Mathematical Biosciences 283 (2017) 48–59

Contents lists available at ScienceDirect

Mathematical Biosciences

journal homepage: www.elsevier.com/locate/mbs

Mathematical model of Ebola transmission dynamics with relapse and reinfection

F.B. Agusto

Department of Ecology and Evolutionary Biology, University of Kansas, Lawrence, KS, United States

ARTICLE INFO

Article history:
Received 5 April 2016
Revised 27 August 2016
Accepted 1 November 2016
Available online 8 November 2016

MSC:
92B05
93A30
93C15

Keywords:
Ebola
Relapse
Reinfection
Backward bifurcation
Sensitivity analysis
Control intervention

ABSTRACT

The Ebola virus disease is caused by the Ebola virus which belongs to the *filoviridae* virus family. The 2014 outbreaks were estimated to have caused over 11,000 fatalities. In this paper, we formulate and analyze a system of ordinary differential equations which incorporates disease relapse and reinfection. The Ebola model with disease relapse and reinfection is locally-asymptotically stable when the *basic reproduction number* is less than unity. The model exhibits in the presence of disease reinfection, the phenomenon of backward bifurcation, where the stable disease-free equilibrium co-exists with a stable endemic equilibrium when the associated reproduction number is less than unity. The feasibility of backward bifurcation occurring increases with increasing values of both relapse and reinfection. The total number of new cases of Ebola-infected individuals increases with increasing values of the relapse and reinfection parameters. Further simulations show that Ebola transmission models that do not incorporate relapse and reinfection may under-estimate disease burden in the community. Similar under-estimation is observed in models that include only one infected and recovered classes. Using results obtained from sensitivity analysis indicates that Ebola (given disease relapse and reinfection) can be effectively curtailed in the community by using control measures with a high-effectiveness level. This strategy is more effective than either the moderate- or low-effectiveness levels.

1. Introduction

The Ebola virus is caused by the Ebola Virus Disease (EVD); it belongs to the *filoviridae* virus family. It is transmitted person-to-person *via* direct contact with infected bodily fluids, secretions, organs, blood, and contaminated surfaces and materials [44]. The EVD case fatality varied from 25% to 90%, however, the case fatality rate on average is around 50% [44]. The 2014 West Africa EVD outbreak had case fatality rate of about 50% and it was the largest and most devastating Ebola outbreak since the first known outbreaks in 1976 [44], which occurred in Sudan and in the Democratic Republic of Congo (the later outbreak was identified near the Ebola River, where the disease got its name [11,42]). The 2014 EVD outbreak (believed to have started in Guinea in March 2014 [42] is the first to have occurred in West Africa [12]). It ravaged three countries (Guinea, Liberia, and Sierra Leone) and further spread by air and land travels to Nigeria, USA , Senegal and Mali [44].

The incubation period of EBOV is between 2 and 21 days [14,16,42] (some studies have estimated the most common incubation period to be 8–10 days [13]). Ebola-infected humans typically exhibit flu-like symptoms during the first 1–3 days of the infection [14], and can thereafter have, or progress to, other symptoms such as fever, severe headache, muscle aches, weakness, vomiting, diarrhea, stomach pains, loss of appetite and at times bleeding (which may be visible or internal) [13,14,43]. The infected human is capable of transmitting the disease to susceptible individuals at the onset of symptoms [14,42].

Following the 2014 outbreak, Liberia was first declared Ebola free in May 2015. The virus was, however, re-introduced twice, with the latest flare-up in November 2015 [46]. To date, 10 such flare-ups which were not part of the original 2014 outbreak were identified, and these are likely the result of the virus persisting in survivors even after recovery [46]. Evidence shows that the virus disappears relatively quickly from survivors, but can remain in the semen of a small number of male survivors for as long as 1 year, and in rare instances, be transmitted to intimate partners [46]. A number of studies [6,17,25,34,35,41,45] show that Ebola virus can persist in testes, spinal cord and eye chamber, sweat, breast milk, aqueous humor, semen, vaginal fluids, urine, amniotic fluid, the placenta and the central nervous system of survivors. During the 1995 Kikwit outbreak [34], a patient had live virus isolated from the seminal fluid 82 days after disease onset. In another study [17], Ebola virus RNA was shown to be present in the semen of survivors for 2 to 9 months post-onset of EVD, [45]. EVD was also

E-mail address: fbagusto@gmail.com

http://dx.doi.org/10.1016/j.mbs.2016.11.002
0025-5564/

shown to be present in sweat and urine for up to 40 days and in urine culture for 26 days after disease symptoms onset [25]. The persistence of EVD virus poses major risks to the survivors and the community [[29]]. It may lead to reactivation (i.e. relapse) of the illness in affected individuals and onward transmission to others either asymptomatically or symptomatically [[29]]. Animal studies support persistence of Ebola virus and subsequent re-emergence of symptoms [22,37].

Recovery from EVD requires both humoral and cell-mediated immunity [[29]], and there is variability in individuals immune response and between EVD outbreaks [36]. Furthermore, variability in host immunity can determine the susceptibility of the host to reinfection [22]. Recovered mice, who were reinfected with the virus developed lethal infection due to the development of partial immunity [22]. In the trial of ZMab in macaques, 2 of 12 monkeys who had lower immunity succumbed to a reinfection [39]. However, individuals with a more robust immune system, develop subclinical or asymptomatic infection [23,28]. For instance, the virus was detected through PCR in two children in Monrovia, who had recovered clinically and had a negative PCR result at the time of discharge [[29]]. Also, a group of women in Guinea despite repeated exposure to the virus were not infected, with just one of them having the Ebola virus antibodies in her blood [21]. Thus, these points to variability in individual host susceptibility to infection and reinfection, based on the host innate immunity as well as the viral load they are exposed to during an infection or reinfection [[29]].

The Ebola epidemic claimed the lives of more than 11,300 people and infected over 28,500. The disease wrought devastation on families, communities and the health and economic systems of the 3 most affected countries (Guinea, Liberia and Sierra Leone) [46]. According to the World Health Organization, the risk of re-introduction of infection is diminishing as the virus gradually clears from the survivor population, but more flare-ups are still anticipated [46] and that strong surveillance and response systems will be critical in the months to come. Thus, the purpose of the current study is to assess the impact of relapse and reinfection of Ebola on the transmission dynamics of EVD in a population. To achieve this objective, a new deterministic compartmental model, which incorporates the above features and other pertinent epidemiological, demographic and biological aspects of EVD, will be designed and the theoretical properties will be investigated.

A number of mathematical models and statistical methods have been used in an attempt to understand the transmission dynamics of EVD (see, for instance, [3,4,16,20,26,32,38], and some of the references therein). In [16], a compartmental mathematical model was used to estimate the number of secondary cases generated by an index case, in the absence or presence of control measures, for the 1995 Congo and 2000 Uganda Ebola outbreaks. The study further highlighted the importance of basic public health control measures, such as public health education, contact tracing and quarantine of suspected cases, and the role such measures can play in reducing the final size of the epidemics. Most recently, the basic reproduction number for the 2014 Ebola outbreak was estimated in [3,4,20,30,32,38]. Agusto et al. [3], using incidence data from Guinea estimated $\mathcal{R}_0$ for EBOV and investigated the impact of non-pharmaceutical control measures. Their study shows that the disease incidence can be reduced by simple use of non-pharmaceutical measures sure as increasing the duration of healthcare workers' daily work shifts; limiting the length of hospital visitation of members of the public and effectively educating the populace to desist from practicing traditional/cultural beliefs system and customs that aid the spread of Ebola in the affected regions. Althaus [4] estimated $\mathcal{R}_0$ for EBOV using incidence data and a SEIR model. The study emphasizes the heightening of control measures in the three countries (especially in Liberia). Legrand et al. [26], developed a compartmental model, using data from 1995 Democratic Republic of Congo (DRC) and 2000 Uganda epidemic, which allow for EBOV transmission by infected people in the community and in the hospital.

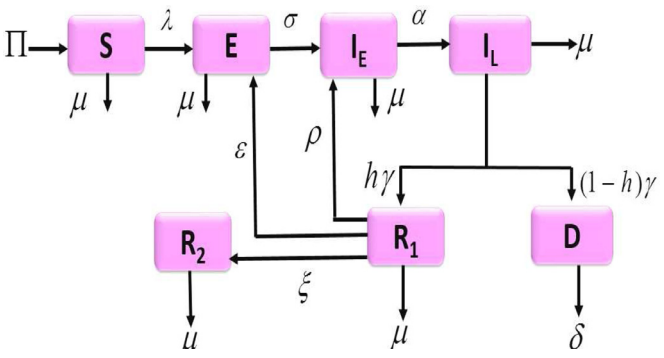

Fig. 1. Flow diagram of the Ebola transmission model.

The paper is organized as follows. The model is formulated in Section 2. In Section 3, we investigate the theoretical properties of the Ebola model with relapse and reinfection and carry out numerical exploration of the model in Section 4. Discussion and conclusions of this study are stated in Section 6.

2. Model formulation

We model the transmission dynamics of the Ebola virus disease (EVD) extending the compartmental framework of the pre-intervention model presented in [3]. The total population, $N_H(t)$, at time t is split into mutually-exclusive sub-populations of individuals who are susceptible ($S(t)$), exposed ($E(t)$), symptomatic individuals in the early-stage of EVD infection ($I_E(t)$), symptomatic individuals in the late-stage of EVD infection ($I_L(t)$), recovered and immune individuals ($R_1(t), R_2(t)$) and Ebola-infected deceased individuals ($D(t)$). So that

$$N(t) = S(t) + E(t) + I_E(t) + I_L(t) + R_1(t) + R_2(t) + D(t)$$

The equations of the mathematical model are given below. The flow diagram of the model is depicted in Fig. 1, and the associated state variables and parameters are described in Table 1.

$$\begin{aligned}
\dot{S}(t) &= \Pi - \lambda(I_E, I_L, R_1, D)S(t) - \mu S(t),\\
\dot{E}(t) &= \lambda(I_E, I_L, D)S(t) + \varepsilon\lambda(I_E, I_L, R_1, D)R_1(t) - (\sigma + \mu)E(t),\\
\dot{I}_E(t) &= \sigma E(t) - (\alpha + \mu)I_E(t) + \rho R(t),\\
\dot{I}_L(t) &= \alpha I_E(t) - (\gamma + \mu)I_L(t),\\
\dot{R}_1(t) &= h\gamma I_L(t) - (\rho + \xi + \mu)R_1(t) - \varepsilon\lambda(I_E, I_L, R_1, D)R_1(t),\\
\dot{R}_2(t) &= \xi R_1(t) - \mu R_2(t),\\
\dot{D}(t) &= (1-h)\gamma I_L(t) - \delta D(t),
\end{aligned} \tag{2.1}$$

where,

$$\lambda(I_E, I_L, R_1, D) = \frac{\beta(I_E + I_L + \tau_1 R_1 + \tau_2 D)}{S + E + I_E + I_L + R_1 + R_2 + D}$$

is the infection rate of the disease, and all other parameters are as defined on Table 1. In particular, β is the effective contact (transmission) rate, τ_1 and τ_2 are modification parameters that account