

Mathematical modeling and comparative analysis of the Ebola epidemic reveal effective control measures

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Abstract

Background The Ebola virus disease (EVD) is a highly contagious disease which is caused by the Ebola virus. Various measures were used to prevent and control the spread of EVD in Guinea, Liberia Sierra and Leone. The aim of this study was to find out the most critical measures to prevent and control the spread of EVD and the effect of control in the three countries. **Methods** We used a novel deterministic compartmental model with the parameters that describes the spreading and control of Ebola, and then the data of confirmed case from the WHO was fitted to obtain the effect estimation of control measures. On the other hand, a comparative analysis also was used to explore the process. **Results** The results of our compartmental model showed that the control parameters (a , c) of pre-infection and post-infection are (0.1827, 0.1091), (0.5832, 0.3278) and (0.3696, 0.1281) in Guinea, Liberia Sierra and Leone, respectively. This means that the control measures in Liberia Sierra works best and that in Guinea works worst. The results of comparative analysis based on the same data showed that the quarantined individuals before infection (R -squared $R^2 = 0.848$, standardized coefficients $\varepsilon = 1.025$), the safe burial teams ($R^2 = 0.772$, $\varepsilon = 0.365$), and the Ebola treatment units (ETU) beds ($R^2 = 0.690$, $\varepsilon = 0.424$) could significantly influence the incidence of EVD. **Conclusion** These findings indicted that a timely and effective quarantine plays a significant role in preventing and controlling the spread of EVD, and the findings would help us prevent and control the epidemic outbreak of new infectious disease in the future.

Background

Ebola virus disease (EVD), previously known as Ebola hemorrhagic fever, is caused by infection of the Ebola virus. Beginning in December 2013 in West Africa, precisely in Guinea, the EVD outbreak spread to Sierra Leone and Liberia at the fatality rates of 73.2%, 43.0% and 52.5%, respectively[1]. Until now, EVD has been known to be a highly contagious disease with a high mortality rate. Ebola virus is classified as a [biosafety level 4](#) agent by the World Health Organization (WHO)[2, 3] A total of 28,616 Ebola cases and 11,310 deaths have been reported in Guinea, Liberia and Sierra Leone[4].

Mathematical modeling has contributed to the investigation of EVD dynamics in recent years. Chowell et al. proposed a stochastic *SEIR* model to fit the data of EVD outbreaks from 1995 to 2000 in Congo and Uganda, respectively [5]. They were able to determine the basic reproduction numbers of the EVD spread in the two countries. Althaus et al. applied an *SEIR* model to study the reproduction numbers of the 2014 EVD spread and predicted the control measure effects through the results obtained [6, 7]. Following these studies, the specific circumstances of the infectious disease spread were taken into account. For example, thanks to improvements in medical treatment, management, and monitoring, mathematical models were improved by adding these components. Adnan Khan et al. established an $S_L S_H E I H R$ model and obtained the reproduction numbers for Liberia and Sierra Leone [1]. In this model, the susceptible individuals were divided into low-risk (S_L) and high-risk (S_H) groups according to their geographical differences. According to the data of Congo and Uganda, an *SEIHDR* model was established in which H , F , and R represented the hospitalized status, dead (not buried) patients, and buried patients, respectively [8]. Camacho et al. proposed an $SE_{pp} E_h I H D B R$ model and estimated that the human-to-human reproduction

number was 1.34 in the EVD early phase [9]. Especially, they suggested that Ebola control would be difficult when counting on hospital-based control measures alone.

Recently, some researchers focused on the control measures in the breakout and analyzed the effect of the measures. Pandey et al. highlighted the Ebola spread in funerals through different space compartments that represented different groups [10]. They considered that control measures at different times had different impacts, which allows for further discussion. Lewnard et al. developed a model to assess the effectiveness of expanding EVD treatment centre, increasing case ascertainment, and allocating protective kits for controlling the outbreak in Montserrado [11]. The authors in reference [12] studied how many cases were averted as a result of the introduction of additional treatment beds in each area. An *SEIR* type model which characterizes the impact of contact tracing on the effective reproduction number of Ebola was represented [13].

To estimate the control measures adopted by the three countries and analyze which types of efforts they should make, we propose an $SE_f E_c I_f I_{fc} R$ model, in which the exposed and infectious individuals are classified into several compartments according to their controlled situations to assess their intervention strategies. We estimate the two parameters of the model, that is, the efficiencies of the pre-infected and post-infected control measures, by fitting the model to the weekly confirmed case data from the WHO. Our results show that the pre-infected and post-infected control measures in Liberia are the best among the three countries. Further analysis shows that more effort should be made in Guinea because the relative rates of change (the predicted confirmed cases with respect to the two parameters) are the largest.

During the spreading and control process of the breakout, too many factors determine the state of system. In fact, modeling the process quantitatively and exactly is an impossible task. From another perspective, we use comparative analysis to estimate the effect of these control measures.

Methods

The $SE_f E_c I_f I_{fc} R$ model

When few efficient control measures were taken for the early phase of EVD outbreak, we only used the classical *SEIR* model as the early dynamic model. For the middle and late phases of the epidemic, a new model is necessary to capture the key characteristics of the control measures.

The population transmission diagram of the model is depicted in **Figure-1**. Considering the quarantine and isolation measures, the compartments E_c , I_c and I_{fc} are added to the *SEIR* model. The subscript *c* represents the control state (quarantined or isolated), and *f* stands for the control-free state. For example, the compartment E_c represents the quarantined latent subpopulation. An individual with state E_c will naturally become an individual with an isolated infectious state after several days, that is, I_c . The subscript *fc* represents the isolated status after a control-free status. I_{fc} stands for those previously

control-free individuals who were infected and then were sent to a hospital for isolation and treatment after further Ebola testing and diagnosis due to their Ebola symptoms.

Fig.1. State transitions of individuals in the $SE_f E_c I_f I_{fc} R$ model.

In Fig.1, the parameter a describes the ability of a country and the government to identify and quarantine high-risk individuals. A larger value for a means that a government can more efficiently identify a high-risk individual before the person is infectious. The parameter c describes the ability of a country and the government to control the epidemic for the infected individuals. Also, a larger value of c means that people can isolate the infective individuals earlier. The system's differential equations are shown as follows: (see Equation 1 in the Supplementary Files)

Data sources

Data fitting is done using the weekly confirmed case data reported by the WHO in Guinea, Liberia and Sierra Leone [14]. The value of $I(t)$ is the sum of the compartments I_f , I_{fc} and I_c in the model.

Parameter values

The parameters σ and γ in the model can be obtained from published papers (or data), as described in Table 1.

Table 1. The parameters used in the models.

Estimation scheme

To obtain the infection rate β in the classical $SEIR$ model, we used Runge-Kutta method of order 4 with good precision and speed. The method's formulas are shown as follows: (see Equation 2 in the Supplementary Files)

The $SEIR$ model and preliminary data are used to determine the infection rate β in the three countries. To solve the optimal parameter value, the function $fmincon$ is used in *Matlab*. We optimize β with the constraint condition $0 < \beta < 1$ in the least-squares (OLS) sense. The objective function is in which d is the weekly confirmed cases data in the early phase by the WHO and m is the corresponding simulation obtained. The confirmed cases of the three countries before 40th week, 25th week and 24th week are used.

In the middle and late phases of the outbreak, that is, the period after 40th week, 25th week and 24th week for the three countries, we use the $SE_f E_c I_f I_{fc} R$ model and fit the model to the middle and late phases confirmed cases data of the three countries and get the values of parameter a and c . We fix the other parameters mentioned above and then solve the parameters a and c by $fmincon$ in the objective function with constraints $0 \leq a \leq 1$ and $0 \leq c \leq 1$.

Statistical analysis

Multivariate linear regression analysis are conducted to analyze the relationship between the number of weekly ETU beds, the quarantine number before infection, the number of safe burial teams and increase rates of new cases, R^2 was the correlation coefficient, ε was the standardized parameters. All statistical analysis are two sided and conducted by SPSS 11.0 for Windows. A P value < 0.05 is considered statistically significant.

The comparative analysis of the control measures

To estimate the impacts of pre-infected and post-infected control measures for preventing EVD spread, we conduct a correlation analyses between the growth rates of the confirmed cases and some measures used in West Africa. We use the published data from situation reports from the WHO from August 2014 to May 2015 over the course of the outbreak. This time period includes all the phases of the EVD epidemic, from the rapid spread of EVD; that is, the height of the outbreak, to the time when the epidemic situation has been gradually controlled. Throughout this period, the control measures become comprehensive and standardized step by step; however, it is notable that there are differences between the three countries in the effects of the epidemic situation control. We evaluate the correlation between the measures adopted in different phases and the increases in the rates of EVD. We estimate it from the 34th week of the epidemic outbreak when the WHO first issued an Ebola epidemic situation report (August 29, 2014) to the 70th week when the epidemic situation had been apparently curbed (May 13, 2015). The reason why we choose this time period for the study is that it includes the gradual increase-to-decrease process of intervention measures that are described in detail, despite some data deficiency. On the basis of having confirmed the favorable linear relationship between different measures and the increase rates of new confirmed cases, respectively, we use a multivariate linear regression to compare the effect of intensities of different measures on the increase rates of new confirmed cases.

Results

Numerical results and analysis

Using the $SE_f E_c I_f I_{fc} R$ model with parameters in **Table 1** and the data from the WHO, we show the numerical results of predicted confirmed cases number in the three countries, include the result under control-free and under practical control (**Fig.2**). The blue curve is the predicted confirmed cases number by fitting the early phase weekly data to an $SEIR$ model. The black curve is the result by fitting the data to our $SE_f E_c I_f I_{fc} R$ model. It is clear that the three maximum values of new weekly infected cases are up to about 290, 1,100, and 1,300 in Guinea, Liberia, and Sierra Leone, respectively, which are far more than the confirmed cases from the WHO (171, 364 and 565, in the same order). This result implies that the Ebola prevention and control measures are urgent and important. Evidently, the practical control measures in the three countries are effective.

Fig.2. Comparative between the fitting results of two models and the data from the WHO.

We also obtain the basic reproduction number of the system (1). The basic reproduction number under control $R_c = (1 - a)(1 - c)\beta/\gamma$ by using method in [16]. The estimated parameters in the model are shown in **Table 2**. A larger value of a means that more efforts toward high-risk individuals in the country were made thanks to the pre-infected measures, such as common knowledge of Ebola, laboratory capacity, effective quarantine aimed to probable and suspected patients, contact tracing and Community Care Centre (CCC). The results show that Liberia's pre-infected measure is the most efficient ($a = 0.5832$), follows by Sierra Leone ($a = 0.3696$), and then Guinea ($a = 0.1827$). Meanwhile, a larger value of c means that more efforts toward infectious individuals were made thanks to the post-infected measures, such as laboratory capacity, effective quarantine aimed at patients with a definite diagnosis, and the number of safe burial teams for dead patients, contact tracing team number, and ETU beds number. It is clear that the post-infected measures in Liberia ($c = 0.3278$) worked better than those Sierra Leone ($c = 0.1281$) and in Guinea ($c = 0.1091$), and Guinea achieved the worst outcome in terms of pre-infected and post-infected control measures.

Table 2. The results of key parameters in the model.

To show the impact of the two control parameters, we determine the numerical results of the relation between the predicted accumulated numbers in the model and the two control parameters. In **Fig.3**, the predicted value is a decreasing function of the two parameters. For the three countries, the predicted values of the accumulated infected number will sharply decrease when the two parameters decrease in the field with small a and c . It is shown that the estimated values of Guinea lie in the sharply decreasing field while those of Liberia lie in the gently decreasing field. This means that Liberia conducted a more efficient control strategy and Guinea's control strategy needed improvement.

Fig.3. The predicted accumulated confirmed cases in the model vs. a and c is the control parameters ("*" in the figure is the fitting value in Table 2).

We further studied the sensitivity of parameters a and c . We fixed one parameter at the values shown in **Table 2** and varied the other parameter. As shown in **Fig.4** and in **Table 3**, we can find that Guinea had the largest relative rates of change with respect to a and c , which means that small improvement in the control strategy will sharply decrease the accumulated infected number.

Table 3. The relative rate of change in the three countries.

Fig.4. The sensitivity of parameters a and c in the three countries.

Based on the information on EVD spread control measures in the situation reports provided by the WHO, we obtain the following data: the number of Ebola treatment units (ETU) beds, the number of suspected cases and probable cases, which we defined as the quarantine number before infection, and the number of safe burial teams. First, we conduct a correlation analysis among the three measures above and the weekly EVD increase rates in Guinea, Liberia and Sierra Leone, respectively (**Fig.5, Fig.6 and Fig.7**). The new confirmed case increase rates are all negatively correlated with the three measures, with a

statistically significant difference. The number of weekly ETU beds, the quarantine number before infection, and the number of safe burial teams are modeled separately with the increase rates of new confirmed cases, and the results of which achieve a goodness of fit. R^2 are 0.690 ($P < 0.001$), 0.848 ($P < 0.001$), and 0.772 ($P < 0.001$), respectively. Moreover, to know which of the three measures has the greatest impact on the increase rates of new confirmed cases, we conduct a multivariate linear regression analysis to identify the most relevant factors against the overall backdrop. The results are shown in **Table 4**. The absolute values of the standardized coefficients of quarantine measures before infection is the largest ($\varepsilon = 1.012$, $P < 0.01$), that of increasing the ETU beds number follows ($\varepsilon = 0.432$, $P < 0.05$), and that of increasing the safe burial teams is the smallest ($\varepsilon = 0.385$, $P < 0.05$).

Fig.5. The correlation analysis between established ETU beds and the weekly EVD increase rates in Guinea.

Fig.6. The correlation analysis between quarantine before infection and the weekly EVD increase rates in Liberia.

Fig.7. The correlation analysis between safe burial teams and the weekly EVD increase rates in Sierra Leone.

Table 4. Standardized coefficients of the three measures.

All of the three measures have a favorable linear relationship with the increase rates of new cases. The results of multivariate linear regression analysis indicate that expanding the quarantine before infection is the most effective control measure. The following figures demonstrate the results above. Apparent differences are observed in the quarantine number before disease among the three countries (**Fig.8, Fig.9 and Fig.10**). Within the statistical data we obtained, the ranking of the maximum proportion of the quarantine number before infection of the total quarantine number is as follows: Liberia (79.31%) > Sierra Leone (31.35%) > Guinea (25.62%), and the differences among the three countries are all statistically significant ($P < 0.05$).

Fig.8. The quarantine number before EVD outbreak in Guinea.

Fig.9. The quarantine number before EVD outbreak in Liberia.

Fig.10. The quarantine number before EVD outbreak in Sierra Leone.

Discussion

The outbreak of EVD began in December 30, 2013 in Guinea, and it is considered as the largest, the most serious, and the most complex international crisis by the WHO. Then, it spread into the three countries (Liberia, Guinea, and Sierra Leone) in West Africa within a very short time, although they are not first occurrence locations. The climate environment, religion, customs, poverty, population density and so on,

are all potential factors causing the outbreak of Ebola virus in West Africa. Contact is the main route of transmission for EVD.

Many control measures were used in the breakout in west Africa three countries. A model that can describe all these effects will guide the action of government and individual. But it is almost impossible to construct this model. We distinguished the control measures and composed their effects into two parameters: pre-infection effect a and post-infection effect c . The results of model can evaluate the effect of control in the three countries by using the parameters and our analysis on the relative rate of change of the predicted infection number with respect to the parameters can point out which country need more effort in the control. Of course, more overall and careful work about the method in our model need advance in the future. Furthermore, we used comparative analysis point out the effect of the three types control measures, the quarantined individuals before infection, the safe burial teams and the ETU beds.

Admittedly, besides the three measures discussed in this paper, there are many measures that could have effects on the epidemic situation. For example, the laboratory capacity will influence the detection rate and speed of patients' blood sample testing and in this way it will influence the reaction time of taking effective measures such as quarantine and treatments on real EVD patients as well as self-protection of medical care workers; the number of professional personnel involved in contact tracing could influence the probability of second transmission by infected people, thus affecting transmission control. However, because of data deficiency, quantitative analysis in these regards will not be included.

Following our paper, further work can continue with following aspects: the development and impact of an Ebola vaccine on prevention and control measures; the effects of population behaviors, such as commerce, tourism and others; detailed numbers of hospitals, ETUs and isolation in the community; more accurate analysis of the effects of specific prevention and control measures; the availability of beds in ETUs estimated from the observed data; the limitations in the amount and timely payment numbers of hospital patients who could be accommodated; and the allocation of Ebola patient beds and so on.

Conclusion

In this study, we mainly evaluated the effects of Ebola intervention strategies. By comparing the infected number of patients before and after the interventions through the model, it is evident that timely and accurate intervention strategies, such as quarantine ability, isolation, and hospitalization, can effectively control the outbreak and transmission of EVD in the three countries in West Africa. However, the most important intervention is quarantine, which has an obvious influence on infection rates. Our model is designed to capture the key characteristics of Ebola spread and determine the effect of control measures. This is an innovative result for Ebola disease models, which has not been presented before and will be useful for investigations of effective epidemic control measures in the future as well. The three countries' prevention and control measures in West Africa are estimated and compared quantitatively.

To determine the effects of a and c obtained in the model in practical epidemic situation control, we classify the control measures in the situation reports of the WHO—the measures related to a include

common knowledge of Ebola, laboratory capacity, effective quarantine aimed to probable and suspected patients, contact tracing and Community Care Centre (CCC). All of these are targeted at probable and suspected individuals without a definite diagnosis. The measures related to c include laboratory capacity, effective quarantine aimed at patients with a definite diagnosis, and the number of safe burial teams for dead patients, contact tracing team number, and ETU beds number. However, incomplete data on the control measures during the epidemic expansion impose restrictions on the integrated and comprehensive analysis. Consequently, although we can only conduct quantitative analysis on the ETU beds number, the number of quarantined individuals before infection, and the numbers of safe burial teams, the three measures act as the core measures in epidemic situation control.

The effectiveness ranking of the three measures we obtained from the multivariate regression analysis is: quarantine before infection > the number of ETU beds > safe burial. We find that the result supports the result of our $SE_f E_c I_f I_{fc} R$ model. The epidemic situation control in Liberia is the best among the three countries in West Africa.

Abbreviations

SEIR model: susceptible-exposed-infected-recovered model;

$S_L S_H E I H R$ model: low-risk susceptible individuals, high-risk susceptible individuals, exposed individuals, infected individuals, hospitalized individuals, and recovered individuals R .

$SE_{pp} E_h I H D B R$ model: susceptible to infection (S); entering an incubation period (E); symptomatic and infectious in the community (I); entering a recovered state (R); remain infectious and go into hospital (H); or die and remain infectious (D) until buried (B).

$SE_f E_c I_f I_{fc} R$ model: susceptible to infection (S); control-free exposed individuals (E_f); exposed individuals quarantined (E_c); control-free infected individuals (I_f); infected individuals isolated (I_c); The subscript fc represents the isolated status after a control-free status; isolated infected individuals who were infected and control-free and then were sent to a hospital for isolation due to their Ebola symptoms (I_{fc}); and recovered individuals R .

Declarations

Ethics approval and consent to participate

Because this study constituted public health rather than research in human beings, ethical approval from institutional review boards was waived by the ethic committee of Southwest Hospital, Third Military Medical University. Data collected from participants in this study are weekly confirmed case data reported by the WHO in Guinea, Liberia and Sierra Leone [16].

Consent for publish

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' Contributions

LSW and JYY established the $SE_f E_c I_f I_{fc} R$ model, JLL did statistical analysis and wrote the original manuscript, LSW and JLL contributed equally to this work and listed as the first authors. HW conceived the study and obtained financial support. CPS, JMZ, LNZ, ZJZ, JP, YL, HYZ and YGW did the literature search and data collection. All authors have reviewed and approved the final manuscript.

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Tables

Table 1. The parameters used in the models.

Country	Parameter	Meaning	Value	References
Guinea	$1/\sigma$	the incubation period	10.9	[15]
	$1/\gamma$	the infection period	6.4	[15]
Liberia	$1/\sigma$	the incubation period	11.7	[15]
	$1/\gamma$	the infection period	7.9	[13] [15]
Sierra Leone	$1/\sigma$	the incubation period	10.8	[15]
	$1/\gamma$	the infection period	6.7	[13] [15]

Table 2. The results of key parameters in the model.

Country	β	Parameter	Value	R_c
Guinea	0.2131	a	0.1827	0.9930
		c	0.1091	
Liberia	0.2414	a	0.5832	0.5343
		c	0.3278	
Sierra Leone	0.2062	a	0.3696	0.7593
		c	0.1281	

Table 3. The relative rate of change in the three countries.

Liberia	-0.1750	-0.1746
Sierra Leone	-0.1628	-0.1726
Guinea	-0.5139	-0.5050

Table 4. Standardized coefficients of the three measures.

Measure	Standardized coefficients ε	P value
Established ETU beds number	0.424	$P < 0.05$
Quarantine before infection	1.025	$P < 0.01$
Safe burial team number	0.364	$P < 0.05$

Figures

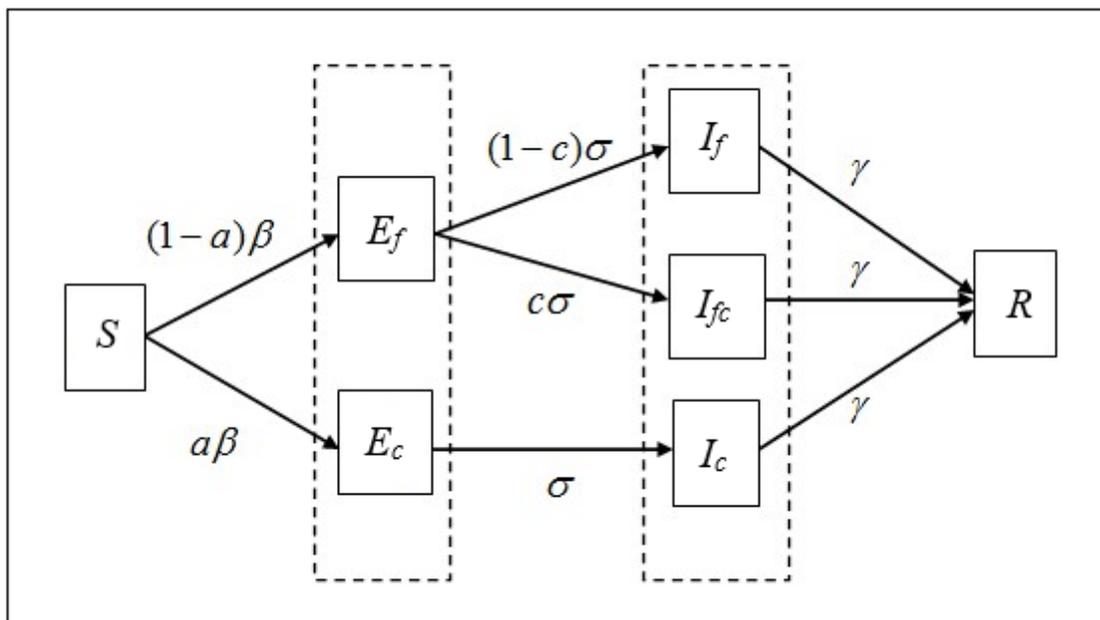


Figure 1

State transitions of individuals in the SEfEclfcR model

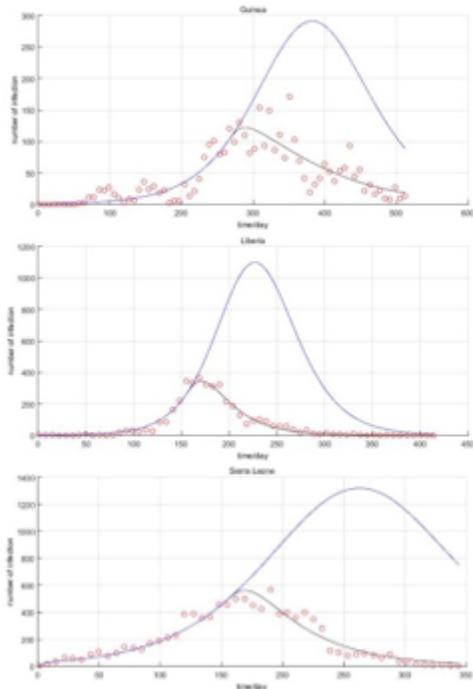


Figure 2

Comparisons between the fitting results of two models and the data from the WHO. The blue curve is the predicted confirmed cases number by fitting the early phase weekly data to an SEIR model. The black curve is the result by fitting the data to our SEfEclflcR model. The red circles are the data of confirmed cases from the WHO.

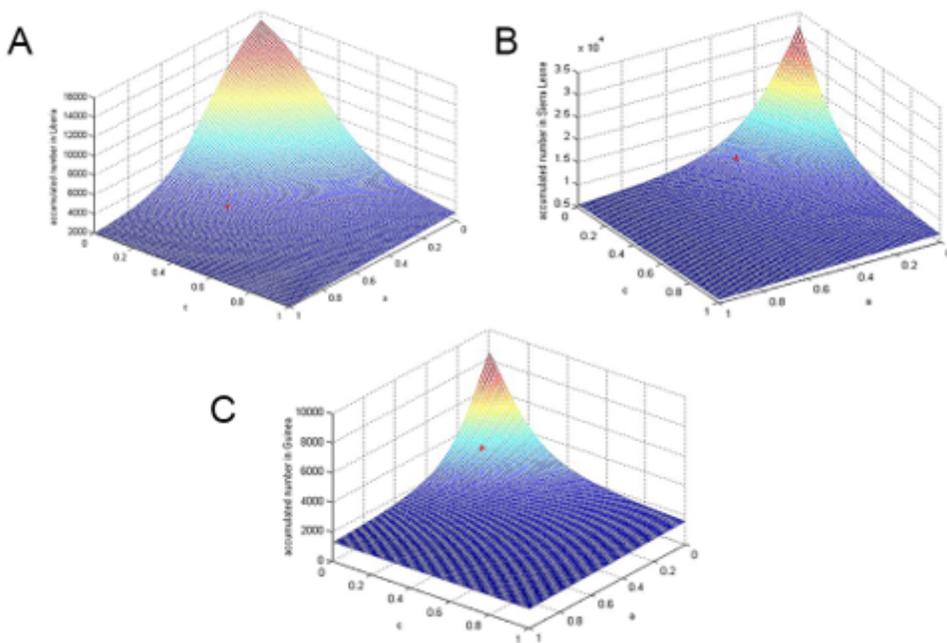


Figure 3

The predicted accumulated infected number in the model.

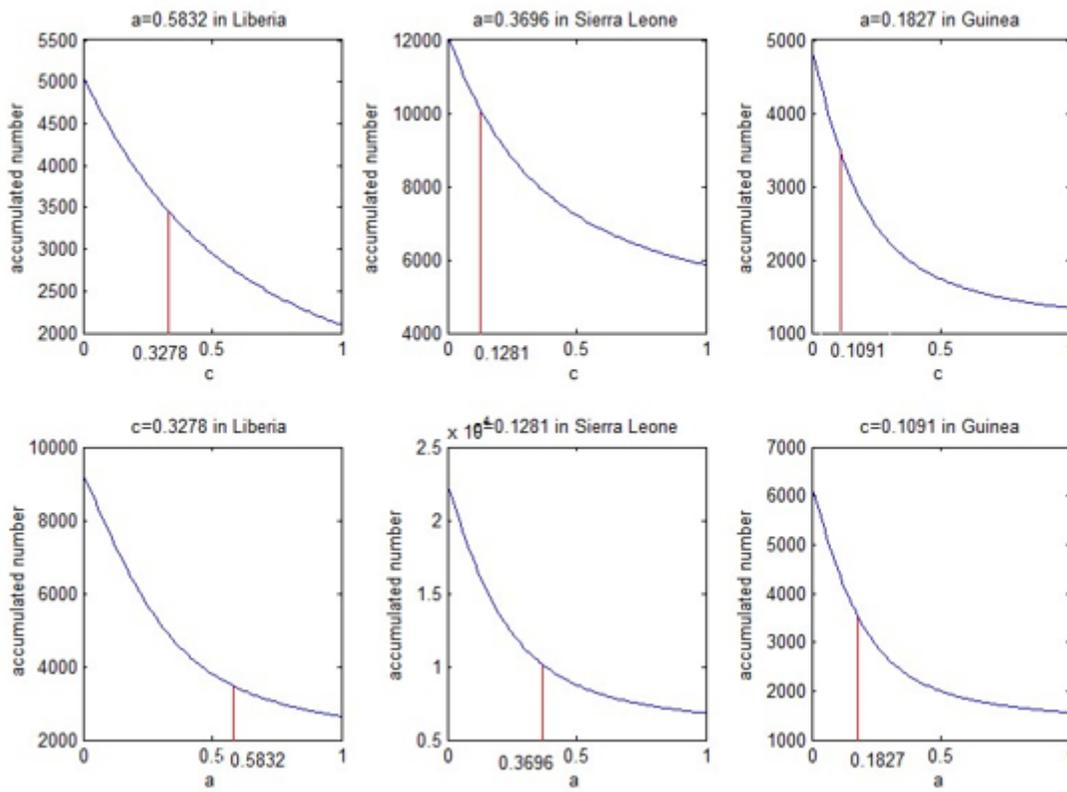


Figure 4

The sensitivity of parameters a and c in the three countries.

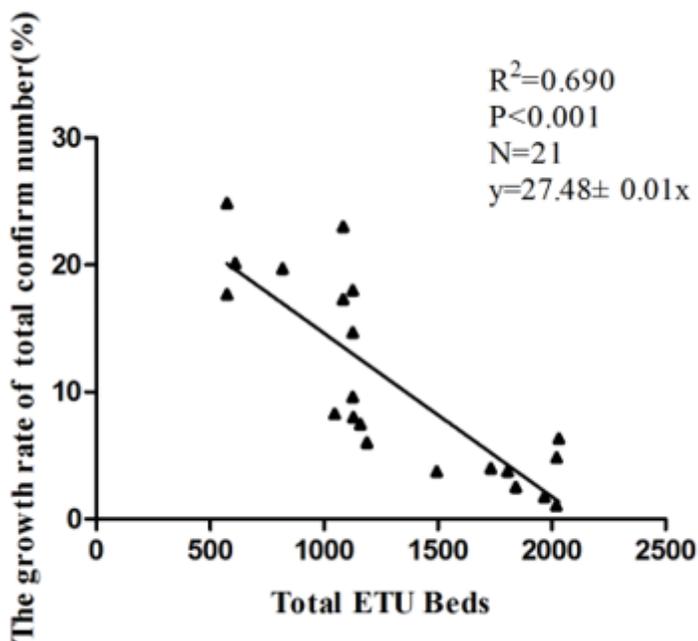


Figure 5

The correlation analysis between established ETU beds and the weekly EVD increase rates in Guinea.

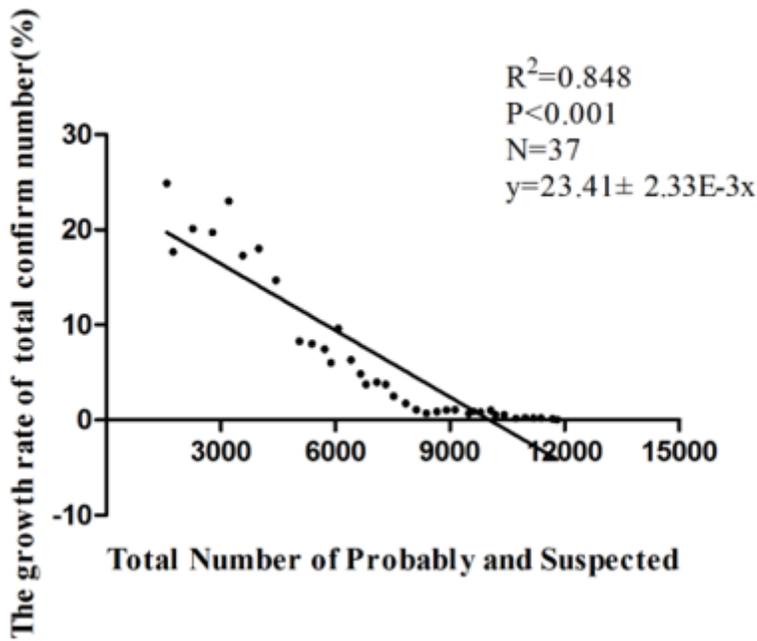


Figure 6

The correlation analysis between quarantine before infection and the weekly EVD increase rates in Liberia

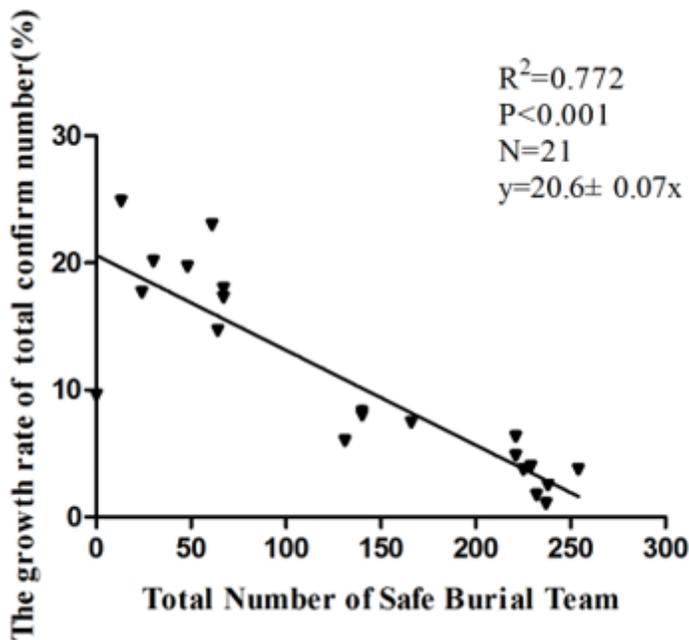


Figure 7

The correlation analysis between safe burial teams and the weekly EVD increase rates in Sierra Leone

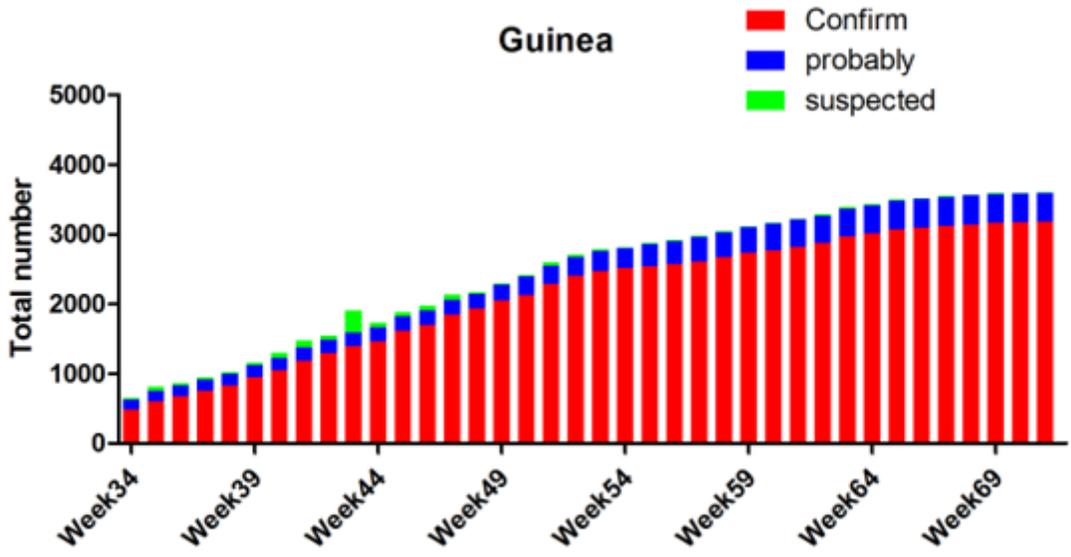


Figure 8

The quarantine and isolated number (include confirmed, probably and suspected number) in Guinea.

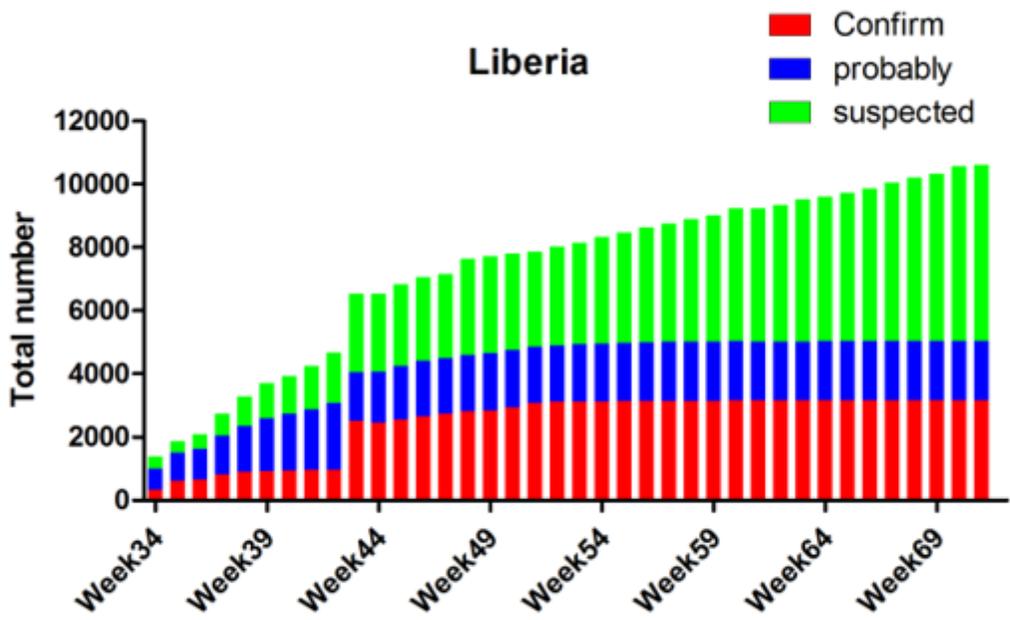


Figure 9

The quarantine and isolated number (include confirmed, probably and suspected number) in Liberia.

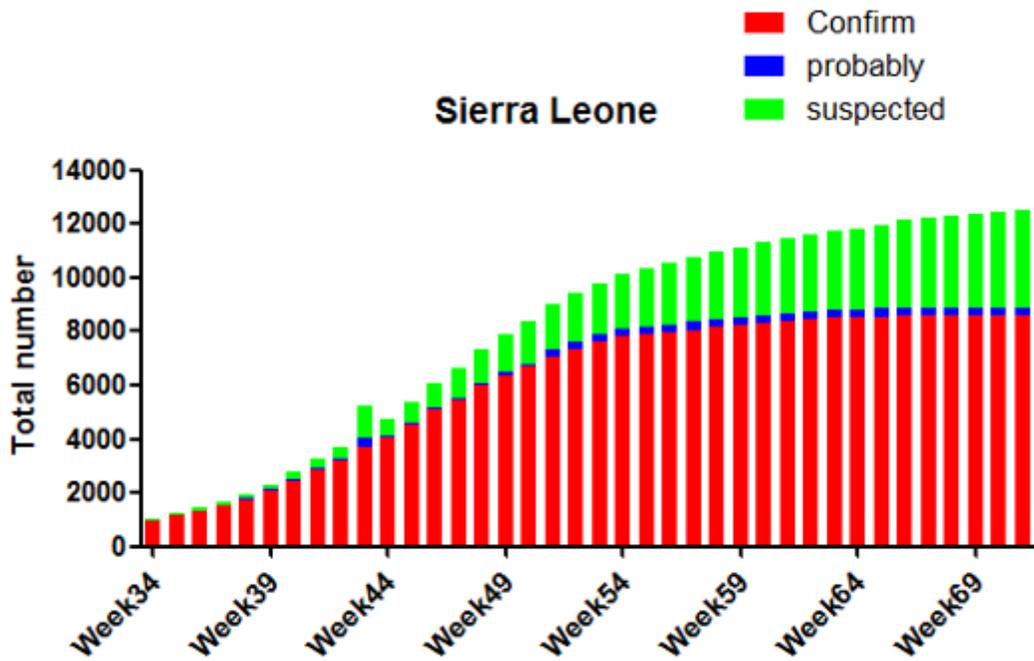


Figure 10

The quarantine and isolated number (include confirmed, probably and suspected number) in Sierra Leone.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Equation2.jpg](#)
- [Equation1.jpg](#)