Cost-effectiveness of community-based screening and treatment for chronic hepatitis B in The Gambia: an economic modelling analysis

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Summary

Background **Despite the high burden of hepatitis B virus (HBV) infection in sub-Saharan Africa, absence of widespread screening and poor access to treatment leads to most people remaining undiagnosed until later stages of disease when prognosis is poor and treatment options are limited. We examined the cost-effectiveness of community-based screening and early treatment with antiviral therapy for HBV in The Gambia.**

Methods **In this economic evaluation, we combined a decision tree with a Markov state transition model to compare a screen and treat intervention consisting of adult community-based screening using a hepatitis B surface antigen (HBsAg) rapid test and subsequent HBV antiviral therapy versus current practice, in which there is an absence of publicly provided screening or treatment for HBV. We used data from the PROLIFICA study to parameterise epidemiological, primary screening, and cost information, and other model parameter inputs were obtained from a literature search. Outcome measures were cost per disability-adjusted life-year (DALY) averted; cost per life-year saved; and cost per quality-adjusted life-year (QALY) gained. We calculated the incremental cost-effectiveness ratios (ICERs) between current practice and the screen and treat intervention. Costs were assessed from a health provider perspective. Costs (expressed in 2013 US$) and health outcomes were discounted at 3% per year.**

Findings **In The Gambia, where the prevalence of HBsAg is 8·8% in people older than 30 years, adult screening and treatment for HBV has an incremental cost-effectiveness ratio (ICER) of $540 per DALY averted, $645 per life-year saved, and $511 per QALY gained, compared with current practice. These ICERs are in line with willingness-to-pay levels of one times the country's gross domestic product per capita ($487) per DALY averted, and remain robust over a wide range of epidemiological and cost parameter inputs.**

Interpretation **Adult community-based screening and treatment for HBV in The Gambia is likely to be a cost-effective intervention. Higher cost-effectiveness might be achievable with targeted facility-based screening, price reductions of drugs and diagnostics, and integration of HBV screening with other public health interventions.**

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Introduction

An estimated 250 million people worldwide are chronically infected with hepatitis B virus (HBV), which is often asymptomatic during the early stages of disease.[1] If left untreated, about 25% of infected individuals will progress to cirrhosis or hepatocellular carcinoma, for which prognosis is poor. Approximately 1 million people die every year from HBV-related end-stage liver disease; the burden is concentrated in resource-poor settings, including West Africa, where more than 70% of cases of hepatocellular carcinoma in people younger than 50 years are caused by HBV.[2] Screening, which aims to identify people with asymptomatic infection and offer early intervention with antiviral therapy, could be an important public health measure to prevent HBV-related morbidity and mortality.

International recommendations, including the new WHO guidelines, recommend treatment for chronic HBV infection.[3] However, in practice, publicly funded treatment for HBV mono-infection is not available in sub-Saharan Africa.[4] Poor infrastructure, high diagnostic and treatment costs, limited community awareness, and absence of trained health-care professionals are just a few of the possible contributing factors that account for this discrepancy. Treatment for chronic HBV infection, without active screening, has been shown to be cost-effective in many settings;[5,6] however, screening studies have focused on high-risk target groups in high-income countries rather than the general population in highly endemic low-income countries.[7] The advent of potent antiviral drugs such as tenofovir, now available at generic prices for HIV treatment but effective in the treatment of both HIV and HBV, makes screening and treatment for chronic HBV infection potentially feasible in more low-income and middle-income countries.

To our knowledge, this study is the first economic evaluation of a community screening and treatment

Research in context

Evidence before this study

We searched PubMed for articles published before September, 2015, with terms incorporating "Hepatitis B", "HBV", or "CHB" and "Cost*" or "Economic" and "Screen*", "Test*", or "Diagnosis". We found no previous studies describing costs or cost-effectiveness of community-based screening for hepatitis B virus (HBV) infection in low-income or middle-income countries. Research in high-income countries included two previous community-based studies of cost-effectiveness of screening, and further studies of screening in groups classified as high risk, including immigrant populations, many of which were based on hypothetical cohorts, rather than real-life screening data.

Added value of this study

To our knowledge, this study is the first to investigate the cost-effectiveness of adult screening and treatment for HBV at the community level in a low-income or middle-income setting. Furthermore, the study includes real-life cost and effectiveness parameter data from a large-scale screening and treatment programme in The Gambia. The model incorporates clinically salient features and is unique in presenting results using three different outcome measures.

Implications of all the available evidence

Ambitious targets for improving testing and treatment for HBV form part of the recent WHO Global Health Sector Strategy for viral hepatitis. Evidence on how to achieve these targets will be needed to help guide national policies. Screening and treatment for hepatitis B has been shown to be a feasible and cost-effective intervention in The Gambia and should be considered as a public health strategy to reduce mortality and morbidity from cirrhosis and liver cancer. Our study helps to inform such decisions, and highlights the need for further similar analyses in other highly endemic countries.

strategy for chronic HBV infection in a low-income or middle-income setting. It aims to inform decisions on health policy and resource allocation by presenting the possible costs and benefits of improving rates of diagnosis and treatment of people with asymptomatic HBV infection in sub-Saharan Africa, a strategy that has so far had a very limited evidence base.

Methods

Model structure

We developed a decision tree representing the intervention characteristics of screening and treatment and combined this tree with Markov models representing the untreated and treated natural history of chronic HBV infection (appendix). We identified eight mutually exclusive health domains to represent the clinical states of the natural history of chronic HBV infection, in accordance with internationally accepted definitions.[60] These stages were based on HBeAg status (a serological marker representing high infectivity), HBV viral load, alanine aminotransferase concentration, and degree of liver fibrosis. Transition parameters between health states were obtained from results of a literature review (table 1). The model was created in Tree Age Pro 2014 and was used to simulate disease progression in the cohorts, in annual cycles for a period of 40 years. We used data from the PROLIFICA study to parameterise epidemiological, screening, and cost information, and other model parameter inputs were obtained from a literature search.

See Online for appendix

Study setting

The multicentre PROLIFICA study assessed the feasibility of a screen and treat HBV intervention programme across the western part of The Gambia (NCT02129829). Study methods are described in detail elsewhere.[61] The study was approved by The Gambia Government/MRC Joint Ethics committee.

Comparator strategies

In this economic evaluation, we compared the screen and treat intervention versus current practice. Our baseline strategy reflects current practice—specifically, the absence of publicly provided screening or treatment for HBV in The Gambia. Therefore, costs for this strategy reflect those incurred if and when patients present at the later stages of disease because of morbidity from cirrhosis and hepatocellular carcinoma, when patient outcomes are also poorer.

For the screen and treat intervention, community-based screening consisted of initial community sensitisation, door-to-door household registration of eligible participants (aged ≥30 years), and testing for hepatitis B surface antigen (HBsAg; a marker of being infected with HBV), by use of a rapid point-of-care test.[61] This part of the intervention was carried out by field workers. Individuals with a positive test result were offered outpatient review for diagnostic assessment including routine blood tests, HBV viral load, screening for co-infection with HIV, hepatitis C virus (HCV), or hepatitis delta virus (HDV), liver ultrasound scan, and transient elastography (FibroScan) for assessment of liver fibrosis. Patients meeting European Association for the Study of the Liver (EASL) criteria[60] for treatment were prescribed tenofovir monotherapy. Standard monitoring was done in accordance with international guidelines and we assumed lifelong treatment. We assumed that there was no resistance to tenofovir[13] and that antiviral treatment would halt disease progression (if patients were completely adherent to treatment). However, for individuals with already established cirrhosis, there

	Base-case value	Deterministic range	PSA distribution	PSA parameters	Source*	Further description
Intervention costs						
One-off activity						
Screening cost per person (US$)	7·43	3·72–14·9	Gamma†	a=100; λ=13·4	Primary data, PROLIFICA	..
Initial assessment visit (US$)	120	60–200	Gamma	±20% range for each component part	Primary data, PROLIFICA	Initial assessment visit includes routine blood tests, virology, ultrasound scan, transient elastography (FibroScan), and staff costs
Annual management						
Drug treatment (US$)	48	24–207	Point estimate	..	Ref 8	Treatment consisted of antiviral therapy with daily tenofovir at generic price
Monitoring on treatment (US$)	36·88	30–44	Gamma	±20% range for each component part	Primary data, PROLIFICA	Monitoring is done every 6 months in the treated stages of chronic HBV infection
Monitoring not on treatment (US$)	15·77	13–32	Gamma	±20% range for each component part	Primary data, PROLIFICA	Monitoring is done yearly in the untreated stages of chronic HBV infection
Costs of hospital admission						
Cost per day of hospital stay (US$)	6·66	..	..	..	Ref 9	WHO-CHOICE values are given minus drug and laboratory costs; therefore, we have multiplied by a factor of two to account for these
Average length of hospital stay (days)	7·15	..	..	..	Ref 9	..
Cost per hospital admission (US$)	47·24	..	Gamma†	a=3·57; λ=0·0756	Ref 9	Average cost per hospital admission in stages of compensated cirrhosis, decompensated cirrhosis, and hepatocellular carcinoma is equal to the average length of stay multiplied by the cost per day of hospital stay
Number of hospital admissions per year for compensated cirrhosis	2	..	Uniform	low=0; high=4	Assumption	..
Number of hospital admissions per year for decompensated cirrhosis	3	..	Uniform	low=0; high=6	Assumption	..
Number of hospital admissions per year for hepatocellular carcinoma	3	..	Uniform	low=0; high=6	Assumption	..
Average annual cost of hospital admission for compensated cirrhosis (US$)	95·24	0–190	..	..	Based on above	Annual cost of hospital admission in each stage is equal to the cost per hospital admission multiplied the number of hospital admissions per year
Average annual cost of hospital admission for decompensated cirrhosis (US$)	142·86	48–286	..	..	Based on above	Annual cost of hospital admission in each stage is equal to the cost per hospital admission multiplied the number of hospital admissions per year
Average annual cost of hospital admission for hepatocellular carcinoma (US$)	142·86	48–286	..	..	Based on above	Annual cost of hospital admission in each stage is equal to the cost per hospital admission multiplied the number of hospital admissions per year
Epidemiological parameters‡						
HBsAg prevalence (%)	8·8%	0–15%	Point estimate	..	PROLIFICA	..
Screening uptake (%)	68·9%	63–97%	Point estimate	..	PROLIFICA (ref 10)‡	Intervention coverage reported in the PROLIFICA study was used as a proxy for uptake of screening, as we can assume all eligible individuals were offered screening, given the study design
Linkage to care (%)	81·3%	62–95%	Point estimate	..	PROLIFICA (ref 11)‡	Defined as attendance at the first clinic appointment after being tested HBsAg positive in the community
Adherence to treatment in year 1 (%)	80·9%	77–95%	Point estimate	..	PROLIFICA (ref 12)‡	Adherence to antiviral therapy in the first year of treatment
Annual rate of drop-out of treatment after year 1 (%)	2%	1–5%	Point estimate	..	Assumption	Yearly drop-out rate from second year of antiviral treatment onwards
Annual resistance to treatment (%)	0%	0–2% (after year 6)	Point estimate	..	Ref 13	..

(Table 1 continues on next page)

	Base-case value	Deterministic range	PSA distribution	PSA parameters	Source*	Further description
(Continued from previous page)						
Annual risk of developing hepatocellular carcinoma in individuals with compensated cirrhosis on antiviral therapy (%)	0·5%	0–1%	Beta	a=0·747; b=149	Refs 14, 15	..
Annual risk of developing hepatocellular carcinoma in individuals with decompensated cirrhosis on antiviral therapy (%)	1%	0–4·4%	Beta	a=0·808; b=80·0	Refs 14, 15	..
Sensitivity of HBsAg POC test (%)	88·5%	85·1–98·2%	Point estimate	..	PROLIFICA (refs 16,17)‡	Patients with false-positive results on screening are seen in clinic and have full diagnostic assessment including confirmatory HBsAg serology; they are then discharged from care and do not receive unnecessary treatment. Patients with false-negative results are those who tested HBsAg negative at screening, and are therefore not followed up in clinic and do not receive treatment; they progress in the model as per the untreated natural history of HBV
Specificity of HBsAg POC test (%)	100%	99·03–100%	Point estimate	..	PROLIFICA (refs 16,17)‡	See previous row for description of false-positive and false-negative cases
Start age of cohort (years)	38	15–50	Point estimate	..	PROLIFICA	Screening was offered to all individuals older than 30 years; however, the start age of our modelled cohort was 38 years to correspond with the median age of HBV-positive patients screened in the community
Discount rate: costs (%)	3%	0–6%	Point estimate		Refs 18, 19	..
Discount rate: health outcomes (%)	3%	0–6%	Point estimate		Refs 18, 19	..
Annual disease transition rates§						
From immune tolerant to:						
Immune reactive	0·1	0·03–0·2	Beta	a=5·063; b=45·57	Refs 20–22	..
Hepatocellular carcinoma	0·003	0–0·006	Beta	a=3·985; b=1324·35	Assumption	..
From immune reactive to:						
Inactive carrier	0·05735	0·0458–0·06882	Beta	a=11·971; b=196·76	Refs 23,24	..
HBeAg-negative chronic HBV	0·005	0–0·05	Beta	a=0·154; b=30·69	Assumption	..
Compensated cirrhosis	0·0277	0·01–0·054	Beta	a=6·138; b=215·45	Refs 25–31	..
Hepatocellular carcinoma	0·0065	0·0027–0·01	Beta	a=12·596; b=1925·30	Refs 26–28, 32–35	..
From inactive carrier to:						
HBeAg-negative chronic HBV	0·0268	0·0155–0·0471	Beta	a=11·173; b=405·74	Refs 24, 36–41	..
Hepatocellular carcinoma	0·00065	0–0·001	Beta	a=0·057; b=94·89	Ref 42	..
HBsAg negative	0·01	0·0097–0·0226	Beta	a=17·146; b=1257·65	Refs 23, 38, 39, 43	..
From HBeAg-negative chronic HBV to:						
Compensated cirrhosis	0·04	0·01–0·052	Beta	a=11·173; b=300·92	Refs 25–31, 37, 43, 44	..
Hepatocellular carcinoma	0·00616	0·0027–0·01	Beta	a=11·300; b=1824·50	Refs 43	..
From compensated cirrhosis to:						
Decompensated cirrhosis	0·039	0·032–0·046	Beta	a=2·848; b=70·18	Refs 35, 45–47	..
Hepatocellular carcinoma	0·0366	0·008–0·08	Beta	a=3·947; b=103·88	Refs 20, 28, 32, 35, 46, 48–56	..
Death	0·039	0·039–0·507	Beta	a= 0·270; b= 6·66	Ref 57	..
From decompensated cirrhosis to:						
Hepatocellular carcinoma	0·0376	0·023–0·071	Beta	a=9·411; b=240·88	Refs 45, 48–52, 58	..

(Table 1 continues on next page)

	Base-case value	Deterministic range	PSA distribution	PSA parameters	Source*	Further description
(Continued from previous page)						
Death	0·314	0·043–0·57	Beta	a=3·583; b=7·83	Ref 57	..
From hepatocellular carcinoma to:						
Death	0·5	0·4–1	Beta	a=5·056; b=5·06	Ref 57	..
Disability weights¶						
Immune tolerant	0·053	..	Beta	a=20·13; b=359·73	GBD 2010[59]	Disability weight for "HIV receiving ARV" was used as proxy
Immune reactive	0·053	..	Beta	a=20·13; b=359·73	GBD 2010[59]	Disability weight for "HIV receiving ARV" was used as proxy
Inactive carrier	0·053	..	Beta	a=20·13; b=359·73	GBD 2010[59]	Disability weight for "HIV receiving ARV" was used as proxy
HBeAg-negative chronic HBV	0·053	..	Beta	a=20·13; b=359·73	GBD 2010[59]	Disability weight for "HIV receiving ARV" was used as proxy
Compensated cirrhosis	0·127	..	Beta	a=10·02; b=68·90	GBD 2010[59]	Disability weight for "Decompensated cirrhosis of the liver" was used as proxy (lower CI used)
Decompensated cirrhosis	0·194	..	Beta	a=21·67; b=90·05	GBD 2010[59]	Disability weight for "Decompensated cirrhosis of the liver" was used
Hepatocellular carcinoma	0·519	..	Beta	a=18·10; b=16·77	GBD 2010[59]	Disability weight for "Terminal phase: without medication (for cancers, end-stage kidney or liver disease)" was used
Treated immune reactive	0·053	..	Beta	a=20·13; b=359·73	GBD 2010[59]	Disability weight for "HIV receiving ARV" was used as proxy
Treated HBeAg-negative chronic HBV	0·053	..	Beta	a=20·13; b=359·73	GBD 2010[59]	Disability weight for "HIV receiving ARV" was used as proxy
Treated compensated cirrhosis	0·053	..	Beta	a=20·13; b=359·73	GBD 2010[59]	Aassumed returns to same disability weight as untreated chronic HBV stages
Treated decompensated cirrhosis	0·127	..	Beta	a=10·02; b=68·90	GBD 2010[59]	Assumed returns to same disability weight as untreated chronic HBV stages

See appendix for starting state distributions of chronic HBV infection and for health utilities used for quality-adjusted life-year calculations. ARV=antiretroviral. HBeAg=hepatitis B envelope antigen. HBsAg=hepatitis B surface antigen. HBV=hepatitis B virus. POC=point-of-care. PSA=probabilistic sensitivity analysis. PROLIFICA=Prevention of Liver Fibrosis and Cancer in Africa. Ref=reference number. *If more than one reference is given, the final value represents a summary value. †In the gamma distributions, the λ parameter is equal to mean/SD^2. ‡The references provided represent the sources of the parameter ranges used in the sensitivity analyses. §For transition rates used from the review by Lin and colleagues,[57] the original articles are individually referenced. ¶The equivalent category in the Global Burden of Disease Study 2010,[59] which was used for the disability weight of each of these health states, is described.

Table 1: **Main model parameters**

remained an ongoing risk of developing hepatocellular carcinoma despite antiviral therapy.[14,15]

Cohort characteristics

Although screening was offered to all individuals living in study areas who were aged 30 years or older, the start age of our modelled cohort was 38 years, corresponding with the median age of HBV-positive patients screened in the community, in an attempt to avoid overestimation of health benefits. We assumed that all individuals offered screening had not been vaccinated against HBV, because the universal infant vaccination programme only began in 1990 in The Gambia.[2] The starting distribution of the infected cohort across different clinical states was based on PROLIFICA data (appendix). We assumed that natural history and cost parameters were independent of age and sex, but applied an age-structured Gambia-specific mortality rate.[62]

Costs

Costs were assessed from a health provider perspective, and were based on the PROLIFICA study budget, public health facility activity data, and interviews with key health personnel regarding time and resource use. Costs consisted of personnel, equipment, materials, and maintenance. The cost components of the screen and treat intervention included one-off costs for screening of US$7·43 per person offered screening and initial diagnostic assessment cost of $120 per patient. Annual costs were $48 for drugs, $36·88 for monitoring on antiviral therapy, and $15·77 for monitoring if not on antiviral therapy (table 1).

We used data from WHO-CHOICE to estimate costs of hospital admission in The Gambia.[9] All costs are expressed in 2013 US$. Future costs and health outcomes were discounted at 3% per year, as per WHO guidelines and Gates Reference Case.[18,19]

Outcome measures

We present three outcome measures to allow for greater comparability with existing literature and to acknowledge that each one has limitations: cost per disability-adjusted life-year (DALY) averted; cost per life-year saved; and cost per quality-adjusted life-year (QALY) gained. When available, we used disability weights from the Global Burden of Disease Study 2010,[59] and approximated from other diseases if liver-specific weights were not available. Health utilities are not well defined for HBV in low-income and middle-income countries, but we used mean cross-country utilities from a multi-country study by Levy

and colleagues[63] for our base-case QALY. Life-years represent an objective measure, but do not take into account morbidity.

Measurement of cost-effectiveness

We calculated an incremental cost-effectiveness ratio (ICER) between current practice and the screen and treat intervention, which was defined as ($cost_{screen\ and\ treat\ intervention}$–$cost_{current\ practice}$)/($effectiveness_{screen\ and\ treat\ intervention}$–$effectiveness_{current\ practice}$). A new intervention is often deemed cost-effective if the ICER is below a willingness-to-pay (WTP) threshold. However, these thresholds and their use are contested, especially in low-income and middle-income countries where various thresholds have been suggested, including multiples of a country's gross domestic product (GDP) per capita[64] and a World Bank threshold of $240 per DALY averted.[65,66] We therefore present a range of WTP thresholds to allow the decision maker to put the results of our study into the context of these various thresholds—namely, one times GDP per capita ($487),[67] three times GDP per capita ($1460), and a more stringent World Bank threshold of $240 per DALY averted.

Sensitivity analysis

We performed a series of one-way deterministic sensitivity analyses that varied the parameters individually over plausible ranges to test the robustness of our findings and to identify key uncertainties and data collection priorities (table 1). Multiple combinations of health utility values were also explored in the sensitivity analysis (appendix). We did a multivariate probabilistic sensitivity analysis to characterise the overall combined uncertainty of all the model parameters using second order Monte Carlo simulations. Distributions for parameter values were specified by a gamma distribution for costs (range of ±20%) and beta distribution for probabilities (range taken from published literature, or if unavailable ±0·2, constrained between 0 and 1). Uncertainty in the model is presented in a cost-effectiveness acceptability curve.

Role of the funding source

The funder of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to the data in the study and had final responsibility for the decision to submit for publication.

Results

The projected total health benefit that a round of screening will impart on this cohort of 8170 people compared with no screening is an additional 498 DALYs averted, 417 life-years gained, or 526 QALYs saved.

The screen and treat intervention has ICERs of $540 per DALY averted, $645 per life-year saved, and $511 per QALY gained, compared with current practice (table 2). The cost per DALY averted compares favourably to a three times GDP per capita threshold in The Gambia

	Average per person				ICER		
	Cost (US$)	Life-years saved	QALY	DALY	US$ per DALY averted	US$ per QALY gained	US$ per life-year saved
Current practice	11·15	19·84	16·98	4·28	..	..	..
Screen and treat intervention	44·08	19·89	17·04	4·22	540	511	645

DALY=disability-adjusted life-year. ICER=incremental cost-effectiveness ratio. QALY=quality-adjusted life-year.

Table 2: **Summary results for each strategy**

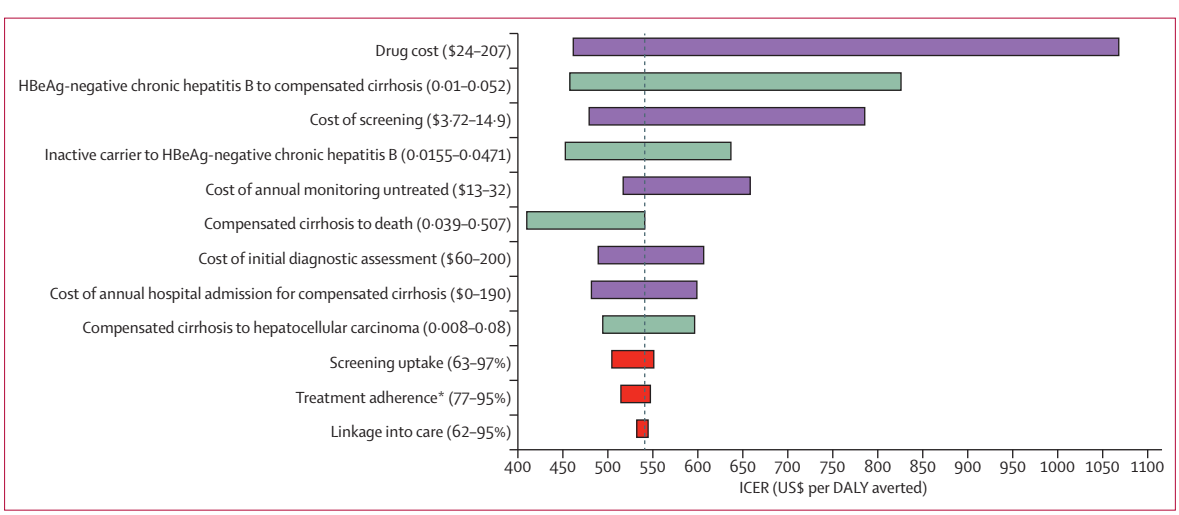

Figure 1: **Tornado diagram showing one-way sensitivity analyses of parameters that affect the ICER**

The first nine parameters affect the ICER by greater than US$100 over the ranges specified. The bottom three parameters affect the ICER to a lesser extent, but are included because they are important for programmatic implementation. Parameter categories are grouped by colour: purple represents costs, green represents transition rates, and red represents patient behaviours. The values representing the lower and higher ranges over which the parameter was varied are shown in parentheses. The dashed vertical black line represents the base case value. DALY=disability-adjusted life-year. ICER=incremental cost-effectiveness ratio.
*Treatment adherence refers to adherence in the first year, when the subsequent yearly drop-out rate was kept constant at 2% per year.

and is in line with a one times GDP per capita threshold, implying that the screening and treatment strategy is likely to be cost-effective. However, if the highly conservative World Bank threshold of $240 per DALY averted is used, this strategy is not cost-effective.

One way-sensitivity analyses showed that the ICER remained below three times GDP per capita per DALY averted, irrespective of outcome measure, for most plausible ranges of parameters (figure 1). Here, we discuss the parameters that had most effect on the ICERs, were most uncertain, or are important for programmatic implementation.

Varying HBsAg prevalence to 10%, 5%, 2%, and 1% increased the ICER to $526, $633, $955, and $1492 per DALY averted, respectively, with a sharp increase in the ICER at a prevalence lower than 2% (figure 2). When the age of the cohort screened was increased from 15 to 50 years, the ICER increased from $443 to $824 per DALY averted.

A two-fold or three-fold increase in the cost of community screening per person from the baseline of $7·43 increased the ICER to $662 or $784 per DALY averted, respectively. The generic price of tenofovir available for HIV programmes in The Gambia of $48 per year[8] was used for the base case, but increasing the drug price to $207, which represents the current pharmaceutical price of tenofovir offered to countries in sub-Saharan Africa,[68] increased the ICER to $1064 per DALY averted. A reduction in drug cost by half would reduce the ICER to $461 per DALY averted.

Our baseline rate of treatment adherence in the first year was 80·9% (recorded in the PROLIFICA study) and varying this between 77% to 95% (while maintaining a subsequent treatment drop-out rate of 2% per year) changed the ICER by $32, from $515 to $547 per DALY averted. Similarly, when screening uptake was varied over a wide range between 63% and 97%, which is in broad agreement with the ranges seen in the Demographic and Health Surveys of HIV screening in sub-Saharan Africa,[10] the effect on the ICER was only $46. Varying linkage to care (defined here as attendance to first outpatient consultation) between 62% and 95% also had only a small effect on the ICER ($13).

The natural history transition parameter with the greatest effect on the ICER was the rate of progression from HBeAg-negative chronic HBV infection to compensated cirrhosis. Changing this from 0·01 to 0·052 moved the ICER from $458 to $824 per DALY averted. The next most influential transition rates were from inactive carrier to HBeAg-negative chronic HBV infection, compensated cirrhosis to death, and compensated cirrhosis to hepatocellular carcinoma, which affected the ICERs by $183, $130, and $102 per DALY averted, respectively.

The use of different health utilities for QALY calculations gave a range of ICERs from $307 to $627 per QALY gained, the lowest ICER when utilities specific to China (with a standard gamble technique)[63] were used and the highest ICER when utilities from Singapore (with EuroQol-5D technique)[69] were used (appendix). Sensitivity analysis on the discount rate for costs and health benefits showed an ICER as low as $221 per DALY averted when costs were discounted at 6% and health benefits undiscounted (appendix, Table S4).

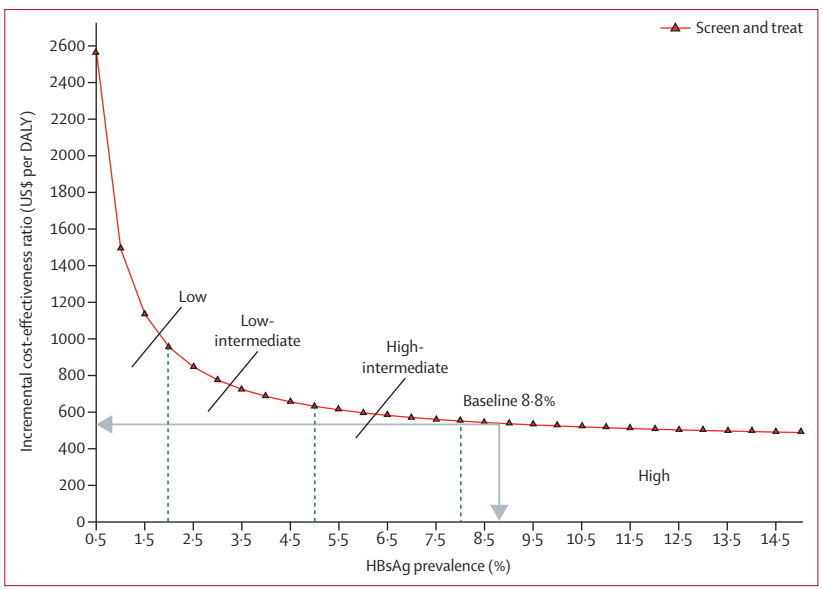

***Figure 2*: Effect of varying HBsAg prevalence on incremental cost-effectiveness ratio**
The boundaries of hepatitis B virus endemicity categories are marked by dashed green lines: low (HBsAg prevalence <2%), low-intermediate (2–5%), high-intermediate (5–8%), and high (>8%). The baseline HBsAg prevalence in The Gambia is represented by a solid grey line. HBsAg=hepatitis B surface antigen. DALY=disability-adjusted life-year.

The following parameters representing effectiveness of treatment had minimal effect (<$20) on the ICER: varying resistance to treatment between 0·5% to 2% per year after 6 years of treatment initiation, varying failure of reduction in disease progression on antiviral treatment between 0 to 2% per year, and varying the continued annual risk of development of hepatocellular carcinoma for individuals with cirrhosis on antiviral therapy, between 0 to 2% per year for compensated cirrhosis and 0 to 4% per year for decompensated cirrhosis.

For 2000 Monte-Carlo simulations, mean cost was $44·70 (95% CI 44·39–45·00) for the screen and treat intervention and $12·45 (95% CI 12·00–12·91) for current practice. Mean DALYs were 4·215 (95% CI 4·213–4·217) for the screen and treat intervention and 4·27 (95% CI 4·268–4·272) for current practice. Mean ICER was $621 (95% CI 612·8–629·6) per DALY averted (see appendix for ICER scatter plot).

The cost-effectiveness acceptability curve in figure 3 represents the probability that the new intervention will be cost-effective over a range of decision makers' WTP thresholds per additional DALY averted. At a WTP threshold of $1460, there is a 99·7% probability that the screening and treatment strategy will be cost-effective; this probability reduces to 95%, 20%, and <1% if the WTP threshold is $974, $487, or $240, respectively.

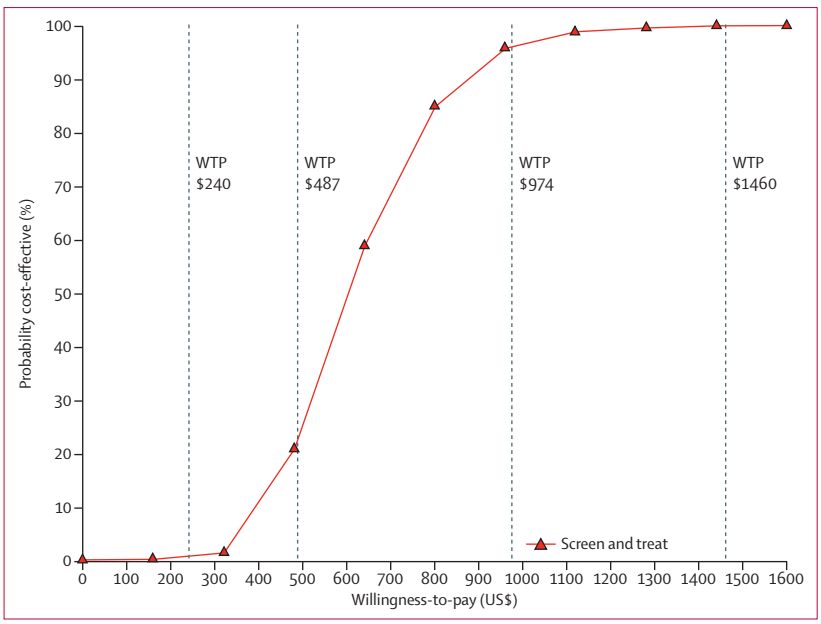

Figure 3: **Cost-effectiveness acceptability curve**
This figure represents the probability that the screen-and-treat intervention will be cost-effective over a range of willingness-to-pay (WTP) thresholds per disability-adjusted life-year (DALY) averted. The dashed lines represent different WTP thresholds that can be applied to The Gambia: US$1460 (represents three times the gross domestic product [GDP] per capita of The Gambia), $974 (represents two times the GDP per capita of The Gambia), $487 (represents one times the GDP per capita of The Gambia), and $240 (World Bank threshold).

The modelled HBV-negative, untreated HBV-positive, and treated HBV-positive cohorts had median survival ages of 70 years, 62 years, and 69 years, respectively. This finding is consistent with the average life expectancy at age 30 years in The Gambia of 68 years,[62] and the assumption that treatment for chronic HBV infection restores a near normal life expectancy. This concordance adds strength to the validity of the model.

Discussion

Screening and treatment for HBV in The Gambia, where the adult HBsAg prevalence is 8·8%, has ICERs of $540 per DALY averted, $645 per life-year saved, and $511 per QALY gained, compared with current practice. Whether this intervention represents a cost-effective strategy must be judged in light of the WTP threshold adopted. The screen and treat intervention remains well below the commonly used benchmark WTP threshold of less than three times the country's GDP per capita. However, because the use of this high threshold is increasingly questioned, we are also able to show that the ICERs remain in line with a much more stringent criteria of one times GDP per capita. Uncertainty exists around the chance that such an intervention will be cost-effective at lower WTP thresholds. Low screening costs, highly effective and relatively low cost antiviral therapy at generic price, and only a small proportion of people requiring antiviral therapy help drive the cost-effectiveness of the screening and treatment strategy. However, these factors have to be balanced against lifelong treatment and the fact that a high proportion of individuals with chronic HBV infection will survive without treatment. Recent trials are showing promising results with finite treatment courses in some patient groups,[70] and this could help increase cost-effectiveness further.

Existing economic evaluations of HBV interventions in low-income and middle-income countries focus on prevention of HBV infection through vaccination. To our knowledge, our study is the first to assess the cost-effectiveness of active population-level screening and treatment for HBV in a low-income or middle-income setting, using primary data from a large community-based implementation study in The Gambia. Furthermore, our model is unique in incorporating all stages of chronic HBV, thereby taking into account the dynamic natural history of chronic HBV infection and allowing separation into treated and monitored categories, which have differing associated costs and outcomes. Although the paucity of data in sub-Saharan Africa can make accurate cost-effectiveness analyses challenging, sensitivity analyses have shown that the intervention remains cost-effective across a wide range of parameter inputs and WTP thresholds.

The cost of community-based HBV screening falls at the lower end of the broad range of community-based HIV screening costs in sub-Saharan Africa presented in a systematic review by Suthar and colleagues (cost per person tested $2·45–33·54).[71] Despite being perceived as a resource-intensive and labour-intensive strategy, in our study screening costs represented only 3–5% of the overall costs of HBV assessment and annual treatment and monitoring costs. Furthermore, costs are likely to be overestimated in our study because of field teams dedicated entirely to HBV screening as it formed part of a research programme. Integration of HBV screening with testing for other diseases such as hepatitis C virus or HIV could potentially reduce these costs further. Understanding how the quality of the intervention outside trial settings will impact costs and effects will be essential.

Downstream costs of diagnosis, antiviral therapy, and monitoring represent a larger proportion of the total costs than the screening part of the intervention. Generic-price tenofovir ($48) was used for our analysis, but a recent study has shown that entecavir, which is due to come off patent in 2017, can be manufactured for a lower cost of $36,[72] and could be an alternative cost-effective therapy to tenofovir. If The Gambia had to purchase tenofovir at the current pharmaceutical price of $207 offered to countries in sub-Saharan Africa, this would substantially decrease cost-effectiveness.[68]

Prevalence of chronic HBV infection can be divided into regions of low (<2%), low-intermediate (2–5%), high-intermediate (5–8%), and high (>8%) endemicity.[1] Although The Gambia is classified as a highly endemic country, our analysis shows that community screening and treatment remains below three times GDP per capita per DALY averted, even at an HBV prevalence as low as 1·5%.

This finding has implications for the decision of whether to offer widescale screening in the post-vaccination era, in which the overall prevalence of chronic HBV carriage has begun to decrease,[73] and for policy makers considering the potential cost-effectiveness of similar interventions in neighbouring countries with different HBV prevalence patterns.

Although increased uptake of interventions and patient engagement are needed to maximise health gains, in our study, uptake of screening, linkage to care, and adherence to therapy were not big drivers of cost-effectiveness. Our baseline adherence of 80·9%, although higher than the reported adherence of 77% to HIV treatment in sub-Saharan Africa,[12] is lower than the reported adherence of 87·8% to HBV treatment in North America.[74] Our base-case estimate of 81·3% potentially overestimates linkage to care in routine practice, because it was measured within a research study that provided reimbursement of transportation fees, clinics held in rural sites to facilitate access to treatment, active reminders about appointments, and good sensitisation and counselling of screened participants. However, variations in these parameters had little effect on cost-effectiveness because low rates reduce both the impact, as well as the costs, which scale together. These losses and frailties are similar to what is seen in the HIV care cascade.

Our model is of a static cohort and assumes homogeneity of the population with respect to age and sex, rather than a dynamic transmission model. The model therefore potentially underestimates the impact and cost-effectiveness of treatment, to the extent that treatment can reduce transmission in the population, especially through prevention of mother-to-child transmission by antiviral therapy. However, because only a small proportion of adults in The Gambia are HBeAg-positive, suggesting lower infectivity risk (which is consistent with data from other regions in sub-Saharan Africa), this extra benefit might be limited.[75]

A health provider perspective was used in this study, hence household costs of accessing screening and treatment were excluded. In a setting in which most people die at home, and end-of-life costs are borne by family members acting as caregivers, a societal perspective analysis would likely show a higher cost-effectiveness of the intervention. Furthermore, in The Gambia, where the median age of patients diagnosed with hepatocellular carcinoma is 40 years,[76] people of working age are often affected; thus, the economic impact is potentially greater to the household and society.

Although care must be taken before generalising the results of this study to other regions in sub-Saharan Africa, the fact that our model results were robust over a wide range of HBV prevalence, transition probabilities, and cost parameters suggests that screening and treatment strategies should be considered in other countries. Direct economic comparison between countries and across disease areas can help put our results into context, but should be interpreted with caution. Our findings suggest that the cost-effectiveness of a screening and treatment strategy for HBV is comparable to other interventions in The Gambia—for example, the introduction of the pneumococcal vaccine.[77] A unique feature of HBV screening is that, when combined with vaccination, it only requires once-a-lifetime testing, which contrasts with HIV, where a negative individual still remains at risk of reinfection.

Finally, although the screen and treat intervention was found to lie within cost-effective thresholds, it must be recognised that the WTP threshold is a theoretical one, especially in low-income and middle-income countries, to indicate whether an intervention should be entitled to be set as a priority in the health-care agenda. However, affordability and how the intervention will be funded (whether by governments, out-of-pocket, insurance systems, or external donor funding), in addition to cost-effectiveness, need to be considered before an intervention is adopted on a national level.

Poor access to testing and antiviral treatment remains a major barrier to reducing morbidity and mortality from HBV-related disease in sub-Saharan Africa. Our analysis has shown that community-based screening and treatment for chronic HBV infection is likely to be cost-effective if generic-priced tenofovir is used, which is currently only available for HIV treatment programmes in sub-Saharan Africa. Furthermore, integration of HBV screening with screening for other diseases, using the already established infrastructure for addressing HIV in sub-Saharan Africa, as well as simplifying diagnostic assessment and monitoring, might make this an even more cost-effective intervention. The combination of vaccination, screening, and treatment raises the possibility of advancing the date of elimination of HBV-related morbidity and mortality as a public health threat.[78]

Contributors

SN, LC, TBH, and MT designed the study. SN collected the costing data, developed the model, carried out the analysis, and wrote the report. ES and LC assisted with the economic analyses. ML, YS, and RN were responsible for the PROLIFICA clinical trial. HN, PS, and ST helped with collecting costing data. All authors read and approved the final manuscript.

Declaration of interests

MT has accepted fees for advisory boards and lectures from AbbVie, BMS, Gilead, Janssen, and Merck. All other authors declare no competing interests.

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