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MODELING AND OPTIMAL CONTROL OF A MULTI-STRAIN EPIDEMIC APPLIED TO COVID-19 WITH AN UNDERLYING CHRONIC DISEASE CONDITION

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Abstract. Our co-infection model made it possible to study the dynamics of two viruses, diabetes and Covid-19 with several strains of Covid-19, within a population. After determining our dynamic system, we showed that it admits a unique solution in an invariant domain. We then calculated the basic reproduction number, determined the stability of the equilibrium points. We established the conditions of extinction of the co-infection within the population. Finally, to confirm our theoretical results, we carried out a numerical simulation using matlab. Using numerical simulations, it was concluded that diabetic individuals who suffered from Covid-19 would die significantly more than those whitout diabetes. Moreover, the number of deaths is higher when there are many strains.

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1. Introduction

The last two decades have been marked by three major zoonotic epidemics caused by betacoronaviruses : SARS-CoV , MERS-CoV , and SARS-CoV-2 for the first time in China [1], [2], [3], [4], [5]. As of March 15, 2020, there were an estimated 150,000 confirmed cases with nearly 6,000 deaths, and these figures will quickly reach 2.4 million confirmed cases compared to 165,000 deaths worldwide [6].

Phylogenetic analyses have shown that $SRS - CoV$ and $SARS - CoV - 2$ viruses are highly related with a genomic nucleotide sequence identity of approximately 80%. In addition, they both use angiotansin-converting enzyme 2 (ACE2) as a receptor for cell entry and infection ([7]- [10]). Coronaviruses have a spike (S) glycoprotein on their surface that forms a trimetric complex categorized into two subunits, S1 and S2, separated by a protease cleavage site [11], [12] $SARS - CoV - 2$ is highly transmissible. The reproduction number is a very determining epidemiological variable. Defined as

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the expected number of infectious cases generated by a single average case in a given fully susceptible population, it is generally noted R_0.

It therefore characterizes the capacity of an infection to spread ([13]- [15]) and [16]. Estimates of the mortality rate of Covid-19 vary depending on the region between 4.5% and 16% in the ten most affected countries [16]. This pandemic has caused enormous challenges to public health and the global economy. According to the WHO, more than 768 million people worldwide have been infected with $covid-19$ as of July 27, 2023, with more than 69 million deaths [17].

This rapid expansion of the disease has prompted enormous researchers to set up epidemiological models in order to provide assistance in decision-making with the aim of slowing down or even eliminating its spread. Preliminary results of the work on Covid-19 already show that people who suffer from underlying health problems or other factors of respiratory infections are exposed to higher risks of complicated forms of the disease leading to their death. Thus, W. Choi showed according to a study that nearly 12% of cases of infected individuals with comorbidity died 4 times more than patients who did not have underlying conditions [18].

Similar results were obtained in Italy by G. Giangreco [7]. Individuals of all ages with the following diseases are at risk of developing the most severe forms of COVID-19: chronic kidney disease, obesity, serious heart diseases such as heart failure, coronary artery disease or cardiomyopathy, sickle cell disease, type 2 diabetes, hypertension, and neurological diseases. The prevalence of type 2 diabetes remains higher in patients with severe COVID-19 [19], [20]. According to estimates from WHO, more than 42 million people suffer from diabetes worldwide with 1.5 million deaths per year and 18% of deaths from $covid-19$ are linked to diabetes [21], [22].

Based on health data collected in 13 African countries regarding comorbidities among Africans who tested positive for $Covid-19$, it appears that the virus is fatal with a rate of 10.2% among diabetics compared to only 2.5% among non-diabetics. It has a result, the mortality rate is twice as high among diabetics compared to other $Covid-19$ patients with other comorbidities such as heart failure, coronary artery disease, hypertension, diabetes [6], [23]. For the sake of simplicity and without losing sight of the general case, we consider diabetes as a chronic disease in the development of models in our work.

The mathematical modeling of epidemiological diseases has attracted much attention in recent years. A. Kouidere [24] proposed an optimal control strategy to determine the impact of complications caused by diabetes. Most models that focus on COVID-19 emphasize the dynamics of transmission in a population without considering the underlying conditions of patients and the diversity of viral strains. F. Aruda and al. studied an optimal control model that simultaneously takes into consideration several viral strains and reinfection due to a waning immunity in England and Amazonas, Brazil [25]. S. Y. Tchoumi and al. studied a model with two COVID-19 strains with vaccination but without a comorbidity

condition [26]. O. Khyar and al. as for them have studied the overall stability of the SEIR model with two viral strains and two general incidence rates while [28].

Similarly, A. Omame and al. analyzed the mathematical model of the dynamics of $Covid-19$ with reinfection in order to assess the impact of previous comorbidity, diabetes mellitus on complications of $covid-19$ and were able to show that the peak of the disease decreases with increasing reinfection among those who have recovered from a COVID-19 infection [29] . C. Yang and al. proposed a model that integrates the impact of chronic health conditions in the host population, to study the transmission dynamics of COVID-19, which takes into account two groups, depending on whether they have underlying conditions or not, and which describes COVID-19 transmission in the United States of America [30] .

S. Okyere and J. Ackora-Prah [19], as well as F. Özköse and al. [31], studied a deterministic diabetes-COVID-19 comorbidity model, Chang, Y. C and all a stochastic multi strain [27] . The results of S. Okyere, after simulation based on statistical data from Ghana, in the period from March to September 2020, show that a greater number of people die when infected with both diabetes and COVID-19, and that the lockdown control minimizes the mortality rate of diabetic individuals at best, while vaccination provides them with immunity against COVID-19. Since the 2020s, seven strains of COVID-19 have been identified [32], but few authors have focused on the case of co-infection, taking into account the numerous strains.

This work is inspired by the SEIRCD model of S. Okyere and that of Chang Y. C. and al. [27] taking into account the plurality of COVID-19 strains, which is structured as follows: First, we will have an introduction, then the formulation of the multi-strain deterministic mathematical model with a comorbidity of diabetes, followed by its analysis. In the fourth part of our work, we will conduct a numerical study of the model, and the fifth part will be devoted to the study of deterministic controls, and we will conclude.

2. Formulation of a mathematical model

Let $V = \{1; 2; 3; ...; n\}$ denote the set of strains of the disease virus within the population considered. Let $j \in V$ and $t \geq 0$. Apart from patient zero, all non-immune individuals are likely to contract the disease. Let's $S(t)$ denote the set of individuals likely to contract the virus at time t within the population considered. Individuals who enter compartment $S(t)$ have had contact either with those in $I_j(t)$ or $C_j(t)$. All individuals having contact with strain j of the virus take a time before noticing the signs of the disease which is called the incubation period and are said to be exposed. $E_j(t)$ is the set of individuals exposed to the virus within the population considered. These are the individuals who are tested positive for the virus and who show symptoms of the disease or not after the incubation period. We denote by $I_j(t)$ the set of individuals infected by the j strain of the virus within the population

considered. It is the set of individuals tested positive symptomatic or asymptomatic cured, i.e. having had a negative test afterwards. $R(t)$ is the set of individuals recovered from Covid-19, $D(t)$ is the set of individuals suffering from diabetes and $C(t)$ is the set of diabetic individuals infected by the virus strain within the population considered. If $N(t)$ is the set of the population studied, we obtain the following system:

$$\frac{dS(t)}{dt} = \Omega + \delta R(t) - \beta(\frac{C(t)+\sum_1^n I_j(t)}{N})S(t) - (\mu+\lambda)S(t) \tag{2.1}$$

$$\frac{dD(t)}{dt} = \lambda S(t) + \gamma C(t) - \beta(\frac{C(t)+\sum_1^n I_j(t)}{N})D(t) - (\delta_2+\mu)D(t) \tag{2.2}$$

$$\frac{dE(t)}{dt} = \beta(\frac{C(t)+\sum_1^n I_j(t)}{N})(S(t)+D(t)) - (\mu+\phi)E(t) \tag{2.3}$$

$$\frac{dI_j(t)}{dt} = \alpha\varphi_j E(t) - (\mu_j+\gamma_j+\mu)I_j(t) \tag{2.4}$$

$$\frac{dC(t)}{dt} = (1-\alpha)\phi E(t) - (\mu+\delta_1+\gamma)C(t) \tag{2.5}$$

$$\frac{dR(t)}{dt} = \sum_1^n \gamma_j I_j(t) - (\delta+\mu)R(t) \tag{2.6}$$

$$N(t) = S(t) + E(t) + \sum_1^n I_j(t) + R(t) + C(t) + D(t) \tag{2.7}$$

with $\phi = \sum_1^n \varphi_j$ and the initial condition following: $S(0) = S_0$; $E(0) = E_0$; $I_j(0) = I_{j,0}$; $R(0) = R_0$; $D(0) = D_0$; $C(0) = C_0$ $\forall j \in V$.

The different parameters are described in the following table:

Table 1. Table of parameters.

Prarameters	Description	Values
Ω	Proportion of the population studied	28.452
α	Fraction of exposed individuals who became infected Covid-19	0.3
β	Covid-19 tranmission rate	0.9
δ	Rate of individuals who lost their immunity	0.011
μ	Natural mortality rate	0.4252912×10^{-4}
γ	Rate of diabetics cured of Covid-19	$\frac{1}{14}$
φ_j	Rate of infection by strain j of exposed individuals	[0.127,0.527]
δ_1	Death rate from Covid-19 among diabetics	0.0144
λ	Rate of diabetics who become susceptible	0.2
δ_2	Death rate from diabetes	0.05
γ_j	Rate of individuals cured of strain j of Covid-19	$[\frac{1}{30}, \frac{1}{4}]$
μ_j	Mortality rate due to strain j	6.83×10^{-5}

The diagram that represents the transmission dynamic is as follows:

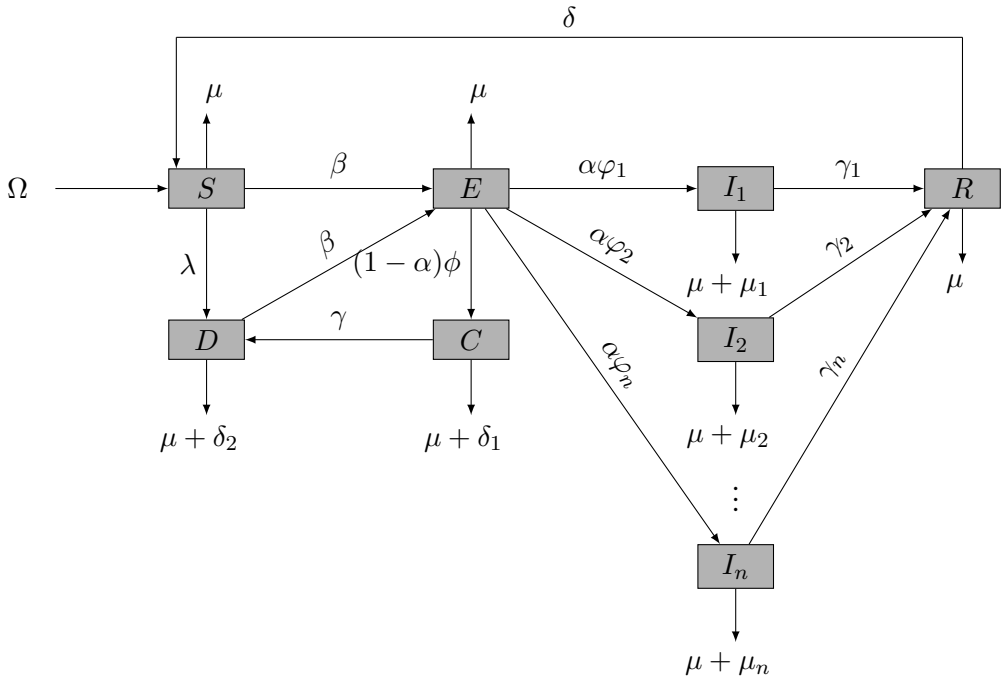

FIGURE 1. Transmission diagram of the model.

3. Analysis of the mathematical model

In this part, we will discuss the calculation of the invariant region, of the basic reproduction number and the study of the locally asymptotic stability of the equilibrium points of the mathematical model. The biological validity of the mathematical model $(2.1)-(2.7)$ depends on the following elements: the solution of the dynamic system is positive and bounded at any given time t.

3.1. Existence and uniqueness of the solution in an invariant domain.

The following results show that the system is well-posed from the epi- semiological and mathematical in a feasible domain U defined by:

$$\mathcal{U} = \{(S; D; E; I_j; C; R) \in \mathbb{R}^6_+; N \leq \frac{\Omega}{\mu}\}_{j\in V} \tag{3.1}$$

Theorem 3.1. (*Positivity*) *Given the following initial conditions:* $S(0) = S_0 > 0$; $E(0) = E_0 > 0$; $I_1(0) = I_{1,0} > 0$; $I_2(0) = I_{2,0} > 0$; ...; $I_n(0) = I_{n,0} > 0$;
$R(0) = R_0 > 0$; $D(0) = D_0 > 0$; $C(0) = C_0 > 0$ *and all* $t_0 > 0$ *then for*
$t \in [0; t_0]$, *there exists a domain* $\mathcal{U}$ *in which the solution* $(S; D; E; I; C; R)$ *of the differential system* $(2.1)-(2.6)$ *belongs.*

Proof. *Assuming all parameters of the system* $(2.1)-(2.7)$ *to be positive, we can establish the following inequalities:*

$$\frac{dS(t)}{dt} > -[\beta(\frac{C + \sum_1^n I_j}{N}) + \mu + \lambda]S(t)$$

$$\frac{dD(t)}{dt} > -[\beta(\frac{C+\sum_1^n I_j}{N}) + \mu + \delta_2]D(t)$$

$$\frac{dE(t)}{dt} > -(\mu+\varphi)E(t)$$

$$\frac{dI_j(t)}{dt} > -(\mu_j+\gamma_j+\mu)I_j(t)\ \forall\ j \in V$$

$$\frac{dC(t)}{dt} > -(\gamma+\mu+\delta_1)C(t)$$

$$\frac{dR(t)}{dt} > -(\mu+\delta)R(t)$$

After solving, we obtain:

$$S(t) > S_0 exp[-\beta \int (\frac{C+\sum_1^n I_j}{N})tdt - (\mu+\lambda)t] > 0$$

$$D(t) > D_0 exp[-\beta \int (\frac{C+\sum_1^n I_j}{N})tdt - (\mu+\lambda_2+\delta_2)t] > 0$$

$$E(t) > E_0 exp[-(\mu+\varphi)t] > 0$$

$$I_j(t) > I_{j,0} exp[-(\mu_j+\gamma_j+\mu)t] > 0; \forall j \in V$$

$$C(t) > C_0 exp[-(\gamma+\mu+\delta_1)t] > 0$$

$$R(t) > R_0 exp[-(\mu+\delta)t] > 0$$

We then conclude that $(S; D; E; I; C; R) \in \mathbb{R}_+^6$ □

Theorem 3.2. (*Bornitude*) *For any function* $S(t)$, $E(t)$,$C(t)$,$D(t)$, $R(t)$,$I_j(t)$; $\forall j \in V$ *of the differential system* $(2.1) - (2.7)$, *there exist positive constants* R_M, S_M, E_M, C_M, D_M, I_M *such that:*

$$\lim_{t\to+\infty} supS(t) \leq S_M$$

$$\lim_{t\to+\infty} supE(t) \leq_M$$

$$\lim_{t\to+\infty} supC(t) \leq C_M$$

$$\lim_{t\to+\infty} supD(t) \leq D_M$$

$$\lim_{t\to+\infty} supR(t) \leq_M$$

$$\lim_{t\to+\infty} supI_J(t) \leq S_M; \quad \forall\ j \in V\ ; t \in [0; t_0]\ et\ t_0 \geq 0.$$

Proof. *We have:*

$$\frac{dN(t)}{dt} = \frac{dS(t)}{dt} + \frac{dE(t)}{dt} + \sum_{1}^{n} \frac{dI_j(t)}{dt} + \frac{dR(t)}{dt} + \frac{dC(t)}{dt} + \frac{dD(t)}{dt} \tag{3.2}$$

We then deduce that

$$\frac{dN(t)}{dt} = \Omega - \mu N(t) - \delta_2 D(t) - \sum_{1}^{n} \mu_j I_j(t)$$

Which gives us

$$\frac{dN(t)}{dt} < \Omega - \mu N(t) \tag{3.3}$$

After solving (3.3) *we obtain respectively*

$$N(t) \leq N_0 e^{-\mu t} + \frac{\Omega}{\mu}(1 - e^{-\mu t}) \tag{3.4}$$

and

$$N(t) \leq N_0 e^{-\mu t} + \frac{\Omega}{\mu} \tag{3.5}$$

We subsequently obtain that

$$N(t) \leq \lim_{t \to +\infty} sup N_0 e^{-\mu t} + \frac{\Omega}{\mu} = \frac{\Omega}{\mu} \; si \; N_0 \leq \frac{\Omega}{\mu} \tag{3.6}$$

Setting $R_M = S_M = E_M = C_M = D_M = I_M = \frac{\Omega}{\mu}$, *we can thus conclude,hat all possible solutions of* $(2.1) - (2.6)$ *are bounded and positive in the set* $\mathcal{U}$ *and the domain* $\mathcal{U}$ *is positively invariant for the model* $(2.1) - (2.6)$. *Indeed, if* $N(0) > \frac{\Omega}{\mu}$ *either the solutions of* $(2.1) - (2.6)$ *are either in* $\mathcal{U}$ *with finite values, or* $N(t)$ *approach asymptotically* $\frac{\Omega}{\mu}$ *Oh . So* $\mathcal{U}$ *attracts the solutions of* $(2.1) - (2.6)$. □

Theorem 3.3. (*Existence and unicity*) *With the initial conditions* $S(0) = S_0 > 0$; $E(0) = E_0 > 0$; $I_1(0) = I_{1,0} > 0$; $I_2(0) = I_{2,0} > 0$; ...; $I_n(0) = I_{n,0} > 0$; $R(0) = R_0 > 0$; $D(0) = D_0 > 0$; $C(0) = C_0 > 0$ *and* $t_0 > 0$, *then for the differential system* $(2.1) - (2.7)$ *admits a positive solution* $(S(t); D(t); E(t); Ij(t); C(t); R(t))$ *for all* $j \in V$ *and all* $t \in \mathbb{R}$

. Proof. Let us rewrite $(2.1) - (2.6)$ as follows:

$$\dot{X}(t) = f(t, X(t)) \tag{3.7}$$

with $\dot{X}(t) = \begin{pmatrix} \dot{S}(t) \\ \dot{D}(t) \\ \dot{E}(t) \\ \dot{I}_j(t) \\ \dot{C}(t) \\ \dot{R}(t) \end{pmatrix}_{j \in V}$ and $f(t, X(t)) = \begin{pmatrix} \Omega + \delta R(t) - \beta(\frac{C + \sum_1^n I_j}{N})S(t) - (\mu + \lambda)S(t) \\ \lambda S(t) + \gamma C(t) - \beta(\frac{C + \sum_1^n I_j}{N})D(t) - (\delta_2 + \mu)D(t) \\ \beta(\frac{C + \sum_1^n I_j}{N})(S(t) + D(t)) - (\mu + \phi)E(t) \\ \alpha\varphi_j E(t) - (\mu_j + \gamma_j + \mu)I_j(t) \\ (1 - \alpha)\phi E(t) - (\mu + \delta_1 + \gamma)C(t) \\ \sum_1^n \gamma_j I_j(t) - (\delta + \mu)R(t) \end{pmatrix}_{j \in V}$

Since f is differentiable and its first derivative is continuous, then it is locally Lipschitzian in $\mathbb{R}^6_+$. By the fundamental theorem of existence and uniqueness , the differential system $(2.1)-(2.6)$ admits a unique bounded and positive solution in $\mathcal{U}$.

3.2. **Stability of equilibrium points.** In the resolution of the differential system $(2.1)-(2.6)$, we obtain two equilibrium points:

(1) The disease-free equilibrium point X_0 which is the solution of the system $(2.1)-(2.6)$ in steady state where there are no individuals with COVID-19 within $E^0=0; I_1^0=0; I_2^0=0; ...; I_n^0=0$; $R^0=0; C^0=0$.
$D^0=\dfrac{\lambda(\delta_2+\mu)\Omega}{(\delta_2+\mu)[\mu(\lambda+\delta_2+\mu)+\lambda\delta_2]}$ and $S^0=\dfrac{(\delta_2+\mu)\Omega}{\mu(\lambda+\delta_2+\mu)+\lambda\delta_2}$.
Which then gives us
$X^0=(\dfrac{(\delta_2+\mu)\Omega}{\mu(\lambda+\delta_2+\mu)+\lambda\delta_2};\dfrac{\lambda(\delta_2+\mu)\Omega}{(\delta_2+\mu)[\mu(\lambda+\delta_2+\mu)+\lambda\delta_2]};0;0;0;0)$.

(2) The endemic equilibrium point $X_j^*=(S^*;D^*;E^*;I_j^*;C^*;R^*)$ obtaineed by takin secound member of the system equal to zero. Which then gives us:

$$\begin{cases} S^*=\dfrac{\delta_2R^*+\Omega}{\beta(C^*+\sum_1^n I_j^*)/N+\lambda+\mu};\\ D^*=\dfrac{\lambda S^*+\gamma C^*}{\beta(C^*+\sum_1^n I_j^*)/N+\delta_2+\mu};\\ E^*=\dfrac{\beta(C^*+\sum_1^n I_j^*)/N(S^*+D^*)}{\mu+\phi}\\ C^*=\dfrac{\phi(1-\alpha)E^*)}{\mu+\gamma+\delta_1};\quad R^*=\dfrac{\sum_1^n I_j^*}{\mu+\gamma_j+\mu_j};\\ I_j^*=\dfrac{\alpha\varphi_jE^*}{\mu+\phi}\ \forall\ j\in V \end{cases}.$$

3.2.1. *The basic reproduction number.* The basic reproduction number denoted R_0 is defined as the number of secondary infections appearing in a sensitive area of the population from an infected individual. We will now determine the basic reproduction number for the system $(2.1)-(2.6)$. It is a threshold in epidemiology which allows to predict or evaluate control strategies. The uninfected and infected classes are respectively (S,D,R) and (E,Ij,C) with $j\in V$. The vectors of new infections and transfers between compartments are similarly respectively defined by

$$\mathcal{F}=\begin{pmatrix}\beta(\frac{C+\sum_1^n I_j}{N})(S(t)+D(t))\\ \alpha\varphi_jE\\ (1-\alpha)\sum_1^n\varphi_jE\end{pmatrix}_{j\in V}\quad\text{and}\quad\mathcal{V}=\begin{pmatrix}(\mu+\sum_1^n\varphi_j)E\\ (\mu_j+\gamma_j+\mu)I_j\\ (\mu+\delta_1+\gamma)C\end{pmatrix}_{j\in V}.$$

We then use the P.V.D. Driessche method [33] to calculate the basic reproduction number R_0. The vectors of new infections and transfers between compartments are defined respectively by:

$$\frac{\partial\mathcal{F}}{\partial x_i}=F=\begin{pmatrix}0&\frac{\beta(S^0+D^0)}{N}&\frac{\beta(S^0+D^0)}{N}\\ \alpha\varphi_j&0&0\\ (1-\alpha)\sum_1^n\varphi_j&0&0\end{pmatrix}_{j\in V}$$

and $\dfrac{\partial \mathcal{V}}{\partial x_i} = V = \begin{pmatrix} \mu + \sum_1^n \varphi_j & 0 & 0 \\ 0 & \mu_j + \gamma_j + \mu & 0 \\ 0 & 0 & \mu + \delta_1 + \gamma \end{pmatrix}_{j \in V}$

with $x_i = E, I_j, C$.

$$FV^{-1} = \begin{pmatrix} 0 & \frac{\beta(S^0+D^0)}{N(\mu+\mu_j+\gamma_j)} & \frac{\beta(S^0+D^0)}{N(\mu+\delta_1+\gamma)} \\ \frac{\alpha\varphi_j}{\mu+\sum_1^n \varphi_j} & 0 & 0 \\ \frac{(1-\alpha)\sum_1^n \varphi_j}{\mu+\sum_1^n \varphi_j} & 0 & 0 \end{pmatrix}_{1 \le j \le n}.$$

The basic reproduction number $\mathcal{R}_0$ is $\mathcal{R}_0 = max\{\mathcal{R}_j^0\}$ with

$$\mathcal{R}_j^0 = \sqrt{\frac{\beta(S^0+D^0)(1-\alpha)\sum_1^n \varphi_j}{N(\mu+\delta_1+\gamma)(\mu+\sum_1^n \varphi_j)} + \frac{\beta(S^0+D^0)\alpha\varphi_j}{N(\mu+\mu_j+\gamma_j)(\mu+\sum_1^n \varphi_j)}} \quad \forall\, j \in V \tag{3.8}$$

3.2.2. *Local stability of equilibrium points.* The following theorems state the conditions necessary for the state of equi- free is established.

(1) 1. Local stability of the disease-free steady state

Theorem 3.4. *The disease-free steady state*
$X^0 = (\dfrac{(\delta_2+\mu)\Omega}{\mu(\lambda+\delta_2+\mu)+\lambda\delta_2}; \dfrac{\lambda(\delta_2+\mu)\Omega}{(\delta_2+\mu)[\mu(\lambda+\delta_2+\mu)+\lambda\delta_2]}; 0; 0; 0; 0)$
of the system $(2.1)-(2.6)$ *is locally asymptotically stable if and only if* $\mathcal{R}_0 < 1$.

Proof. *The Jacobian matrix associated with the system* $(2.1)-(2.6)$ *at the disease-free equilibrium point is given by:*

$$\mathcal{J}_{def} = \begin{bmatrix} J_{11} & 0 & 0 & -\frac{\beta S}{N} & -\frac{\beta S}{N} & \delta \\ \lambda_1 & J_{22} & 0 & -\frac{\beta D}{N} & \gamma - \frac{\beta D}{N} & 0 \\ J_{31} & J_{32} & -\mu-\phi & \frac{\beta(S+D)}{N} & \frac{\beta(S+D)}{N} & 0 \\ 0 & 0 & \alpha\varphi_j & -\mu_j-\gamma_j-\mu & 0 & 0 \\ 0 & 0 & (1-\alpha)\sum_1^n \varphi_j & 0 & -\mu-\delta_1-\gamma & 0 \\ 0 & 0 & 0 & \gamma_j & 0 & -\mu-\delta \end{bmatrix}_{j \in V} \tag{3.9}$$

with

$$J_{11} = -\frac{\beta(C+\sum_1^n I_j)}{N} - \mu;\ J_{31} = \frac{\beta(C+\sum_1^n I_j)}{N};\ J_{22} = -\frac{\beta(C+\sum_1^n I_j)}{N} - \mu - \delta_2;\ J_{32} = \frac{\beta(C+\sum_1^n I_j)}{N}$$

The Jacobian matrix in the absence of disease is:

$$\mathcal{J}_{N^0} = \begin{bmatrix} -\mu-\lambda & 0 & 0 & -\frac{\beta S^0}{N} & -\frac{\beta S^0}{N} & \delta \\ \lambda & -\mu-\delta_2 & 0 & -\frac{\beta D^0}{N} & \gamma - \frac{\beta D^0}{N} & 0 \\ 0 & 0 & -\mu-\phi & \frac{\beta(S^0+D^0)}{N} & \frac{\beta(S^0+D^0)}{N} & 0 \\ 0 & 0 & \alpha\varphi_j & J_{55} & 0 & 0 \\ 0 & 0 & (1-\alpha)\phi & 0 & J_{55} & 0 \\ 0 & 0 & 0 & \gamma_j & 0 & -\mu-\delta \end{bmatrix}_{j \in V} \tag{3.10}$$

with

$$J_{44} = -\mu_j - \gamma_j - \mu;\ J_{55} = -\mu - \delta_1 - \gamma$$

Let us now determine the eigenvalues of the disease-free Jacobian matrix. The first is given by $-(\mu+\delta)$. *The others are those of the following matrix:*

$$\mathcal{J}_0 = \begin{bmatrix} -(\mu+\lambda) & 0 & 0 & -\frac{\beta S^0}{N} & -\frac{\beta S^0}{N} \\ \lambda & -(\mu+\delta_2) & 0 & -\frac{\beta D^0}{N} & \gamma - \frac{\beta D^0}{N} \\ 0 & 0 & -(\mu+\phi) & \frac{\beta(S^0+D^0)}{N} & \frac{\beta(S^0+D^0)}{N} \\ 0 & 0 & \alpha\varphi_j & -(\mu_j+\gamma_j+\mu) & 0 \\ 0 & 0 & (1-\alpha)\phi & 0 & J_{55} \end{bmatrix}_{j\in V} \tag{3.11}$$

$$J_{55} = -(\mu + \delta_1 + \gamma)$$

The characteristic polynomial of this matrix is given:

$P(X) = (X^2 + A_1X + A_0)(X^3 + B_2X^2 + B_1X + B_0)$ *with*

$A_1 = \lambda_1 + \delta_2 + 2\mu$;

$A_0 = \mu(\mu + \lambda + \delta_2) + \lambda\delta_2$;

$B_0 = (\mu+\phi)(\mu+\mu_j+\gamma_j)(\mu+\delta_1+\gamma)(1-\mathcal{R}_0^2)$;

$B_1 = \mu_j + \gamma_j + \gamma + \delta_1 + \phi + 3\mu$

$B_2 = (\mu+\phi)(\mu_j+\gamma_j+\delta_1+\gamma+2\mu) +$

$(\delta_1+\mu+\gamma)(\mu_j+\gamma_j+\mu)[1 - \frac{(\mu+\phi)(\alpha\varphi_j+(1-\alpha)\phi)\mathcal{R}_0^2}{\alpha\varphi_j(\mu+\delta_1+\gamma)+(1-\alpha)\phi(\mu+\mu_j+\gamma_j)}]$.

We have $A_0 > 0$, $A_1 > 0$, $B_0 > 0$, $B_1 > 0$ *and* $B_2 > 0$. *In addition,*

$B_1B_2 - B_0 = (\mu+\phi)(\mu_j+\gamma_j+\delta_1+\gamma+\phi+3\mu)(\mu_j+\gamma_j+\delta_1+\gamma+2\mu) +$

$(\mu_j+\gamma_j+\delta_1+\gamma+\phi+3\mu)(\mu+\delta_1+\gamma)(\mu_j+\gamma_j+\mu) -$

$(\mu+\phi)(\mu+\delta_1+\gamma)(\mu_j+\gamma_j+\mu)[\frac{(\mu_j+\gamma_j+\delta_1+\gamma+\phi+3\mu)(\alpha\varphi_j+(1-\alpha)\phi)\mathcal{R}_0^2}{\alpha\varphi_j(\mu+\delta_1+\gamma)+(1-\alpha)\phi(\mu+\mu_j+\gamma_j)} + 1 - \mathcal{R}_0^2] > 0$

si $\mathcal{R}_0 < 1$ *and if we designate by* X_1 *and* X_2 *the roots of* $X^2 + A_1X + A_0$, *we have:*

$X_1 + X_2 = -A_1 < 0$ *and* $X_1X_2 = A_0 > 0$

According to the Routh-Hurwitz [34] *stability criterion all eigenvalues of the matrix* J_0 *have negative real parts. Therefore* X_0 *is stable.* □

(2) 2. Local stability of the endemic equilibrium state

Theorem 3.5. *The endemic equilibrium state*

$N_j^* = (S^*; D^*; E^*; I_j^*; C^*; R^*)$ *of the system*$(2.1) - (2.6)$ *is locally asymptotically stable if and only if* $\mathcal{R}_0 > 1$.

Proof. *Assume that the endemic equilibrium state exists and assume that* $\mathcal{R}_0 > 1$. *Let the candidate Lyapunov function* L [35] *be defined by*

$L(S,D,E,I_j,C,R) = (S - S^* - S^* ln\frac{S}{S^*}) + (D - S^* - D^* ln\frac{D}{D^*}) + (E - E^* - E^* ln\frac{E}{E^*}) + (I_j - I_j^* - I_j^* ln\frac{I_j}{I_j^*}) + (C - C^* - C^* ln\frac{C}{C^*}) + (R - R^* - R^* ln\frac{R}{R^*})$ *with* $1 \leq j \leq n$. *The differential of L is given by*

$\frac{dL}{dt} = (\frac{S-S^*}{S})\dot{S} + (\frac{D-D^*}{D})\dot{D} + (\frac{E-E^*}{E})\dot{E} + (\frac{I_j-I_j^*}{I_j})\dot{I}_j + (\frac{C-C^*}{C})\dot{C} + (\frac{R-R^*}{R})\dot{R}$ *with* $1 \leq j \leq n$. *Which gives the following:*

$\frac{dL}{dt} = (\frac{S-S^*}{S})[\Omega + \delta R - \beta\frac{C+\sum_1^n I_j}{N}S - (\mu+\lambda)S] + (\frac{D-D^*}{D})[\lambda S + \gamma C - \beta\frac{C+\sum_1^n I_j}{N}D - (\delta_2+\mu)D] + (\frac{E-E^*}{E})[\beta\frac{C+\sum_1^n I_j}{N}(S+D) - (\mu+\phi)E)] + (\frac{I_j-I_j^*}{I_j})[\alpha\varphi_j E - (\mu_j+\gamma_j+\mu)I_j] + (\frac{C-C^*}{C})[(1-\alpha)\phi E - (\mu+\delta_1+\gamma)C] + (\frac{R-R^*}{R})[\sum_1^n \gamma_j I_j - (\delta+\mu)R] = (\frac{S-S^*}{S})[\Omega + \delta R - \beta\frac{C+\sum_1^n I_j}{N}(S-S^*) - (\mu+\lambda)(S-S^*) - (\beta\frac{C+\sum_1^n I_j}{N}S^* + (\mu+\lambda)S^*)] + (\frac{D-D^*}{D})[\lambda S + \gamma C - \beta\frac{C+\sum_1^n I_j}{N}(D-D^*) - (\delta_2+\mu)(D-D^*) - (\beta\frac{C+\sum_1^n I_j}{N}D^* + (\delta_2+\mu)D^*)] + (\frac{E-E^*}{E})[\beta\frac{C+\sum_1^n I_j}{N}(S+D) - (\mu+\phi)(E-E^*) - (\mu+\phi)E^*] + (\frac{I_j-I_j^*}{I_j})[\alpha\varphi_j E - (\mu_j+\gamma_j+\mu)(I_j-I_j^*) - (\mu_j+\gamma_j+\mu)I_j^*] + (\frac{C-C^*}{C})[(1-\alpha)\phi E - (\mu+\delta_1+\gamma)(C-C^*) - (\mu+\delta_1+\gamma)C^*] + (\frac{R-R^*}{R})[\sum_1^n \gamma_j I_j - (\delta+\mu)(R-R^*) - (\delta+\mu)R^*]$
$= -\frac{(S-S^*)^2}{S}(\beta\frac{C+\sum_1^n I_j}{N} + \mu + \lambda) - \frac{(D-D^*)^2}{D}(\beta\frac{C+\sum_1^n I_j}{N} + \delta_2 + \mu) - \frac{(E-E^*)^2}{E}(\mu+\phi) - \frac{(I_j-I_j^*)^2}{I_j}(\mu_j + \gamma_j + \mu) - \frac{(C-C^*)^2}{C}(\mu+\delta_1+\gamma) - \frac{(R-R^*)^2}{R}(\delta+\mu) + \Omega + \delta R - (\beta\frac{C+\sum_1^n I_j}{N} + \mu + \lambda)S^* - (\beta\frac{C+\sum_1^n I_j}{N} + \delta_2 + \mu + \lambda_2)D^* + \lambda S + \gamma C + \beta\frac{C+\sum_1^n I_j}{N}(S+D) - (\mu+\phi)E^* + \alpha\varphi_j E - (\mu_j+\gamma_j+\mu)I_j^* + (1-\alpha)\phi E - (\mu+\delta_1+\gamma)C^* + \sum_1^n \gamma_j I_j - (\delta+\mu)R^* - (\Omega+\delta R)\frac{S^*}{S} + (\beta\frac{C+\sum_1^n I_j}{N} + \mu + \lambda)\frac{S^{*2}}{S} + (\beta\frac{C+\sum_1^n I_j}{N} + \delta_2 + \mu)\frac{D^{*2}}{D} + (\mu+\phi)\frac{E^{*2}}{E} + (\mu_j+\gamma_j+\mu)\frac{I_j^{*2}}{I_j} + (\mu+\delta_1+\gamma)\frac{C^{*2}}{C} + (\delta+\mu)\frac{R^{*2}}{R} - (\lambda_1 S + \gamma C)\frac{D^*}{D} - \beta\frac{C+\sum_1^n I_j}{N}(S+D)\frac{E^*}{E} - \alpha\varphi_j E\frac{I_j^*}{I_j} - (1-\alpha)\phi E\frac{C^*}{C} - \sum_1^n \gamma_j I_j \frac{R^*}{R}$ *with* $1 \leq j \leq n$.

Let's pose $\Delta_1 = \Omega + \delta R + \alpha\varphi_j E + \alpha\varphi_j E + (1-\alpha)\phi E + \lambda S + \gamma C + \beta\frac{C+\sum_1^n I_j}{N}(S+D) + \sum_1^n \gamma_j I_j + (\beta\frac{C+\sum_1^n I_j}{N} + \mu + \lambda)\frac{S^{*2}}{S} + (\beta\frac{C+\sum_1^n I_j}{N} + \delta_2 + \mu)\frac{D^{*2}}{D} + (\mu+\phi)\frac{E^{*2}}{E} + (\mu_j+\gamma_j+\mu)\frac{I_j^{*2}}{I_j} + (\mu+\delta_1+\gamma)\frac{C^{*2}}{C} + (\delta+\mu)\frac{R^{*2}}{R}$ *and* $\Delta_2 = \frac{(S-S^*)^2}{S}(\beta\frac{C+\sum_1^n I_j}{N} + \mu + \lambda) + \frac{(D-D^*)^2}{D}(\beta\frac{C+\sum_1^n I_j}{N} + \delta_2 + \mu) + \frac{(E-E^*)^2}{E}(\mu+\phi) + \frac{(I_j-I_j^*)^2}{I_j}(\mu_j+\gamma_j+\mu) + \frac{(C-C^*)^2}{C}(\mu+\delta_1+\gamma) + \frac{(R-R^*)^2}{R}(\delta+\mu) + (\beta\frac{C+\sum_1^n I_j}{N} + \mu + \lambda)S^* + (\beta\frac{C+\sum_1^n I_j}{N} + \delta_2 + \mu)D^* + (\mu+\phi)E^* + (\mu_j+\gamma_j+\mu)I_j^* + (\mu+\delta_1+\gamma)C^* + (\delta+\mu)R^* + (\Omega + \delta R)\frac{S^*}{S} + (\lambda S + \gamma C)\frac{D^*}{D} + \beta\frac{C+\sum_1^n I_j}{N}(S+D)\frac{E^*}{E} + \alpha\varphi_j E\frac{I_j^*}{I_j} - (1-\alpha)\phi E\frac{C^*}{C} + \sum_1^n \gamma_j I_j \frac{R^*}{R}$.

We therefore obtain

$\frac{dL}{dt} = \Delta_1 - \Delta_2$. *Since all parameters of the system* $(2.1) - (2.6)$ *are all positive, it goes without saying that* $\frac{dL}{dt} \leq 0$ *if and only* $\Delta_1 \leq \Delta_2$ *and* $\frac{dL}{dt} = 0$ *when* $\Delta_1 = \Delta_2$. *This implies* $\frac{dL}{dt} = 0$ *if and only* $S = S^*$, $D = D^*$,$E = E^*$,$C = C^*$,$R = R^*$ *et* $I_j = I_j^*$ $\forall j \in V$. *Accodrding to the La Salle invariannce principle* [36], *the endemic equilibrium state is therefore globally asymptotically stable.* □

4. Controllability of the mathematical model

Control measures can significantly mitigate the transmission and control of the Covid-19 disease. We introduce two preventive control measures into model $(1.1) - (1.6)$ which are: u_1 which represents confinement and u_2 vaccination. Regarding confinement, it will be a question of reducing population

movements as much as possible. In this case, the interactions between susceptible individuals, susceptible diabetics, infected with covid-19 and infected diabetics must be reduced as much as possible. To take confinement into account in our model, we will replace the parameter β by $(1-u_1)\beta$. By incorporating these two controls into our model, we obtain the following state equation:

$$\frac{dS(t)}{dt} = \Omega + \delta R(t) - (1-u_1)\beta(\tfrac{C+\sum_1^n I_j}{N})S(t) - (\mu+\lambda)S(t) - u_2 S(t) \tag{4.1}$$

$$\frac{dD(t)}{dt} = \lambda S(t) + \gamma C(t) - (1-u_1)\beta(\tfrac{C+\sum_1^n I_j}{N})D(t) - (\delta_2+\mu)D(t) - u_2 D(t) \tag{4.2}$$

$$\frac{dE(t)}{dt} = (1-u_1)\beta(\tfrac{C+\sum_1^n I_j}{N})(S(t)+D(t)) - (\mu+\phi)E(t) \tag{4.3}$$

$$\frac{dI_j(t)}{dt} = \alpha\varphi_j E(t) - (\mu_j+\gamma_j+\mu)I_j(t) \tag{4.4}$$

$$\frac{dC(t)}{dt} = (1-\alpha)\phi E(t) - (\mu+\delta_1+\gamma)C(t) \tag{4.5}$$

$$\frac{dR(t)}{dt} = \textstyle\sum_1^n \gamma_j I_j(t) - (\delta+\mu)R(t) \tag{4.6}$$

4.1. **Analysis of the optimal control model.** In this part our objective is to minimize the cost function defined over a limited time interval t_f . The function that minimizes the number of susceptible cases S, the number of diabetic cases D, the number of infected cases I_j , the number of infected diabetic cases C and the number of exposed cases E is defined over the finite time interval $[0; t_f]$ by:

$$J(u_1,u_2) = \int_0^{t_f} [c_1 S(t) + c_2 E(t) + c_3 I_j(t) + c_4 C(t) + c_5 D(t) + \frac{1}{2}(b_1 u_1^2 + b_2 u_2^2)]dt \tag{4.7}$$

c_1, c_2, c_3, c_4, and c_5 are weight functions that contribute to balancing the different factors while b_1 and b_2 measure the relative costs of the intervention strategies associated with u_1 and u_2 respectively and t_f denotes the control time limit. The necessary and sufficient conditions for the existence of optimal control are established by the Pontryagin maximum principle [17]. Our objective is to minimize the cost function (4.7) i.e. to find the controls u_1^* and u_2^* such as

$$J(u_1^*, u_2^*) = \min_{u_1,u_2 \in U} J(u_1,u_2), \tag{4.8}$$

the controls are taken from the set U defined by
$U = \{u_1(t), u_2(t)/0 \le u_1(t), u_2(t) \le 1, 0 \le t \le t_f\}$ which is subject to the constraints of the system $(4.1) - (4.6)$. The necessary requirementsmet for a control to be optimal are those of the Pontryagin maximum principle [17] which consists in transforming the problem $(4.1) - (4.6)$ into a problem of pointwise minimization of a Hamiltonian$H$ with respect to the controls $u_1(t)$ and $u_2(t)$ with

$$H(y,u_1(t),u_2(t),\Gamma_j,t) = h_0 S(t) + h_1 D(t) + h_2 E(t) + h_3 I_j(t) + h_4 C(t) + \frac{1}{2}(b_1 u_1^2 + b_2 u_2^2)$$
$$+ \Gamma_S\{\Omega + \delta R(t) - (1-u_1)\beta(\tfrac{C+\sum_1^n I_j}{N})S(t) - (\mu+\lambda)S(t) - u_2 S(t)\}$$
$$+ \Gamma_D\{\lambda S(t) + \gamma C(t) - (1-u_1)\beta(\tfrac{C+\sum_1^n I_j}{N})D(t) - (\delta_2+\mu)D(t) - u_2 D(t)\}$$
$$+ \Gamma_E\{(1-u_1)\beta(\tfrac{C+\sum_1^n I_j}{N})(S(t)+D(t)) - (\mu+\phi)E(t)\}$$

$+\Gamma_{I_j}\{\alpha\varphi_j E(t)-(\mu_j+\gamma_j+\mu)I_j(t)\}$
$+\Gamma_C\{(1-\alpha)\phi E(t)-(\mu+\delta_1+\gamma)C(t)\}$
$+\Gamma_R\{\sum_1^n \gamma_j I_j(t)-(\delta+\mu)R(t)\}$
where $y=(S,D,E,I_j,C,R)$ and $\Gamma_k, k\in\{S,D,E,I_j,C,R\}$ representing the adjoint variables obtained by a differentiation of the Hamiltonian function with respect to the compartment variables S, D, E, I_j , C, R. Which gives $\dot{\Gamma}_S=\Gamma_S((1-u_1)\beta(\frac{C+\sum_1^n I_j}{N})+\mu+\lambda+u_2)+\Gamma_D\lambda-\Gamma_E(1-u_1)\beta(\frac{C+\sum_1^n I_j}{N})-h_0$
$\dot{\Gamma}_D=\Gamma_D((1-u_1)\beta(\frac{C+\sum_1^n I_j}{N})+\delta_2+\mu+u_2)-\Gamma_E(1-u_1)\beta(\frac{C+\sum_1^n I_j}{N})-h_1$
$\dot{\Gamma}_E=\Gamma_E(\mu+\phi)E(t)-\Gamma_{I_j}\alpha\varphi_j-\Gamma_C(1-\alpha)\phi-h_2$
$\dot{\Gamma}_{I_j}=\Gamma_{I_j}(\mu_j+\gamma_j+\mu)+\Gamma_S(1-u_1)\beta\frac{S(t)}{N}+\Gamma_D(1-u_1)\beta\frac{D(t)}{N}-\Gamma_E(1-u_1)\beta\frac{S(t)+D(t)}{N}-h_3$
$\dot{\Gamma}_C=\Gamma_C(\mu+\gamma+\delta_1)+\Gamma_S(1-u_1)\beta\frac{S(t)}{N}+\Gamma_D(1-u_1)\beta\frac{D(t)}{N}-\Gamma_E(1-u_1)\beta\frac{S(t)+D(t)}{N}-h_4$
$\dot{\Gamma}_R=\Gamma_R(\delta+\mu)$
Taking into account the transversality condition
$\Gamma_S(t_f)=\Gamma_D(t_f)=\Gamma_E(t_f)=\Gamma_{I_j}(t_f)=\Gamma_C(t_f)=\Gamma_R(t_f)=0$ we obtain respectively the optimal control and the optimality condition defined by :
$\frac{\partial H}{\partial u_1}=0$ and $\frac{\partial H}{\partial u_2}=0$ from where
$-b_1u_1-\Gamma_S\beta(\frac{C+\sum_1^n I_j}{N})S(t)-\Gamma_D\beta(\frac{C+\sum_1^n I_j}{N})D(t)+\Gamma_E\beta(\frac{C+\sum_1^n I_j}{N})(S(t)+D(t))=0$
$-b_2u_2+\Gamma_S S(t)+\Gamma_D D(t)=0$
which gives

$$\begin{cases} u_1=\frac{\Gamma_E\beta(\frac{C+\sum_1^n I_j}{N})(S(t)+D(t))-\Gamma_S\beta(\frac{C+\sum_1^n I_j}{N})S(t)-\Gamma_D\beta(\frac{C+\sum_1^n I_j}{N})D(t)}{b_1} \\ u_2=\frac{\Gamma_S S(t)+\Gamma_D D(t)}{b_2} \end{cases} \tag{4.9}$$

And we subsequently obtain

$$\begin{cases} u_1^*=min(1,max(0;\frac{\Gamma_E\beta(\frac{C+\sum_1^n I_j}{N})(S(t)+D(t))-\beta(\frac{C+\sum_1^n I_j}{N})(\Gamma_S S(t)+\Gamma_D D)}{b_1})) \\ u_2^*=min(1,max(0;\frac{\Gamma_S S(t)+\Gamma_D D(t)}{b_2})) \end{cases} \tag{4.10}$$

Thus, the equation of state, the adjoint system , the characterization of the optimal control and the transversality condition constitute an optimality system. In the following, we will do the numerical simulation of the optimal control.

4.2. **Numerical simulation of the optimal control model.** In this part, we are dealing with the numerical simulation of the solution of the optimality system taking into account the initial conditions for the different values of the equation of state. To do this, we use Matlab 2016b to make the numerical simulation of the equation of state constrained by the adjoint equation system as well as the transversality condition and the characterization equation of the optimal control. We will use the Runge- Kutta order 4 scheme. The model highlighted the contribution of intervention measures in mitigating multi-strain COVID-19 in a diabetic and non-diabetic population using two intervention measures as controls. In

order to establish a comparison between the results of the numerical simulations, we will only consider the Alpha, Delta and Omicron variants.

(1) Model without control measures

The strategies are optimal and the results are as follows:

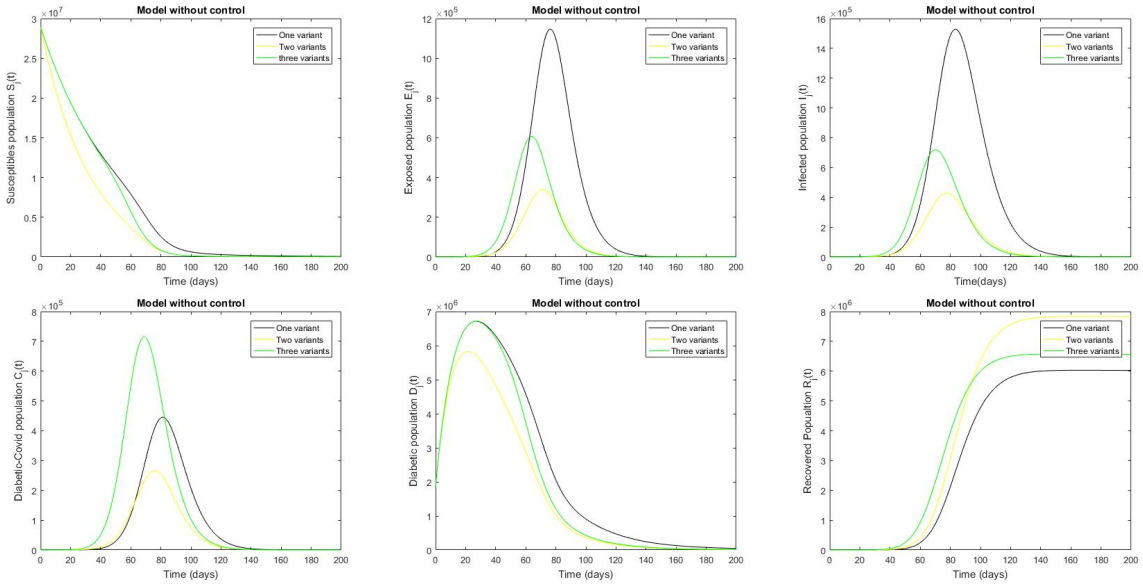

FIGURE 2. Population without control

Figure 2 shows that among non-diabetic individuals, there are more individuals infected with a single variant than those infected with two or three variants at a time. In contrast, diabetics are more susceptible to higher infection with all three strains at a time. In both cases, the disease peaks after 60 days. The following figure illustrates the death cases according to the number of covid strains and without control measures.

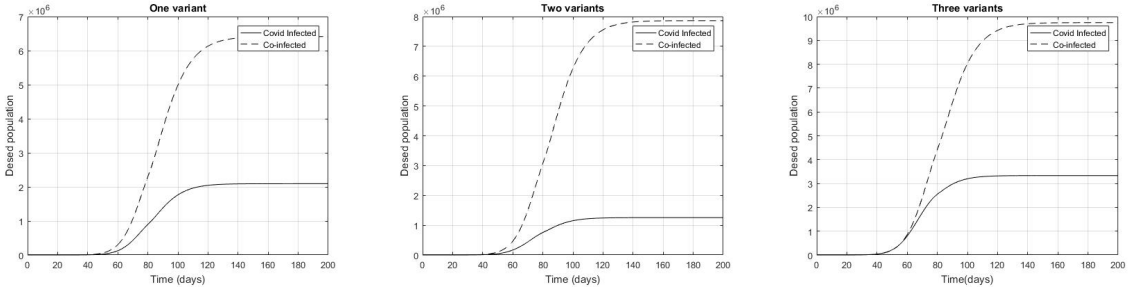

FIGURE 3. Deceded population without control

The curves in Figure 3 show that there are significantly more deaths in the case of coinfection after 60 days of illness. In addition, more deaths are recorded when the number of variants is high in diabetic individuals.

(2) Model with control measure

In this, case we consider the controls $u_1(t) = 0.03$; $u_2(t) = 0.95$. The results obtained are as follow:

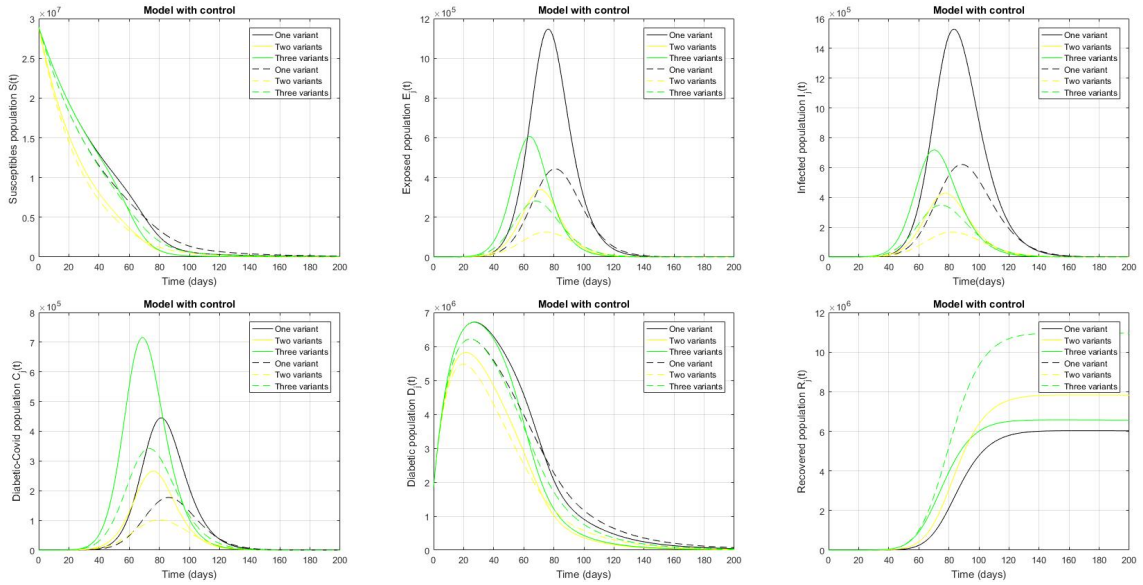

FIGURE 4. Population with control

The following figure illustrates the cases of death according to the number of strains of covid and with two control measures.

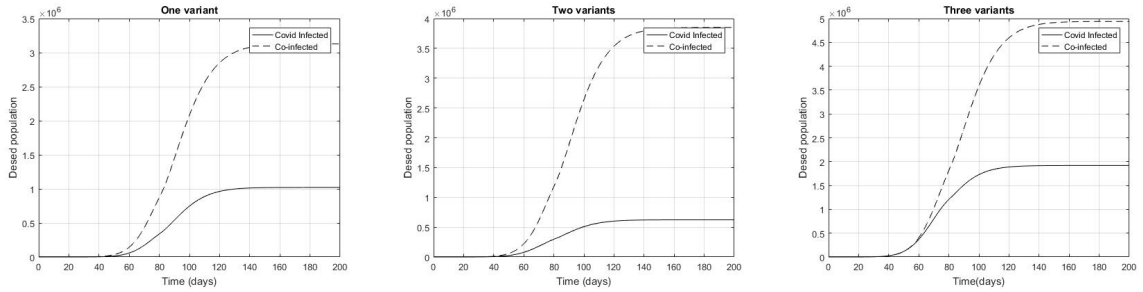

FIGURE 5. Deceded population with control

Figure 2 shows that these controls help reduce the number of individuals exposed by the strain and other strains have maintained populations decreasing. Similarly, these two controls have enabled populations to decrease considerably, while the number of diabetics has also increased.

5. CONCLUSION

In this article, we studied a deterministic control problem which describes the transmission of different strains of covid19 in a population with diabetics. After showing that the system admits a unique positive solution, the stability of the equilibrium points was confirmed by numerical simulation

our theoretical results. For the numerical simulation, we considered only three Alpha, Beta and Gamma strains. It appears that co-infection leads to more deaths. So, diabetic individuals suffering from covid are more exposed to death than non-diabetics.

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Conflicts of Interest. The authors declare that there are no conflicts of interest regarding the publication of this paper.

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