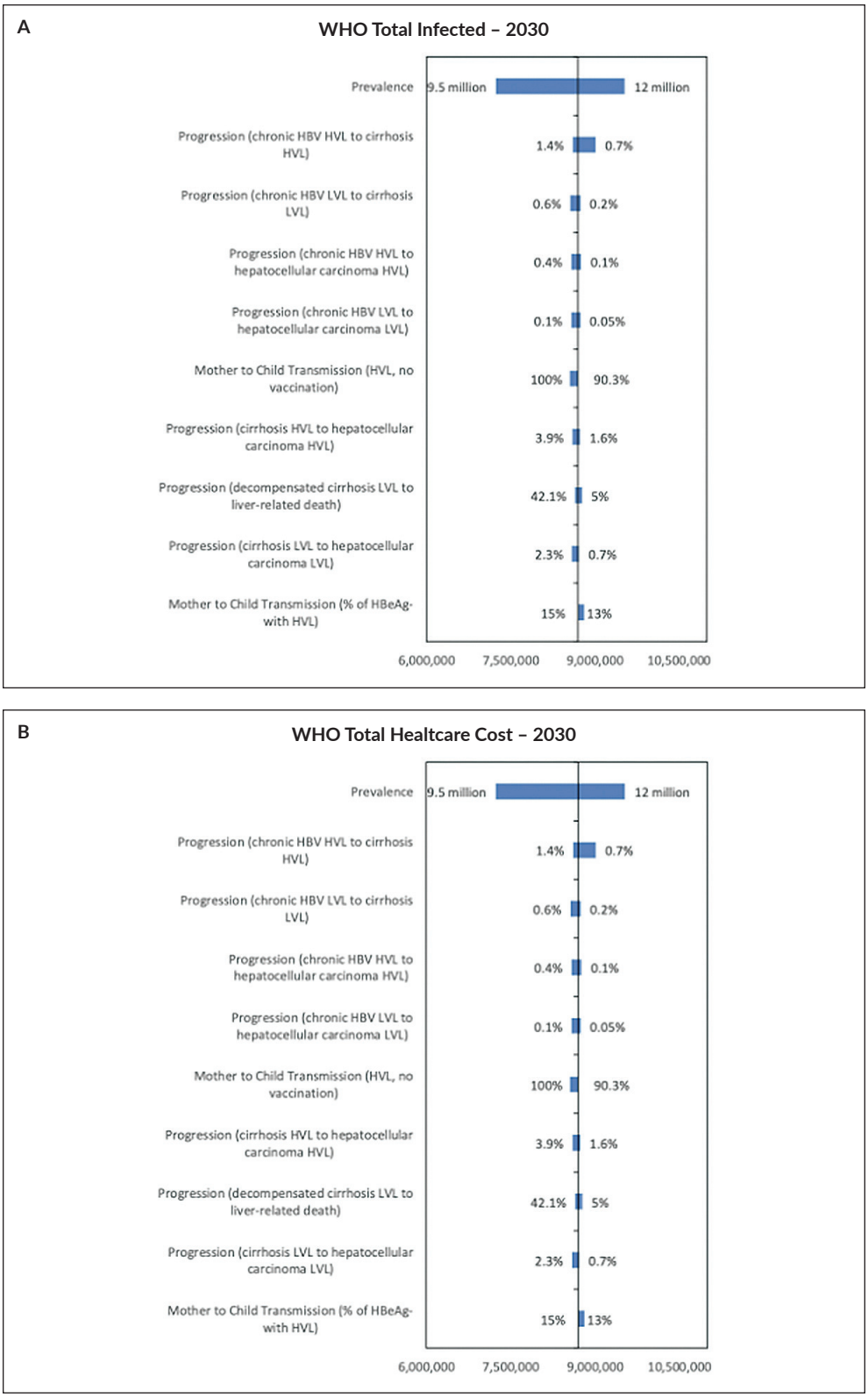

Figure 8. **(A)** Tornado diagram for the WHO Elimination Targets scenario for total infected from 2018 to 2030. **(B)** Tornado diagram for the WHO Elimination Targets scenario for healthcare costs from 2018 to 2030.

HBV – hepatitis B virus, LVL – low viral load, HVL – high viral load, HBeAg- – hepatitis B e Antigen negative

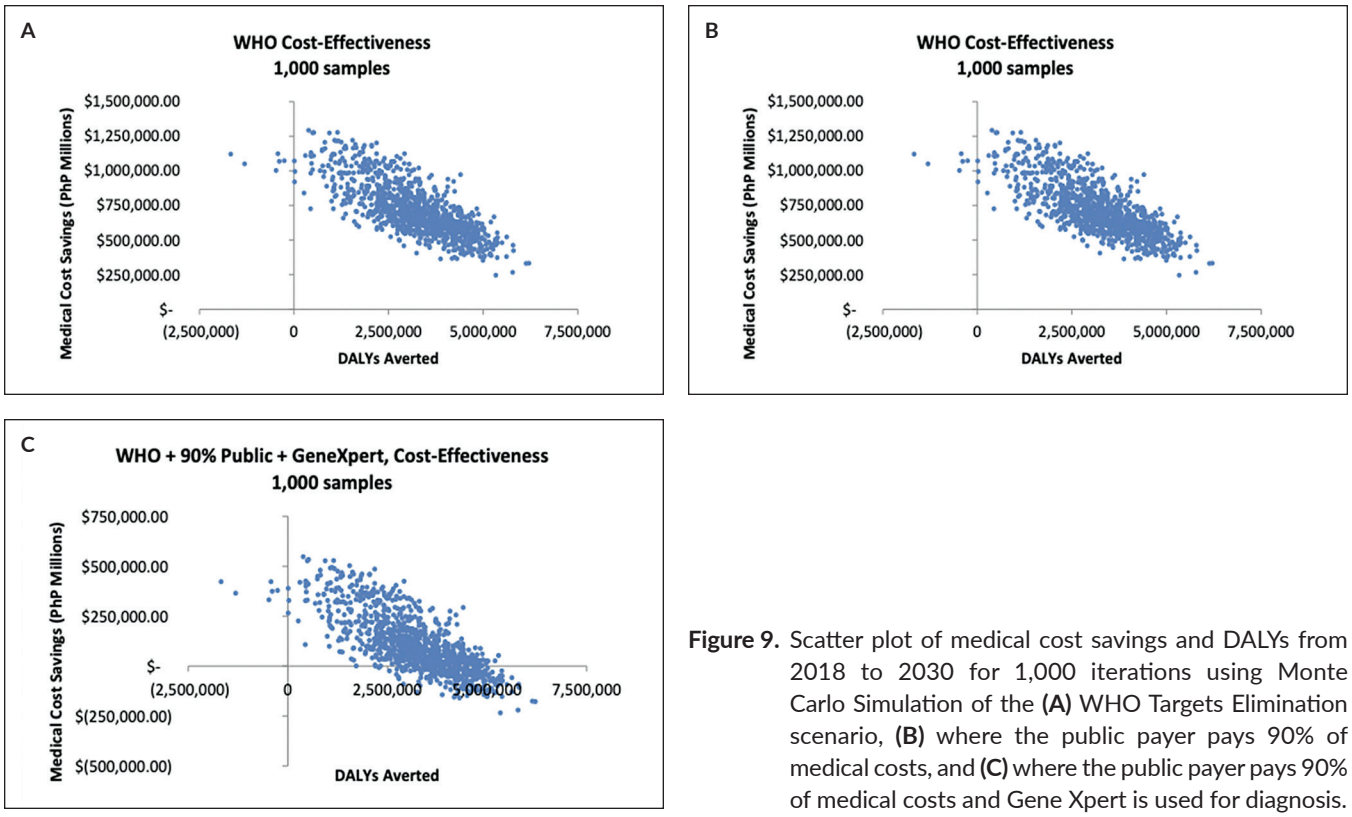

Figure 9. Scatter plot of medical cost savings and DALYs from 2018 to 2030 for 1,000 iterations using Monte Carlo Simulation of the **(A)** WHO Targets Elimination scenario, **(B)** where the public payer pays 90% of medical costs, and **(C)** where the public payer pays 90% of medical costs and Gene Xpert is used for diagnosis.

Stakeholder engagement played a crucial role in enriching the study design and data collection process by ensuring the inclusion of diverse perspectives and region-specific insights. By consulting experts such as gastroenterologists and hepatologists through RTDs across Luzon, NCR, Visayas, and Mindanao, the study team validated key model inputs, refined methodologies, and enhanced the applicability of findings. The involvement of public and private health facilities further strengthened data reliability by capturing cost variations in diagnostics and medications across different healthcare settings. Moving forward, incorporating stakeholder feedback earlier in the research process—such as in study design formulation and periodic validation checkpoints—can improve model accuracy, enhance policy relevance, and ensure more comprehensive, regionally representative analyses.

CONCLUSION

Despite inherent limitations of mathematical models, results manifested that it will be cost-effective to adhere to the WHO elimination targets for HBV. By complying to these models run with WHO elimination targets, the country will be significantly lowering incidence, prevalence, morbidity, and mortality for hepatitis B. Furthermore, all the three WHO scenario will substantially lower DALYs and this consequently will result in incremental cost per DALY averted at lower than 1x GDP.

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Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

All authors declared no conflicts of interest related to this research. No financial or non-financial relationships exist with any entities that may have influenced the study. All authors have no relevant financial ties, affiliations, or competing interests were identified, except for one author

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