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A review on West African Ebola epidemic dynamics models

Philemon Manliura Datilo, Zuhaimy Ismail*
Mathematical Sciences Dept., Universiti Teknologi Malaysia, Malasia.
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ABSTRACT

Background and aims: The world is threatened by disease outbreak that reaches a public health emergency of international concern, studies to inform public and agencies for effective containment strategy are necessary. Several studies provided vital information of the dynamics and control of Ebola epidemic outbreak in West Africa. Methodologies and techniques in those researches have to be reviewed for purposes of synthesis of published research in this area, insight into how to carry out similar studies and future research direction.
Methods: In this report we adopted a thematic review of recent studies that covered topical issues of epidemic model theories and applications used in Ebola investigations. Models for studying severity and prevalence of the disease, statistics, and growth threshold parameters, efficacy of intervention measures, and uncertainty and sensitivity analysis of the disease models were reviewed.
Results: In 1966, 6.34% of the national total population was over 60 years compared to Ebola dynamics is widely investigated, covering topical epidemiological problems that involves mathematical model for purposes of providing quantitative information for epidemic control decisions.
Conclusion: Mathematical models play great role in modelling epidemics,. Therefore, a comprehensive survey of mathematical theories, methodologies and models in Ebola growth studies will provide standpoints for future epidemic investigation.

Keywords: Ebola, Epidemic model, Epidemic optimal control, Sensitivity analysis.

Review Article

INTRODUCTION

The world is threatened by outbreaks of epidemics, MERS in Arabian Peninsula and South Korea, SARS in South East Asia and Canada, Ebola in Africa, HIV/AIDS the world over, dengue in South East Asia, Western Pacific, Zika virus in Africa and Asia, Lassa fever in Africa, and many others.[1] Epidemic outbreaks spanned the period of human existence, with differing fatality rates in infected countries' populations. Ever since Ebola broke out in Zaire in 1976, it had continually re-emerged in countries in Africa and other part of the world killing over 1542.[2] In the recent West Africa (Guinea, Liberia, Sierra Leone, Nigeria, Mali and Senegal) outbreak the death toll is nearly half the infected population.

Mathematical models that govern overall behaviour of epidemic growth, so that correct parameter estimates that can be used to

*Corresponding author: Zuhaimy Ismail, Mathematical Sciences Dept., Universiti Teknologi Malaysia, Malasia, Tel: 0060143101974, E-mail: zuhaimyi@yahoo.com

simulate epidemic process using stable relations in the epidemic growth model, and appropriate sensitivity or uncertainty for control factor influence analysis upon epidemic dynamics is an inevitable exercise for stopping epidemics. However, it is challenging to determine right tools for analyzing epidemic growth model. Therefore a comprehensive survey of mathematical theories, methodologies and models in Ebola growth studies will provide guideline for future epidemic investigation. This survey provided insight into Ebola epidemic model by several authors with resolved mathematical models and tools selection problems.

The recent outbreak of Ebola had prompted research interest in developing its dynamics models and control strategies. In this report a thematic review of methodologies and techniques used by several authors in investigating the transmission and dynamics and control strategy mix. The review presented underlying mathematical theory, methods, and application Ebola investigations. It attempts to provide analysis of epidemic models, disease prevalence, control and sensitivity analysis of Ebola control and model parameters. Articles in this review are sourced from different journals, with related search key term of Ebola epidemic. The period of search is from 2013 to date. Necessary theoretical background overviews are sourced from related fundamental and related topical studies of subject matter. The number of articles or journal type is not predetermined; this is because of the broad interest in the Ebola outbreak. Application of newer techniques under some heterogeneous assumptions or condition are underway; Therefore, this review only provided a threshold in understanding of Ebola disease dynamics model, and sensitivity analysis of implementable model parameters and control measures.This review is organized into 5 sections. Section one highlighted the symptoms and transmission modes of Ebola and its global risk. In section two, epidemic dynamics models were summarized, including transmission models, parameters estimation, epidemic model stability analysis, Ebola epidemic growth, scale and prevalence. In section three epidemic control modelling, factors and analysis, and optimal control were reviewed. Finally section four covers the sensitivity and uncertainty analysis for determining control factor influence upon the performance of the epidemic. Lastly conclusion is drawn on the review.

The recent West African Ebola virus disease outbreak is the largest and most complex outbreak. The first case of West African Ebola was a small boy in Meliandou Guinea on December 2, 2013 who died with an illness characterised by fever, black stool, and vomiting.[3] With increasing spread and transmission in the communities and countries Nigeria (July), Senegal (August) and Mali (October), on August 8, 2014 the WHO declared Ebola as epidemic to be a public health emergency of international concern.[2,4,5] The disease continued to spread into neighbouring West African countries, against efforts to control it. The West African Ebola outbreak has caused more cases and deaths than the total previous Ebola epidemics, with average fatality rate of over 48%.[3,5,6]

The increasing rate of transmission and spread of Ebola virus disease threatens the world. Ebola continued to spread, reaching an exponential growth rate[3,7] across West Africa.[8-10] High risk of transmitting Ebola into Africa countries of the world was eminent because of air traffic intensity and border crossing between the affected countries and other countries of the world (Figure 1).[11] If the epidemic continues to remain unchecked to the point that it affects 1% of population of Africa, the outbreak would then clearly pose a global hazard.[12,13]

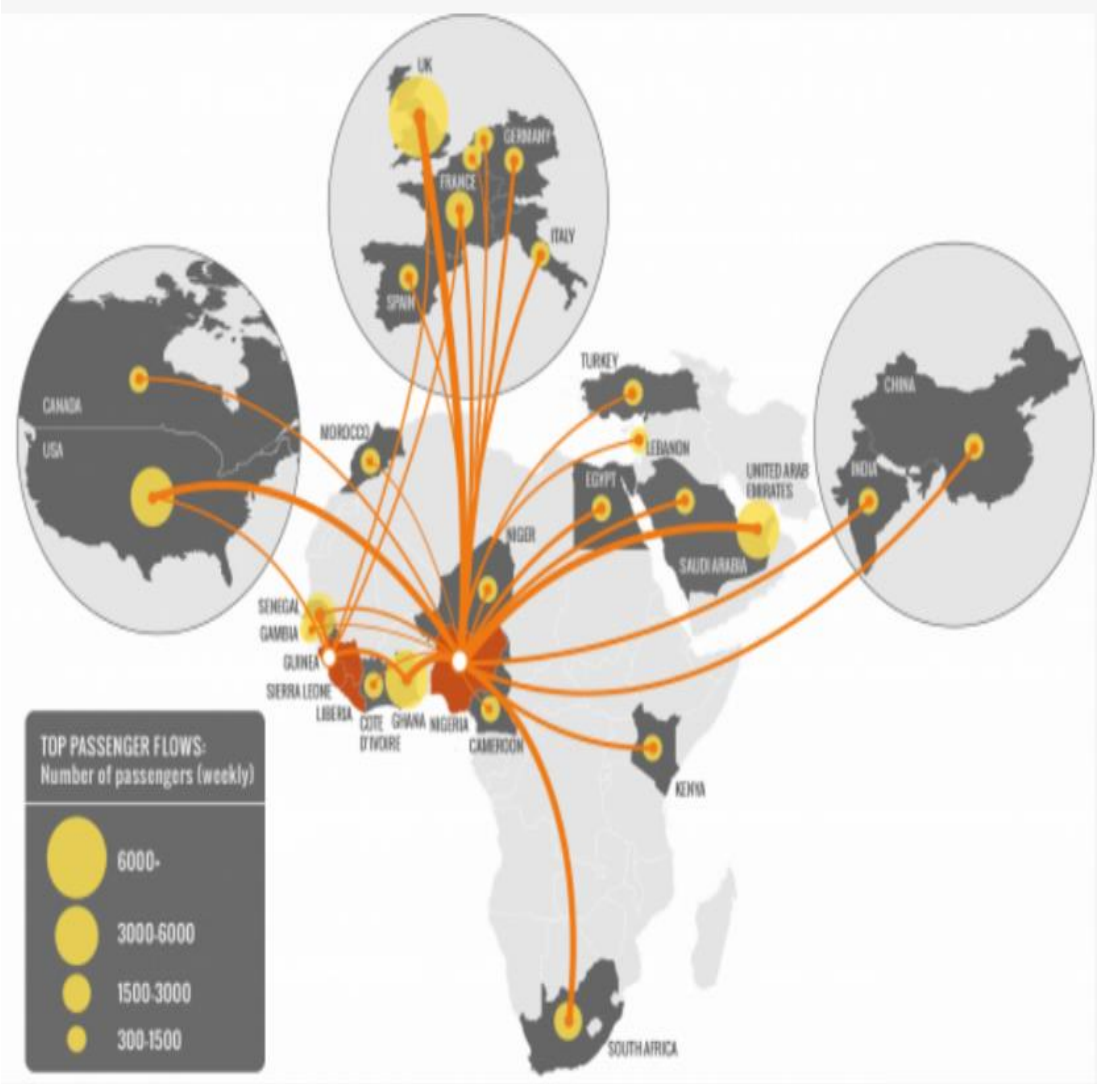

Figure 1: Air traffic connections from West African countries with the rest of the world

Predicting the risk of Ebola in other parts of the world has been widely studied China[14,15] and Europe [8]. To minimize this risk, public health efforts in the European Union and WHO focus on early case detection and isolation, investigation and management of confirmed and suspected cases.[16] A potential response to controlling the spread is to suppress flights, ban cross-border travelling among counties and countries within and outside affected countries.[16]

Parameters of epidemic models influence disease dynamics which is used to explain characteristics of transition and transmission of the disease. Epidemic parameters could be evaluated or observed by clinical values.[17] Basic assumptions have to underline parameter used in epidemic models. Applications of these parameters values in epidemic modelling range from disease dynamics, forecasting and optimization of epidemic control.[18,19] Epidemic parameters are evaluated within certain degree of uncertainty or confidence. More parameters can be incorporated in disease dynamics models with refinement of epidemic transmission and control problem. Some basic parameters that characterize Ebola are presented in Table 1.

Table 1: Ebola parameters estimates summary for the most affected countries

Parameter		Estimate	Reference*
Susceptible (N)	Guinea	10.6M	19,20
	Liberia	4.1M	
	S/Leone	6.2M	
Index case**	Guinea	Dec 2, 3013	19,21-23
	Liberia	Mar 31, 2014/Apr 14	
	S/Leone	April 8, 2014/Mar 23	
Transmission rate (β)	Guinea	0.27	22,24
	Liberia	0.45	
	S/Leone	0.71	
#average infectious period (1/γ)		7.5 days (6-16)	20,24-26
#average incubation period (1/α)		6.3 days	4,20,24,27,28
#average length time from onset to death		10 days	26,27,29
growth rate (r)		Exponential (0.022, 0.12, 0.035)	6,27,30,31

**: Fully or partly evaluated the parameter that fell within the range indicated; **: Different dates have been used by different authors to evaluate dynamics of the disease; #mean length time involving some interventions or control structure are defined based on the dynamics equations.*

SEIR (susceptible-exposed-infectious-recovered) deterministic compartmental structure is commonly used to investigate Ebola. SEIR model divides the population into susceptible, Exposed, Infectious and Recovered individuals. Diseases that have incubating period include among other HIV, influenza, tuberculosis, measles sexually transmitted diseases, the window of incubation varies.[20] Many studies had been carried out to relate the Ebola epidemic to SEIR compartment model as is summarized in Table 2.[21] Due to incorporation of different stages of disease transmission and control measures newer SEIR structure emerges. These structures are not limited, but advances in redefining and simplifying assumptions or disease situations can give more unique variants.

Table 2: Ebola Transmission SEIR Variant Models and control measures investigated

Model	Transmissions	Control	Reference
SEI(HF)R	Hospital, funeral	Isolation safe burial	18,26
SEIH(DB)R	Hospital, dead, funeral	Quarantine, isolation and safe burial	33
SEIIFR	Community, hospital, Funeral	Isolation and safe burial, ETU	24
SEIIIHR	Isolated in hospital	Isolation	34
SEIRD	Dead	Safe burial	31
SEIT	Community	Case management in isolation	35
SEICIsR	Isolated, contaminated	Isolation and Quarantining	36,37
SEIIHFR	Community, hospital, funeral	Media, isolation, quarantine, safe burial	38
SVEEIJDR	Community, hospital, funeral	Vaccination, media, isolation, quarantine, safe burial	39
SEIHRDB	Community, hospital, funeral	Isolation, safe burial	40
SEI-(CCC/ETC)R	Community centres	Quarantine and Isolation	41

S=susceptible; E=exposed; I=infected; infectious; Is=isolated; R=recovered; H=hospitalised; V=vaccinated; CCC=community care centre; D=dead; B=buried; F=funeral; T=treatment.

The rate at which susceptible become infected is called the transmission rate. Transmission rate is one important epidemic parameter that helps accurately analyze the epidemiological characteristic of a disease. It varies with time of epidemic generation. In evaluating transmission of Ebola virus in community, hospital and dead not buried in a SEIR compartment structure establish that transmission rate declines with time, derived transmission rate to be $\beta(t)=\begin{cases}\beta & t<t_* \\ \beta_0 \exp^{-q(t-t_*)} & t\geq t_*\end{cases}$ Where t*, is the time point at which control measure are introduced, β is the initial transmission rate, and is the rate at which decays as.[22-24] Disease transmission model is essential for assessing the risk, spread and fatality of an epidemic outbreak. Ebola transmission rates enabled fits of the epidemic parameters for growth forecasts and spread.[19,21,22,25-28] Transmission rate tends to decline with time due to the impact of intervention and control measures, so that disease growth rate declines accordingly. A logistic or Richards sigmoid function can be used to evaluate Ebola transmission in community, hospital and funeral for time-dependent smooth decreasing function of the transmission rate.[21,22]

Parameters are estimated to gauge whether epidemic model correctly represent the biological process understudy. Epidemic parameters can be fitted, pre-estimated or fixed, based on the disease dynamics and demographic or clinical observation data.[29] Different parameter estimation methods for linear or nonlinear models are used based on convenience, consistency, bias and variance, provision of extra statistical information criteria is necessary. Common estimation techniques that are used for epidemic studies are the least square and maximum likelihood estimation procedure.

Least Squares method estimates epidemic parameters by minimizing the sum of the squared errors. $S=\sum(y_i-f(x_i,\theta))^2$, where is the observed value, $f(x_i,\theta)$ is the model function, with being the vector of unknown parameters. The basic idea behind it is to test different values of parameters in order to find the best fit model for the given data set.

Maximum likelihood fits epidemic model by maximizing a likelihood function, defined as the probability of a given dataset having occurred. The likelihood function is characterized as $L(\theta|x_1,x_2,....x_n)=f(x_1,x_2,...x_n|\theta)=\prod_{i=1}^{n}f(x_i|\theta)$ For convenience the negative log likelihood function is usually minimized as: $\text{neglog}L(\theta|x_1,x_2,....x_n)=-\sum_{i=1}^{n}\log f(x_i|\theta)$, where xi is the observed data points, θ is the vector of unknown parameters and $f(x|\theta)$ is the associated probability density function. Maximum Likelihood estimation is robust, having better sufficiency conditions and smaller errors than other methods. Maximum likelihood estimation provides confidence interval values for uncertainties associated with estimated parameters.[30]

If estimation is done to fit a particular distribution which has insufficient parameters for the biological process there will be un identifiability problem in interpreting the disease dynamics. There are different methods for assessing how well a given model parameter fits particular data-set or distribution, they differ based on how they handle over fitting/under fitting, outliers, and number of parameters to be estimated.[31] Statistics like the coefficient of determination (R^2), standard error (SE), Information Criterion (or AICc) are used to measure performance of parameter estimators of epidemic model.

$$R^2=1-\frac{SS_{res}}{SS_{tot}}$$

$$AIC=n\left[\ln\left(\frac{SSE}{n}\right)\right]+2k$$

$$AIC_C = n\left[\ln\left(\frac{SSE}{n}\right)\right] + 2k + \frac{2k(k+1)}{n-k-1}$$

Reproduction number is the average number of secondary cases produced by a typical infectious host at the onset of an outbreak[32] given as $R_0 = \beta/\gamma$. As an outbreak progresses, transmission rate began to change with epidemic time.[32] If is at threshold ($R_0 = 1$), the number of cases stays constant thus the disease is in endemic stage. If R_0 drops below unity the epidemic eventually stops, otherwise the disease will continue to spread.[33-35] Table 3 summarises reproduction numbers of Ebola in the most affected countries.

Table 3: Summary of R0 values of West African EVD infected nations

Guinea	S' Leone	Liberia	Reference
1.79	1.32	1.81	[24]
1.51	2.53	1.59	[22]
	3.07	1.96	[27]
1.71	2.02	1.83	[4]
	1.85	1.94	[29].
1.11	1.26	1.54	[36]
1.2	1.3	1.9	[19]
1.116	1.181	1.226	[25]
2.75	3	3.2	[34]
1.52	2.42	1.65	[49,50]

Different models and methodologies gave different values of basic reproduction number, partly due to different assumptions[36], timeline and size of data, intervention control programs, incomplete and inaccurate data, demographic or contact rates.[18,21,27] Estimating R_0 from individual parameters is not always feasible, as they may be unknown or impossible to estimate. Alternatively basic reproduction ratio can be estimated from epidemic time series[37] given that, if the exponential growth rate of the initial phase r is available, then. $R_0 = 1 + rD$.

If doubling time of the number of infected individual td is known, $R_0 = 1 + \frac{D\ln 2}{t_d}$.

If the number of susceptible is considered before the outbreak and the number of susceptible after the epidemic dies out, then $R_0 = \frac{\ln(S_0) - \ln(S_\alpha)}{S_0 - S_\alpha}$.

Though R_0 estimates can misrepresent the disease situation[32], it remained an important threshold parameter in determining size of epidemic, control efficiency, epidemic burnout. Epidemiologists use it to gauge control requirement.[36,38,39]

Another important approach to determining the reproduction number is the use of next generation matrix approach, method in which system of ordinary (or partial) differential equations of an infectious disease dynamics model is converted to an operator that translate from one generation of infectious individuals to the next.[40] The reproduction number R_0 is computed as the largest positive eigen value of the next-generation matrix. Hence is given by the largest eigenvalue (or spectral radius) of the matrix. FV^{-1} $R_0 = \rho(FV^{-1})$ Next generation operator approach helps to determine the reproduction number for epidemic models that incorporated proportionate mixing, preferred mixing, heterosexual transmission, host-vector groups, multiple mixing groups, vaccination, and age structure.[41] This method was explored.[24,38,39,42,43] in determining Ebola control reproduction numbers in the community, isolation and funeral.

Stability analysis of an epidemic dynamics model is to establish a disease free equilibrium or endemic equilibrium state. The reproduction number R_0 gives a threshold condition for the stability of the disease-free equilibrium.[29] With the proposition that if, $R_0 < 1$, then the disease free equilibrium is

locally asymptotically stable but if, the disease free equilibrium is unstable.[32]

The Lyapunov theorem is used for two dimensional disease dynamics stability analysis. Stability is determined by evaluating the Jacobian of the disease dynamics' system of differential equations at equilibrium. So, it is determined by solving the characteristic equation $|J - \lambda I| = 0$.

When incorporating public enlightenment and isolation into the disease model[44] evaluated Ebola stability growth model. With higher dimension of disease dynamics Lyapunov theorem using Jacobian approach fails to calculate the R_0, Routh-Hurwitz criterion overcomes this problem. The criteria for stability depends on eigenvalues of Jacobian matrix evaluated at X, $J(X)$. Eigenvalues are determined by finding the roots of polynomial characteristic equation $|J - \lambda I| = 0$. According to the Routh-Hurwitz criterion necessary and sufficient conditions that all eigenvalues of J have negative real parts are $\text{trace(J)} < 0$; $\det(J) < 0$ and $trM - \det < 0$, where M is the sum of second order principal minors of J. If all of the eigenvalues have negative real part, then the equilibrium is locally asymptotically stable.[29] The next generation matrix approach is simpler to evaluate the stability of disease model, and determination of reproduction number.

The early phase of Ebola epidemic is characterized by exponential growth rate. Changes in growth rate measure the effectiveness of intervention or control measures upon the disease transmission. Transmission rate can be used to evaluate R_0. Different growth models including exponential, logistics, delayed logistic, Richards, and delayed logistic or Richards are used to fit and estimate growth rate of an epidemic with few or longer sequence data points.[21] Epidemic growth can be estimated using the phenomenal growth functions which are defined as: Exponential $X(t) = X_0 e^{rt}$

Logistics $c(t) = K((1+[K/c_0)-1]\exp^{-rt})^{-1}$

Richards

$$c(t) = K \Big/ \left(1 + \left[\left(K/c_0 \right)^a - 1 \right] \exp \left\{ -r_0 t \Big/ \left[1 - \left(c_0/K \right)^a \right] \right\} \right)^{1/a}$$

The parameters intrinsic growth rate and the final size K need to be estimated, with initial cases, x_0, c_0, Ebola cumulative is sigmoid characterised, it initially grew exponentially, but later began to decline with a lower intrinsic growth rate.[36] In fitting the early incidences of Ebola, found significant differences in the growth pattern of the disease across infected countries or counties and districts.[45] Logistic model was preferred for modelling epidemic growth against Richards, because of identifiability problem.[46] When used Richards for Ebola, the study revealed multiple waves, at varying lengths, of infection in the most affected countries.[47]

This is a relation that can be used to predict total number of cases during an outbreak, it provides reliable approximation when parameters and the total population do not change after some time T, as often is the case when the interventions are effective.24 Different methods based on different distributions can be used to evaluate the final size of an epidemic48. The standard epidemic size relation is given as49: $\ln \frac{S_0}{S_\infty} = R_0 \left(1 - \frac{S_\infty}{S_0} \right)$.

In the case of effective intervention and control, the final size50 is $\ln \frac{S_0}{S_\infty} = R_c \left(1 - \frac{S_\infty}{N} \right)$ where R_c is the control reproduction number. The notation S_∞ expresses the number of susceptible at the end of the outbreak. It can be used to forecast the total number of cases during the outbreak when effective interventions are in place. It can help determine sensitivity of the total number of cases to the intervention parameters and relative importance of each measure.[24]

A long term state of disease dynamics can be determined using burnout relation. The burnout is a scalar result that determines the

number of susceptible that will remain uninfected throughout the epidemic generation or until the disease dies out. Firstly, it has been observed that there will always be a certain number of susceptible individuals who do not get infected. Using disease dynamics system of ordinary differential equations[50], $\frac{dS}{dR} = -\frac{\beta S}{\gamma} = -R_0 S$ Integrating with respect to R to obtain: $S(t) = S(0)e^{-R(t)R_0}$ Therefore if $R \leq 1$, $\Rightarrow S(t) = e^{-R_0} > 0$.

This shows that always stays positive, that is there will always be some susceptible who escape infection. The conclusion that emerges from this result is rather counter-intuitive: the chain of transmission eventually breaks due to the decline in infective, not due to a complete lack of susceptible.[51]

If population mixes randomly and homogenously among themselves, diseases with high force of infection tend to infect more susceptible person, thereby spreading rapidly and widely across borders. The threshold parameter R_0 implies that in order for an epidemic to spread, the initial number of susceptible must exceed a certain threshold $S(0) < \gamma/\beta$ commonly referred to as relative removal rate which must be small enough to allow infection to spread. The inverse of this rate is called the basic reproductive ratio, R_0 ($R_0 > \gamma/\beta$). Therefore the epidemic will spread if and only if R_0>1. With most (Table 2) R_0 values above unity, it confirms that Ebola epidemic continued to grow and spread if nothing is done to reverse the index. Different methods are used to assess the speed of spread of an epidemic in populations.[52] In small world networks, most contacts between individuals are local, but some long-distance contacts ensure rapid global spread of epidemic.[10] For a simple nearest neighbour mixing model in spatiotemporal disease spread model, rate of infection between the populations in j is $s_j \frac{\beta}{\sum M_{ji} I_i} \sum_{i=1}^{K} M_{ji} I_i$.

Where M_{ji} is the mixing rate between j and its neighbouring area i, I_j and is the number of infectious individuals in I, K is the total number of areas, N_i the total population in i, β the transmission coefficient.[52] Using scaled network[53] model and determine the early growth and spread of Ebola among households and communities. Travel restriction in the most affected countries was modelled, it was found that restrictive measures were insufficient to prevent the exportation of Ebola cases.[17] Morbidity and spread of Ebola in 15 counties of Liberia[25] modelled and determine estimates of transmission coefficients in the community, hospital and at traditional burial. It defined total rate of mobility in each county as $s_c(\bar{X}) = \sum_{c \neq j} \frac{x^j}{N_j} r_{jc} - \frac{x^c}{N_c} r_{cj}$ where $x^j(x^c)$ is the number of individuals (susceptible or exposed) in county $j(x)$, $N_j(N_c)$ the total population of county $j(or\ c)$ and r_{jc} and r_{cj}, mobility rates from county $j \to c$ and from county $c \to j$ respectively.

Several standard measures are used to measure and describe the frequency of disease. Each measure has its appropriate uses, depending on situation and information available to epidemiologist.[54,55] Morbidity and mortality measure disease intensity in population. While mortality measures the rate and volume of deaths occurring as a result of the disease, morbidity (incidence or sick rate) is the ratio of the diseased to the number of residents of a given location during the epidemic period. Morbidity and prevalence rates can be measured by:

$$\theta_{IR} = \frac{number\ of\ new\ cases\ of\ disease}{population\ at\ risk} x\ 10^n$$

.

$$\theta_p = \frac{number\ of\ existing\ cases\ of\ disease}{total\ population} x\ 10^n$$

Existing cases will comprise of pre-existing and new cases.

When Ebola broke out in Guinea, it spread into neighbouring countries, cases increased, with Sierra Leone recording the highest morbidity.[56] Hence[57] modelled the morbidity rate of Ebola to assess the effects of using or not using drugs for treatment and vaccination and defines individual's morbidity rate in a country i as:

$$P_i' = \begin{cases} k_N = k_2(1-a)l \\ h_i k_1 \frac{N_{i-ill}}{N_{i-total}} k_2 & (0 < t < t_1) \\ h_i k_1 \frac{N_{i-ill}}{N_{i-total}} k_N (1 - b\frac{t-t_1}{t_2-t_1}) & (t_1 < t < t_2) \\ N_{T-i-ill} = N_{0-i-ill} + N_{i-total} \cdot \int_0^T P_i' dt - N_{i-total} a - N_{i-death} \end{cases}$$

Richards model was used to gauge the temporal variability in the morbidity and spread of the Ebola in West Africa in terms of its reproduction number.[47] Prevalence rate among men and women was also analyzed to determine risk of infection, survival and how to deploy control measures with sex specific differences.[58]

Epidemics have to be controlled rapidly through surveillance and identification, contact tracing, isolation quarantine and case treatment of infected individuals, public enlightenment, vaccine.[3,19,59] Control measures reduce contact rate, transmission probability or average period of infectiousness. To halt Ebola, several interventions and control measures have been used. Because of limited treatment facilities and vaccines against Ebola disease, non pharmaceutical interventions (public enlightenment, quarantining, isolation, or contact tracing) were mostly used.[26,35,36,42,60-64] Several studies investigated the impact of interventions and control upon Ebola growth (Table 2).

In modelling vaccination it is assumed that vaccine is available prior to outbreak of disease. The most important factors to model vaccination are critical vaccination coverage and vaccination efficiency. Since vaccinating each and every individual in susceptible class is practically not feasible for economically backward countries, a critical fraction or proportion of population that needs to be vaccinated should be determined.[65] A critical vaccination coverage, v_c is the fraction (of susceptible) that should be vaccinated in order to surely prevent an outbreak.[66] If prior to outbreak, a fraction v is vaccinated, the number of infections caused by a typical individual is reduced to $R_0(1-v)$.[67] Since only the fraction $(1-v)$ of all contact result in infection, new R_0 will be $R_v = R_0(1-v)$. In terms of v, this is equivalent to be $v > 1 - \frac{1}{R_0}$ if $R_0 > 1$, otherwise, $v_c = 0$ vaccination efficiency is the effectiveness of vaccine to induce immunity. It is measured relative to susceptible and/or exposed individuals. This offers information for preferred implementation strategy of immunizing susceptible is given by the following relations $VE_{Rf}(t) = 1 - \frac{R_f(t)}{R_0}$ $VE_{Rf}(t)$ is the overall effect of a vaccination strategy in a population. Vaccination efficacy can be measure against infectiousness (VE_I) and susceptibility (VE_S) of an epidemic.[35,66] If $R_f(t)$ is the reproductive number at time and the fraction of populations is vaccinated. Effect of a vaccination strategy in a population can be measured by relative reduction in (basic) reproductive number after the campaign compared with one before vaccination campaign. Efficacy of vaccine had often been simulated, with hypothetic results to measure the impact of vaccination on Ebola epidemic[68-70]. Trial vaccines in Guinea (rSV-ZEBOV), Liberia and Sierra Leone[71] were administered to assess how effective this factor can control Ebola growth. These

vaccines are tried in Europe for a similar evaluation.[72]

Contact tracing is able to reduce prevalence of diseases. The WHO had outlined broad plans56,[73] for tracing contacts, its efficacy tends to vary with location and epidemic stages[42]. The influence of contact tracing on Ebola was studied by[74], effective reproduction number in relation to contact tracing was given as. $R_e = \frac{k(1-q)}{q} + k_m$ where k is the number of secondary traced infected contacts per primary untraced reported case, km is the number of secondary traced infected contacts per primary traced reported case and (1−q)/q is the odds that a reported case is not a traced contact. Though contact tracing has lot of challenges[75], but is a most critical preliminary control measures to spread of infectious disease.

In the absence of effective vaccine or treatment, symptom-based public control measures involves tracing and quarantining asymptomatic and isolating and contact tracing.[29,35] Isolation is often employed as a control strategy in epidemic models than quarantine. In control, average time to quarantine and isolation is usually optimized. Isolation is done to reduce average time to infectiousness and recovery, thereby reducing virus transmission rate. Effective isolation requires full BPE practices, sufficient personnel, facilitated labs and treatment centres, sufficient support treatment pharmaceuticals, effective restrictions in and around infectious individuals.[5,61]

In order to control rumours and misinformation by broadcasting news about control measures, a rapid communication between media, public and health personnel should be conducted at every stage of epidemic. An objective of media campaigns against a disease is to increase population awareness of the disease and reverse misperceptions about how it is spread. It enlightens people of personal and environmental health conditions. This measure will require a correct media-strategy, community involvement in grass root media coverage for educative and psychological enlightenment. Media efficacy on Ebola growth has been widely attempted.[38,39]

Since virus is transmitted through contact with infectious body fluids of individual or cadavers. Ebola tends to be transmitted during funeral because of observed burial traditions. Interventions in safe burial will reduce disease transmission. Safe burial is to minimise average period from death to traditional burial. Post-death transmission control comprises of early and safe removal of cadavers into deep and safe burial grounds, safe disposal of fomites by trained personnel. Effective reproduction number due to efficacy of safe burial has been well assessed by Shen for the most affected countries[38]. Reduction in post death transmission will reduce overall epidemic spread so that effective reproduction number due to efficacy of safe burial will be $R_e = (1-\rho_D)R_0$, where ρ_D is post-death transmission rate.[27]

Optimal control enforces restriction of economic constraints imposed by limited resources when analyzing control strategies. Optimal control has been recently used in series of epidemiological problems[69,76-79], aimed at minimizing the number of infected and at the same time minimizes cost of implementing controls.[69] In studying control of cholera[78] outlined procedure of evaluation of optimal control in an epidemiological model. To determine the control such that we minimize prevalence cost of controlling disease, the payoff (objective) function is given as $J(u) = \int_0^T g(x(t), u(t))dt,$ where $x(t)$ solves the system of differential equations for the specified control for all $u(t)$, $0 \le u(t) \le 0.9$. The function g is the running payoff. To determine control u*(t) that minimizes payoff function the following is solved.

$$J(u^*) = \min_{u \in A} \{J(u)\}$$

Common approaches of optimal control are the direct and indirect methods. Direct methods are based on the discretization of the optimal control problems, reducing them to nonlinear constrained optimization problems.

Indirect methods are based on the Hamiltonian and the Pontryagin maximum/minimum principle.[70] The Filippov-Cesari existence theorem, Pontryagin's minimum/maximum principle and Mangasarian theorem can be used to determine the existence of optimal control in disease dynamics model.[29,70,80] There are challenges to optimal control process. Ideal weights are very hard to obtain in practice which requires intensive data mining, analyses, and fitting. Hence, the acquirement of appropriate practical weights becomes a problem.[81] Effective cost analysis[82] is required to assess costs associated to deployment of control measures, because an effective strategy identified does not necessarily mean it is feasible on the grounds of the constraint of resources. Several measures have been investigated to determine optimal control on Ebola including vaccination[69,80], public enlightenment, isolation and treatment for exposed or infectious population[38,61], media[82] case finding and public enlightenment, and hospitalization.[83]

Once a model is formulated, the values of parameters governing transition rules between health states must be determined. Models are calibrated so that their behaviour fits observed data from specific scenario. Varying the parameters changes the output of the model. The goal of sensitivity analysis is to decide qualitatively which parameters are most influential on model output. It provides insight into how the problem understudy will behave when fundamental variables, parameters or conditions changes.

Sensitivity analysis can be performed on epidemic dynamics model, prediction, final size, optimal control, or on thresholds like reproduction number or equilibrial prevalence.[29] Different methods are used for uncertainty and sensitivity analysis in epidemiology. [84] Latin hypercube sample and partial rank correlation coefficients (LHS/PRCC) is commonly[84,85] for assumption-based, non-linear and monotonic, differential and regression or correlation applications. Determining which parameters have the most significant impact on that output, factor-influence analyses have to be performed using LHS/PRCC procedure. This procedure had been widely applied in different epidemics HIV/AIDs, cholera, Ebola.[24,74,78,86-88] LHS is a statistical sampling method that permits simultaneous variation of parameters value in a model. It assesses the accuracy of the sensitivity indices. PRCC determines which statistical relationship exists between each input parameter and the outcome variable. Parameters with larger PRCC are positively correlated with output of the model function the reverse is also true.[85] Sensitivity measures for uncertainty analysis of epidemic model are:

Pearson correlation coefficient is

$$\rho(X_j Y) = \frac{\sum_{i=1}^{N}\left(X_j^{(i)} - E(X_j)\right)\left(Y_i - E(Y)\right)}{\sqrt{\sum_{i=1}^{N}\left(X_j^{(i)} - E(X_j)\right)^2}\sqrt{\sum_{i=1}^{N}\left(Y_i - E(Y)\right)^2}}$$

Standard Regression Coefficient is

$$SRC_j = \beta_j \sqrt{\frac{Var(X_j)}{Var(Y)}}$$

Partial correlation coefficient is

$$PCC_J = \rho(X - X_{-j}, Y - Y_{-j})$$

For nonlinear epidemic models, rank transformation involving replacing the values by their ranks should be applied upon the samples. The importance measure tools become spearman correlation coefficient (ρ^S), standard rank regression coefficient (SRCC), and the partial rank correlation coefficient (PRCC). The LHS/PRCC was used by[24,38,89] to identify which parameters R_0 and Ebola final epidemic size is sensitive to.

CONCLUSION

Ebola affected the West African region, grew exponentially and killed nearly half of the total number infected, with potentials of spreading to other parts of the world. This review provided an overview of Ebola epidemic models that are used to investigate the development of the epidemic. The review highlighted tools and techniques for model stability analysis, parameter estimation, determination of growth and size of epidemic, theories for spread and frequency of diseases and indices of intervention efficacy in the control of the outbreak. Appropriate tools and studies that analysed how sensitive Ebola epidemic and parameters were also reviewed. Exploring epidemiological models/tools will enable analyst to use it to evaluate disease outbreaks, so that findings will facilitate optimal disease control and outbreak management decisions. Controlling epidemic requires that concerted and comprehensive control strategy help to stop epidemic, while there are different approaches to that effect, a review of epidemiologically measurable interventions over the epidemic period provides a strategy mix for containing the disease.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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