



MATHEMATICAL MODEL OF EBOLA VIRUS DISEASE WITH VACCINATION

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ABSTRACT. The continued reoccurrences of Ebola virus disease (EVD) among human population has given a great cause for concern. This paper studied the impact of vaccination on the transmission dynamics of EVD by constructing a deterministic model. A threshold quantity called basic reproduction number, R_0 , is computed and used to discuss the persistent and eradication of disease in the population. The local and global stability of the disease-free equilibrium are established to show the asymptotic behavior of the infection. The stability analysis shown that the disease-free equilibrium is locally and globally asymptotically stable whenever $R_0 < 1$ and unstable whenever $R_0 > 1$. Furthermore, sensitivity analysis is carried out to ascertain the model parameters that have high impact on R_0 for intervention planning. The sensitivity result shown that vaccination rate has high impact compare on R_0 , as the rate of vaccination increases, the disease reduces in the population. The numerical simulations of the model are carried out using fourth order Runge–Kutta scheme in order to investigate the dynamics of EVD in the presence of vaccination. The result shown the important of vaccination in eliminating EVD in the population. It indicates that if a good proportion of the population are vaccinated with a vaccine that does not wane off on time, it will reduce the number of infected individuals in the population and this will help to eradication of EVD in the population.

1. INTRODUCTION

Ebola virus disease (EVD) is a severe, often fatal illness with death rate of up to 90% [1]. The disease is caused by Ebola virus which is named after a river in Democratic Republic of Congo (DRC) in Africa where it originated [2]. It is a ribonucleic acid virus family with no known reservoir, has an incubation period of 2 to 21 days and infectious period of 4 to 10 days [3]. Ebola virus has five strains – Zaire Ebola virus, Budinbugyo Ebola virus, Sudan Ebola virus, Tai Forest Ebola Virus and Reston Ebola virus [4].

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Exposure to Ebola virus occurs when one has direct contact with the blood or secretions from an infected person. It can be also contracted through contact with contaminated objects such as needles. The virus can persist up to eight weeks in the semen of survivors of EVD and could be transmitted through sexual intercourse [5]. Therefore, it has been advocated that men who have recovered from Ebola virus disease should abstain from sex until they are certified safe by physicians [6]. Ebola virus is also present in the breast milk of women who recovered from the disease. It is recommended that such women should not breastfeed until they are declared safe by health officials [7]. The Ebola epidemic recurred in 2018 in the DRC, making it the 9th outbreak and next in severity and scoped to the 2014 to 2016 West African Ebola epidemic [2]. Countries affected during the West African Ebola epidemics included Guinea, Liberia, Nigeria, Senegal, Sierra Leone, Spain and United States of America. 4,555 deaths recorded at the end of October 2014 [8]. Nigeria had her own share on July 20, 2014 and by October 20, 2014, she was certified Ebola-free [5]. According to the WHO [9], there was 3,233 confirmed cases with a total of 2,217 deaths in the DRC just within 21 days during the 9th epidemic. The 10th outbreak also struck in 2020 and new outbreaks are expected in the DRC given the existence of the virus in an animal reservoir in many points of the country [10]. Hence, there is need for aggressive measures to be taken to end Ebola epidemics before they spiral out of control and seriously deplete human population.

There is no certified cure for Ebola yet. Even the experimental drug-Zmapp which used to be effective is now said to be less effective [11]. This was discovered during the August 2018 Ebola outbreak in the DRC when about 50% of the patients given Zmapp died. For now, Ebola is mainly controlled through supportive care. This includes fluid and electrolyte replacement, blood pressure and blood gas monitoring, pain management, antibody and anti-malaria drug as needed [12]. Health experts have suggested many preventive measures including personal hygiene, infection control practices, public health education, and avoidance of hand shaking and administration of vaccination to the susceptible population [13 -16].

Mathematical models have been developed to figure out the interventions that can eradicate EVD. For instance, Legrand et al. [17] used a modified SEIR to showed that rapid implementation of barrier nursing within isolation ward and prompt hospitalization will reduce EVD within the hospital and the community. Rivers et al. [18] evaluated the impact of improved infection control and hypothetical pharmaceutical intervention on EVD. Harrison et al. [19] used a measles' SEIR pre – vaccination model with vital dynamics to study the 2014 Ebola outbreaks in Guinea, Liberia and Sierra – Leone. Okeke et al. [20] focused on diagnostic testing and ascertained that a decrease in the extent of the outbreak can be achieved when all feverish patients or health-care workers are tested on time. Camacho et al. [21] proposed that changes in behaviour of the people made a substantial reduction in both hospitals to community and within community transmission. Rachah and Torres [22] discussed the importance of optimal control strategy on the dynamics of EVD using SIR models with and without vaccination. In addition, Atangana and Goufo [23] developed an SIRD model and found that the population could die out in a very short period of time if there is no good prevention for a small portion of infected individuals. Webb et al. [24] modified a SEIR model for Ebola virus by incorporating contact

tracing term in their model while Li et al. [25] proposed a susceptible-exposed-infected-treatment (SEIT) model of Ebola virus transmission. Madubueze et al. [14] explored a mathematical model for EVD with contact tracing and quarantine measures. Their results showed that the implementation of contact tracing measure will eradicate EVD transmission in the population. Yarus [26] used an SIRD model to study the Ebola-Zaire dynamics, where D is number of dead cases. They suggest an inclusion of vaccination as control measure in the model. Based on the suggestion, this study extends the work by Yarus [26] by incorporating vaccination in the model since there is no approved medication against EVD and much works have not been done for the impact of vaccination for EVD using mathematical modelling approach. Although, Rachah and Torres [22], Brettin et al. [27], Area et al. [28] and Tulu et al. [29] considered vaccination in their work but the proportion of the population to vaccinated and vaccine wane off are not simulated and discussed in details. Since the whole population cannot be vaccine and vaccine wane off is possible, this study therefore consider vaccination as control measure in eradicating the spread EVD. It will find out how many proportion of population will be vaccine and how long people vaccinated are protected.

The rest of this work is organized as follows: In Section 2, we present the model formulation of Ebola with vaccination as a control strategy. Mathematical analysis of EVD model with the stability and sensitivity analyses of the model parameters are presented in Section 3. The numerical simulation was done in Section 4 while the result and discussion are presented in Section 5 and finally the conclusion is in Section 6.

2. MATERIALS AND METHODS

2.1 Model Formation. The model considered in this study is an extension of the work by Yarus [26] with additional assumption that the susceptible population is vaccinated against the virus. The total population, $N(t)$, at any time, t , is subdivided into Susceptible individuals, $S(t)$, Infected individuals, $I(t)$, Vaccinated individuals, $V(t)$, Recovered Individuals, $R(t)$ and Dead individuals, $D(t)$. The susceptible individuals acquire the infection through contact with the infected individuals at a rate, a and move to the infected class while the vaccination rate, $v \in [0,1]$, reduces the transmission rate, a . A proportion, δ , of the susceptible individuals are vaccinated at a rate, v , and progress to the vaccinated individuals, $V(t)$ where the vaccine wanes at a rate, ϕ . Infected individuals recover at a rate, b , or died of Ebola virus at a rate, e . We assumed that there is no permanent immunity for those that recovered of the virus. Thus, c is the rate at which the recovered individuals become susceptible again. We assume that the study is for short period as in the case of Ebola virus outbreak in Nigeria year, 2014. Therefore, natural death rate and birth rate are negligible in this study. The flow diagram of the model formulation is given in Figure 1.

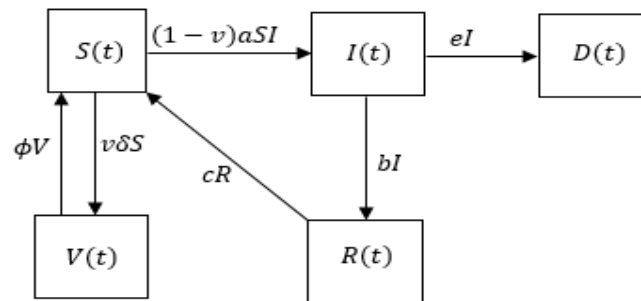


FIGURE 1. Systematic Diagram of the EVD Model.

With the description of the model, additional assumptions to the model of Yarus [26] and the systematic diagram in Figure 1, we present the model for this study as a system of differential equations

$$\left. \begin{aligned} \frac{dS}{dt} &= -(1-v)aSI - v\delta S + \phi V + cR \\ \frac{dI}{dt} &= (1-v)aSI - bI - eI \\ \frac{dV(t)}{dt} &= v\delta S - \phi V \\ \frac{dR(t)}{dt} &= bI - cR \\ \frac{dD(t)}{dt} &= eI \end{aligned} \right\} \quad (2.1)$$

with $S(0) > 0, I(0) \geq 0, V(0) \geq 0, R(0) \geq 0$ and $D(0) \geq 0$ as the initial conditions and $S + I + V + R + D = N$. Note that $\frac{dS}{dt} + \frac{dI}{dt} + \frac{dV}{dt} + \frac{dR}{dt} + \frac{dD}{dt} = \frac{dN}{dt} = 0$ which implies that N is a constant population.

2.2. Model analysis. For model analysis, consider the $S(t), I(t), V(t)$ and $R(t)$ subpopulations since $D(t)$ subpopulation will be determine from the other subpopulations, that is $D = N - S - I - V - R$.

2.2.1. Basic Reproduction number, R_0 . Basic reproduction number, R_0 , is a threshold parameter in mathematical epidemiology. It is the average number of secondary infections caused by a single infective person introduced in an entirely susceptible population during an entire infectious period. R_0 is said to measure the average number of secondary infections (cases) generated by a primary case in mostly susceptible individuals and is also an estimate of epidemic growth at the start of the outbreak if everyone is susceptible [30]. It has implications for disease elimination and persistence in the population. $R_0 > 1$ implies that the infection persists in the population while $R_0 < 1$ means the disappearance of the disease from the population. Basic Reproductive Number, R_0 , of system (2.1) is computed using the next generation method demonstrated in van den Driessche and Watmough [31] at disease-free equilibrium state.

The disease-free equilibrium, E_0 , of the system (2.1) is given by

$$E_0 = \left(S_0, 0, \frac{v\delta S_0}{\phi}, 0 \right). \tag{2.2}$$

Let X be vector of infected classes, such as Infected Individuals class in the study, F be vector of new infection rates of the infected classes, and U be vector of all other rates of the infected classes (not new infection rates).

Now, let $X = I(t)$, $F(X) = (1 - \delta)aSI$, $U(X) = (b + e)I$ and $\frac{dI}{dt} = F(X) - V(X)$. Taking the Jacobian of F and U around the disease-free equilibrium, E_0 , gives $\mathcal{F} = \left. \frac{\partial F}{\partial t} \right|_{E_0} = (1 - \delta)aS_0$ and $\mathcal{U} = \left. \frac{\partial U}{\partial t} \right|_{E_0} = b + e$ with $\mathcal{U}^{-1} = \frac{1}{b+e}$. So the matrix, $\mathcal{F}\mathcal{U}^{-1} = \frac{(1-\delta)aS_0}{b+e}$.

Basic reproduction number, R_0 , which is the spectral radius or maximum eigenvalues of the matrix, $\mathcal{F}\mathcal{U}^{-1}$ is given as

$$R_0 = \frac{(1-v)aS_0}{b+e}. \tag{2.3}$$

2.2.2. Stability analysis of disease-free equilibrium, E_0 . The disease-free equilibrium, E_0 , is established by solving simultaneously the system (2.1) at equilibrium state, that is $\frac{ds}{dt} = \frac{dI}{dt} = \frac{dV}{dt} = \frac{dR}{dt} = \frac{dD}{dt} = 0$. This gives the disease-free equilibrium, E_0 , of equation (2.2).

Theorem 1. The disease-free equilibrium, E_0 , is locally asymptotically stable if $R_0 < 1$ otherwise unstable for $R_0 > 1$.

Proof. Using the linearization method, we have the Jacobian matrix at E_0 of the system (2.1) given as

$$J(E_0) = \begin{bmatrix} -v\delta & -(1-v)aS_0 & \phi & c \\ 0 & (1-v)aS_0 - (b+e) & 0 & 0 \\ v\delta & 0 & -\phi & 0 \\ 0 & b & 0 & -c \end{bmatrix}.$$

The nonzero eigenvalues of the Jacobian matrix, $J(E_0)$, are $-c$, $(1 - v)aS_0 - (b + e)$ and $-(v\delta + \phi)$. The matrix, $J(E_0)$, has negative eigenvalues if $(1 - v)aS_0 - (b + e) < 0$ which implies that $\frac{(1-v)aS_0}{b+e} < 1$. Thus with the definition of R_0 in equation (2.3), we have that the disease-free equilibrium, E_0 , is locally stable if $R_0 < 1$ otherwise it is unstable.

Theorem 2. The disease-free equilibrium, E_0 , is globally asymptotically stable if $R_0 < 1$ otherwise unstable for $R_0 > 1$.

Proof. Using the approach in Shuai and Van den Driessche [32] to construct a Lyapunov function of the form

$$L = \frac{1}{b+e} I.$$

We differentiate L along the trajectory of system (2.1) to give

$$L' = \frac{1}{b+e} I',$$

and this yields

$$L' = \frac{1}{b+e} ((1 - \nu)aSI - (b + e)I). \quad (2.4)$$

Simplifying and expanding equation (2.4) gives

$$L' = \left(\frac{(1-\nu)aS}{b+e} - 1 \right) I.$$

Further simplification with definition of R_0 in equation (2.3) yields

$$L' = \left(\frac{(1-\nu)aS_0}{b+e} - 1 \right) I - \frac{(1-\nu)aS_0}{b+e} \left(\frac{S_0}{S} - 1 \right) I,$$

which is equivalent to

$$L' = (R_0 - 1)I - R_0 \left(\frac{S_0}{S} - 1 \right) I. \quad (2.5)$$

Thus, $L' < 0$ if $R_0 < 1$ since $\frac{S_0}{S} \geq 1$ and $L' = 0$ if $I = 0$. This shows that every solutions of the system (2.1) tends to the singleton set E_0 as $t \rightarrow \infty$. Therefore, by La Salle's invariance principle [33], the disease-free equilibrium, E_0 , is globally asymptotically stable whenever $R_0 < 1$. This completes the proof.

2.3. Sensitivity analysis. Sensitivity Analysis (SA) is performed to determine the robustness of the model predictions to parameter values since there are usually many errors in data collection and the parameter values are assumed [34]. It also determines the relative importance of model parameters on disease transmission [35]. Sensitivity analysis will enable us to find out the parameters that have high impact on R_0 which should be the targeted in case of intervention strategies.

The sensitivity index of a variable, γ that depends differentiable on index of a parameter, p is defined as $r_p^\gamma = \frac{\partial \gamma}{\partial p} \times \frac{p}{\gamma}$.

Analytically, we derive the expression for the SA of R_0 as $r_p^{R_0} = \frac{\partial R_0}{\partial p} \times \frac{p}{R_0}$, where p denotes each of parameters of R_0 . We therefore compute sensitivity indices of every parameters in R_0 and display them in Table 1 with the sources of the parameter values.

TABLE 1. Sensitivity indices of R_0

Parameter	Value	Source	Index sign	Sensitivity value
ν	0.6	[19]	-	1.5
a	0.160	[14]	+	1.0
S_0	0.6	Assumed	+	0.999999997
e	0.0301653	[14]	-	0.3316133
b	0.0608	[14]	-	0.6683867361

The sensitivity indices of R_0 given in Table 1 are arranged in descending order. The indices with positive signs show that the value of R_0 increases when corresponding parameters are increased while those indices having negative signs show that the value of R_0 decreases when the parameters are increased. Hence from the results shown in Table 1, we have that the parameters a and S_0 increase the value of R_0 when they are increased which means the disease will persist in the population. Conversely, the parameters, b, e and ν decrease the value of R_0 when they are increased, implying that the virus will die out in the population in this regard. The most sensitivity parameter is the vaccination rate, ν , with negative index sign follow by transmission rate, a . This implies that increasing the vaccination rate decreases the basic reproduction number, R_0 which in return eliminate EVD in the population while increasing the transmission rate increases R_0 and this increases the spread of EVD in the population. This is shown in Figure 2 that increasing vaccination rate, ν , decreases R_0 while increasing the transmission rate, a , increases R_0 .

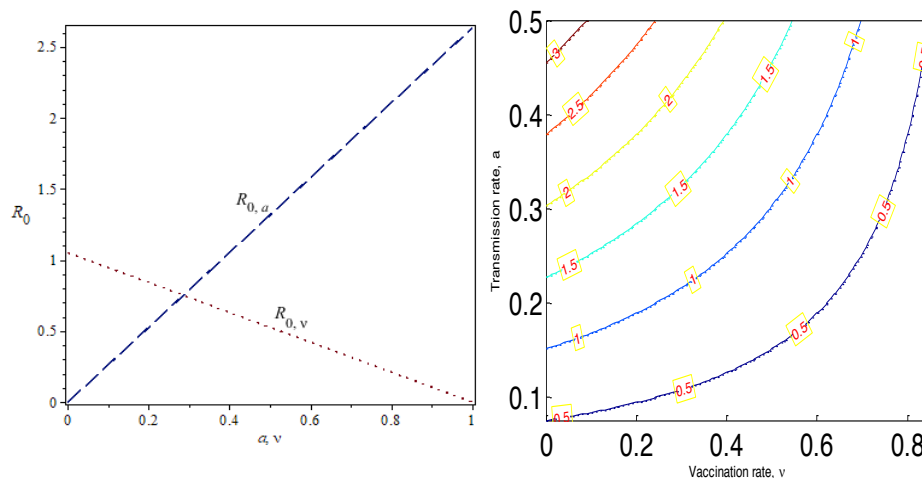


FIGURE 2. Plots displaying the basic reproduction number, (R_0) as function of transmission rate, (a) and vaccination rate, (ν). Here, $R_{0\nu}$ and R_{0a} are the reproduction numbers when the parameters, ν and α are varied.

3. NUMERICAL SIMULATIONS

In this section, we perform numerical experiments of the system (2.1) using the parameter values in Table 1 and $c = 0.0314862$ [14], $\delta \in [0,1]$ varied and $\phi = 0.1$ (assumed). This is solved using the fourth order Runge-Kutta method embedded in MatLab of Ode45. The choice of parameter values is to validate the analytic solutions and to show the impact of vaccination on Ebola virus disease dynamics. Using the values from the Table 1, we have $R_0 = 0.42214$ with vaccination while $R_0 = 1.05535$ without vaccination.

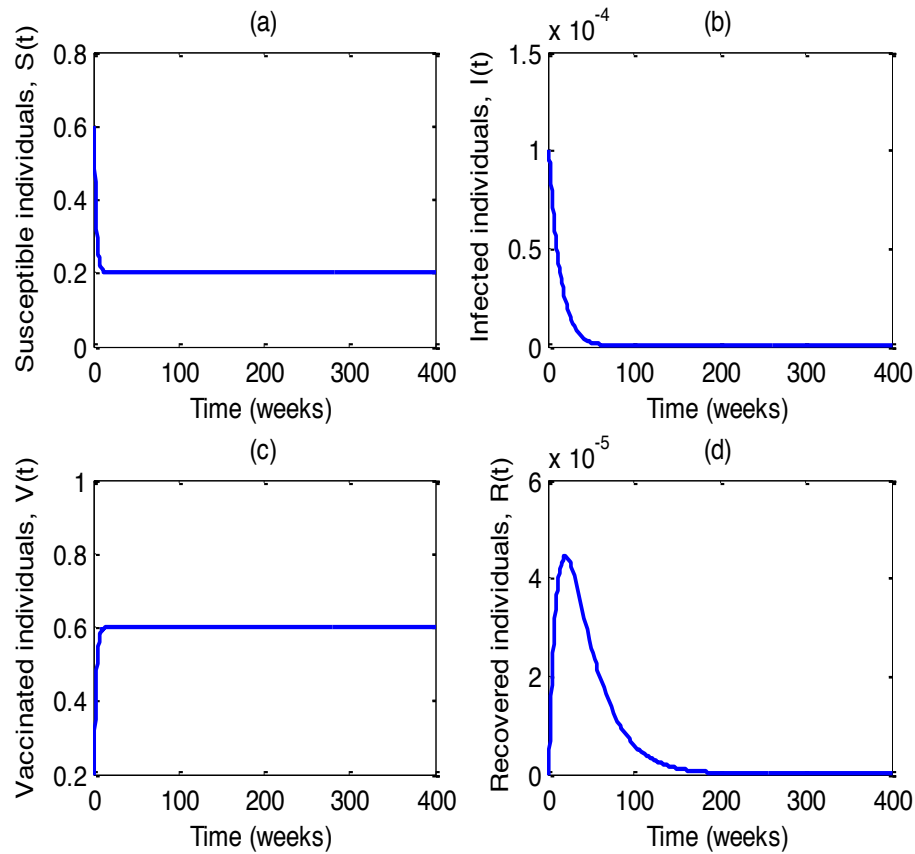


FIGURE 3. Plots displaying the disease-free equilibrium solutions of system (2.1).

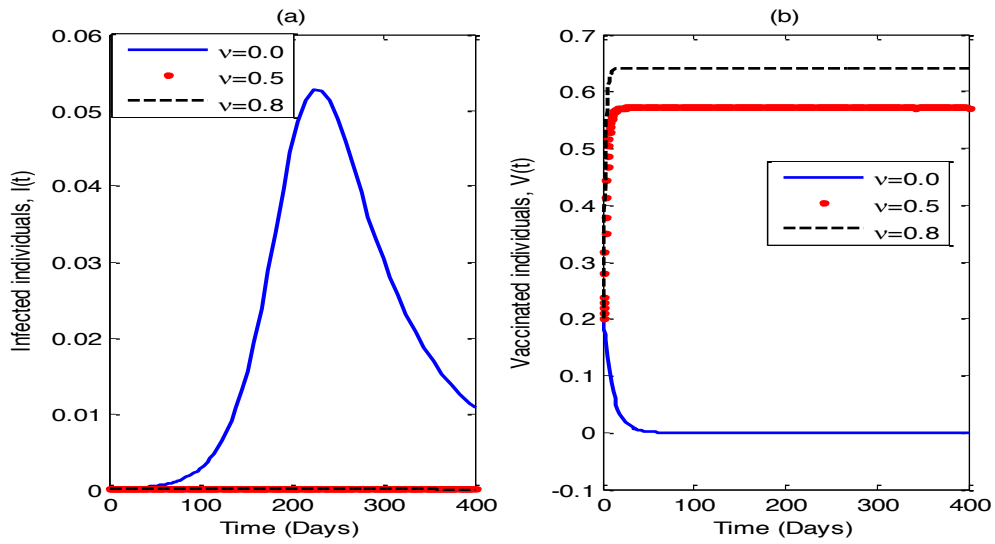


FIGURE 4. Plots showing the effect of vaccination on the infected and vaccinated individuals.

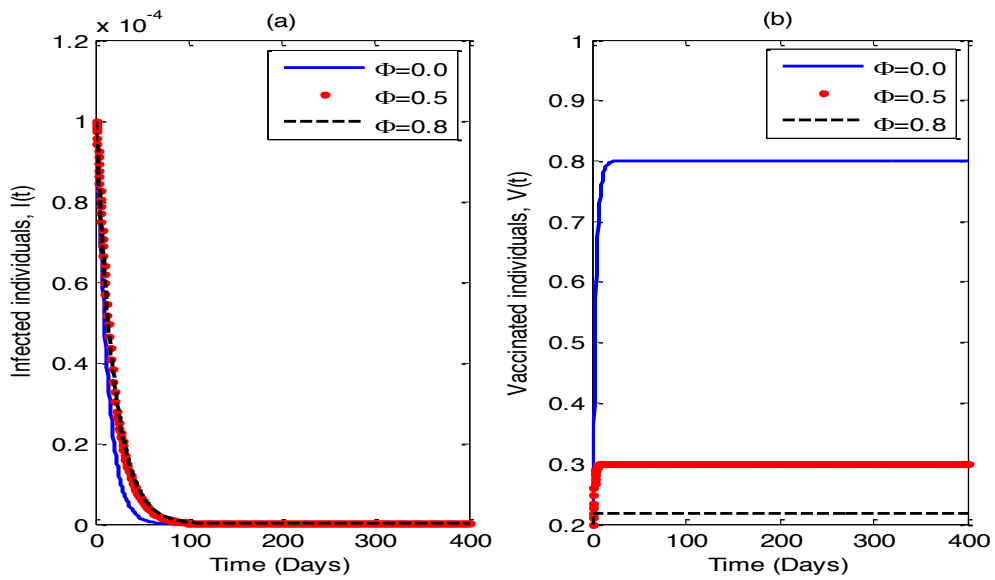


FIGURE 5. Plots showing the effect of vaccine wane on the infected and vaccinated individuals.

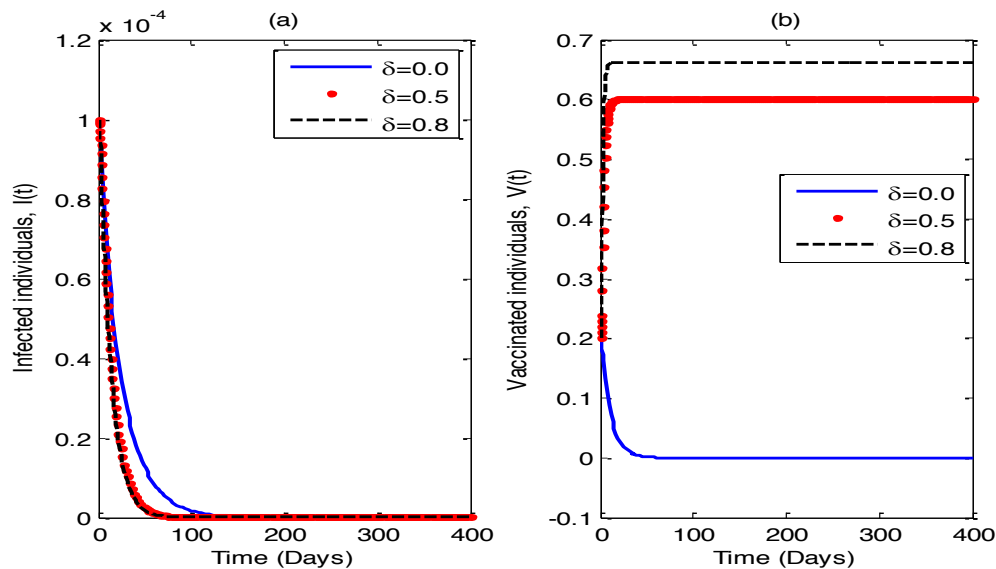


FIGURE 6. Plots showing the proportion of people vaccinated on the infected and vaccinated individuals.

4. RESULTS AND DISCUSSION

Figure 3 displays the stable disease-free equilibrium solution of system (2.1) in the presence of vaccination. We see from Figure 3 that disease-free equilibrium solution is achieved. The population of susceptible (vaccinated) individuals decreases (increases) to a point and remains stable while the Infected population, $I(t)$, decreases sharply and approaches a stable disease-free equilibrium state (see Figure 3(b)) showing elimination of EVD with vaccination in the population. This is the same with the recovery individuals in population that is in the absence of infectives in the population, the recovered population will approach disease-free population after 200 weeks (see Figure 3(d)). It shows that the number of infected individuals reduces with vaccination in place.

The effect of increasing vaccination rate is depicted in Figure 4. We observe that increasing the vaccination rate reduces the number of infected persons while increasing the vaccinated population. For example in the absence of vaccination ($v = 0.0$), the infected population increases sharply and before gradually reduces and becomes endemic in the population (see Figure 4(b)). It also shows that once people are vaccinated in the population against EVD, they are protected and this will reduce the number of infected population and in return lead to eradication of EVD in the population. Figure 5 illustrates the effect of vaccine wane off on the infected and vaccinated individuals. As the waning rate, ϕ , increases, efficacy of the vaccine sags, thus elongating the reduction time of the infected people but not drastically. For instance, a vaccine without waning rate, ($\phi = 0.0$), that is a highly efficacious vaccine reduces the population of Infected Individuals, $I(t)$, in a very short time while increasing the vaccinated people in the population. So, it is not just vaccinating people but it is also good to use vaccine that does not wane in order to achieve the aim of

vaccination. This makes the vaccinated persons to stay protected for long period of time against EVD. Furthermore, the importance of vaccinating more people in the population is considered in Figure 6. It shows that the more people are vaccinated, the more it reduces the number of infected population and increases the vaccinated population and this shows that more people are protected against EVD. So once there is an outbreak of EVD, a good proportion of population should be vaccinated to reduce the spread of EVD in population and the vaccine should be a zero wane vaccine in order to halt the spread of EVD from affecting the population.

5. CONCLUSION

In this work, the important of vaccination is considered by extending the model by Yarus [27]. The basic reproduction number R_0 , is computed using next generation method and it is used to show how vaccine controls the spread of EVD in the population. We observed that R_0 is less than unity in the presence of vaccination while greater than unity in the absence of vaccination. The stability of disease-free equilibrium is analyzed and shown to be locally and globally asymptotically stable whenever $R_0 < 1$ but unstable whenever $R_0 > 1$. Furthermore, the sensitivity analysis is carried out to discuss the importance of the model parameters on R_0 and the result indicates that vaccination rate is the most sensitivity parameter of the model and increasing it will reduce the number of infected individuals in the population. This is supported by numerical simulation which shows that the number of infected persons reduces when more people are vaccinated in the population. Additionally, more people are protected when they are vaccinated with zero wane off vaccine which in return reduce infected population. This will lead to eradication of EVD in the population on time and makes the vaccinated persons to stay protected for long period of time against EVD.

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Authors' Conflicts of interest. The authors declare no conflict of interest, financial or otherwise.

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