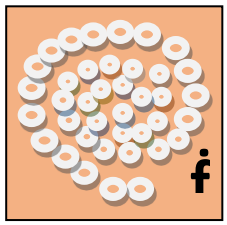

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Optimal control and sensitivity analysis of age-structured mathematical model of Diphtheria infection

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Abstract

The work presented an age-structured deterministic model of a system of ordinary differential equations of diphtheria infection transmission dynamics. Optimal control theory was used to study the impact of personal protection, vaccination and treatment as effective control measures against the epidemics and established necessary conditions for the optimal control of the system. The application of time-dependent controls can reduce the total number of infected (symptomatic and asymptomatic) individuals in the population To determine the most influential parameters of the model that greatly influence the prevalence of diphtheria, sensitivity analysis was carried out on R_b using the normalised forward sensitivity index of R_b that depends differentially on basic reproduction ration parameters. From the sensitivity analysis is was discovered that, the most influential parameters of the model that greatly influence the prevalence of diphtheria are effective rate of transmission, rate of progression from the latent state to the infected state, fraction of new infection that are both symptomatic and asymptomatic, detection rate, natural and infection death rate. The numerical simulations show that there is a significant effect of vaccination (u_2) and isolation (u_1) for susceptible individuals. The number of susceptible infants (S_1) reduces and drops to zero when each of the controls are applied with time. The use of treatment / drug inhibition control could significantly reduce the number of both asymptomatic and symptomatic infected individuals

Keywords and phrases: Diphtheria; Optimal Control; Sensitivity; Asymptomatic; Symptomatic;

1 Introduction

Diphtheria is a highly contagious vaccine-preventable bacterial infection caused by *Corynebacterium diphtheriae* that primarily infects the throat (pharynx and tonsils) and nose. The bacterium has an

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estimated basic reproduction number of 1.7–4.3 [1,2]. Although diphtheria is treatable if detected early, it can lead to severe complications such as respiratory failure, heart problems and even deaths (case-fatality ratio among untreated, never vaccinated cases 28.8–29.2%) [1]. It remains a health problem in low-resource countries, particularly where vaccination uptake and coverage are low and where sanitation conditions remain poor [3].

On December 1, 2022, the Nigeria Centre for Disease Control (NCDC) was notified of suspected diphtheria outbreaks in two of the largest states in Nigeria, Lagos, and Kano, with a combined population of over 30 million. On January 20, 2023, the Director General of the NCDC issued an advisory confirming the outbreaks in Lagos and Kano and the development in two other states, Yobe and Osun, is being monitored. As of February 3, 2023, 216 confirmed cases and 40 persons have died (case fatality rate of 18.5%) from the infection in the current outbreak in Nigeria [4]. This ongoing outbreak mainly occurred in children aged 2 to 14 years (85.2%) and in Kano state (97.7%). It is worth mentioning that only a fraction, 27 (12.5%) of the confirmed cases, were fully vaccinated with diphtheria-tetanus-pertussis (DTP3)—a three-dose vaccine [4]. The Nigerian outbreak has underscored the importance of vaccination and herd immunity, impact of vaccination coverage and sensitisation (media coverage) and effect of complacency in controlling the spread of infectious disease, as emphasized by [5,6,7], blaming it on low vaccination uptake occasioned by COVID-19 in many low-resource countries and consequent opportunistic outbreaks. In Nigeria, case fatality rate among untreated and unvaccinated population is 28.8- 28.2%. because health problem in low resource areas where vaccination uptake and coverage is low and which sanitation conditions remain poor. Diphtheria vaccination coverage estimate in Nigeria have been in the decline. The vaccination rate dropped from 86% in 2019 to 81% in 2021. The overall vaccination coverage of 56% in Nigeria is suboptimal, this is as a result of unavailability of vaccines [4].

Nigeria is currently facing a second wave of diphtheria outbreak. There is an increase in the affected population with a rise in the number of confirmed cases and related death. This is due to the low national vaccination coverage of 56% while vaccination coverage of 80-86% must be maintained to ensure community protection [8].

The control of diphtheria is based on primary prevention of disease by ensuring high population immunity through vaccination. Secondary prevention spread by the rapid investigation of close contacts to ensure prompt treatment of those infected. To effectively contend the spread of Diphtheria, Government has been implementing different control measures, such as isolation of patient, maintenance of one meter between patients, keeping patient care areas well ventilated, the use medical mask and cover any wound/lesions on patient's body by patient who may have to move out of the isolation areas, high risk population such as young children under five years of age, school children, elderly close contact with diphtheria cases and health workers should be vaccinated on a priority basis, epidemiological surveillance ensuring early detection of diphtheria outbreak, administering antitoxin to neutralize the toxin and antibiotics to kill the bacteria, reducing complication and mortality [8].

Mathematical models over the years have become a veritable tool in the hand of mathematicians and epidemiologist in studying, understanding, describing and analysing the dynamics of infectious diseases [9, 10, 11, 12, 13, 14,15, 16, 28, 29, 30,31]. Some mathematical models such as [17, 18] has been formulated for the transmission dynamics of diphtheria, which correctly describe the decreasing

trend of diphtheria cases and predicted the diphtheria outbreak patterns that may occur in the near future. Finds parameters that gives contribution endemic and non-endemic condition

In [17] the SIR mathematical of diphtheria transmission is discussed, simplifying the assumptions and find parameters that give contribution to endemic and nonendemic condition. The model assumes that infected humans can heal by itself. The Basic Reproduction Number was used to analyse the endemic equilibrium.

The work in [18] presented a mathematical model, describing diphtheria transmission in Thailand. Based on the course of diphtheria infection, the population was divided into 8 epidemiological classes, namely, susceptible, symptomatic infectious, asymptomatic infectious, carrier with full natural-acquired immunity, carrier with partial natural-acquired immunity, individual with full vaccine-induced immunity, and individual with partial vaccine-induced immunity.

In this work, the S V E I R age -structured model of diphtheria infection dynamics is presented. Since People who are most susceptible to infection are those who are not completely immunized or have low antitoxin antibody levels and have been exposed to a carrier or diseased individual [26, 27]. The work assumes that those that have been completely vaccinated have no or negligible fatality.
Previous works by other researchers had not taken into consideration age sensitivity in diphtheria infection. This work has successfully structured the susceptible class into two groups: S_1 − Susceptible infant at time t (0-1 year), S_2 − Susceptible school children population at time t (1-15 years) which are the categories that is mostly affected by the infection.

2 Methodology/model formulation

2.1 Assumptions

- The control of diphtheria is based on primary prevention of disease by ensuring high population immunity of the infant ((0-1 year) and school children by vaccination
- Isolation of detected cases (that is confirmed cases are not allowed to interact with the population freely.
- Epidemiological surveillance ensuring early detection through contact tracing is carried out
- Secondary prevention spread by the rapid investigation of close contacts to ensure prompt treatment of those infected

The total population of human at time t under consideration denoted by N_h is split into mutually exclusive sub-population of S_1 Susceptible infant at time t (0-1years), S_2 , Susceptible school children population at time t, V, Vaccination population at time t, E, Exposed population at time t , I_1, Asymptomatic infection population at time t, I_2., Symptomatic infection population at time t, R., Recovered population at time t. I_D., Detected infectious humans at time t (Asymptomatic and symptomatic) population through testing,

$$N_h = S_1 + S_2 + V + E + I_1 + I_2 + R + I_D$$

2.2 State variables

N_h −The total population of human at time t under consideration
S_1 − Susceptible infant at time t (0-1years),
S_2 − Susceptible school children population at time t, (1-15years)
V −Vaccination population at time t,
E − Exposed population at time t , (the exposed are the unvaccinated individuals in S_1 and S_2 who are in contact with the infected individuals)
I_1. − Asymptomatic infection population at time t,
I_2. − Symptomatic infection population at time t,
R − Recovered population at time t.
I_D. − Detected infectious humans at time t (Asymptomatic and symptomatic) population through testing,
Note: It is assume that the age bracket in the classes I_1, I_2, I_D, V and R may range from 0 -15 and above depending on their progression in each of the stages.

2.3 Parameters

σ_1 − progress rate from exposed to I_1, Asymptomatic infection population
σ_2 − progress rate efrom exposed to I_2, symptomatic infection population
δ − fraction of new infection that are I_1, Asymptomatic
$1-\delta$ − fraction of new infection that are I_2, symptomatic
β_1 − effective transmission rate from S_1
β_2 − effective transmission rate from S_2
τ_1 − vaccination coverage for S_1
τ_2 − vaccination coverage for S_2
ε − vaccine efficacy
ρ − maturity rate from S_1 to S_2
b − per capita birth rate of humans
$\varepsilon\tau_1$ − immunization rate in S_1
$\varepsilon\tau_2$ − immunization rate in S_2
θ_1 − detection rate (via contact tracing) for S_1
θ_2 − detection rate (via contact tracing) for S_2
η − death due to infection
α − natural death rate

$$\lambda_1(t) = \frac{\beta_1(\sigma_1 I_1 + \sigma_2 I_2)}{N_h - I_D}$$

$$\lambda_2(t) = \frac{\beta_2(\sigma_1 I_1 + \sigma_2 I_2)}{N_h - I_D}$$

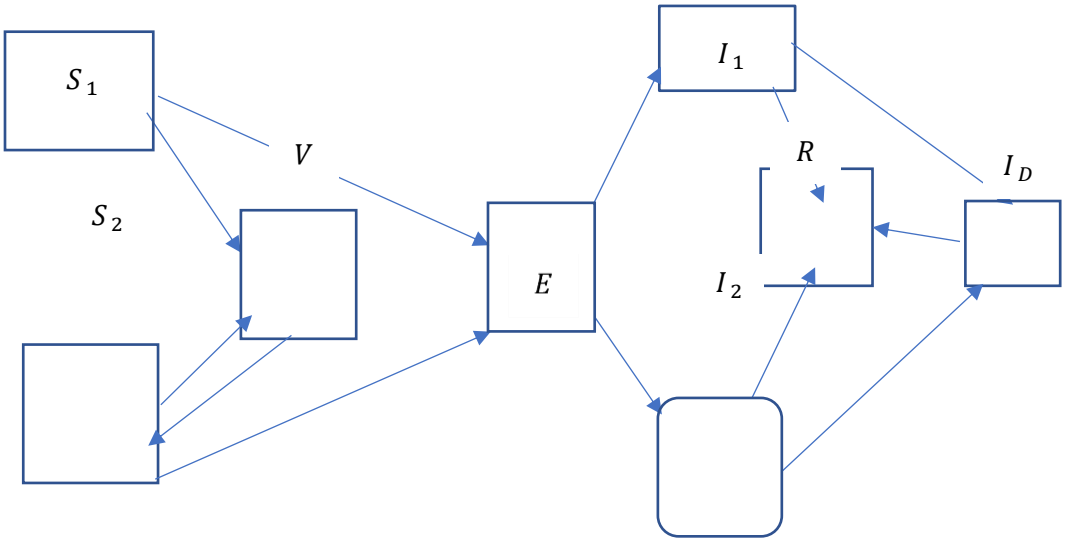

Figure 1: FLOWCHART OF AGE-STRUCTURED DIPHTHERIA DYNAMICS

2.4 Model equations

Using the above-described state variables and parameters together with the schematic diagram in figure 1, the model of the diphtheria infection transmission dynamics results in the following system of deterministic non-linear first order differential equations

$$\frac{dS_1}{dt} = bN_h - \frac{\beta_1(\sigma_1 I_1 + \sigma_2 I_2)}{N_h - I_D} S_1 - \varepsilon\tau_1 S_1 - \rho S_1 - \alpha S_1 \quad (2.1)$$

$$\frac{dS_2}{dt} = \rho S_1 - \frac{\beta_2(\sigma_1 I_1 + \sigma_2 I_2)}{N_h - I_D} S_2 - \varepsilon\tau_2 S_2 - \alpha S_2 \quad (2.2)$$

$$\frac{dV}{dt} = \varepsilon\tau_1 S_1 + \varepsilon\tau_2 S_2 - \alpha V \quad (2.3)$$

$$\frac{dE}{dt} = \frac{\beta_1(\sigma_1 I_1 + \sigma_2 I_2)}{N_h - I_D} S_1 + \frac{\beta_2(\sigma_1 I_1 + \sigma_2 I_2)}{N_h - I_D} S_2 - \sigma_1\delta E - \sigma_2(1-\delta)E - \alpha E \quad (2.4)$$

$$\frac{dI_1}{dt} = \sigma_1\delta E - \gamma_1 I_1 - \theta_1 I_1 - \alpha I_1 - \eta I_1 \quad (2.5)$$

$$\frac{dI_2}{dt} = \sigma_2(1-\delta)E - \gamma_2 I_2 - \theta_2 I_2 - \alpha I_2 - \eta I_2 \quad (2.6)$$

$$\frac{dR}{dt} = \gamma_1 I_1 + \gamma_2 I_2 + \gamma_3 I_D - \alpha R \quad (2.7)$$

$$\frac{dI_D}{dt} = \theta_1 I_1 + \theta_2 I_2 - \gamma_3 I_D - \alpha I_D - \eta I_D \quad (2.8)$$

3 Analysis of the model

This section seeks to study qualitatively the dynamical properties of the Diphtheria model (2.1) – (2.8).

3.1 Basic properties of the model

Before the model (2.1) – (2.8) is epidemiologically meaningful, it is important to show that all its state variables are positive (non-negative) at all time $t > 0$ in the domain $\wp$, and that the domain $\wp$ is indeed bounded. This shall be done through the following theorems and proves.

Theorem 3.1 Let the initial data of the model (2.1) – (2.8) be given as $S_1(0) \geq 0$, $S_2(0) \geq 0, V(0) \geq 0, E(0) \geq 0$, $I_1(0) \geq 0$, $I_2(0) \geq 0$, $R(0) \geq 0$, $I_D(0) \geq 0$. Then the solutions S_1, S_2, V, E, I_1, I_2, R, I_D of the model (2.1) – (2.8) are non-negative $\forall\ t > 0$

Proof: Let $t_1 = sup\{t > 0: S_1 > 0$, $S_2 > 0, V > 0, E > 0$, $I_1 > 0$, $I_2 > 0$, $R > 0$, $I_D > 0 \in [0, t]\}$. Thus, $t_1 > 0$.

We have from (2.1)

$$\frac{dS_1}{dt} = bN_h - \frac{\beta_1(\sigma_1 I_1 + \sigma_2 I_2)}{N_h - I_D} S_1 - \varepsilon\tau_1 S_1 - \rho S_1 - \alpha S_1$$

$$\frac{dS_1}{dt} = bN_h - (\lambda S_1 + \varepsilon\tau_1 + \rho + \alpha) S_1 \qquad where\ \lambda_1(t) = \frac{\beta_1(\sigma_1 I_1 + \sigma_2 I_2)}{N_h - I_D}$$

which can be re-written as

$$\frac{dS_1}{dt} + (\lambda S_1 + \varepsilon\tau_1 + \rho + \alpha) S_1 = bN_h$$

So that $S_1(t) = e^{-(\lambda S_1 + \varepsilon\tau_1 + \rho + \alpha)t} \int_0^t bN_h\, e^{-(\lambda S_1 + \varepsilon\tau_1 + \rho + \alpha)s} ds > 0$

Similarly, it can be shown that: $S_2 > 0, V > 0, E > 0$, $I_1 > 0$, $I_2 > 0$, $R > 0$, $I_D > 0$

Theorem 3.2 : The domain $\wp = \{(S_1, S_2, V, E, I_1, I_2, R, I_D) \in \Re_+^8 : N_h \leq N_h(0)\}$ is positively-invariant for the model (2.1)- (2.8) and attracts all positive solutions of the model.

Proof: adding all the equation of the model (2.1) – (2.8), we have

$$\frac{dN_h}{dt} = bN_h - \alpha S_1 - \alpha S_2 - \alpha V - \alpha E - \alpha I_1 - \eta I_1 - \alpha I_2 - \eta I_2 - \alpha I_D - \eta I_D - \alpha R$$

$$\varphi = \text{Max}\{\alpha, \eta\}$$

$$\frac{dN_h}{dt} \leq bN_h - \varphi N_h = \vartheta N_h,\ \vartheta = b - \varphi$$

$$\frac{dN_h}{dt} \leq \vartheta N_h,$$

$$\int \frac{dN_h}{N_h} \leq \int \vartheta dt$$

$$N_h(t) = N_h(0) e^{\vartheta t}$$

$$N_h(t)\ approaches\ N_h(0)\ as\ t \to \infty\ \forall\ b < \varphi$$

3.2 The basic reproductive ratio

The basic reproductive ratio R_b of the model (2.1) – (2.8) can be established by the use of next generation matrix method on the system (2.1) – (2.8) using the methods in [5,6,19, 20]. Hence, the

transmission matrix F and the transition matrix of the system (2.1) – (2.8) is given respectively as follows:

$$F(E, I_1, I_2, I_D) = \begin{pmatrix} 0 & \sigma_1(\beta_1+\beta_2) & \sigma_2(\beta_1+\beta_2) & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}$$

$$V(E, I_1, I_2, I_D) = \begin{pmatrix} \sigma_1\delta + \sigma_2(1-\delta) + \alpha & 0 & 0 & 0 \\ -\sigma_1\delta & \gamma_1 + \theta_1 + \alpha + \eta & 0 & 0 \\ -\sigma_2(1-\delta) & 0 & \gamma_2 + \theta_2 + \alpha + \eta & 0 \\ 0 & -\theta_1 & -\theta_2 & \gamma_1 + \alpha + \eta \end{pmatrix}$$

From [5,6,19, 20,28, 29], it follows that the basic reproduction number denoted by R_b

ss obtained as $R_b = \frac{\sigma_1^2\delta(\beta_1+\beta_2)}{((\sigma_1\delta+\sigma_2(1-\delta)+\alpha)(\theta_1+\gamma_1+\alpha+\eta)} + \frac{\sigma_2^2(1-\delta)(\beta_1+\beta_2)}{((\sigma_1\delta+\sigma_2(1-\delta)+\alpha)(\theta_2+\gamma_2+\alpha+\eta)}$ or

$$R_b = (\beta_1+\beta_2)\left\{\frac{\sigma_1^2\delta}{((\sigma_1\delta+\sigma_2(1-\delta)+\alpha)(\theta_1+\gamma_1+\alpha+\eta)} + \frac{\sigma_2^2(1-\delta)}{((\sigma_1\delta+\sigma_2(1-\delta)+\alpha)(\theta_2+\gamma_2+\alpha+\eta)}\right\}$$

3.3 Formulation of the optimal control problem for Diphtheria

Given the initial population size $S_1(0), S_2(0), V(0), E(0), I_1(0), I_2(0), I_D(0), R(0)$. of all the eight classes of model (2.1) – (2.8), the aim of this section is to find the best control strategy that would minimize the number of individuals that die as a result of the disease, at the same time minimizing the cost of the strategy.

Introducing the controls strategies $u_1(t)\ u_2(t), u_3(t)$,and $u_4(t)$ representing the efficiency of isolation/prevention, efficiency of the vaccine therapy in preventing new diphtheria infection, the efficiency of testing the exposed, the efficiency of drug in inhibiting the virus strain and effort on infected human to increase the number of recovered individuals respectively, the model (2.1) – (2.8) becomes Eq. (3.1) – (3.8). $u_1(t)$ is defined to be the prevention/isolation control, minimizing the contact among the healthy and infected individuals. $u_2(t)$, is the vaccination control, it represents the effort in the possible vaccination of all the individuals in order to reduce the further spread of diphtheria, thereby reducing the infection in the system. Control u_3 denotes the effort in testing individuals in the exposed stage, to identify the symptomatic and asymptomatic individuals. The control u_4 represents the treatment effort on the $I_1.-$ Asymptomatic infection population $I_2.-$ Symptomatic infection population $I_D.-$ Detected infectious humans (Asymptomatic and symptomatic) population through testing. r_1, r_2, r_D represent the rate of treatment of $I_1.-$ Asymptomatic infection population $I_2.-$ Symptomatic infection population $I_D.-$ Detected infectious humans (Asymptomatic and symptomatic) population through testing respectively. ξ_1, ξ_2

represent the rate of the effect of the control u_2 on the S_1 and S_2 respectively. ξ_3 represent the rate of the effect of control u_3 on E. ρ_1 is the proportion of the effect of control u_3 on E that move to I_1 class. The above illustrations and parameters leads to the following optimal control problem for diphtheria infection.

$$\frac{dS_1}{dt} = bN_h - \frac{\beta_1(\sigma_1 I_1 + \sigma_2 I_2)}{N_h - I_D}(1-u_1)S_1 - \varepsilon\tau_1 S_1 - \rho S_1 - (\alpha + \xi_1 u_2)S_1 \quad (3.1)$$

$$\frac{dS_2}{dt} = \rho S_1 - \frac{\beta_2(\sigma_1 I_1 + \sigma_2 I_2)}{N_h - I_D}(1-u_1)S_2 - \varepsilon\tau_2 S_2 - (\alpha + \xi_2 u_2)S_2 \quad (3.2)$$

$$\frac{dV}{dt} = u_2\xi_1 S_1 + u_2\xi_2 S_2 + \varepsilon\tau_1 S_1 + \varepsilon\tau_2 S_2 - \alpha V \quad (3.3)$$

$$\frac{dE}{dt} = \frac{\beta_1(\sigma_1 I_1 + \sigma_2 I_2)}{N_h - I_D}(1-u_1)S_1 + \frac{\beta_2(\sigma_1 I_1 + \sigma_2 I_2)}{N_h - I_D}(1-u_1)S_2 - \sigma_1\delta E - \sigma_2(1-\delta)E - \alpha E - (1-u_3)\xi_3 E \quad (3.4)$$

$$\frac{dI_1}{dt} = \rho_1 u_3 \xi_3 E + \sigma_1 \delta E - \gamma_1 I_1 - \theta_1 I_1 - \alpha I_1 - \eta I_1 - r_1 u_4 I_2 \quad (3.5)$$

$$\frac{dI_2}{dt} = (1-\rho_1)u_3\xi_3 E + \sigma_2(1-\delta)E - \gamma_2 I_2 - \theta_2 I_2 - \alpha I_2 - \eta I_2 - r_2 u_4 I_2 \quad (3.6)$$

$$\frac{dI_D}{dt} = \theta_1 I_1 + \theta_2 I_2 - \gamma_3 I_D - \alpha I_D - \eta I_D - r_D u_4 I_D \quad (3.7)$$

$$\frac{dR}{dt} = \gamma_1 I_1 + \gamma_2 I_2 + \gamma_3 I_D - \alpha R \quad (3.8)$$

The control functions $u_1(t)\ u_2(t), u_3(t)$,and $u_4(t)$ are bounded lebesgue integrable functions. The control $u_1(t)$ is the time dependent effort on prevention/isolation control, minimizing the contact among the healthy and infected individuals, practiced on the time interval $[0, t_f]$ to reduce the number of individuals that may become fully infected.

The control $u_2(t)$ is the time dependent effort on the efficiency of the vaccine therapy in preventing new diphtheria infection, practiced on the time interval $[0, t_f]$ to reduce the number of individuals that may become fully infected.

The control $u_3(t)$ is the time dependent effort on the efficiency of testing individuals in the exposed stage, to identify the symptomatic and asymptomatic individuals, practiced on the time interval $[0, t_f]$ to reduce the number of individuals that may become fully infected.

The control $u_4(t)$ is the time dependent effort on the treatment effort on the actively infected individuals ($I_1.\ I_2.\ I_D$), practiced on the time interval $[0, t_f]$ to increase the number of recovered individuals.

The optimal control problem in this work, involves that in which the number of vaccinated, exposed and active diphtheria infections and the cost of treatment controls $u_1(t)\ u_2(t), u_3(t), u_4(t)$, are minimized subject to the differential Equations $(3.1) - (3.8)$. This involves the number of individuals with active and latent diphtheria infection respectively as well as the cost of applying the

vaccine therapy in preventing new diphtheria infection, the efficiency of drug in inhibiting the virus strain and effort on infected human to increase the number of recovered individuals
The objective functional is defined as

$$J = \int_0^{t_f} \{A_1E + A_2I_1 + A_3I_2 + A_4I_D + \frac{A_5}{2}u_1^2 + \frac{A_6}{2}u_2^2 + \frac{A_7}{2}u_3^2 + \frac{A_8}{2}u_4^2\}dt \quad \ldots\ldots\ldots\ldots\ldots\ldots (3.9)$$

where t_f is the final time and the coefficient $A_1 > 0$, $A_2 > 0$, $A_3 > 0, A_4 > 0, A_5 > 0$, $A_6 > 0$, $A_7 > 0, A_8 > 0$ are the balancing cost factors.

We seek the minimize the objective functional

$$J = \int_0^{t_f} \{A_1E + A_2I_1 + A_3I_2 + A_4I_D + \frac{A_5}{2}u_1^2 + \frac{A_6}{2}u_2^2 + \frac{A_7}{2}u_3^2 + \frac{A_8}{2}u_4^2\}dt$$

subject to the optimal control system (3,1) –(3.8)

Hence minimizing the number of infected individuals but keeping the cost of vaccination, treatment/drugs low. That is, to find the optimal control $u_1^0, u_2^0, u_3^0, u_4^0$ such that $J(u_1^0, u_2^0, u_3^0, u_4^0) = Min[J(u_1(t)\ u_2(t), u_3(t), u_4(t),)\ /u_1(t)\ u_2(t), u_3(t), u_4(t), u_5(t)\ \epsilon\Omega]$
where $\Omega = \{(u_1(t)\ u_2(t), u_3(t), u_4(t)\ )\ /\ u_1(t)\ u_2(t), u_3(t), u_4(t)$ are measurable$\}$
$a_i < u_1(t)\ \ u_2(t),\ \ u_3(t), u_4(t)\ < b_i, i = 1,2,3,4\ \ t\ \epsilon[0, t_f]$ is the control set. Also $a_i. and\ b_i\ are\ constant\ in\ [0,\ 1]$.

We use the quadratic control functions in this problem because the controls cost of intervention is nonlinear. It means that there is no linear relationship among the cost of intervention among infected individuals and the cost of intervention.

3.4 Characterization of an optimal control

We shall apply the Pontryagin's Maximum Principle [12,21,22,23], to convert the system (3.1) – (3.8) and (3.9) to a problem of minimizing a pointwise a Hamiltonian functional with respect to the controls u_i . And also establish necessary conditions for the optimal control of the system.
We take λ_k, $\forall\ k = S_1, S_2, V, E,\ I_1,\ I_2,\ I_D,\ R$ to be the adjoint variable associated with the state variable $S_1, S_2, V, E,\ I_1,\ I_2,\ I_D,\ R$.

Theorem 3.3: Given the optimal control u_j^0 and solutions $S_1^0,\ S_2^0,\ V^0,\ E^0,\ I_1^0,\ I_2^0,\ I_D^0, R^0$ of the control system (3.1) – (3.8) that minimizes $J(u_j^0)\ over\ \Omega$. Then there exist adjoint variables λ_k satisfying

$$\frac{\partial \lambda_k}{\partial t} = -\frac{\partial H}{\partial i} \quad \ldots\ldots\ldots\ldots\ldots (3.11)$$

with transversality conditions

$$\lambda_k(t_f) = 0, where\ k = S_1, S_2, V, E,\ I_1,\ I_2,\ I_D,\ R \quad \ldots. (3.12)$$

The optimality condition is given by

$$\frac{\partial H}{\partial u_j} = 0, \forall j = 1, 2, 3, 4 \qquad (3.13)$$

with controls $u_1^0 = min\left\{1,\ max\left[0,\ \frac{\left[\left(\lambda_E^*-\lambda_{S_1}^*\right)\beta_1 S_1^0+\ \left(\lambda_E^*-\lambda_{S_2}^*\right)\beta_2 S_2^0\right]\frac{\left(\sigma_1 I_1^0+\sigma_2 I_2^0\right)}{\left(N_h^0-I_D^0\right)}}{A_5}\right]\right\}$

$$u_2^0 = min\left\{1,\quad max\left[0,\quad \frac{\left[\left(\lambda_{S_1}^*-\xi_1\lambda_V^*\right)S_1^0+\ \left(\lambda_{S_2}^*-\xi_2\lambda_V^*\right)S_2^0\right]}{A_6}\right]\right\}$$

$$u_3^0 = min\left\{1,\quad max\left[0,\quad \frac{\lambda_{I_2}^*(\rho_1-1)\xi_3E^0-\lambda_E^*\xi_3E^0-\lambda_{I_1}^*\rho_1\xi_3E^0}{A_7}\right]\right\}$$

$$u_4^0 = min\left\{1,\quad max\left[0,\quad \frac{\lambda_{I_1}^* r_1 I_1^0+\lambda_{I_2}^* r_2 I_2^0+\lambda_{I_D}^* r_D I_D^0}{A_8}\right]\right\}$$

Proof:

Since we have eight state variables, $S_1, S_2, V, E,\ I_1,\ I_2,\ I_D,\ R$, we shall have eight corresponding adjoint variables $\lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5, \lambda_6, \lambda_7, \lambda_8$. Then we obtain the Hamiltonian functional:

$$\begin{aligned}
H\ =\ & A_1E + A_2I_1 + A_3I_2 + A_4I_D\ + \frac{A_5}{2}u_1^2 + \frac{A_6}{2}u_2^2 + \frac{A_7}{2}u_3^2 + \frac{A_8}{2}u_4^2 \\
& + \lambda_1\left\{bN_h - \frac{\beta_1(\sigma_1I_1+\sigma_2I_2)}{N_h-I_D}(1-u_1)S_1 - \varepsilon\tau_1S_1 - \rho S_1 - (\alpha+\xi_1u_2)S_1\right\} \\
& + \lambda_2\left\{\rho S_1 - \frac{\beta_2(\sigma_1I_1+\sigma_2I_2)}{N_h-I_D}(1-u_1)S_2 - \varepsilon\tau_2S_2 - (\alpha+\xi_2u_2)S_2\right\} \\
& + \lambda_3\{u_2\xi_1S_1 + u_2\xi_2S_2 + \varepsilon\tau_1S_1 + \varepsilon\tau_2S_2 - \alpha V\} \\
& + \lambda_4\left\{\frac{\beta_1(\sigma_1I_1+\sigma_2I_2)}{N_h-I_D}(1-u_1)S_1 + \frac{\beta_2(\sigma_1I_1+\sigma_2I_2)}{N_h-I_D}(1-u_1)S_2 - \sigma_1\delta E\right. \\
& \left. - \sigma_2(1-\delta)E - \alpha E - (1-u_3)\xi_3E\right\} \\
& + \lambda_5\{\rho_1u_3\xi_3E + \sigma_1\delta E - \gamma_1I_1 - \theta_1I_1 - \alpha I_1 - \eta I_1 - r_1u_4I_1\} \\
& + \lambda_6\{(1-\rho_1)u_3\xi_3E + \sigma_2(1-\delta)E - \gamma_2I_2 - \theta_2I_2 - \alpha I_2 - \eta I_2 - r_2u_4I_2\} \\
& + \lambda_7\{\theta_1I_1 + \theta_2I_2 - \gamma_3I_D - \alpha I_D - \eta I_D - r_Du_4I_D\} \\
& + \lambda_8\{\gamma_1I_1 + \gamma_2I_2 + \gamma_3I_D - \alpha R\} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (3.10)
\end{aligned}$$

The system of adjoint equation is obtained by taking the appropriate partial derivative of H with respect to the respective state variables.

$$\begin{aligned}
\frac{\partial\lambda_{S_1}}{\partial t}\ &= -\frac{\partial H}{\partial S_1} \\
&= \left(\lambda_{S_1}-\lambda_E\right)\frac{\beta_1(\sigma_1I_1+\sigma_2I_2)}{N_h-I_D}(1-u_1) + \left(\lambda_{S_1}-\lambda_V\right)\varepsilon\tau_1 + \left(\lambda_{S_1}-\lambda_V\right)\xi_1u_2 \\
&+ \left(\lambda_{S_1}-\lambda_{S_2}\right)\rho + \alpha\lambda_{S_1} \\
&\lambda_{S_1}(t_f)\ = 0
\end{aligned}$$

$$\frac{\partial \lambda_{S_2}}{\partial t} = -\frac{\partial H}{\partial S_2}$$

$$= \left(\lambda_{S_2} - \lambda_E\right)\frac{\beta_2(\sigma_1 I_1 + \sigma_2 I_2)}{N_h - I_D}(1-u_1) + \left(\lambda_{S_2} - \lambda_V\right)\varepsilon\tau_2 + \left(\lambda_{S_2} - \lambda_V\right)u_2\xi_2 + \alpha\lambda_{S_2}$$

$$\lambda_{S_2}(t_f) = 0$$

$$\frac{\partial \lambda_V}{\partial t} = -\frac{\partial H}{\partial V} = \lambda_V \alpha V$$

$$\lambda_{S_V}(t_f) = 0$$

$$\frac{\partial \lambda_E}{\partial t} = -\frac{\partial H}{\partial E}$$

$$= \left(\lambda_E - \lambda_{I_1}\right)\sigma_1\delta + \left(\lambda_E - \lambda_{I_2}\right)\sigma_2(1-\delta) - \left(\lambda_E + \lambda_{I_2}\right)u_3\xi_3 + \left(\lambda_{I_2} - \lambda_{I_1}\right)\rho_1 u_3\xi_3 + (\alpha + \xi_3)\,\lambda_E - A_1$$

$$\lambda_E(t_f) = 0$$

$$\frac{\partial \lambda_{I_1}}{\partial t} = -\frac{\partial H}{\partial I_1} = (\lambda_{I_1} - \lambda_R)\gamma_1 + (\lambda_{I_1} - \lambda_{I_D})\theta_1 + (\alpha + \eta + r_1 u_4)\lambda_{I_1} - A_2$$

$$\lambda_{I_1}(t_f) = 0$$

$$\frac{\partial \lambda_{I_2}}{\partial t} = -\frac{\partial H}{\partial I_2} = \left(\lambda_{I_2} - \lambda_R\right)\gamma_2 + \left(\lambda_{I_2} - \lambda_{I_D}\right)\theta_2 + (\alpha + \eta + r_2 u_4)\lambda_{I_2} - A_3$$

$$\lambda_{I_2}(t_f) = 0$$

$$\frac{\partial \lambda_{I_D}}{\partial t} = -\frac{\partial H}{\partial I_D} = (\lambda_{I_D} - \lambda_R)\gamma_3 + (\alpha + \eta + r_D u_4)\,\lambda_{I_D} - A_4$$

$$\lambda_{I_D}(t_f) = 0$$

$$\frac{\partial \lambda_R}{\partial t} = -\frac{\partial H}{\partial R} = \alpha\lambda_R$$

$$\lambda_R(t_f) = 0$$

The optimal control $u_1^0, u_2^0, u_3^0\, u_4^0$ can be solved from optimality conditions

$$\frac{\partial H}{\partial u_1} = A_5 u_1 + \frac{\beta_1(\sigma_1 I_1 + \sigma_2 I_2)}{N_h - I_D} S_1\lambda_1 + \frac{\beta_2(\sigma_1 I_1 + \sigma_2 I_2)}{N_h - I_D} S_2\lambda_2 - \frac{\beta_1(\sigma_1 I_1 + \sigma_2 I_2)}{N_h - I_D} S_1\lambda_4 - \frac{\beta_2(\sigma_1 I_1 + \sigma_2 I_2)}{N_h - I_D} S_2\lambda_4 = 0$$

$A_5 u_1^0 + \left(\{\beta_1 S_1^0 \lambda_{S_1}^* + \beta_2 S_2 \lambda_{S_2}^*\} - \{\beta_1 S_1^0 \lambda_E^* + \beta_2 S_1^0 \lambda_E^*\}\right) \frac{(\sigma_1 I_1^0 + \sigma_2 I_2^0)}{(N_h^0 - I_D^0)} = 0$. Hence $u_1^0 = \frac{\left[\left(\lambda_E^* - \lambda_{S_1}^*\right)\beta_1 S_1^0 + \left(\lambda_E^* - \lambda_{S_2}^*\right)\beta_2 S_2^0\right]\frac{(\sigma_1 I_1^0 + \sigma_2 I_2^0)}{(N_h^0 - I_D^0)}}{A_5}$

$$\frac{\partial H}{\partial u_2} = A_6 u_2 - \lambda_{S_1} S_1 - \lambda_{S_2} S_2 + \lambda_V(\xi_1 S_1 + \xi_2 S_2) = A_6 u_2 - \left[\left(\lambda_{S_1} - \xi_1\lambda_V\right)S_1 + \left(\lambda_{S_2} - \xi_2\lambda_V\right)S_2\right] = 0$$

$A_6 u_2 - \left[\left(\lambda_{S_1}^* - \lambda_V^*\right)S_1^0 + \left(\lambda_{S_2}^* - \lambda_V^*\right)S_2^0\right] = 0 \Rightarrow u_2^0 = \frac{\left[\left(\lambda_{S_1}^* - \xi_1\lambda_V^*\right)S_1^0 + \left(\lambda_{S_2}^* - \xi_2\lambda_V^*\right)S_2^0\right]}{A_6}$

$\frac{\partial H}{\partial u_3} = A_7 u_3 + \lambda_E \xi_3 E + \lambda_{I_1}\rho_1\xi_3 E + \lambda_{I_2}(1-\rho_1)\xi_3 E = A_7 u_3 + \lambda_E\xi_3 E + \lambda_{I_1}\rho_1\xi_3 E - \lambda_{I_2}(\rho_1 - 1)\xi_3 E = 0$

$A_7 u_3 = \lambda_{I_2}^*(\rho_1 - 1)\xi_3 E^0 - \lambda_E^*\xi_3 E^0 - \lambda_{I_1}^*\rho_1\xi_3 E^0 \quad u_3^0 = \frac{\lambda_{I_2}^*(\rho_1-1)\xi_3 E^0 - \lambda_E^*\xi_3 E^0 - \lambda_{I_1}^*\rho_1\xi_3 E^0}{A_7}$

$\frac{\partial H}{\partial u_4} = A_8 u_4 - \lambda_5 r_1 I_1 - \lambda_6 r_2 I_2 - \lambda_7 r_D I_D = 0 \quad u_4^0 = \frac{\lambda_{I_1}^* r_1 I_1 + \lambda_{I_2}^* r_2 I_2 + \lambda_{I_D}^* r_D I_D}{A_8}$

4 Numerical simulations/sensitivity analysis

4.1 Numerical simulations

The numerical simulation was carried out using Matlab 15 to show the effect of the controls on the spread of diphtheria. The parameter values used are shown in the table below

Table 1 Model Parameters and Values

Parameters	Values	Source
B	0.15448/dy	Rahmi &Pratama (2023)
α	0.0000194	Rahmi & Pratama (2023)
r_1, r_2, r_D	0.5, 0.6, 0.7	Assumed
$\varepsilon_1, \varepsilon_2, \varepsilon_3$	0.7,0.7,0.3	Assumed
θ_1, θ_2	0.3, 0.4	Assumed
β_1, β_2	0.57	Izzati & Andriani (2021)
ϵ	0.6	Assumed
ρ	0.7	Assumed
σ_1, σ_2	0.143, 0.140	Rahmi & Pratama (2023)
γ	0.5	Rahmi & Pratama (2023)
δ	0.2	Assumed
τ_1, τ_2	0.5, 0.4	Rahmi & Pratama (2023)

The initial conditions for the variables are; $S_1(0) = 500$, $S_2(0) = 500$, $V(0) = 200$, $E(0) = 700$, $I_1(0) = 100$, $I_2(0) = 200$, $I_D(0) = 400$

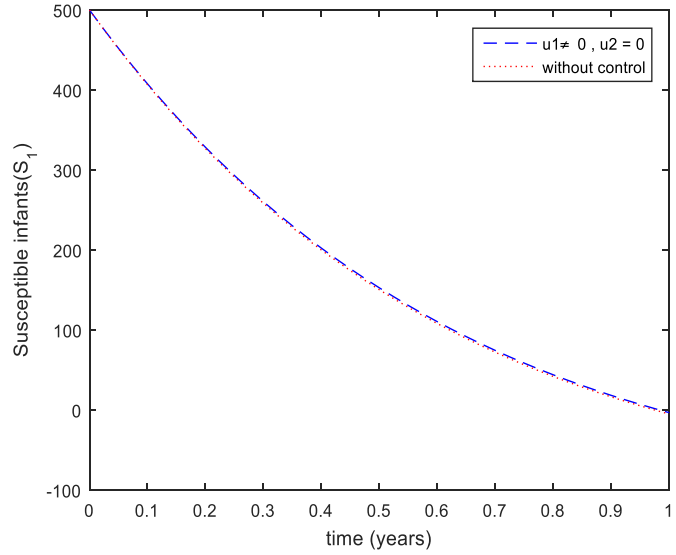

Fig 2. Effect of isolation on S_1

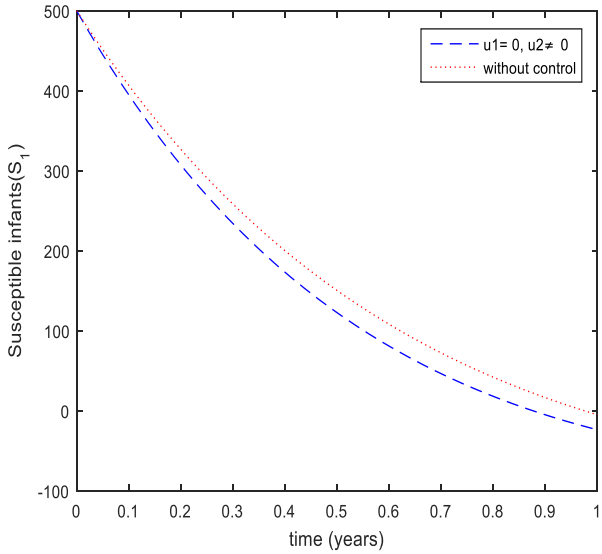

Fig 3. Effect of vaccination on S_1

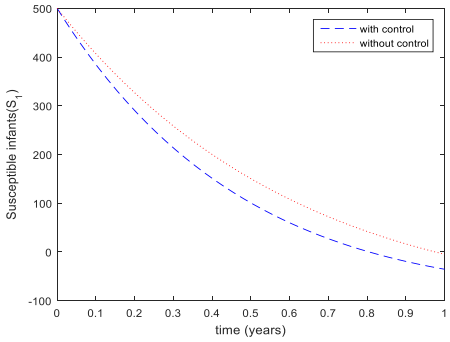

Fig. 4. Effect of vaccination and isolation on S_1

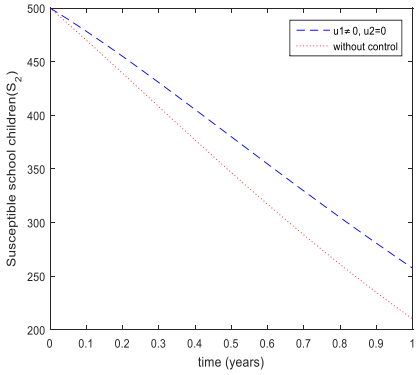

Fig. 5. Effect of isolation on S_2

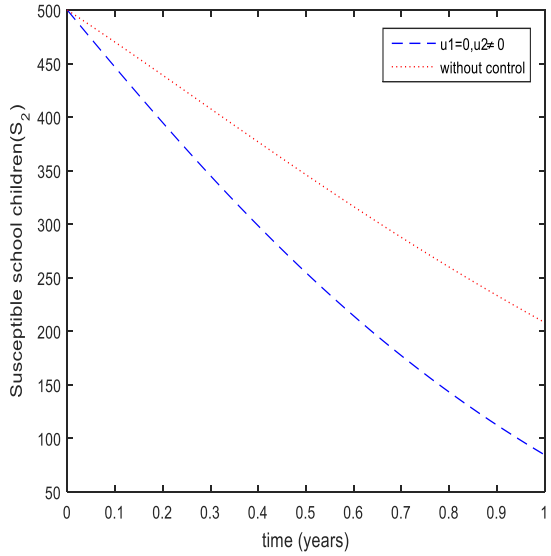

Fig. 6. Effect of vaccination onS_2

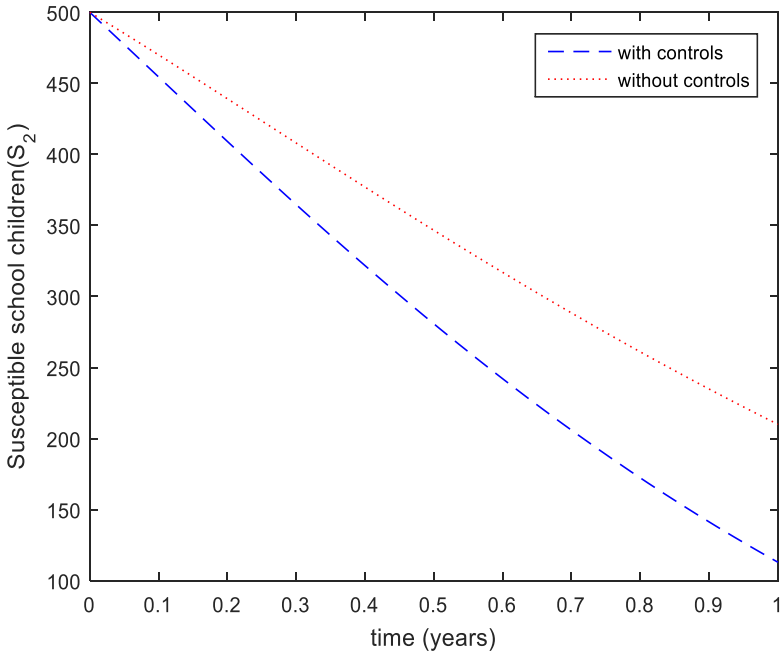

Fig.7. Effect of isolation and vaccination on S_2

The numerical simulations show that there is a significant effect of vaccination (u_2) and isolation (u_1) for susceptible individuals. The number of susceptible infants (S_1) reduces and drops to zero when each of the controls are applied with time as shown in fig 2. However, from Fig. 5 and 6, vaccination (u_2) tends to significantly reduce the number of susceptible school children population (S_2) with time compared to applying only isolation control (u_1).

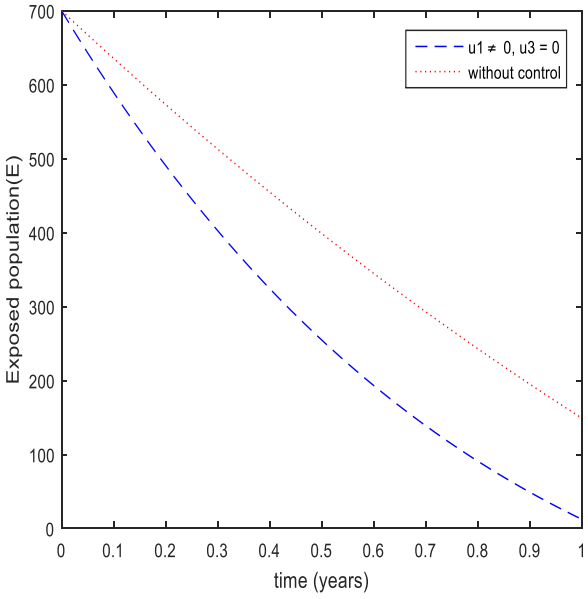

Fig. 8. Effect of Isolation on Exposed population

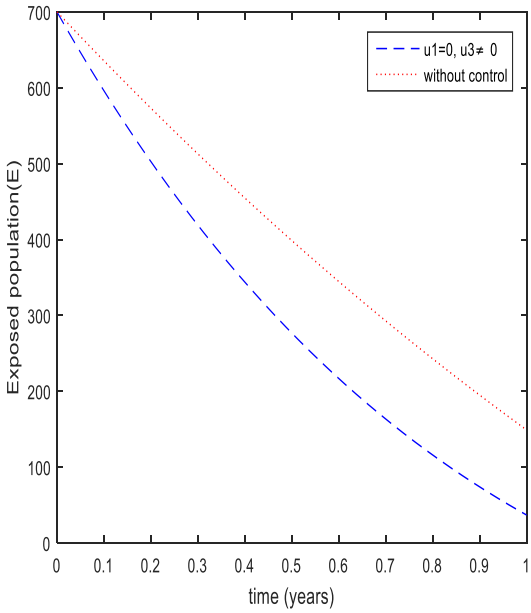

Fig. 9. Effect of testing on Exposed population

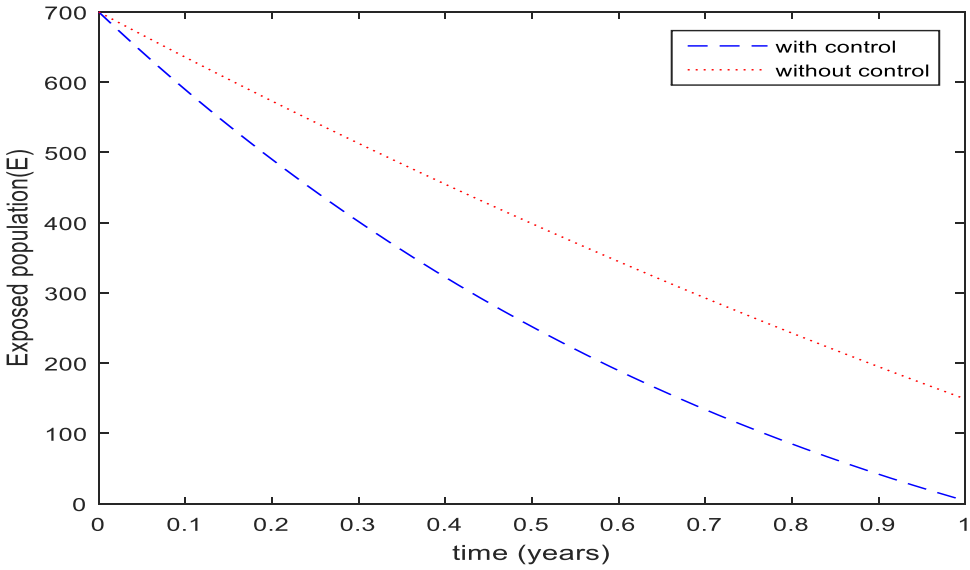

Fig. 10. Effect of Isolation and testing on Exposed population

We can see from Fig. 10 that the isolation of exposed individuals could reduce the number of exposed population to almost zero with time but the combination of isolation (u_1) and testing (u_3) brings the number of exposed individuals to zero after 9years.

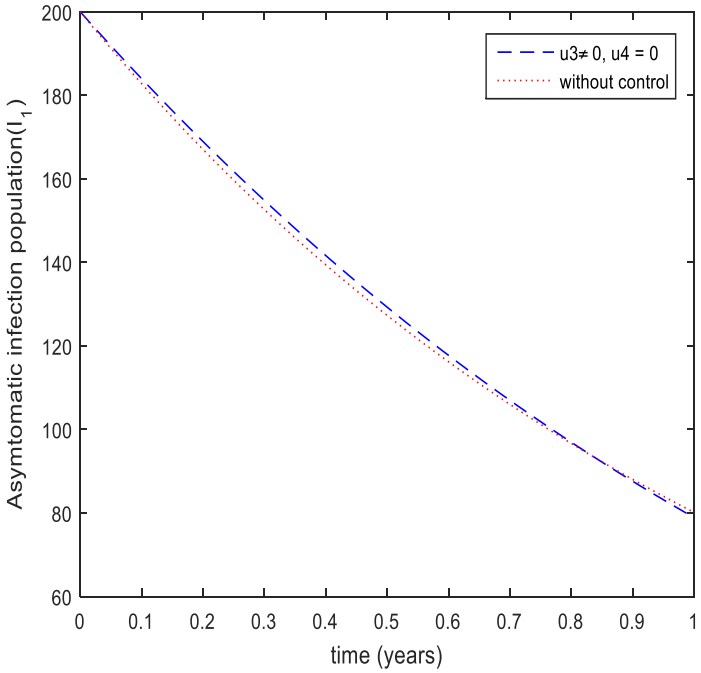

Fig. 11. Effect of testing on I_1

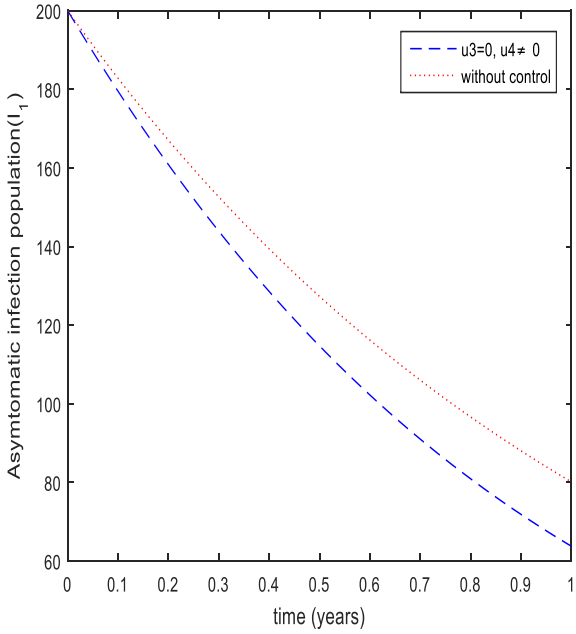

Fig. 12. Effect of treatment on I_1

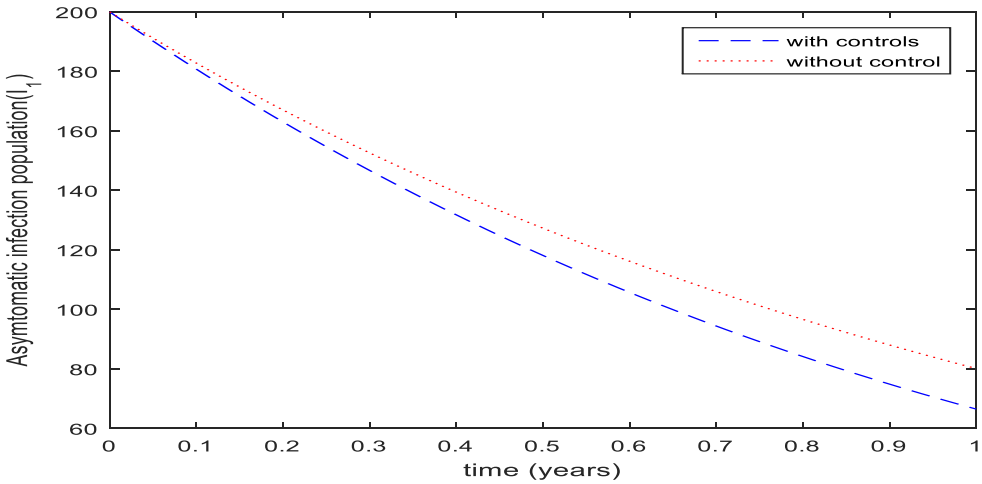

Fig. 13. Effect of testing and treatment on I_1

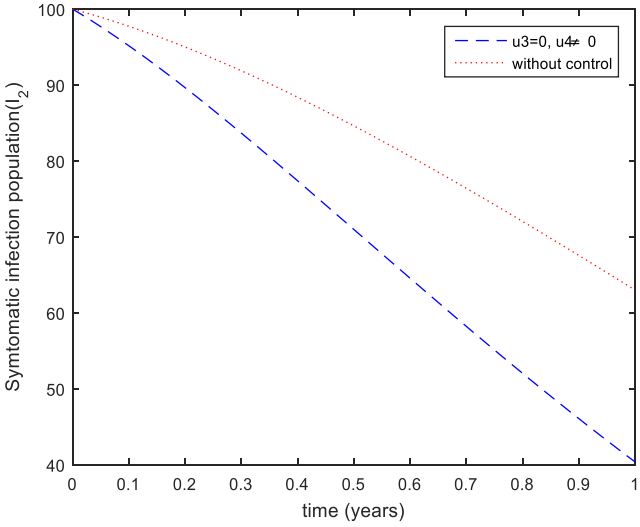

Fig.14. Effect of testing on I_2

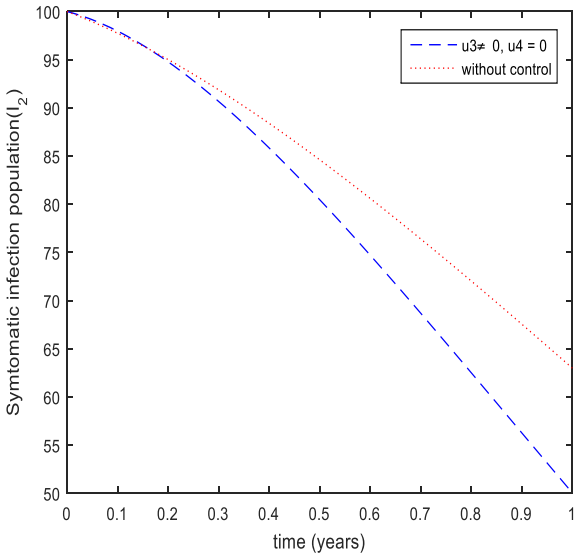

Fig. 15. Effect of treatment on I_2

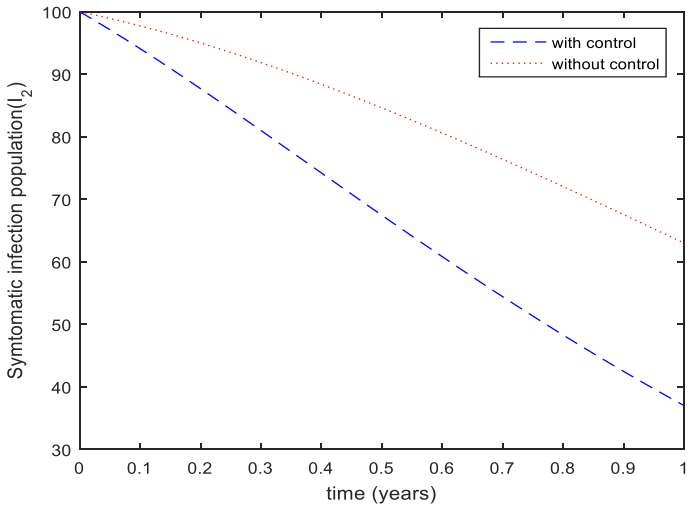

Fig. 16. Effect of treatment and testing on Symptomatic infected population (I_2)

The effect of treatment (u_4) and testing (u_3) of infected individuals can be observed in Figs 11, 12, 13, 14, 15, and 16. The use of treatment / drug inhibition control could significantly reduce the number of both asymptomatic and symptomatic infected individuals as shown in Figs 12 and 15. However the combination of testing and treatment controls could be more effective in reducing the number of symptomatic infected individuals as shown in Fig 16.

4.2 Sensitivity analysis on $\mathbf{R_b}$

A sensitivity analysis is done to determine the parameters most responsible for the transmission and spread of diphtheria and to measure the effect of changes in the dominant factors of the model. Sensitivity analysis of the basic reproductive number is employed to design an intervention strategy to curtail the spread of the infection by reducing R_b. With the basic reproductive number one can discover the parameters that have high impact on the values of R_b, that is the most influential parameters of the model that greatly influence the prevalence of infection. These parameters are then targeted as a means of reducing the value of R_b.

The normalised forward sensitivity index of R_b that depends differentially on a parameter p is defined by

$r_t^{R_b} = \left(\frac{\partial R_b}{\partial t}\right)\left(\frac{t}{R_b}\right)$ $where\ t = \beta_1, \beta_2, \sigma_1, \sigma_2, \delta, \theta_1, \theta_2, \gamma_1, \alpha, \eta)$ is used to compute the sensitivity analysis on the R_b of the system.

In particular, sensitivity indices of the basic reproduction number, R_b, with respect to the model parameters are computed as follows:

$$\left(\frac{\partial R_b}{\partial \beta_1}\right)\left(\frac{\beta_1}{R_b}\right) = \frac{\beta_1}{\beta_1 + \beta_2}$$

$$\left(\frac{\partial R_b}{\partial \beta_2}\right)\left(\frac{\beta_2}{R_b}\right) = \frac{\beta_2}{\beta_1 + \beta_2}$$

$$\left(\frac{\partial R_b}{\partial \sigma_1}\right)\left(\frac{\sigma_1}{R_b}\right) = (\theta_1 + \gamma_1 + \alpha + \eta)(\theta_2 + \gamma_2 + \alpha + \eta)\left\{\frac{2\sigma_1^2\delta((\sigma_1\delta + \sigma_2(1-\delta) + \alpha)}{\sigma_1^2\delta + \sigma_2^2(1-\delta)} - \sigma_1\delta\right\}$$

$$\left(\frac{\partial R_b}{\partial \sigma_1}\right)\left(\frac{\sigma_1}{R_b}\right) = \frac{\sigma_1^3\delta^2 + 2\sigma_1^2\delta(\sigma_2 + \alpha) - \sigma_2^2\sigma_1\delta(1-\delta) - 2\sigma_2\sigma_1\delta^2}{\left((\sigma_1\delta + \sigma_2(1-\delta) + \alpha)\right)\left(\sigma_1^2\delta + \sigma_2^2(1-\delta)\right)}$$

$$\left(\frac{\partial R_b}{\partial \sigma_2}\right)\left(\frac{\sigma_2}{R_b}\right) = \frac{(1-\delta)\sigma_2\{2\sigma_2\sigma_1\delta + \sigma_2^2(1-\delta) + 2\sigma_2\alpha - \sigma_1^2\delta}{\left((\sigma_1\delta + \sigma_2(1-\delta) + \alpha)\right)\left(\sigma_1^2\delta + \sigma_2^2(1-\delta)\right)}$$

$$\left(\frac{\partial R_b}{\partial \delta}\right)\left(\frac{\delta}{R_b}\right)$$

$$= \frac{\delta\left((\sigma_1\delta + \sigma_2(1-\delta) + \alpha)\right)(\theta_1 + \gamma_1 + \alpha + \eta)(\theta_2 + \gamma_2 + \alpha + \eta)\{(\sigma_2 + \alpha)\sigma_1^2 - (\sigma_1 + \alpha)\sigma_2^2 - \sigma_2^3\}}{\left(\sigma_1^2\delta + \sigma_2^2(1-\delta)\right)}$$

$$\left(\frac{\partial R_b}{\partial \alpha}\right)\left(\frac{\alpha}{R_b}\right) = \frac{-\{(\theta_1 + \gamma_1 + \alpha + \eta)(\theta_2 + \gamma_2 + \alpha + \eta) + (\theta_1 + \theta_2 + \gamma_1 + \gamma_2 + 2\alpha + 2\eta)\}}{(\theta_1 + \gamma_1 + \alpha + \eta)(\theta_2 + \gamma_2 + \alpha + \eta\ )}\alpha$$

$$\left(\frac{\partial R_b}{\partial \theta_1}\right)\left(\frac{\theta_1}{R_b}\right) = -\frac{\theta_1}{(\theta_1 + \gamma_1 + \alpha + \eta)}$$

$$\left(\frac{\partial R_b}{\partial \theta_2}\right)\left(\frac{\theta_2}{R_b}\right) = -\frac{\theta_2}{(\theta_2 + \gamma_2 + \alpha + \eta)}$$

$$\left(\frac{\partial R_b}{\partial \eta}\right)\left(\frac{\eta}{R_b}\right) = \frac{-[(\theta_1+\gamma_1+\alpha+\eta)+(\theta_2+\gamma_2+\alpha+\eta)]}{(\theta_1+\gamma_1+\alpha+\eta)(\theta_2+\gamma_2+\alpha+\eta)}\eta$$

The sensitivity index of the basic reproduction number to the model parameters indicates that an increase (or decrease) in value of the following parameters $\beta_1, \beta_2, \sigma_1, \sigma_2, \delta,$ will lead to an increase (or decrease) in the basic reproduction number. On the other hand, an increase (or decrease) in the death rates (α, η) and detection rate, (θ_1, θ_2) leads to a corresponding decrease (or increase) in the basic reproduction number of the disease.

The most influential parameters of the model that greatly influence the prevalence of diphtheria are effective rate of transmission, rate of progression from the latent state to the infected state, fraction of new infection that are both symptomatic and asymptomatic, detection rate, natural and infection death rate.

5 Discussions and conclusion

We summarize some of the main theoretical and epidemiological findings of this study as follows: the work presented an age-structured deterministic model of a system of ordinary differential equations of diphtheria infection transmission dynamics. It was established that the model is epidemiologically meaningful, with theorem and proof that shows that all its state variables are positive (non-negative) at all-time $t > 0$ in the domain $\wp$, and that the domain $\wp$ is indeed bounded.

The basic reproductive ratio R_b of the model (2.1) – (2.8) was established as

$$R_b = (\beta_1+\beta_2)\left\{\frac{\sigma_1^2\delta}{((\sigma_1\delta+\sigma_2(1-\delta)+\alpha)(\theta_1+\gamma_1+\alpha+\eta)} + \frac{\sigma_2^2(1-\delta)}{((\sigma_1\delta+\sigma_2(1-\delta)+\alpha)(\theta_2+\gamma_2+\alpha+\eta)}\right\}$$

by the use of next generation matrix method on the system (2.1) – (2.8) using the methods in [5,6,19, 20,30,31]. To determine the most influential parameters of the model that greatly influence the prevalence of diphtheria, sensitivity analysis was carried out on R_b using the normalised forward sensitivity index of R_b that depends differentially on basic reproduction ration parameters. From the sensitivity analysis is was discovered that, the most influential parameters of the model that greatly influence the prevalence of diphtheria are effective rate of transmission, rate of progression from the latent state to the infected state, fraction of new infection that are both symptomatic and asymptomatic, detection rate, natural and infection death rate.

Optimal control theory was used to study the impact of personal protection, vaccination and treatment as effective control measures against the epidemics. And establish necessary conditions for the optimal control of the system. The application of time-dependent controls can reduce the total number of infected (symptomatic and asymptomatic) individuals in the population.

The numerical simulations show that there is a significant effect of vaccination (u_2) and isolation (u_1) for susceptible individuals. The number of susceptible infants (S_1) reduces and drops to zero when each of the controls are applied with time as shown in fig 2. However, from Fig. 5 and 6, vaccination (u_2) tends to significantly reduce the number of susceptible school children population (S_2) with time compared to applying only isolation control (u_1).

As seen from Fig. 10, the isolation of exposed individuals could reduce the number of exposed population to almost zero with time but the combination of isolation (u_1) and testing (u_3) brings the number of exposed individuals to zero after 9years. The effect of treatment (u_4) and testing (u_3) of infected individuals can be observed in Figs 11, 12, 13, 14, 15, and 16. The use of treatment / drug inhibition control could significantly reduce the number of both asymptomatic and symptomatic infected individuals as shown in Figs 12 and 15. However the combination of testing and treatment controls could be more effective in reducing the number of symptomatic infected individuals as shown in Fig 16.

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