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COST EFFECTIVENESS ANALYSIS ON THE CONTROL OF HEPATITIS C VIRUS INFECTION TRANSMISSION DYNAMICS

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ABSTRACT

In this paper, we proposed a mathematical model for hepatitis C virus (HCV) transmission dynamics. The cost and health benefits of various control strategies for preventing and curtailing the spread HCV infection were assessed via a computational approach. The MATLAB solver ODE45 is used to examine the impact of each strategy on the total number of infected individuals over the planning horizon. It is found that epidemiological impact of the strategies revealed that strategy E which is combination of: enlightening the susceptible and recruit individuals, screening, counselling and treatment is the most effective. Furthermore, the cost effectiveness of each strategy in terms of Incremental Cost Effectiveness Ratio (ICER) is calculated using Quality Adjusted Life Years (QALYs) as health benefit. The result revealed that HCV can be controlled most efficiently by implementing strategy E as it gives a smaller number of infected individuals and is highly cost effective.

Keywords: HCV, Cost effectiveness, QALYs

INTRODUCTION

Hepatitis C Virus (HCV) is a contagious liver disease that ranges in severity from a mild illness lasting a few weeks to a severe, lifelong illness that attacks the liver (CDC, 2016). It results from infection with hepatitis C virus, which primarily spreads through contact with the blood of an infected person. Hepatitis C virus infection is a blood borne virus and the most common mode of transmission is through exposure to infected blood, this may happen through; sharing of injection needles among intravenous drug abusers, the reuse or inadequate sterilization of medical equipment, especially syringes and needles in health care settings and the transfusion of poorly screened blood and blood products . Based on the report by World Health Organization (WHO) in 2017, globally, an estimated 71 million have chronic HCV infection and approximately 399,000 people die each year from HCV mostly cirrhosis and hepatocellular carcinoma (HCC) (WHO, 2017). Most of newly infected persons are asymptomatic therefore, are unaware of their infection with minorities having symptoms such as jaundice, dark urine, fatigue, nausea, vomiting, and abdominal pain (Kamal, 2008).

The good news about HCV is that antiviral medicine can cure more than 95% of

persons with hepatitis C infection, thereby reducing the risk of death from liver cancer and cirrhosis (WHO, 2019). The bad news is that access to the treatment is very low due the cost of the medicine, especially in low- and middle-income countries. However, unlike HBV infection, there is currently no vaccine for hepatitis C virus infection, but research is ongoing in the direction.

Numerous mathematical models were designed to study the spread of hepatitis C disease in order to suggest some effective strategies to curtail its transmission. For instance, Martcheva and Castillo present an epidemiological model with a chronic infectious phase and variable population size (Martcheva & Castillo-Chavez, 2003). This model was further extended by (Das, Mukherjee, & Sarkar, 2005) by incorporating the immune class. Also, it was later extended by Yuan who consider the latent period (Yuan & Yang, 2008). Furthermore, an epidemic model of hepatitis C considering an isolation class is formulated by Imran and analysed the effects of the isolation class on the transmission dynamics of the disease (Imran, Hassan, & Khan, 2013). Mathematical modelling of hepatitis C treatment for drug injecting users was studied (see, (Zeiler, Langlands, Murray, & Ritter, 2010; Martin, et al., 2011; Nyabadza & Mukandavire, 2011; Edward, Shachter, & Owens, 1998)) where the treated individuals are assumed not to infect the susceptible individuals. There are researches like (Zhang & Zhou, 2012; Shen, Xiao, Zhou, & Li, 2015) about hepatitis C epidemic cases which suggest some measures to control hepatitis C infection in continental China. However, all the aforementioned studies focused on the transmission dynamics and effectiveness of control strategies of HCV, while the cost associated to the implementation of intervention strategies is not discussed. Considering the challenges of limited resources and budget constraints on health sector of developing countries, there is a need to identify the most cost-effective strategy so as to avoid wasting of resource. Thus, in this work we proposed a mathematical model to investigate the epidemiologic and economic impact of control strategies of HCV infection which include: public enlightenment, screening and treatment. We consider the prevalence of HCV of Egypt in 2014 to study the model.

THE MODEL FORMULATION

The total population at time *t* is given by $N(t)$ which is divided into eight mutual exclusive classes; Susceptible unenlightened $S_u(t)$, Susceptible enlightened $S_e(t)$, acute HCV infected undiagnosed $I_u(t)$, acute HCV infected diagnosed $I_a(t)$, chronic HCV infected undiagnosed $C_u(t)$, chronic HCV infected diagnosed $C_a(t)$, infected Individuals with liver cirrhosis undiagnosed $X_u(t)$ and infected Individuals with liver cirrhosis diagnosed $X_a(t)$ so that the total population become;

$$N(t)=S_u(t)+S_e(t)+I_u(t)+I_a(t)+C_u(t)+C_a(t)+X_u(t)+X_a(t).$$

The susceptible unenlightened individuals are generated by the proportion of new entrant that were not enlightened given by $(1-\rho)\Lambda$. The population is decreased by those who acquire infection (at rate λ), those who become enlightened (at rate ε) and the natural mortality (at rate μ). Thus, we have;

$$\dot{S}_u(t) = (1-\rho)\Lambda - (\lambda + \varepsilon + \mu)S_u$$

Where λ is the force of infection define as;

$$\lambda = \frac{\beta\left((\eta_1 I_u + \eta_2 C_u + X_u) + (1-\phi_1)(1-\phi_2)(\eta_3 I_a + \eta_4 C_a + X_a)\right)}{N}$$

The susceptible enlightened population is generated by the proportion of new entrant that are enlightened given by $\rho\Lambda$, the susceptible not enlighten who become enlightened (at rate ε). Indeed, this population further increased due to recovery of individuals in I_a and C_a classes at the rates τ_1 and τ_2 respectively. The population is reduced by those who acquire infection at reduced rate due enlightenment given by $(1-\theta)\lambda$ and natural mortality (at rate μ). So that we have;

$$\dot{S}_e(t) = \rho\Lambda + \varepsilon S_u + \tau_1 I_a + \tau_2 C_a - [(1-\theta)\lambda + \mu)]S_e$$

The population of acute HCV infected undiagnosed is generated due to the infection of individuals in S_u and S_e classes at rates λ and $(1-\theta)\lambda$ respectively. The population is reduced due progression to chronic HCV undiagnosed (at rate σ_1) and screening and counselling (at rate γ_1). However, HCV induced death and natural mortality further decrease this population at the rates δ_1 and μ respectively. This is given as;

$$\dot{I}_u(t) = \lambda[S_u + (1-\theta)S_e] - (\sigma_1 + \gamma_1 + \delta_1 + \mu)I_u$$

The population of acute HCV infected diagnosed is generated by screening and counselling of individuals in I_u (at rate γ_1). The reduction of this population occur due to progression to chronic HCV diagnosed at a reduced rate σ_2 as compared with individuals in I_u class, meaning that ($\sigma_2 < \sigma_1$). Treatment (at rate τ_1), disease induced and natural deaths at the rates δ_2 and μ further reduced the population. Thus, we have

$$\dot{I}_a(t) = \gamma_1 I_u - (\sigma_2 + \tau_1 + \delta_2 + \mu)I_a$$

The population of chronic HCV infected undiagnosed is generated due progression of individuals in I_u class (at rate σ_1) and diminished as a result of screening and counselling (at rate γ_2), progression to liver cirrhosis undiagnosed (at a rate σ_3), disease induced and natural deaths at the rates δ_3 and μ. Thus, we have;

$$\dot{C}_u(t) = \sigma_1 I_u - (\gamma_2 + \sigma_3 + \delta_3 + \mu)C_u$$

The population of chronic HCV infected diagnosed is generated due to screening and

counselling of individuals in C_u class (at rate γ_2) and progression of individuals in I_a class (at rate σ_2). This population is reduced due to treatment (at rate τ_2), progression to liver cirrhosis diagnosed (at a rate σ_4), disease induced and natural deaths at the rates δ_4 and μ correspondingly. Thus, we obtain

$$\dot{C}_a(t) = \gamma_2 C_u + \sigma_2 I_a - (\tau_2 + \sigma_4 + \delta_4 + \mu)C_u$$

The population of individuals who progressed to liver cirrhosis undiagnosed is generated by the progression of individuals in C_u (at a rate σ_3). The population reduced as a result of screening and counselling (at a rate γ_3). It further diminished due to disease induced and natural deaths at the rates δ_5 and μ respectively. So that we have;

$$\dot{X}_u(t) = \sigma_3 C_u - (\gamma_3 + \delta_5 + \mu)X_u$$

Lastly the population of individuals diagnosed with liver cirrhosis is generated by screening and counselling of individual in X_u class (at a rate γ_3) and progression of individuals in class C_a (at a rate σ_4) note that $\sigma_4 < \sigma_3$. The population is reduced as a result of disease induced and natural deaths at the rates δ_6 and μ respectively. So that we have;

$$\dot{X}_a(t) = \gamma_3 C_u + \sigma_4 C_a - (\delta_6 + \mu)X_u$$

Table 1: The Description of Variable of the Model

Variables	Description	Initial Values
$S_u(t)$	Susceptible unenlightened	67,200,000
$S_e(t)$	Susceptible enlightened	16,800, 000
$I_u(t)$	Acute HCV infected undiagnosed	3,000,000
$I_a(t)$	Acute HCV infected diagnosed	300,000
$C_u(t)$	chronic HCV infected undiagnosed	1,800,000
$C_a(t)$	chronic HCV infected diagnosed	600,000
$X_u(t)$	Liver Cirrhosis undiagnosed	200, 000
$X_a(t)$	Liver Cirrhosis diagnosed	100,000
$N(t)$	To population	90,000,000

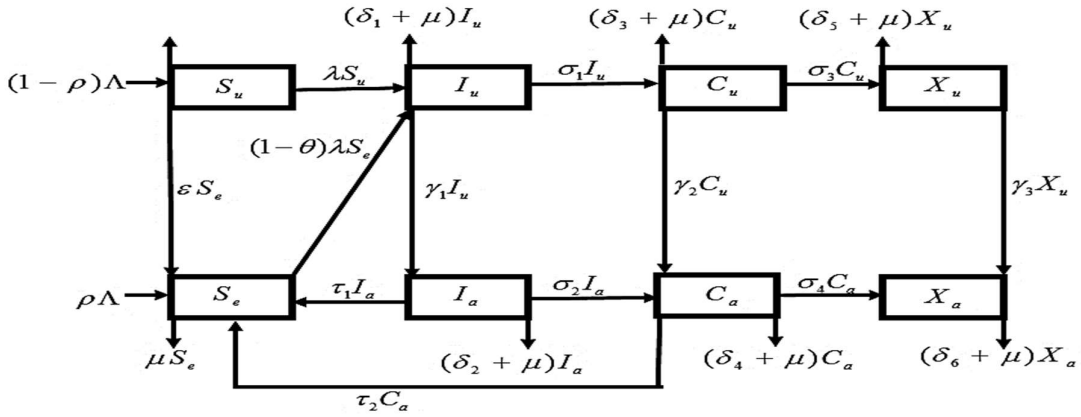

Figure 1: Schematic Diagram

Table 2: The Description of Parameters of the Model

Parameters	Description	Values	Source
Λ	Recruitment rate	1980000	Estimated
μ	Natural mortality rate	0.014	Estimated
ε	Rate of enlightening the susceptible	0.65	Assumed
ρ	Proportion of new entrant that are enlightened	0.55	Estimated
$\gamma_1,\gamma_2,\gamma_3$	Rates at which individuals in $I_u(t), C_u(t)$ and $X_u(t)$ are screened and enlightened	0.05, 0.3, 0.6	Assumed
β	Effective contact rate	0.35	(Khan, Sial, & Imran, 2014)
η_1,η_2	Modification parameters for reduction in transmission due low viral load.	0.3, 0.4	Assumed
$\sigma_1,\sigma_2,\sigma_3,\sigma_4$	Progression rates to Chronic and Compensated Liver Cirrhosis	0.8, 0.45, 0.3, 0.1	(Khan, Sial, & Imran, 2014)
θ	Level of protection due awareness in preventing the susceptible from getting infection	0.8	Assumed
$\delta_1,\delta_2,\delta_3,\delta_4,\delta_5,$	Disease induced death rates of I_u, I_a, C_u, C_a, X_u and X_a classes respectively	0.005, 0.002, 0.008, 0,0031,0.035, 0.021	Assumed
τ_1,τ_2	Treatment rates of I_a and C_a classes	0.85, 0.75	Assumed
ϕ_1,ϕ_2	Efficacies of condom, screening and counselling of infected individuals	0.2, 0.7	(Abu-Raddad, et al., 2010)

The Model Equations

The model is governed by the following system of first order nonlinear ordinary differential equations

$$\dot{S}_u(t) = (1-\rho)\Lambda - (\lambda + \varepsilon + \mu)S_u$$

$$\dot{S}_e(t) = \rho\Lambda + \varepsilon S_u + \tau_1 I_a + \tau_2 C_a - [(1-\theta)\lambda + \mu)]S_e$$

$$\dot{I}_u(t) = \lambda[S_u + (1-\theta)S_e] - (\sigma_1 + \gamma_1 + \delta_1 + \mu)I_u$$
$$\dot{I}_a(t) = \gamma_1 I_u - (\sigma_2 + \tau_1 + \delta_2 + \mu)I_a \qquad (1)$$
$$\dot{C}_u(t) = \sigma_1 I_u - (\gamma_2 + \sigma_3 + \delta_3 + \mu)C_u$$
$$\dot{C}_a(t) = \gamma_2 C_u + \sigma_2 I_a - (\tau_2 + \sigma_4 + \delta_4 + \mu)C_u$$
$$\dot{X}_u(t) = \sigma_3 C_u - (\gamma_3 + \delta_5 + \mu)X_u$$
$$\dot{X}_a(t) = \gamma_3 C_u + \sigma_4 C_a - (\delta_6 + \mu)X_u$$

Where λ is the force of infection define as

$$\lambda = \frac{\beta\left((\eta_1 I_u + \eta_2 C_u + X_u) + (1-\phi_1)(1-\phi_2)(\eta_3 I_a + \eta_4 C_a + X_a)\right)}{N}$$

EPIDEMIOLOGIC AND ECONOMIC IMPACT

In this work, we consider public enlightenment by targeting the susceptible individuals, screening and counselling of infected individuals and treatment as the main intervention for the control of HCV infection in a population. However, these interventions were further arranged based on the following strategies.

Strategy A: Enlightening the new entrant into population and the susceptible individuals only.

Strategy B: Screening and counselling the infected individuals only.

Strategy C: Screening and counselling and treating the infected individuals only.

Strategy D: Implementing strategies A and B only.

Strategy E: implementing strategies A and C only.

Quality Adjusted Life Year (QALY)

Quality adjusted life year is the most widely used technique for estimating quality of life benefit in health economic evaluation. It measures the impact of an intervention on the state of health for a given disease. In this approach, quality of life weight is assigned to each health state.

The discounted QALY for strategy *k* is given by;

$$QALY_k = \int_0^T (q_1 S_u + q_2 S_e + q_3 I_u + q_4 I_a + q_5 C_u + q_6 C_a + q_7 X_u + q_8 X_a) e^{-rt} dt$$

Where $q_i\,(i = 1,...,8)$ are the quality of life weights of individuals in $S_u, S_e, I_u, I_a, C_u, C_a,$ X_u and X_a classes correspondingly as shown in table 3.

Table 3: The Quality of Life weights for Health states

Health state	Quality of Life
S_u	1.0
S_e	1.0
I_u	1.0
I_a	0.94
C_u	0.94
C_a	0.82
X_u	0.84
X_a	0.74

Source: Australia Health Department, 2002

The Cost of Strategies

The cost of resources used for each of the strategies is presented below:

The Cost of Public enlightenment

The total cost of public enlightenment is obtained by taking the product of per unit cost per year of enlightenment denoted by c_p, and the number of people to be enlightened. So that the total cost of public awareness associated with any strategy *k*is presented as;

$$C_k^p(t) = c_p(\rho\Lambda + \varepsilon S_e)$$

The Cost of Condom

The total cost of condom is the product of per unit cost of condom given by c_c, and the proportions of people who use condom in $S_e(t)$, $I_a(t)$, $C_a(t)$and $X_a(t)$ classes. Thus, the total cost of condom for strategy *k* is given by;

$$C_k^c(t) = c_c(\alpha_1 S_e + \alpha_2 I_a + \alpha_3 C_a + \alpha_4 X_a)$$

The Cost of Screening and Counselling

The total cost of screening and counselling at time t is the product of per capita cost of screening, c_s, and the number of people to be screened. Thus, the total cost for screening associated with strategy *k* is given by;

$$C_k^s(t) = c_r(\gamma_1 I_u + \gamma_2 C_u + \gamma_3 X_u)$$

Cost of Treatment

Treatment costs of acute HCV, chronic HCV and liver cirrhosis are the product of the number of screened and treated and cost of treatment.Per capita cost per year of treating acute HCV diagnosed, chronic HCV diagnosed and liver cirrhosis diagnosed are c_{ta}, $c_{tc}$and $c_m$respectively. Thus, the total cost for treatment associated with strategy *k* is given by;

$$C_k^t(t) = c_{ta}(\tau_1 I_a) + c_{tc}(\tau_2 C_a) + c_m X_u$$

The total cost associated with strategy *k* is presented as;

$$C_k^T(t) = C_k^p(t) + C_k^c(t) + C_k^s(t) + C_k^t(t) + c_r$$

Here c_r is the general running cost and other related administrative issues such as training of educators, printing of booklets, etc.

Thus, total discounted cost associated with strategy *k* over the planning horizon (0, T) is given as;

$$Cost(t)_k = \int_0^T C_k^T(t) e^{-rt} dt$$

Table 4: Cost of Resources used

Parameter	Description	Value (per capita cost)	Source
c_p	Cost of public enlightenment	\$0.97	(Hove-Musekwa, Nyabadza, Mambili-Mamboundou, Chiyaka, & Mukandavire, 2014)
c_s	Cost of screening	\$42.3	(Saab, Ahn, Mcdaniel, Yanny, & Tong, 2018)
c_{ta}	Cost of treating acute HCV	\$20, 000	(NATAP, 2018)
c_{tc}	Cost of treating chronic HCV	\$26, 338	(NATAP, 2018)
c_m	Cost of treating liver cirrhosis	\$27, 987	(NATAP, 2018)
R	Discount rate	5%	(Hove-Musekwa, Nyabadza, Mambili-Mamboundou, Chiyaka, & Mukandavire, 2014)
c_r	Running cost	\$5000	(Hove-Musekwa, Nyabadza, Mambili-Mamboundou, Chiyaka, & Mukandavire, 2014)
c_c	Cost of condom	\$2.5	(Hove-Musekwa, Nyabadza, Mambili-Mamboundou, Chiyaka, & Mukandavire, 2014)
$\alpha_1, \alpha_2, \alpha_3, \alpha_4$	Proportions of individuals in S_e, I_a, C_a and X_a using condom	0.55, 0.65, 0.75, 0.90	(Hove-Musekwa, Nyabadza, Mambili-Mamboundou, Chiyaka, & Mukandavire, 2014)

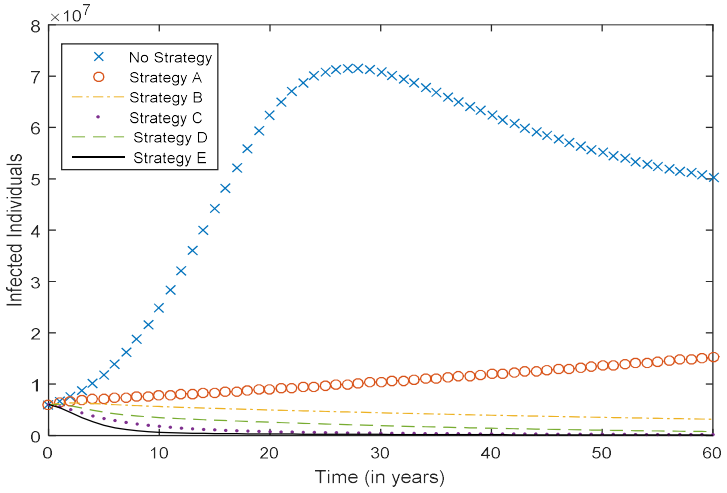

Figure 2: Impact of the Strategies on the Infected Population

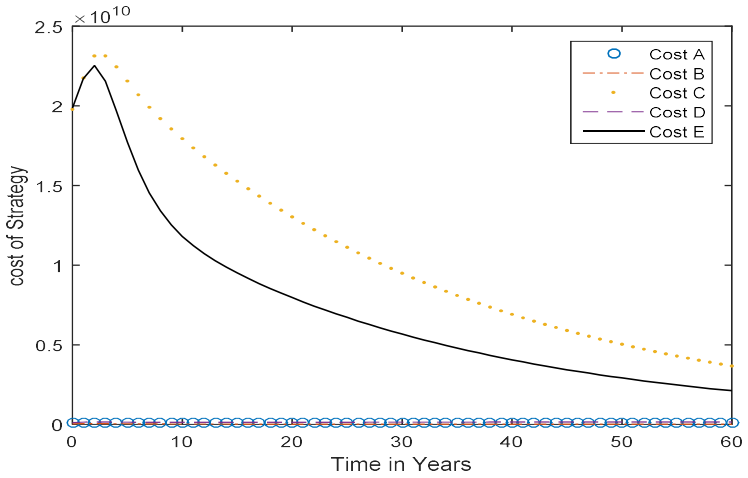

Figure 3: The Trend in the Cost of the Strategies over the Planning

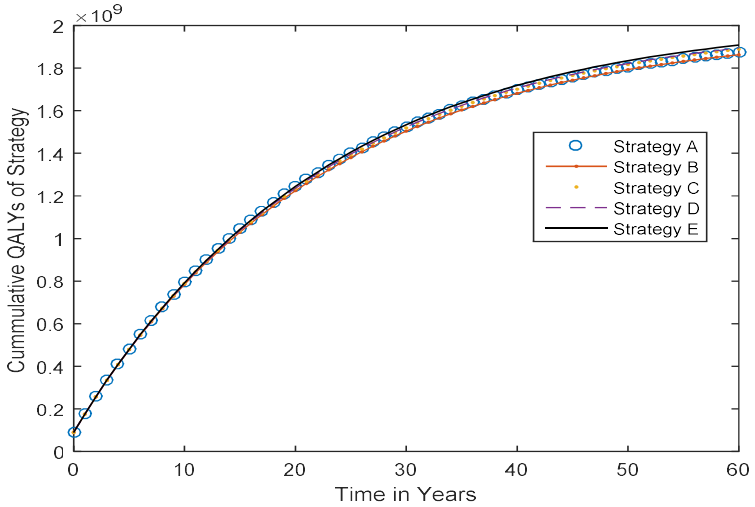

Figure 4: Cumulative QALYs Gained by each Strategy

Incremental Cost Effectiveness Ratio (ICER)

In order to compare the effectiveness of two competing strategies k and k' we use the incremental cost effectiveness ratio (ICER) as used by (Weinstein, 1996) is given by

$$ICER = \frac{\text{cost}_k - \text{cost}_{k'}}{\text{QALY}_k - \text{QALY}_{k'}}$$

Table 4: The ICER of the Strategies

	Discounted Total		
Strategies	**QALY**	**Cost ($)**	**ICER($)/QALY**
A	1.1526E+11	1.4270E+11	**Dominated**
B	1.1691E+11	2.1323E+10	74
C	1.1962E+11	1.2728E+13	**Dominated**
D	1.2000E+11	1.6693E+11	33055
E	1.2114E+11	8.7017E+12	7487

RESULTS AND DISCUSSION

We carryout numerical simulation using ODE45 solver in MATLAB to examine the impact of each strategy on the total number of infected individuals over the planning horizon and the results are presented in figure 2. The result revealed that, when there is no strategy the total number of infected individuals increase rapidly and later drop slowly and at the long run the infection persists in the population. However, with the introduction of the strategies, the outcomes of strategies C, D and E indicate significance reduction in the number of infected persons and the greatest reduction is observed in strategy E. This result revealed that the implementing all the strategies is the most effective strategies in the fight against this deadly infection. Indeed, strategy B indicates less reduction in the number of infected individuals and this indicates that the strategy is not effective and strategy A is the most less effective strategy as it shows no reduction in the number of infected individuals.

The economic impact of the strategies was also investigated and the result in figure 3 shows the trend of cost of the strategies over the planning horizon. The cost of all the strategies i.e. E at the beginning was the most expenses and later become cheaper than strategy C. Furthermore, the cost of strategies A, B and D remain cheaper throughout the periods.

The cumulative discounted QALYs gained for each of the strategy was computed and the result was plotted as seen in figure 4. The greatest QALY gained is observed in strategy E. In order to calculate the incremental cost effectiveness ratio of the strategies the total discounted QALYs and cost of the strategies were computed and the result is presented in table 4.

We compute the incremental cost effectiveness ratio of each strategy considering QALY as health benefit. The result is shown in table 4. The strategies are arranged in order of increasing QALY (i.e. from least effective to the most effective). It was observed that strategies A and C were less effective and more costly than strategies B and D respectively, this implies that strategies A and C are dominated. According to (Sachs, 2001) the cost effectiveness threshold (cost per health benefit) is usually determine using per capita gross domestic product (GDP) of a region or country. The three approaches for selecting the most cost-effective strategy are:

a. Highly cost effective if the ICER of the strategy < 1 x (GDP per capita).
b. Cost effective, if 1 x (GDP per capita) < ICER < 3 x (GDP per capita).
c. Not cost effective if ICER >3 x (GDP per capita).

The per capita GDP of Egypt as at 2015 was estimated by CIA to be $12,800.00. In order to choose the most cost-effective strategy we consider the ICER of the non-dominated strategies as seen in table 5. It is obvious from table 5, that strategies B and E are highly cost effective since their ICER are less than one-time per capita GDP. However, strategy D is just cost effective since its ICER is less than three times per capita GDP of the country. Since strategy E is the most effective strategy (i.e. highest QALY gained). Therefore, strategy E is the most cost-effective strategy based on the above criteria.

Table 5: The ICER of Non- dominated Strategies

Strategies	Discounted Total QALY	Cost ($)	ICER($)/QALY
B	1.1691E+11	2.1323E+10	74
D	1.2000E+11	1.6693E+11	33055
E	1.2114E+11	8.7017E+12	7487

CONCLUSION

In this work, we evaluate the costs and effects of public enlightenment, screening and counselling as well as treatment in the control of HCV and liver cirrhosis using the data from Egypt. The epidemiological impact of the strategies revealed that strategy E is the most effective as the results shows the greatest reduction in the total number of infected individuals and accrued the highest QALY as compared with the other strategies. Furthermore, we computed the ICER of all the strategies using QALYs as the health benefit and the result shows that strategy A and C are less cost effective hence were dominated. Also, in order to determine the most cost effective strategy out of the non-dominated strategies, we use the criteria by (Sachs, 2001) and the outcome shows that strategy E is highly cost effective. We therefore recommend the universal strategy E i.e. strategy E to the policy makers for implementation.

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