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MATHEMATICAL MODEL ANALYSIS FOR THE TRANSMISSION DYNAMICS OF BACTERIAL MENINGITIS DISEASE INCORPORATING DRUG-RESISTANCE CLASS

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Abstract. In this paper, a deterministic compartmental bacterial meningitis model including drug resist class is formulated. Primarily, the invariant region and positivity of solutions of the model, the equilibria and their stability are examined. The effective reproduction number (R_{ef}) of the system also computed using Routh-Hurwize criteria. From the stability analysis studied the disease free equilibrium (DFE) is both locally and globally asymptotically stable. The center manifold theory is used to examined the local stability of endemic equilibrium (EE), and the system shows forward bifurcation at $R_{ef} = 1$. With the help of normalized forward sensitivity index approach, the most influential parameters on the system are identified. Simulations of the model are performed using fourth-order Runge-Kutta method to demonstrate stability behaviours of DFE and EE as well as the impact of the most sensitive parameters on the bacterial meningitis disease transmission, which are presented graphically. These results showed that as time goes large trajectories of the state variables are close to DFE whenever $R_{ef} < 1$, and a unique EE when $R_{ef} > 1$, respectively. Moreover, decreasing effective transmission per contact rate, enhancing vaccine uptake rate for susceptible individuals, increasing first line treatment rate for infected and second line treatment rate for drug-resistance individuals using suitable measure mechanisms have a powerful role in reducing the burden of bacterial meningitis disease in the community.

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1. INTRODUCTION

Meningitis is an attack of the meninges which are membranes that shields the brain and the spinal cord. This disease is caused by different organisms like; viruses,bacteria, parasites, protozoa, and fungi, while the seriousness of the disease is depend on the organism causing the disease [1, 2]. Bacterial meningitis is a serious disease if not diagnosed and treated early. It is mainly spread from one individual to another through coughing, sneezing, or closed contact with an individual who carries the bacterium [3]. The main pathogens that can motive bacterial meningitis are *Neisseria meningitidis (meningococcal meningitis), Streptococcus pneumoniae (pneumococcal meningitis), Haemophilus influenzae (haemophilus meningitis), Group B Streptococcu, Listeria monocytogenes* , *Escherichia coli*and *Myobacterium tuberculosis (Tuberculous meningitis)*. Among these pathogens the most significantly recognized types of bacteria that caused bacterial meningitis are *Streptococcus pneumoniae*, which is primarily found in the respiratory tract, sinuses, and nasal pit; *Neisseria meningitidis* is transmit through saliva and other respiratory fluids [4, 5].

Even though bacterial meningitis is endemic across the world, the majority occur in Sub-Saharan Africa in the area called the meningitis belt, which includes 26 countries. This epidemic region spans across from Senegal in the west to Ethiopia in the east with 1.2 million people affected each year, 135,000 of which are fatal. The case mortality rate can be from 3% to 10% in developed countries, and as high as 20% in Africa meningitis belt countries, and up to 20% of survivors developing neurological sequelae like deafness, epilepsy, cerebral palsy, speech disorders, loss of limbs, and mental retardation [6, 7].

Quick detection and early use of a proper vaccine against the predominant bacterial meningitis is the best way to control the disease. An important and mandatory examination for bacterial meningitis is Cerebrospinal fluid (CSF) examination. After obtaining CSF using lumbar puncture; administrating antibiotics like, penicillin, cephalosporin, and ciprofloxcin are among the

important treatments of bacterial meningitis infected individuals. But nowadays, these antibiotics are ineffective against *pneumococcal meningitis*, *meningococcal meningitis* and *Tuberculous meningitis*. According to [8], out of $4,122$ meningocaccal meningitis disease caused by *Neisseria meningitidis* isolates, 113 were penicillin-resistant, five were ciprofloxacin-resistant, two were rifampicin-resistant, and one was cefotaximeresistant; moreover *Streptococcus pneumoniae* is also resistance to one or more clinically relevant antibiotics in more than 30% of cases [9]. Thus, the efficiency of globally available antibiotics is endangered by the universal emergence of multidrug-resistance bacteria like *Streptococcus pneumoniae* and *Neisseria meningitidis* [10, 11]. It is, therefore, important to study the dynamics of bacterial meningitis disease incorporating drug-resistance class.

A mathematical model is a crucial tool in understanding how diseases spread and are transmitted. It can also be used to forecast how diseases will affect communities; explain key aspects of the disease transmission process; suggest efficient control and prevention strategies; and estimate the severity and potential scope of an epidemic [12]. Several mathematical models have been investigated in order to study the dynamics of bacterial meningitis disease. In this regards, [13] constructed a non-linear compartmental mathematical model for transmission of bacterial meningitis with two control strategies vaccine and treatment; where the whole population was divided into four classes: susceptible, carrier, ill individuals and recovered individuals. Results of their study concluded that the bast way to regulate bacterial meningitis was mixing use of vaccine, treatment and public health education. The work done by [14] proposed SCIR model of meningococcal meningitis disease with variable total population size. According to his simulation results, control measures that can lower the rate of disease transmission and immunity waning as well as raise the rate of vaccination and treatment success would be successful in containing and possibly curing the meningitis epidemic. Agusto & Leite [15], studied a Mathematical model of bacterial meningitis outbreaks in Nigeria by classifying the total population into five classes namely: susceptible, vaccinated, carrier, infected and recovered. They obtained from the sensitivity analysis of the basic reproductive number suggested that identification of transmission probability per contact, the recovery rate of the carrier population, the vaccine efficacy rate, and the disease progression rate were had high impact on disease transmission.

The research worked by [16] constructed a deterministic mathematical model for transmission of bacterial meningitis by incorporating standard incident rate and non-linear recovery rate. Numerical results suggested that suppressing bacterial meningitis in an endemic environment, the efficient providing of successful antibiotics for treatment with efficient providing of hospital beds including vaccine was much better than concentrating on only vaccine or providing of hospital beds. Similarly, [17] proposed a deterministic compartmental model of bacterial meningitis disease depending on susceptible-vaccination-carrier-infected-treated-recovered. Examined from sensitivity analysis an increase in vaccine waning, modification parameter of infectiousness the carrier population, progression rate from carrier to infected, and transmission probability will increase the spread of the disease. Moreover, results from numerical simulation indicated that disease can be eradicated with effective vaccination and treatment. Afolabi [18] created a mathematical model to illustrate how effective contact rate affects the transmission dynamics of bacterial meningitis disease. Their simulation analysis demonstrated that effective contact rate has a positive impact on increasing basic reproduction number. Other researchers such as [19, 20, 21, 22, 23] have also studied on dynamics of bacterial meningitis disease.

In this study, we proposed a model for bacterial meningitis adopted from [15] by incorporating drug-resistant compartment, which is different from models mentioned above. Considering this new compartment together with other two infectious classes namely, carrier and infected classes are more useful to study the dynamics of this disease. The model we consider is formulated based on bacterial meningitis transmission among population. This paper is organized as follows. In section 2, the description of state variables and parameters, and model formulation are done. In section 3, we study the qualitative analysis those are, positivity and boundedness of the system; stability of disease free and endemic equilibrium points; and sensitivity analysis of the effective reproduction number. In section 4, simulation analysis of the system is done. We generalized in section 5 with conclusions.

2. Model Formulation

In this section, we develop a non-linear compartmental mathematical model for the transmission process of bacterial meningitis epidemic. The total population at the time t, denoted by $N(t)$, and partitioned it into six independent epidemiological classes such as, $S(t)$, $C(t)$, $I(t)$,

$V(t)$,$D_r(t)$ and $R(t)$. Hence, the total population defined as follows.

$$N(t) = S(t) + C(t) + V(t) + I(t) + D_r(t) + R(t) \tag{1}$$

Moreover, description of the variables of the model are in the Table 1 below:

TABLE 1. Description of Variables of the bacterial meningitis disease model

Variable	Description
$S(t)$	The susceptible individuals; Individuals who are not yet infected, but will be infected easily,
$C(t)$	Carrier individuals; Individuals who are infectious but not showing symptoms,
$I(t)$	Infected individuals;Individuals who are infectious and showing symptoms,
$V(t)$	Vaccinated individuals; Those who have immunity from the disease,
$D_r(t)$	Drug resistant individuals; Individuals who adopting the first line antibiotics of bacterial meningitis,
$R(t)$	Recovered individuals; Those individuals have recovered from the disease and have got temporary immunity.

In the development of the model, the following assumptions are made:

(i) We assume that new entry to susceptible populations may be newborns or immigrants at the constant rate of Π,

(ii) Disease induce death rate exists at $I(t)$ compartment,

(iii) Both susceptible and vaccinated classes are infected through interaction of carrier, symptomatically, infected or drug resist individuals.

(iv) There is a homogeneous mixing between populations,

(v) Recovered individuals can be reinfected,

(vi) All parameters are non-negative.

The model assumes that a fraction of the population was vaccinated at a rate of $\kappa\Pi$ before the illness breakout, and the remaining individuals $(1-\kappa)\Pi$ are susceptible, where Π recruitment rate and κ is the proportion of vaccinated. Susceptible class is infected through carrier, symptomatically infected or drug resist individuals with a force of infection $\lambda = \beta(q_1 C + q_2 I + q_3 D_r)$, where $0 < q_1 < 1$, $0 < q_3 < 1$, and $0 < q_2 \leq 1$ are the modification parameters of C, D_r and I respectively and β is the effective transmission probability per contact.

Populations in the infected class can recover at a per capita rate of η with α proportion of populations join the recovered class by use of proper treatment or join the drug resist class

with $(1-\alpha)$ proportion,because of improper use of treatment. Since the vaccine does not provide immunity to all vaccine recipients, vaccinated people become infected at a lesser rate than unprotected people with force of infection $\varepsilon\lambda$, where ε is the proportion of the serotype not covered by the vaccine. and $0 < \varepsilon < 1$. Further explanation of parameters in the model are described in the Table 2 below:

TABLE 2. Description of parameters of Bacterial Meningitis Disease model

Parameter	Description
Π	The recruitment rate of susceptible populations
μ	Natural death rate
σ	The death rate due to the disease at infected class
ϑ	Rate of recovery individuals waning immunity
δ	Rate of carrier move to infected class by developing symptoms or screen themselves
ω	Natural recovery rate from carrier class
θ	Recovery rate after second line treatment
γ_1	Vaccine waning rate
γ_2	Vaccine uptake rate

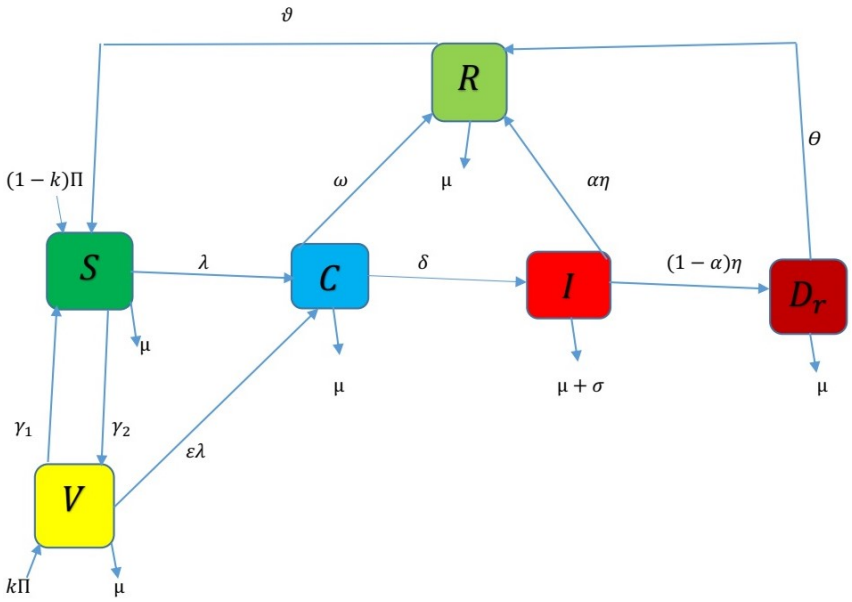

FIGURE 1. *Compartmental flow diagram of bacterial meningitis disease transmission*

From the Figure 1, we can obtain the following non-linear first order system of ordinary differential equations:

$$
\begin{cases}
\dfrac{dS}{dt} = \Pi(1-\kappa) + \vartheta R + \gamma_1 V - (\lambda + \mu + \gamma_2)S \\
\dfrac{dV}{dt} = \Pi\kappa + \gamma_2 S - (\mu + \varepsilon\lambda + \gamma_1)V \\
\dfrac{dC}{dt} = \lambda S + \varepsilon\lambda V - (\delta + \omega + \mu)C \\
\dfrac{dI}{dt} = \delta C - (\eta + \sigma + \mu)I \\
\dfrac{dD_r}{dt} = (1-\alpha)\eta I - (\theta + \mu)D_r \\
\dfrac{dR}{dt} = \omega C + \alpha\eta I + \theta D_r - (\vartheta + \mu)R
\end{cases} \tag{2}
$$

With the initial conditions: $S(0) = S_0 \geq 0$,$C(0) = C_0 \geq 0$,$I(0) = I_0 \geq 0$,$V(0) = V_0 \geq 0$,$D_r(0) = D_{r,0} \geq 0$,and $R(0) = R_0 \geq 0$.

3. Model Analysis

3.1. Invariant Region.

Theorem 1. *All solutions of bacterial meningitis model in* (2) *remains in* $\Omega_m = \left\{(S,V,C,I,D_r,R) \in R_+^6 : 0 \leq N(t) \leq \frac{\Pi}{\mu}\right\}$.

Proof: The total population at any time t is given by

$$N(t) = S(t) + C(t) + V(t) + I(t) + D_r(t) + R(t) \tag{3}$$

After differentiating both sides of N and we obtained,

$$\frac{dN}{dt} = \frac{dS}{dt} + \frac{dV}{dt} + \frac{dC}{dt} + \frac{dI}{dt} + \frac{dD_r}{dt} + \frac{dR}{dt} = \Pi - \mu N - \sigma I \tag{4}$$

Since the parameter σ, and the state variable I are non-negative in (4), we have

$$\frac{dN}{dt} \leq \Pi - \mu N \tag{5}$$

Using separation of variables rule equation (5) changes to,

$$\frac{dN}{\Pi - \mu N} \leq dt \tag{6}$$

By the help of [24] integrating both sides of equation (6),

$$\int \frac{dN}{\Pi - \mu N} \leq \int dt \tag{7}$$

After further simplification and applying the initial condition $N(0) = N_0$ we get,

$$N \leq \frac{\Pi}{\mu} - \frac{1}{\mu}(\Pi - \mu N_0)e^{-\mu t} \tag{8}$$

As $t \to \infty$ in equation (8) the population size $N \to \frac{\Pi}{\mu}$, which implies that $0 \leq N \leq \frac{\Pi}{\mu}$. Thus the feasible solution of set of the system equation of the model enter and remain in the region:

$$\Omega_m = \left\{ (S,V,C,I,D_r,R) \in R_+^6 : 0 \leq N \leq \frac{\Pi}{\mu} \right\} \tag{9}$$

Hence, the model is well posed epidemiologically as well as mathematically. Hence, it is sufficient to study the dynamics of the basic model in Ω_m.

3.2. Positivity of Solutions.

Theorem 2. *Let* $\Omega_m(0) = \Big(S(0),V(0),C(0),I(0),D_r(0),R(0)\Big) \in R_+^6$ *be the initial condition for the model* (2)*. Then, the set of solutions* $\Big\{S(t),V(t),C(t),I(t),D_r(t),R(t)\Big\}$ *of the model is non-negative for all* $t > 0$*.*

Proof: Let $t_1 = \sup\Big\{t > 0 : S(t_0) > 0, V(t_0) > 0, C(t_0) > 0, I(t_0) > 0, D_r(t_0) > 0, R(t_0) > 0, \forall t_0 \text{ in } [0,t]\Big\}$. From the system of the differential equation in (2) let us take each equation step by step. From the first equation of model (2), it follows that,

$$\frac{dS}{dt} + \big(\lambda(t) + \mu + \gamma_2\big)S = \Pi(1-\kappa) + \vartheta R(t) + \gamma_1 V(t)$$

Which can be rewritten as,

$$\frac{d}{dt}\left[S(t)e^{(\mu+\gamma_2)t+\int_0^t \lambda(m)dm}\right] = \Big(\Pi(1-\kappa) + \vartheta R(t) + \gamma_1 V(t)\Big)e^{(\mu+\gamma_2)t+\int_0^t \lambda(m)dm}.$$

Hence,

$$S(t_1)e^{(\mu+\gamma_2)t_1+\int_0^{t_1} \lambda(m)dm} - S(0) = \int_0^{t_1} \left(\Pi(1-\kappa) + \vartheta R(z) + \gamma_1 V(z)\right)\left[e^{(\mu+\gamma_2)z+\int_0^z \lambda(m)dm}\right]dz.$$

Therefore,

$$S(t_1) = S(0)e^{(-\mu-\gamma_2)t_1-\int_0^{t_1}\lambda(m)dm}+$$
$$\left[e^{(-\mu-\gamma_2)t_1-\int_0^{t_1}\lambda(m)dm}\right]\times\int_0^{t_1}\left(\Pi(1-\kappa)+\vartheta R(z)+\gamma_1 V(z)\right)\left[e^{(\mu+\gamma_2)z+\int_0^{z}\lambda(m)dm}\right]dz\geq 0.$$

Taking the second equation from (2),

$$\frac{dV}{dt}+(\gamma_1+\varepsilon\lambda+\mu)V=\Pi\kappa+\gamma_2 S$$

We can write it as follows,

$$\frac{d}{dt}\left[V(t)e^{(\mu+\gamma_1)t+\int_0^{t}\varepsilon\lambda(m)dm}\right]=\left(\Pi\kappa+\gamma_2 S(t)\right)e^{(\mu+\gamma_1)t+\int_0^{t}\varepsilon\lambda(m)dm}.$$

Thus,

$$V(t_1)e^{(\mu+\gamma_1)t_1+\int_0^{t_1}\varepsilon\lambda(m)dm}-V(0)=\int_0^{t_1}\left(\Pi\kappa+\gamma_2 S(z)\right)\left[e^{(\mu+\gamma_1)z+\int_0^{z}\varepsilon\lambda(m)dm}\right]dz.$$

Therefore,

$$V(t_1) = V(0)e^{(-\mu-\gamma_1)t_1-\int_0^{t_1}\varepsilon\lambda(m)dm}+$$
$$\left[e^{(-\mu-\gamma_1)t_1-\int_0^{t_1}\varepsilon\lambda(m)dm}\right]\times\int_0^{t_1}\left(\Pi\kappa+\gamma_2 S(z)\right)\left[e^{(\mu+\gamma_1)z+\int_0^{z}\varepsilon\lambda(m)dm}\right]dz\geq 0.$$

Let us take the third equation of the model

$$\frac{dC}{dt}=\lambda S+\varepsilon\lambda V-(\delta+\omega+\mu)C$$
$$\frac{dC}{dt}\geq-(\mu+\delta+\omega)C$$

By separation of variable

$$\frac{dC}{C}\geq-(\mu+\delta+\omega)dt$$
$$\ln\mid C\mid\geq-(\mu+\delta+\omega)t+m_3$$
$$C(t)\geq A_3e^{-(\mu+\delta+\omega)t}$$

Applying the initial condition $C(0)$ to obtained the value A_3,

$$C(t)\geq C(0)e^{-(\mu+\delta+\omega)t}\geq 0$$

Similarly,

$$\begin{cases} I(t) \geq I(0)e^{-(\eta+\sigma+\mu)t} \geq 0, \forall t \geq 0, \\ D_r(t) \geq D_r(0)e^{-(\theta+\mu)t} \geq 0, \forall t \geq 0, \\ R(t) \geq R(0)e^{-(\vartheta+\mu)t} \geq 0, \forall t \geq 0. \end{cases} \tag{10}$$

Therefore, all solutions of the system in (2) remain non-negative for all non-negative initial conditions.

3.3. Disease Free Equilibrium. It is a point at which the epidemic is eradicated from the population. By setting the left sides of systems of ordinary differential equations in (2) to zero and substituting zero to all infective class variables we obtain,

$$\Pi(1-\kappa) + \gamma_1 V - (\mu+\gamma_2)S = 0 \tag{11}$$

$$\Pi\kappa + \gamma_2 S - (\mu+\gamma_1)V = 0 \tag{12}$$

By using equation (11) and (12) simultaneously we obtain

$$S^0 = \frac{\Pi(\mu(1-\kappa)+\gamma_1)}{\mu(\mu+\gamma_1+\gamma_2)} = \frac{\Pi D_1}{\mu}, D_1 = \frac{\mu(1-\kappa)+\gamma_1}{(\mu+\gamma_1+\gamma_2)}$$

$$V^0 = \frac{\Pi(\kappa\mu+\gamma_2)}{\mu(\mu+\gamma_1+\gamma_2)} = \frac{\Pi D_2}{\mu}, D_2 = \frac{\kappa\mu+\gamma_2}{(\mu+\gamma_1+\gamma_2)}$$

Hence the disease free equilibrium point is given by $E_0 = (S^0, V^0, 0, 0, 0, 0) = \left(\frac{\Pi D_1}{\mu}, \frac{\Pi D_2}{\mu}, 0, 0, 0, 0\right)$. We used Routh-Hurwiz criteria to compute the effective reproduction number(R_{ef}). It can be obtained from the constant term of the characteristics equation after computing the Jacobian of the system at the disease free equilibrium [25].

Computing the Jacobian of (2) at the disease- free equilibrium gives,

$$J(E_0) = \begin{bmatrix} -m_1 & \gamma_1 & -\beta q_1 S^0 & -\beta q_2 S^0 & -\beta q_3 S^0 & \vartheta \\ \gamma_2 & -m_6 & -\varepsilon\beta q_1 V^0 & -\varepsilon\beta q_2 V^0 & -\varepsilon\beta q_3 V^0 & 0 \\ 0 & 0 & \beta q_1 m_2 - m_4 & \beta q_2 m_2 & \beta q_3 m_2 & 0 \\ 0 & 0 & \delta & -m_7 & 0 & 0 \\ 0 & 0 & 0 & m_8 & -m_5 & 0 \\ 0 & 0 & \omega & \alpha\eta & \theta & -m_9 \end{bmatrix} \tag{13}$$

Where $m_1 = (\mu+\gamma_2), m_2 = S^0 + \varepsilon V^0, m_4 = \delta+\mu+\omega, m_5 = \theta+\mu, m_6 = \mu+\gamma_1, m_7 = \eta+\sigma+\mu, m_8 = (1-\alpha)\eta, m_9 = \vartheta+\mu$.

Expanding the determinant of the characteristic equation $| J(E_0) - \lambda I | = 0$ by the first column twice and then by the last column, respectively, gives equation (14).

$$[(-m_1-\lambda)(-m_6-\lambda)-\gamma_1\gamma_2](m_9+\lambda)\begin{vmatrix} \beta q_1 m_2 - m_4 - \lambda & \beta q_2 m_2 & \beta q_3 m_2 \\ \delta & -m_7-\lambda & 0 \\ 0 & m_8 & -m_5-\lambda \end{vmatrix} = 0 \tag{14}$$

We can rewrite equation (14) as follows.

$$[(-m_1-\lambda)(-m_6-\lambda)-\gamma_1\gamma_2](m_9+\lambda) = 0 \tag{15}$$

Or

$$\begin{vmatrix} \beta q_1 m_2 - m_4 - \lambda & \beta q_2 m_2 & \beta q_3 m_2 \\ \delta & -m_7-\lambda & 0 \\ 0 & m_8 & -m_5-\lambda \end{vmatrix} = 0 \tag{16}$$

The characteristic equation of (16) after simplification gives equation (17).

$$\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0 \tag{17}$$

Where,

$$a_1 = m_5 + m_7 + m_4 - \beta q_1 m_2$$

$$a_2 = m_7 m_5 + m_4(m_7 + m_5) - \beta q_1 m_2(m_7 + m_5) + \delta\beta q_2 m_2$$

$$a_3 = m_4 m_7 m_5 - \beta q_1 m_2 m_7 m_5 - \delta\beta q_2 m_2 m_5 - \delta\beta q_3 m_2 m_8$$

The condition $R_{ef} < 1$ should be equivalent to the condition $a_3 > 0$, hence, we define the effective reproductive number of the model in (2) as follows.

$$m_4 m_7 m_5 - \beta q_1 m_2 m_7 m_5 - \delta\beta q_2 m_2 m_5 - \delta\beta q_3 m_2 m_8 > 0$$

$$m_4 m_7 m_5 > \beta q_1 m_2 m_7 m_5 + \delta\beta q_2 m_2 m_5 + \delta\beta q_3 m_2 m_8$$

$$1 > \frac{\beta q_1 m_2}{m_4} + \frac{\delta\beta q_2 m_2}{m_4 m_7} + \frac{\delta\beta q_3 m_2 m_8}{m_4 m_7 m_5}$$

$$R_{ef} = \frac{\beta q_1 m_2}{m_4} + \frac{\delta\beta q_2 m_2}{m_4 m_7} + \frac{\delta\beta q_3 m_2 m_8}{m_4 m_7 m_5}$$

After substitution the values of m_2, m_4, m_5 and m_7 the effective reproduction number becomes,

$$\begin{aligned}
R_{ef} &= \left(\frac{\beta q_1}{\delta+\mu+\omega} + \frac{\delta\beta q_2}{(\delta+\mu+\omega)(\eta+\sigma+\mu)} + \frac{\delta\beta q_3(1-\alpha)\eta}{(\delta+\mu+\omega)(\eta+\sigma+\mu)(\theta+\mu)}\right)(S^0+\varepsilon V^0) \\
&= \left(\frac{\beta q_1}{\delta+\mu+\omega} + \frac{\delta\beta q_2}{(\delta+\mu+\omega)(\eta+\sigma+\mu)} + \frac{\delta\beta q_3(1-\alpha)\eta}{(\delta+\mu+\omega)(\eta+\sigma+\mu)(\theta+\mu)}\right)\left(\frac{\Pi}{\mu}D_1 + \varepsilon\frac{\Pi}{\mu}D_2\right) \\
&= \left(\frac{\beta q_1}{\delta+\mu+\omega} + \frac{\delta\beta q_2}{(\delta+\mu+\omega)(\eta+\sigma+\mu)} + \frac{\delta\beta q_3(1-\alpha)\eta}{(\delta+\mu+\omega)(\eta+\sigma+\mu)(\theta+\mu)}\right)\frac{\Pi}{\mu}D_1 + \\
&\varepsilon\left(\frac{\beta q_1}{\delta+\mu+\omega} + \frac{\delta\beta q_2}{(\delta+\mu+\omega)(\eta+\sigma+\mu)} + \frac{\delta\beta q_3(1-\alpha)\eta}{(\delta+\mu+\omega)(\eta+\sigma+\mu)(\theta+\mu)}\right)\frac{\Pi}{\mu}D_2
\end{aligned}$$

Then the effective reproduction number can be written as;

$$R_{ef} = R_C + R_I + R_{D_r} = R_s + R_v \tag{18}$$

Where,

$$\begin{aligned}
R_s &= \left(\frac{\beta q_1}{\delta+\mu+\omega} + \frac{\delta\beta q_2}{(\delta+\mu+\omega)(\eta+\sigma+\mu)} + \frac{\delta\beta q_3(1-\alpha)\eta}{(\delta+\mu+\omega)(\eta+\sigma+\mu)(\theta+\mu)}\right)\frac{\Pi D_1}{\mu} \\
R_v &= \varepsilon\left(\frac{\beta q_1}{\delta+\mu+\omega} + \frac{\delta\beta q_2}{(\delta+\mu+\omega)(\eta+\sigma+\mu)} + \frac{\delta\beta q_3(1-\alpha)\eta}{(\delta+\mu+\omega)(\eta+\sigma+\mu)(\theta+\mu)}\right)\frac{\Pi D_2}{\mu}
\end{aligned}$$

The threshold quantity R_s represents the reproduction number when all individuals are susceptible whereas R_v denotes reproduction number when all hosts are vaccinated. Furthermore, the effective reproduction number (R_{ef}) consists of the sum of three terms. The first term denoted by (R_C), gives the number of secondary infectious produced by one carrier, the second term (R_I) gives the number of secondary infectious produced by one infectious individual , and the third term (R_{D_r}) gives the number of secondary infectious produced by one drug resistance individual in totally susceptible and vaccinated individuals.

3.4. Local Stability of Disease Free Equilibrium.

Theorem 3. *The disease free equilibrium point is locally asymptotically stable if* $R_{ef} < 1$ *and unstable if* $R_{ef} > 1$.

Proof: As we obtained in the previous section expanding the determinant of the characteristic equation $| J(E_0) - \lambda I | = 0$ from equation (13) we get;

$$(\lambda^2 + (2\mu+\gamma_1+\gamma_2)\lambda + \mu(\mu+\gamma_1+\gamma_2))(\vartheta+\mu+\lambda)\left(\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3\right) = 0 \tag{19}$$

Next computing the possible eigenvalues in equation (19) separately as follows,

$$(\lambda^2+(2\mu+\gamma_1+\gamma_2)\lambda+\mu(\mu+\gamma_1+\gamma_2))(\vartheta+\mu+\lambda)=0$$

Thus, $\lambda_1=-(\vartheta+\mu)$ and, λ_2 and λ_3 are negative by the help of Routh-Hurwiz criteria.The remanding three eigenvalues are obtained from,

$$\lambda^3+a_1\lambda^2+a_2\lambda+a_3=0$$

where,

$$\begin{aligned}
a_1 &= m_5+m_7+m_4-\beta q_1 m_2 = m_5+m_7+m_4(1-R_C)>0\\
a_2 &= m_7m_5+m_4(m_7+m_5)-\beta q_1 m_2(m_7+m_5)+\delta\beta q_2 m_2\\
&= m_7m_5+m_4(m_7+m_5)(1-R_C)+\delta\beta q_2 m_2>0\\
a_3 &= m_4m_7m_5(1-Ref)>0
\end{aligned}$$

$a_1a_2=(m_5+m_7+m_4(1-R_c))(m_7m_5+m_4(m_7+m_5)(1-R_c)+\delta\beta q_2m_2)>m_4m_7m_5(1-R_c)-\delta\beta q_2m_2m_5-\delta\beta q_3m_2m_8=a_3$, therefore $a_1a_2>a_3$, and also $a_3>0$, whenever $R_{ef}<1$. Thus, using Routh-Hurwiz principle the disease free equilibrium is locally asymptotically stable if $R_{ef}<1$.

3.5. Global Stability of Disease Free Equilibrium.

Theorem 4. *The disease-free equilibrium point,$E_0=(S^0,V^0,0,0,0,0)$, is globally asymptotically stable (GAS) whenever $R_{ef}<1$.*

Proof: To prove this we use the method of Lyapunov function defined as,

$$L=k_1C+k_2I+k_3D_r \tag{20}$$

where,

$$\begin{aligned}
k_1 &= \frac{q_1m_7m_5+q_2\delta m_5+q_3\delta(1-\alpha)\eta}{q_3m_4m_7}\\
k_2 &= \frac{m_5q_2+(1-\alpha)\eta q_3}{q_3m_7}\\
k_3 &= 1
\end{aligned}$$

Notice that $L(E_0)=0$ and $L(C,I,D_r)>0\forall(C,I,D_r)\in U/E_0$, where $U\subset\Omega_m$. It remains to prove $\frac{dL}{dt}\leq 0$. Differentiating (20) we obtain,

$$\begin{aligned}
\frac{dL}{dt} &= k_1\dot{C}+k_2\dot{I}+k_3\dot{D}_r \\
&= \left(\frac{[q_1m_7m_5+q_2\delta m_5+q_3\delta(1-\alpha)\eta]m_5}{q_3m_4m_7m_5}\right)[\beta(q_1C+q_2I+q_3D_r)(S+\varepsilon V)-m_4C] \\
&+\left(\frac{m_5q_2+(1-\alpha)\eta q_3}{q_3m_7}\right)[\delta C-m_7I]+(1-\alpha)\eta I-m_5D_r \\
&\leq \left(\frac{[q_1m_7m_5+q_2\delta m_5+q_3\delta(1-\alpha)\eta]m_5}{q_3m_4m_7m_5}\right)\left[\beta(q_1C+q_2I+q_3D_r)(S^0+\varepsilon V^0)-m_4C\right] \\
&+\left(\frac{m_5q_2+(1-\alpha)\eta q_3}{q_3m_7}\right)[\delta C-m_7I]+(1-\alpha)\eta I-m_5D_r, \qquad \text{Since,} S\leq S^0, V\leq V^0 \\
&= \left(\frac{[q_1m_7m_5+q_2\delta m_5+q_3\delta(1-\alpha)\eta]m_5\beta q_1C(S^0+\varepsilon V^0)}{q_3m_4m_7m_5}-\frac{q_1m_5C}{q_3}\right) \\
&+\left(\frac{[q_1m_7m_5+q_2\delta m_5+q_3\delta(1-\alpha)\eta]m_5\beta q_2I(S^0+\varepsilon V^0)}{q_3m_4m_7m_5}-\frac{q_2m_5I}{q_3}\right) \\
&+\left(\frac{[q_1m_7m_5+q_2\delta m_5+q_3\delta(1-\alpha)\eta]m_5\beta D_r(S^0+\varepsilon V^0)}{m_4m_7m_5}-m_5D_r\right) \\
&= \frac{m_5q_1}{q_3}(R_{ef}-1)C+\frac{m_5q_2}{q_3}(R_{ef}-1)I+m_5(R_{ef}-1)D_r
\end{aligned}$$

Where, $R_{ef}=\frac{(q_1m_7m_5+q_2\delta m_5+q_3\delta(1-\alpha)\eta)\beta(S^0+\varepsilon V^0)}{m_4m_7m_5}$. Thus, $\frac{dL}{dt}<0$ if $R_{ef}<1$, and $\frac{dL}{dt}=0$. Therefore, according to La Salle invariant principle presented in [26], we conclude that the point, E_0 is GAS in Ω_m if $R_{ef}<1$.

3.6. Endemic Equilibrium. Endemic equilibrium point of the system (2) is the steady state solution where the bacterial meningitis persist in the population and it is denoted by E^*=$(S^*,V^*,C^*,I^*,D_r^*,R^*)$. This can be obtained by equating the system of equation (2) to zero.

From the fourth, fifth and sixth equations of the model (2) respectively we obtain,

$$C^*=\frac{(\eta+\sigma+\mu)I^*}{\delta} \tag{21}$$

$$D_r^*=\frac{(1-\alpha)\eta I^*}{\theta+\mu} \tag{22}$$

$$R^* = \left(\frac{\omega(\theta+\mu)(\eta+\sigma+\mu)+\delta\alpha\eta\mu+\delta\theta\eta}{\delta(\theta+\mu)(\vartheta+\mu)}\right)I^* \tag{23}$$

Using the first and second equations of the system (2),

$$V^* = \frac{\Pi\kappa+\gamma_2 S^*}{\mu+\varepsilon\lambda^*+\gamma_1} \tag{24}$$

$$S^* = \frac{(\mu+\varepsilon\lambda^*+\gamma_1)(\Pi(1-\kappa)+\vartheta R^*)+\gamma_1\Pi\kappa}{(\lambda^*+\mu+\gamma_2)(\mu+\varepsilon\lambda^*+\gamma_1)-\gamma_1\gamma_2} \tag{25}$$

By substituting the expression of C^*, V^*, and S^* above into the third equation in the system (2) and rearranging it we get;

$$H_1 I^{*3} + H_2 I^{*2} + H_3 I^* + H_4 = 0 \tag{26}$$

Where

$$\begin{aligned}
H_1 &= (\theta\vartheta(\eta\mu+\sigma\delta+\sigma\mu+\mu\delta+\mu^2)+\mu\vartheta(\eta\delta+\eta\mu+\sigma\delta+\sigma\mu+\mu\delta+\mu^2)\\
&\quad+(\theta\mu+\mu^2)(\eta\delta+\eta\mu+\eta\omega+\sigma\delta+\sigma\mu+\sigma\omega+\mu\delta+\mu^2+\mu\omega)-\vartheta\mu\delta\alpha\eta)A^3\beta^3\varepsilon^2\\
H_2 &= d_3d_5d_1d_2(\varepsilon^2d_6+2d_7)\beta^2A^2-(\delta d_3d_5\pi\varepsilon^2\beta^3A^3+2\vartheta(\omega d_1d_3+\delta d_3\alpha\eta+\theta d_4\delta)(2d_7+\varepsilon\gamma_2)\varepsilon A^2\beta^2)\\
H_3 &= d_1d_2d_3d_5\varepsilon(d_7(d_6+d_7+1)-\gamma_1\gamma_2)\beta A-((2\delta d_3d_5d_7\pi(1-\kappa)+\pi\kappa\gamma_1)A^2\beta^2\varepsilon+\delta d_3d_5\pi(\gamma_2(1-\kappa)\\
&\quad+\kappa(d_6+d_7))\varepsilon^2\beta^2A^2+\vartheta(\omega d_1d_3+\delta d_3\alpha\eta+\theta d_4\delta)(d_7+\varepsilon))\\
H_4 &= (\vartheta+\mu)(\mu+\gamma_1)(1-R_{ef})
\end{aligned}$$

$d_1 = \eta+\sigma+\mu, d_2 = \delta+\mu+\omega, d_3 = \theta+\mu, d_4 = (1-\alpha)\eta, d_5 = \vartheta+\mu, d_6 = \mu+\gamma_2$, $d_7 = \mu+\gamma_1$ and $A = \frac{q_1d_1d_3+\delta d_3q_2+q_3d_4\delta}{\delta d_3}$.

The coefficient H_1 is positive while the sign of H_4 is depend on the values of R_{ef}. We use the Descarte's rule of signs presented in [27] to analyse the existence of possible positive roots of the polynomial equation in (26).

Theorem 5. *Model* (2)

(i) has a unique positive endemic equilibrium if the case $(2,4,6)$ *are satisfied,*

(ii) has a unique, or would have three positive endemic equilibrium if the case 8 *is satisfied,*

(iii) would have two , or has no positive endemic equilibrium if the case $(3,5,7)$ *are satisfied and,*

(iv) has no endemic equilibrium if the case 1 *is satisfied.*

TABLE 3. Number of possible positive real roots of I^*

Cases	H_1	H_2	H_3	H_4	R_{ef}	No. of sign change	No.of positive real roots
1	+	+	+	+	$R_{ef}<1$	0	0
2	+	+	+	−	$R_{ef}>1$	1	1
3	+	+	−	+	$R_{ef}<1$	2	0,2
4	+	+	−	−	$R_{ef}>1$	1	1
5	+	−	−	+	$R_{ef}<1$	2	0,2
6	+	−	−	−	$R_{ef}>1$	1	1
7	+	−	+	+	$R_{ef}<1$	2	0,2
8	+	−	+	−	$R_{ef}>1$	3	1,3

3.7. Local Stability of the Endemic Equilibrium.

Theorem 6. *The endemic equilibrium E^* of the system in* (2)*, is locally asymptotically stable for $R_{ef}>1$(but near to* 1*).*

Proof: To investigate the possibility of backward or forward bifurcation of the model (2) we use the method introduced by [28]. This is done by assigning the variables as follows;

$$S=x_1, V=x_2, C=x_3, I=x_4, D_r=x_5, R=x_6.$$

Then the system (2) can be written as;

$$\begin{cases} \frac{dx_1}{dt} = \Pi(1-\kappa)+\vartheta x_6+\gamma_1 x_2-(\lambda+\mu+\gamma_2)x_1 \\ \frac{dx_2}{dt} = \Pi\kappa+\gamma_2 x_1-(\mu+\varepsilon\lambda+\gamma_1)x_2 \\ \frac{dx_3}{dt} = \lambda x_1+\varepsilon\lambda x_2-(\delta+\omega+\mu)x_3 \\ \frac{dx_4}{dt} = \delta x_3-(\eta+\sigma+\mu)x_4 \\ \frac{dx_5}{dt} = (1-\alpha)\eta x_4-(\theta+\mu)x_5 \\ \frac{dx_6}{dt} = \omega x_3+\alpha\eta x_4+\theta x_5-(\vartheta+\mu)x_6 \end{cases} \tag{27}$$

choosing β as bifurcation parameter and solving for $\beta=\beta^*$ in (18), when $R_{ef}=1$ yields;

$$\beta^* = \frac{(\delta+\mu+\omega)(\eta+\sigma+\mu)(\theta+\mu)(\mu+\gamma_1+\gamma_2)\mu}{\pi\left[q_1(\eta+\sigma+\mu)(\theta+\mu)+q_2\delta(\theta+\mu)+q_3\delta(1-\alpha)\eta\right]\left[\mu(1-\kappa)+\gamma_1+\varepsilon(\mu\kappa+\gamma_2)\right]}$$

The linearization matrix of system in (27) around the disease free equilibrium when $\beta = \beta^*$ is;

$$J(E_0,\beta^*) = \begin{bmatrix} -m_1 & \gamma_1 & -\beta^* q_1 S^0 & -\beta^* q_2 S_0 & -\beta^* q_3 S^0 & \vartheta \\ \gamma_2 & -m_6 & -\varepsilon\beta q_1 V_0 & -\varepsilon\beta^* q_2 V_0 & -\varepsilon\beta^* q_3 V^0 & 0 \\ 0 & 0 & \beta^* q_1 m_2 - m_4 & \beta^* q_2 m_2 & \beta^* q_3 m_2 & 0 \\ 0 & 0 & \delta^* & -m_7 & 0 & 0 \\ 0 & 0 & 0 & m_8 & -m_5 & 0 \\ 0 & 0 & \omega & \alpha\eta & \theta & -m_9 \end{bmatrix} \tag{28}$$

Where $m_1 = (\mu+\gamma_2), m_2 = S^0 + \varepsilon V^0, m_4 = \delta+\mu+\omega, m_5 = \theta+\mu, m_6 = \mu+\gamma_1, m_7 = \eta+\sigma+\mu, m_8 = (1-\alpha)\eta, m_9 = \vartheta+\mu$.

The Jacobian matrix in (28) has a simple zero eigenvalues, hence the center manifold theory will be used to analyses the dynamic of the system (27) near $\beta = \beta^*$.

Next, we obtain the left and the right eigenvector of $J(E_0,\beta^*)$ associated with the zero eigenvalue. The right eigenvector is given by $w = (w_1, w_2, w_3, w_4, w_5, w_6)^T$ from (28);

$$\begin{bmatrix} -m_1 & \gamma_1 & -\beta^* q_1 S_0 & -\beta^* q_2 S_0 & -\beta^* q_3 S_0 & \vartheta \\ \gamma_2 & -m_6 & -\varepsilon\beta q_1 V_0 & -\varepsilon\beta^* q_2 V_0 & -\varepsilon\beta^* q_3 V_0 & 0 \\ 0 & 0 & \beta^* q_1 m_2 - m_4 & \beta^* q_2 m_2 & \beta^* q_3 m_2 & 0 \\ 0 & 0 & \delta^* & -m_7 & 0 & 0 \\ 0 & 0 & 0 & m_8 & -m_5 & 0 \\ 0 & 0 & \omega & \alpha\eta & \theta & -m_9 \end{bmatrix} \begin{bmatrix} w_1 \\ w_2 \\ w_3 \\ w_4 \\ w_5 \\ w_6 \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}$$

The system of this equation becomes,

$$\begin{cases} -m_1 w_1 + \gamma_1 w_2 - \beta^* q_1 S_0 w_3 - \beta^* q_2 S_0 w_4 - \beta^* q_3 S_0 w_5 + \vartheta w_6 = 0 \\ \gamma_2 w_1 - m_6 w_2 - \varepsilon\beta^* q_1 V_0 w_3 - \varepsilon\beta^* q_2 V_0 w_4 - \varepsilon\beta^* q_3 V_0 w_5 = 0 \\ (\beta^* q_1 m_2 - m_4) w_3 + \beta^* q_2 m_2 w_4 + \beta^* q_3 m_2 w_5 = 0 \\ \delta w_3 - m_7 w_4 = 0 \\ m_8 w_4 - m_5 w_5 = 0 \\ \omega w_3 + \alpha\eta w_4 + \theta w_5 - m_9 w_6 = 0 \end{cases} \tag{29}$$

Solving system of (29) we obtain;

$$w_1 = \frac{\varepsilon m_4(\kappa\mu+\gamma_2)w_3}{\gamma_2(\mu(1-\kappa)+\gamma_1+\varepsilon(\kappa\mu+\gamma_2))} + \frac{m_6 w_2}{\gamma_2}$$

$$w_2 = \frac{1}{\mu(\mu+\gamma_1+\gamma_2)}\left(\frac{\gamma_2\vartheta(\omega m_7 m_5+\alpha\delta\eta m_5+\theta\delta m_8)}{m_7 m_5 m_9} - \frac{m_4\mu\varepsilon(\kappa\mu+\gamma_2)}{\mu(1-\kappa)+\gamma_1+\varepsilon(\kappa\mu+\gamma_2)} - \gamma_2 m_4\right) w_3$$

$$w_3 = w_3 > 0$$

$$w_4 = \frac{\delta w_3}{m_7}$$

$$w_5 = \frac{m_8\delta w_3}{m_7 m_5}$$

$$w_6 = \left(\frac{\omega m_7 m_5+\alpha\delta\eta m_5+\theta\delta m_8}{m_7 m_5 m_9}\right) w_3$$

Similarly, we have the left eigenvectors of $J_{E_0\beta^*}$ associated with the zero eigenvalues. It is given by $v=(v_1,v_2,v_3,v_4,v_5,v_6)^T$ where;

$$\begin{bmatrix} -m_1 & \gamma_2 & 0 & 0 & 0 & 0 \\ \gamma_1 & -m_6 & 0 & 0 & 0 & 0 \\ -\beta^* q_1 S_0 & -\varepsilon\beta^* q_1 V_0 & \beta^* q_1 m_2 - m_4 & \delta & 0 & \omega \\ -\beta^* q_2 S_0 & -\varepsilon\beta^* q_2 V_0 & \beta^* q_2 m_2 & -m_7 & m_8 & \alpha\eta \\ -\beta^* q_3 S_0 & -\varepsilon\beta^* q_3 V_0 & \beta^* q_3 m_2 & 0 & -m_5 & \theta \\ \vartheta & 0 & 0 & 0 & 0 & -m_9 \end{bmatrix} \begin{bmatrix} v_1 \\ v_2 \\ v_3 \\ v_4 \\ v_5 \\ v_6 \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}$$

The system of equation becomes;

$$\begin{cases} -m_1 v_1 + \gamma_2 v_2 = 0 \\ \gamma_1 v_1 - m_6 v_2 = 0 \\ -\beta^* q_1 S_0 v_1 - -\beta^* q_1 V_0 v_2 + (-\beta^* q_1 m_2 - m_4) v_3 + \delta v_4 + \omega v_6 = 0 \\ -\beta^* q_2 S_0 v_1 - \varepsilon\beta^* q_2 V_0 v_2 + \beta^* q_2 S m_2 v_3 - m_7 v_4 + m_8 v_5 + \alpha\eta v_6 = 0 \\ -\beta^* q_3 S_0 v_1 - \varepsilon\beta^* q_3 V_0 v_2 + \beta^* q_3 m_2 v_3 - m_5 v_5 + \theta v_6 = 0 \\ \vartheta v_1 - m_9 v_2 = 0 \end{cases} \tag{30}$$

Solving system of equation (30) simultaneously we obtain;

$$v_1 = v_2 = v_6 = 0$$

$$v_3 = v_3 > 0$$

$$v_4 = \frac{(m_4 - \beta^* q_1 m_2)v_3}{\delta}$$

$$v_5 = \frac{\beta^* q_3 m_2 v_3}{m_5}$$

Furthermore, by the help of $w.v = 1$ we can determine for v_3 and w_3 as,

$$w_3 = \frac{m_7 m_5^2(q_1 m_7 m_5 + q_2\delta m_5 + q_3\delta m_8)}{m_7 m_5^2(q_1 m_7 m_5 + q_2\delta m_5 + q_3\delta m_8) + m_4 m_5^2(q_2\delta m_5 + q_3\delta m_8) + m_4 m_7 m_5 m_8 q_3}$$

$$v_3 = 1$$

Now, we compute the coefficient a and b which defined in Castillo-Chavez and Song as follows,

$$a = \sum_{k,i,j=1}^{6} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(E_0) \tag{31}$$

$$b = \sum_{k,i=1}^{6} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \beta}(E_0) \tag{32}$$

Where,

$$\begin{cases} f_1 = \Pi(1-\kappa) + \vartheta x_6 + \gamma_1 x_2 - (\lambda + \mu + \gamma_2)x_1 \\ f_2 = \Pi\kappa + \gamma_2 x_1 - (\mu + \varepsilon\lambda + \gamma_1)x_2 \\ f_3 = \lambda x_1 + \varepsilon\lambda x_2 - (\delta + \omega + \mu)x_3 \\ f_4 = \delta x_3 - (\eta + \sigma + \mu)x_4 \\ f_5 = (1-\alpha)\eta x_4 - (\theta + \mu)x_5 \\ f_6 = \omega x_3 + \alpha\eta x_4 + \theta x_5 - (\vartheta + \mu)x_6 \end{cases} \tag{33}$$

We obtained by examining only the non-zero components of the left eigenvectors v_3,v_4 and v_5 and taking into account the corresponding second-order partial derivatives of the system in (33);

$$a = -2v_3 w_3^2 \beta \left(q_1 + \frac{\delta q_2}{\eta + \sigma + \mu} + \frac{(1-\alpha)\eta\delta q_3}{(\eta + \sigma + \mu)(\theta + \mu)}\right)\left(\frac{\varepsilon m_4(\kappa\mu + \gamma_2)(1-\varepsilon)}{\gamma_2(\mu(1-\kappa) + \gamma_1 + \varepsilon(\kappa\mu + \gamma_2))(\mu + \gamma_1 + \gamma_2)}\right.$$
$$\left. + \left(\frac{m_6 + \varepsilon\gamma_2}{\mu(\mu + \gamma_1 + \gamma_2)}\right)\left(\frac{\vartheta\mu\eta\delta(1-\alpha) + \vartheta\delta(\sigma + \mu)m_5 + \vartheta\mu m_7 m_5 + \mu m_4 m_7 m_5}{m_7 m_5 m_9}\right)\right) < 0.$$

$$b = w_3 v_3 \Pi \left(q_1 + \frac{\delta q_2}{\delta + \mu + \omega} + \frac{(1-\alpha)\eta\delta q_3}{(\eta+\sigma+\mu)(\theta+\mu)} \right) \left(\frac{[\mu(1-\kappa)+\gamma_1+\varepsilon(\kappa\mu+\gamma_2)]}{\mu(\mu+\gamma_1+\gamma_2)} \right) > 0$$

Since $a < 0$ and $b > 0$, by the help of [28], the system (2) exhibits a forward bifurcation at $R_{ef} = 1$ (see Figure 2), and the endemic equilibrium is locally asymptotically stable for $R_{ef} > 1$, but near to 1. Its biological meaning is that as long as $R_{ef} < 1$ the disease can be eradicated from the population.

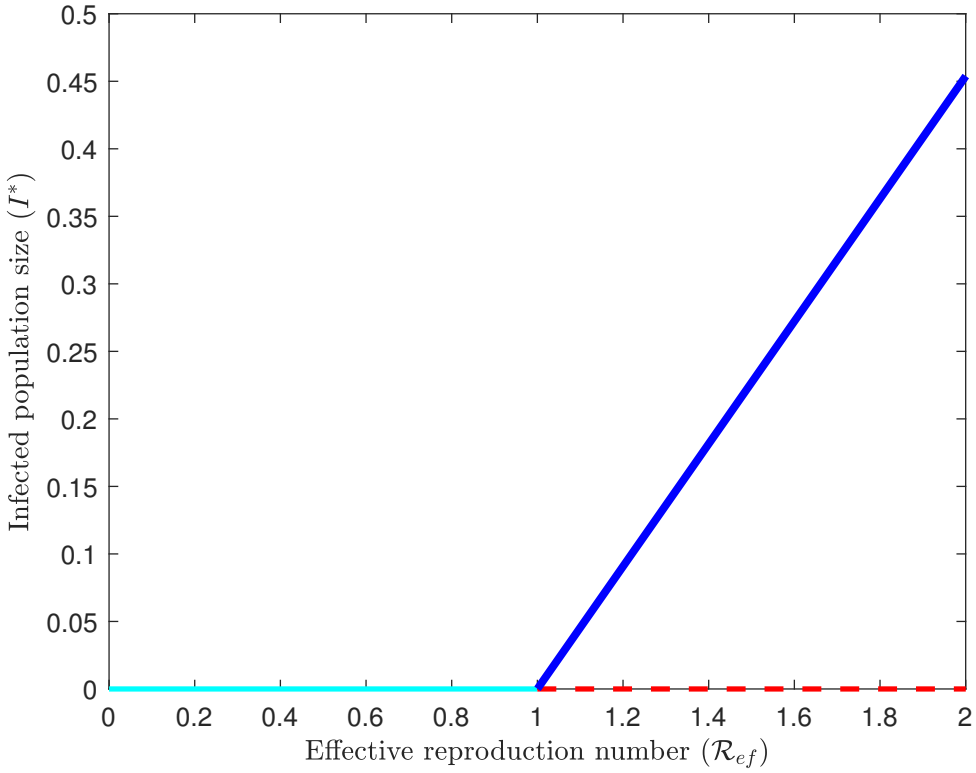

FIGURE 2. *Forward bifurication*

3.8. Sensitivity Analysis. In this section, we examined the sensitivity of the parameters for the effective reproduction number of the model using the idea presented in [29, 30, 31]. This helped us in identifying the parameters that have a significant impact on the effective reproductive number R_{ef}. To compute the sensitivity index of R_{ef} to a given parameter Ψ we use the following formula,

$$\Lambda_{\Psi}^{R_{ef}} = \left(\frac{\partial R_{ef}}{\partial \Psi} \right) \left(\frac{\Psi}{R_{ef}} \right) \tag{34}$$

Thus, we compute the sensitivity index of R_{ef} corresponding to each parameters in (18) as follows.

$$\Lambda_{\beta}^{R_{ef}} = 1 = \Lambda_{\Pi}^{R_{ef}}$$

$$\Lambda_{q_1}^{R_{ef}} = \frac{q_1(\eta+\sigma+\mu)(\theta+\mu)}{q_1(\eta+\sigma+\mu)(\mu+\theta)+\delta q_2(\theta+\mu)+\delta q_3(1-\alpha)\eta}$$

$$\Lambda_{q_2}^{R_{ef}} = \frac{q_2\delta(\theta+\mu)}{q_1(\eta+\mu+\sigma)(\mu+\theta)+\delta q_2(\theta+\mu)+\delta q_3(1-\alpha)\eta}$$

$$\Lambda_{q_3}^{R_{ef}} = \frac{\delta(1-\alpha)\eta q_3}{q_1(\eta+\sigma+\mu)(\mu+\theta)+\delta q_2(\theta+\mu)+\delta q_3(1-\alpha)\eta}$$

$$\Lambda_{\alpha}^{R_{ef}} = \frac{-\alpha\delta\eta q_3}{q_1(\eta+\sigma+\mu)(\mu+\theta)+\delta q_2(\theta+\mu)+\delta q_3(1-\alpha)\eta}$$

$$\Lambda_{\kappa}^{R_{ef}} = \frac{\kappa\mu(\varepsilon-1)}{\mu(1-\kappa)+\gamma_1+\varepsilon(\mu\kappa+\gamma_2)}$$

$$\Lambda_{\varepsilon}^{R_{ef}} = \frac{\varepsilon(\mu\kappa+\gamma_2)}{\mu(1-\kappa)+\gamma_1+\varepsilon(\mu\kappa+\gamma_2)}$$

$$\Lambda_{\omega}^{R_{ef}} = \frac{-\omega}{\delta+\mu+\omega}$$

$$\Lambda_{\theta}^{R_{ef}} = \frac{-\theta\delta q_3(1-\alpha)\eta}{[q_1(\eta+\sigma+\mu)(\mu+\theta)+q_2\delta(\theta+\mu)+\delta q_3(1-\alpha)\eta](\theta+\mu)}$$

$$\Lambda_{\gamma_1}^{R_{ef}} = \frac{\gamma_1(\gamma_2-\mu+\mu\kappa-\varepsilon(\mu\kappa+\gamma_2))}{[\mu(1-\kappa)+\gamma_1+\varepsilon(\kappa\mu+\gamma_2)](\mu(\mu+\gamma_1+\gamma_2)^2)}$$

$$\Lambda_{\gamma_2}^{R_{ef}} = \frac{\gamma_2(\varepsilon(\mu+\gamma_1+\gamma_2)-(\mu(1-\kappa)+\gamma_1+\varepsilon(\mu\kappa+\gamma_2)))}{(\mu+\gamma_1+\gamma_2)(\mu(1-\kappa)+\gamma_1+\varepsilon(\kappa\mu+\gamma_2)}$$

$$\Lambda_{\delta}^{R_{ef}} = \frac{\delta[(q_2(\theta+\mu)+q_3(1-\alpha)\eta)(\delta+\mu+\omega)-(q_1(\eta+\sigma+\mu)(\theta+\mu)+\delta q_2(\mu+\theta)+\delta q_3(1-\alpha)\eta)]}{(\delta+\omega+\mu)[q_1(\eta+\sigma+\mu)(\theta+\mu)+q_2\delta(\theta+\mu)+q_3\delta(1-\alpha)\eta]}$$

$$\Lambda_{\eta}^{R_{ef}} = \frac{\eta[(q_1(\theta+\mu)+\delta q_3(1-\alpha))(\eta+\sigma+\mu)-(q_1(\eta+\mu+\sigma)(\theta+\mu)+\delta q_2(\theta+\mu)+\delta q_3(1-\alpha)\eta)]}{(\eta+\sigma+\mu)[q_1(\eta+\sigma+\mu)(\theta+\mu)+q_2\delta(\theta+\mu)+\delta q_3(1-\alpha)\eta]}$$

$$\Lambda_{\sigma}^{R_{ef}} = \frac{\sigma[q_1(\eta+\sigma+\mu)-(q_1(\eta+\sigma+\mu)(\mu+\theta)+q_2\delta(\theta+\mu)+q_3\delta(1-\alpha)\eta)]}{(\eta+\mu+\sigma)[q_1(\eta+\sigma+\mu)(\mu+\theta)+\delta q_2(\theta+\mu)+q_3\delta(1-\alpha)\eta]}$$

$$\Lambda_{\mu}^{R_{ef}} = \frac{\mu(\Phi\Psi+\varphi(1-\kappa+\varepsilon\kappa))}{\varphi\Psi} - \frac{\mu(\tau\rho-\iota\zeta)}{\iota\rho}$$

where,

$$\Phi = q_1(2\mu+\theta\eta+\sigma)+\delta q_2$$

$$\Psi = \mu(1-\mu)+\gamma_1+\varepsilon(\kappa\mu+\gamma_2)$$

$$\varphi = q_1(\eta+\sigma+\mu)(\mu+\theta)+\delta q_2(\theta+\mu)+\delta q_3(1-\alpha)\eta$$

$$\tau = 2\mu+\gamma_1+\gamma_2$$

$$\rho = (\delta+\mu+\omega)(\mu+\theta)(\eta+\sigma+\mu)$$

$$\iota = \mu(\mu+\gamma_1+\gamma-2)$$

$$\zeta = \theta(\eta+\sigma)+\delta\theta+2\mu\theta+\omega\theta+(\eta+2\mu+\omega)(\eta+\sigma)+(2\delta\mu+3\mu^2+2\omega\mu).$$

The values of sensitivity indices of the effective reproduction number (R_{ef}) to each of its parameter values are itemized in Table 4. Thus, the sensitivity indices of the parameters $(\Pi,\beta,\gamma_1,q_1,q_2,q_3,\varepsilon)$ will have a corresponding percentage increase in severity of the disease. For instance, the effective transmission probability per contact (β) and recruitment rate (Π) which have a sensitivity indices of 1 have a positive impact on the effective reproduction number and $x\%$ increase in both β and Π will leads to a $2x\%$ increase in disease burden. Similarly increasing the value of q_2 by 10% results in increase in the value R_{ef} by 8.533%. Thus, the effective reproduction number is most sensitive the effective transmission probability per contact (β), the recruitment rate (Π) and q_2. Similarly from Table (4), demonstrates that the effective reproduction number R_{ef}, can be decreased through an increase in the values $(\eta,\sigma,\theta,\alpha,\omega,\mu,\gamma_2,\kappa)$. However, since σ and μ represent disease induce death rate from infected class and natural death rate from all compartments respectively, we cannot use them as intervention measures. In contrast, $\Lambda_{\eta}^{R_{ef}} = -0.394$, means that a 0.394 increase in η will produce 0.651 decrease in R_{ef} based on treatment. Furthermore, the disease burden will decreased by 6.8% if the vaccine uptake rate of susceptible individuals (γ_2) increase by 10%. Epidemiological implication of this section is that preventive and control should be targeted on the most sensitive parameters to reduce the burden of bacterial meningitis on populations.

4. SIMULATIONS OF THE SYSTEM

In this section, authors use some numerical simulations to illustrate the previous theoretical analysis and discuss more dynamical behaviour of the system(2). Fourth-order Runge-Kutta method in the MATLAB program is used to solve the system and the results are represents graphically. The initial condition $(S_0,V_0,C_0,I_0,D_{r0},R_0) = (5550,4100,1620,210,180,350)$, and $\Pi = 111$, $\beta = 0.03$ and $\vartheta = 0.0839$ are used for the simulation of figures (5,6, and 7), in addition to parameter values given in Table 4.

Figure (3) shows simulation results converge to the disease free equilibrium point for the total

TABLE 4. Sensitivity indices

Parameter	Value	Source	Sensitivity indices
Π	Varied		1
β	Varied		1
η	0.56	Assumed	-0.394
δ	$0.1-0.52$	[13]	0.17
γ_1	0.32	Assumed	0.65
γ_2	0.92	Assumed	-0.68
μ	0.02	[32]	-0.00006
κ	0.21	Assumed	-0.012
ω	0.1118	[15]	-0.174
σ	$0.05-0.5$	[16]	-0.44
q_1	0.0016	Assumed	0.0358
q_2	0.08	Assumed	0.8533
q_3	0.02	Assumed	0.111
α	0.22	Assumed	-0.0313
ε	$[0.019-0.15]$	Assumed	0.05
θ	0.82	Assumed	-0.1083

number of susceptible, vaccinated, carrier, infected and drug-resistant individuals using various initial conditions, $\beta = 0.025$ and $\Pi = 30$ (in such manner $R_{ef} = 0.7323$) and $\vartheta = 0.0839$. All other parameters are as in Table (4). This result shows that bacterial meningitis can be eliminated from the population as long as effective reproduction number $(R_{ef}) < 1$. Since the unique positive endemic equilibrium is locally asymptotically stable in Figure (4) all solution trajectories of carrier,infected and drug-resistant individuals converge to the endemic equilibrium using different initial conditions, $\beta = 0.03$, $\Pi = 111$ and all other parameters are as in table(4) (in such manner $R_{ef} = 3.2513$) and $\vartheta = 0.0839$. This indicated that the disease persist in the community because $R_{ef} = 3.2513 > 1$. The effective transmission probability per contact rate (β) plays a powerful role in expanding of bacterial meningitis disease transmission by maximizing

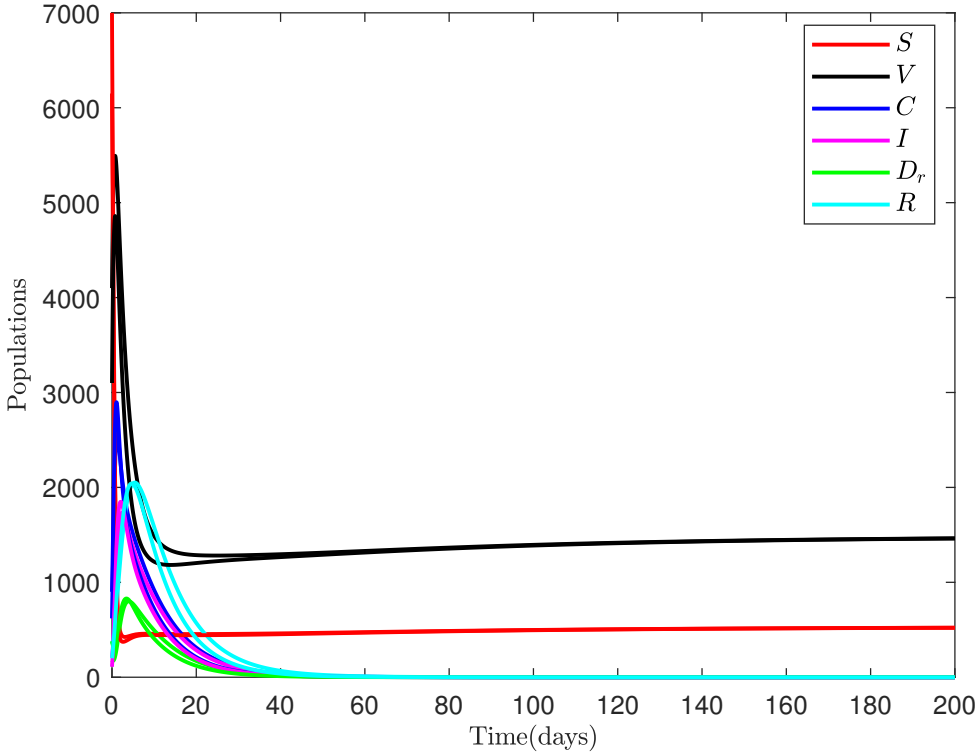

FIGURE 3. *Simulation of system(2) showing the total number of populations as a function of time ,using various initial conditions when* $\beta = 0.025$ *and* $\Pi = 30$ *(in such a manner* $R_{ef} = 0.7323$*) and* $\vartheta = 0.0839$*. All other parameters are as in Table (4).*

the incidence rate in the infectious populations. Figure 5(a and b) demonstrates that maximizing the effective transmission probability per contact rate (β) which value significantly increase the number of susceptible and vaccinated individuals getting infectious (or decrease the number of susceptible and vaccinated), respectively and vice versa. Thus, the maximization of effective transmission probability per contact rate (β) result in increase in the size of carrier, infected and drug-resistant population as shown in Figure $5(c-e)$ respectively. In Figure (6), the change in vaccinated, carrier, infected and drug-resistant populations are shown for different values of vaccine uptake rate (γ_2). It is found that as the intervention vaccine uptake rate increases the vaccinated individuals in Figure (6) (a) increases and remains stable, while,the carrier, infected and drug-resistant individuals decreases after some time as shown from Figure (6) $(b-d)$ respectively. It indicates that by increasing the intervention vaccine uptake rate, the spread of the infectious disease can be reduced.

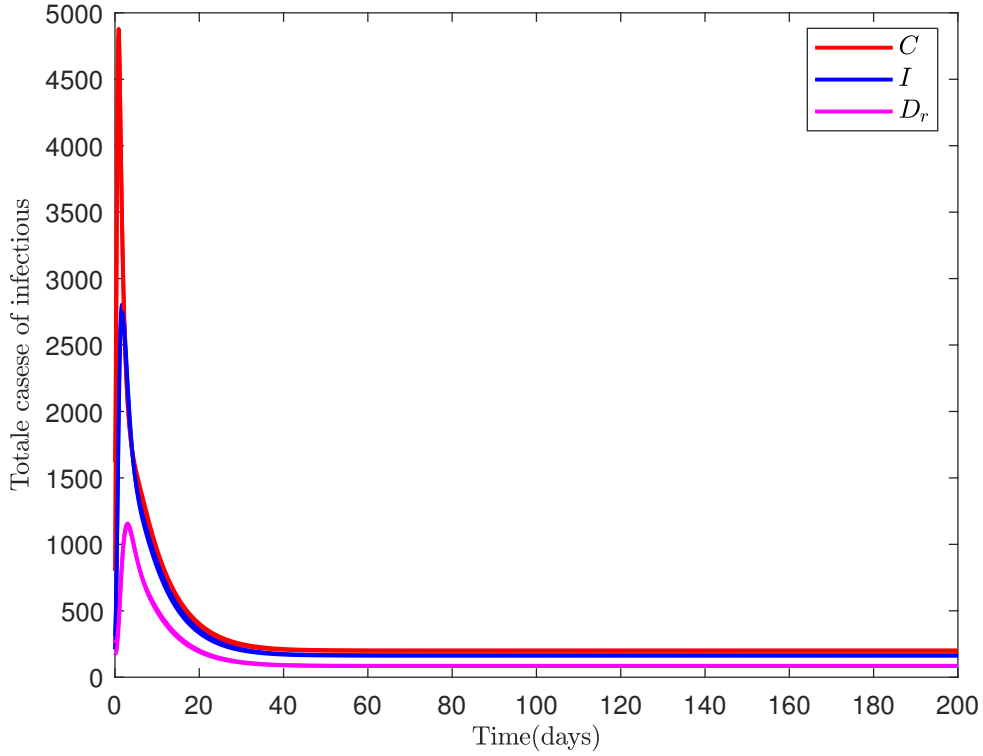

FIGURE 4. *Simulation of system(2) showing the total number of infectious individuals as a function of time ,using various initial conditions when* $\beta = 0.03$ *and* $\Pi = 111$ *(in such a manner* $R_{ef} = 3.2513$*) and* $\vartheta = 0.0839$*. All other parameters are as in Table (4).*

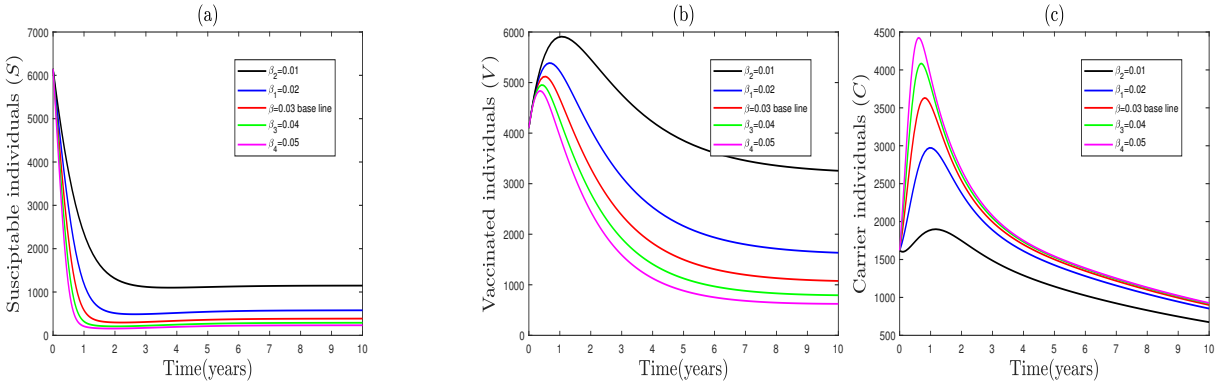

Figure (7) demonstrates that the trajectories of infected, drug-resistant and recovered individuals for different values of treatment rates η and θ. It found out that the increment in both treatments results the minimization of both infected individuals in Figure (7) (a) and drug-resistant population in (7) (b) ,and vice versa. Moreover, increasing the treatment rates results, in more individuals get recovering as shown in (7)(c). Thus, the spread of bacterial

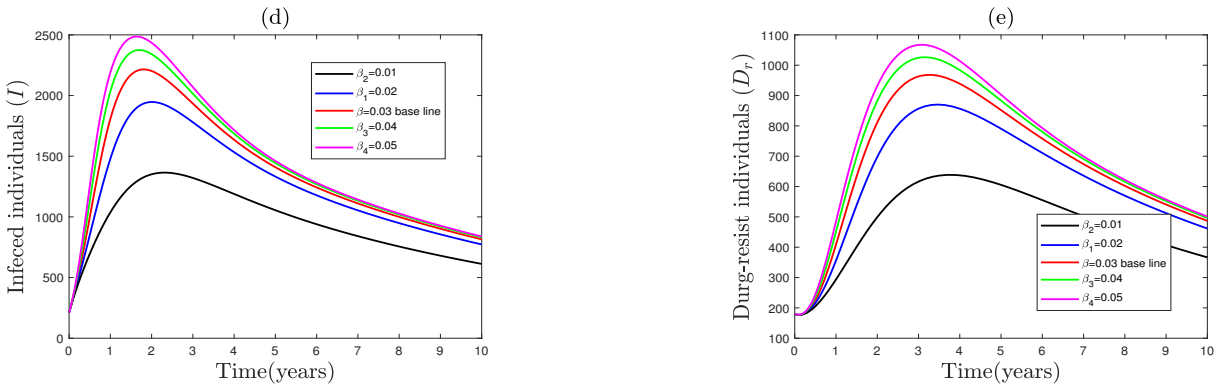

FIGURE 5. The impact of effective transmission probability per contact rate on susceptible, vaccinated, carrier, infected and drug-resist populations.

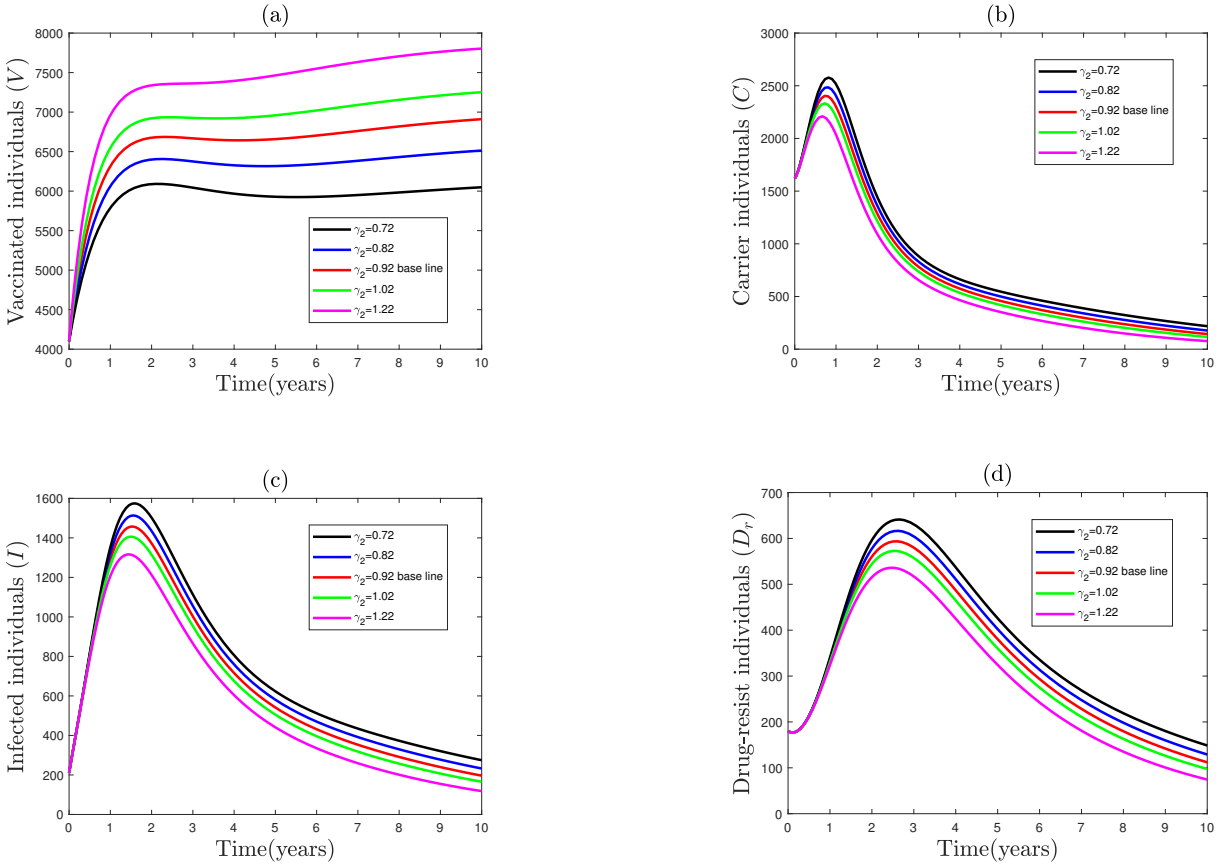

FIGURE 6. The effect of vaccine uptake rates on vaccinated, carrier, infected and drug-resist individuals.

meningitis can be control by enhancing both first and second lines of bacterial meningitis treatments.

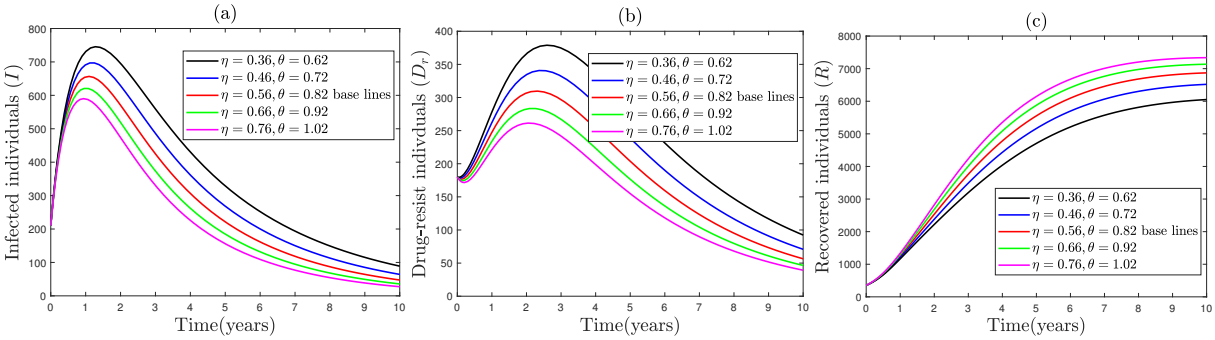

FIGURE 7. The effect of treatment rates on infected, drug-resistant and recovered individuals

5. CONCLUSIONS

In this work, a compartmental mathematical model for the dynamics of bacterial meningitis in the presence of drug-resistant class are formulated, and extensively examined to understand dynamical characteristics associated with its epidemiological thresholds. Investigation of the model demonstrated that there exists a feasible region where the model is epidemiologically meaningful and mathematically well-posed. Using Routh-Hurwize criteria the effective reproduction number(R_{ef}), of the model was computed. Existence and stability of the associated equilibria were examined. Based on Lyapunov function approach, we demonstrated that the disease-free equilibrium (DFE) is globally asymptotically stable if $R_{ef} < 1$ and unstable otherwise. Furthermore, using center manifold theory, an endemic equilibrium (EE) is locally asymptotically stable when R_{ef} is greater than one. The sensitivity analysis of the model was examined using normalized forward sensitivity index method. Among other parameters, the recruitment rate (Π), effective transmission per contact rate (β), modification rate(q_2), vaccine uptake rate(γ_2),first line treatment (η) and second line treatment(θ) are the most sensitive on effective reproduction number (R_{ef}). This demonstrates that minimizing the number of infectious individuals depends on the reduction of β and q_2 on susceptible and vaccinated individuals; maximizing vaccine uptake rate (γ_2) for susceptible and enhancing first line treatment rate (η) and second line treatment rate(θ) for infected and drug-resistance individuals respectively. Biological implication of this illustration is preventive and control measures should be addressed on the parameters, effective transmission per contact rate (β),vaccine uptake rate(γ_2), modification rate(q_2), and treatment rates $(\eta$ and $\theta)$ to reduce the difficulty of the disease. The

simulations of the system was conducted using fourth-order Runge-Kutta method in the MATLAB program. From simulation of the system,it is shown that as time goes large trajectories of the state variables are close to disease free equilibrium point whenever $R_{ef} = 0.7323 < 1$, and a unique endemic equilibrium point for $R_{ef} = 3.2513 > 1$ respectively, moreover the model shows forward bifurcation at $R_{ef} = 1$. The biological implication of this is that if effective reproduction number less than unity, the bacterial meningitis disease disappeared from the population.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interests.

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