Cost-Effectiveness Analysis of Optimal Control Strategies for Malaria Transmission in Bubanza Province, Burundi.

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***Abstract*: Malaria is a parasitic infection ranked among the leading causes of mortality and morbidity in Sub-Sahara African countries. If recommended interventions measures are well applied, malaria can be prevented and controlled. In many cases, the budget allocated to malaria prevention and treatment project is not enough, using malaria intervention measures properly will guarantee the reduction of infected population while the intervention costs is minimized. This saves the budget and produces the results in economical way. The aim of this article is to understand the cost so that decision makers are well informed when they determine budget allocated to malaria interventions. After ordering different possible strategies from the smallest to the highest, utilizing Incremental Cost-Effectiveness Ratio (ICER), we studied the Cost-effectiveness of each strategy. This study analyses the cost-effectiveness of all possible optimal control measures to identify which is the intervention strategy is going to save available resources and cost-effective. After analysis, this study shows that malaria can be minimized in Bubanza using preventive measures at the most cost effective way.**

***Keywords*: Mathematical model, Stability, Disease-free equilibrium, Endemic Equilibrium, Basic Reproductive number, Optimal control, cost effectiveness Analysis, Malaria intervention strategies.**

I. INTRODUCTION

Malaria is a parasitic infection which is one of the leading cause of mortality and morbidity in Sub-Sahara Africa where the most affected are under five years and pregnant women (Bawa et *al*., 2021; Otieno et *al*., 2016). The high need of money to prevent and control malaria calls for the analysis of malaria cost effectiveness to contribute in the race of Burundi government to control the spread of malaria. Malaria spread is very high in Burundi due to many factors favoring malaria transmission (Nkurunziza et *al*., 2011. The reduction of malaria cases in Burundi is due to the use of preventive measures, rapid diagnostic test, cases management and treatment on time of confirmed cases. Cost-effective analysis became a tool which very important to make decisions regarding disease control intervention program (Robinson, R., 1993; Otieno, G., et *al*., 2016; Levin, H. M. et *al*., 2000). The aims of Cost-effectiveness analysis is to path decision makers who are going to be assigned responsibilities of making decisions on how to allocate budget for malaria intervention mostly in case where fund allocated is insufficient.

The cost analysis balances prices and deduces the most effective cheapest intervention strategy (Okosun et *al*., 2013). Even if the use of Cost-effectiveness analysis in the domain health appear as irrelevant when monetizing health outcomes (Otieno et *al*., 2016). The choice of the most effective intervention strategy is made by analyzing cost-effectiveness which is possible by calculating the incremental cost-effectiveness ratio (ICER) and comparing prices (Guerra, C. A., et *al*., 2008).

Okosun et *al*.(2013) used ICER to investigate the cost effective analysis by comparing for three malaria intervention strategies in his research , he did not consider the most exposed category.

Otieno et *al*. (2016) modeled cost-effectiveness of malaria intervention.

In his study, Stukey et *al*. (2014) modelled the cost effectiveness to control malaria spread using simulation modeling but at risk population were not considered in his study. Hansena et *al*. (2012) did research where he investigated cost effectiveness of three health interventions strategies considering low transmission settings for the pregnant women as the most exposed group. However, there is not a general cost effectiveness investigation which was done so far on malaria intervention strategies for the optimal control strategies in Bubanza province.

In this study, we investigated the general cost-effectiveness for all possible combinations strategies to control malaria to guide decision makers of Bubanza province when proposing resources to be allocated to malaria interventions.

II. MODEL FORMULATION

A standard SIRS-SI model considered is a transformation of the model of malaria transmission as given in Otieno et *al*.(2016); Mojeeb et *al*. ,(2017)**,** Appiah, P. (2020) but it is not a generalized of one of these ones.

The used model is divided in five compartments: S_h, I_h, R_h for human population and S_v, I_v for vector population.

In this model, following assumptions were considered:

- The total number of humans and mosquitoes is constant (No immigrants).
- There is not recovery for infected mosquitoes.
- There is not death of mosquitoes due to infection.
- Parameters of model are all positives.
- There is not infection transmission between Recovered human and susceptible mosquitoes.
- New born with infection enter directly the group of Infected human.
- Human can die at any time due to other causes.
- Recovered humans become Susceptible by partially loosing immunity

The model is given by the following system of Ordinary differential Equation:

$$\frac{dS_h}{dt} = \Lambda_h + \omega R_h - \frac{\beta_{vh} I_v S_h}{N} - \mu_h S_h$$

$$\frac{dI_h}{dt} = \frac{\beta_{vh} I_v S_h}{N} - (a + u_1 + \mu_h + \delta_h - \kappa) I_h$$

$$\frac{dR_h}{dt} = (a + u_1) I_h - (\mu_h + \omega) R_h \qquad \textbf{(1)}$$

$$\frac{dS_v}{dt} = \Lambda_v - \frac{\beta_{hv} h S_v}{N} - (u_2 + \mu_v) S_v$$

$$\frac{dI_v}{dt} = \frac{\beta_{hv} h S_v}{N} - (u_2 + \mu_v) I_v$$

Initial conditions are:

$$S_h > 0, I_h \geq 0, R_h \geq 0, S_v > 0, I_v \geq 0$$

with $I_h + I_v > 0$, $u_2 = u_1 = 0$

The total host population is:

$$N = S_h + I_h + R_h$$

$$\frac{dN(t)}{dt} = \frac{dS_h}{dt} + \frac{dI_h}{dt} + \frac{dR_h}{dt} = \Lambda_h - \mu_h N - (\delta_h - k) I_h$$

The total vector population is: $M = S_v + I_v$

$$\frac{dM(t)}{dt} = \frac{dS_v}{dt} + \frac{dI_v}{dt} = \Lambda_v - (u_2 + \mu_v) M$$

Table 1: Identification, description of the Basic Parameters and variables used in the Model

Parameters	Description
$S_h(t)$	:Susceptible Individuals at time t
$I_h(t)$	: Infectious Humans at time t
$R_h(t)$	:Recovered(Immunized) humans at time t
$S_v(t)$	:Susceptible mosquitoes at time t
$I_v(t)$	:Infectious mosquitoes at time t
N(t)	:Total number of humans at time t
M (t)	: Total mosquitoes population at time t
β_{vh}	:Mosquitoes-Humans infection transmission
β_{hv}	:Humans-mosquitoes infection transmission
μ_h	: Human Natural mortality and birth rates
μ_v	: Mosquitoes Natural mortality and Birth rates
ω	: Rate of loss of immunity
Λ_h	:Recruitment rate of human
Λ_v	:Recruitment rate of mosquitoes
δ_h	:Death rate for humans due to the disease
a	:Recovery rate due to immunity
u_1	:Control using treatment
u_2	:Control using preventive measures

II. PROPERTIES OF THE MODEL

II.A. Positivity and invariant region.

To capture the fact that the dynamical system is epidemiologically and mathematically well posed, there a need to show that the solutions to the system (1) are not negative since we are considering population and also find the boundary of existences solutions.

Lemma 1: If initial condition are such that at t=0,

$S_{h0} > 0$ $I_{h0} \geq 0$ $R_{h0} \geq 0$ $S_{v0} > 0$ $I_{v0} \geq 0$ then for all

t>0, $S_h > 0$ $I_h \geq 0$ $R_h \geq 0$ $S_v > 0$ $I_v \geq 0$

Proof: Considering the susceptible human population S_h, from the system of differential equations;

We have:

$$\frac{dS_h}{dt} = \Lambda_h + \omega R_h - \frac{\beta_{vh} I_v S_h}{N} - \mu_h S_h$$

$$> -(\frac{\beta_{vh} I_v}{N} + \mu_h) S_h(t)$$

Assuming that a constant C for all time is such that:

$$\frac{I(t)}{N} \leq C,$$

We get:

$$\frac{dS_h(t)}{dt} > -(C\beta_{vh} + \mu_h) S_h(t)$$

The use of variable separation technique gives:

$$\int \frac{dS_h(t)}{S_h(t)} > -\int (C\beta_{vh} + \mu_h) dt$$

$$\log S_h(t) > -(C\beta_{vh} + \mu_h)t + K$$

$$S_h(t) > \exp[-(C\beta_{vh} + \mu h)t + K]$$

With initial condition $S_h(0) = S_0$ where $S_0 > 0$, we get

$$S_h(t) > S_0 \exp(-(C\beta_{vh} + \mu h)t)$$

As t= ∞,

$$S_h(t) > S_0 > 0$$

From above computations, we conclude that the susceptible population is always positive.

Using the same technique, the proof is completed by showing that:

$I_h \geq 0, R_h \geq 0 \quad S_v > 0 \; I_v \geq 0.$

Similarly, using the same method, it can be concluded that all parameters S_h, I_h, R_h, S_v, I_v are all positive.

Lemma 2 (Invariant region): the region

$\Omega = \{(S_h, I_h, R_h, S_v, I_v) \in R^5_+ : (S_h, S_v) > 0, (I_h, R_h, I_v) \geq 0; N \leq \frac{\Lambda_h}{\mu_h}; M \leq \frac{\Lambda_v}{u_2 + \mu_v}\}$ is positively invariant.

Since $t \to \infty$,

The rate of change of the total humans N from the system of equations (1) which is given by:

$$\frac{dN(t)}{dt} = \frac{dS_h}{dt} + \frac{dI_h}{dt} + \frac{dR_h}{dt}$$
$$= \Lambda_h - \mu_h N - (\delta_h - k) I_h \qquad (2)$$
$$\geq \Lambda_h - \mu_h N$$

The inequation (2) becomes

$$\frac{dN(t)}{dt} \geq \Lambda_h - \mu_h N$$

With factor integrating methods, we get:

$$\frac{d}{dt}(e^{\mu_h t} N) dt \leq e^{\mu_h t} \Lambda_h$$
$$\int \frac{d}{dt}(e^{\mu_h t} N) dt \leq \int e^{\mu_h t} \Lambda_h$$
$$e^{\mu_h t} N \leq e^{\mu_h t} \Lambda_h + K$$
$$N \leq \frac{\Lambda_h}{\mu_h} + K$$

With initial condition $N(0)=N_0$, where $N_0 > 0$, we get:

$$N(t) \leq \frac{\Lambda_h}{\mu_h} + (N_0 - \frac{\Lambda_h}{\mu_h}) e^{-\mu t}$$

Since $t \to \infty$,

$$N(t) \leq \frac{\Lambda_h}{\mu_h}$$

Since $N(t) \leq \frac{\Lambda_h}{\mu_h}$ if $t \to \infty$ under the dynamic system described by the system (1), we have the region

$\Omega = \{(S_h, I_h, R_h, S_v, I_v) \in R^5_+ :$

$(S_h, S_v) > 0, (I_h, R_h, I_v) \geq 0; N \leq \frac{\Lambda_h}{\mu_h}; M \leq \frac{\Lambda_v}{u_2 + \mu_v}\}\}$ is positively invariant.

There is a subsequence $t_i \to \infty$ if $(S_h, I_h, R_h, S_v, I_v)$ is a Ω limit point of an orbit in R^5_+ such that:

$\lim_{i \to \infty}\{(S_h(t_i), I_h(t_i), R_h(t_i))\} = (S_h^*, I_h^*, R_h^*)$ and

$\lim_{i \to \infty}\{S_v(t_i), I_v(t_i)\} = (S_v^*, I_v^*)$

Hence,

$$\lim_{i \to \infty} N(ti) = N^* = S_h^* + I_h^* + R_h^*$$
$$\lim_{i \to \infty} M(t_i) = M^* = S_v^*, + I_v^*$$

Thus from the lemma 1 and lemma 2, for initial conditions $(S_{h0}, I_{h0}, R_{h0}, S_{v0}, I_{v0})$, the trajectory lies in Ω and this prove that the system (1) is epidemiologically and mathematically well posed.

II.B. Equilibrium points and Basic Reproductive Number

The disease-free equilibrium and the endemic equilibrium points of (1) are respectively given by:

$E_0 = (\frac{\Lambda h}{\mu_h}, 0, 0, \frac{\Lambda v}{\mu_v + u_2}, 0)$ and $E_1 = (S_h^*, I_h^*, R_h^*, S_v^*, I_v^*)$

Where:

$S_h^* = \frac{W[(\Lambda_h \beta_{hv} + (\mu_h + \omega) + H(a + \mu_h + u_1 - k + \delta_h) + \omega(\mu_h + \delta_h)]}{Yh + Zh}$

$I_h^* = \frac{\Lambda_v \Lambda_h B hv \beta_{vh} (\mu_h + \omega) X}{Y_h + Z_h}$

$R_h^* = \frac{\Lambda_v \Lambda_{hBhv} \beta_{vh} (a + u_1) + W[\Lambda_v \Lambda_h \beta_{hv} - d]}{Y_h + Z_h}$

$d = H\mu_h(\mu_v + u_2)(\delta_h - (-a + u_1 + k)$

$S_v^* = \frac{N[(\mu_h + \delta_h + \omega) + \delta_h \omega] + \mu_h W N(\mu_h + \omega)}{Y_v + Zv}$

$I_v^* = \frac{\Lambda_v \Lambda_h \beta_{hv} \beta_{vh} (\mu_h + \omega) X}{Yv + Zv}$

where:

$W = (a + \mu_h + \delta_h + u_1 - k)(\mu_v + u1)N$

$X = [N\mu_h(\mu_h + \omega)(a + \mu_h + \delta_h + u_1 - k)(\mu_v + u_2)^2$

$Y_h = \Lambda_v[(a + \mu_h + \delta_h + u_1 - k)(\mu_h + \omega) - \delta_h \omega]$

$Z_y = \beta_{hv} \mu_h (a + \mu_h + \delta_h + u_1 - k)(\mu_v + u_2)$
$(\mu_h + \omega)$

$Y_v = \Lambda_v \beta_{hv} \beta_{vh} (\mu_h + \omega)(\mu_h + u_2)[$
$(a + \mu_h + \delta_h + u_1 - k)(\mu_h + \omega) - N(a + u1)]$

$Z_h = \beta_{hv} H(\mu_v + u_2)[(a + \mu_h + u_1 - k + \delta_h)$
$(\mu_h + \omega) - (a + u_1)]$

The Basic reproduction number (R_0) of the system (1) is computed using the next generation method (Bawa, M et *al.*, 2021)

Let Y= $(S_h, I_h, R_h, S_v, I_v)^T$

$$A^* = \begin{bmatrix} \frac{\beta_{vh} I_v S_h}{N} \\ \frac{\beta_{hvI} h S_v}{N} \\ \mathbf{0} \\ \mathbf{0} \\ \mathbf{0} \end{bmatrix} \qquad B^* = \begin{bmatrix} (a + u_1 + \mu_h + \delta_h - \kappa) I_h \\ (u_2 + \mu_v) I_v \\ -(a + u_1) I_h + (\mu_h + \omega) R_h \\ -\Lambda_v + \frac{\beta_{hvI} h S_v}{N} + (u_2 + \mu_v) S_v \\ -\Lambda_h - \omega R_h + \frac{\beta_{vh} I_v S_h}{N} + \mu_h S_h \end{bmatrix}$$

DA and DB are expressed respectively as follow:

$$DA^*_{E_0} = \begin{bmatrix} 0 & F \\ 0 & 0 \end{bmatrix} \qquad DB^*_{E_0} = \begin{bmatrix} V & 0 \\ P_2 & P_3 \end{bmatrix}$$

$$F = \begin{bmatrix} 0 & \frac{\beta_{vh} \Lambda h}{N \mu_h} \\ \frac{\beta_{hv} \Lambda v}{N(\mu_v + u_2)} & 0 \end{bmatrix}$$

$$V = \begin{bmatrix} a + u_1 + \mu_h + \delta_h - \kappa & 0 \\ 0 & u_2 + \mu_v \end{bmatrix}$$

The computation of the basic reproduction number is as follows:

$G = FV^{-1}$

Where G is the Next generation matrix.

$$V^{-1} = \begin{bmatrix} \frac{1}{a + u_1 + \mu_h + \delta_h - \kappa} & 0 \\ 0 & \frac{1}{u_2 + \mu_v} \end{bmatrix}$$

$$G = \begin{bmatrix} 0 & \frac{\beta_{vh} \Lambda h}{N \mu_h (u_2 + \mu_v)} \\ \frac{\beta_{hv} \Lambda v}{N(\mu_v + u_2)(a + u_1 + \mu_h + \delta_h - \kappa)} & 0 \end{bmatrix}$$

$$R_0 = \frac{\sqrt{\beta_{vh} \Lambda h \beta_{hv} \Lambda v}}{N(u_2 + \mu_v)\sqrt{\mu_h (a + u_1 + \mu_h + \delta_h - \kappa)}}$$

Theorem 1: The disease free-equilibrium point E_0 is locally asymptotically stable if $R_0<0$ and Unstable otherwise

Proof: The Jacobean of the system (1) is given by the following matrix:

$$J = \begin{bmatrix} -n_1 & 0 & \omega & 0 & -\frac{\beta_{vh} I_v}{N} \\ \frac{\beta_{vh} I_v}{N} & -n_2 & 0 & \frac{\beta_{vh} I_v}{N} & 0 \\ 0 & a + u_1 & -\mu_h - \omega & 0 & 0 \\ -\frac{\beta_{hv} S_v}{N} & 0 & 0 & n_3 & 0 \\ \frac{\beta_{hv} S_v}{N} & 0 & 0 & \frac{\beta_{vh} I_h S_v}{N} & n_4 \end{bmatrix}$$

$$n_1 = \frac{\beta_{vh} I_v}{N} - \mu_h, \qquad n_2 = (a + u_1 + \mu_h + \delta_h - \kappa)$$

$$n_3 = -\frac{\beta_{hvI} h}{N} - u_2 - \mu_v, \; n_4 = -(u_2 + \mu_v)$$

The eigenvalues are given by the characteristics equation $|J_{E_0} - \lambda I| = 0$ and it is implies that:

$$\lambda_1 = -\mu_h, \; \lambda_2 = -\mu_h - \omega \quad , \lambda_3 = -(u_2 + \mu_v)$$

$$\lambda_4 = -P(Q + \sqrt{W}), \quad \lambda_5 = -P(Q - \sqrt{W})$$

Where:

$$P = \frac{1}{2N\mu_h (u_2 + \mu_v)(\mu_h + \omega)}$$

$$Q = N^2 \mu_h (u_2 + \mu_v)(a + u_1 + \mu_h + u_2 + \delta_h - \kappa)(\mu_h + \omega)$$

$$W = 4\mu_h \beta_{vh} \Lambda_h \beta_{hv} \Lambda_v (u_2 + \mu_v)(\mu_h + \omega) + N^2 (u_2 + \mu_v)^2 [(a + u_1 + \mu_h + u_2 + \delta_h - \kappa) - \mu_h (u_2 + \mu_v)^2 (\mu_h + \omega)]$$

It very clear that $\lambda_1, \lambda_2, \lambda_3, \lambda_4$ are all non-positive and λ_5 is negative if:

$$Q^2 - W > 0$$

$$-4\beta_{hv} \beta_{vh} \Lambda_h \Lambda_v (\mu_h + \omega) + 4\mu_h N^2 (\mu_h + \omega) - [(a + u_1 + \mu_h + u2 + \delta_h - \kappa)(u_2 + \mu_v)^2 > 0$$

$$\frac{\beta_{vh} \Lambda_h \beta_{hv} \Lambda_v}{N^2 (a + u_1 + \mu_h + u2 + \delta_h - \kappa)(u_2 + \mu_v)^2} < 1$$

$$R_0^2 < 1$$

As the threshold is less than one, we have that the point E_0 is asymptotically stable.

Theorem 2: The disease free equilibrium point is globally asymptotically stable if R<1.

Let consider the Lyapnov function:

$L(S_h, I_h, R_h, S_v, I_v) = \phi I_h + I_v$,

where ϕ is a positive number defined by:

$$\phi = \frac{N\mu_h (u_2 + \mu_v)^2}{\Lambda_h \beta_{hv} \Lambda_v}$$

$$\frac{dL}{dt} = \phi \frac{dIh}{dt} + \frac{dI_v}{dt}$$

$$\frac{dL}{dt} = \phi \left(\frac{\beta_{vh} I_v S_h}{N} - (a + u_1 + \mu_h + \delta_h - \kappa) I_h \right) + \frac{\beta_{hvI} h S_v}{N} - (u_2 + \mu_v) I_v$$

$$\leq [\frac{\beta_{hv} S_v}{N(\mu_v + u2)} - N\phi(a + u_1 + \mu_h + \delta_h - \kappa)/N] I_h$$

$$N2(u_2 + \mu_v) 2R_0 \mu_h (a + u_1 + \mu_h + \delta_h - \kappa) = \beta_{vh} \Lambda h \beta_{hv} \Lambda v$$

$$\frac{4N(u_2 + \mu_v) R_0^2 \mu_h (a + u_1 + \mu_h + \delta_h - \kappa)}{\Lambda_h \beta_{hv} \Lambda_v} = \beta_{vh}$$

$$\frac{dL}{dt} \leq [\frac{2R_0^2 \mu_h N(u_2 + \mu v)(a + u_1 + \mu_h + \delta_h - \kappa)}{(\mu_v + u2) \Lambda h \beta_{hv}} - \frac{N\mu_h (u_2 + \mu v)^2}{\Lambda_h \beta_{hv} \Lambda_v} (a + u_1 + \mu_h + \delta_h - \kappa)] I_h$$

$$\leq \frac{N\mu_h(a+u_1+\mu_h+\delta_h-\kappa)(u_2+\mu v)2(R_0^2-1)}{\Lambda_h\beta_{hv}\Lambda_v}$$

As all parameters are positive, it is clear that $\frac{dL}{dt}$<0 if R_0<1 and $\frac{dL}{dt}$=0 if $I_h = I_v = 0$.

Therefore, the largest compact invariant is included in $(S_h, I_h, R_h, S_v, I_v) \in R^5_+$, when $R_0 < 1$.

Therefore, the largest compact invariant is included in

$$\Omega$$

$$(S_h, I_h, R_h, S_v, I_v) \in R^5_+ : |(S_h+I_h+R_h) \leq \frac{\Lambda_h}{\mu h}; (S_v + I_v) = < \frac{\Lambda_v}{\mu v+u2}\}$$

when $R_0 < 1$.

According to LaSalle's invariant principle (La Salle, 1976, cost), E_0 is globally asymptotically stable.

Theorem 3: The endemic equilibrium point (E_1) is locally asymptotically stable if R_0>1 and unstable if R_0<0.

To examine the local stability, the change of infectious class was used by elaborating on the theorem expressing the infectious class of E_1 on the subject of the basic reproductive number.

The infectious classes of the endemic equilibrium point are given by:

$$I_h^* = \frac{X(R_0^2-1)}{Y_h + Z_h} \quad , \quad I_v^* = \frac{X(R_0^2-1)}{Y_v + Z_v}$$

Since the denominators of both I_h^* and I_v^* are positives, the endemic conditions exist if and only if $R_0 > 1$.

Hence the point E_1 is locally asymptotically stable *if and only* $R_0 > 1$ and it is unstable if $R_0 < 0$

Theorem 6: The endemic equilibrium E_1 of the dynamic system (1) is globally asymptotically stable inside of the feasible region R_+^5 if $R_0 > 1$.

Proof: According to Abioye et *al*. (2020). Olaniyi and *al*. (2018), Shuai&Driessche (2013) and Ojo et *al*. (2017), the equation of Lyaponov is made referring to Goh-Volterra type Lyapunov function where for the SIRS-SI Con Goh-Volterra type sidering $R_h \to R_h^*$ as time t→ ∞ the system (1). The Lyapunov function is given by:

$$T = S_h - S_h^* - S_h^* log\frac{S_h}{S_h^*} + I_h - I_h^* - I_h^* log\frac{I_h}{I_h^*}$$

$$+ h_1(S_v - S_v^* - S_v^* log\frac{S_v}{S_v^*}) + h_2(I_v - I_v^* - I_v^* log\frac{I_v}{I_v^*})$$

Where $h_1 = h_2 = \frac{S_h^* I_h^* \beta_{vh}}{I_v^* S_v^* \beta_{hv}}$

The differentiation of *T* with respect to time,

$$\frac{dT}{dt} = \left(1 - \frac{S_h^*}{Sh}\right) + \left(1 - \frac{I_h^*}{I_h}\right) + h_1\left(1 - \frac{S_v^*}{S_v}\right)$$

$$+ h_2\left(1 - \frac{I_v^*}{I_v}\right)$$

Replacing h_1 and h_2; then substituting and simplifying:

$$\frac{dT}{dt} = \mu_h S_h^*(2 - \frac{S_h^*}{Sh} - \frac{S_h}{S_h^*}) + S_h^* I_h^* \beta_{vh}(2 - \frac{S_v^*}{Sv} - \frac{S_v}{S_v^*}) +$$

$$S_h^* I_v^* \beta_{hv}(4 - \frac{S_h^*}{Sh} - \frac{S_h I_h^*}{S_h^* I_v^* I_h} - \frac{S_v^*}{S_v} - \frac{S_v I_v^*}{S_v^* I_h^* I_v})$$

According to Abioye et *al*. (2020) , from the rule of geometry, the geometric mean is less than the arithmetic mean therefore the following inequalities holds:

$$2 - \frac{S_h^*}{Sh} - \frac{S_h}{S_h^*} \leq 0 \quad , \quad 2 - \frac{S_v^*}{Sv} - \frac{S_v}{S_v^*} \leq 0$$

$$,4 - \frac{S_h^*}{Sh} - \frac{S_h I_v^*}{S_h^* I_v^*} - \frac{S_v^*}{S_v} - \frac{S_v I_h^*}{S_v^* I_h^*} \leq 0$$

Therefore $\frac{dT}{dt}$<0 if R0 > 1 and $\frac{dT}{dt}$=0 if $S_h = S_h^*$, $I_h = I_h^*$, $S_v = S_v^*$, $I_v = I_v^*$ Since all the parameters are non-negative and so according to LaSalle's invariance principle (La Salle. ,1976) the point E_1 is globally asymptotically stable whenever $R_0 > 1$. The theorem 6 means that epidemiologically, that there will be persistence of malaria in the neighborhood of E_1 whenever $R_0 > 1$.

IV.THE ECONOMIC INVESTIGATION OF THE COST-EFFECTIVENESS.

IV.A. Economic Evaluation

The purpose of the cost-effectiveness economic investigation is to know among all interventions strategies used to minimize or eradicate malaria disease the one which gives best results at the cheapest cost.

The following cost objective function was used:

$$C(u_1(t), u_2(t)) = min_{u1,u2 \in U}\{\int_0^T [B_1 u_1(S_h(t) + I_h(t)) + B_2 u_2(S_v(t) + I_v(t))] e^{-\theta t} dt$$

Where $(S_h(t), I_h(t)), S_v(t), I_v$ (t) denote infectious and susceptible humans and mosquitoes at the end of treatment and preventive measures application, the integral term represents the harmful effect of drugs and other products used to reduce mostiquoes

The controls u_1 and u_2 representing the control parameters for treatment of infectious and preventive measures respectively depend on relative amount of resources for each control action to be executed.

The cost weights B_1 and B_2 depend on the importance of the control measures in reducing malaria transmission, as well as the cost of each control per unit being implemented. The term $B_1 u_1$ and $B_2 u_2$ represent the costs associated with prevention and treatment respectively where θ is the cut-rate of 3-5%

Hamiltonian equation representing cost is given by:

$$H_c = [B_1u_1(S_h(t) + I_h(t)) + B_2u_2[(I_v(t) + S_v(t))]e^{-\theta t} + \lambda_{S_h}(\Lambda_h + \omega R_h - \frac{\beta_{vh}I_vS_h}{N} - \mu_{hS_h}) + \lambda_{I_h}[\frac{\beta_{vh}I_vS_h}{N} - (a + \mu_h + \delta_h + u_1 - k)I_h] + \lambda_{R_h}[(a + u_1)I_h - (\mu_h + \omega)R_h] + \lambda_{S_v}[(\Lambda_v - \frac{\beta_{hv}I_hS_v}{N} - (\mu_v + u_2)S_v] + \lambda_{I_v}[\frac{\beta_{hv}I_hS_v}{N} - (\mu_v + u_2)I_v].$$

Co-state variables are given by:

$$\frac{d\lambda_{S_h}}{dt} = -\frac{\partial H_c}{\partial S_h}, \frac{d\lambda_{I_h}}{dt} = -\frac{\partial H_c}{\partial I_h}, \frac{d\lambda_{R_h}}{dt} = -\frac{\partial H_c}{\partial R_h},$$

$$\frac{d\lambda_{S_v}}{dt} = -\frac{\partial H_c}{\partial S_v}, \frac{d\lambda_{I_v}}{dt} = -\frac{\partial H_c}{\partial I_v}$$

$$\frac{d\lambda_{S_h}}{dt} = -\frac{\partial H_c}{\partial I_v} = -B_1u_1e^{-\theta t} + \frac{\beta_{vh}I_v}{N}(\lambda_{S_h} - \lambda_{I_h}) + \mu_h\lambda_{S_h}$$

$$\frac{d\lambda_{I_h}}{dt} = -\frac{\partial H_c}{\partial I_v} = -B_1u_1e^{-\theta t} + (a + u_1)(\lambda_{I_h} - \lambda_{R_h}) + (\delta_h - k + \mu_h)\lambda_{I_h} + \frac{\beta_{hv}S_v}{N}(\lambda_{S_v} - \lambda_{I_v})$$

$$\frac{d\lambda_{R_h}}{dt} = -\frac{\partial Hc}{\partial R_h} = \omega(\lambda_{R_h} - \lambda_{S_h}) + \mu_h\lambda_{R_h}$$

$$\frac{d\lambda_{S_v}}{dt} = -\frac{\partial Hc}{\partial S_v} = -B_2u_2e^{-\theta t} + \frac{\beta_{hv}I_h}{N}(\lambda_{S_v} - \lambda_{I_v}) + (\mu_v + u_2)\lambda_{S_v}$$

$$\frac{d\lambda_{I_v}}{dt} = -\frac{\partial Hc}{\partial I_v} = -B_2u_2e^{-\theta t} + \frac{\beta_{vh}S_h}{N}(\lambda_{S_h} - \lambda_{I_h}) + (\mu_v + u_2)\lambda_{I_v}$$

With $\lambda_{S_h}, \lambda_{R_h}, \lambda_{S_v}, \lambda_{I_v}, \lambda_{I_h}$ representing shadow prices.

The application of Pontryagin's Maximum Principal (Pontryagin et *al*., 2018) and according to Fleming and Rishel (2012), Otieno et *al*. (2016), the optimal controls u_1^* and u_2^* that minimize u_1 and u_2 :

$$\frac{\partial H}{\partial u_1} = B_1Ne^{-\theta t} + I_h(\lambda_{R_h} - \lambda_{I_h})$$

$$\frac{\partial H}{\partial u_2} = B_2Me^{-\theta t} - S_v\lambda_{S_v} - I_v\lambda_{I_v}$$

By the bounds on the controls norms arguments, it is deduced that the optimal policies for treatment and prevention are respectively given by:

$$u_1 = 0 \quad if \quad B_1Ne^{-\theta t} > Ih(\lambda_{R_h} - \lambda_{I_h})$$

$$u_1[0,1] \quad if \quad B_1Ne^{-\theta t} = I_h(\lambda_{R_h} - \lambda_{I_h}) \qquad (3)$$

$$u_1 = 1 \quad if \quad B_1Ne^{-\theta t} < Ih(\lambda_{R_h} - \lambda_{I_h}$$

$$u_2 = 0 \quad if \quad B_2Me^{-\theta t} > S_v\lambda_{S_v} + I_v\lambda_{I_v}$$

$$u_2 = \epsilon[0,1] \quad if \quad B_2Me^{-\theta t} = S_v\lambda_{S_v} + I_v\lambda_{I_v} \qquad (4)$$

$$u_2 = 1 \quad if \quad B_2u_2e^{-\theta t} < S_v\lambda_{S_v} + I_v\lambda_{I_v}$$

B_1N and $I_h(\lambda_{R_h} - \lambda_{I_h})$ Represent marginal benefits and marginal cost respectively for malaria treatment

B_2M and $S_v\lambda_{S_v} + I_v\lambda_{I_v}$ represent marginal benefits and marginal cost respectively for malaria prevention.

From (3), all infected human will have to be treated if only if the marginal cost is less than the marginal benefit and if not, only a small number of infected humans are going to be treated.

From (4), the optimal policy is the prevention of malaria if and only if the marginal benefits is greater than the marginal cost and this means that prevention will be the preferred method to minimize malaria than treatment.

IV.B. Optimal control Analysis

The optimal control u_1^* , u_2^* are such that:

$$J(u_1^*, u_2^*) = min_{u1,u2 \in U}](u_1, u_2)$$

With U is a measurable function defined from [0, T] onto [0, 1].

Hamiltonian equation is given by the following equation:

$$H = \{I_h + S_h + I_v + 1/2B_1u_1^2 + 1/2B_1u_1^2\} + \lambda_{S_h}(\Lambda_h + \omega R_h - \frac{\beta_{vh}I_vS_h}{N} - \mu_{hS_h}) + \lambda_{I_h}[(\frac{\beta_{vh}I_vS_h}{N} - (a + \mu_h + \delta_h + u_1 - k)I_h] + \lambda_{R_h}[(a + u_1)I_h - (\mu_h + \omega)R_h] + \lambda_{S_v}[(\Lambda_v - \frac{\beta_{hv}I_hS_v}{N} - (\mu_v + u_2)S_v] + \lambda_{I_v}[\frac{\beta_{hv}I_hS_v}{N} - (\mu_v + u_2)I_v]\}e^{-\theta t}$$

Co-state variables are given by:

$$\frac{d\lambda_{S_h}}{dt} = -\frac{\partial H}{\partial S_h} = \frac{\beta_{vh}I_v}{N}(\lambda_{S_h} - \lambda_{I_h}) + \mu_h\lambda_{S_h}$$

$$\frac{d\lambda_{I_h}}{dt} = -\frac{\partial H}{\partial I_h} = e^{-\theta t} + (a + u_1)(\lambda_{I_h} - \lambda_{R_h}) + (\delta_h - k + \mu_h)\lambda_{I_h} + \frac{\beta_{hv}S_v}{N}(\lambda_{S_v} - \lambda_{I_v})$$

$$\frac{d\lambda_{R_h}}{dt} = -\frac{\partial H}{\partial R_h} = \omega(\lambda_{R_h} - \lambda_{S_h}) + \mu_h\lambda_{R_h}$$

$$\frac{d\lambda_{S_v}}{dt} = -\frac{\partial H}{\partial S_v} = e^{-\theta t} + \frac{\beta_{hv}I_h}{N}(\lambda_{S_v} - \lambda_{I_v}) + (\mu_v + u_2)\lambda_{S_v}$$

$$\frac{d\lambda_{I_v}}{dt} = -\frac{\partial H}{\partial I_v} = e^{-\theta t} + \frac{\beta_{vh}S_h}{N}(\lambda_{S_h} - \lambda_{I_h}) + (\mu_v + u_2)\lambda_{I_v}$$

The transversality conditions are:

$$\lambda_{S_h} = \lambda_{R_h} = \lambda_{S_v} = \lambda_{I_v} = \lambda_{I_h}$$

The application of Pontryagin's Maximum Principal (Pontryagin et *al*., 2018) and optimal control as described by

Fleming and Rishel (2012), Otieno et *al*. (2016), we have the optimal control u_1^* and u_2^* that minimize u_1 and u_2.

$$u_1^* = \min\{\max(0, \frac{(\lambda_{S_v} - \lambda_{I_h})e^{\theta t}}{B_1}, u_{1max}\}$$

$$u_1^* = \min\{\max(0, \frac{(\lambda_{S_v}S_v - \lambda_{I_v}I_v)e^{\theta t}}{B_2}), u_{2max}\}$$

This can be written by:

$$u_1^* = \begin{cases} 0 & if \quad \frac{(\lambda_{S_v} - \lambda_{I_h})e^{\theta t}}{B_1} < 0 \\ \frac{(\lambda_{S_v} - \lambda_{I_h})e^{\theta t}}{B_1} & if \quad 0 < \frac{(\lambda_{S_v} - \lambda_{I_h})e^{\theta t}}{B_1} < 1 \\ 1 & if \quad \frac{(\lambda_{S_v} - \lambda_{I_h})e^{\theta t}}{B_1} \geq 1 \end{cases}$$

$$u_2^* = \begin{cases} 0 & if \quad \frac{(\lambda_{S_v}S_v - \lambda_{I_v}I_v)e^{\theta t}}{B_2} < 0 \\ \frac{(\lambda_{S_v}S_v - \lambda_{I_v}I_v)e^{\theta t}}{B_2} & \text{if } 0 < \frac{(\lambda_{S_v}S_v - \lambda_{I_v}I_v)e^{\theta t}}{B_2} < 1 \\ 1 & if \quad \frac{(\lambda_{S_v}S_v - \lambda_{I_v}I_v)e^{\theta t}}{B_2} \geq 1 \end{cases}$$

IV.C. Analysis of Cost-Effectiveness

The cost effectiveness analysis was done using ICER classical approach of the 15 alternative strategies **(**Otieno et *al*., 2016**,** Okosun et *al*., 2013) to reach the comparison of prices and the effects results on health of each intervention strategy competing for available means.

To calculate the ICER, we use the following formula:

$$ICER\ for\ B = \frac{\text{Price of Intervention B} - \text{Price of Intervention A}}{\text{Impact of Intervention B} - \text{Impact of Intervention A}}$$

The two intervention strategies A and B with their advantages on health rating are going to be compared. Their measurement is done considering quality life years benefited or lost. After Simulation, strategies are ranked from the smallest to the highest effectiveness measured as the sum of infections averted.

V. NUMERICAL RESULTS AND DISCUSSION

Parameters used in the model (1) are estimated using data from the Department of National Health Information System of Burundi. Unavailable data are estimated referring to published literature on malaria in other countries where malaria is endemic compared to Burundi.

Table 3: values of parameters of the model (1)

Parameter	Estimated value	Source
Λ_h	19	Estimated (Minisante,2020)
Λ_v	727.26	Estimated UNDP(2020)
μ_h	0.0000557989	Estimated
a	0.23608349	Estimated
δ_h	0.27033533	Estimated(Minisante,2020)
κ	0.20910926	Estimated(Minisante, 2020)
ω	0.53193937	Estimated
β_{vh}	0.05024818	Estimated
β_{hv}	0.47460852	Estimated
μ_v	0.000710736	Estimated UNDP(2020)
N	338033	Minisante,2020
M	1701800	Assumed
B1	\$2.5-5	Estimated (Minisante,2020)
B2	\$6	Estimated (Minisante, 2020)

The estimation of intervention measures are: u_1= 0.1904, u_2 =0.265 and the initial state variables are: $S_h(0)$= 850 , $I_h(0)$= =25, $R_h(0)$=0, $S_v(0)$= 600, $I_v(0)$= 560

The numerical simulation was done using Python.

V.A. Economic Evaluations Numerical Simulations Economic Evaluations

For illuminative purpose, a case of the endemic area was chosen**.** Evaluation of the shadow prices at the beginning of epidemic and as a function of the numbers of protected (**R**) at that period, the simulation is done to illustrate the impact of marginal benefits and shadow prices.

The incremental cost and effect of the intervention measures simulation was done considering the Endemic spread settings and the simulation results are given in following figure:

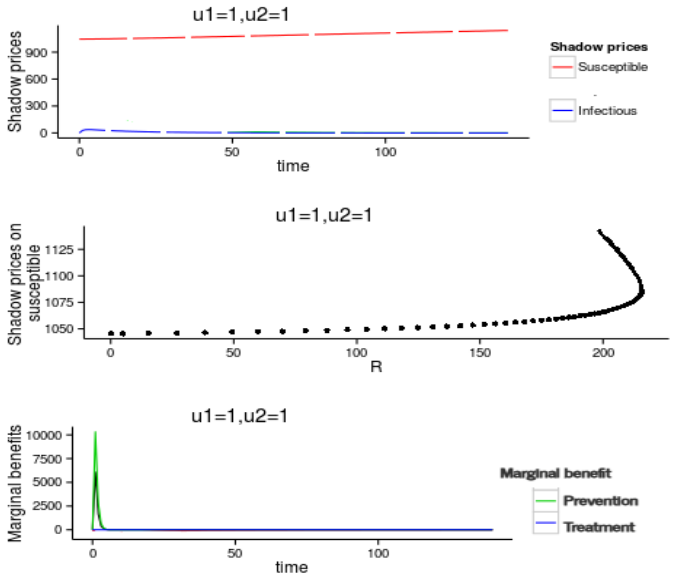

Fig. Shadow prices evaluation at the beginning of malaria with their Marginal benefits

From above figures, it is very clear that the value of marginal of the infected human is much less demanding than the values of marginal of the Susceptible human. The shadow price on humans who are susceptible humans increases with time and meanwhile; at the third day the shadow price on the infectious humans begins to decrease. On the figure, it is noticeable that the shadow price on susceptible humans begins at higher non-negative values, it increases to stabilize at the maximal prices tight to the total susceptible population.

As shown on figures, the cost of recovered individuals (R) is still higher, treatment is the preferable way to eliminate malaria as the needed amount for treatment is smaller than the amount needed for prevention.

In order to quantify the cost effectiveness of the control strategies, Infection Averted Ratio, the Numerical Simulation of the Optimal Malaria Control Strategies and Cost-Effectiveness Analysis was done using the following formula:

$$\text{Infection Averted Ratio (IAR)} = \frac{\text{Number of Averted Ratio}}{\text{Number of sucessifully Recovered}}$$

Assuming that there is a direct proportionality between of the price of the controls measures and the control number, this assumption help us to understand the goals of the use of preventive measures when reducing infection.

Numerical simulations showing the ration of averted infections and the associated corresponding prices to the averted infections by the intervention strategies for the four different transmission settings and rankings of the number averted infections were investigated to apply ICER.

Different intervention strategies and associated averted infections of the optimal solutions were computed.

The strategies were chosen as follows:

A= No Intervention measures, B= Preventive measures only, C= Treatment only, D Treatment and Preventive measures

Table 4: Averted infections with allocated cost corresponding to Intervention strategies.

Strategy	**IAR**	**Cost (USD)**
A	0	0
B	1.58750613	4.7613
C	100.7392	600.4357
D	121.7351	67.7985

Table 5: Incremental cost-effectiveness ratios

Strategy	SE	Cost ($)	IC	IE	ICER
A	0	0	0	0	0
B	1.587 5	4.7613	4.7613	1.587 5	2.9923
C	100.7392	600.4357	595.6744	99.1517	6.0169
D	121.7351	67.7985	-532.6372	20.9959	-26.2891

From the table **5** if strategies B and C are compared, it is very clear that there is a saving of $2.992325 if the strategy B is used compared to C. B has the lower ICER and this means that the strategy C is dominated. Hence, the strategy C is the more expensive and the least effective than B.

Thus, it must be removed because it consume much resources without good results.

After C is excluded, we get:

Table 6: Incremental cost-effectiveness ratios after C is excluded

Strategy	SE	Cost ($)	IC	IE	ICER
B	1.5875	4.7613	4.7613	1.5875	2.992325
D	121.7351	67.7985	-532.6372	20.9959	-26.2891

From the results given in table 6, it is deduced that the strategy D (treatment and preventive measures), has the least ICER and therefore it is more cost-effective than strategy B.

V.B. Discussion

This paper studied the cost-effectiveness of possible separated or combined strategies for malaria spread settings with purpose of identifying the most beneficial and cost effective strategies. The simulation of optimal control of the four strategies with associated cost-effectiveness were done. The rank of possible strategies was done beginning from the strategy which has the least effect among the identified four strategies: strategy where there is no intervention measure, strategy where only Preventive measures are only considered, strategy where only Treatment is considered, strategy where there is a combination of Treatment and Preventive measures. There had been marginal and cost benefits investigations using ICER results comparison of economic benefits of the different possible intervention strategies with their health effects. Results of numerical simulation gave the comparison of the marginal value and marginal effect for the four intervention strategies.

The results of the study has shown that combining treatment and prevention is the cheapest way to control the spread of malaria while preventive measures are the cheapest way to minimize or eradicate malaria transmission.

As these findings prove that Health beneficial and cost-effectiveness must be considered when choosing different disease transmission settings and this a very important information for decision makers when allocating hearth resources.

These findings are a very useful too that may inform decision makers when developing malaria prevention guidelines in Bubanza province, in Burundi and they can be generalized to other countries.

As this study was done based on pre-existent data, there is a need of doing deep study to verify the accuracy of these findings using primary data.

V.C. Conclusion

In this paper, we determined and investigated a deterministic model representing the transmission of malaria incorporating the intervention strategies. After the Cost-effectiveness analysis of the optimal control strategies was done, we summarized the model analysis as follows:

1. The disease-free equilibrium point of the system (1) is locally asymptotically stable if the basic reproduction number (R_0) is less than one and it is unstable if $R_0>0$.
2. The endemic equilibrium point of the system (1) is locally asymptotically stable if and only if the basic reproduction number (R_0) is greater than one and it is unstable if $R_0 >0$.

3. The optimal control strategies cost effectiveness analysis showed that the combination of prevention and treatment are the most effective and health beneficial while prevention is the cheapest method.

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