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Optimal control strategy for the administration of the third vaccine dose in the treatment of pandemic COVID-19

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In this paper, we propose a mathematical model of COVID-19 infection, taking into account the division of the population according to vaccination criteria. Our goal is to demonstrate the positive effect of receiving the third dose of the Corona vaccine. We proposed two strategies to limit the spread of the COVID-19 pandemic respectively awareness programs on the importance of the third dose of the vaccine and the delivery of treatment to infected individuals who have health problems. Pontryagin's maximum principle is applied in order to characterize the optimal controls, and the optimality system is resolved using an iterative approach. At last, numerical simulations are executed to verify the theoretical analysis using MATLAB.

Keywords: *optimal control; mathematical model; COVID-19; the third dose — Corona vaccine.*

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1. Introduction

Commensurate with the World Health Organization (WHO), the severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) otherwise called new corona virus (2019-nCoV) is reckoned as the etymology of a contagious disease denominated as (COVID-19). As part of its response to the outbreak, WHO has stopped up its Research and Development (R&D) Program to hasten elaboration of diagnostics, vaccines and medicines. Beside a wide variety of organizations involved in development, from largest pharma companies to academic centers and non-profit groups. Hence, vaccination for the susceptible host is predominantly contemplated as the only reliable procedure to control SARS-CoV-2.

However, the sense of exigency in rummaging vaccines was not shared across all demographics. Vaccine hesitancy emerges as ubiquitous phenomenon threatening the global health. This refusal although accessibility of vaccination services is altered by a variety of determinants as confidence (belief in vaccination safety, efficacy, and the proficiency of healthcare systems), convenience (accessibility, competitiveness and distribution of vaccines in a well-provided conditions), and complacency (points out the deficient awareness of the pandemic risk; wherefore, vaccination interpreted as unwarranted process) [1].

A survey of the United Kingdom ascertained a representative UK sample and elicited the join between vaccine knowledge and vaccination willingness. Thus, results perceived the crucial aspect in vaccine hesitancy among respondents which was anxiety rather than familiarity with vaccines. In modern society, mass media and social networks involve an immense influence on perceived knowledge regarding vaccines along with vaccination refusal, based on irresponsible anti-vaccination propaganda sparked by misleading information. Henceforward, rumors and homemade remedies were perceptibly propagated on social platforms, adjoining mass distribution of worldwide post describing vaccine severe side effects, the latter forced vaccination and overestimation of the number of vaccinated people [2]. A large community-based study concerning COVID-19 vaccine hesitancy in the United States, discerned that almost 22% of respondents delayed acceptance of vaccination predicated on assortment of criteria as ethnicity, sex, educational status, financial position, and zone of habitation. Subsequently, political affiliations beside presumed COVID-19 threat were observed as a vital aspects of vaccine hesitancy [3].

Lazarus et al. provided a global survey revealed that 71% of 13 426 randomly selected individuals among 19 countries with a high COVID-19 burden respondents exhibit their ability to get vaccinated in case of vaccine effectiveness and safety [4]. Further up-to-date analysis was implemented by [1] concerning the global COVID-19 vaccination acceptance rates. Accordingly, lower COVID-19 vaccine acceptance rates were sighted in the Eastern Europe, Middle East, and Russia. Whereas high acceptance rates in East and South East Asia may control the complicated course of the SARS-CoV-2. Thereby, government officials should provide comprehensible and consistent communication to build public confidence, listing vaccine process and development explanation during the course of recruitment to regulatory approval built on efficiency and safety. On the other hand, influential vaccination campaigns should certainly emphasize a vaccine's degree of effectiveness, beside duration required for protection and the essential effect of population-wide coverage to attain and maintain public immunity.

Therefore, many studies have been effectuated to assess VE (Vaccine Effectiveness) across the globe: vaccines against SARS-CoV-2 have been expanding extensively through divers technical routes, along with the traditional inactivated vaccine, viral vector vaccine, DNA vaccine, recombinant protein vaccine, and mRNA vaccine. The first study proving the Vaccine Effectiveness of heterologous prime booster vaccination has been accomplished in Brazil, exploiting an inactivated vaccine and an mRNA vaccine booster. Results have shown that VE of the two-dose regimen resistant to either infection or severe outcomes declined for all ages; whereas, vaccine-induced antibodies enhanced remarkably when an mRNA booster dose fulfilled the two-dose of inactivated vaccine (after the booster dose VE resistant to infection appeared 88.8%, and VE resistant to severe outcomes was 90.1%) [5]. The findings of a similar study in Israel provide supportive evidence for a marked increase in protection after the third dose, this analysis examined elderly individuals after the third dose of vaccine in comparison with those who had not received the boosters. Immunity against COVID-19 was improved dramatically after the booster vaccine, likewise protection against severe illness and death [6]. This study has also mentioned the value of vaccine duration as people who got vaccinated in the beginning of the year tended to have additional risk of severe illness contrasted with immunized more recently. These results correspond utterly with Mizrahi research, relevant to the correlation between time-from-vaccine and prevalence of breakthrough infection. A considerable decrease in immune system, beside higher risk for hospitalization for early vaccines compared to later vaccinated people [7]. Introductory data from UK and Qatar corroborate the Israeli research. Boosters provide superior improvement to antibodies and T cells assuring the effectiveness of vaccination [6].

On the grounds that COVID-19 is caused by a new virus, the possible impact of certain biologic medications on the increase of infection severity was effect was unapprehended. A CLARITY IBD research study, from 92UK hospitals covered patients with inflammatory bowel diseases (2279 infliximab-treated and 1031 vedolizumab-treated patients), the study revealed that infliximab-treated patients without antecedent SARS-CoV-2 infection have significantly lower anti-SARS-CoV-2 spike antibody concentrations following two doses of vaccines than patients taking the alternative biologic vedolizumab. However, the study deemed much higher antibody levels in individuals treated with vedolizumab and infliximab with a history of SARS-CoV-2 infection prior to vaccination [8]; this suggests that prioritizing a third strengthening dose of vaccine boosts and sustains the serological immune responses. The latest epidemiological studies elucidate the crucial association between SARS-CoV-2 infections and high frequency of hospitalization in intensive therapy. Almost all communities are faced with a large number of all levels of the health system. Subsequently, healthcare workers (HCWs) are the first group with the highest risk of acquiring infection and emerging physical and mental health disadvantages due to virus high concentration. Medical assistants are in close proximity to infected patients and susceptible not just to infection, but to receive the virus in large doses. China reported 3387 infected HCWs and a percentage of 0.6% of death cases. Europe in turn computes high rates of health workers infection, in France above 50 deaths occurred amongst emergency workers. To shield the wellness of HCWs, an implementation of strategy measures will strengthen lessening the burden of health consequences: as strict control procedures, shorter shift length and arrangement of mental health and support services [9].

Mass vaccination has ascertained its effectiveness in lowering SARS-CoV-2 infections among vaccinated groups. Nevertheless, preventing vaccinated people from spreading the virus to their household members and close contacts remains open to question. Hypothetically, if a 70 to 80% of people get vaccinated and resistant to COVID-19, herd immunity established conceivably to cease the rest of unvaccinated population from SARS-CoV-2 infection. This theory has been experimentally proven in [10], the observational cohort analysis assessed the cumulative amount of COVID-19 infections within vaccinated beside unvaccinated medical workers, supplementary to their unvaccinated household members. The study conceived that mRNA-based vaccines succeed not only in minimizing COVID-19 infections among vaccinated healthcare assistants but also induce a significant decrease in infections within unvaccinated partners and children living in the same household.

Eventually, vaccination has proven its impact on susceptibility in vaccinated individuals and the possibility to cease propagation of infection to unvaccinated ones. However, the cross-protection of new current vaccines resistant to emerging COVID-19 variants has been deemed to be the recent worldwide concern; SARS-CoV-2 accumulates mutations at about the same rate as the causative agent of influenza, with new characteristics as immune escape, rapid transmission and virulence. The strain of Alpha variant detected in South-Eastern England in September 2020, characterized by its upraised transmissibility, in addition, preliminary studies suggest an increase in mortality. Mechanistic demonstration correlate this high transmission characteristic with higher nasopharyngeal viral load combined with lengthened viral shedding; howbeit, Monel et al. asserts that alpha variant does not develop neither viral RNA content nor lengthened viral shedding [11]. Significantly, the correlation between this VOC and the disease severity is neglected, both for alpha or other virus mutations. Whilst most researchers associate the alpha variant transmissibility with higher hospitalization rates. Based on the WHO definition of vaccine efficacy ($>50\%$), an experiment elucidates the ability of COVID-19 inactivated vaccine to generate protection against emerging VOCs variants, and to reduce SARS-CoV-2 severity and mortality [12].

The world is currently dominated by many strains of the pandemic, delta, due to several mutations, turned out to be the most contagious and caused the rise of a new wave of COVID-19. The first discovery of delta strain was in October 2020 in India, and by the beginning of July 2021, WHO recorded the delta strain in 98 countries. In this case, a third boost dose of vaccine could arise antiviral immune responses, bearing in mind the challenge of limited vaccine supply around the world, particularly in developing countries. WHO reviewed the available evidence, and advised on fractional dosing to combat the epidemic; thus, in most dose-finding studies for SARS-CoV-2 vaccines, the intradermal (ID) fractional dose has evinced its potential to enhance immunogenicity similarly with standard intramuscular (IM) dose. The ID fractional third dose was similar as IM third dose within vaccinated groups despite the fact that neutralizing antibody responses after low-dose vaccination were about half as strong as those seen with registered vaccination [13].

The pandemic has greatly advanced biotechnical science and its application in practical health care, giving rise to variety of challenges including time; thus, full genome sequencing is a critical tool for identifying the cause of a hereditary disease beyond higher effect sizes across all variants. Contrasted to microarray genotyping, GenOMICC sequenced almost the entire human genome to analyze and identify complications occurred during a viral infection. The process which initially took more than a decade along with financial cost. Genomic sequencing determines public health decisions as each new variant becomes available. For example, sequencing the genome of the omicron variant allowed researchers to detect more than 30 mutations in a spiny protein that allows the virus to bind to cells in the human body [14]. In [15] the S-LV vaccination revealed $10-20$ times higher peak antibody titres after the third immunization in comparison with inactivated virus vaccines, Adenovirus-based vaccines, DNA vaccine, and an mRNA vaccine. The study illustrates that S-LV vaccination induces strong neutralization of Alpha, Beta, and Gamma, the approach is considered as an effective strategy aiming at saving macaques from high-dose defeat. Results have also suggested the efficacy of the third dose in S-protein Ab titers enhancement, which conceivably affects the neutralization of multiple variants.

The high complexity of an epidemic spread requires mathematical modeling process, recognized as a valuable procedure integrating into the public health decision-making. The application of epidemic modeling submits numerous fundamental perceptions into an outbreak and its control; yet, these assumptions are nearly considerably challenging to conclude only from infection data. A study was effectuated to evaluate fighting policies against corona using a two scale compartmental model, in addition of 20 categories correspondent to 10 human population states beside 10 viruses locations. The model denoted SEIQHTRDDIB reffering to Susceptible (S), Infected (E), Infectious (I), Quarantined (Q), Hospitalized (H), Treated (T), Recovered (R), Non-Infectious dead (D), Infectious dead (DI), Buried (B). Final observations marked social distancing as an essential aspect of the control measures for its ability to eliminate restriction and to assure mobility. Moreover, wearing mask is recognized as a further fruitful control strategy; yet not emergent in case of regular social distancing and disinfection [16]. An extra epidemic model is proposed in [17], the variant SIR model aims at analyzing the impact of heterogeneity on the dynamics, taking into consideration two criteria availability of vaccines and the constant rate of transmission; thus, the vaccination measure transformed regarding epidemic dynamics. As a result, the heterogeneous hysteretic response contributes to the convergency to an endemic equilibrium situation, wherefore, the homogeneity of hysteretic response could induce periodic outbreaks of the SARS-CoV-2 pandemic. Some control systems can be found in the following references [18–21].

The remaining parts of the paper are organized as follows. In Section 2, we present the discrete-time mathematical model taking into account the division of the population according to the vaccination criteria. The optimal control problem of the considered model is studied in Section 3. The results and discussion are provided to ensure the effectiveness of the control strategies in Section 4. To conclude our paper, a conclusion is given in Section 5.

2. Presentation of the model

Due to the current circumstances regarding the spread of the Corona epidemic, which resulted in the division of the population into several groups according to the vaccination criterion. We propose a simple SIR model [22] in which we decompose three compartments into three parts. The first category is formed by unvaccinated individuals, due to the ineffectiveness of the first dose of the vaccine [23], we considered that people who received one dose of the vaccine are also not vaccinated. The second category is those who received two doses of the vaccine. The third group is individuals who took the third dose of the vaccine. We thought that people who received all three doses of vaccine died naturally [24], and that those who recovered become susceptible to infection again.

Therefore we obtain the following system

$$\begin{cases} S_{i+1} = \Lambda_1 + S_i - \beta_1 S_i P_i - \beta_2 S_i J_i - \mu S_i + \theta_1 R_i - \phi_1 S, \\ E_{i+1} = \Lambda_2 + E_i - \gamma_1 E_i P_i - \gamma_2 E_i J_i - \mu E_i + \theta_2 Y_i + \phi_1 S - \phi_2 E, \\ T_{i+1} = \Lambda_3 + T_i - \alpha_1 T_i P_i - \alpha_2 T_i J_i - \mu T_i + \theta_3 W_i + \phi_2 E, \\ P_{i+1} = P_i + \beta_1 S_i P_i + \beta_2 S_i J_i - (\mu + \delta_1 + r_1) P_i, \\ J_{i+1} = J_i + \gamma_1 E_i P_i + \gamma_2 E_i J_i - (\mu + \delta_2 + r_2) J_i, \\ K_{i+1} = K_i + \alpha_1 T_i P_i + \alpha_2 T_i J_i - (\mu + r_3) K_i, \\ R_{i+1} = R_i + r_1 P_i - \mu R_i - \theta_1 R_i, \\ Y_{i+1} = Y_i + r_2 J_i - \mu Y_i - \theta_2 Y_i, \\ W_{i+1} = W_i + r_3 K_i - \mu W_i - \theta_3 W_i, \end{cases} \tag{1}$$

with $i \in \{0, \ldots, N-1\}$, $S_0 \geqslant 0$, $E_0 \geqslant 0$, $T_0 \geqslant 0$, $P_0 \geqslant 0$, $J_0 \geqslant 0$, $K_0 \geqslant 0$, $R_0 \geqslant 0$, $Y_0 > 0$ and $W_0 \geqslant 0$ are the given initial states. The meaning of each compartment is given in Table 1, the meanings of the parameters considered in the model is given in Table 2 and a graphic representation of the proposed model is shown in Fig. 1.

Table 1. The meaning of the compartment considered in the model.

Compartment	Meaning
S_i	Unvaccinated or once-vaccinated susceptible individuals
E_i	Susceptible individuals vaccinated two times
T_i	Susceptible individuals vaccinated three time
P_i	Unvaccinated or once-vaccinated infected individuals
J_i	Infected individuals vaccinated two times
K_i	Infected individuals vaccinated three time
R_i	Unvaccinated or once-vaccinated recovered individuals
Y_i	Recovered individuals vaccinated two times
W_i	Recovered individuals vaccinated three time

Table 2. The meanings of the parameters considered in the model.

Parameter	Meaning
Λ_1	The recruitment rate of unvaccinated susceptible individuals
Λ_2	The recruitment rate of susceptible individuals vaccinated two times
Λ_3	The recruitment rate of susceptible individuals vaccinated three times
μ	Natural mortality rate
β_1	The rate of people unvaccinated who were infected through contact with unvaccinated infected people
β_2	The rate of people unvaccinated who were infected by contact with people vaccinated two times
γ_1	The rate of twice-vaccinated persons who became infected through contact with unvaccinated infected people
γ_2	The rate of twice-vaccinated persons who became infected through contact with persons who were vaccinated two times
α_1	The rate of triple-vaccinated individuals who became infected through contact with unvaccinated infected individuals
α_2	The rate of triple-vaccinated individuals who became infected through contact with infected individuals who were vaccinated two times
δ_1	Mortality rate of unvaccinated people due to COVID-19 health problems
δ_1	Mortality rate of twice vaccinated people due to COVID-19 health problems
r_1	The rate of unvaccinated people who recovered from the virus
r_2	The rate of people who were vaccinated two times and recovered from the virus
r_3	The rate of people who were vaccinated three times and recovered from the virus
ϕ_1	The rate of vaccination with the second dose of the vaccine
ϕ_2	The rate of vaccination with the third dose of the vaccine
θ_1	The rate at which unvaccinated individuals recovered return to the susceptible class
θ_2	The rate at which twice-vaccinated recovered individuals return to the susceptible class
θ_3	The rate at which thrice-vaccinated individuals recovered back to the susceptible class

3. The optimal control problem

3.1. Presentation of the controls

As the world lives with the impact of the Corona epidemic, several efforts have been undertaken to stop it or limit its spread. Among these efforts is vaccination, which has proven to be effective in reducing the spread of the epidemic and the death rate from it. But the problem is that the demand for the vaccine is low and some people may receive one or two doses of the vaccine when they have not completed the third dose, which has a negative effect on the spread of the epidemic. Our control

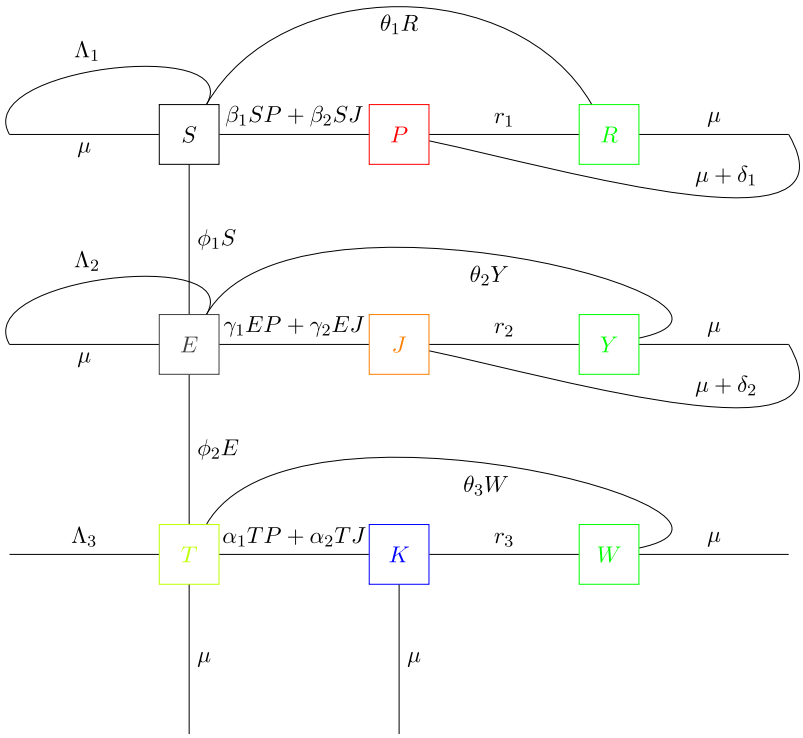

Fig. 1. Graphical representation of the proposed model.

strategy is based on two elements, the first (control u) being awareness of the importance of receiving the coronavirus vaccine in general and the importance of the third booster dose, through awareness programs and flyers. The second control (v) is the treatment of those infected by the epidemic who have complications such as shortness of breath or difficulty breathing and pneumonia.

Then, the controlled discrete time mathematical model is given as follows,

$$\begin{cases} S_{i+1} = \Lambda_1 + S_i - \beta_1 S_i P_i - \beta_2 S_i J_i - \mu S_i + \theta_1 R_i - \phi_1 S - u_i S_i, \\ E_{i+1} = \Lambda_2 + E_i - \gamma_1 E_i P_i - \gamma_2 E_i J_i - \mu E_i + \theta_2 Y_i + \phi_1 S - \phi_2 E + -u_i E_i, \\ T_{i+1} = \Lambda_3 + T_i - \alpha_1 T_i P_i - \alpha_2 T_i J_i - \mu T_i + \theta_3 W_i + u_i S_i + +\phi_2 E + u_i E_i, \\ P_{i+1} = P_i + \beta_1 S_i P_i + \beta_2 S_i J_i - (\mu + \delta_1 + r_1) P_i - v_i P_i, \\ J_{i+1} = J_i + \gamma_1 E_i P_i + \gamma_2 E_i J_i - (\mu + \delta_2 + r_2) J_i - v_i J_i, \\ K_{i+1} = K_i + \alpha_1 T_i P_i + \alpha_2 T_i J_i - (\mu + r_3) K_i, \\ R_{i+1} = R_i + r_1 P_i - \mu R_i - \theta_1 R_i + v_i P_i, \\ Y_{i+1} = Y_i + r_2 J_i - \mu Y_i - \theta_2 Y_i + v_i J_i, \\ W_{i+1} = W_i + r_3 K_i - \mu W_i - \theta_3 W_i, \end{cases} \tag{2}$$

with $i \in \{0, \ldots, N-1\}$, $S_0 \geqslant 0$, $E_0 \geqslant 0$, $T_0 \geqslant 0$, $P_0 \geqslant 0$, $J_0 \geqslant 0$, $K_0 \geqslant 0$, $R_0 \geqslant 0$, $Y_0 > 0$ and $W_0 \geqslant 0$ are the given initial states.

3.2. Objective functional

Our plan is to reduce the number of unvaccinated patients with three doses and maximize the number of recovered patients with minimal cost. Therefore, the problem is to minimize the objective functional given by

$$J(u,v) = \alpha P_N + \beta J_N - \zeta R_N - \theta Y_N - \eta W_N + \sum_{j=0}^{N-1} \left(\alpha P_j + \beta J_j - \zeta R_j - \theta Y_j - \eta W_j + \tfrac{1}{2} A u_j^2 + \tfrac{1}{2} B v_j^2 \right), \tag{3}$$

where α, β, ζ, θ, η are positive parameters and $A > 0$, $B > 0$ are the weight constants of the controls, $u = (u_0, \ldots, u_{N-1})$, $v = (v_0, \ldots, v_{N-1})$ and N is the final time of our control strategy. Our

objective is to minimize the number of unvaccinated individuals with three doses, minimize the cost of implementing controls, and increase the number of recovered individuals. In other words, we search for optimal controls u^* and v^* in such a way that

$$J(u^*, v^*) = \min\left\{J(u, v)/u \in \mathcal{U},\, v \in \mathcal{V}\right\}, \tag{4}$$

where $\mathcal{U}$ and $\mathcal{V}$ are the control sets defined by

$$\mathcal{U} = \{u\colon u_{\min} \leqslant u_i \leqslant u_{\max},\, i = 0, \ldots, N-1\}, \tag{5}$$

$$\mathcal{V} = \{v\colon v_{\min} \leqslant v_i \leqslant v_{\max},\, i = 0, \ldots, N-1\}. \tag{6}$$

3.3. Sufficient conditions

The sufficient condition of existence of an optimal control (u^*, v^*) for the problem 2 and 4 is derived from the following theorem.

Theorem 1. *There exists an optimal control $(u^*, v^*) \in \mathcal{U} \times \mathcal{V}$ such that*

$$J(u^*, v^*) = \min\{J(u, v)/u \in \mathcal{U},\, v \in \mathcal{V}\}$$

subjected to the control system 2 with initial conditions.

Proof. Given that the parameters of the system are bounded and there exist a finite number of time steps, i.e. S, E, T, P, J, K, R, Y and W are uniformly bounded for any (u, v) in the control set $\mathcal{U} \times \mathcal{V}$, so $J(u, v)$ is also bounded for any $(u, v) \in \mathcal{U} \times \mathcal{V}$. This implies that $\inf_{(u,v)\in\mathcal{U}\times\mathcal{V}} J(u, v)$ is finite, and there exists a sequence $(u^n, v^n) \in \mathcal{U} \times \mathcal{V}$ such as that

$$\lim_{n\to+\infty} J(u^n, v^n) = \inf_{(u,v)\in\mathcal{U}\times\mathcal{V}} J(u, v)$$

and corresponding sequences of states S, E, T, P, J, K and R. Since there is a finite number of uniformly bounded sequences, then there exists $(u^*, v^*) \in \mathcal{U} \times \mathcal{V}$ and S^*, E^*, T^*, P^*, J^*, R^*, Y^* and W^* such as, over a sequence

$$\begin{array}{lllll} (u^n, v^n) \to (u^*, v^*), & S^n \to S^*, & E^n \to E^*, & T^n \to T^*, & P^n \to P^*, \\ J^n \to J^*, & K^n \to K^*, & R^n \to R^*, & Y^n \to Y^*, & W^n \to W^*. \end{array}$$

Finally, as a result of the finite dimensional structure of the system 2 and the objective function $J(u, v)$, we obtain that (u^*, v^*) is an optimal control with corresponding states S^*, E^*, T^*, P^*, J^*, R^*, Y^* and W^*, which complete the proof. ∎

3.4. Necessary conditions

We now have the Hamiltonian $\mathcal{H}$ in time step i, given by

$$\begin{aligned} \mathcal{H}_i = {} & \alpha\, P_i + \beta\, J_i - \zeta\, R_i - \theta Y_N - \eta W_N + \tfrac{1}{2} A {u_i}^2 + \tfrac{1}{2} B {v_i}^2 \\ & + \zeta_{i+1}^1 \left(\Lambda_1 + S_i - \beta_1\, S_i P_i - \beta_2\, S_i J_i - \mu\, S_i + \theta_1 R_i - \phi_1 S - u_i S_i\right) \\ & + \zeta_{i+1}^2 \left(\Lambda_2 + E_i - \gamma_1\, E_i P_i - \gamma_2\, E_i J_i - \mu\, E_i + \theta_2 Y_i + \phi_1 S - \phi_2 E - u_i E_i\right) \\ & + \zeta_{i+1}^3 \left(\Lambda_3 + T_i - \alpha_1\, T_i P_i - \alpha_2\, T_i J_i - \mu\, T_i + \theta_3 W_i + u_i S_i + \phi_2 E + u_i E_i\right) \\ & + \zeta_{i+1}^4 \left(P_i + \beta_1\, S_i P_i + \beta_2\, S_i J_i - (\mu + \delta_1 + r_1)\, P_i - v_i P_i\right) \\ & + \zeta_{i+1}^5 \left(J_i + \gamma_1\, E_i P_i + \gamma_2\, E_i J_i - (\mu + \delta_2 + r_2)\, J_i - v_i J_i\right) \\ & + \zeta_{i+1}^6 \left(K_i + \alpha_1\, T_i P_i + \alpha_2\, T_i J_i - (\mu + r_3)\, K_i\right) + \zeta_{i+1}^7 \left(R_i + r_1\, P_i - \mu\, R_i - \theta_1 R_i + v_i P_i\right) \\ & + \zeta_{i+1}^8 \left(Y_i + r_2 J_i - \mu\, Y_i - \theta_2 Y_i + v_i J_i\right) + \zeta_{i+1}^9 \left(W_i + r_3 K_i - \mu\, W_i - \theta_3 W_i\right). \end{aligned} \tag{7}$$

Theorem 2. *Given optimal controls u^*, v^* and solutions S^*, E^*, T^*, P^*, J^*, K^*, R^*, Y^* and W^* of corresponding state system 2, there exists ζ_i^j, $i = 0, \ldots, N-1$, $j = 1, 2, \ldots, 9$, the adjoint variables that satisfy the following equations*

$$\Delta\zeta_{i+1}^1 = -\left[\zeta_{i+1}^1 \left(-\beta_1\, P_i - \beta_2\, J_i - \mu - \phi_1 - u_i + 1\right) + \zeta_{i+1}^2 \phi_1 + \zeta_{i+1}^3 \cdot u_i + \zeta_{i+1}^4 \left(\beta_1\, P_i + \beta_2\, J_i\right)\right],$$

$$\Delta\zeta_{i+1}^2 = -\left[\zeta_{i+1}^2 \left(-\gamma_1\, P_i - \gamma_2\, J_i - \mu - \phi_2 - u_i + 1\right) + \zeta_{i+1}^3 \left(u_i + \phi_2\right) + \zeta_{i+1}^5 \left(\gamma_1\, P_i + \gamma_2\, J_i\right)\right],$$

$$
\begin{aligned}
\Delta\zeta_{i+1}^{3} &= -\left[\zeta_{i+1}^{3}\left(-\alpha_1 P_i - \alpha_2 J_i - \mu + 1\right) + \zeta_{i+1}^{6}\left(\alpha_1 P_i + \alpha_2 J_i\right)\right],\\
\Delta\zeta_{i+1}^{4} &= -\big[\alpha - \zeta_{i+1}^{1}\beta_1 S_i - \zeta_{i+1}^{2}\gamma_1 E_i - \zeta_{i+1}^{3}\cdot\alpha_1 T_i + \zeta_{i+1}^{4}\left(\beta_1 S_i - \mu - r_1 - \delta_1 - v_i + 1\right)\\
&\quad + \zeta_{i+1}^{5}\gamma_1 E_i + \zeta_{i+1}^{6}\alpha_1 T_i + \zeta_{i+1}^{7}\left(v_i + r_1\right)\big],\\
\Delta\zeta_{i+1}^{5} &= -\big[\beta - \zeta_{i+1}^{1}\beta_2 S_i - \zeta_{i+1}^{2}\gamma_2 E_i - \zeta_{i+1}^{3}\cdot\alpha_2 T_i + \zeta_{i+1}^{4}\beta_2 S_i + \zeta_{i+1}^{5}\left(\gamma_2 E_i - \mu - r_2 - \delta_2 - v_i + 1\right)\\
&\quad + \zeta_{i+1}^{6}\alpha_2 T_i + \zeta_{i+1}^{8}\left(v_i + r_2\right)\big],\\
\Delta\zeta_{i+1}^{6} &= -\left[\zeta_{i+1}^{6}\left(-\mu - r_3 + 1\right) + \zeta_{i+1}^{9}\cdot r_3\right],\\
\Delta\zeta_{i+1}^{7} &= -\left[-\zeta + \zeta_{i+1}^{1}\theta_1 + \zeta_{i+1}^{7}\left(-\mu - \theta_1 + 1\right)\right],\\
\Delta\zeta_{i+1}^{8} &= -\left[-\theta + \zeta_{i+1}^{2}\theta_2 + \zeta_{i+1}^{8}\left(-\mu - \theta_2 + 1\right)\right],\\
\Delta\zeta_{i+1}^{9} &= -\left[-\eta + \zeta_{i+1}^{3}\theta_3 + \zeta_{i+1}^{9}\left(-\mu - \theta_3 + 1\right)\right],
\end{aligned}
$$

with the conditions of transversality at time N

$$\zeta_N^1 = 0, \quad \zeta_N^2 = 0, \quad \zeta_N^3 = 0, \quad \zeta_N^4 = \alpha, \quad \zeta_N^5 = \beta, \quad \zeta_N^6 = 0, \quad \zeta_N^7 = -\zeta, \quad \zeta_N^8 = -\theta \quad \text{and} \quad \zeta_N^9 = -\eta.$$

In addition, for $i = 0, 1, \ldots, N-1$ *we obtain the optimal control* (u^*, v^*) *as*

$$u_i = \min\left\{u_{\max}, \max\left\{-\frac{-\zeta_{i+1}^{2}E_i - \zeta_{i+1}^{1}S_i + \zeta_{i+1}^{3}\cdot(E_i+S_i)}{A}, u_{\min}\right\}\right\}, \tag{8}$$

$$v_i = \min\left\{v_{\max}, \max\left\{-\frac{-\zeta_{i+1}^{5}J_i - \zeta_{i+1}^{4}P_i + \zeta_{i+1}^{7}P_i + \zeta_{i+1}^{8}J_i}{B}, v_{\min}\right\}\right\}. \tag{9}$$

Proof. The Hamiltonian $\mathcal{H}_i$ at time step i is obtained by 7. For $i = 0, \ldots, N-1$, the adjoint equations and transversality conditions can be derived by using the discrete-time Pontryagin maximum principle given in [22, 25–27] as follows

$$
\begin{aligned}
\Delta\zeta_i^1 &= -\frac{\partial\mathcal{H}_i}{\partial S_i}, \quad \zeta_N^1 = \frac{\partial\left(\alpha P_N + \beta J_N - \zeta R_N - \theta Y_N - \eta W_N\right)}{\partial S_N} = 0,\\
\Delta\zeta_i^2 &= -\frac{\partial\mathcal{H}_i}{\partial E_i}, \quad \zeta_N^2 = \frac{\partial\left(\alpha P_N + \beta J_N - \zeta R_N - \theta Y_N - \eta W_N\right)}{\partial E_N} = 0,\\
\Delta\zeta_i^3 &= -\frac{\partial\mathcal{H}_i}{\partial T_i}, \quad \zeta_N^3 = \frac{\partial\left(\alpha P_N + \beta J_N - \zeta R_N - \theta Y_N - \eta W_N\right)}{\partial T_N} = 0,\\
\Delta\zeta_i^4 &= -\frac{\partial\mathcal{H}_i}{\partial P_i}, \quad \zeta_N^4 = \frac{\partial\left(\alpha P_N + \beta J_N - \zeta R_N - \theta Y_N - \eta W_N\right)}{\partial P_N} = \alpha,\\
\Delta\zeta_i^5 &= -\frac{\partial\mathcal{H}_i}{\partial J_i}, \quad \zeta_N^5 = \frac{\partial\left(\alpha P_N + \beta J_N - \zeta R_N - \theta Y_N - \eta W_N\right)}{\partial J_N} = \beta,\\
\Delta\zeta_i^6 &= -\frac{\partial\mathcal{H}_i}{\partial K_i}, \quad \zeta_N^6 = \frac{\partial\left(\alpha P_N + \beta J_N - \zeta R_N - \theta Y_N - \eta W_N\right)}{\partial K_N} = 0,\\
\Delta\zeta_i^7 &= -\frac{\partial\mathcal{H}_i}{\partial R_i}, \quad \zeta_N^7 = \frac{\partial\left(\alpha P_N + \beta J_N - \zeta R_N - \theta Y_N - \eta W_N\right)}{\partial R_N} = -\zeta,\\
\Delta\zeta_i^8 &= -\frac{\partial\mathcal{H}_i}{\partial Y_i}, \quad \zeta_N^7 = \frac{\partial\left(\alpha P_N + \beta J_N - \zeta R_N - \theta Y_N - \eta W_N\right)}{\partial Y_N} = -\theta,\\
\Delta\zeta_i^9 &= -\frac{\partial\mathcal{H}_i}{\partial W_i}, \quad \zeta_N^7 = \frac{\partial\left(\alpha P_N + \beta J_N - \zeta R_N - \theta Y_N - \eta W_N\right)}{\partial W_N} = -\eta.
\end{aligned}
$$

For $i = 0, \ldots, N-1$, the optimal controls (u^*, v^*) can be determined from the optimality conditions

$$
\begin{aligned}
\frac{\partial\mathcal{H}}{\partial u_i} &= Au_i - \zeta_{i+1}^{1}S_i - \zeta_{i+1}^{2}E_i + \zeta_{i+1}^{3}\left(E_i + S_i\right) = 0,\\
\frac{\partial\mathcal{H}}{\partial v_i} &= Bv_i - \zeta_{i+1}^{4}P_i - \zeta_{i+1}^{5}J_i + \zeta_{i+1}^{7}P_i + \zeta_{i+1}^{8}J_i = 0,
\end{aligned} \tag{10}
$$

thus, we obtain $u_i = -\frac{-\zeta_{i+1}^{2}E_i - \zeta_{i+1}^{1}S_i + \zeta_{i+1}^{3}\cdot(E_i+S_i)}{A}$, $v_i = -\frac{-\zeta_{i+1}^{5}J_i - \zeta_{i+1}^{4}P_i + \zeta_{i+1}^{7}P_i + \zeta_{i+1}^{8}J_i}{B}$. By the bounds in $\mathcal{U}$ and $\mathcal{V}$ of the controls, it is simple to obtain u and v in the form of (8) and (9). ∎

4. Numerical simulation and discussion

In this section, we present numerical simulations for the above-mentioned optimization problem. We write the program in MATLAB 1, and we simulate our work with various data. The optimality systems are solved using a discrete iterative approach that converges after an adequate test similar to the FBSM. First, the system of the state is solved with the initial hypothesis forward in time, and then the adjoint system is solved backward in time because of the transversality conditions. Next, we are updating our optimum control values with the state and co-state resources derived in the preceding steps. Finally, we execute the above steps until the standard tolerance is achieved.

Algorithm 1 Determination of u, v, S, E, T, P, J, K, R, Y, W.

REQUIRE S_0, E_0, R_0, T_0, P_0, J_0, K_0, R_0, Y_0, W_0, N, $u_0 = v_0 = 0$, $\zeta_N^1 = 0$, $\zeta_N^2 = 0$, $\zeta_N^3 = 0$, $\zeta_N^4 = \alpha$, $\zeta_N^5 = \beta$, $\zeta_N^6 = 0$, $\zeta_N^7 = -\zeta$, $\zeta_N^8 = -\theta$, $\zeta_N^9 = -\eta$.

FOR $i = 0, \ldots, N-1$

$$
\begin{cases}
S_{i+1} = \Lambda_1 + S_i - \beta_1 S_i P_i - \beta_2 S_i J_i - \mu S_i + \theta_1 R_i - \phi_1 S - u_i S_i, \\
E_{i+1} = \Lambda_2 + E_i - \gamma_1 E_i P_i - \gamma_2 E_i J_i - \mu E_i + \theta_2 Y_i + \phi_1 S - \phi_2 E + -u_i E_i, \\
T_{i+1} = \Lambda_3 + T_i - \alpha_1 T_i P_i - \alpha_2 T_i J_i - \mu T_i + \theta_3 W_i + u_i S_i + +\phi_2 E + u_i E_i, \\
P_{i+1} = P_i + \beta_1 S_i P_i + \beta_2 S_i J_i - (\mu + \delta_1 + r_1) P_i - v_i P_i, \\
J_{i+1} = J_i + \gamma_1 E_i P_i + \gamma_2 E_i J_i - (\mu + \delta_2 + r_2) J_i - v_i J_i, \\
K_{i+1} = K_i + \alpha_1 T_i P_i + \alpha_2 T_i J_i - (\mu + r_3) K_i, \\
R_{i+1} = R_i + r_1 P_i - \mu R_i - \theta_1 R_i + v_i P_i, \\
Y_{i+1} = Y_i + r_2 J_i - \mu Y_i - \theta_2 Y_i + v_i J_i, \\
W_{i+1} = W_i + r_3 K_i - \mu W_i - \theta_3 W_i,
\end{cases}
$$

$$
\begin{cases}
\zeta_{N-i}^1 = \zeta_{N-i+1}^1 + \big[\zeta_{N-i+1}^1(-\beta_1 P_i - \beta_2 J_i - \mu - \phi_1 - u_i + 1) + \zeta_{N-i+1}^2 \phi_1 \\
\qquad + \zeta_{N-i+1}^3 u_i + \zeta_{N-i+1}^4(\beta_1 P_i + \beta_2 J_i)\big], \\
\zeta_{N-i}^2 = \zeta_{N-i+1}^2 + \big[\zeta_{N-i+1}^2(-\gamma_1 P_i - \gamma_2 J_i - \mu - \phi_2 - u_i + 1) + \zeta_{N-i+1}^3(u_i + \phi_2) \\
\qquad + \zeta_{N-i+1}^5(\gamma_1 P_i + \gamma_2 J_i)\big], \\
\zeta_{N-i}^3 = \zeta_{N-i+1}^3 + \big[\zeta_{N-i+1}^3(-\alpha_1 P_i - \alpha_2 J_i - \mu + 1) + \zeta_{N-i+1}^6(\alpha_1 P_i + \alpha_2 J_i)\big], \\
\zeta_{N-i}^4 = \zeta_{N-i+1}^4 + \big[\alpha - \zeta_{N-i+1}^1 \beta_1 S_i - \zeta_{N-i+1}^2 \gamma_1 E_i - \zeta_{N-i+1}^3 \alpha_1 T_i \\
\qquad + \zeta_{N-i+1}^4(\beta_1 S_i - \mu - r_1 - \delta_1 - v_i + 1) + \zeta_{N-i+1}^5 \gamma_1 E_i + \zeta_{N-i+1}^6 \alpha_1 T_i + \zeta_{N-i+1}^7(v_i + r_1)\big], \\
\zeta_{N-i}^5 = \zeta_{N-i+1}^5 + \big[\beta - \zeta_{N-i+1}^1 \beta_2 S_i - \zeta_{N-i+1}^2 \gamma_2 E_i - \zeta_{i+1}^3 \alpha_2 T_i + \zeta_{N-i+1}^4 \beta_2 S_i \\
\qquad + \zeta_{N-i+1}^5(\gamma_2 E_i - \mu - r_2 - \delta_2 - v_i + 1) + \zeta_{N-i+1}^6 \alpha_2 T_i + \zeta_{N-i+1}^8(v_i + r_2)\big], \\
\zeta_{N-i}^6 = \zeta_{N-i+1}^6 + \big[\zeta_{N-i+1}^6(-\mu - r_3 + 1) + \zeta_{N-i+1}^9 r_3\big], \\
\zeta_{N-i}^7 = \zeta_{N-i+1}^7 + \big[-\zeta + \zeta_{N-i+1}^1 \theta_1 + \zeta_{N-i+1}^7(-\mu - \theta_1 + 1)\big], \\
\zeta_{N-i}^8 = \zeta_{N-i+1}^8 + \big[-\theta + \zeta_{N-i+1}^2 \theta_2 + \zeta_{N-i+1}^8(-\mu - \theta_2 + 1)\big], \\
\zeta_{N-i}^9 = \zeta_{N-i+1}^9 + \big[-\eta + \zeta_{N-i+1}^3 \theta_3 + \zeta_{N-i+1}^9(-\mu - \theta_3 + 1)\big],
\end{cases}
$$

$$
u_i = \min\left\{u_{\max}, \max\left\{-\frac{-\zeta_{N-i+1}^2 E_i - \zeta_{N-i+1}^1 S_i + \zeta_{i+1}^3 \cdot (E_i + S_i)}{A}, u_{\min}\right\}\right\},
$$

$$
v_i = \min\left\{v_{\max}, \max\left\{-\frac{-\zeta_{N-i+1}^5 J_i - \zeta_{N-i+1}^4 P_i + \zeta_{N-i+1}^7 P_i + \zeta_{N-i+1}^8 J_i}{B}, v_{\min}\right\}\right\}.
$$

END FOR

4.1. Strategy one: Awareness of the importance of the third dose

We use only optimum control $u(t)$.

This strategy is aimed at increasing the number of people vaccinated three times, through Figures 8, 9 and 12, we can see that after applying this strategy through an awareness program via awareness campaigns to all citizens, to inform them of the danger of the disease COVID-19, through the media, and instruct them on the importance of taking the third booster dose. The results of this strategy will reduce the number of patients not vaccinated or vaccinated with two doses and increase the number of those who recovered.

4.2. Strategy two: Treatment

We use only optimum control $v(t)$.

Because of the risk of serious complications in individuals infected with the Corona epidemic who have not received three doses, we proposed a strategy based on the provision of treatment at home for those with minor complications and provide treatment in hospitals to those with serious complications. From Figures 8, 9, 10, and 11, we can see the effectiveness of this strategy in reducing the number of patients who did not receive the booster dose and increasing the number of those who recovered in this category.

4.3. Strategy three: Awareness of the importance of the third dose and treatment

We combine the optimal controls $u(t)$ and $v(t)$.

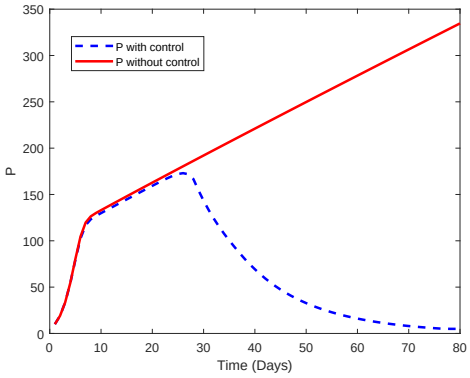

Fig. 2. The number of infected unvaccinated without and with the two controls.

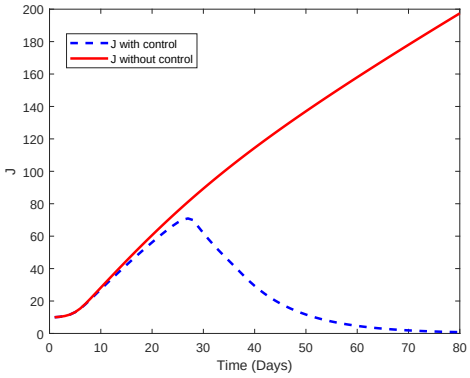

Fig. 3. The number of infected vaccinated two times without and with the two controls.

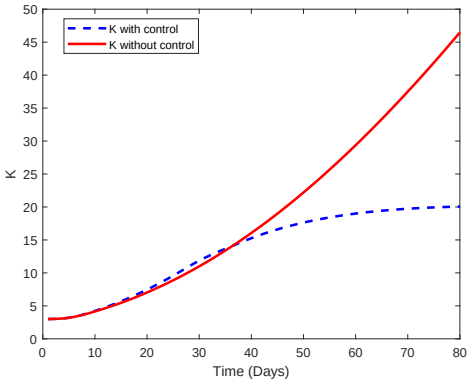

Fig. 4. The number of infected vaccinated three times without and with the two controls.

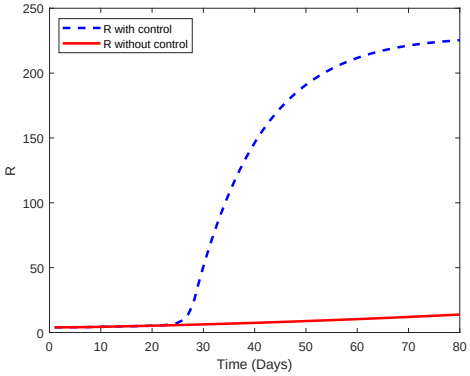

Fig. 5. The number of recovered unvaccinated without and with the two controls.

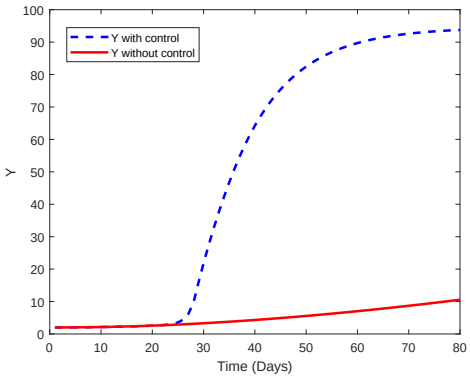

Fig. 6. The number of recovered vaccinated two times without and with the two controls.

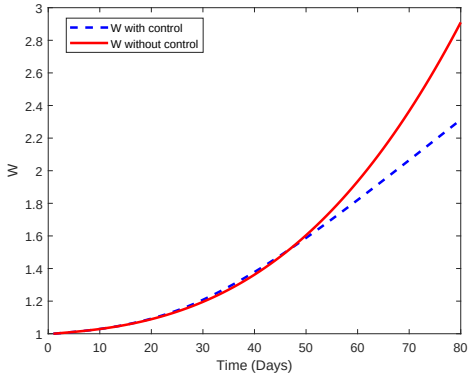

Fig. 7. The number of recovered vaccinated three times without and with the two controls.

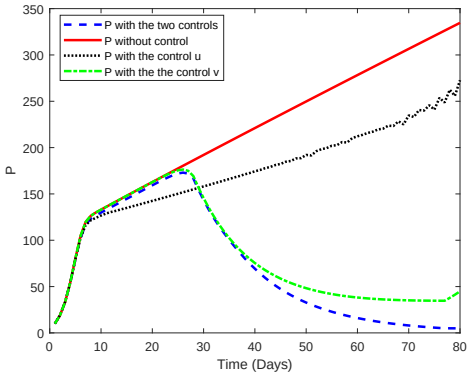

Fig. 8. The number of infected unvaccinated without and with the two controls.

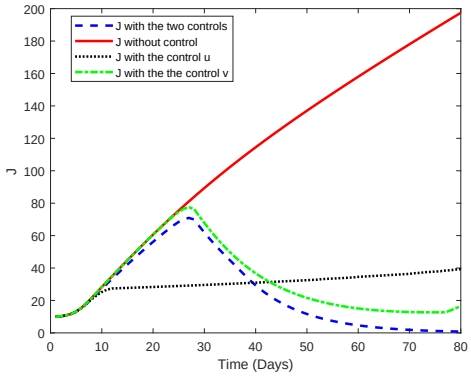

Fig. 9. The number of infected vaccinated two times without and with the two controls.

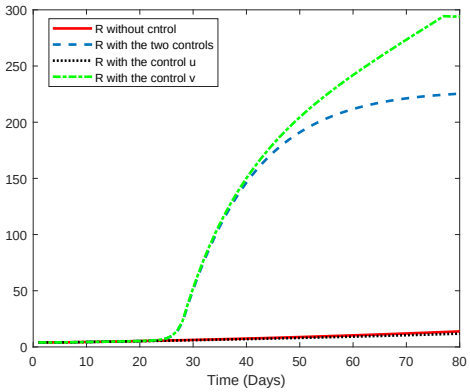

Fig. 10. The number of recovered unvaccinated without and with the two controls.

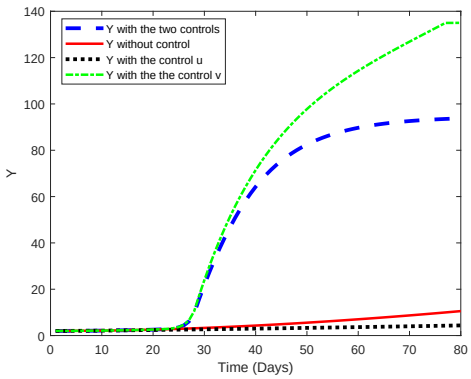

Fig. 11. The number of recovered vaccinated two times without and with the two controls.

In this new strategy, two optimal controls $u(t)$ and $v(t)$ are applied at the same time to improve the statistical performance of two proposed strategies. Based on Figures 2, 3, 5 and 6, after applying both strategies, we obtained the suggested results, with a decrease in the number of unvaccinated infected people that tended towards 0 after 80 days, and an increase in the number of people recovering from the virus. Hence, the definitive elimination of the virus and the restriction the spread of COVID-19.

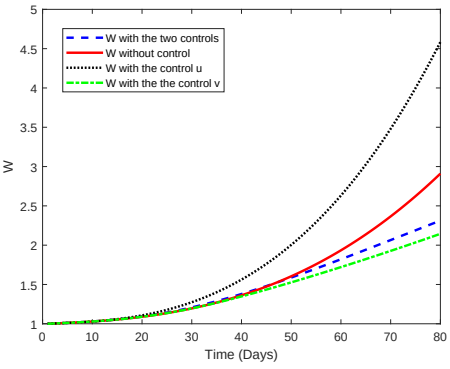

Fig. 12. The number of recovered vaccinated three times without and with the two controls.

5. Conclusion

In this paper, we propose a mathematical model of COVID-19 infection, taking into account the division of the population by vaccination criteria. Our objective is to demonstrate the positive effect of receiving all three doses of the Corona vaccine. We also proposed several strategies to limit the spread of the COVID-19 pandemic. We also introduced two controls, respectively, awareness programs on the importance of the third dose of the vaccine and the delivery of treatment to infected people who have health problems. We applied the control theory results and successfully obtained the characterizations of the optimum controls. The numerical simulation of the obtained results demonstrated the effectiveness of the proposed control strategies.

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Оптимальна стратегія керування за введенням третьої дози вакцини при лікуванні пандемії COVID-19

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У цій роботі пропонується математична модель інфікування COVID-19 з урахуванням поділу населення за критеріями вакцинації. Наша мета — продемонструвати позитивний ефект від отримання третьої дози вакцини проти коронавіруса. Запропоновано дві стратегії для обмеження поширення пандемії COVID-19, відповідно програми інформування про важливість третьої дози вакцини та надання лікування інфікованим особам, які мають проблеми зі здоров'ям. Принцип максимуму Понтрягіна застосовано для характеристики оптимального керування, а система оптимальних рівнянь розв'язана за допомогою ітераційного підходу. Накінець чисельне моделювання виконується для перевірки теоретичного аналізу за допомогою MATLAB.

Ключові слова: *оптимальне керування; математична модель; COVID 19; третя доза – вакцина від коронавіруса.*