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Cost-effectiveness model for hepatitis C screening and treatment: Implications for Egypt and other countries with high prevalence

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Abstract

Hepatitis C Virus (HCV) infection is a major cause of cirrhosis and liver cancer, and many developing countries report intermediate-to-high prevalence. However, the economic impact of screening and treatment for HCV in high prevalence countries has not been well studied. Thus, we examined the cost-effectiveness of screening and treatment for HCV infection for asymptomatic, average-risk adults using a Markov decision analytic model. In our model, we collected age-specific prevalence, disease progression rates for Egyptians, and local cost estimates in Egypt, which has the highest prevalence of HCV infection (~15%) in the world. We estimated the incremental cost-effectiveness ratio (ICER) and conducted sensitivity analyses to determine how cost-effective HCV screening and treatment might be in other developing countries with high and intermediate prevalence. In Egypt, implementing a screening program using triple-therapy treatment (sofosbuvir with pegylated interferon and ribavirin) was dominant compared to no screening because it would have lower total costs and improve health outcomes. HCV screening and treatment would also be cost-effective in global settings with intermediate costs of drug treatment (~\$8,000) and a higher sustained viral response rate (70–80%).

Keywords

Cost effectiveness; Hepatitis C; screening; treatment; Egypt

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Introduction

Hepatitis C Virus (HCV) infection is a major cause of cirrhosis and liver cancer, affecting as many as 170 million individuals globally, and about 350,000 die annually from HCV-related diseases. (WHO, 2011). Because of the progressive nature of HCV infection, infected individuals are at a higher risk of developing complicated liver diseases, accounting for 27% and 25% of the worldwide prevalence of cirrhosis and hepatocellular carcinoma (HCC). (Perz, Armstrong, Farrington, Hutin, & Bell, 2006; Tong, el-Farra, Reikes, & Co, 1995). Around the globe, Egypt, Bolivia, Mongolia and Cameroon have the highest HCV prevalence (>10%), and other areas of South America, Southeast Asia, and Sub-Saharan Africa regions report high to intermediate HCV prevalence of 2.5–10%. (Fung, Brand, Newhouse, & Hsu, 2011). One particular country having a major problem with both liver cancer and HCV is Egypt. The prevalence of HCV infection among Egyptians is about 10–15%, and the rate is much higher in the older population aged forty to sixty (Shepard, Finelli, & Alter, 2005; Strickland, 2006; Wasley & Alter, 2000). The origin of this ‘epidemic’ was linked to the use of unsterilized and contaminated needles during intravenous mass treatment of populations in Egypt for endemic Schistosomiasis from 1961 to 1985. (Frank et al., 2000; Rao et al., 2002). However, despite the high prevalence of HCV, the level of awareness of HCV is very low, with 78.7% of the Egyptian population having never been tested for HCV infection, and 17.5% of the population have never even heard about hepatitis C. (El-Zanaty & Way, 2009). This underscores the importance and urgency of implementing a national-wide screening and treatment programme for HCV infection in Egypt.

Considering that HCV infection has a long pre-symptomatic period, screening during this period may allow patients to receive treatment before chronic complications develop. (Freeman et al., 2001; Jafferbhoy, Gashau, & Dillon, 2010; Lavanchy, 2009). Recently, a more effective drug, called sofosbuvir, has also come on the market. In combination with other therapies, sofosbuvir dramatically improved a sustained viral response (SVR), compared to a traditional combination therapy of peginterferon and ribavirin (Lawitz et al., 2013). This new therapy has dramatic costs in the developed world, but the manufacturer has given price breaks in Egypt at \$900 for a 12-week course of treatment (Fick & Hirschler, 2014). A recent analysis of this new therapy suggests it may be cost-effective to treat patients already identified with the disease (Obach et al., 2014).

Nonetheless, the economic impact of screening and treatment for chronic HCV in higher prevalence countries has not been well studied. Previous economic analyses have primarily focused on the U.S. population. Those studies did not recommend screening for HCV in the general population and suggested targeted birth-cohort or high-risk population screening only due to the low prevalence of HCV in the United States (Eckman, Talal, Gordon, Schiff, & Sherman, 2013; Liu, Cipriano, Holodniy, & Goldhaber-Fiebert, 2013; Moyer, 2004; Rein et al., 2012; Salomon, Weinstein, Hammitt, & Goldie, 2003; Singer & Younossi, 2001; USPSTF, 2004)).

In this paper, we first use the case of Egypt to estimate the cost-effectiveness of an intervention to provide one-time screening and follow-up treatment for HCV infection,

compared to the current strategy of no screening. We then examine how the conclusions might be generalisable to other developing countries with intermediate-to-high HCV prevalence. Because there are few existing local or national programmes for screening and treating for HCV in the developing world, we analysed the costs and effectiveness of implementing such programmes using local data from Egypt and using a mathematical modelling approach with international standards for economic evaluation.

Methods

Decision analytic model

We developed a Markov model for HCV disease progression to evaluate the cost-effectiveness of universal one-time screening followed by treatment. We used a societal perspective to capture all costs and health effects, and applied a three percent annual discount rate to both cost and effectiveness to convert future dollars and future health outcomes to their present values (Gold, Siegel, Russell, & Weinstein, 1996). Quality-adjusted life years (QALYs) were used as a measure of health outcomes. We evaluated the provision of one-time screening for 40-year-old, asymptomatic, average-risk adults in Egypt, and followed the hypothetical cohorts for 40 years to evaluate long-term disease progression and costs. In the sensitivity analyses, different time horizons and age cohorts were examined. This model followed the natural history of HCV and used the best-available sources of evidence. (Deuffic-Burban, Mohamed, Larouze, Carrat, & Valleron, 2006; Lehman & Wilson, 2009)

Figure 1a provides a schematic diagram of the decision tree for the screening and treatment strategy. Screening involves third generation enzyme-linked immunosorbent assay (ELISA), followed by confirmation with polymerase chain reaction (PCR). The specificity and sensitivity of ELISA are 99% and 98.6% respectively, whereas both the sensitivity and specificity of PCR are 100% (Pawlotsky et al., 1998). Because PCR is 100% specific, 'False Positive' individuals only incur extra testing costs and then advance to the 'Healthy' category in the Markov model (Figure 1b). 'True Positive' individuals are recommended for treatment although they may not choose to receive treatment. 'False Negative' individuals follow the natural history of HCV progression. 'True Negative' individuals follow age-specific mortality patterns of 40-year-old Egyptians (WHO, 2010). In the treatment phase, patients with HCV infection receive up to 48 weeks of treatment. If the treatment is successful, patients move into the recovery stage, following the general age-specific mortality patterns. Successfully-treated individuals have a chance to be re-infected with HCV following age-specific annual incidence rates of HCV. We assume that unsuccessfully-treated individuals do not have a second opportunity to be treated. If the treatment fails, infected patients follow the natural history of HCV disease progression (Figure 1b).

Progression, prevalence and incidence of HCV infection

To simulate disease progression, we used HCV age-gender-specific annual probabilities of progression from chronic HCV to compensated cirrhosis (Deuffic-Burban et al., 2006). In the sensitivity analysis, we varied the rate of progression to examine how variations in this

rate might influence the results. We included the age-specific prevalence of HCV in Egypt ranging from 4.1 to 39.4% (El-Zanaty & Way, 2009), as well as the annual age-specific HCV incidence in a range of 0.002% – 0.025% (Lehman & Wilson, 2009). We obtained age-gender-specific mortality rates in Egypt from the WHO life tables (WHO, 2010). Detailed tables are provided in the technical appendix.

HCV treatment & quality of life

After screening, we assumed that only 20% of HCV-positive patients choose to receive treatment due to ineligibility for treatment, financial inability or personal preferences to avoid treatment side-effects. A French study reported that only 21.5% of HCV-positive patients received treatment (Piton et al., 1998). Clinical experience of the authors suggested that the probability of receiving treatment might be lower in Egypt than the published estimate. Therefore, we examined a broader range of 10–50% in the sensitivity analysis.

Considering that HCV genotype 4 is dominant among Egyptians, we modelled dual-therapy with pegylated interferon alpha-2b and ribavirin because this combination therapy has shown to be effective in the treatment of HCV genotype 4 (Hasan et al., 2004; Ray, Arthur, Carella, Bukh, & Thomas, 2000). Because of the lack of published studies about the efficacy of treatment in Egypt, Egyptian clinicians provided efficacy estimates based on their clinical experiences. After 48 weeks of treatment, 45% of patients achieved a sustained viral response (SVR), then assumed to be fully recovered from HCV. In addition, based on the clinical data available to the authors, we included a one-time 2.5% chance of relapse after successful treatment. In terms of treatment attrition, all patients had weekly treatment for four weeks followed by lab testing. Only 60% of the original patients continued treatment beyond eight weeks, and then after 12 weeks, 45% of them continued treatment until completion. To evaluate the cost-effectiveness of the new drug, we also included triple-therapy of sofosbuvir in combination with interferon and ribavirin. The limited efficacy data on Egyptian-descent patients with genotype 4 reported 80% of having a SVR. (Kowdley et al., 2013; Ruane et al., 2013)

Liver transplant is the only treatment option for patients with decompensated cirrhosis and HCC (Fink & Jacobson, 2011). Due to little data on liver transplantation in Egypt, we assumed that 10% of patients with decompensated cirrhosis and HCC need liver transplants annually. Among patients who need liver transplants, we assumed 10% of them annually receive transplants with 91.7% success rate of liver transplantation (OPTN/SRTR, 2011).

We assigned health-related quality of life to each stage of liver disease and treatment to assess patient's quality of life over time (Singer & Younossi, 2001). We assumed no loss in quality of life from being identified as HCV-positive. Nevertheless, we examined disutility from the identification of HCV infection with a range from 0.00 to –0.05 because previous studies identified disutility from HCV identification as one of the most significant driver in their models (Plunkett & Grobman, 2005; Rodger, Jolley, Thompson, Lanigan, & Crofts, 1999; Singer & Younossi, 2001). Other parameters related to disease progression, treatment probabilities, and utilities were presented in Table 1.

http://www.ustransplant.org/annual_reports/current/912b_li.pdf

Cost data

We included direct medical costs and lost productivity in this analysis (Table 1). In the base model, we initially used the government hospital costs of drugs and treatment, and then we examined the private hospital costs, which were higher than the government hospital costs. The Egyptian authors provided annual medical costs for patients in each of the disease progression stages. Direct medical costs included hospitalisations, outpatient visits, and laboratory tests. Since we assumed that unidentified patients with chronic hepatitis C receive no treatment, they do not incur any costs at the stage of having asymptomatic HCV infection. After the unidentified HCV-infected patients progress to cirrhosis or liver cancer, they incur much higher costs associated with the progressed diseases.

Treatment costs included liver biopsy, blood count, liver profile, ultrasound, and level 3 patient visits. The cost of dual-therapy was based on receiving one treatment per week over 48 weeks with interferon and ribavirin, including the patient attrition through the treatment process. The cost for each treatment is \$72 at the government hospital and \$225 at the private hospital. Patients with triple-therapy receive 12 weeks of sofosbuvir, which costs \$900 in Egypt, plus the other drugs (Fick & Hirschler, 2014). Sofosbuvir is expected to be available in Egypt by August 2014 and covered by the Ministry of Health and National Insurance Plan.

We also included productivity losses due to side effects from treatment using the average wage of Egyptian workers (ECAPMS, 2011). We assumed that 40% of patients miss three days of work over the four weeks of the initial treatment, and then 15% of patients miss four days over the next eight weeks treatment. The rest of the patients complete 48 weeks of treatment while missing seven days of work. Considering the lack of available data for productivity losses for untreated or unsuccessfully treated individuals who progress to late state liver disease and can no longer work due to severe illness, we only incorporated productivity losses over the treatment period. All costs were converted to 2014 U.S. dollars using the GDP deflator (FRED, 2014; World Bank, 2012) and the exchange rate (OANDA Corporation, 2014) (1 LE=0.14 USD on May 21, 2014).

Secondary analyses

To address various issues arising in Egypt, we examined three different screening scenarios: 1) comparing treatment in the government hospital vs. the private hospital, 2) treatment with dual- versus triple-therapy and 3) screening only males, females, or both.

Sensitivity analyses

To analyse the robustness of the study results, we varied every parameter within plausible ranges based on literature reviews and expert opinions through one-way sensitivity analysis, and we conducted two-way sensitivity analysis on key parameters. Table 1 provided the ranges of each parameter used in the sensitivity analyses. In addition, we addressed parameter uncertainty using probabilistic sensitivity analysis (PSA) that allowed us to vary all of the parameters in the model simultaneously. In the PSA, we used the beta distribution for probability and health-utility parameters, and applied the gamma distribution to cost parameters. Further details of the distributions are presented in the technical appendix.

Global impact analysis

To assess the cost-effectiveness of screening and treatment for HCV infection in other high to intermediate prevalence regions (HCV prevalence > 2.5%), we varied the prevalence of HCV in a range of 2.5% to 10%, and modified the total costs of drug and treatment from low (~\$2,000) to intermediate (~\$8,000) to high (~\$20,000) accordingly. The dual-therapy of pegylated interferon with ribavirin is the standard of care for all HCV genotypes, but there is much promise for the triple-therapy including sofosbuvir. The dual- and triple-therapies would be relevant treatment options for other genotypes in other countries (Fried et al., 2002; Hadziyannis et al., 2004; Manns et al., 2001). Differential response rates to treatment based on each genotype, however, were used in the global impact analysis. Over the 48 weeks of treatment, we used a SVR for HCV genotype 1 in the range of 40 to 50% for dual-therapy, whereas treatment for 24 weeks in patients with genotype 2 or 3 reported higher response rates of about 70–80% (Davis, Alter, El-Serag, Poynard, & Jennings, 2010; Hadziyannis et al., 2004). While new, triple-therapy is promising with 67%–90% of patients achieving a SVR (Lawitz et al., 2013). In this analysis, we varied the response rate from 40%–90% in different regions.

Results

Baseline analysis

Under the base case assumptions, not screening would cost \$1,840 for 19.179 QALYs for a 40-year-old Egyptian over a 40-year time horizon. Implementing a screening programme using triple-therapy was dominant compared to no screening because it would have lower total costs (\$1,816) and lead to higher QALYs (19.229). If 10,000 individuals were screened, we project there to be 360 cases of SVR, 20 fewer cases of decompensated cirrhosis, four averted cases of hepatocellular carcinoma (liver cancer), and one liver transplant averted over the next 40 years. Screening and treatment with dual-therapy was dominated by screening and treatment with triple-therapy since the dual-therapy cost more (\$1,890) and had fewer QALYs (19.206). However, if triple-therapy were not available, the ICER of screening and dual-therapy compared to no screening was \$1,856/QALY. Screening and treatment were effective at lowering costs of disease between \$94 to \$156 per person.

Secondary analyses

As we examined different scenarios of screening and treatment options, screening in a government hospital with triple-therapy was a dominant strategy, mainly due to the averted costs of disease and relatively low costs of therapy. Even the scenario with the highest ICER of \$8,312/QALY (screening females and treating them in the private hospital with dual-therapy) might still be considered to be cost-effective. This ICER was lower than the current WHO guideline that suggests interventions costing less than three times Gross domestic product (GDP) per capita would be considered cost-effective, which is about \$10,000/QALY in Egypt (IMF, 2014; Sachs, 2001).

Sensitivity analyses

One-way sensitivity analyses confirmed that screening and treatment for hepatitis C in Egypt would be cost-effective under most assumptions. Results, however, were highly sensitive to the disutility of being identified as having HCV through screening. If the disutility from being identified as HCV-positive is greater than 0.013, the intervention would not be considered to be cost-effective since the utility loss from becoming aware of one's HCV status would outweigh the utility gain due to treatment. Therefore, the potential psychologically-negative impact from screening would make this screening and treatment programme for HCV in Egypt less favourable. Sensitivity analysis on age shows that screening and treatment with triple-therapy is likely to be cost-saving or highly cost-effective for most age groups. Although the programme is more expensive and gains fewer quality-adjusted life-years in populations of older individuals, it would still be considered cost-effective to screen and treat individuals up to age 60 (Table 5).

Two-way sensitivity analysis showed that the probability of successful treatment with triple-therapy and the cost of triple-therapy may also have significant impacts on the results. If the effectiveness of triple-therapy were much lower (60%, for example) and the cost of triple-therapy were several times higher (\$5,000, for example), the preferred strategy would be to continue to screen the population, but treat them with dual-therapy the willingness-to-pay for a QALY were less than \$10,000.

The cost-effectiveness acceptability curves from the PSA are presented in Figure 3. Among 1,000 iterations of the Monte Carlo simulation, 75% of iterations showed that screening and treatment with triple-therapy would be considered highly cost-effective ($<1 \times \text{GDP}$). Also, the figure shows an 83% chance of screening being cost-effective at $< 3 \times \text{GDP}$.

Global impact analysis

For other countries with intermediate-to-high HCV prevalence, screening and treating HCV may also be cost-effective. Treatment costs have a significant impact on the cost-effectiveness of this policy. The sustained viral response rates can also have a moderate impact, and the prevalence has a small impact on cost-effectiveness of the intervention. For example, in the high HCV prevalence regions ($> 10\%$), high costs of treatment and drug with a lower SVR rate ($\sim 40\%$) would lead a HCV screening and treatment policy to have an ICER of \$33,981/QALY while having low costs and a higher SVR rate would lead to screening and treatment with triple-therapy being dominant (lower costs and better health). We found the highest ICER of \$35,102/QALY in intermediate HCV prevalence regions ($\sim 2.5\%$) with higher costs of treatment and drug ($\sim \$20,000$) and a lower SVR rate ($\sim 40\%$).

Discussion

This study used Egypt as a case study of hepatitis C screening and treatment in the developing world. We found implementing hepatitis C screening and treatment for asymptomatic, average-risk Egyptian adults would be cost-saving with triple-therapy and very cost-effective with dual-therapy. Sensitivity analysis shows that the results are robust to most assumptions. In varying assumptions about costs and HCV prevalence, we found

insights about screening in other developing countries with intermediate-to-high HCV prevalence. The cost of HCV treatment drives cost-effectiveness of HCV screening and treatment in regions with intermediate-to-high HCV prevalence. However, considering that most of the high-intermediate HCV prevalence regions are developing countries where the combined cost of treatment and drugs would be lower, implementing a screening and treatment program for HCV may be cost-effective in those regions. In global settings, countries with higher HCV prevalence, lower costs of treatment, and a higher SVR rate after treatment may find it cost-effective to implement HCV screening and treatment programmes.

Nationwide screening and treatment for HCV in Egypt could have substantial costs, but with corresponding large health benefits. If a screening and treatment programme were implemented for the population aged between 40–44 in all of Egypt – 5.9 million people in this age group (U.S. Census Bureau, 2014), the screening and treatment program would have a cost of 778 million dollars, but save \$920 million in costs of disease and saving 1,697,328 quality-adjusted life years over 40 years. If expanded to most of the population in Egypt screening and treatment could save almost 1.7 million life years from chronic hepatitis C related liver disease over 40 years (Table 5). The immediate plans in Egypt after registering the new drug are to focus on treating HCV patients with liver cirrhosis identified in the past few years, eventually followed by screening and treatment programs for at-risk groups. The last stage will include national screening and treatment of patients from the general population.

Our model was the most sensitive to disutility in being identified as having HCV after screening. It is mostly a psychological, rather than a physical factor, but people may feel worse when they find out that they have HCV. Although a previous study used the value of 0.02 for the disutility (Singer & Younossi, 2001), this value is from the era where treatment consisted of nearly year-long interferon. Without much evidence about this factor, specifically for Egyptians, we left it at zero. We also believe that if treatment were more readily available through a national screening and treatment programme with triple-therapy, any disutility associated with knowledge of HCV infection would be very low because a cure would now be attainable with fewer side effects than in the past. However, if there is compelling evidence that the disutility is real and significant, screening for HCV may cause a net loss in overall quality of life.

The study has some limitations. Our study relied on the international literature to define the clinical progression from HCV infection to chronic liver diseases and relied on clinical experts' opinions. Having more information on this for Egyptian patients would have added to the strength of the conclusions for Egypt. Although using Egyptian data is strength for making conclusions about Egypt, it also may be a limitation to making broader conclusions about other developing countries with intermediate-to-high prevalence. Also, due to the complexity of modelling, our model didn't incorporate dynamic effects on the onward transmission of HCV. Including such effects would only make the screening and treatment programme more favourable. Our use of a model-based approach allows us to use sensitivity analysis on costs and prevalence to examine the anticipated effects in other countries. Also, due to the lack of data on future treatments for HCV, we had to predict future events based

on current data and treatment paradigms. Changes such as advances in treatment options or an unprecedented reduction of HCV prevalence could change our results.

Conclusion

Implementing screening and treatment programmes for HCV in Egypt can be cost-effective methods to reduce the burden of liver disease. Early detection of HCV can lead to appropriate treatment and reduction in the long-term burden of cirrhosis and liver cancer. Screening and treatment may also be cost-effective in regions with high to intermediate HCV prevalence (2.5%–10%). Lower costs of HCV treatment along with a higher sustained response rate after treatment, would be favourable conditions for implementing screening and treatment programmes.

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Appendix

Decision analytic model

We implemented the decision analytic model in TreeAge Pro 2014 Suite (TreeAge Software, Williamstown, Massachusetts).

Incremental cost-effectiveness ratio

The incremental cost-effectiveness ratio (ICER) is defined as the difference in costs divided by the difference in health benefit when two strategies are compared. For example, in this analysis, we evaluated the cost-effectiveness of implementing the screening and treatment programme for HCV infection compared with no screening and treatment program provided. We estimated the ICER using the following formula:

$$ICER = \frac{\text{Costs with the Programme} - \text{Costs without the Programme}}{\text{Benefits (measured in QALYs) with the Programme} - \text{Benefits without the Programme}}$$

The ICER should be not confused with the average cost-effectiveness ratio, which is defined as the cost of an intervention divided by the benefit. Based on microeconomic theory called 'The Marginal Principle: The additional units of a good should be consumed as long as the marginal benefit exceeds the marginal cost', the ICER, not the average cost-effectiveness ratio should be used for resource allocation decisions.

Screening and genotyping for hepatitis C

Considering that hepatitis C is a viral infection of the liver, Hepatitis C Virus (HCV) infection is usually suspected when a blood test shows the presence of hepatitis C antibody. One of the most common blood test is the Enzyme-Linked Immunosorbent Assay (ELISA). The ELISA detects antibodies against recombinant antigens. However, there are concerns about false-positive tests. In this analysis, the specificity of ELISA was 99%, and the sensitivity was 98.6%. We varied these parameters from 95% to 100% in the sensitivity analysis. Therefore, Polymerase Chain Reaction (PCR), which is a laboratory method used to detect circulating HCV RNA in the blood, is conducted to confirm positive ELISA results. Patients who receive positive results on ELISA, but negative results on PCR were considered false positive in this analysis, showing that there was no evidence of HCV infection (Healthy) while they incur costs for screening tests. Based on the results from PCR, doctors determine patients' HCV genotype.

Multiplier for probabilities of progression from HCV to cirrhosis

In this analysis, we presented age-gender specific annual probabilities of progression among Egyptian population. With the limited Egyptian data, we relied on estimates from one published study (Table A). Although the study provided a range around the baseline value, we included a multiplier in the decision analytic model to address uncertainty associated with the study itself.

$$\text{Prob. of Progression from HCV to Cirrhosis} = \text{Multiplier} * \text{Baseline Value}$$

Consequently, the probability of progression from HCV to Cirrhosis was estimated from multiplying baseline values with the multiplier. In the base case scenario, the multiplier was set to 1 so that we assumed that the estimates from the previous study were reasonable. In the sensitivity analysis, however, the multiplier was varied from 0.5 to 1.5. As the multiplier is equal to 0.5, we assumed that the probability of progression from HCV to cirrhosis might be half of the reported estimates. With the multiplier of 1.5, we assumed that the probability of progression was 50% higher than what was reported in the previous study. As we expected, higher multipliers led to more favorable results to the screening and treatment programme since more people were likely to progress cirrhosis from HCV, yielding higher benefits of implementing the screening and treatment programme.

Table A
Age-gender specific annual probabilities of progression
among Egyptian population

(Source: Deuffic-Burban et al, 2006)

Probabilities of progression	Baseline	Range
(1) From chronic hepatitis to cirrhosis		
Women, 0–20	0.0000	0.0000–0.0003
Women, 21–50	0.0068	0.0031–0.0075
Women, 51–70	0.0038	0.0029–0.0101
Women, >70	0.0101	0.0063–0.0365
Men, 0–20	0.0000	0.0000–0.0000
Men, 21–50	0.0073	0.0037–0.0134
Men, 51–70	0.0062	0.0046–0.0162
Men, >70	0.0102	0.0043–0.0407
(2) From cirrhosis to death from liver failure		
All ages	0.0241	0.0317–0.1001
(3) From cirrhosis to HCC		
0–50	0.0020	0.0042–0.0058
51–60	0.0120	0.0127–0.0363
61–70	0.0180	0.0127–0.0434
>70	0.0324	0.0155–0.0511

Table B
Age specific HCV prevalence and incidence in Egypt

(Source: El-Zanaty & Way, 2009 and Lehman & Wilson, 2009)

Age	Prevalence (El-Zanaty, 2009)	Incidence (SD) (Lehman, 2009)
5–9	-	0.010 (0.01)

Age	Prevalence (El-Zanaty, 2009)	Incidence (SD) (Lehman, 2009)
10–14	-	0.014 (0.01)
15–19	4.1	0.021 (0.01)
20–24	4.9	0.029 (0.01)
25–29	6.1	0.041 (0.03)
30–34	11.8	0.056 (0.03)
35–39	13.8	0.076 (0.04)
40–44	23	0.010 (0.05)
45–49	28.6	0.127 (0.06)
50–54	38.3	–
55–59	39.4	–
60+	-	–

Table C
Age-gender specific mortality rates among Egyptian population

(Source: WHO Life Table)

Age Group	Male	Female	Both Sexes
<1	0.0194	0.0171	0.0183
1–4	0.0008	0.0007	0.0008
5–9	0.0002	0.0002	0.0002
10–14	0.0004	0.0002	0.0003
15–19	0.0007	0.0004	0.0005
20–24	0.0010	0.0005	0.0007
25–29	0.0010	0.0006	0.0008
30–34	0.0011	0.0008	0.0010
35–39	0.0015	0.0011	0.0013
40–44	0.0022	0.0016	0.0019
45–49	0.0039	0.0026	0.0032
50–54	0.0071	0.0040	0.0055
55–59	0.0121	0.0063	0.0091
60–64	0.0190	0.0104	0.0145
65–69	0.0314	0.0194	0.0250
70–74	0.0513	0.0357	0.0428
75–79	0.0839	0.0650	0.0731
80–84	0.1370	0.1158	0.1246
85–89	0.2144	0.1917	0.2007
90–94	0.3276	0.3049	0.3133
95–99	0.4573	0.4625	0.4607
100+	0.5487	0.4709	0.4966

Government hospital costs vs. private hospital costs

In Egypt, there are two types of hospitals: public hospitals that provide most of the population who are relatively poor with medical care and private-owned hospitals. Public hospitals are financed and managed by the governmental Ministry of Health and Population (MOHP). There are about 1,000 public hospitals and 2,000 private hospitals in Egypt, but the utilisation of public hospitals far outweighs that of private hospitals, because costs of treatment are much cheaper in public hospitals, and most of the Egyptians cannot afford treatment in private hospitals. For example, drug costs for treating HCV infection are three times higher in private hospitals and treatment costs are twice as much as costs in public hospitals. Although the quality of care in public hospitals has been questioned, such as improper circulation, personal hygiene, and physicians' smoking, the quality issue has not been incorporated into this analysis. Considering that most of Egyptians who have HCV infection are poor and not able to afford treatment at private hospitals, we assumed that patients receive treatment in government hospitals in the base case model.

Probabilistic sensitivity analyses

In order to address parameter uncertainty, we conducted probabilistic sensitivity analyses (PSA) that allowed us to vary all of the parameters in the model simultaneously. In PSA, all parameters in the model were sampled from their parametric distributions. We used a beta distribution for probability and health utility parameters, which is bounded by 0 and 1, and applied a gamma distribution to cost parameters to account for the skewness of cost data. (Table D) We conducted 1,000 Monte Carlo simulations. For each strategy in each simulation, the ICER was estimated, and the cost-effectiveness acceptability curve was constructed to show the probability that a given strategy would be cost-effective at various willingness-to-pay thresholds.

Table D

Distributions used in probabilistic sensitivity analyses

Variable name	Baseline value	Distribution	Parameters
	Base case		
<i>Costs (2014 US dollars)</i>			
Chronic hepatitis C (annual)	139	Gamma	$\alpha = 3.4, \lambda = 0.025$
Compensated cirrhosis (annual)	1,053	Gamma	$\alpha = 7.9, \lambda = 0.0075$
Decompensated cirrhosis (annual)	8,424	Gamma	$\alpha = 9.4, \lambda = 0.0011$
Hepatocellular Carcinoma (annual)	10,421	Gamma	$\alpha = 7.7, \lambda = 0.00074$
Liver transplant (1st year)	51,947	Gamma	$\alpha = 7.7, \lambda = 0.00015$
Liver transplant (annual, after 1st year)	16,848	Gamma	$\alpha = 7.3, \lambda = 0.00043$
Third generation ELISA (one-time)	11	Gamma	$\alpha = 3.1, \lambda = 0.28$
PCR and genotyping (one-time)	184	Gamma	$\alpha = 3.4, \lambda = 0.018$
Treatment	139 (GH)	Gamma	$\alpha = 1.5, \lambda = 0.011$

Variable name	Baseline value	Distribution	Parameters
Dual therapy drugs	244 (PH) 1,795 (GH) 5,616 (GH)	Gamma	$\alpha = 3.2, \lambda = 0.0018$
Triple therapy drugs	1,540 (GH) 2,732 (PH)	Gamma	$\alpha = 2.4, \lambda = 0.0015$
Productivity loss	44	Gamma	$\alpha = 4.8, \lambda = 0.11$
Annual disease progression and treatment probabilities			
Mortality from compensated cirrhosis	0.035	Beta	$a = 12, b = 320$
Mortality from decompensated cirrhosis	0.186	Beta	$a = 3.5, b = 15$
Mortality from hepatocellular carcinoma	0.95	Beta	$a = 19, b = 1.0$
Mortality from liver transplant (year 2 +)	0.03	Beta	$a = 8.7, b = 280$
Progression rate from CC to DC	0.065	Beta	$a = 4.3, b = 62$
Multiplier for HCV to CC progression rate	1	Gamma	$\alpha = 16, \lambda = 16$
Requesting liver transplant	0.1	Beta	$a = 6.3, b = 57$
Receiving liver transplant from waitlist	0.1	Beta	$a = 2.2, b = 20$
Successful liver transplant	0.917	Beta	$a = 49, b = 4.4$
Receiving treatment after HCV identification	0.2	Beta	$a = 51, b = 200$
Successful HCV treatment with dual therapy	0.45	Beta	$a = 6.7, b = 8.2$
Successful HCV treatment with triple therapy	0.8	Beta	$a = 9.3, b = 2.3$
Relapse after successful HCV treatment (one-time)	0.005	Beta	$a = 0.005, b = 0.99$
Sensitivity (ELISA)	0.986	Beta	$a = 86, b = 1.2$
Specificity (ELISA)	0.99	Beta	$a = 62, b = 0.62$
Utilities			
Chronic hepatitis C	0.96	Beta	$a = 22, b = 0.92$
Compensated cirrhosis	0.8	Beta	$a = 12, b = 3.0$
Decompensated cirrhosis	0.56	Beta	$a = 6.0, b = 4.7$
Hepatocellular carcinoma	0.25	Beta	$a = 4.4, b = 13$
Liver transplant (1st year)	0.8	Beta	$a = 12, b = 3$
Liver transplant (after 1st year)	0.95	Beta	$a = 31, b = 1.6$
Dual therapy treatment including side effects	0.9	Beta	$a = 20, b = 2.2$
Triple therapy treatment including side effects	0.95	Beta	$a = 71, b = 3.8$

Figure 1a.

Figure 1b.

Figure 1.

Figure 1a. Schematic for intervention

Figure 1b. Markov model of disease progression

HCV: Hepatitis C; HCC: hepatocellular carcinoma

Boxes represent health states and arrows represent transitions between states.

Figure 2. Two-way sensitivity analysis varying the probability of successful treatment with triple-therapy and the cost of sofosbuvir

The base case assumptions are that treatment success is 80% and the cost of triple-therapy is \$1540 for the course of treatment.

Figure 3.
Probabilistic sensitivity analysis—cost-effectiveness acceptability curve

Table 1

Baseline values, ranges and respective ICER for model variables

Variable name	Baseline value			Range		Reference
	Base case	ICER (Base)	min	max	ICER (min)	ICER (max)
GENERAL						
Perspective of analysis	Societal	Dominant	N/A	N/A	N/A	N/A
Annual discount rate	0.03	Dominant	0.00	0.05	Dominant	318
Population age to be screened (yrs)	40	Dominant	10	60	Dominant	1,418
Time horizon (yrs)	40	Dominant	20	60	Dominant	698
GDP per capita (2014 US Dollars)	3333	Dominant	N/A	N/A	N/A	(IMF, 2014)
COSTS (2014 US Dollars)						
Chronic Hepatitis C (Annual)	139	Dominant	100	400	Dominant	Dominant
Compensated cirrhosis (Annual)	1,053	Dominant	500	2000	Dominant	Dominant
Decompensated cirrhosis (Annual)	8,424	Dominant	4000	15000	Dominant	8
Hepatocellular carcinoma (Annual)	10,421	Dominant	5000	20000	Dominant	Dominant
Liver transplant (1st year)	51,947	Dominant	25000	100000	Dominant	Dominant
Liver transplant (Annual, after 1st year)	16,848	Dominant	5000	30000	Dominant	Dominant
Third generation ELISA (one-time)	11	Dominant	5	30	Dominant	Dominant
PCR and genotyping (one-time)	184	Dominant	100	500	Dominant	1,012
Treatment	139 (GH)	Dominant	50	500	Dominant	Dominant
	244 (PH)	Dominant			Dominant	Dominant
Dual-therapy drugs	1795 (GH)	Dominant	1000	10000	Dominant	Dominant
	5616 (PH)	Dominant			Dominant	Dominant
Triple-therapy drugs	1540 (GH)	Dominant	1000	10000	Dominant	7,225
	2732 (PH)	610			Dominant	Dominant
Productivity loss	44	Dominant	20	100	Dominant	Dominant
ANNUAL DISEASE PROGRESSION AND TREATMENT PROBABILITIES						
Mortality from compensated cirrhosis	0.035	Dominant	0.01	0.05	Dominant	Dominant
Mortality from decompensated cirrhosis	0.186	Dominant	0.05	0.40	Dominant	29

Variable name	Baseline value			Range		Reference
	Base case	ICER (Base)	min	max	ICER (min)	ICER (max)
Mortality from hepatocellular carcinoma	0.95	Dominant	0.80	0.99	Dominant	Dominant (Lehman, 2009)
Mortality from liver transplant	0.083	Dominant	0.01	0.1	Dominant	Dominant (US OPTN/SRTR, 2011)
Age-specific general mortality rate (20–80 yrs old)	0.00081–0.12046	Dominant	N/A	N/A	N/A	N/A (WHO, 2011)
Age-specific HCV incidence rate (20–50 yrs old)	0.00585–0.02547	Dominant	N/A	N/A	N/A	N/A (Lehman, 2009)
Age-specific HCV prevalence (20–60 yrs old)	0.049–0.394	Dominant	N/A	N/A	N/A	N/A (Egypt DHS, 2008)
Age-specific progression rate from HCV to CC (20–80 yrs old)	0.00705–0.01015	Dominant	N/A	N/A	N/A	N/A (Deuffic-Burban, 2006)
Age-specific progression rate from CC to HCC (20–80 yrs old)	0.002–0.0324	Dominant	N/A	N/A	N/A	N/A (Deuffic-Burban, 2006)
Progression rate from CC to DC	0.065	Dominant	0.03	0.15	Dominant	Dominant (Lehman, 2009)
Multiplier for HCV to CC progression rate	1	Dominant	0.50	1.50	Dominant	327 N/A
Requesting liver transplant	0.1	Dominant	0.05	0.20	Dominant	Dominant Estimate
Receiving liver transplant from waitlist	0.1	Dominant	0.05	0.30	Dominant	Dominant Estimate
Successful liver transplant	0.917	Dominant	0.80	0.95	Dominant	Dominant (US OPTN/SRTR, 2011)
Receiving treatment after HCV identification	0.2	Dominant	0.05	0.50	-	7,130 (Piton, 1998)
Successful HCV treatment with dual-therapy	0.45	Dominant	0.20	0.70	Dominant	Dominant Expert
Successful HCV treatment with triple-therapy	0.8	Dominant	0.5	0.95	Dominant	921 (Kowdley, 2013), (Levin, 2013)
Sensitivity (ELISA)	0.986	Dominant	0.95	1.00	Dominant	Dominant (Pawlotsky, 1998)
Specificity (ELISA)	0.99	Dominant	0.95	1.00	Dominant	Dominant (Pawlotsky, 1998)
UTILITIES						
Chronic Hepatitis C	0.96	Dominant	0.84	1.00	Dominant	Dominant (Singer, 2001)
Compensated cirrhosis	0.8	Dominant	0.50	0.90	Dominant	Dominant (Singer, 2001)
Decompensated cirrhosis	0.56	Dominant	0.30	0.88	Dominant	Dominant (Singer, 2001)
Hepatocellular carcinoma	0.25	Dominant	0.10	0.50	Dominant	Dominant (Singer, 2001)
Perfect health	1	Dominant	N/A	N/A	N/A	N/A (Singer, 2001)
Liver transplant (1st Year)	0.8	Dominant	0.50	0.90	Dominant	Dominant (Singer, 2001)
Liver transplant (After 1st year)	0.95	Dominant	0.80	0.95	Dominant	Dominant (Singer, 2001)
Dual-therapy treatment including side effects	0.9	Dominant	0.70	0.95	Dominant	Dominant (Singer, 2001)
Triple-therapy treatment including side effects	0.95	Dominant	0.9	1.0	Dominant	Dominant (Obach, 2014)
Awareness of HCV positive infection	0	Dominant	0.00	–0.05	Dominant	211* (Singer, 2001)

The ICER values are for screening and treatment with triple-therapy. Dominant: Compared to the non-screening strategy, the screening and treatment programme costs less with better quality of life. Dominated: Compared to the non-screening strategy, the screening and treatment programme costs more with worse quality of life. N/A=not applicable. With a decrement of 0.05 utility accompanying awareness of HCV infection, the screening and triple-therapy alternative would still be the least expensive, but it would have fewer QALYs than no screening. No screening would cost more, and would provide 0.135 those additional QALYS at an incremental cost of \$29 for an incremental cost-effectiveness ratio of \$210 per QALY gained over screening and triple therapy.

Cost-Effectiveness Result

Table 2

Intervention	Costs of screening and treatment	Costs of disease	Total cost (\$)	SVR	DC	HCC	LT	Total effectiveness (QALYs)	Incr. Cost (\$)	Incr. Effectiveness (QALYs)	Incr. C-E Ratio (\$/QALY)	Dominance
Discounted results (5% annual discount for both cost and effectiveness)												
No ccreening	-	1,326	1,326	0	0.028	0.0072	0.0011	15.187				
Screening and triple-therapy	132	1,205	1,338	0.036	0.026	0.0068	0.0010	15.223	11	0.036	318	
Screening and dual-therapy	144	1,253	1,397	0.020	0.027	0.0070	0.0010	15.206	59	-0.017		Dominated
Discounted results (3% annual discount for both cost and effectiveness)—Standard												
No Screening	-	1,840	1,840	0	0.028	0.0072	0.0011	19.179	24	-0.05		Dominated
Screening and triple-therapy	132	1,684	1,816	0.036	0.026	0.0068	0.0010	19.229				Dominated
Screening and dual-therapy	144	1,746	1,890	0.020	0.027	0.0070	0.0010	19.206	74	-0.023		Dominated
Undiscounted results												
No Screening	-	3,281	3,281	0	0.028	0.0072	0.0011	29.522	115	-0.089		Dominated
Screening and triple-therapy	132	3,034	3,166	0.036	0.026	0.0068	0.0010	29.611				Dominated
Screening and dual-therapy	144	3,135	3,279	0.020	0.027	0.0070	0.0010	29.572	112	-0.039		Dominated

Cost measured in 2014 USD, Effectiveness measured in QALY, and ICER measured in 2014 USD/QALY.

SVR: Sustained Viral Response. DCC: Decompensated cirrhosis. HCC: Hepatocellular carcinoma (liver cancer). LT: Liver transplant

Dominant: Compared to the no screening strategy, the screening and treatment program costs less with better quality of life

Dominated: Compared to the screening strategy with triple-therapy, the screening and treatment programme with dual-therapy (or no screening) costs more with worse quality of life.

Table 3

ICER under different treatment scenarios

		Male	Female	Both
Government hospital	Triple-therapy	Dominant	Dominant	Dominant
	Dual-therapy	1,633	1,920	1,852
Private hospital	Triple-therapy	454	649	610
	Dual-therapy	7,763	8,312	8,272

Both ICERs are compared to no screening and treatment.

If screening with triple-therapy is available, it dominates screening with dual-therapy in all cases.

Table 4

Global impact of implementing a screening and treatment programme in high to intermediate HCV prevalence regions

	HCV prevalence	Combined cost of treatment and drug	Successful treatment (sustained response rate)	ICER (\$/QALY)
HCV high to intermediate regions	10%	High (~\$20,000)	40 – 90%	33,981–14,472
		Intermediate (~\$8,000)		13,319–4,702
		Low (~\$2,000)		2,988-Dominant
	5%	High (~\$20,000)	40 – 90%	35,102–15,003
		Intermediate (~\$8,000)		14,440–5,232
		Low (~\$2,000)		4109–347
	2.5%	High (~\$20,000)	40 – 90%	37,344–16,063
		Intermediate (~\$8,000)		16,682–6,292
		Low (~\$2,000)		6,351–1,407

Table 5

National impact of implementing a screening and treatment programme with triple-therapy

Age group	Incr. Cost	Incr. Eff.	Population in Egypt (U.S. Census Bureau, 2014)	Total incremental cost (\$ Millions)	Total incremental effectiveness	ICER (\$/QALYs)
10–14	\$2.69	0.00908	8,162,860	\$22.0	74,119	\$297
15–19	(\$0.68)	0.0108	8,639,088	(\$5.8)	93,302	dominant
20–24	(\$6.70)	0.01493	7,863,878	(\$52.7)	117,408	dominant
25–29	(\$8.19)	0.01746	7,586,398	(\$62.1)	132,459	dominant
30–34	(\$20.15)	0.031	7,698,463	(\$155.2)	238,652	dominant
35–39	(\$15.62)	0.03244	7,480,012	(\$116.8)	242,652	dominant
40–44	(\$16.40)	0.04696	5,895,930	(\$96.7)	276,873	dominant
45–49	(\$0.25)	0.0491	4,492,842	(\$1.1)	220,599	dominant
50–54	\$26.01	0.05332	4,013,418	\$104.4	213,995	\$488
55–59	\$133.61	0.02321	3,760,004	\$502.4	87,270	\$5,757
Total			65,592,893	\$138.3	1,697,328	\$0

(\$) represents negative dollars, which mean saving money from the intervention

Incr. Cost/Effectiveness: Costs spent / QALYs gained per person for a screening/treatment programme over 40 years, compared to no-screening

Total Cost/Effectiveness: Total costs / QALYs gained by expanding a screening and treatment programme to each age group.