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Cost and cost-effectiveness of a simplified treatment model with direct-acting antivirals for chronic hepatitis C in Cambodia

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Abstract

Background & Aims: In 2016, Médecins Sans Frontières established the first general population Hepatitis C virus (HCV) screening and treatment site in Cambodia, offering free direct-acting antiviral (DAA) treatment. This study analysed the cost-effectiveness of this intervention.

Methods: Costs, quality adjusted life years (QALYs) and cost-effectiveness of the intervention were projected with a Markov model over a lifetime horizon, discounted at 3%/year. Patient-level resource-use and outcome data, treatment costs, costs of HCV-related healthcare and EQ-5D-5L health states were collected from an observational cohort study evaluating the effectiveness of DAA treatment under full and simplified models of care compared to no treatment; other model parameters were derived from literature. Incremental cost-effectiveness ratios (cost/QALY gained) were compared to an opportunity cost-based willingness-to-pay threshold for Cambodia ($248/QALY).

Results: The total cost of testing and treatment per patient for the full model of care was $925(IQR $668-1631), reducing to $376(IQR $344-422) for the simplified model of care. EQ-5D-5L values varied by fibrosis stage: decompensated cirrhosis had the lowest value, values increased during and following treatment. The simplified model of care was cost saving compared to no treatment, while the full model of care, although cost-effective compared to no treatment ($187/QALY), cost an additional $14 485/QALY compared to the simplified model, above the willingness-to-pay threshold for Cambodia. This result is robust to variation in parameters.

Abbreviations: DAA, direct-acting antiviral; DALY, disability adjusted life years; DC, decompensated cirrhosis; FMC, full model of care; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ICER, incremental cost-effectiveness ratio; IQR, interquartile range; LMIC, low- and middle-income countries; MSF, Médecins Sans Frontières; QALY, quality adjusted life years; SMC, simplified model of care; SVR12, sustained virological response at 12 weeks after the end of treatment; WHO, World Health Organization; WTP, willingness to pay.

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Conclusions: The simplified model of care was cost saving compared to no treatment, emphasizing the importance of simplifying pathways of care for improving access to HCV treatment in low-resource settings.

KEYWORDS

cost-effectiveness, direct-acting antiviral treatment, healthcare costs, hepatitis C, low-income population, Markov process, treatment costs

1 | INTRODUCTION

The World Health Organization (WHO) estimated that 71 million people were infected with the Hepatitis C virus (HCV) globally in 2015.[1] Most (80%) HCV infections are in low- and middle-income countries (LMIC),[2] but fewer than 5% of these patients are diagnosed.[3]

HCV is a major contributor to liver cancer and overall cancer deaths in Cambodia and Asia.[4,5] Southeast Asia has the second highest burden of viral hepatitis mortality globally.[1] More than 11 million people are estimated to have antibodies to HCV in this region,[6] with 2.3% of Cambodians exposed to HCV.[7]

Direct-acting antivirals (DAAs) offer an effective cure for HCV with few side effects. Access to these medicines, however, has been limited by their high cost, alongside the cost of diagnostics and the infrastructure required for scaling up treatment.[3,8] In Cambodia, healthcare expenditure per capita is low ($69 in 2012); of this 60% comes from patient out of pocket expenses.[9] Despite limited funding, ongoing government health initiatives provide tuberculosis, malaria and HIV/AIDS treatment free at the point of care. However, there is no national HCV strategy, with procurement of HCV drugs left entirely to the private sector.

In 2016, in collaboration with the Ministry of Health, Médecins Sans Frontières (MSF) established the first general population HCV testing and treatment site in Phnom Penh, Cambodia, offering free DAA treatment. The initial model of care for HCV treatment, based on 2016 European Association for the Study of the Liver guidelines,[11] was subsequently simplified in 2017 by reducing the number of patient visits and treatment monitoring conducted, with data suggesting this did not adversely affect patient outcomes (cure rate and incidence of serious adverse events).[10]

In this study, we evaluate the cost-effectiveness of both the full and simplified models of care implemented by MSF. To our knowledge, this is the first study to conduct a full costing and cost-effectiveness analysis of a real-world HCV treatment intervention in a LMIC. This includes Cambodian patient-level data on EQ-5D-5L health states for different HCV disease stages and the cost of healthcare for HCV-related liver disease.

Lay Summary

- Access to treatment for Hepatitis C virus (HCV) has been limited in low and middle-income countries because of the high cost of drugs and complex treatment protocol.
- Médecins Sans Frontières screened and treated patients for HCV in Phnom Penh, Cambodia, with a simple treatment protocol with fewer visits (than standard of care), point of care testing and task shifting from doctors to nurses.
- The simple treatment protocol saved money and had better outcomes projected over the lifetime of the cohort patients compared to if they had not received HCV screening and treatment.

2 | METHODS

This study evaluated the cost-effectiveness of MSF's HCV treatment program in Cambodia[10] in terms of cost per quality adjusted life year (QALY) gained using a Markov state-transition model representing the lifetime disease progression of a cohort of HCV-infected patients. Model parameters, health state values and costs were based on data from the cohort of patients screened and treated as part of the program, as well as from the literature. Compared to a counterfactual of no treatment, we evaluated two strategies implemented by MSF: the initial full model of care (FMC), and simplified model of care (SMC).

2.1 | Setting and models of care

Patient characteristics, costs and quality of life data were collected from an observational cohort study evaluating the 'real-world' effectiveness of DAAs for the treatment of chronic HCV infection in adults (≥18 years). This study was conducted at MSF's HCV clinic, embedded within the gastroenterology department of the Preah Kossamak Hospital in Phnom Penh.[10] Clinic staff were employed by MSF, with a small number of nurses and doctors seconded from the Ministry of Health.

The FMC and SMC both included processes for HCV diagnosis and liver disease staging, following which patients either began treatment, were referred for further tests to determine eligibility or control comorbidities, or were determined to be ineligible for treatment.[10] Treatment regimens were based on sofosbuvir with daclatasvir or sofosbuvir with ledipasvir, with sofosbuvir/daclatasvir used as a pan-genotypic regimen in the SMC. Each patient was tested for sustained virological response at 12 weeks after the end of treatment (SVR12) to determine if treatment was successful. The SMC used point of care tests (SD Bioline and GeneXpert) for diagnostics while the FMC used an external lab for ELISA and PCR confirmation. In the SMC, compared to the FMC, the number of sessions where nurse-counsellors discussed risk factors, adherence and lifestyle education with patients were reduced (from ten to two),

genotype testing was eliminated, three blood tests for monitoring during treatment were removed, patient visits during treatment were reduced from eight to four, with some tasks shifted from doctors to nurses and pharmacists (Figure 1, Table S1). The FMC includes patients initiated on treatment from September 2016 through March 2017, and the SMC includes patients initiated on treatment from August 2017 through April 2018. March to August 2017 was a transition phase in which the model of care was gradually simplified—this phase is not considered here.

Written consent was obtained from all patients. Ethics approval for this study was obtained from the French Comité de Protection des Personnes of Saint-Germain-en-Laye (reference: 16049) and the National Ethical Committee for Health Research of the Cambodian MoH (reference: 005 NECHR). Official permission for this study was obtained from the Director of Kossamak Hospital.

2.2 | Costing methods

The costs of HCV diagnosis and treatment were estimated from the provider's perspective in 2017 US dollars, using a retrospective cohort-based approach over a 9-month period (September 2016–May 2017). Data on costs came from MSF's expenditure records and price lists, which were allocated to activities making up the FMC as described above, with subtotals calculated for clinic visits, laboratory tests, DAA and other medicines and diagnosis costs.

2.2.1 | Patient-level resource use

Detailed patient-level data on the numbers and types of visits and tests undertaken for patients receiving each model of care were collected from electronic individual patient records.[12] Costs of case-finding were included as the cost of testing patients who were not found to be chronically infected. Data on the quantity of DAAs and other medicines received by each patient during the intervention came from pharmacy dispensing records. Staff time was allocated for each activity through the use of staff time sheets completed over the course of one week by patient-facing staff, direct observation and interviews with staff and according to the number of patient interactions in the observation period.

2.2.2 | Valuation of resources

Valuation of the resources used in the intervention was based on detailed financial records provided by MSF using activity-based costing. The cost per activity within the intervention, for example the baseline treatment visit, was estimated as the sum of ingredients (Table S5). These ingredients, such as cost per minute of doctor or counsellor time or cost of clinic facilities per patient visit, were estimated from the financial records during the observation period when the FMC was implemented. Activity cost estimates from the FMC during the observation period were adapted to estimate the costs of the SMC based on interviews with project staff to determine how activities and their ingredients differed between the models of care. Unit costs for medicines were derived using the 2017 MSF Access campaign negotiated costs for DAAs and other medications. The costs of laboratory tests contracted outside of the intervention were gathered from hospital price lists and from invoices billed to MSF (Table S6). In the base case we exclude costs specific to MSF and replace staff costs for international staff with what local staff would be paid by MSF for the

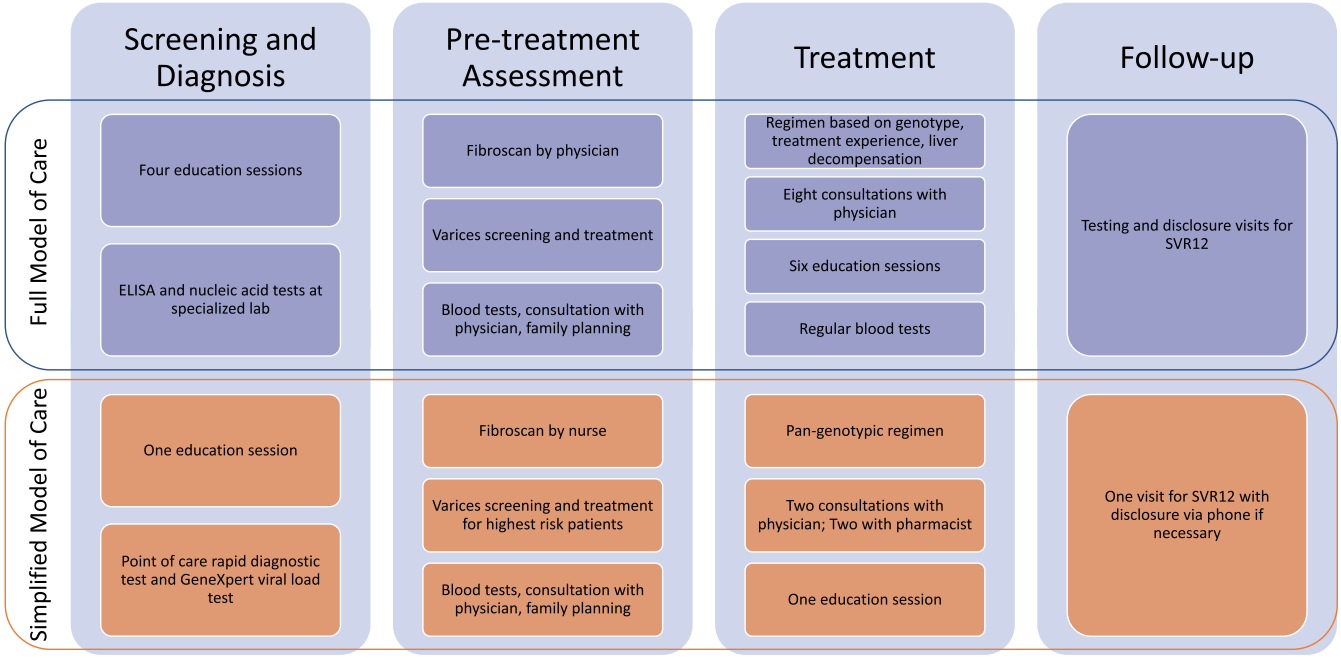

FIGURE 1 Summary of differences between full (top, blue) and simplified (bottom, orange) models of care at each phase of the screening and treatment process. Full details included in Table S1

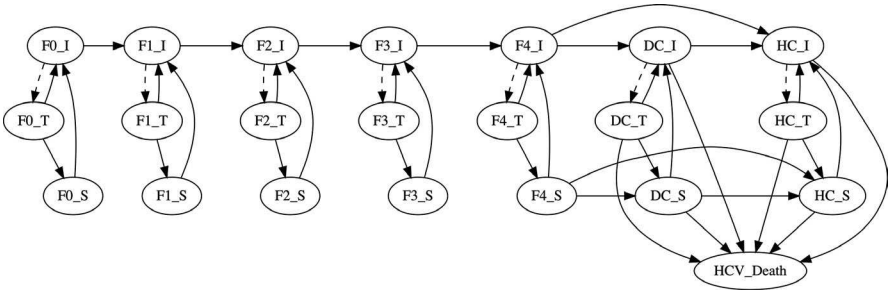

FIGURE 2 Schematic of Markov model showing how patients progress through infection and liver disease states. Dashed lines indicate initiation on treatment. I = infected; T = on treatment; S = susceptible. Baseline mortality occurs according to cohort age, with equal death rates for all compartments (not shown in figure)

TABLE 1 Model parameters and their distributions for the probabilistic sensitivity analysis

Variable	Base-case value	Distribution in PSA	Distribution parameter(s)[a]	Source
Fibrosis progression (annual transition probability)				
Mild fibrosis (F0) to Mild fibrosis (F1)	0.117	Normal	0.005	36
Mild fibrosis (F1) to Moderate fibrosis (F2)	0.085	Normal	0.004	36
Moderate fibrosis (F2) to Moderate fibrosis (F3)	0.121	Normal	0.0046	36
Moderate fibrosis (F3) to Severe fibrosis (F4)	0.115	Normal	0.004	36
F4 to DC	0.039	Beta	14.6, 360.2 (95% CI 0.022-0.046)	37
F4 or DC to HCC	0.014	Beta	1.9, 136.1 (95% CI 0.0016- 0.039)	37
F4 to DC after SVR achieved	0.070 * F4 to DC	Triangle [95% CI of base case 0.03-0.2 *F4 to DC]	0.00066, 0.00922, 0.00273	37,38
F4 or DC to HCC after SVR achieved	0.230 * F4 or DC to HCC	Triangle [95% CI of base case 0.16-0.35 *F4 to DC]	0.000256, 0.01365, 0.00322	37,39
Liver-related mortality (annual transition probability)				
DC to liver death	0.130	Beta	147.03, 983.97 (95% CI 0.11-0.15)	37
HCC to liver death	0.430	Triangle	0.40,0.44	37
Viral re-infection (annual transition probability)	0	Triangle	0, 0, 0.01	
SVR12 rate				Cohort
Full	0.968	Binomial	0.968, 624 (95% CI 0.950-0.980)	
Simplified	0.940	Binomial	0.940, 1324 (95% CI 0.925-0.952)	
Cohort initial age	55.9	Normal	10.6	Cohort

[a]Distribution parameters for PSA: Normal: standard deviation; Triangle: lower, peak, upper; Beta: α [shape1], β [shape2]; Binomial: proportion, sample size.

same role. More details on costing methods can be found in the supplementary material (Methods S1).

2.2.3 | Cost of hepatitis C-related disease

Information on patient access to healthcare for HCV-related liver disease prior to treatment was gathered through a resource-use questionnaire administered to a subset (n = 144, liver disease stages F0-F4) of diagnosed patients at their initial visit. The questionnaire asked patients to recall the number of hospital inpatient or outpatient and clinic visits (health system contacts) in the 6 months prior to coming to the MSF clinic. We assumed that contacts in 6 months represented half of the annual number of contacts. For each type of visit, the patient was further asked to recall the reason and the price paid for the most recent visit. We use patient-reported costs to represent the cost of care in the base case because prior to the MSF program, all relevant costs would be the responsibility of the patient (Methods S2).

Patients with fibrosis stage F0 (no liver damage) were assumed to represent a baseline number of health system contacts (visits) for those without liver disease, with the number of visits for more advanced disease states being modelled using Poisson regression from the questionnaire data. The patient-reported mean cost per visit was then multiplied by the modelled annual number of visits to calculate the annual cost of liver disease care for each fibrosis stage (Methods S2). Estimates of the yearly cost of decompensated cirrhosis (DC) and hepatocellular carcinoma (HCC) were based on reviews of patient records in three hospitals analysed and adjusted through a WHO-facilitated expert discussion. In the base case, we assume that 70% of patients with these disease stages access this care based on expert opinion (Methods S2). The estimated costs of healthcare are assumed to apply to infected patients of all disease stages and cured patients with F4, DC and HCC.

2.3 | Simulation model

The costs and outcomes of each treatment strategy were projected for a cohort of diagnosed patients using a Markov model with annual time steps. The cohort is defined by the number of individuals diagnosed with chronic HCV infection, allocated to liver disease severity categories according to the distribution found among patients who had a fibrosis score recorded. The model schematic (Figure 2) shows progression characterized by different stages of liver disease severity. The modelled health states include stages for METAVIR fibrosis scores F0, F1, F2, F3, F4 (cirrhosis),[14] DC and HCC. Each of the seven modelled health states has three possible HCV states (infected, on treatment and cured/susceptible). Patients are modelled to receive treatment in the first year of the simulation, with the proportion treated in each fibrosis stage matching the treatments in the intervention data.

Liver disease-related mortality (assumed to occur in the DC and HCC states only) and background age-dependent mortality (Figure S1) were modelled as absorbing health states. The number of liver transplants performed in Cambodia is negligible, and so was not modelled. The model was implemented in R version 3.6.1 using the *heemodpackage*.[15,16]

2.3.1 | Disease progression rates

Parameter values for progression through disease states were sourced from previous studies (Table 1). Each patient started in one of seven liver disease states according to the distribution in the cohort. At the end of each cycle, patients either remain in the same state, move into a more advanced disease state or die from background or HCV-related mortality (Figure 2). In the base case we assume there is no re-infection following curative treatment. The SVR12 rate was calculated for the FMC and SMC from patients who were due to complete treatment at least 12 weeks before the data export date (17 July 2018), with those not tested for SVR12 for any reason, including loss to follow-up and death, counted as not achieving SVR12 (treatment failure). Patients who fail treatment return to the infected states and are assumed to face the same risks of liver disease progression as untreated patients, while cured patients move to a susceptible compartment in the same liver disease stage they were treated in. Being cured stops disease progression in pre-cirrhotic patients while it is slowed in cirrhotic patients.

2.4 | Outcomes

The Khmer version of EQ-5D-5L[17] was used to collect health-related quality of life measures for patients (4934 total individuals) with chronic HCV infection prior to treatment initiation, during treatment and at the SVR12 visit after treatment. Where multiple records were available for a patient at a given treatment stage, we combined these into a single measure using a time-weighted average. Patients who failed treatment (n = 62) were not included in the after-treatment analysis. EQ-5D-5L measures were stratified by fibrosis stage and converted to health state values using the EQ-5D-5L value set available for Indonesia,[18] as this is the closest country in the same World Bank income group where a value set is available. Health state values for each model compartment were estimated using a linear mixed-effects model with patient as a random effect and fibrosis stage and treatment stage as fixed effects.

2.5 | Cost-effectiveness analysis

We evaluated the cost-effectiveness of the FMC and SMC compared to no HCV treatment in the study population. The model was run for 100 years to cover the full lifetime of the cohort, with a baseline discount rate of 3% for both future costs and outcomes.[19] Cost-effectiveness was evaluated in terms of lifetime costs per QALY gained, or the incremental cost-effectiveness ratio (ICER) for each strategy. This was compared to an empirical opportunity cost-based willingness-to-pay (WTP) threshold of $248 per QALY gained[20] and to the commonly used threshold of GDP per capita ($1270).[21]

2.6 | Sensitivity analysis

We accounted for uncertainty in key parameters by conducting a probabilistic sensitivity analysis, in which 1000 parameter sets were sampled from their statistical distributions (Table 1). The cost of treatment for each fibrosis stage was varied according to the data in a triangular distribution of the median and inter-quartile range (IQR, Table S4). Cost of care was varied in a triangular distribution according to the bootstrapped 95% confidence interval for F1-F4 (Table 2) and according to the range of consensus values for DC and HCC. Health state values were varied in a triangular distribution of the mean and 95% confidence interval for each fibrosis stage and time point (Table 3).

In addition, we conducted one-way sensitivity analyses by varying key parameters in the model to minimum or maximum values to test model assumptions. This included changing the DAA cost to be $120 per treatment course for every patient instead of varying by individual, removing or doubling the cost of care for liver disease, using WHO-CHOICE estimates of the cost of care instead of patient-reported costs for F0-F4[22] (Methods S2) and varying the percentage of end stage liver disease patients (DC or HCC) accessing care from 70% to 40% or 100%. In addition, we analyse the inclusion of MSF-specific indirect costs, alternative discount rates of 0% or 7%, reducing the time horizon to 10 years from 100 years, allowing for re-infection with HCV at 1% or 10% per year (except for patients with HCC) and changing the initial age of the cohort to 45 or 65. We evaluated how the cost-effectiveness of treatment would vary if screening yielded antibody prevalences of 2.3% (the national estimate[7]), 10% or 30%, compared to 65% as observed in the cohort. For these sensitivity analyses, we assumed 72% chronic infection among those that are antibody positive, as found in the cohort. We also present results using an alternative EQ-5D-5L value set from Thailand[23] and disability values from the 2016 Global Burden of Disease study to estimate health state values in the form of disability adjusted life years (DALY, Table S10). We evaluate the effect of patients having equal treatment rate across all fibrosis stages, matching the overall treatment rate in the cohort of 64%, or if the cost of treatment is assumed to be the overall average mean cost rather than varying by fibrosis stage. We evaluate the result if core antigen testing ($20/test[24]) was used in a one-step screening process (no antibody testing) or to replace the confirmatory test and if the SVR rates for both models of care were reduced by 20% (to 75% and 77% for the SMC and FMC respectively).

3 | RESULTS

3.1 | Cohort treatment outcomes

Of 15 112 patients screened, 7131 patients were diagnosed with chronic HCV (47%), 6831 referred to care and 4550 (64% of diagnosed) initiated treatment between 19 September 2016 and 30 April 2018 (Figure S4). The mean age of those treated was 55.9 (SD 10.6) years and 57% were female. Patients with cirrhosis (F4), DC or HCC made up 32.8% of diagnosed patients and 44.5% of treated patients (Table S2).

Under the FMC and SMC, 624 and 1324 patients initiated treatment and were followed-up to at least 12 weeks post treatment respectively. These individuals were included in the costing and outcomes analysis, while patients treated during the transitional phase between the models of care were excluded from analysis (Figure S4). Characteristics of patients treated under each model of care are presented in Table S3. In the FMC, 96.8% (95% confidence interval 95.0%-98.0%) of patients achieved SVR12, while 94.0% (92.5%-95.2%) achieved SVR12 in the SMC. Treatment regimens were based on sofosbuvir with daclatasvir in 56% and 98% of patients in the FMC and SMC, respectively, with the remaining treatments being sofosbuvir with ledipasvir.

3.2 | Costs of HCV treatment

The median total cost of HCV testing and treatment for the FMC was $925 (IQR $668-1,631) and $376 (IQR $344-422) for the SMC (Figure 3, Table S4). The biggest contributor to the overall cost in both models was DAA costs, making up 26% and 42% of the total treatment cost for the FMC and SMC respectively.

3.3 | Cost of hepatitis C-related disease

The number of health system contacts reported in the resource-use questionnaire is presented in Table 2 and Figure S2. The mean cost per visit was $72.34 (bootstrapped 95% CI $49.35-$110.81) and the annual cost of care ranged from $39.06 for F0 to $226.42 for F4 (Table 2). From the WHO-facilitated expert discussion, the annual cost of inpatient care for a patient with decompensated cirrhosis was $347 (varying from $236 to $457 in provincial versus national hospital settings) and for hepatocellular carcinoma was

TABLE 2 Reported health system contacts by fibrosis stage, with Poisson modelled annual number of health system contacts, in addition to the contacts by an F0 patient

Disease stage	N	Mean, (IQR) reported health system contacts in last 6 months	Modelled annual number of health system contacts attributable to liver disease, relative to F0 (95% CI)	Mean annual healthcare cost (95% CI)
F0	17	1.0, (0-1)	0	$0.00
F1	42	1.2, (0-1)	0.54 (0.016-1.19)	$39.06 ($9.63-$84.65)
F2	29	1.8, (0-2)	1.22 (0.032-3.05)	$88.25 ($19.27-$227.88)
F3	14	3.4, (0-6)	2.07 (0.048-5.94)	$149.74 ($48.93-$418.25)
F4	37	2.3, (0-3)	3.13 (0.065-10.45)	$226.42 ($73.91-$728.10)

TABLE 3 Health state values (mean and 95% CI) by disease stage and treatment time point estimated from mixed-effects model with patient as a random effect

	Health state value		
Disease stage	Before treatment	During treatment	After treatment (cured)
F0	0.86 (0.85-0.88)	0.90 (0.89-0.91)	0.93 (0.92-0.94)
F1	0.86 (0.85-0.87)	0.90 (0.89-0.91)	0.93 (0.92-0.94)
F2	0.85 (0.84-0.86)	0.89 (0.87-0.90)	0.92 (0.90-0.93)
F3	0.87 (0.86-0.87)	0.91 (0.90-0.91)	0.94 (0.93-0.94)
F4	0.85 (0.84-0.85)	0.88 (0.88-0.89)	0.91 (0.91-0.92)
DC	0.75 (0.74-0.77)	0.79 (0.77-0.81)	0.82 (0.80-0.84)
HCC	0.78 (0.75-0.81)	0.82 (0.79-0.85)	0.85 (0.82-0.88)

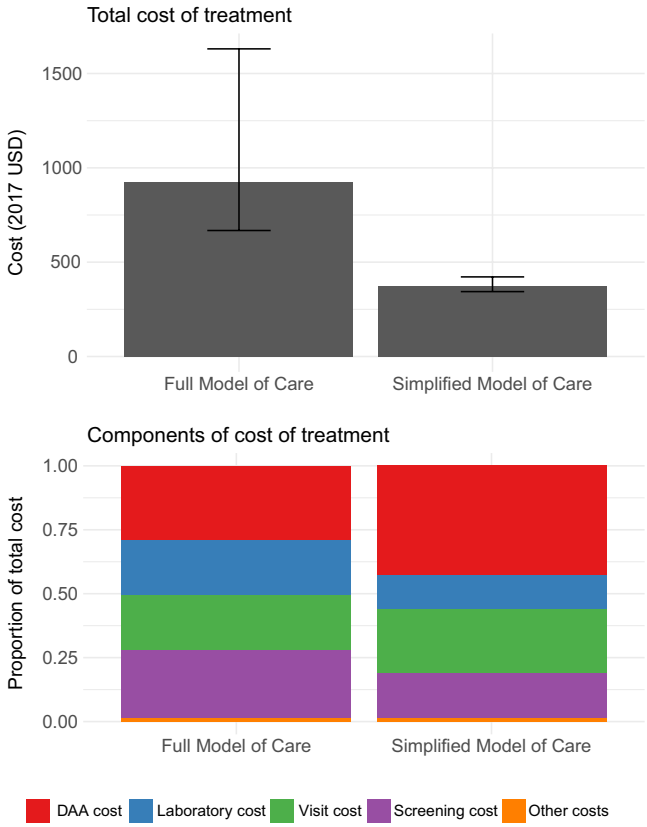

FIGURE 3 Median and interquartile range of overall cost of treatment (top) and median proportion of overall cost of treatment attributable to different activities (bottom) under the full and simplified models of care. DAA, direct-acting antivirals

$424 ($368-$576). The alternative estimates based on WHO-CHOICE gave an annual cost of care for F0-F3 of $28.27 and $216.51 for F4.

3.4 | Health state values

Health state values generated through EQ-5D-5L varied by fibrosis stage and treatment status. The health state value increased by 0.039 (95% CI 0.032-0.046) during treatment and 0.068 (95% CI 0.061-0.075) after treatment, compared to pretreatment levels. Patients with DC had the lowest health state values, 0.11 (95% CI 0.090-0.13) lower than patients in F0, while patients with HCC had health state values 0.083 (95% CI 0.050-0.12) lower than patients in F0. Fitted health state values for each disease and treatment state used in the model are shown in Table 3. The health profiles (proportion of individuals with each level for the five dimensions) reported in EQ-5D-5L are presented in Tables S7-S9.

3.5 | Cost-effectiveness

The FMC compared to no treatment was cost-effective ($187/QALY) compared to the opportunity cost WTP threshold ($248) and GDP threshold ($1270). The SMC was cost-saving (−$91/QALY, Table 4) compared to no treatment. The incremental benefit of implementing the FMC compared to the SMC costs $14 485/QALY. These results are robust to parameter variation in the probabilistic sensitivity analysis, with 94.0% of runs for the SMC being cost-saving and 99.7%

TABLE 4 Incremental cost-effectiveness of full and simplified models of care for the base case. Time horizon is 100 years and discount rate is 3%

	Cost (USD) per capita		QALY per capita		ICER
Strategy	Total	Incremental	Total	Incremental	Cost/QALY
No treatment	$1,298	–	7.49	–	Dominated
Simplified Model of Care	$1,185	−$113	8.72	1.24	−$91
Full model of care	$1,534	$350	8.75	0.024	$14,485

being cost-effective compared to the opportunity cost threshold (Figure S3).

3.6 | Sensitivity analysis

When key model parameters are varied the SMC generally remains cost-saving compared to no treatment (Figure 4), while the FMC is never cost-effective compared to the SMC (Table S11). The only changes which make the SMC not cost-saving are reducing the cost of care for all HCV-related liver disease to $0 ($205/QALY), using WHO-CHOICE costs for F0-F4 liver disease care ($29/QALY), increasing re-infection rate to 10% per year ($39/QALY), or reducing screening prevalence to 2.3% ($28/QALY), all of which are still cost-effective compared to the opportunity cost WTP threshold ($248). The SMC would remain cost-saving at an antibody prevalence of 3% or a re-infection rate up to 6%/year.

4 | DISCUSSION

Our analyses suggest that an HCV testing and treatment intervention undertaken among the general population in Cambodia could be cost-saving when a simplified model of care is used. This simplified model of care provides similar high rates of cure to the initially implemented but more costly full model of care.[10] Although the full model of care resulted in a small incremental benefit of 0.03 QALYs per person compared to the simplified model, this occurred at approximately triple the cost per treatment, and was not cost-effective compared to the simplified model of care.

4.1 | Strengths and limitations

The main strength of this study is the use of detailed data from a real-life implementation of HCV testing and treatment in a LMIC, including a full activity-based costing analysis instead of expert opinion to calculate the costs of screening and treatment. We also surveyed patients directly about their healthcare resource use prior to seeking HCV treatment in order to estimate the cost of medical care for patients living with HCV; to our knowledge this is the first time this has been done in a LMIC. Unfortunately, these estimates are limited by the long recall period used, and reliance on patient-reported expenditure. This is likely to be an underestimate of the full costs of care, resulting in a conservative ICER. A better understanding of the proportion of individuals who access different

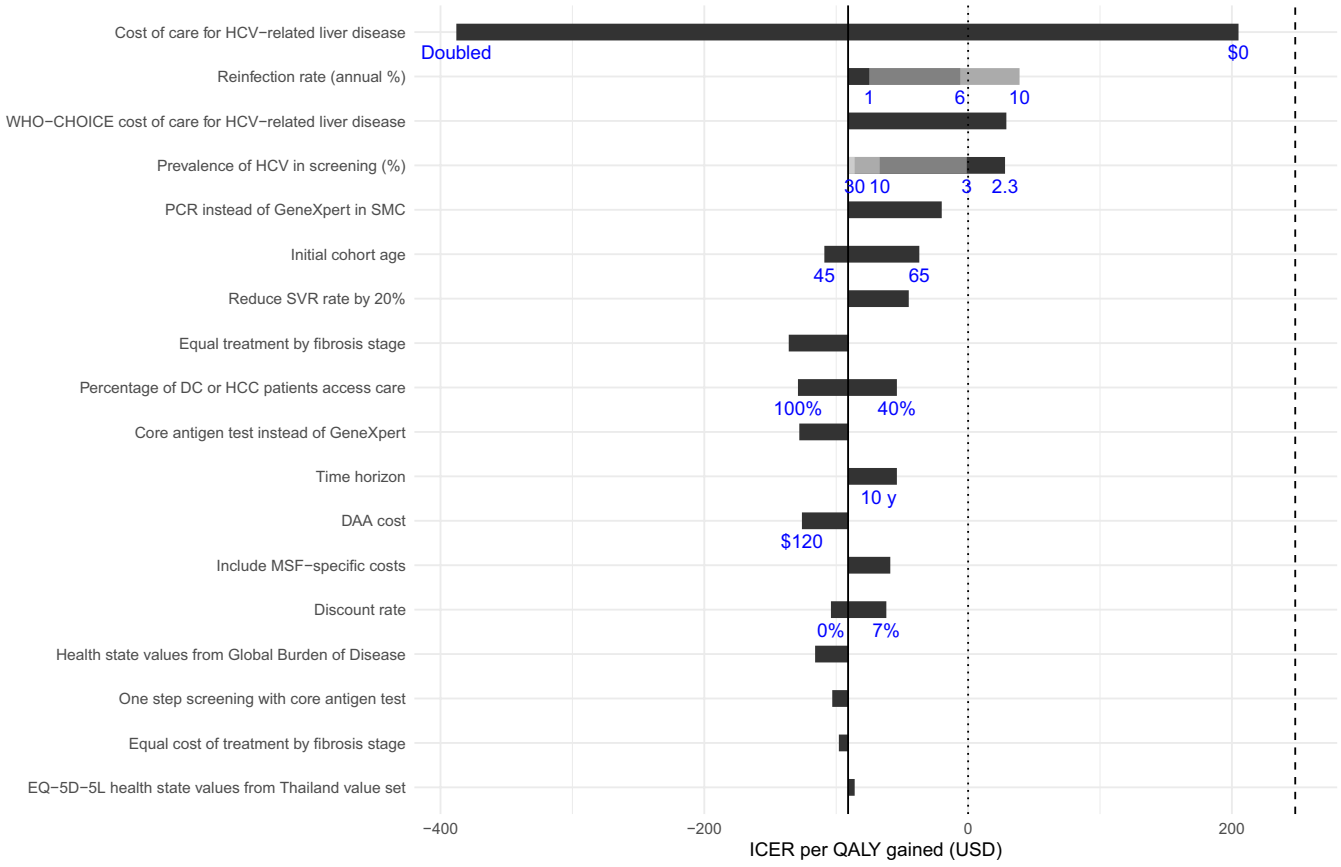

FIGURE 4 Deterministic sensitivity analysis showing simplified model of care ICER compared to no treatment when parameters are varied one at a time. Text on plot shows new parameter value where relevant. Solid vertical line shows baseline ICER of −$91/QALY, dotted line shows $0/QALY (cost-saving threshold), and dashed line shows opportunity cost threshold for Cambodia ($248/QALY). The full set of sensitivity analysis results are shown in Table S11

levels of healthcare, and how this will change in the future, is crucial to improving the accuracy of cost-effectiveness estimates for HCV treatment.

Another strength is that we directly estimated health state utility weights for each stage of liver disease and treatment using EQ-5D-5L questionnaires collected from the treated population. Self-reported quality of life improved during treatment and at SVR12 as compared to baseline, similar to what has been observed in a cohort of patients treated with DAAs in Japan,[25] but with our data adding important information for LMICs.

A main limitation of this analysis is that, because of a lack of information on current re-infection risk we did not account for changes in disease incidence over time in our analysis. However, as a result of the advanced age and fibrosis observed in our cohort of patients, it is likely that many individuals were infected decades ago rather than being at current risk of infection and re-infection. Including a constant re-infection rate made little difference to the result.

Furthermore, the population involved in this intervention were self-selecting, and were therefore highly motivated to receive treatment. The 65% antibody prevalence rate among screened patients indicates many were aware or suspected they were infected with HCV. Globally, fewer than 5% of those infected with HCV are aware of their status,[26] indicating that this high screening yield is not likely to be maintained once individuals who are aware of their status have been treated (warehousing effect). Importantly, though, our projections suggest the intervention remains cost saving even if the screening yield reduces to 3%, with the estimated prevalence for Cambodia being 2.3%.[7] A new sero-prevalence study in rural Cambodia found similar results to the previous estimate, with 2.6% (95% CI 2.3-3.0) prevalence in people 18 years or older, and 5.1% (4.6%-5.7%) in those 45 years or older.[27] This suggests that targeting screening towards older people would help the intervention to be cost-saving, while the intervention would remain highly cost-effective ($28/QALY) with no targeting.

The intervention implemented by MSF demonstrates the feasibility and cost-effectiveness of a general population screening and treatment intervention for HCV implemented by an international NGO. If the intervention were expanded by the Ministry of Health or other local organizations, costs are likely to be different as MSF procured some equipment and consumables outside of Cambodia, and although they set local staff salaries based on competitive local rates, salaries may still vary by organization. To make a detailed implementation plan for HCV screening and treatment, local organizations can evaluate where their costs will differ from MSF. Also, the landscape of diagnostic tools and cost for HCV drugs are both rapidly changing as countries aim to achieve HCV elimination, so it is likely that new technologies will be available for consideration in future implementations.

Although we demonstrate that this intervention is cost-saving, the upfront cost of treatment with the simplified model of care ($311 excluding screening) for an estimated 270 000 chronic infections in Cambodia would be $84 million. The full cost of scaling up screening and treatment will be highly dependent on antibody screening yield, which can be maximized through targeting treatment to groups known to be more likely to be infected, such as the older population.[27]

4.2 | Comparison with other studies

Previous evidence on the cost-effectiveness of treatment with DAA-only regimens for HCV in LMIC is limited, but in agreement with our results. Studies in Egypt[28] and India[29-32] have found HCV screening and treatment to be cost-saving, and cost-effective in Lebanon[33] and Indonesia.[34] The WHO Hep C Calculator,[35] which allows a user to input the cost of treatment, finds HCV treatment (not including testing) in Cambodia to be cost-effective when default values are used and cost-saving when input values from this study are used. However, these previous models do not use data from a real-world intervention, while ours is the first to use data from a local treatment intervention to estimate the costs of testing, treatment and healthcare, as well as quality of life utilities for different stages of HCV disease. Our analysis is therefore an important addition to the literature.

4.3 | Implications and conclusions

Much of the effort towards expanding access to HCV treatment in LMIC has focused on reducing and simplifying the cost of testing and DAA medication. In this cohort, simplification of the treatment pathway quadrupled the number of people that could be treated and cured,[10] reduced the cost of treatment by two-thirds and resulted in the intervention becoming cost-saving. This remained so even if the prevalence of HCV was as low as 3%, suggesting this model of care could be used to expand screening and treatment across Cambodia. Although our study was implemented by MSF, the Ministry of Health in Cambodia and other LMIC can be empowered by these results to scale-up HCV treatment access using a simplified model of care relative to standard international guidelines.[11] Urgent scale-up of treatment access for all infected individuals is necessary to prevent HCV-related mortality and reach HCV elimination as proposed by WHO.[3]

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CONFLICTS OF INTEREST

PV has received unrestricted research grants from Gilead and honoraria from Gilead and Abbvie. MI, JPD, SK, MLP, TM, SB, AL and DM

were employed by MSF and/or by Epicentre, an association created by MSF in 1986 to provide epidemiological expertise to underpin MSF operations. They participated in planning this study, carrying out the research and writing the report. The other authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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