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Combined Drug Interventions and its Efficacy in the Reduction of COVID-19 Burden : A Within-Host Modeling Study with reference to HCQ and BCG Vaccination

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ABSTRACT

The COVID-19 pandemic has resulted in more than 28.05 million infections and 9, 08, 475 deaths in 212 countries over the last few months. Different drug interventions acting at multiple stages of the pathogenesis of COVID-19 can substantially reduce infection-induced mortality. The current within-host mathematical modeling studies deals with the optimal combined drug intervention strategy and its efficacy in reducing the burden of COVID-19. The drug interventions considered here include Hydroxychloroquine (HCQ), the first BCG vaccine dose, and a booster dose of BCG administered at a later stage. In this work, we consider two scenarios involving the administration of these interventions. In the first scenario, we study the efficacy of drug interventions such as HCQ and BCG first dose administered at present. Initially, we study their efficacy when administered individually and, later we study the efficacy of the combined therapy involving the administration of these two interventions HCQ, BCG first dose simultaneously at present. In the second scenario, we assume that the BCG primary dose has been administered at birth to the individual and we study the efficacy of the drug interventions HCQ and BCG booster dose administered either individually or in combination at present. In both these scenarios, the optimal intervention strategy is proposed based on two methods. In the first method, these medical interventions are modeled as control interventions and a corresponding objective function and optimal control problem is formulated and discussed. Later, using the comparative effectiveness method the optimal drug intervention strategy is proposed based on basic reproduction number and viral count. The findings of these studies include the following: The average infected cell count and viral load decreased the most when both the HCQ and BCG interventions were applied together in both scenarios. On the other hand, the average susceptible cell count decreased the best when HCQ alone was administered in both these scenarios. The basic reproduction number and viral count decreased the best when HCQ and BCG booster interventions were applied together, reinstating the fact obtained earlier in the optimal control setting. These findings may help physicians with decision making in the treatment of life-threatening COVID-19 pneumonia.

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KEYWORDS

COVID-19; Inflammatory Mediators; BCG Vaccine; HCQ; Optimal Control Problem;

1 INTRODUCTION

The humanity at this point of time is facing one the worst crisis in the last century in the form of pandemic COVID-19 caused by the *Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2)*, which engulfed the lives of 28.05 million in 212 countries as of September 10, 2020, and continues to worsen [6]. Doctors, scientists, leaders of the states and many other professionals are working round the clock to root out the virus from our society. At this juncture mathematical modeling can play a crucial role in this journey as they are helpful in multi-fold. Firstly, they help in understanding the dynamics of infection and its spread in the society. They help in studying the success of various control measures that can be implemented in order to avoid the further damage. Secondly, the within-host mathematical modeling helps to study the dynamics of virus in the human body and can help us in understanding efficacy of different drug intervention acting at multiple stages of pathogenesis which in turn can help in identification of potential vaccine candidates. Some works dealing with population level studies and within-host studies for diseases such as Dengue, HIV, Influenza include [11, 19] and references within. Recent works dealing with population level studies and within-host studies for COVID-19 can be found in [14, 16, 18, 21, 25].

The Bacillus Calmette-Guerin (BCG) vaccine was first mass produced in 1924 for tuberculosis disease. The BCG tuberculosis vaccine boosts the production of immune cells. A study proves that Century-old BCG vaccine used to eradicate tuberculosis does reduce the chance of death from COVID-19 [2, 4]. It is found out that the countries with a 10 per cent greater prevalence of the BCG vaccine also had a 10.4 per cent reduction in COVID-19 mortality [12, 9]. Recent work [8] showed that mandated BCG vaccination can be effective in fight against COVID-19. In fact mandated BCG predicted flattened curves for the spread of COVID-19. Also, the anti-malarial drug Hydroxychloroquine (HCQ) has demonstrated in-vitro activity against SARS-CoV2 [3]. HCQ along with other drugs like Azithromycin was administered initially to COVID-19 patients [7]. Later medical guidelines were modified to administer HCQ alone to treat COVID-19 patients at the early course of the disease [3].

Recently the author's team worked on a within-host model involving crucial inflammatory mediators and the host immune response [1]. This work dealt with the natural history and course of infection of COVID-19. The authors also briefly discussed about combined drug therapy in [1].

Motivated by the above in the present work we work on optimal drug intervention strategy and the efficacy of combined therapy in reducing the burden of COVID-19. The drug interventions considered include HCQ, BCG first dose and BCG booster dose. We consider two scenarios involving administration of these interventions. In the first scenario we study the efficacy of drug interventions such as HCQ and BCG first dose administered at the present time. Initially we study their efficacy when administered individually and later we study the efficacy of the combined therapy involving administration of these two interventions HCQ, BCG first dose simultaneously at present. In the second scenario we assume that the BCG primary dose has been administered at birth to the individual and we study the efficacy of the drug interventions HCQ and BCG booster dose administered either individually or in combination at the present time. In both these scenarios the optimal intervention strategy is proposed based on two methods. In the first method

these medical interventions are modeled as control interventions and a corresponding objective function and optimal control problem is formulated and discussed. Later using the comparative effectiveness method the optimal drug intervention strategy is proposed based on basic reproduction number and viral count. The findings of these studies include the following. The average infected cell count and viral load decreased the most when both the HCQ and BCG interventions were applied together in both the scenarios. On the other hand the average susceptible cell count decreased the best when HCQ alone was administered in both these scenarios. The basic reproduction number and viral count decreased the best when HCQ and BCG booster interventions were applied together reinstating the fact obtained earlier in the optimal control setting. These findings may help physicians with decision making in treatment of life-threatening COVID-19 pneumonia.

RESEARCH IN CONTEXT

Evidence before the study: The efficacy of drugs in the treatment of COVID-19 infection was assessed and reported in a few clinical trials and observational studies. The role of combination of anti-microbial agents in achieving the favorable outcome is very well established in several viral diseases including HIV, dengue hemorrhagic fever etc. To determine the utility of combined anti-microbials through the clinical studies will take a long way and considering the current mortalities due to COVID-19 cannot be awaited for.

Added value of this study: The current research study is the first hand evidence for the efficacy of combined anti-microbial agents for the treatment of COVID-19. The study assessed the combined efficacy of three therapeutic interventions namely HCQ, BCG first dose and BCG booster dose. Optimal reduction in the viral load and the number of infected cells can be significantly achieved when the above four interventions used in combination as compared with the efficacy of individual therapeutic agent.

Implications of all the available evidence: The mathematical evidence generated out of this study will pave a way for developing a standardized clinical treatment regimen both on therapeutic and research avenues.

OBJECTIVES OF THE PROPOSED STUDY

1. To investigate the role of medical interventions such as HCQ and BCG vaccine by incorporating them as controls at specific sites in the pathogenesis.
2. To study and compare the dynamics of susceptible, infected cells and viral load with and without these control interventions.
3. To propose the optimal drug strategy in scenarios involving administration of single drug intervention, two drug interventions based on the average susceptible, infected cell count and average viral load.
4. To propose the optimal drug strategy using the comparative effectiveness studies.

METHODS

A within-host mathematical model incorporating drug interventions was studied as an optimal control problem. The *Fillipov Existence Theorem* was used to obtain an optimal solution [20]. Characterization of optimal controls is done using Maximum Principle [20]. Numerical simulations involving with and without control interventions were performed for obtaining optimal drug regimen. Comparative effectiveness method [13] was used to study the change in basic reproduction number and virus count for single and multiple interventions.

2 MODEL WITH HCQ AND BCG FIRST DOSE

In similar lines to [1], in this section, we consider a control problem with the drug interventions HCQ and BCG first dose as controls given by

$$\frac{dS}{dt} = \omega - \beta SV - \mu_{1hcq}(t)S - \mu S \tag{2.1}$$

$$\frac{dI}{dt} = \beta SV - \Big(d_1 + d_2 + d_3 + d_4 + d_5 + d_6\Big)I - \Big(\mu_{2hcq}(t) + \mu_{2bcgfd}(t)\Big)I - \mu I \tag{2.2}$$

$$\frac{dV}{dt} = \alpha I - \Big(b_1 + b_2 + b_3 + b_4 + b_5 + b_6\Big)V - \mu_1 V - \Big(\mu_{3hcq}(t) + \mu_{3bcgfd}(t)\Big)V \tag{2.3}$$

Parameters	**Biological Meaning**
S	Healthy Type II Pneumocytes
I	Infected Type II Pneumocytes
ω	Natural birth rate of Type II Pneumocytes
V	Viral load
β	Rate at which healthy Pneumocytes are infected
α	Burst rate of virus particles
μ	Natural death rate of Type II Pneumocytes
μ_1	Natural death rate of virus
d_1, d_2, d_3, d_4, d_5, d_6	Rates at which Infected Pneumocytes are removed because of the release of cytokines and chemokines IL-6 TNF-α, INF, CCL5, CXCL8 , CXCL10 respectively
b_1, b_2, b_3, b_4, b_5, b_6	Rates at which Virus is removed because of the release of cytokines and chemokines IL-6 TNF-α, INF, CCL5, CXCL8 , CXCL10 respectively
u_{1hcq}, u_{2hcq}, u_{3hcq}	Rates at which susceptible cells, infected cells and viral load are reduced due to HCQ drug.
u_{2bcgfd}, u_{3bcgfd}	Rates at which infected cells and the viral load are reduced due to BCG first dose

Definition of the objective function

Let $U_1 = (\mu_{1hcq}, \mu_{2hcq}, \ \mu_{3hcq}), U_2 = (\mu_{2bcgfd}, \mu_{3bcgfd})$

$$J(U_1, U_2) = \int_0^T \Big(A_1 U_1^2 + A_2 U_2^2 - I(t) - V(t) \Big) dt \tag{2.4}$$

To reduce the complexity of the problem here we choose to model the control efforts via a linear combination of the quadratic terms. Also when the objective function is quadratic with respect to the control, differential equations arising from optimization have a known solution. Other functional forms sometimes lead to systems of differential equations that are difficult to solve [10], [17].

The integrand of the cost function (2.4), denoted by

$$L(S, I, V, U_1, U_2) = \Big(A_1 U_1^2 + A_2 U_2^2 - I(t) - V(t) \Big)$$

is called the Lagrangian of the running cost.

Here the cost function (2.4) represents the benefits of each of the interventions and the number of infected cells and viral load throughout the observation period. Our goal is to maximize the benefits of each of the interventions and minimize the infected and viral load.

The coefficients A_i, for $i = 1, 2$ are the constants related to the benefits of each of the interventions.

The admissible solution set for the optimal control problem (2.1) - (2.4) is given by,

$$\Omega = \{(S, I, V, U_1, U_2) \mid S, I \ and \ V \text{that satisfy } (2.1) - (2.3) \ \forall \ U_i \in U\}$$

where U is the set of all admissible controls given by

$U = \{U_1 = (\mu_{1hcq}(t), \mu_{2hcq}(t), \mu_{3hcq}(t)), U_2 = (\mu_{2bcgfd}(t), \mu_{3bcgfd}(t))\}$:

$\mu_{1hcq}(t)) \in [0, \mu_{1hcq}max], \ \mu_{2hcq}(t) \in [0, \mu_{2hcq}max], \ \mu_{3hcq}(t) \in [0, \mu_{3hcq}max], \ \mu_{2bcgfd}(t) \in [0, \mu_{2bcgfd}max], \ t \in [0, T]\}$.

2.1 *Existence of Optimal Controls*

Theorem 2.1. *There exists a 5-tuple of optimal controls* $(\mu^*_{1hcq}(t), \mu^*_{2hcq}(t), \mu^*_{3hcq}(t), \mu^*_{2bcgfd}(t), \mu^*_{3bcgfd}(t)$ *in the set of admissible controls* U *such that the cost functional is maximized i.e.,*

$J = \max_{(\mu_{1hcq}, \mu_{2hcq}, \mu_{3hcq}, \mu_{2bcgfd}, \mu_{3bcgfd}) \in U} \Big\{ J[\mu_{1hcq}(t), \mu_{2hcq}(t), \mu_{3hcq}(t)), \mu_{2bcgfd}(t)), \mu_{3bcgfd}(t))] \Big\}$ *corresponding to the optimal control problem (2.1) - (2.4).*

Proof. In order to show the existence of optimal control functions, we will show that the following conditions are satisfied :

1. The solution set for the system (2.1) - (2.4) along with bounded controls must be non-empty, *i.e.*, $\Omega \neq \phi$.

2. U is closed and convex and system should be expressed linearly in terms of the control variables with coefficients that are functions of time and state variables.

3. The Lagrangian L should be convex on U and $L(S, I, V, U_1, U_2) \geq g(U_1, U_2)$, where g is a continuous function of control variables such that $|(\mu_{1hcq}, \mu_{2hcq}, \mu_{3hcq}, \mu_{2bcgfd}, \mu_{3bcgfd})|^{-1}$
$g(\mu_{1hcq}, \mu_{2hcq}, \mu_{3hcq}, \mu_{2bcgfd}, \mu_{3bcgfd}) \to \infty$
whenever $|(\mu_{1hcq}, \mu_{2hcq}, \mu_{3hcq}, \mu_{2bcgfd}, \mu_{3bcgfd})| \to \infty$, where $|.|$ is an $l^2(0, T)$ norm.

Now we will show that each of the conditions are satisfied :

1. From positivity and boundedness of solutions of the system (2.1) - (2.3) [1], all solutions are bounded for each bounded control variable in U.

Also, the right hand side of the system (2.1) - (2.3) satisfies Lipschitz condition with respect to state variables.

Hence, using the positivity and boundedness condition and the existence of solution from Picard-Lindelof Theorem [22], we have satisfied condition 1.

2. U is closed and convex by definition. Also, the system (2.1) - (2.3) is clearly linear with respect to controls such that coefficients are only state variables or functions dependent on time. Hence condition 2 is satisfied.

3. Choosing $g(\mu_{1hcq}, \mu_{2hcq}, \mu_{3hcq}, \mu_{2bcgfd}, \mu_{3bbcgfd})$
$= c(\mu_{1hcq}, \mu_{2hcq}, \mu_{3hcq}, \mu_{2bcgfd}, \mu_{3bcgfd})$ such that $c = min\{A_1, A_2\}$, we can satisfy the condition 3.

Hence there exists a control 5-tuple $(\mu_{1hcq}, \mu_{2hcq}, \mu_{3hcq}, \mu_{2bcgfd}, \mu_{3bcgfd}) \in U$
that maximizes the cost function (2.4). □

2.2 *Characteriztion of Optimal Controls*

We now obtain the necessary conditions for optimal control functions using the Pontryagin's Maximum Principle [20] and also obtain the characteristics of the optimal controls.

The Hamiltonian for this problem is given by

$$H(S, I, V, U_1, U_2, \lambda) = L(S, I, V, U_1, U_2) + \lambda_1 \frac{\mathrm{d}S}{\mathrm{d}t} + \lambda_2 \frac{\mathrm{d}I}{\mathrm{d}t} + \lambda_3 \frac{\mathrm{d}V}{\mathrm{d}t}$$

Here $\lambda = (\lambda_1, \lambda_2, \lambda_3)$ is called co-state vector or adjoint vector.

Now the Canonical equations that relate the state variables to the co-state variables are given by

$$\begin{aligned} \frac{\mathrm{d}\lambda_1}{\mathrm{d}t} &= -\frac{\partial H}{\partial S} \\ \frac{\mathrm{d}\lambda_2}{\mathrm{d}t} &= -\frac{\partial H}{\partial I} \\ \frac{\mathrm{d}\lambda_3}{\mathrm{d}t} &= -\frac{\partial H}{\partial V} \end{aligned} \tag{2.5}$$

Substituting the Hamiltonian value gives the canonical system

$$\begin{aligned}
\frac{\mathrm{d}\lambda_1}{\mathrm{d}t} &= \lambda_1(\beta V + \mu + \mu_{1hcq}) - \lambda_2\beta V \\
\frac{\mathrm{d}\lambda_2}{\mathrm{d}t} &= 1 + \lambda_2\bigg(x + (\mu_{2hcq} + \mu_{2bcgfd} + \mu)\bigg) - \lambda_3\alpha \\
\frac{\mathrm{d}\lambda_3}{\mathrm{d}t} &= 1 + \lambda_1\beta S - \lambda_2\beta S + \lambda_3(y + \mu_{3bcgfd} + \mu_{3hcq} + \mu_1)
\end{aligned} \tag{2.6}$$

where $x = d_1 + d_2 + d - 3 + d_4 + d_5 + d_6$and $y = b_1 + b_2 + b_3 + b_4 + b_5 + b_6$ along with transversality conditions $\lambda_1(T) = 0,\ \lambda_2(T) = 0,\ \lambda_3(T) = 0.$

Now, to obtain the optimal controls, we will use the Hamiltonian minimization condition $\frac{\partial H}{\partial u_i} = 0$, at μ^*.

Differentiating the Hamiltonian and solving the equations, we obtain the optimal controls as

$$\begin{aligned}
\mu^*_{1hcq} &= \min\left\{\max\left\{\frac{\lambda_1 S}{2A_1}, 0\right\}, u_{1hcq}max\right\} \\
\mu^*_{2hcq} &= \min\left\{\max\left\{\frac{\lambda_2 I}{2A_1}, 0\right\}, u_{2hcq}max\right\} \\
\mu^*_{3hcq} &= \min\left\{\max\left\{\frac{\lambda_3 V}{2A_1}, 0\right\}, u_{3hcq}max\right\} \\
\mu^*_{2bcgfd} &= \min\left\{\max\left\{\frac{\lambda_2 I}{2A_2}, 0\right\}, u_{2bcgfd}max\right\} \\
\mu^*_{3bcgfd} &= \min\left\{\max\left\{\frac{\lambda_3 V}{2A_2}, 0\right\}, u_{3bcgfd}max\right\}
\end{aligned}$$

3 OPTIMAL DRUG REGIMEN WITH HCQ AND BCG FIRST DOSE AS DRUG INTERVENTIONS

In this section, we perform numerical simulations to understand the efficacy of single and two drug interventions and propose the optimal drug regimen in these scenarios. This is done by studying the effect of the corresponding controls on the dynamics of the system (2.1) - (2.3).

The efficacy of combinations of controls considered are:

1. Single drug intervention administration.

2. Two drug interventions administration.

For our simulations, we have taken the total number of days as $T = 30$ and the parameter values from the following table which are as in [1].

ω	β	μ	μ_1	α	d_1	d_2	d_3	d_4	d_5	d_6	b_1	b_2	b_3	b_4	b_5	b_6
10	0.05	.1	1.1	.5	0.027	0.22	.1	0.428	0.01	0.01	0.1	.1	.08	.11	.1	.07

Table 1. Parameter Values

We first solve the state system numerically using Fourth Order Runge-Kutta method in MATLAB without any interventions. We take the initial values of state variables to be $S(0) = 3.2 \times 10^5, I(0) = 0, V(0) = 5$ and the initial values of the control parameters as zeros.

Now, to simulate the system with controls, we use the Forward-Backward Sweep method stating with the initial values of controls and solve the state system forward in time. Following this we solve the adjoint state system backward in time due to the transversality conditions, using the optimal state variables and initial values of optimal control.

Now, using the values of adjoint state variables, the values of optimal control are updated and with these updated control variables, we go through this process again. We continue this till the convergence criterion is met [20].

We observed that HCQ was administered in the initial stages of the disease to avoid adverse conditions and seems to perform fairly well [3]. Another study shows that the countries with a 10 percent greater prevalence of the BCG vaccine also has a 10.4 percent less reduction in COVID-19 mortality[4]. It is also found that in an in-vitro study, the booster dose of BCG vaccine along with a protein performs better in reducing the coronavirus count by boosting the immune system[2, 4]. Based on these evidences, we choose the positive weights for objective coefficients as $A_1 = 150, A_2 = 100$.

3.1 *WITHOUT ANY DRUGS / INTERVENTIONS*

In this section we simulate the behaviour of susceptible, infected cells and viral load over time. As can be seen from figure 1 the susceptible cells reduce and the infected cells increase exponentially due to the increase in viral load over a period of time.

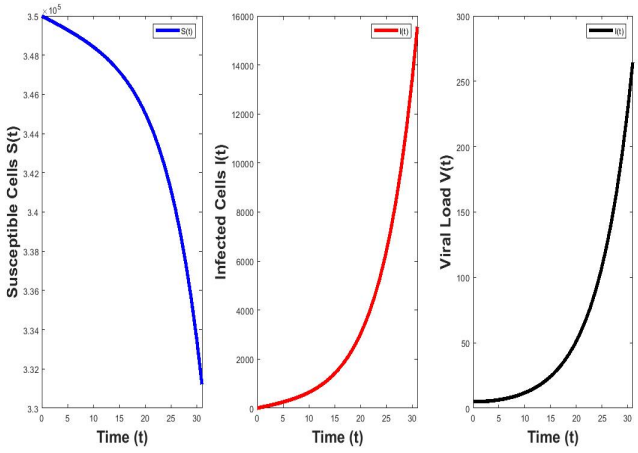

Figure 1. Figure depicting the S, I, V populations for the system (2.1) - (2.3) without control interventions over the time. The exponential growth of the infected cells and viral load can be observed.

3.2 *SINGLE DRUG INTERVENTION*

In this section we study the dynamics of susceptible, infected cells and viral load when HCQ and BCG first dose are administered individually. Figures 2, 3, 4 depict the susceptible, infected population and viral load.

Drug Combinations	Avg Suceptible cells	Avg Infected cells	Avg Viral load
$U_1 = U_1^*, U_2 = 0$	3.2682×10^5	2.9208×10^3	52.0672
$U_1 = 0, U_2 = U_2^*$	3.4534×10^5	3.1071×10^3	53.1666
$U_1 = 0, U_2 = 0$	3.4507×10^5	3.3999×10^3	58.3429

Table 2. Table depicting the average values of the susceptible cells, infected cells and the viral load with respect to each of the drug interventions HCG and BCG first dose when administered individually.

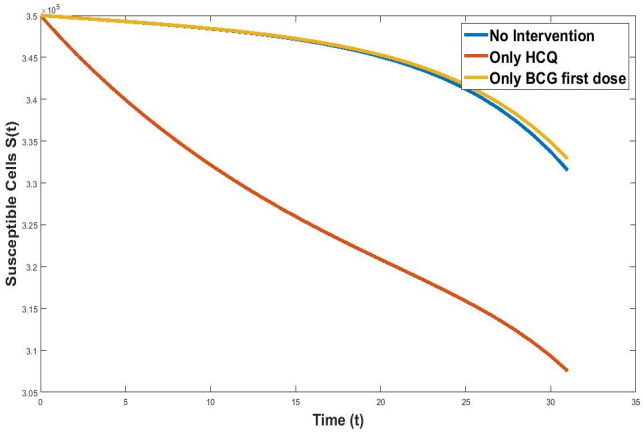

Figure 2. Figure depicting the dynamics of Susceptible cells (S) under the optimal controls U_1^*, U_2^*. Each curve represents the dynamics of susceptible cells with respect to a single control intervention.

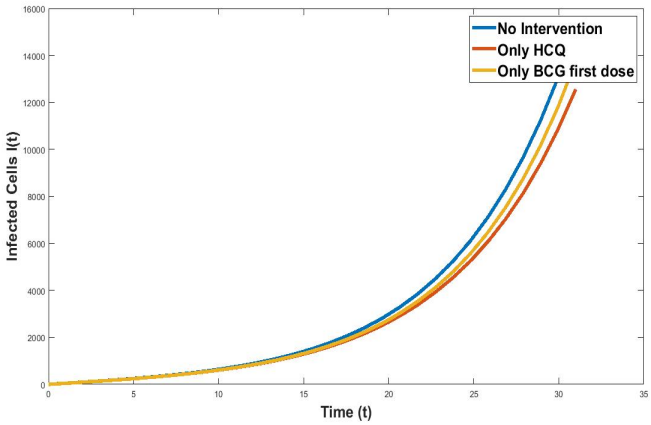

Figure 3. Figure depicting the dynamics of Infected cells (I) under the optimal controls U_1^*, U_2^*. Each curve represents the dynamics of infected cells with respect to a single control intervention.

In table 2 the average values of the susceptible cells, infected cells and the viral load with respect to each of the drug interventions HCQ, BCG first dose when administered individually is listed. From this table 2 it can be seen that the drug HCQ ($U_1 = U_1^*$) reduces the infected cells and viral load the best compared to other combinations when administered individually followed by BCG first dose ($U_2 = U_2^*$). Also HCQ ($U_1 = U_1^*$) does the best job in reducing the susceptible cells.

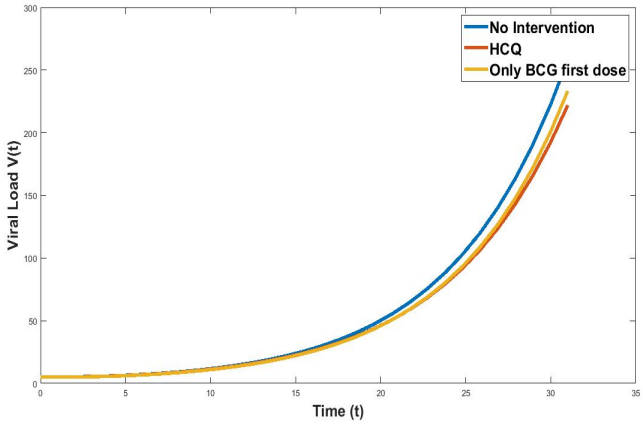

Figure 4. Figure depicting the dynamics of Viral load (V) under the optimal controls U_1^*, U_2^*. Each curve represents the dynamics of viral load with respect to a single control intervention.

3.3 *TWO DRUGS / INTERVENTIONS*

In this section we study the dynamics of susceptible, infected cells and viral load when two control interventions are administered at a time. Figures 5, 6, 7 depict the susceptible, infected population and viral load.

Drug Combinations	**Avg Susceptible cells**	**Avg Infected cells**	**Avg Viral load**
$U_1 = U_1^*, U_2 = U_2^*$	3.2759×10^5	2.8079×10^3	50.1007
$U_1 = U_2 = 0$	3.4507×10^5	3.3999×10^3	58.3429

Table 3. Table depicting the average values of the susceptible cells, infected cells and the viral load with respect to two control interventions administered at a time.

In table 3 the average values of the susceptible cells, infected cells and the viral load with respect to two control interventions administered at a time is listed. From this table 3 it can be seen that the combination of HCQ and BCG first dose ($U_1 = U_1^*, U_2 = U_2^*$) reduces the infected cells and viral load the best. Also the drug combination of HCQ and BCG first dose ($U_1 = U_1^*$) does a better job in reducing the susceptible cells compared to no intervention case.

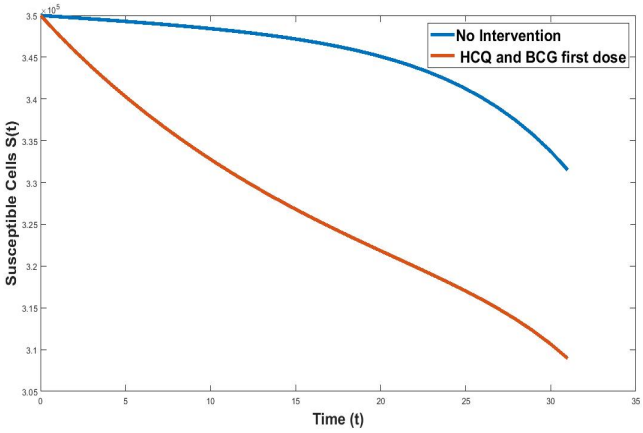

Figure 5. Figure depicting the dynamics of Susceptible cells (S) under the optimal controls U_1^*, U_2^* Each curve represents the dynamics of susceptible cells with respect to two control interventions administered at a time.

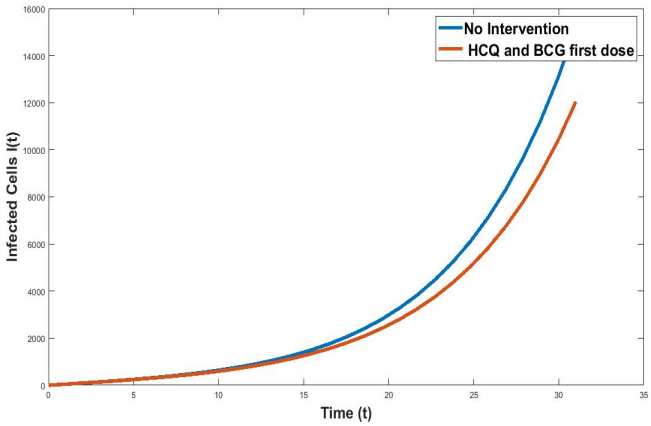

Figure 6. Figure depicting the dynamics of Infected cells (I) under the optimal controls U_1^*, U_2^* Each curve represents the dynamics of infected cells with respect to two control interventions administered at a time.

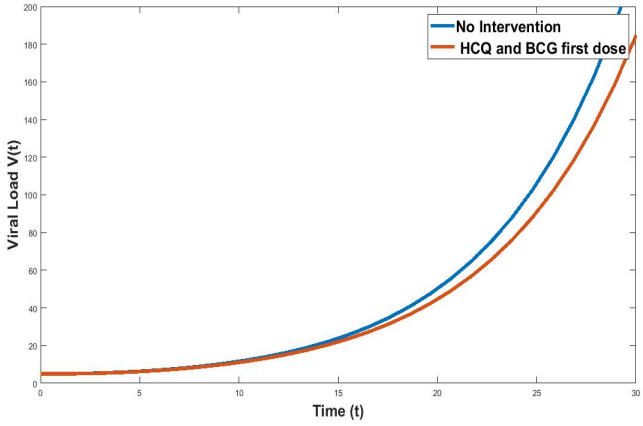

Figure 7. Figure depicting the dynamics of Viral load (I) under the optimal controls U_1^*, U_2^* Each curve represents the dynamics of viral load with respect to two control interventions administered at a time.

4 MODEL WITH HCQ AND BCG BOOSTER DOSE

In similar lines to section 2, in this section, we consider a control problem with the drug interventions HCQ and BCG booster dose as controls. The natural history for this model is in similar lines with the model presented by authors in [1]. We assume that the BCG primary dose is already administered to the patient at birth or in childhood at some point of time. Because of administration of BCG primary dose the individual will be now having an additional immunity component acquired due to BCG vaccine first dose. Incorporating this aspect the modified control problem is now given by

$$\frac{dS}{dt} = \omega - \beta SV - \mu_{1hcq}(t)S - \mu S \tag{4.1}$$

$$\frac{dI}{dt} = \beta SV - \Big(d_1 + d_2 + d_3 + d_4 + d_5 + d_6\Big)I - \Big(\mu_{2hcq}(t) + \mu_{2bcgbd}(t)\Big)I - \alpha_1 I - \mu I \tag{4.2}$$

$$\frac{dV}{dt} = \alpha I - \Big(b_1 + b_2 + b_3 + b_4 + b_5 + b_6\Big)V - \alpha_2 V - \mu_1 V - \Big(\mu_{3hcq}(t) + \mu_{3bcgbd}(t)\Big)V \tag{4.3}$$

Here the parameters α_1 and α_2 represent the rates of decrease of the infected and viral load because of the immunity gained due to BCG primary dose. Evidence from animal and human studies shows that there are significant differences in the immune response induced by different BCG vaccine strains [24]. Among the six widely used BCG vaccine strains, BCG Tice is the most efficacious BCG vaccine[15]. The values for α_1, α_2 will be based on the efficacy of the particular BCG vaccine strain. Here their values are estimated to be 0.1 and .01 as for other parameter values estimated in [1].

Also, the control interventions u_{2bcgbd}, u_{3bcgbd} are the rates at which infected cells and viral load are reduced due to BCG booster dose.

Definition of the objective function

Let $U_3 = (\mu_{1hcq}, \mu_{2hcq}, \ \mu_{3hcq}), U_4 = (\mu_{2bcgbd}, \mu_{3bcgbd})$

$$J(U_3, U_4) = \int_0^T \Big(A_3 U_3^2 + A_4 U_4^2 - I(t) - V(t)\Big)dt \tag{4.4}$$

To reduce the complexity of the problem here we choose to model the control efforts via a linear combination of the quadratic terms. Also when the objective function is quadratic with respect to the control, differential equations arising from optimization have a known solution. Other functional forms sometimes lead to systems of differential equations that are difficult to solve [10], [17].

The integrand of the cost function (4.4), denoted by

$$L(S, I, V, U_3, U_4) = \Big(A_3 U_3^2 + A_4 U_4^2 - I(t) - V(t)\Big)$$

is called the Lagrangian of the running cost.

Here the cost function (4.4) represents the benefits of each of the interventions and the number of infected cells and viral load throughout the observation period. Our goal is to maximize the benefits of each of the interventions and minimize the infected and viral load.

The coefficients A_i, for $i = 3, 4$ are the constants related to the benefits of each of the interventions.

The admissible solution set for the optimal control problem (4.1) - (4.4) is given by,

$$\Omega = \{(S, I, V, U_3, U_4) \mid S, I \; and \; V \text{that satisfy } (4.1) - (4.3) \; \forall \; U_i \in U\}$$

where U is the set of all admissible controls given by

$U = \{U_3 = (\mu_{1hcq}(t), \mu_{2hcq}(t), \mu_{3hcq}(t)),\ U_4 = (\mu_{2bcgbd}(t), \mu_{3bcgbd}(t))\}$:

$\mu_{1hcq}(t)) \in [0, \mu_{1hcq}max],\ \mu_{2hcq}(t) \in [0, \mu_{2hcq}max],\ \mu_{3hcq}(t) \in [0, \mu_{3hcq}max],\ \mu_{2bcgbd}(t) \in [0, \mu_{2bcgbd}max],\ \mu_{3bcgbd}(t) \in [0, \mu_{3bcgbd}max],\ t \in [0, T]\}$.

The existence of optimal controls and characterization of optimal controls for the model (4.1) - (4.3) are in similar lines to sections 2.1 and 2.2 and they are discussed in Appendix.

5 OPTIMAL DRUG REGIMEN WITH HCQ AND BCG BOOSTER DOSE AS DRUG INTERVENTIONS

In this section, we perform numerical simulations to understand the efficacy of single and two drug interventions and propose the optimal drug regimen in these scenarios. This is done by studying the effect of the corresponding controls on the dynamics of the system (4.1) - (4.3).

The efficacy of various combinations of controls considered are:

1. Single drug intervention administration.

2. Two drug interventions administration.

For our simulations, we have taken the total number of days as $T = 30$ and the parameter values from the table 1.

We take the initial values of state variables to be $S(0) = 3.2 \times 10^5, I(0) = 0, V(0) = 5$ and the initial values of the control parameters as zeros. Also we choose the positive weights for objective coefficients as $A_3 = 150, A_4 = 200$.

5.1 *WITHOUT ANY DRUGS / INTERVENTIONS*

In this section we simulate the behaviour of susceptible, infected cells and viral load over time. As can be seen from figure 8 the susceptible cells reduce and the infected cells increase exponentially due to the increase in viral load over a period of time.

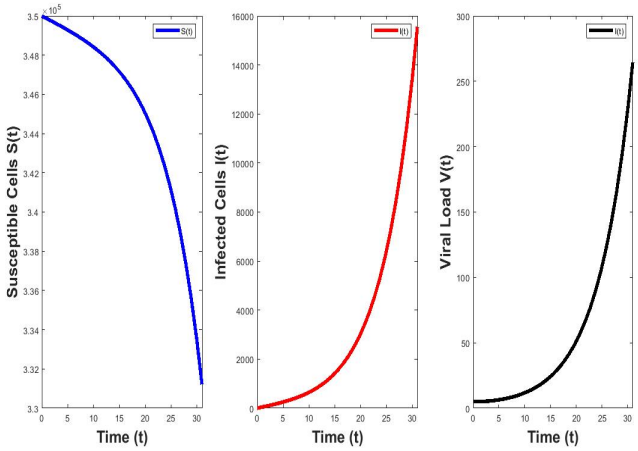

Figure 8. Figure depicting the S, I, V populations for the system (4.1) - (4.3) without control interventions over the time. The exponential growth of the infected cells and viral load can be observed. This figure is qualitatively same as figure 1 but its quantitaively different because of the additional aquired immunity due to BCG primary administered at birth/childhood.

5.2 *SINGLE DRUG INTERVENTION*

In this section we study the dynamics of susceptible, infected cells and viral load when each of these drugs is administered individually. Figures 9, 10, 11 depict the susceptible, infected population and viral load.

Drug Combinations	**Avg Suceptible cells**	**Avg Infected cells**	**Avg Viral load**
$U_3 = U_3^*, U_4 = 0$	3.2694×10^5	2.9019×10^3	51.8034
$U_3 = 0, U_4 = U_4^*$	3.4523×10^5	3.2185×10^3	55.2208
$U_3 = 0, U_4 = 0$	3.4509×10^5	3.3752×10^3	58.0082

Table 4. Table depicting the average values of the susceptible cells, infected cells and the viral load with respect to each of these drug interventions when administered individually.

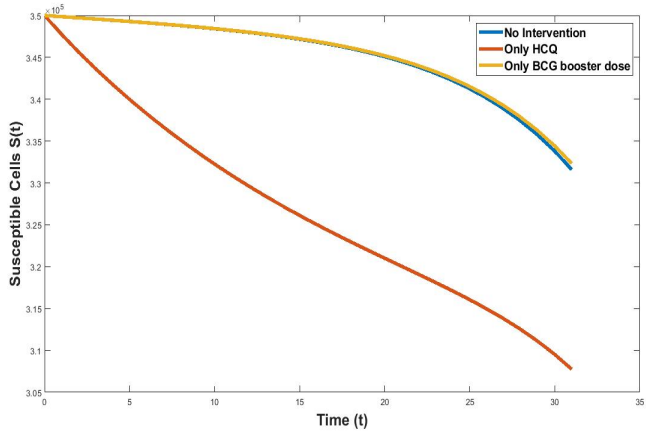

Figure 9. Figure depicting the dynamics of Susceptible cells (S) under the optimal controls U_3^*, U_4^*. Each curve represents the dynamics of susceptible cells with respect to a single control intervention.

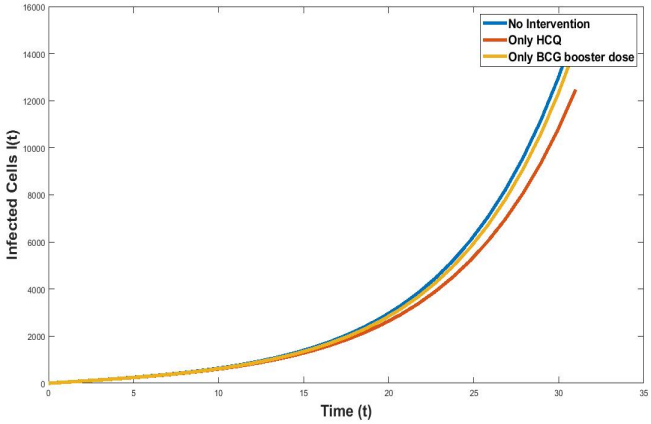

Figure 10. Figure depicting the dynamics of Infected cells (I) under the optimal controls U_3^*, U_4^*. Each curve represents the dynamics of infected cells with respect to a single control intervention.

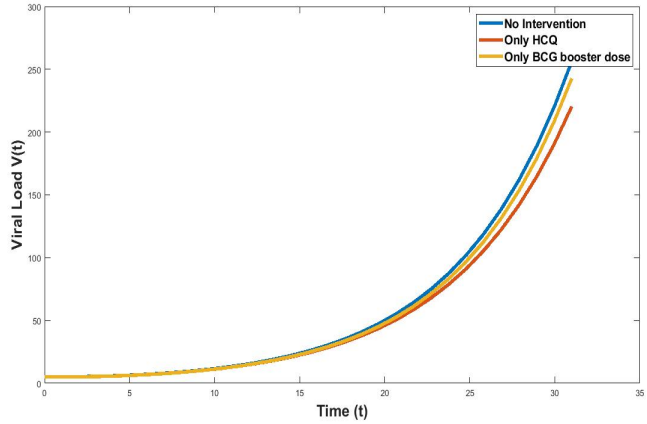

Figure 11. Figure depicting the dynamics of Viral load (I) under the optimal controls U_3^*, U_4^*. Each curve represents the dynamics of viral load with respect to a single control intervention.

In the table 4 the average values of the susceptible cells, infected cells and the viral load with respect to each of these drug interventions when administered individually is listed. From this table 4 it can be seen that the drug HCQ ($U_3 = U_3^*$) reduces the infected cells and viral load the best followed by drug BCG booster dose ($U_4 = U_4^*$). Also HCQ ($U_3 = U_3^*$) does the best job in decreasing the susceptible cells.

5.3 *TWO DRUGS / INTERVENTIONS*

In this section we study the dynamics of susceptible, infected cells and viral load when two control interventions are administered at a time. Figures 12, 12, 14 depict the susceptible, infected population and viral load.

Drug Combinations	**Avg Susceptible cells**	**Avg Infected cells**	**Avg Viral load**
$U_3 = U_3^*, U_4 = U_4^*$	3.2734×10^5	2.8447×10^3	50.8041
$U_3 = U_4 = 0$	3.4509×10^5	3.3752×10^3	58.0082

Table 5. Table depicting the average values of the susceptible cells, infected cells and the viral load with respect to two control interventions administered at a time.

In the table 5 the average values of the susceptible cells, infected cells and the viral load with respect to two control interventions administered at a time is listed. From this table 5 it can be seen when both HCQ and BCG booster dose ($U_3 = U_3^*, U_4 = U_4^*$) when administered together reduce the average infected cells and viral load the best even when compared to the single drug intervention case. They also reduce susceptible cells better compared to no intervention case.

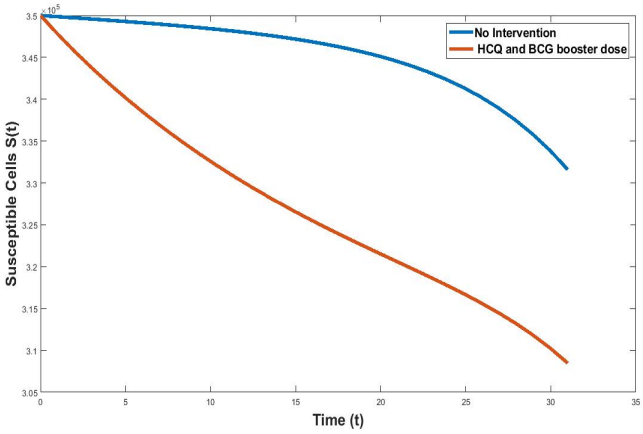

Figure 12. Figure depicting the dynamics of Susceptible cells (S) under the optimal controls U_3^*, U_4^*. Each curve represents the dynamics of susceptible cells with respect to two control interventions administered at a time.

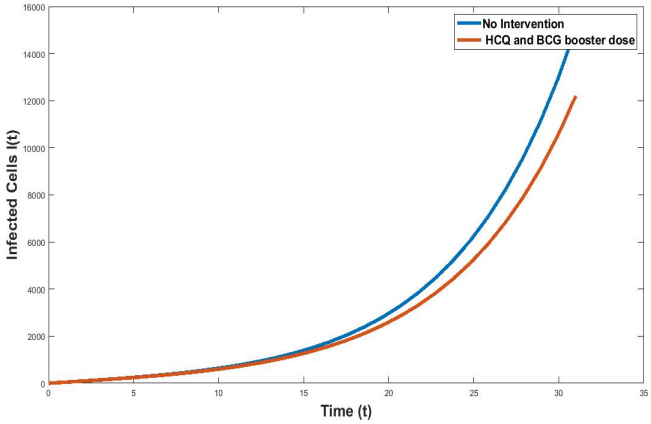

Figure 13. Figure depicting the dynamics of Infected cells (I) under the optimal controls U_3^*, U_4^*. Each curve represents the dynamics of infected cells with respect to two control interventions administered at a time.

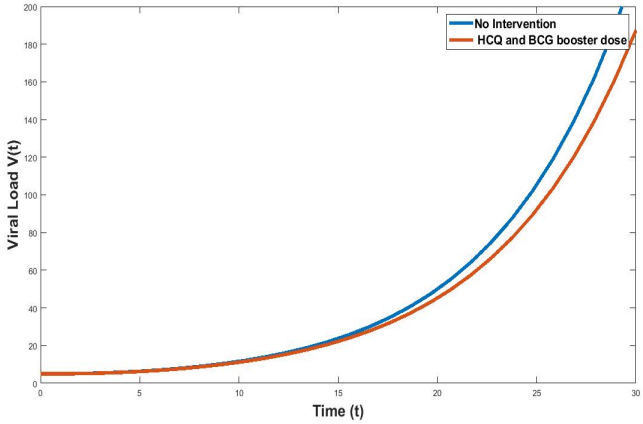

Figure 14. Figure depicting the dynamics of Viral load (V) under the optimal controls U_3^*, U_4^*. Each curve represents the dynamics of viral load with respect to two control interventions administered at a time.

6 COMPARATIVE EFFECTIVENESS STUDY

In this section we do the comparative effectiveness study for the system

$$\frac{dS}{dt} = \omega - \beta SV - \mu S \tag{6.1}$$

$$\frac{dI}{dt} = \beta SV - \Big(d_1 + d_2 + d_3 + d_4 + d_5 + d_6\Big)I - \mu I \tag{6.2}$$

$$\frac{dV}{dt} = \alpha I - \Big(b_1 + b_2 + b_3 + b_4 + b_5 + b_6\Big)V - \mu_1 V \tag{6.3}$$

The basic reproductive number for the system (6.1) - (6.3) as obtained in [1] is given by

$$\mathcal{R}_0 = \frac{\beta\alpha\omega}{\mu(b_1 + b_2 + b_3 + b_4 + b_5 + b_6 + \mu_1)(d_1 + d_2 + d_3 + d_4 + d_5 + d_6 + \mu)} \tag{6.4}$$

The disease-free equilibrium for the system can be seen to be

$$E^0 = \left(S^0, I^0, V^0\right) = \left(\frac{\omega}{\mu}, 0, 0\right) \tag{6.5}$$

and the endemic equilibrium to be

$$\begin{aligned}
\overline{S} &= \frac{(b_1 + b_2 + b_3 + b_4 + b_5 + b_6 + \mu_1)\,(d_1 + d_2 + d_3 + d_4 + d_5 + d_6 + \mu)}{\alpha\beta} \\
\overline{I} &= \frac{\alpha\beta\omega - \mu\,(b_1 + b_2 + b_3 + b_4 + b_5 + b_6 + \mu_1)\,(d_1 + d_2 + d_3 + d_4 + d_5 + d_6 + \mu)}{\alpha\beta\,(d_1 + d_2 + d_3 + d_4 + d_5 + d_6 + \mu)} \\
\overline{V} &= \frac{\alpha\beta\omega - \mu\,(b_1 + b_2 + b_3 + b_4 + b_5 + b_6 + \mu_1)\,(d_1 + d_2 + d_3 + d_4 + d_5 + d_6 + \mu)}{\beta\,(b_1 + b_2 + b_3 + b_4 + b_5 + b_6 + \mu_1)\,(d_1 + d_2 + d_3 + d_4 + d_5 + d_6 + \mu)}
\end{aligned} \tag{6.6}$$

Broadly we consider three kinds of interventions for this comparative effectiveness study.

1. Drugs that inhibit viral replication : Hydroxychloroquine(HCQ) does this job. So we now choose α to be $\alpha(1-\epsilon_1)$, where ϵ_1 is the efficacy of HCQ.
2. Drugs that block virus binding to susceptible cells : Hydroxychloroquine(HCQ) does this job. So we now choose β to be $\beta(1-\epsilon_1)$, where ϵ_1 is the efficacy of HCQ.
3. Possible Immunotherapies : BCG vaccine does this job. So we now choose $(d_1+d_2+d_3+d_4+d_5+d_6)$ to be $(d_1+d_2+d_3+d_4+d_5+d_6)(1+\epsilon_2)$, where ϵ_2 are the efficacy of BCG dosage.

$\mathcal{R}_0$ plays a crucial role in understanding the spread of infection in the individual and $\overline{V}$ determines the infectivity of virus in an individual. Taking the three kinds of interventions into consideration, we now have modified basic reproductive number $\mathcal{R}_E$ and modified virus count $\overline{V}_E$ of the endemic equilibrium to be

$$\begin{aligned}
\mathcal{R}_E &= \frac{\alpha(1-\epsilon_1)\beta(1-\epsilon_1)\omega}{\mu(b_1 + b_2 + b_3 + b_4 + b_5 + b_6 + \mu_1)((d_1 + d_2 + d_3 + d_4 + d_5 + d_6)(1+\epsilon_2) + \mu)} \\
\overline{V_E} &= \frac{\alpha(1-\epsilon_1)\omega}{(b_1 + b_2 + b_3 + b_4 + b_5 + b_6 + \mu_1)\,((d_1 + d_2 + d_3 + d_4 + d_5 + d_6)\,(1+\epsilon_2) + \mu)} - \frac{\mu}{\beta(1-\epsilon_1)}
\end{aligned} \tag{6.7}$$

The efficacy of these interventions is taken as follows : For HCQ, we choose $\epsilon_1 = 0.6$;
The efficacy of two BCG doses are different. So, we choose them as follows :
for BCG first dose, we choose $\epsilon_2 = 0.3$;
for BCG booster dose, we choose $\epsilon_2 = 0.9$;

We now do the comparative effectiveness study of these interventions by calculating the percentage reduction of $\mathcal{R}_\prime$ and $\overline{V}$ for single and multiple combination of these interventions. Percentage reduction of $\mathcal{R}_0$ and $\overline{V}$ are given by

$$\text{Percentage reduction of } \mathcal{R}_0 = \left[\frac{\mathcal{R}_0 - \mathcal{R}_{E_j}}{\mathcal{R}_0}\right] \times 100$$

$$\text{Percentage reduction of } \overline{V} = \left[\frac{\overline{V} - \overline{V}_{E_j}}{\overline{V}}\right] \times 100$$

where j stands for ϵ_1, ϵ_2 or combinations thereof.

Since we have 2 interventions, we consider 4 $(= 2^2)$ different combinations of these drugs.

No.	**Intervention**	**%age change in $\mathcal{R}_0$**	**Rank**	**%age change in $\overline{V}$**	**Rank**
1	Nil	0	1	0	1
	HCQ and BCG First Dose				
2	ϵ_1	84	3	367.6	3
3	ϵ_2	21.04	2	51.86	2
4	$\epsilon_1\epsilon_2$	87.37	4	388.34	4
	HCQ and BCG Booster Dose				
5	ϵ_1	84	3	367.6	3
6	ϵ_2	44.43	2	109.5	2
7	$\epsilon_1\epsilon_2$	91.11	4	411.4	4

Table 6. Comparative Effectiveness Study

In the table 6 the comparative effectiveness is calculated and measured on a scale from 1 to 4 with 1 denoting the lowest comparative effectiveness while 4 denoting the highest comparative effectiveness. The conclusions from this study are the following.

1. When single drug intervention is administered, HCQ outperforms BCG vaccination for either of the dosages w.r.t reduction in both $\mathcal{R}_0$ and $\overline{V}$ (refer rows $2, 3, 5, 6$ in table 6).
2. When HCQ and BCG vaccine are both administered together, the best reduction in $\mathcal{R}_0$ and $\overline{V}$ is seen (refer rows 4,7 in table 6).

7 DISCUSSIONS AND CONCLUSIONS

In this work we have considered three drugs interventions namely, HCQ, BCG first dose and BCG booster dose and studied their efficacy for treatment of COVID-19 when applied individually or in combination. This study is done in two ways. The first by modeling these interventions as control interventions and studying the optimal control problem. The second study was the comparative effectiveness study.

Conclusions from the optimal control studies and comparative effectiveness studies suggest the following.

1. All HCQ and BCG interventions when administered individually or in combination reduce the infected cells and viral load significantly.
2. The average infected cell count and viral load decreased the best when both the HCQ and BCG interventions were applied together.
3. The average susceptible cell count decreased the best when HCQ alone was administered.
4. The basic reproduction number and viral count decreased the best when HCQ and BCG booster interventions were applied together reinstating the fact obtained earlier in the optimal control setting.

This study supports the findings in the recent work [8, 23, 5] which state that

- "Mandated BCG vaccination can be effective in fight against COVID-19. Mandated BCG predicted flattened curves for the spread of COVID-19."
- "BCG vaccination might be associated with a decrease in the incidence of sickness during the COVID-19 pandemic."
- "A combination of hydroxychloroquine, vitamin and zinc tablets along with homeopathic medicines apart from separate medical facilities for policemen and women who contract COVID-19 has helped control the virus among the uniformed personnel."

AUTHORS CONTRIBUTIONS

- First author : Performed research; contributed for theoretical analysis and numerical simulations; analyzed data
- Second/Corresponding author : Conceived the idea; contributed for theoretical analysis and numerical simulations; majorly wrote the entire manuscript
- Third author : Contributed for theoretical analysis; almost did the entire comparative effectiveness study
- Fourth/Senior author : Conceived the idea; contributed for theoretical analysis; gave intellectual inputs; proof read the entire manuscript

DEDICATION

The authors from SSSIHL dedicate this paper to the founder chancellor of SSSIHL, Bhagawan Sri Sathya Sai Baba on the occasion of his 95^{th} Birthday Celebrations. The corresponding author also dedicates this paper to his loving elder brother D. A. C. Prakash who still lives in his heart and the first author also dedicates this paper to his loving father Purna Chhetri.

REFERENCES

[1] *https://arxiv.org/abs/2005.02261.*

[2] *https://www.dailymail.co.uk/sciencetech/article-8509655/bcg-does-protect-against-covid-19-study-confirms.html.*

[3] *https://www.ndtv.com/india-news/health-ministry-okays-anti-malarial-drug-hcq-for-early-course-of-covid-19-2245829.*

[4] *https://www.newscientist.com/article/2242866-bcg-vaccine-helps-fight-infections-by-boosting-immune-cell-production/.*

[5] *https://www.tribuneindia.com/news/nation/hcq-vitamin-tablets-help-mumbai-cops-beat-covid-19-96751.*

[6] *https://www.worldometers.info/coronavirus/.*

[7] Samia Arshad, Paul Kilgore, Zohra S Chaudhry, Gordon Jacobsen, Dee Dee Wang, Kylie Huitsing, Indira Brar, George J Alangaden, Mayur S Ramesh, John E McKinnon, et al., *Treatment with hydroxychloroquine, azithromycin, and combination in patients hospitalized with covid-19*, International Journal of Infectious Diseases (2020).

[8] Martha K Berg, Qinggang Yu, Cristina E Salvador, Irene Melani, and Shinobu Kitayama, *Mandated bacillus calmette-guérin (bcg) vaccination predicts flattened curves for the spread of covid-19*, Medrxiv (2020).

[9] Camila Covián, Angello Retamal-Díaz, Susan M Bueno, and Alexis M Kalergis, *Could bcg vaccination induce protective trained immunity for sars-cov-2?*, Frontiers in Immunology **11** (2020), 970.

[10] Ramses Djidjou-Demasse, Yannis Michalakis, Marc Choisy, Micea T Sofonea, and Samuel Alizon, *Optimal covid-19 epidemic control until vaccine deployment*, medRxiv (2020).

[11] Jeffrey W Eaton, Leigh F Johnson, Joshua A Salomon, Till Bärnighausen, Eran Bendavid, Anna Bershteyn, David E Bloom, Valentina Cambiano, Christophe Fraser, Jan AC Hontelez, et al., *Hiv treatment as prevention: systematic comparison of mathematical models of the potential impact of antiretroviral therapy on hiv incidence in south africa*, PLoS Med **9** (2012), no. 7, e1001245.

[12] Luis E Escobar, Alvaro Molina-Cruz, and Carolina Barillas-Mury, *Bcg vaccine protection from severe coronavirus disease 2019 (covid-19)*, Proceedings of the National Academy of Sciences (2020).

[13] Winston Garira and Dephney Mathebula, *Development and application of multiscale models of acute viral infections in intervention research*, Mathematical Methods in the Applied Sciences **43** (2020), no. 6, 3280–3306.

[14] Giulia Giordano, Franco Blanchini, Raffaele Bruno, Patrizio Colaneri, Alessandro Di Filippo, Angela Di Matteo, and Marta Colaneri, *Modelling the covid-19 epidemic and implementation of population-wide interventions in italy*, Nature Medicine (2020), 1–6.

[15] Marcus A Horwitz, Günter Harth, Barbara Jane Dillon, and Saša Masleša-Galić, *Commonly administered bcg strains including an evolutionarily early strain and evolutionarily late strains of disparate genealogy induce comparable protective immunity against tuberculosis*, Vaccine **27** (2009), no. 3, 441–445.

[16] Adam J Kucharski, Timothy W Russell, Charlie Diamond, Yang Liu, John Edmunds, Sebastian Funk, Rosalind M Eggo, Fiona Sun, Mark Jit, James D Munday, et al., *Early dynamics of transmission and control of covid-19: a mathematical modelling study*, The lancet infectious diseases (2020).

[17] Sunmi Lee, Gerardo Chowell, and Carlos Castillo-Chávez, *Optimal control for pandemic influenza: the role of limited antiviral treatment and isolation*, Journal of Theoretical Biology **265** (2010), no. 2, 136–150.

[18] Chentong Li, Jinhu Xu, Jiawei Liu, and Yicang Zhou, *The within-host viral kinetics of sars-cov-2*, bioRxiv (2020).

[19] Xiaowei Li, Manman Geng, Yizhao Peng, Liesu Meng, and Shemin Lu, *Molecular immune pathogenesis and diagnosis of covid-19*, Journal of Pharmaceutical Analysis (2020).

[20] Daniel Liberzon, *Calculus of variations and optimal control theory: a concise introduction*, Princeton University Press, 2011.

[21] Yingxia Liu, Yang Yang, Cong Zhang, Fengming Huang, Fuxiang Wang, Jing Yuan, Zhaoqin Wang, Jinxiu Li, Jianming Li, Cheng Feng, et al., *Clinical and biochemical indexes from 2019-ncov infected patients linked to viral loads and lung injury*, Science China Life Sciences **63** (2020), no. 3, 364–374.

[22] Evgeny Makarov and Bas Spitters, *The picard algorithm for ordinary differential equations in coq*, International Conference on Interactive Theorem Proving, Springer, 2013, pp. 463–468.

[23] Simone JCFM Moorlag, Rosanne C van Deuren, Cornelis H van Werkhoven, Martin Jaeger, Priya Debisarun, Esther Taks, Vera P Mourits, Valerie ACM Koeken, L Charlotte J de Bree, Thijs Ten Doesschate, et al., *Safety and covid-19 symptoms in individuals recently vaccinated with bcg: a retrospective cohort study*, Cell Reports Medicine (2020), 100073.

[24] Nicole Ritz, Willem A Hanekom, Roy Robins-Browne, Warwick J Britton, and Nigel Curtis, *Influence of bcg vaccine strain on the immune response and protection against tuberculosis*, FEMS microbiology reviews **32** (2008), no. 5, 821–841.

[25] Esteban Abelardo Hernandez Vargas and Jorge X Velasco-Hernandez, *In-host modelling of covid-19 kinetics in humans*, medRxiv (2020).

8 APPENDIX

8.1 *Existence of Optimal Controls*

Theorem 8.1. *There exists a 5-tuple of optimal controls* $(\mu^*_{1hcq}(t), \mu^*_{2hcq}(t), \mu^*_{3hcq}(t), \mu^*_{2bcgbd}(t), \mu^*_{3bcgbd}(t)$ *in the set of admissible controls* U *such that the cost functional is maximized i.e.,*

$J = \max_{(\mu_{1hcq},\mu_{2hcq},\mu_{3hcq},,\mu_{2bcgbd},\mu_{3bcgbd})\in U} \left\{ J[\mu_{1hcq}(t), \mu_{2hcq}(t), \mu_{3hcq}(t)), \mu_{2bcgbd}(t)), \mu_{3bcgbd}(t))] \right\}$ *corresponding to the optimal control problem (4.1) - (4.4).*

Proof. In order to show the existence of optimal control functions, we will show that the following conditions are satisfied :

1. The solution set for the system (4.1) - (4.4) along with bounded controls must be non-empty, *i.e.*, $\Omega \neq \phi$.

2. U is closed and convex and system should be expressed linearly in terms of the control variables with coefficients that are functions of time and state variables.

3. The Lagrangian L should be convex on U and $L(S, I, V, U_3.U_4) \geq g(U_3, U_4)$, where g is a continuous function of control variables such that $|(\mu_{1hcq}, \mu_{2hcq}, \mu_{3hcq}, \mu_{2bcgbd}, \mu_{3bcgbd})|^{-1}$
$g(\mu_{1hcq}, \mu_{2hcq}, \mu_{3hcq}, \mu_{2bcgbd}, \mu_{3bcgbd}) \to \infty$
whenever $|(\mu_{1hcq}, \mu_{2hcq}, \mu_{3hcq}, \mu_{2bcgbd}, \mu_{3bcgbd})| \to \infty$, where $|.|$ is an $l^2(0, T)$ norm.

Now we will show that each of the conditions are satisfied :

1. From positivity and boundedness of solutions of the system (4.1) - (4.3) [1], all solutions are bounded for each bounded control variable in U.

Also, the right hand side of the system (4.1) - (4.3) satisfies Lipschitz condition with respect to state variables.

Hence, using the positivity and boundedness condition and the existence of solution from Picard-Lindelof Theorem [22], we have satisfied condition 1.

2. U is closed and convex by definition. Also, the system (4.1) - (4.3) is clearly linear with respect to controls such that coefficients are only state variables or functions dependent on time. Hence condition 2 is satisfied.

3. Choosing $g(\mu_{1hcq}, \mu_{2hcq}, \mu_{3hcq}, \mu_{2bcgbd}, \mu_{3bcgbd})$
$= c(\mu_{1hcq}, \mu_{2hcq}, \mu_{3hcq}, \mu_{2bcgbd}, \mu_{3bcgbd})$ such that $c = min\{A_3, A_4\}$, we can satisfy the condition 3.

Hence there exists a control 5-tuple $(\mu_{1hcq}, \mu_{2hcq}, \mu_{3hcq}, \mu_{2bcgbd}, \mu_{3bcgbd}) \in U$
that maximizes the cost function (4.4). □

8.2 *Characterization of Optimal Controls*

We now obtain the necessary conditions for optimal control functions using the Pontryagin's Maximum Principle [20] and also obtain the characteristics of the optimal controls.

The Hamiltonian for this problem is given by

$$H(S, I, V, U_3, U_4, \lambda) = L(S, I, V, U_3, U_4) + \lambda_1 \frac{\mathrm{d}S}{\mathrm{d}t} + \lambda_2 \frac{\mathrm{d}I}{\mathrm{d}t} + \lambda_3 \frac{\mathrm{d}V}{\mathrm{d}t}$$

Here $\lambda = (\lambda_1, \lambda_2, \lambda_3)$ is called co-state vector or adjoint vector.

Now the Canonical equations that relate the state variables to the co-state variables are given by

$$\begin{aligned} \frac{\mathrm{d}\lambda_1}{\mathrm{d}t} &= -\frac{\partial H}{\partial S} \\ \frac{\mathrm{d}\lambda_2}{\mathrm{d}t} &= -\frac{\partial H}{\partial I} \\ \frac{\mathrm{d}\lambda_3}{\mathrm{d}t} &= -\frac{\partial H}{\partial V} \end{aligned} \tag{8.1}$$

Substituting the Hamiltonian value gives the canonical system

$$\begin{aligned}
\frac{\mathrm{d}\lambda_1}{\mathrm{d}t} &= \lambda_1(\beta V + \mu + \mu_{1hcq}) - \lambda_2 \beta V \\
\frac{\mathrm{d}\lambda_2}{\mathrm{d}t} &= 1 + \lambda_2\Big(x + (\mu_{2hcq} + \mu_{2bcgbd} + \alpha_1 + \mu)\Big) - \lambda_3 \alpha \\
\frac{\mathrm{d}\lambda_3}{\mathrm{d}t} &= 1 + \lambda_1 \beta S - \lambda_2 \beta S + \lambda_3(y + \alpha_2 + \mu_{3bcgbd} + \mu_{3hcq} + \mu_1)
\end{aligned} \tag{8.2}$$

where $x = d_1 + d_2 + d - 3 + d_4 + d_5 + d_6$and $y = b_1 + b_2 + b_3 + b_4 + b_5 + b_6$ along with transversality conditions $\lambda_1(T) = 0,\ \lambda_2(T) = 0,\ \lambda_3(T) = 0.$

Now, to obtain the optimal controls, we will use the Hamiltonian minimization condition $\frac{\partial H}{\partial u_i} = 0$, at μ^*.

Differentiating the Hamiltonian and solving the equations, we obtain the optimal controls as

$$\begin{aligned}
\mu^*_{1hcq} &= \min\left\{ \max\left\{ \frac{\lambda_1 S}{2A_3}, 0 \right\}, u_{1hcq}max \right\} \\
\mu^*_{2hcq} &= \min\left\{ \max\left\{ \frac{\lambda_2 I}{2A_3}, 0 \right\}, u_{2hcq}max \right\} \\
\mu^*_{3hcq} &= \min\left\{ \max\left\{ \frac{\lambda_3 V}{2A_3}, 0 \right\}, u_{3hcq}max \right\} \\
\mu^*_{2bcgbd} &= \min\left\{ \max\left\{ \frac{\lambda_2 I}{2A_4}, 0 \right\}, u_{2bcgbd}max \right\} \\
\mu^*_{3bcgbd} &= \min\left\{ \max\left\{ \frac{\lambda_3 V}{2A_4}, 0 \right\}, u_{3bcgbd}max \right\}
\end{aligned}$$