Efficient disease control strategy in metropolitan area using sensitivity analysis of basic reproduction ratio R0	八島健太, 佐々木顕	平成26年度九州大学IMI共同利用研究・研究集(I)「感染症数理モデルの実用化と産業及び政策での活用のための新たな展開」	2014年10月1日-10月3日	国内
Construction of Lyapunov functions and functionals for models in ecology, 口頭	Toru Sasaki and Tsuyoshi Kajiwara	Joint Annual Meeting of the Japanese Society for Mathematical Biology and the Society for Mathematicl Biology	2014年7月	国内
免疫変数を含む病原体ダイミクスモデルのリアプノフ関数の構成	佐々木徹, 梶原毅	研究集会「理論生物学に現れる多成分系数理モデルの熱力学と数理解析」	2014年8月	国内
生態モデルのリアプノフ関数/汎関数について	佐々木徹, 梶原毅	研究集会「第 11 回生物数学の理論とその応用」	2014年9月	国内
How can the spatial structure affect complex dynamical behavior of the population?(口頭)	佐藤一憲	JSMB/SMB OSAKA 2014	2014年7月	国内(大阪)
APOBEC3F potently promotes HIV-1 diversification and evolution in humanized mouse model(口頭)	Sato, K., Shibata, J., Izumi, T., Misawa, N., Kobayashi, T., Kimura, Y., Ito, M., Pathak, V. K., Koyanagi,	Cold Spring Harbor Laboratory Meeting on Retroviruses	2015年5月	国外
Quantification of acute viral infection dynamics in HIV-1 infected humanized mouse using delay differential equations(口頭)	Ikeda, H., Nakaoka, S., Sato, K., Iwami, S.	日本数理生物学会	2015年7月	国内
レンチウイルスと宿主の進化的軍拡競争の分子メカニズム(口頭、招待ワークショップ)	佐藤佳, 竹内(柴田)潤子, 小林朋子, 吉川禄助, 山田英里, 中野雄介, 任鳳蓉, 田中博, 小	日本進化学会第16回大会	2015年8月	国内
HIV感染ヒト化マウスモデルにおける宿主因子-ウイルス因子の相克(口頭)	佐藤佳.	第11回湯河原キャンプ	2015年9月	国内

FIVサブタイプ間におけるVifタンパク質の機能的相違性(口頭)	吉川禄助, 竹内(柴田)潤子, 山田英里, 中野雄介, 木村雄一, 宮沢孝幸, 佐藤	第62回日本ウイルス学会学術集会	2015年11月	国内
ヒト化マウスモデルを用いたエイズウイルス適応進化メカニズムの解明(口頭)	佐藤佳, 竹内(柴田)潤子, 小林朋子, 三沢尚子, 山田英里, 中野雄介, 吉川禄助, 小柳義	第62回日本ウイルス学会学術集会	2015年11月	国内
TetherinとNefの相克から読み解く霊長類レンチウイルスの進化的軍拡競争(ポスター)	山田英里, 竹内(柴田)潤子, 吉川禄助, 小林朋子, 任鳳蓉, 松田健太, 中野雄介, 木村雄一, 三沢尚子, 田中博, Hirsch Vanessa, 佐	第62回日本ウイルス学会学術集会	2015年11月	国内
ネコAPOBEC3Z3の遺伝子多型とFIV Vif感受性の関連(ポスター)	吉川禄助, 山田英里, 中野雄介, 任鳳蓉, 田中博, 宮沢孝幸, 佐藤佳, 小柳義	第37回日本分子生物学会年会	2015年11月	国内
異種レンチウイルスVifのCBFb要求性の差異(ポスター)	山田英里, 吉川禄助, 竹内(柴田)潤子, 中野雄介, 任鳳蓉, 田中博, 宮沢孝幸, 佐藤佳, 小	第37回日本分子生物学会年会	2015年11月	国内
霊長類レンチウイルスのNef タンパク質の機能的進化とその意義(口頭)	中野雄介, 吉川禄助, 山田英里, 小林朋子, 竹内(柴田)潤子, 三沢尚子, 佐藤佳, 小柳義	第28回日本エイズ学会学術集会・総会	2015年12月	国内
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Impact of Intracellular Delay, Immune Activation Delay and Nonlinear Incidence on Viral Dynamics （口頭）	Yasuhiro Takeuchi	The Joint Annual Meeting of the Japanese Society for Mathematical Biology and the Society for Mathematical Biology	2014年8月	国内
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2．学会誌・雑誌等における論文掲載

掲載した論文（発表題目）	発表者氏名	発表した場所（学会誌・雑誌等名）	発表した時期	国内・外の別
EMタイプIRTによる不完全マトリクスの完全化とその応用	作村，徳永，廣瀬	情報処理学会論文誌，数理モデル化と応用	2014年11月	国内
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（注１）発表者氏名は、連名による発表の場合には、筆頭者を先頭にして全員を記載すること。
（注２）本様式はexcel形式にて作成し、甲が求める場合は別途電子データを納入すること。

V章

Early transmission dynamics of Ebola virus disease (EVD), West Africa, March to August 2014

H Nishiura (nishiurah@m.u-tokyo.ac.jp)1, G Chowell2,3
1. Graduate School of Medicine, The University of Tokyo, Tokyo, Japan
2. School of Human Evolution and Social Change, Arizona State University, Tempe, Arizona, United States
3. Division of International Epidemiology and Population Studies, Fogarty International Center, National Institutes of Health, Bethesda, Maryland, United States

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The effective reproduction number, R_t, of Ebola virus disease was estimated using country-specific data reported from Guinea, Liberia and Sierra Leone to the World Health Organization from March to August, 2014. R_t for the three countries lies consistently above 1.0 since June 2014. Country-specific R_t for Liberia and Sierra Leone have lied between 1.0 and 2.0. R_t<2 indicate that control could be attained by preventing over half of the secondary transmissions per primary case.

Introduction

The largest and first regional outbreak of Ebola virus disease (EVD) has been unfolding in West Africa since approximately December 2013, with the first cases traced back to southern Guinea [1]. However, the outbreak was not recognised until March 2014 [1], which facilitated the spread to neighbouring Sierra Leone and Liberia through porous borders as well as Nigeria via a commercial airplane on 20 July [2]. The World Health Organization (WHO) declared this EVD epidemic a Public Health Emergency of International Concern on 8 August 2014 [3]. According to phylogenetic analyses, the causative Ebola virus strain is closely related to a strain associated with past EVD outbreaks in Central Africa, and could have been circulating in West Africa for about a decade [4].

A total of 3,707 cases (including 2,106 confirmed, 1,003 probable and 598 suspected cases, respectively) and 1,848 deaths (concerning 1,050 confirmed and 557 probable cases, as well as 241 suspected cases and deaths, respectively) have been reported in Guinea, Sierra Leone, Liberia, Nigeria, and Senegal as of 31 August 2014 [5]. The total number of cases in Guinea, Sierra Leone, Liberia, Nigeria and Senegal have been 771, 1,216, 1,698, 21 and one, respectively. By contrast, the great majority of past outbreaks have been associated with small numbers of reported cases and have been confined to isolated rural areas in Central Africa. For reference, the largest outbreaks in Central Africa generated 315 cases in Congo in 1976 and 425 cases in Uganda in 2000 [6,7].

The effective reproduction number, R_t, which measures the average number of secondary cases generated by a typical primary case at a given calendar time, can be helpful to understand the EVD transmission dynamics over time in affected countries as well as gauge the effect of control interventions [8]. Values of R_t<1 indicate that the epidemic is in a downward trend. By contrast, an epidemic is in an increasing trend if R_t>1. The mean reproduction number for EVD has been estimated at 1.83 for an outbreak in Congo in 1995 and 1.34 in Uganda in 2000 prior to the implementation of control interventions [9]. Here we sought to estimate the R_t, in real time in order to assess the current status of the evolving outbreak across countries affected in 2014. We also compare our estimates of the reproduction number for the current outbreak with those previously published for the largest outbreaks in Central Africa and discuss our findings from a public health perspective.

Methods

Case data

We analysed the cumulative case counts reported by the WHO [10] as of 26 August 2014. Case counts are classified into three categories, i.e. confirmed, probable and suspected cases. Confirmed cases are laboratory diagnosed by polymerase chain reaction (PCR), positive IgM antibody or viral isolation while suspected cases correspond to individuals presenting fever (≥38.5°C (101°F)) and no favourable response to treatment for usual causes of fever in the area, and at least one of the following clinical signs: bloody diarrhoea, bleeding from gums, bleeding into skin (purpura), bleeding into eyes and urine. Probable cases are suspected cases of EVD with an epidemiological link to a confirmed EVD case [11]. We analysed two different sets of grouped data, i.e. (i) confirmed plus probable

cases and (ii) the total number of reported cases (i.e. confirmed, probable and suspected cases).

Because case counts were reported in irregular time intervals, we estimated daily incidence curves of EVD cases in order to estimate R_t. For this purpose, we first fit a smoothing spline to country-specific cumulative curves of reported cases. Next we took the daily difference of the cumulative counts to obtain daily incidence time series. Of note, the cumulative case series reflects the diagnostic process (among suspected and probable cases) and sometimes declined as a function of time (e.g. 5 April and 12 July in Guinea and Sierra Leone, respectively). When the difference was negative, we replaced it by 0. The smoothing spline was chosen to obtain a coefficient of determination R^2 at 0.995. Data from Nigeria and Senegal have been omitted due to a limited number of cases recorded in these countries thus far.

Mathematical model

We employed mathematical modelling together with time- and country-specific incidence data to estimate the R_t. Thus, here we model the transmission dynamics of EVD using a country-specific next-generation matrix $\{k_{ij,t}\}$ representing the average number of secondary cases in country i at time τ generated by a single primary case in country j. Let g_τ represent the probability density function of the generation time of length t days for EVD. Hence, the expected value of EVD incidence in country i at time t is modelled as

$$E(c_{i,t}) = \sum_j k_{ij,t} \sum_{\tau=1}^{\infty} c_{j,t-\tau} g_\tau$$

The univariate version of Equation 1 has been employed by White and Pagano [12,13] in order to jointly estimate R_0 and the generation time distribution of EVD. Assuming that EVD incidence follows a Poisson distribution, the likelihood to estimate $\{k_{ij,t}\}$ is

$$\prod_t \prod_i \frac{\left(\sum_j k_{ij,t} \sum_{\tau=1}^{\infty} r_{j,t-\tau} g_\tau\right)^{r_{i,t}} \exp\left[-\left(\sum_j k_{ij,t} \sum_{\tau=1}^{\infty} r_{j,t-\tau} g_\tau\right)\right]}{r_{i,t}!}$$

where $r_{i,t}$ is the estimated daily incidence in country i on day t derived from the difference of the smoothing spline fit to the cumulative data as explained above.

Each element of the next-generation matrix is interpreted as the average number of secondary cases generated by a single primary case at time t. We assume that the per-contact probability of infection and the average generation time do not differ by country. Thus, the contact matrix regulates the relative difference between each pair of entries of the next-generation matrix, and because the contact patterns within and between countries cannot be directly observed, we made a qualitative assumption for the matrix $\{k_{ij,t}\}$ to approximately capture the pattern of (domestic and transnational) transmission [14], i.e.

$$M_t = \begin{pmatrix} k_{g,t} & \alpha & \alpha \\ \alpha & k_{s,t} & \alpha \\ \alpha & \alpha & k_{l,t} \end{pmatrix}$$

The matrix M_t qualitatively assumes that there are more frequent within-country transmissions (denoted by $k_{g,t}$, $k_{s,t}$ and $k_{l,t}$, where the subscripts g, s and l represent Guinea, Sierra Leone and Liberia, respectively) compared with transnational spread. The transnational spread is modelled by a single parameter a. We employed a piecewise constant model and change the parameters for the above-mentioned elements every seven days. Maximum likelihood estimates of the parameters were obtained by minimising the negative logarithm of Equation 2. Using the most recent incidence estimate i_0 and the exponential growth rate r as calculated from $r=(R-1)/12$ (where R is the most recent reproduction number and 12 is the mean generation time), the expected number of additional cases in 2014 was calculated as

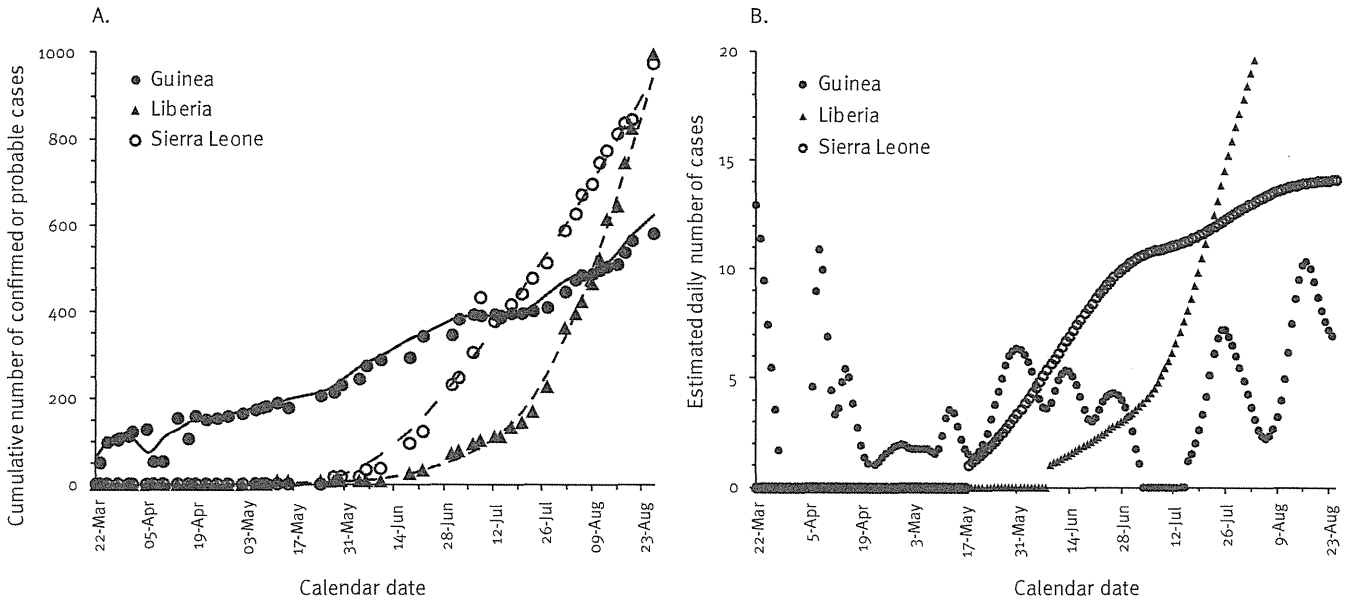
$$I = i_0 \int_0^{120} \exp(rt)\, dt$$

. The expected cases represent a 'worst-case' scenario based on the current situation by assuming a fixed reproduction number R for the remainder of the year (i.e. approximately 120 days remaining in 2014).

We also computed the R_t for all countries (hereafter referred to as the 'global' estimate of the reproduction number) by calculating the dominant eigenvalue of the estimated next-generation matrices. Moreover, we calculated column sums of the matrices to estimate the average number of secondary transmissions arising in and from a specific country and also extracted estimates of 2α, the value that governs the transnational spread generated by a single primary case. Although White and Pagano achieved the joint estimation of R_0 and generation time distribution [12,13], we assumed that the generation time is known, because our analysis relies solely on the cumulative number of reported cases with irregular reporting intervals. The generation time was assumed to follow an exponential distribution with a mean of 12 days [15], which is known to be close to the mean incubation period [16]. Based on empirical data of the serial interval distribution [15], we also carried out a sensitivity analysis of reproduction numbers by varying the mean generation time between nine and 15 days. The 95% confidence intervals of the R_t can be computed via bootstrapping methods. However, our study focused on examining model uncertainty associated with the transnational mixing patterns and the mean generation time as model uncertainty in our study is likely more influential on R_t compared to uncertainty relating to measurement error. In sensitivity analyses, we also examined the impact of varying specified time interval on R_t. For this purpose, we also

FIGURE 1

Cumulative and daily epidemic curves of Ebola virus disease (EVD) in Guinea, Liberia, and Sierra Leone, 23 March–26 August 2014



A)Cumulative number of confirmed or probable cases of EVD reported to the World Health Organization [10]. Solid lines are the smoothing spline fits to cumulative curves for each country with a coefficient of variation R^2 at 0.995.

B) Estimated daily incidence curves based on the smoothing spline model. Data from Nigeria and Senegal have been omitted due to the limited number of cases recorded in these countries thus far.

analysed the piecewise constant model for every six and eight days instead of seven days.

Results

Figure 1 illustrates the process of deriving daily EVD incidence curves by country from cumulative curves of reported cases. Multiple fluctuations are evident from the incidence curve for Guinea (Figure 1). In Liberia, the early transmission phase did not appear to exhibit sustained growth and was probably driven by case importations during first epidemic month. Exponential growth was subsequently seen, reflecting self-sustaining transmission. Similarly, the incidence curve for Sierra Leone also displayed steady growth since early June. Most recent EVD incidence data for Guinea also showed an increasing pattern.

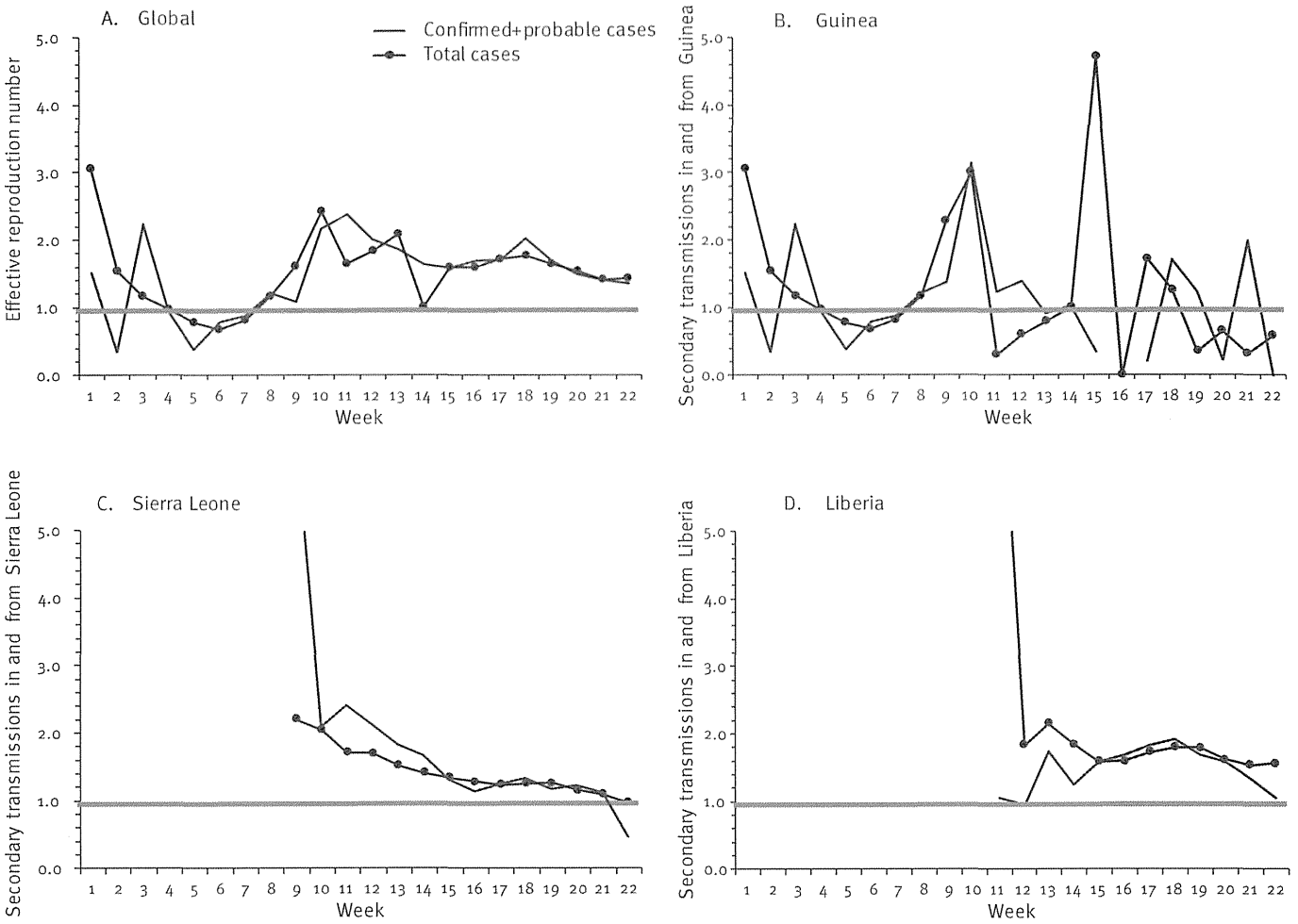
Our weekly maximum likelihood estimates of the R_t for each affected country and for the global system in West Africa are displayed in Figure 2. Results indicate that the reproduction number for all countries reached levels below unity in April and May, but has appeared to be continuously above one since early June (Figure 2A). This pattern was robust when using two different datasets (including and excluding suspected cases). Estimates of R_t using total case reports from June to July 2014, a period during which exponential growth of cases has been observed in Sierra Leone and Liberia, ranged from 1.4 to 1.7, respectively. In the hypothetical worst-case scenario that the current situation with an estimated reproduction number R ranging from 1.4 to 1.7 continues for the remainder of the year, we would expect to observe a total of 77,181 to 277,124 additional cases within 2014.

Maximum likelihood estimates of R_t in Guinea appeared to have fluctuated around 1.0 (Figure 2B), which reflects the observed variation in the corresponding incidence curve. Importantly, R_t in this country has not been continuously below 1.0, which supports the view that in this country the outbreak is not yet under control. Estimates of R_t in Sierra Leone and Liberia appeared to be consistently above 1.0 up to week 22 (i.e. the week starting on 18 August) (Figure 2C and 2D). Although R_t in Sierra Leone has been declining with the highest estimates obtained for early June, R_t has not been consistently below 1.0 in this country, including estimates for the latest reporting week (Figure 2). The pattern of R_t in Liberia shows values well above 1.0 since July 2014. In this country, the estimates of R_t reaching values up to 2.0 indicate that the outbreak could only be brought under control if more than half of secondary transmissions per primary case were prevented.

Figure 3A shows the estimated average number of transnational transmissions per single primary case as a function of time (calculated by 2α). α has been high in early June, but has declined dramatically since late June. Nevertheless, most recent model estimates still suggest a non-negligible number of cross-border

FIGURE 2

Effective reproduction number of Ebola virus disease (EVD) estimated for Guinea, Sierra Leone, Liberia, and for the global system in West Africa, 23 March–26 August 2014



A) Global (maximum likelihood) estimates of the effective reproduction number of EVD based on data from all affected countries (Guinea, Sierra Leone and Liberia) were derived from the dominant eigenvalue of the next generation matrix.

B-D) The average number of secondary transmissions arising from Guinea, Sierra Leone and Liberia, was calculated from the corresponding column sum of the next generation matrix. The horizontal grey solid line indicates the reproduction number at 1.0 for reference, below which the epidemic follows a declining trend. Estimates were derived using either confirmed cases plus probable cases or the total reported case counts (confirmed, probable plus suspected cases). Data from Nigeria and Senegal have been omitted due to limited number of cases recorded thus far. Epidemic week 0 corresponds to the week that includes 22 March 2014.

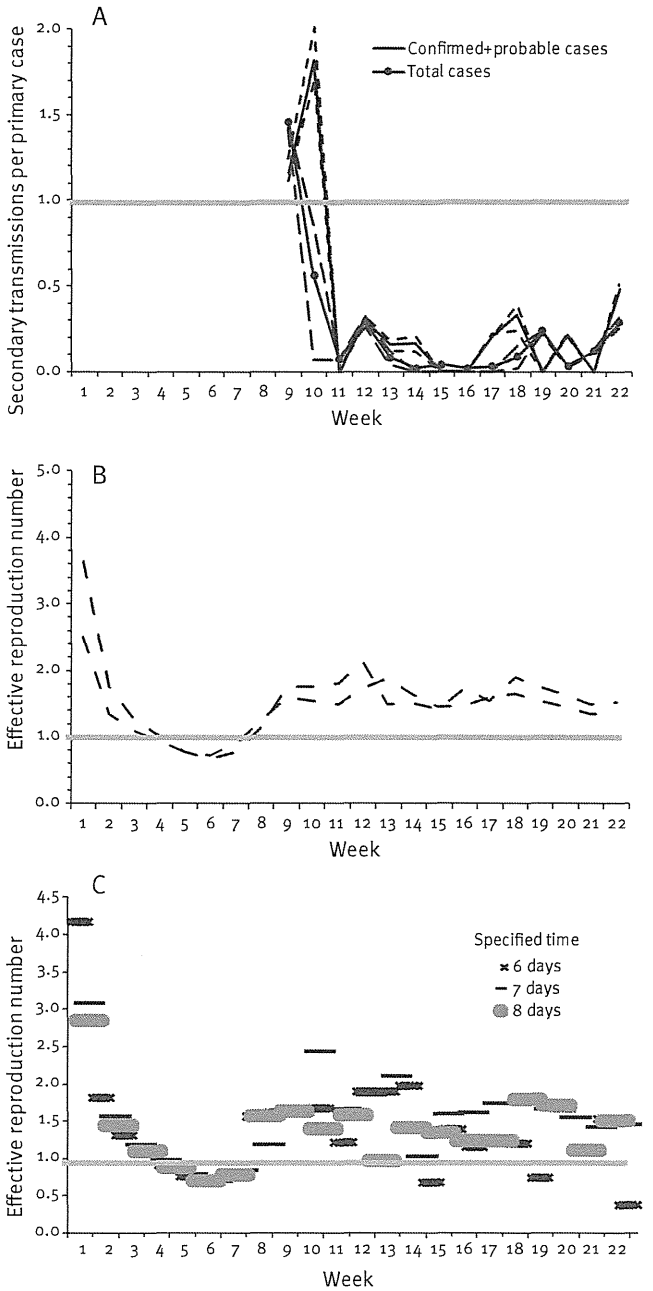
transmissions. Figure 3B examines the sensitivity of R_t for all countries to changes in the mean generation time. Although the absolute values of R_t are positively correlated with the mean generation time, the above-mentioned qualitative patterns of R_t are preserved, which indicates that the ongoing EVD epidemic has yet to be brought under control. Figure 3C examines the sensitivity of R_t to a specified time interval of the piecewise constant model. Perhaps not surprisingly, as the interval is shortened, fluctuations in R_t tend to increase, perhaps due to stochastic effects. Nevertheless, all models roughly provide qualitatively similar patterns in R_t.

Discussion

We have derived global and country-specific estimates of the R_t of EVD for the ongoing outbreak in West Africa. Our global estimates of the R_t appear to be continuously above one since early June, indicating that the epidemic has been steadily growing and has not been brought under control as of 26 August 2014. The country-specific estimates for Sierra Leone and Liberia were also above one, perhaps reflecting the increasing trend in cases in these countries since June. Our estimated reproduction numbers, broadly ranging from one to two, are consistent with published estimates from prior outbreaks in Central Africa [9,17]. Our estimates of R_t<2 indicate that the outbreak could

FIGURE 3

Sensitivity analysis of the effective reproduction number of Ebola virus disease (EVD), West Africa, 23 March–26 August 2014



A) The estimated average number of secondary cases per single primary case arising from transnational spread. Solid lines represents estimates derived from the mean generation time of 12 days, while dashed lines correspond to estimates derived using nine and 15 days as the mean generation time.

B) Upper and lower bounds of the effective reproduction number (R_t)for the global dynamics in West Africa are shown assuming a mean generation time of EVD ranging from nine to 15 days. The horizontal grey line is shown as a reference for the reproduction number at 1.0 below which the epidemic follows a declining trend.

C) Sensitivity of R_t to varying specified time intervals of the piecewise constant model. Estimates in B and C were derived using the total number of reported EVD cases (confirmed, probable plus suspected cases). Epidemic week 0 corresponds to 22 March 2014. Of note, estimates overlap at week 9 as these were derived from epidemiological data for a single country (i.e. Guinea).

be brought under control if more than half of secondary transmissions per primary case are prevented.

Our statistical analysis of the reproduction number of EVD in West Africa has demonstrated that the continuous growth of cases from June to August 2014 signalled a major epidemic, which is in line with estimates of the R_t above 1.0. Moreover, the timing of R_t reaching levels above one is in line with a concomitant surge in cases in Sierra Leone and Liberia. In a worst-case hypothetical scenario, should the outbreak continue with recent trends, the case burden could gain an additional 77,181 to 277,124 cases by the end of 2014. Although such numbers must be interpreted with caution (as they rest on an assumption of continued exponential growth within 2014, which is unlikely), our study supports the notion that the ongoing EVD epidemic must be regarded as a Public Health Emergency of International Concern [3]. This finding also implies that transnational spread of EVD might have hindered control efforts, suggesting that preparedness plans for potential case introductions is critical particularly for countries at high risk of EVD case importations [18] with suboptimal public health systems. The transnational spread per person appears to have been reduced over time, but our most recent model estimates still suggest a non-negligible number of secondary cases arising from transnational spread. Uncontrolled cross-border transmission could fuel a major epidemic to take off in new geographical areas (e.g. as seen in Liberia). Unaffected countries at risk of transnational spread should be on high alert for potential EVD introductions and be ready to launch comprehensive and timely containment responses to avert outbreaks.

Our analysis is not exempted of limitations. First, the epidemic is ongoing in multiple geographical locations, and no simple mixing matrix can capture the complex geographical patterns of spread in the region. Second, cases may be under-ascertained, and hence reported cases may represent only a portion of the total number of infected individuals. However, our estimates of the reproduction number are not affected whenever the diagnosis and reporting rates have not dramatically changed over time. Third, the reporting delays are known to induce a downward bias in incidence in the latest observation, which can complicate real-time analyses. Several studies have successfully addressed this bias [19-22], but we were unable to incorporate this delay into our analyses due to a lack of empirical data to characterise the reporting delay distribution.

Despite the above-mentioned limitations, we believe that our findings are useful to demonstrate that the cases have been steadily growing in the last three months with an R_t above one. Close monitoring of this evolving epidemic should continue in order to assess the status of the outbreak in real time and guide control interventions in the region. Reviewing possible countermeasures for countries at risk of transnational

spread [18] would be of utmost importance to confront the ongoing propagation of cases over time and space.

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Conflict of interest

None declared.

Author contributions

HN conceived mathematical modeling method and analyzed the data. HN and GC drafted and revised the manuscript.

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