ANALYSIS OF NON-LINEAR TRANSMISSION OF EBOLA VIRUS DISEASE AND THE IMPACT OF PUBLIC HEALTH CONTROL INTERVENTIONS IN HOSPITAL: The *case of Guinea (West Africa) outbreak 2014.*

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ABSTRACT

Epidemiological data on infection outbreaks are challenging to analyze, despite improved control interventions Ebola virus Disease (EVD) remains a serious risk in Guinea (West Africa) with 607 reported cases and 406 deaths recorded (66.8%) as of 20th August, 2014.In this study we use modified epidemiological modeling SEIR to analyze data from an Ebola outbreak in Guinea from 22nd march – 20th August,2014 We use Bayesian inference with non – linear transmission times incorporated into augmented dataset as latent variables. Despite the lack of detailed data, most data sets record the time on symptom onset but transmission time is not observable. We inferred from such dataset records using structured Hidden Markov Models HMMS. Infectivity is determined before and after public health interventions for hospitalized cases. We estimate the number of secondary cases generated by an index case in the absence of control interventions (R_o). Our estimate of R_o is 1.57 (CI_{95} 0.82-1.92) and the mean value of estimated detection rate is 0.75 (CI_{95} 0.59 -0.93) with a coefficient of correlation between β and v as – 0.23. We perform sensitivity analysis of the final epidemic size tothe time of intervention, which ensures the uniqueness and the global stability of the positive endemic equilibrium state.

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Key words: *Epidemiological, control interventions, Ebola, disease, Bayesian inference, incorporated, Markov models, sensitivity analysis, equilibrium state*

INTRODUCTION

On 26 August, WHO reported that more than 240 health workers have developed Ebola in Guinea, Liberia, Nigeria and Sierra Leone, and more than 120 have died. Caring for the infected is greatly scary. WHO endorsed the use of interventions with as – yet – unknown effects for treatment and for prevention of Ebola? Health care providers caring for Ebola patients, family and friends in close contact with Ebola patients are at the highest risk of

getting infected because they may come on direct contact with the blood or body fluids of sick patients. Nosocomial cases are rampant in Guinea owning to the explanation lack of the number of medical staff needed to manage such a large outbreak, shortages of protective equipment, or improperly using what is available [42].Also, without recent past experience with the disease, people have become intensely fearfully and have in some cases, attacked medical staff, believing that they cause the disease [42].In late August, medicine Sans Frontiers (MSF) called the situation "Chaotic" and medical response " inadequate" calling the situation " an emergency within emergency" MSF reports that many hospitals have had to shut down due to lack of staff or fear of the virus among patients and staff " The poor living conditions and lack of water and sanitation in most districts of Conakry pose a serious risk that the epidemic escalate into a crisis. People do not think to wash their hands when they do not have enough water to drink" [18].

Forecasts of economic growth have been reduced [33]. An initial world Bank-IMF assessment of Guinea projects a full percentage point drop in GDP from 4.5 percent to 3.5 percent [22]. Foreign mining companies have withdrawn non-essential personnel, deferred new investment and cut back operating [25][8][41].Guinea closed its border with both Liberia and Sierra Leone to help contain the spread of the disease, as more cases were being reported in those countries than in Guinea [30]. The virus re-surfaces in September the new cases were related to persons returning to Guinea from neighboring Liberia or sierra Leone [21]. According to Dr Peter Piot, the scientist who co– discovered the Ebola virus, Ebola is not following its usual linear patterns as mapped out in previous outbreaks. This time the virus is "hopping" all over the West African Epidemic region.

Mathematical models can be useful in the area of hospital control for two reasons. Firstly, they can be used to predict quantitatively the course of an epidemic, predicting its total size; and time to peak and the impact of infection control interventions including non-linear interactions that occur when multiple interventions are undertaken. Secondly; they can inform the design of trial and structure statistical analysis to avoid assumptions of serial independence and difficulties with interval censoring and unknown number of infectious cases. In recent years, a number of authors studied epidemiological models with non-linear incidence rates. The most common non-linear incidence rate takes the form $\beta I^p S^q$ (where P and Q are positive constants). Models with incidence rate have been studied by[40] and later by [32],[17],[36], and many others. [40]Proposedmore sophisticated forms of the non – linear incidence rate(KI^{p}S)(I + α I^l)

[11] Who studied infection of insects considered a non – linear pathogens transmission of the form $Sln\,(I + V\frac{P}{K})$ (Where P is the density of the pathogen particles). [37] Studied the global properties of a SEIR model with the incidence rate of the form $g(I)S$; they also extended some of their results for a SEIRS model. [35] Considered a variety of models with the incidence rate of the form $g(I)h(S)$;the most general case was considered by [24] who considered properties of a model with arbitrarily many stages of infection. They found the condition for existence of a unique endemic equilibrium state for its local stability. Our objective is to formulate and analyze a model for Ebola virus (EBOV) that includes relevant Biological strategy not considered before in Ebola models. The overall objectives of this study are to develop statistical models in order to improve the understanding of the transmission of infection agents in the hospital and to use these models to inform infection control practitioners in public health as to the existence of endemic equilibrium under some conditions and analyze the stability of disease – free equilibrium

As of 20th October 2014 [12] has it that nosocomial transmission has been typical as patients are often treated by unprepared hospital personal (barrier nursing techniques need to be observed) individuals exposed to the virus who become infectious do so after a mean incubation of 6.3 days (1-21days) [6] Ebola is characterized by initial flu –like symptoms which rapidly progress to vomiting, diarrhea, rash, and internal and external bleeding. Infected individuals received limited careand no specific treatment or vaccine exists. Most infected persons die within 10days of their initial infection [5] (50%-90%) mortality (WHO, 2003).

Using modified SEIR (susceptible exposed – infectious – removed) epidemic model in (fig2) and data from well – documented Ebola outbreak[31]. We use Bayesian inference with non-linear transmission times incorporated into augmented dataset as latent variables and inferring the data set into structured Hidden Marker Models HMMs. We estimate the number of secondary cases generated by an under case in the absence of control interventions (R_o). Our estimate is 1.57(CI95 0.82-1.92) and the mean value for estimated detection rate is 0.75 (CI95 0.59-0.93) with a coefficient correlation between β and V as – 0.23. We perform sensitivity analysis of the final epidemic size to the time to intervention, which ensures the uniqueness and the global stability of the positive endemic equilibrium state.

METHODS

We fit data from Ebola virus disease out breaks in Guinea (2014) to a simple deterministic (Continuous time) SEIR epidemic model Fig 1. The fit of the model provides estimate for parameters. The fitted model can then be used to estimate the basic reproductive number Ro and quantify the impact of intervention measures on the transmission rate of the disease. Interpreting the fitted model as an expected value of a structured Hidden Marker Model HMM, process, we use multiple stochastic realization of the epidemic to estimate a distribution of the final epidemic size to the timing of intervention. We used the Bayesian framework to estimate posterior probability of the transmission parameter. We perform sensitivity analysis on R_o to account for high variability in disease related parameter in our model to ensure the uniqueness and the global stability of the positive endemic equilibrium state.

FIG: 1 2014 EBOLA OUTBREAK IN WEST AFRICA-OUTBREAK DISTRIBUTION MAP

	Conakry, Coyah, Forecariah, Gueckedou, Kouroussa, Macenta, Siguiri, Pita, Nzerekore,Dubreka,Yomou,Kerouane,Kindia,Dalaba,Lola,Beyla
Affected areas in Guinea	***No longer active due to intervention control**: Boffa, Dabola, Dinguiraya, Kissidougou, Telimele, Boke*

On 28 August, the WHO released its first estimate of the possible total cases (20,000) from the outbreak as part of its roadmap for stopping the transmission of the virus.[3] The WHO roadmap states "[t]his Roadmap assumes that in many areas of intense transmission the actual number of cases may be two- to fourfold higher than that currently reported. It acknowledges that the aggregate case

load of EVD could exceed 20,000 over the course of this emergency. The Roadmap assumes that a rapid escalation of the complementary strategies in intense transmission, resource-constrained areas will allow the comprehensive application of more standard containment strategies within 3 months."[3] It has been reported that some people in this area believe that health workers have been purposely spreading the disease to the people, while others believe that the disease does not exist. Riots recently broke out in the regional capital, Nzérékoré, when rumors were spread that people were being contaminated when health workers were spraying a market area to decontaminate it.[31]

On 18 September, it was reported that the bodies of a team of Guinean health and government officials, accompanied by journalists, who had been distributing Ebola information and doing disinfection work, were found in a latrine in the town of Womey near Nzérékoré.[4] The workers had been murdered by residents of the village after they initially went missing after a riot against the presence of the health education team. Government officials said "the bodies showed signs of being attacked with machetes and clubs" and "three of them had their throats slit."[26]

WHO estimated on 21 September that Guinea's capacity to treat EVD cases falls short by the equivalent of 40 beds.[39] On 13 October, France indicated it would build more treatment centers[26] On 18 October, Egypt sent three tons of medical aid, consisting of medicine and medical equipment.[23]

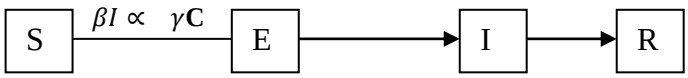

Fig 2: A schematic representation of the flow of individual between epidemiology classes βI is the transmission rate to susceptible S from I, E I the class of infected (not yet infectious) individuals; K is the rate at which E – individuals move to the symptomatic and infectious class I: infectious individuals (I) either die or recover at rate γ. C is not an epidemiological state but keeps track of the cumulative number of cases after the time of onset of symptoms.

TABLE: 1 showing major Ebola virus outbreaks by country and by date – 25 August

To most recent WHO/Gov update .***Note*: These reflect official confirmations only. The actual numbers are estimated to be three times as high.**

Date	Total		Guinea		Liberia		Sierra Leone	
	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths
24 Oct 2014	12,008	5,078	1,598	981	6,253	≥2,704	4,017	1,341
19 Oct 2014	9,936	4,877	1,540	926	≥4,665	≥2,705	3,706	1,259
17 Oct 2014	9,693	4,811	1,501	886	≥4,607	≥2,689	3,560	1,227
12 Oct 2014	8,997	4,493	1,472	843	≥4,249	≥2,458	3,252	1,183
7 Oct 2014	8,386	3,988	1,350	778	≥4,076	≥2,316	2,937	885
5 Oct 2014	8,033	3,865	1,298	768	≥3,924	≥2,210	2,789	≥879
1 Oct 2014	7,492	3,439	1,199	739	≥3,834	≥2,069	2,437	623
28 Sep 2014	7,192	3,286	1,157	710	≥3,696	≥1,998	2,317	570
25 Sep 2014	6,808	3,159	1,103	668	≥3,564	≥1,922	2,120	561
23 Sep 2014	6,574	3,043	1,074	648	≥3,458	≥1,830	2,021	557
21 Sep 2014	6,263	2,900	1,022	635	≥3,280	≥1,707	1,940	550
17 Sep 2014	5,762	2,746	965	623	≥3,022	≥1,578	1,753	537
14 Sep 2014	5,339	2,586	942	601	≥2,720	≥1,461	1,655	516
10 Sep 2014	4,848	2,376	899	568	2,415	1,307	1,509	493
7 Sep 2014	4,391	2,177	861	557	2,081	1,137	1,424	476
3 Sep 2014	4,001	2,059	823	522	1,863	1,078	1,292	452
31 Aug 2014	3,707	1,808	771	494	1,698	871	1,216	436
25 Aug 2014	3,071	1,553	648	430	1,378	694	1,026	422

EPEDEMIC MODEL

Our model accommodates the diverse and complex dynamics of an Ebola virus (EBOV) outbreak in West Africa 2014 determined by population – specific parameters such as the effective contact rate β. The general epidemic model assumes that people begin susceptible to an infective disease, may become infected by exposure to an infected person becoming immediately infectious themselves and after a time period either recover or die. Recovery constitutes immunity to further infection and they are said to be removed. The

simplest version of this SEIR model assumes homogenous mixing and a fixed population size $N = S(t) + E(t) + I(t) + R(t)$ $WhereS(t)\ E(t), I(t), and\ R(t)$ Are the numbers in the population who are susceptible, infectious and removed at time t [7]. The homogenous mixing is invalid, in this case the necessary population structure and heterogeneous mixing may be incorporated into a model with a specific form of non – linear transmission and the non –linear incidence rate βSI and arises from

$$\frac{ds}{dt} = -\beta SI$$

$$\frac{dE}{dt} = \beta SI - \alpha E$$

$$\frac{dI}{dt} = \alpha E - \gamma I$$

$$\frac{dR}{dt} = \gamma I$$

Where $\alpha, \beta,$ and γ are positive constant. Linearising the system about a steady state (S, E, I) taking S = S + s̄ Ē = E + e and Ī = I + i leads to

$$\begin{pmatrix} \bar{S} \\ e \\ \dot{\imath} \end{pmatrix} = \begin{pmatrix} -\beta I & O & -\beta S S \\ \beta I & -\alpha & \beta S\ e \\ O & \alpha & -\gamma\ i \end{pmatrix} \begin{pmatrix} \\ \\ \end{pmatrix}$$

TABLE: 2showing effects and transmission rate according to the model

Events	Effect	Transmission Rate
Exposure	(S,E, I,R) ⟶ (S-I, E+I, IR)	β(t) S $\frac{I}{N}$
Infection	(S,E, I,R) ⟶ (S,E, I,I+I,R)	$\propto E$
Removal	(S,E, I,R) ⟶ (S-E, I-i,R+I)	γI

The dominant eigenvalue of the Jacobian at the steady state (S = N, E = 0, I = 0) gives the growth rate of the epidemic curves.

$\lambda = \frac{(-\gamma + \alpha) + \sqrt{(\alpha - \gamma)^2 + 4\beta N\alpha}}{2}$ [5]

Note: The growth of the epidemic is dependent on the rate of transmission from the latent infectious periodα.

MODEL ASSUMPTIONS

The model makes the following assumptions

1. The ward is of fixed size, *N*.
2. The model parameters are time invariant
3. Each observation is conditionally independent given the corresponding hidden state.
4. The hidden states follow a first order time homogenous Markov process, that is $Pr(C(t_k) \mid C(t_1), \ldots, (C(t_k - 1)$ = Pr $(C(t_k) \mid C(t_{k-1}) = Pr(C\ t_k - t_{k-1}) \mid C(0)$.
5. Homogenous mixing of patients takes place.

saturation effects[13]. If the proportion of the infective host in a population is very high, so exposure to the disease agents is virtually setting, the transmission rate may respond more slowly than linear to increase in the number of effectives. Each contact between the susceptible and the exposed – those individuals have acquired infections but not yet infectious can be simulated numerically. A simple system of questions from classical system of ordinary differential equations (ODES) can be used to describe the model.

$$\Pr(S(t+dt) = i-I, E(t+dt) = j+I\ S(t) = i, E(t) = j) = \frac{\beta S(t) I(t) dt,}{N(t)}$$

Where β is a constant? In the simplest version of the SEIR model, transition between subsequent model compartments occurs at a constant rate, becoming infectious as they move into the I compartment and being neither infectious nor susceptible after being removed (see Figure 2). This leads to

$$\Pr(E(t+dt) = j-1, I(t+dt) = k+1 \mid E(t) = j, I(t) = k) = \delta E(t) dt$$

$$\Pr(I(t+dt) = k-1 \mid I(t) = k) = \gamma I(t) dt,$$

Where δ *and* γ are constants?

The assumption of a constant transition rate in the basic SEIR model is adopted for ease of calculation, leads to an exponential distribution of the probability density function for the time to transition. Other distributions, parametric or not parametric could be used to model sojourn times [19]. Assuming an exponentially distributed $p(y, z/\theta) = p(y/z, \theta)p(z/\theta)$. The marginal distribution of y is given by.$p(y/\theta) = \int p(y, z/\theta) dz$. The value of introducing the latent variable z into the model is clear when the complete likelihood, $p(y, z/\theta)$, has a much simpler of a dataset. Latent variables can be used to extend the range of distributions that can be modeled [16] and simplify model computations. They have also been shown to enhance convergence [10].The integral required to evaluate the marginal distribution is often difficult or intractable. The following discussion reviews methods used to tackle latent variable problems.

MODEL OF TRANSMISSION OF VIRUS IN THE HOSPITAL WARD

We base our transmission model on the susceptible infected (SI) model with migration, described by [6]. Modified versions of this model have been used previously to analyze nosocomial transmission data. A schematic of the model is shown in Figure 2. The rate of cross transmission of EBOV colonization (per colonized per incubation period, with a mode of zero (when in fact the mode of the incubation period is considerably greater than zero) leads to under – estimation of infectivity inferred from the early epidemic growth curve λ.

LATENT VARIABLES

Missing data in stochastic epidemic models can be imputed using latent variables. A set of latent variables, *z*, and a set of observations, *y*, form an augment dataset. Latent variables could be missing data, an unobservable process or an auxiliary variable introduced into the model for convenience. The probability of observations, given the augmented data and the model parameters, *p(y/z, θ),* is called the conditional probability of the observations. The joint probability of the unobserved data and the observations, the complete likelihood, is given by

form than the marginal likelihood, $p(y/\theta)$, as is the case when there are missing data and one wishes to apply the piecewise constant hazard to determine the likelihood

susceptible patient per day) is denoted by β. It is assumed that the ward is of fixed size, N, hence the number of uncolonised patients is N – C. Colonised patients are assumed to remain colonized for their entire hospital stay, therefore transmission from the colonized to uncolonised compartments occurs via discharge of a colonized patient and replacement with an uncolonised patient, which occurs at a rate μC. Duration of stay of colonized patients was available from the dataset. Acquisition of EBOV that is transmitted is described by the mass – action term, $\beta C(N-C)$. EBOV acquisition that is sporadic can arise through ward admission of a colonized patient or any other process that is not related to the number of colonized patients, and occurs at a rate, $v(N-C)$.

$$\beta C(N-C) + v\,(N-C)$$

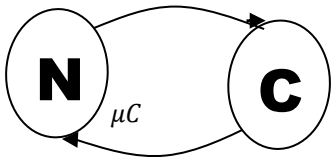

Figure 3: The transmission of bacteria pathogens in the hospital ward.

The probability of a change in the number of colonized patients, *C*, in short time period, h is given by

$$\left.\begin{aligned}
&\Pr[C(t+h) = i+1 \,|C(t) = i] = \beta i(N-i)h + v\,(N-i)h + o(h),\\
&\Pr[C(t+h) = i-1 \,|C(t) = i] = \mu ih + o(h),\\
&\Pr[C(t+h) = i \,|C(t) = i] = 1 - \beta i(N-i)h - v\,(N-i)h - \mu ih + o(h),\\
&\Pr[C(t+h) = j\ (j \neq i-1, i, i+1)|C(t) = i] = o(h).
\end{aligned}\right\}$$

BAYESIAN INFERENCE TO ESTIMATE Ø

Estimate of Ebola cross – transmission were complicated by interval censoring of colonization times. Colonization events are asymptomatic so observations of EBOLA acquisition consisted of the time of first detection. We used Bayesian frame work to estimate the posterior probability of the transmission parameter, ø. The parameter of transmitted β, and sporadic EBOV, v, estimated using a Bayesian framework. Let $\theta_p = \{\beta, v, d\}$ be the vector of model parameters. [5] Recursionformula was used to determine the likelihood of the data, L(Y $|\theta_p$). Union U[0,0.1] prior probability distributions were assigned toβ *and* v, because little works known about these parameters other than that negative values or values higher than 0.1 were completely implausible. The posterior probability distribution is given by. $p(\theta_p|Y) \propto \pi(\theta_p)$ L (Y $|\ \theta_p$), **)**

Where $\pi(\theta_p)$ is the prior probability distribution of θ_p. This was estimated using a Monte – Carlo Markov chain algorithm. The Bayesian framework can provide estimates (and full posterior probability density) of any function of model parameters including functions which depend upon knowledge of hidden states. Let θ_h be the vector of ***n*** inferred hidden states $C_1 \ldots, C_n$ and let θ = { θ_p, θ_h). The proportion of EBOV acquisitions due to ward transmission, $f(\theta)$, is given by:

$$f(\theta) = \frac{\sum_{k=1}^{n} \beta C_k (N - C_k)}{\sum_{k=1}^{n} \beta C_k\,(N-C_k) + v\,(N-C_k)}$$

We evaluate the expectation, $E[\ f\ (\theta)\,|\,Y]$, by drawing samples θ_k, k=1,…,*m* from $p(\theta\,|Y)$ and using the approximation of [29] $E[\ f(\theta)\,|\,Y] \approx \frac{1}{m}\sum_{k=1}^{m} f(\theta_k)$

HIDDEN MARKOV MODEL

We aim to estimate parameters associated with sporadic colonization, *v*, and the colonization caused by ward transmission, β, using the structured HMM illustrated in Figure 4

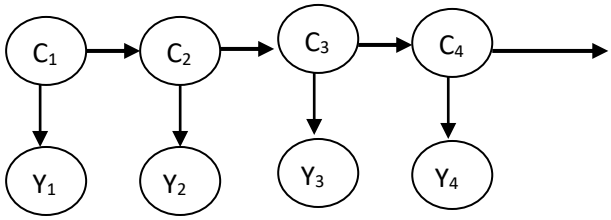

Figure 4 Hidden Markov Model. Here C represents the number of colonized patients in the ward (detected or undetected), Y represents the number of patients detected at each time point. The horizontal arrows represent the transition from one state to the next, and the vertical arrows represent the relationship between the hidden state and the corresponding observation

Our Hidden Markov Model (HMM) consists of: observation, ***Y***, the number of patients detected at each time point; underlying hidden states, C, the number of colonized patients in the ward; a transition model linking each hidden state with its adjacent states, represented by the horizontal lines in figure 4 and observation model linking the data with the hidden sate, represented by the vertical lines in Figure 4. There is one hidden state for each observation, denoted $C_1, C_2, \ldots C_n$

The full conditional probability of any node depends only on neighboring nodes to which it is connected directly. The observation component of the HMM, denoted by Y, consists of 200 data inputs of weekly Ebola prevalence taken over 6 months and the vector of time points, $t - t_1, \ldots, t_n$,

corresponding to each observation time. The vector C consists of the $n=200$ hidden states. To construct the transition probability matrix for an arbitrary time interval, following the theory of [15], we developed a transition probability matrix, $\boldsymbol{\Gamma}(t_k-t_{k-1})$ *The i* j^{th}element of $\Gamma(t_k-t_{k-1})$ gives the probability of having j colonized patients on the ward at time t_k, given that there were I colonized patients on the ward at time t_{k-1}. Firstly we developed a discrete time transition probability matrix, $\boldsymbol{A}$, for a small time interval, h. let $\boldsymbol{A}$ be the matrix in which the i j^{th} element is given by

$Pr(C(t+h) = j/C(t) = i)$. A is given using the system of equations

$$\Pr[C(t+h) = i+1 \,|C(t) = i] = \beta i(N-i)h + v\,(N-i)h + o(h),$$

$$\Pr[C(t+h) = i-1 \,|C(t) = i] = \mu ih + o(h),$$

$$\Pr[C(t+h) = i \,|C(t) = i] = 1 - \beta i(N-i)h - v\,(N-i)h - \mu ih + o(h),$$

$$\Pr[C(t+h) = j\ (j \neq i-1, i, i+1)|C(t) = i] = o(h).$$

Here, i *and* j are the number of patients colonized in the ward and can take on values $0,\ldots,N$.

The mean value for the estimated detection rate was 0.75 with a 95% credible interval of 0.59 to 0.93.

MODEL FORTHEIMPACTOFINTERVENTION FOR HOSPITALIZED AND COMMUNITY SYMPTOMATIC CASES

We used attack rate as the outcome measures to model the effect of a number of interventions: Improving hand hygiene compliance, decolonization, and health care workers / patients ratios with and without patient cohorting, ward size and patient discharge rate on the attack rate. We examined both deterministic and stochastic model predictions.

Estimated means of the parameters derived from the data were used as the default parameters. The ward in the study was not fixed, however the ward ran at near maximum capacity much of the time, therefore new administrations were often limited by the rate of patient discharge. This justified the use of a simplifying assumption of fixed ward size to estimate the impact of interventions. We used the mean occupancy derived from the data to determine the number of patients in the ward, n_p = 15 (here we used a fixed value of occupancy as a parameter, N_p, rather than the variable, N_p). We also assumed that $N_h = P^{n}{}_{p}$, where ρ is the health – care / patient ratio. This simplifies the mathematical equations to

$$\left.\begin{aligned}\frac{dY_p}{dt} &= cp_{hp}(n_p - Y_p)Y_h - (\gamma + \mu_{Y(1-\sigma)})Yp + \mu_x\sigma(n_p - Y_p),\\ \frac{dY_h}{dt} &= cp_{ph}(pn_p - Y_h)\,Y_p - kY_h.\end{aligned}\right\}$$

Note that we have now allowed decolonization of patients, γ, to be non – zero. The equilibrium attack rate is given by $AR = cp_{hp}\,Y_{he}$, Where Y_{he} *is the equilibrium value for* Y_h, obtained when $\frac{dY_p}{dt} = \frac{dY_h}{dt} =$ o. In the stochastic version of the model, the probability during a small time interval, δ, of transiting from one state to another is described by the equations

$$\left.\begin{aligned}Pr(\,Y_p(t+\delta) = i+1 \,|\, Y_p(t) = i) &= Cp_{hp}(n_p - i)\,Y_h\delta + \mu_x\sigma(n_p - i)\delta + o(\delta)\\ Pr(\,Y_p(t+\delta) = i-1 \,|\, Y_p(t) = i) &= (\gamma - \mu_y)\,(1-\sigma)i\delta + o(\delta)\\ Pr(\,Y_p(t+\delta) = i \,|\, Y_p(t) = i) &= 1 - Cp_{hp}(n_p - i)\,Y_h\delta - \mu_x\sigma(n_p - i)\delta - (\gamma - \mu_y)\,(1-\sigma)i\delta + o(\delta)\end{aligned}\right\}$$

Where $o(\delta)$ is the Landau symbol, denoting lower order terms ofδ. It was a summed that $\frac{dY_h}{dt} = 0$. All other probabilities are $o(\delta)$.

Table 3: showing parameters used in the model for the impacts intervention for hospitalized and community symptomatic cases (pt = patients HCW = health care workers)

Parameter	Symbols	Units
Contact rate	c	Contacts $Pt^{-1}HCW^{-1}$ day^{-1}
Decolonization rate	γ	Pt^{-1} day^{-1}
Admission prevalence	σ	-
Admission rate (patients per day)	Ω	pt day^{-1}
Discharge rate of colonized patients	μ_Y	day^{-1}
Discharge rate of uncolonized patients	μ_x	day^{-1}
Transmission patients → Health care workers	P_{ph}	Colonization $contact^{-1}$
Transmission health care workers → patients per contact	P_{hp}	Colonization HCW^{-1}
Hand hygiene rate per health care workers	k	HCW^{-1} day^{-1}

THEOREM

(i) if the function f(*S,I)* monotonically grows with respect to *S* and *I* and is concave with respect to the variable *I* (that is if $\partial^2 f \leq 0$), and $R_o > I$, then the system (I) has an unique ∂I^2

Positive endemic equilibrium state Q* which is globally asymptotically stable

(ii)If $R_o \leq 1$, then there is no positive endemic equilibrium state, and the infection – free equilibrium state Q_o is globally asymptotically stable.

Proof: Existence of a positive equilibrium state.

At fixed of the system, the equalities $\delta I = \mu S = \mu \; and \; \delta I = f\,(S,I)$ hold. These equalities define a negatively sloped straight line q_1 and a curve q_2 on the *I S*plane. The equality $\delta I = f(S.I)$ defined also a function

$S = h\,(I)$. *If* $\frac{\partial f(s.I)}{\partial S}$ is strictly positive, then, by the implicit function theorem, the function $h\,(I)$ is defined and continuous for all $I > 0$. It is obvious that is $S_* = h\,(0) \leq S_o = 1$ then there is at least one

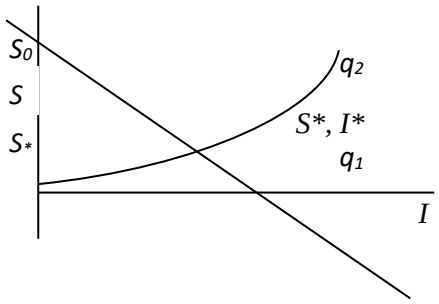

Figure 5: The straight line q_1 and the curve q_2

Point of intersection of the lines q_1 andq_2. The function $f(S,I)$ grows monotonically with respect of both variable, and hence $S_o / S_* > 1$ if

$$Lim_{I \to 0} \frac{f\,(S_o, I)}{f\,(S_*, I)} = \lim_{I \to 0} \frac{f\,(S_0, I)}{\delta I} = \frac{1}{\delta} \frac{\partial f\,(S^o, 0)}{\partial I} = R_o > 1.$$

We assumed now that apart from the equilibrium Q^*, the system has another positive equilibrium state $Q_1 = (S_1,I_1)$. Then $f\,(S_1,I_1) + \mu S_1 = \mu$ and $\delta I_1 = f\,(S_1,I_1)$ hold. The derivative of a Lyapunov function is equal to zero at any equilibrium state, and therefore $\frac{dv}{dt} = 0$ at Q_1. Therefore, S_1 *and* I_1 must satisfy the equalities.

$$\left.\begin{aligned} \left(1 - \frac{S_1}{S^*}\right)\left(1 - \frac{f\,(S^*, I^*)}{f\,(S_1, I^*)}\right) &= 0 \quad \text{(i)} \\ \left(1 - \frac{f\,(S^*, I^*)}{f\,(S_1, I^*)}\right)\left(1 - \frac{f\,(S_1, I)}{f\,(S^*, I)}\right) &= 0 \quad \text{(ii)} \end{aligned}\right\}$$

$\frac{I_1}{I^* f(S_1, I^*)} - \frac{f(S_1, I_1)}{f(S^*, I_1)} \frac{f(S^*, I^*)}{} - 1 = 0$ (iii)

$\frac{\partial v}{\partial s} = 1 - \frac{f(S^*, I^*)}{f(S, I^*)} \frac{\partial v}{\partial I} = 1 - \frac{f(S^*, I^*)}{f(S^*, I)}$ (iv)

Where v is a function defined as

$V(S, I) = S - \int_{\varepsilon}^{S} \frac{f(S^*, I^*)}{f(\tau, I^*)} d\tau + 1 - \int_{\varepsilon}^{I} \frac{f(S^*, I^*)}{f(S^*, \tau)} d\tau,$

It is obvious that for a monotonic function (or for a function satisfying condition (iv), the equality (i) holds only when $S_1 = S^*$. Then $I_1 = I^*$ is necessary to satisfy fixed point of the system.

Furthermore, it is also obvious that for a monotonic (or satisfying condition (iv) function, the point Q* is the only invariant set the system (1) in the set $\frac{dv}{dt} = 0$.

Therefore, by the Lyapunov assumption the point Q* is asymptotically stable for all $S \geq \varepsilon$.

The parameter ε may be made as small as required, and therefore the endemic equilibrium Q* is a asymptotically stable in the non –negative quadrant R^2_+.

To prove the global stability of the infection – free equilibrium states $Q_0 = (1,0)$ we consider the Lyampunov function.

$U(S,I) = S - \int_{\varepsilon}^{S} \lim_{I \to 1_o} \frac{f(S_o, I)}{f(\tau, I)} d\tau + I$

(We cannot consider the function $U = S - \int_{\varepsilon}^{S} \frac{f(S_o, I_o)}{f(\tau, I_o)} d\tau + I$, because $f(S,0) = 0$)

In this case of the SIR system (1), the Lyampunov function satisfies

$\frac{dU(S,I)}{dt} = \mu - f(S, I - \mu S - \mu \lim \frac{f(S_o, I_o)}{f(S, I_o)} + f(S, I) \lim \frac{f(S_o, I_o)}{f(S, I_o)} + \mu S \lim \frac{f(S_o, I_o)}{f(S, I_o)} - \delta I$

$= \mu - \mu \frac{S}{S_o} - \mu \lim \frac{f(S_o, I_o)}{f(S, I_o)} + f(S, I) \lim \frac{f(S_o, I_o)}{f(S, I_o)} + \mu \frac{S}{S_o f(S, I_o)} \lim \frac{f(S_o, I_o)}{f(S, I_o)} - \delta I$

$= \mu \left(1 - \frac{S}{S_o f(S, I_o)}\right) 1 - \left(\frac{f(S_o, I_o)}{\delta I}\right) + \delta I \, f(S, I) \left(\lim \frac{f(S_o, I_o)}{f(S, I_o)} - 1\right)$

(Here we denote $\lim \frac{f(S_o, I_o)}{f(S, I_o)} = \lim_{I \to I_o} \frac{f(S_o, I)}{f(S, I)}$ *For a monotonic function*

$\left(1 - \frac{S}{S_o f(S, I_o)}\right) 1 - \lim \frac{f(S_o, I_o)}{} \leq 0$ *for all S>0*

Concavity of the function f (S.I) ensures that $f(S.I) \leq 1 \frac{\partial f(S, 0)}{\partial I}$ *for al* $1 > 0$, *and hence*

$\delta I \quad \frac{f(S. I)}{1 \to I_o f(S, I)} \quad 1 - \lim \frac{f(S_o, I)}{\delta I} = f(S. I)$ [

$$\frac{\partial f(So, Io)}{\partial I} \leq \frac{1}{\delta}\frac{\partial f(So, Io)}{\partial I} = R_o \Big]$$
$$\frac{\partial f(S, Io)}{\partial I}$$

Therefore, $R_o \leq 1$ ensures that $\frac{dU(S.I)}{dt} \leq 0$ for all S, $I>\varepsilon$, and hence by the asymptotic stability theorem , the equilibrium state Q_o is globally a asymptotically stable in this case.

We proved that for all $R_o \leq 1$ there exists a unique and globally stable positive equilibrium state Q^*, and that for $Ro \leq 1$ the infection – free equilibrium Q_o is globally stable. At $R_0 = 1$ for any function $f(S, I)$ monotonic with respect to S. These two equilibriumQ_o and Q^*, meet and exchange their stability; that is a transcritical bifurcation occurs at this point. Indeed, it is easy to see (cf. Proof, part 1) that, for a monotonic function $f(S,I)$, S_o, At S_*(and hence S*) tends to S_o as R_o tends to I, and that R_o = 1 implies $S_* = S_o$. At $R_o = 1$ the point (S_o, I_o) is, therefore, the point ofintersection of the lines q_1 and q_2 (see Fig.5) For $R_o<1$ the equilibrium Q^* moves in the quadrant $S > 0, 1 < 0$.

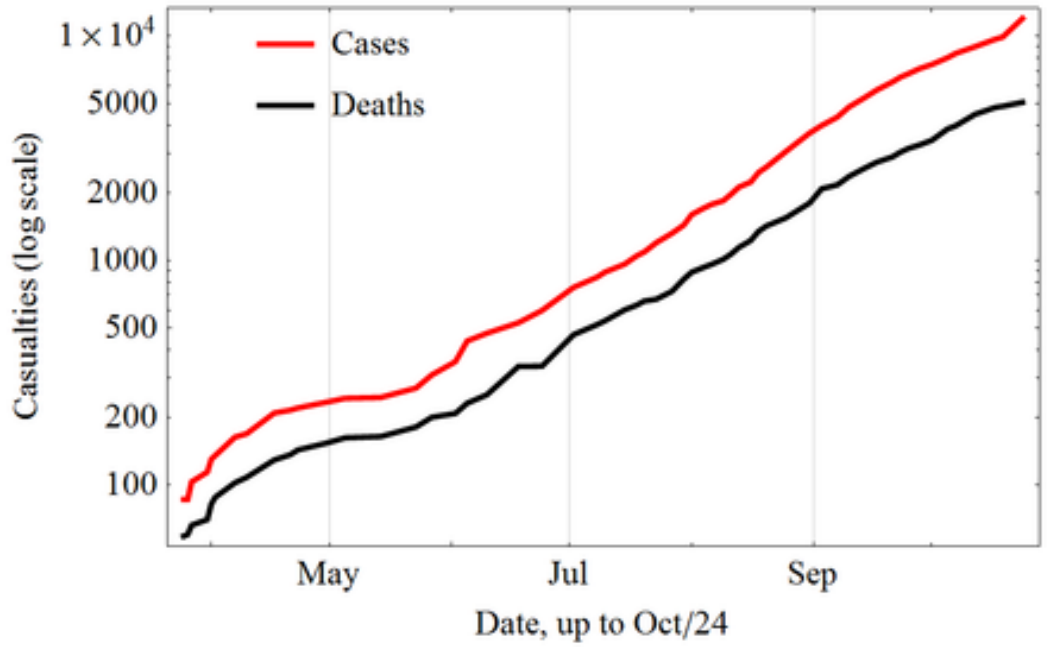

Fig: 6 Cumulative totals of cases and deaths over time

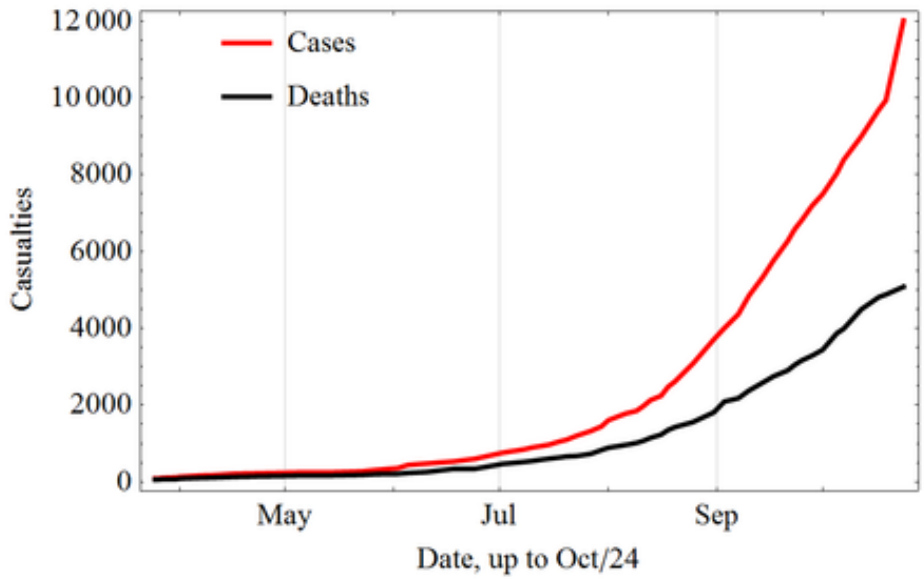

Fig: 7 Cumulative totals in log scale

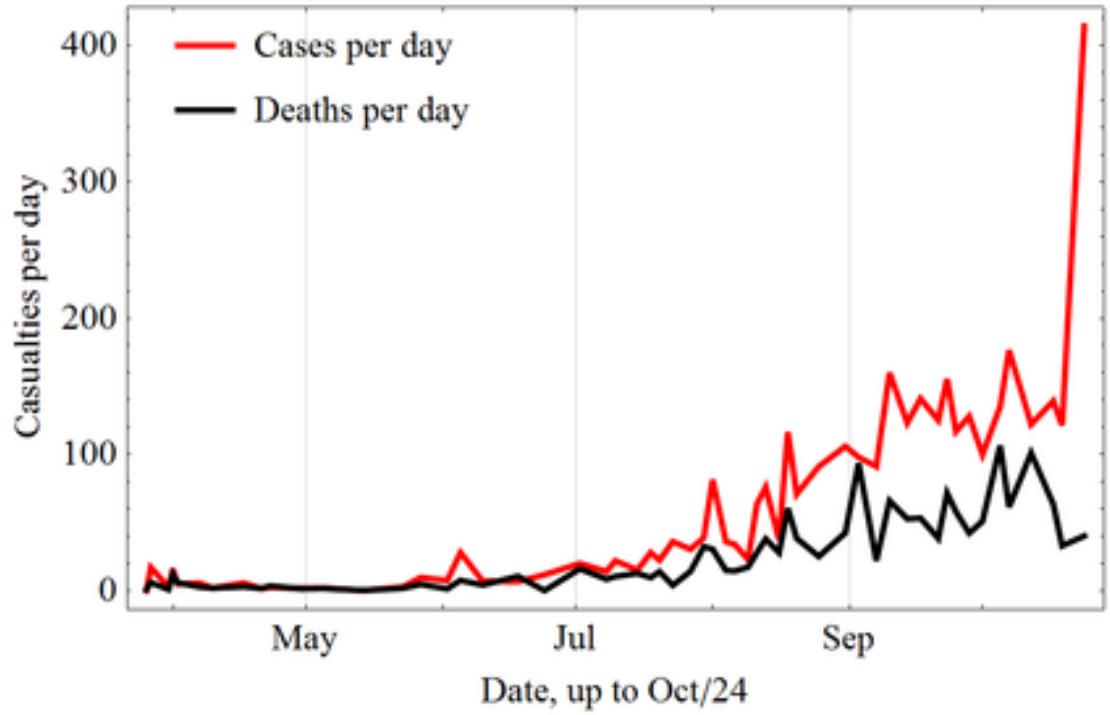

Fig: 8 Average new cases and deaths per day (between WHO reporting dates)

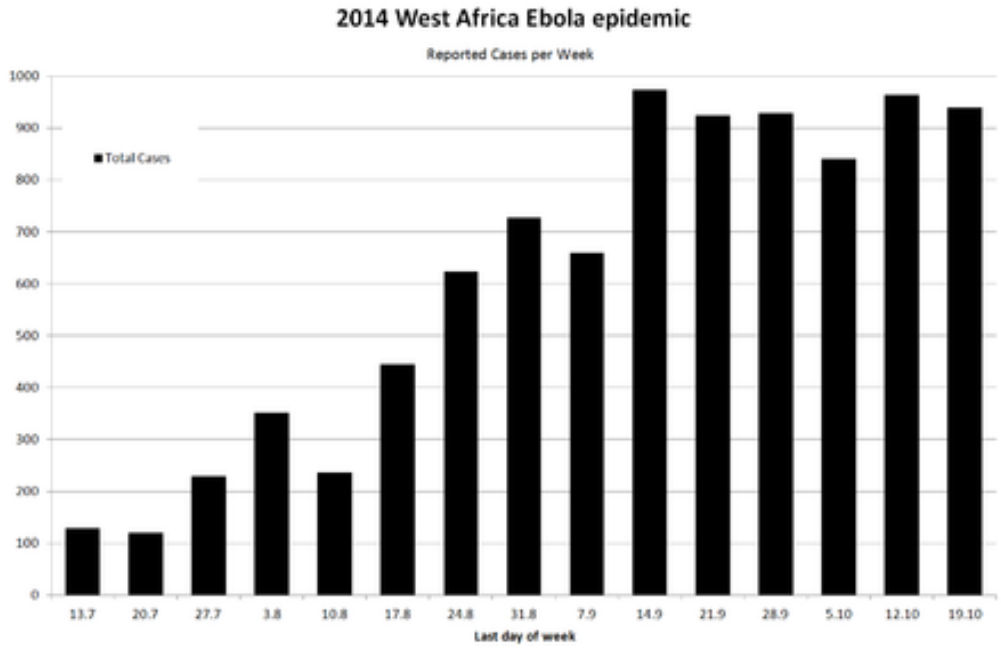

Fig:9 The reported weekly cases of Ebola in West Africa as listed on Wikipedia Ebola virus epidemic in West Africa**; some values are interpolated**

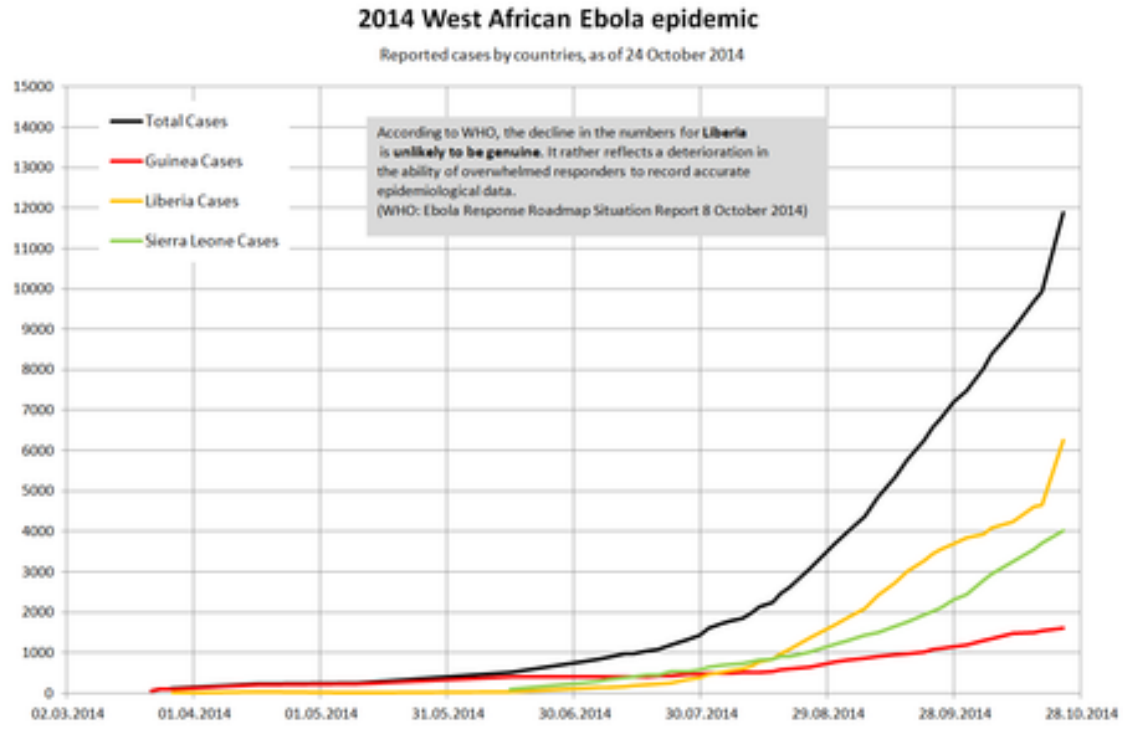

Fig: 10 Cumulative numbers of cases by country, using a linear scale

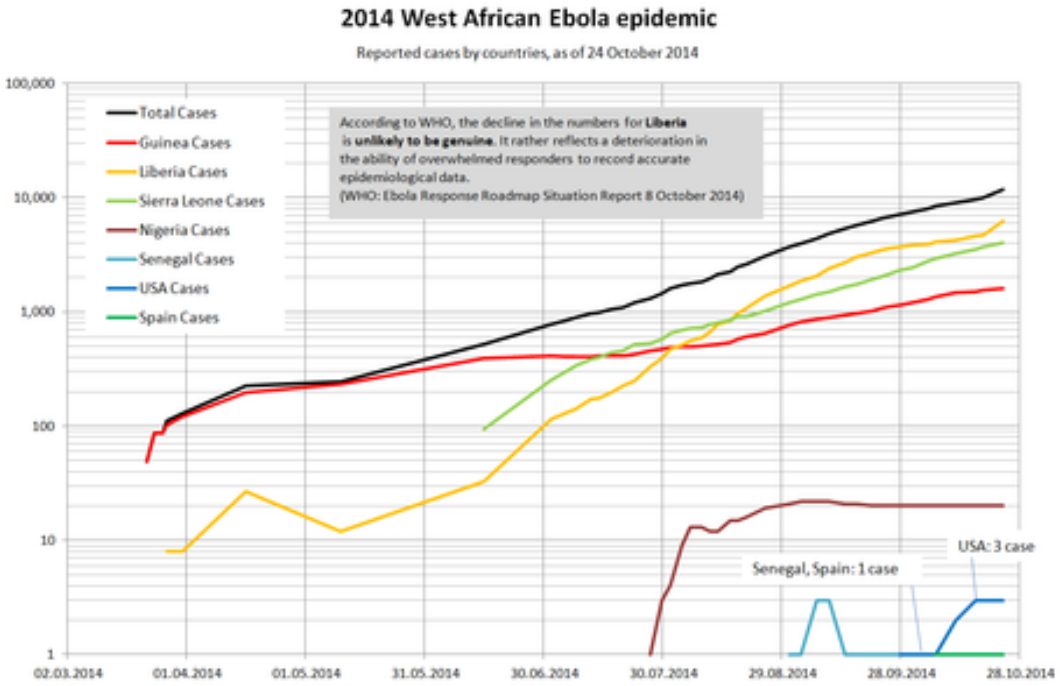

Fig: 11Cumulative numbers of cases by country, using a logarithmic scale

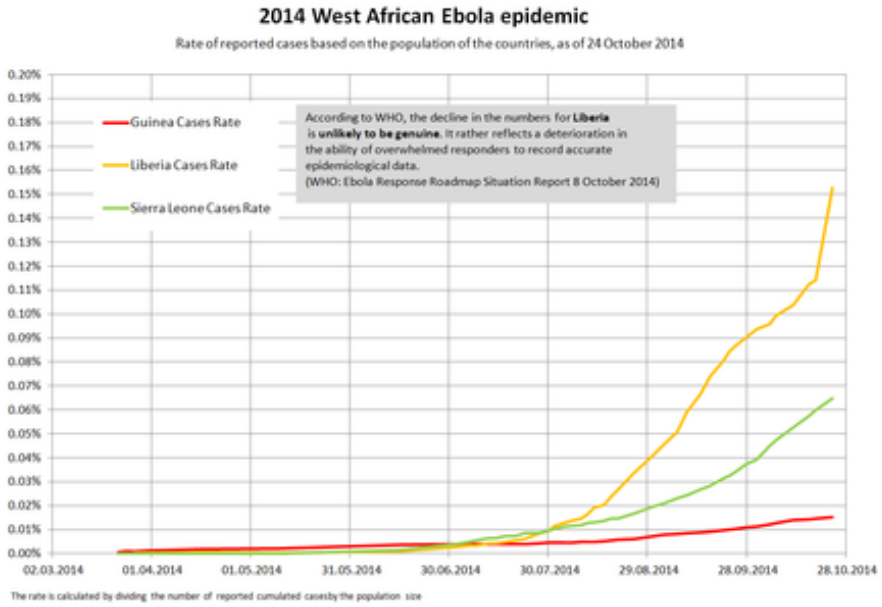

Fig: 12Cases based on population, using a linear scale

MODEL ADEQUACY AND SENSITIVITY ANALYSIS

Due to the degree of uncertainty in the parameter values, we consider a range of parameters to examine the dependence of R_o on parameter variation. The parametric bootstrap analysis was used to determine model adequacy, this process involves simulating data from the model using ward observations (number of uncolonized number of patients and admission of known colonized patients) and the estimated transmission parameter. The methodology described in this paper was then applied to the simulated data to estimate the mean of the marginal posterior distribution of the transmission parameter. The study found that this gave an unbiased estimate of the transmission parameter. We also used Latin Hypercube sampling and Partial Rank Correlation Coefficients (PRCCs) to identify which parameters R_o is most sensitive. Latin Hypercube sampling is a statistical sampling

method that evaluates sensitivity of an outcome variable to all input variable. PRCCs measure the relative degree of sensitivity to each parameter regardless of whether the parameter has a positive or negative influence on the outcome variable. This demonstrates that R_o is most sensitive to variations in $\mu_Y, \mu_x, P_{ph}, P_{hp}, k, \beta, \mu, v$ and d respectively, shows that the disease is reliably controlled at early detection.

RESULTS AND DISCUSSION

The default value for the health care workers / patients ration, ρ, was unity. The default value for the decolonization rate, γ, was zero. Other default values were admission prevalence, σ = 0.03, discharge rate of colonized patients $\mu_Y = \frac{1}{11}$ corresponding to a length of stay of 11 days, discharge rate of uncolonised patients $\mu_x = \frac{1}{5}$ corresponding to a length of stay of 5 days, probability of transmission from colonized to health care workers per contacts p_{ph}= 0.13,hand hygiene compliance, h = 0.59. In the simulations, for each set of parameters, the ward was assumed to start with no colonized patients, the burn – in period was 200 days and the predicted attack rate was derived from the next 139 simulated days. Stochastic results were based on 200 simulations for each set of parameters, and the 2.6-96.5 percentile ranges were determined. By leaving all other parameters at their default values and modifying h, μ_Y, μ_x andσ, we simulated the effects of changes in hand hygiene compliance, discharge rate of colonized and uncolonised patients and admission prevalence respectively. By changing γ from zero to 0.05, we simulated the effect of decolonization.Cohorting was simulated by reducing the number of "effective contacts". We assumed that cohorting was non – selective. That is that health care workers cared for a cohort of patients who could be a mix of colonized and uncolonised patients. The smaller the group in the cohort, the more likely that a given contact is a return contact and thus not an "effective contact". When maximum co-horting is taking place, we assume that a proportion of contacts equal to the health care workers / patients, ρ, pose no risk (When $\rho \geq 1$ all cohorted contacts pose no risk).

Our model defined c as the number of contacts per patient per health care taker. By examining the effect of increasing staff patient ratio, ρ, we assume that each health care worker has fixed number of contacts and increasing staff increases contacts. To extend this simulation to allow for charges in patient numbers but continuing to assume a fixed number of contacts per Health care worker, one could modify the contact rate, $c^* = c\,\underline{n_p}$, where n_p is the default number of patients

Np

and N_p is the actual number of patients. We could alternatively simulate a situation where patients have a fixed number of contacts and increasing staff does not increase contacts.

Such a simulation would require modifying the contact rate to c* c/ρ. This model predicts that the attack rate will increase dramatically should the hand hygiene compliance fall below 40%. A hand hygiene compliance of 48% would increase the ward of production ratio to unity and changing the discharge rate of colonized patients μ_Y, leading to a reciprocal change in expected duration of stay. The response curve was sigmoidal in shape. Increasing the mean time on ward following colonization to 21 days would lead to the ward of reproduction ratio exceeding unity.

The response of attack rates to doubling the admission prevalence from the current 3% to 6% is predicted increase in attack rate from one transmission per 160 uncolonised patients' days to one per 105 uncolonised patient's day. We investigated the predicted impact of changing the health care worker / patient ratio increasing health care worker number increases cross transmission. The study included 1698 patients of these 120 patients were known to be colonized on admission.

Given the following parameters number of patient N = 75, removal rate of colonized patients $\mu \frac{1}{21}$days, contact / transmission rate β = 1.0 x 10^{-3}, Sporadic acquisition rate v = 2.0 x 10^{-4}, detention probability d = 0.58 – 0.97 where N, μ are directly from the data set, $\beta$and v are fitted using HMM, and d is from literature review.The estimated value for the transmission coefficient β was 10 x 10^{-4} (CI_{95}7.9 x 10^{-4}, 13x10^{-4}) and the sporadic acquisition rate v was 2.0 x 10^{-4} (CI_{95} 0.85 x 10^{-4}, 3.8 x 10^{-4}). The coefficient of correlation between β and v was estimated to be -0.23.The basic reproduction ratio,

R_o, is "the average number of persons directly infected by an infectious case during its entire infectious period, after entering a totally susceptible population" [18]. In this model it can be shown to be $R_o = \frac{\beta N}{\mu}$. The basic reproduction ratio is estimated to be 1.57(CI_{95} 0.82-1.95).

In our model people are either susceptible infected or recovered. Recovered individuals return only temporary immunity before becoming susceptible again. Ebola virus, (Ebov) grows logistically with a given carrying capacity. The transmission of Ebola virus during single contact in the hospital setting. Hospital infection surveillance data is often less detailed than data collected for epidemiological studies. This study uses modified epidemical models (SEIR) to analyze data from Ebola outbreak that are specific to virus. We proposed and investigated an impulsive statistical model in an attempt to understand the effects of some intrinsic variables controlling Ebola. The disease – free equilibrium is shown to be globally stable considering Lyapunov function, proved that for all $R_o > 1$ there exist a unique and global stable positive equilibrium state Q*, and there for $R_o < 1$ the infection – free equilibrium Q_0 is globally stable. At $R_o = 1$ for any function *f(S, I) monotonic* with respect to S these two equilibrium, $Q_o$and Q*, meet and exchange their stability, that is a transcritical bifurcation occurs at this point. The comparison theorem is used to prove the global stability for DFE. The theory is employed to show that if a unique positive endemic equilibrium states Q^*, exists then it's globally asymptotically stable when the $R_o > 1$ and if $R_o < 1$ then there is no positive endemic equilibrium states, and the DFE state Q_0 is globally a asymptotically stable. Due to the degree of uncertainty in the parameter values, we considered a range of parameters to examine the dependence of R_0 on parameter variation.

We perform sensitivity analysis which ensures the uniqueness and the global stability of the positive endemic equilibrium state which demonstrates that R_o is most sensitive to variation in $\mu_Y, \mu_x, P_{ph}, P_{hp}, k, \beta, \mu, v$ *and* d respectively. This shows that the disease is reliably controlled at early detection. The basic reproduction ration $0.82 < R_0 < 1.95$ *at 95%* credible interval and the mean value for the estimated detection rate was 0.75 with a 95% credible interval of 0.59 – 0.93. Important conclusion regarding the infectivity of Ebola virus can be drawn from this analysis. The estimated daily infectivity of the hospitalized patients was lower than community patients. Despite this, it was estimated that early in the epidemic, a larger number of secondary cases resulted from hospitalized patients. These results support, the conclusion that interventions were effective at controlling the Ebola epidemic in West Africa. The Bayesian approach was adopted in this study because the main questions posed by the studies were "how does the information, provided in this single dataset, modify our belief regarding the transmission of the virus?" Such a question does not have meaning in a frequentist context. MSF closed its treatment centers in May leaving only a small skeleton staff to handle the Macenta region. However, high numbers of new cases reappeared in the region in late August. According to Marc Poncin, a coordinator for MSF, the new cases were related to persons returning to Guinea from neighboring Liberia or Sierra Leone.[21].By our analysis there is an impact of public health control interventions in hospital.

CONCLUSSION/RECOMMENDATION

We have explored the sensitivity of the epidemic size to the starting time of interventions. The exponential increase of the final epidemic size with the time of start of interventions as seen on the figures above supports the idea that the rapid implementation of control measures should be considered as a critical component in any contingency plan against disease outbreaks especially for Ebola case which have no specific treatment or vaccine exists. Our model has some limitations, which should be noted one limitation is the estimation of the parameters, a number of which were assumed. Our model also ignored some important factors like nutrition among poor communities. For example, the disease is more fatal for poor people with inadequate nursing and running water with sanitizer for hand washing. We also conflated the effect of household sensitizing and cleaning into the saturation constants. In summary despite the lack of detailed data set transmission characteristics was inferred using Hidden Markov models (HMMs a symptomatic case which are specific to the virus.We thus recommend the development of such models to determine infectivity with health interventions for early detection, The Markov Chain Monte – Carlo

algorithm is a very convenient tool for numerical integration of complex expressions derived from incorporation of latent variables into transmission models. Bayesian inference also allowed us to incorporate prior information into models. In this study the prior probabilities were vague. Mostly, this was because little was known about the model parameters. In the cases where a small amount of independent data was available, these were used to independently validate our model to conclusion.

The results of our model assumption revealed that the basic reproduction number will surely be a function of the contribution of the interaction of the human effective population. Our findings are very significant contribution to the disease transmission dynamics of non-linear form and serve as an improvement of the models earlier reviewed as literature. Our estimate of R_o=1.57(0.82 < R_o< 1.95) at 95% confidence interval, means R_o> 1 which is in conformity to standard principle in epidemiology and this ensures the uniqueness and the global stability of the positive endemic equilibrium state. We shall shift focus to the analysis of the endemic equilibrium of our model in the subsequent papers.

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