Spatiotemporal Evolution of Ebola Virus Disease at Sub-National Level during the 2014 West Africa Epidemic: Model Scrutiny and Data Meagreness

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Abstract

Background

The Ebola outbreak in West Africa has infected at least 27,443 individuals and killed 11,207, based on data until 24 June, 2015, released by the World Health Organization (WHO). This outbreak has been characterised by extensive geographic spread across the affected countries Guinea, Liberia and Sierra Leone, and by localized hotspots within these countries. The rapid recognition and quantitative assessment of localised areas of higher transmission can inform the optimal deployment of public health resources.

Methods

A variety of mathematical models have been used to estimate the evolution of this epidemic, and some have pointed out the importance of the spatial heterogeneity apparent from incidence maps. However, little is known about the district-level transmission. Given that many response decisions are taken at sub-national level, the current study aimed to investigate the spatial heterogeneity by using a different modelling framework, built on publicly available data at district level. Furthermore, we assessed whether this model could quantify the effect of intervention measures and provide predictions at a local level to guide public health action. We used a two-stage modelling approach: a) a flexible spatiotemporal growth model across all affected districts and b) a deterministic SEIR compartmental model per district whenever deemed appropriate.

Findings

Our estimates show substantial differences in the evolution of the outbreak in the various regions of Guinea, Liberia and Sierra Leone, illustrating the importance of monitoring the
outbreak at district level. We also provide an estimate of the time-dependent district-specific effective reproduction number, as a quantitative measure to compare transmission between different districts and give input for informed decisions on control measures and resource allocation. Prediction and assessing the impact of control measures proved to be difficult without more accurate data. In conclusion, this study provides us a useful tool at district level for public health, and illustrates the importance of collecting and sharing data.

Introduction

The Ebola epidemic in West Africa was detected in March, 2014. On 8 August, 2014, WHO declared the event a Public Health Emergency of International Concern [1] and the UN General Assembly declared the epidemic a threat to global health and security [2]. On 9 May, 2015, Liberia was declared free of Ebola virus transmission but on 30 June, 2015, a new case was detected from an unknown chain of transmission [3,4]. In Guinea and Sierra Leone, the epidemic persists in a number of districts mainly between Conakry and Freetown [5]. As of 24 June, 2015, it has caused 27,443 probable, confirmed, and suspected cases of EVD in Guinea, Liberia and Sierra Leone, including 11,207 deaths [6].

A number of, mainly deterministic, SEIR transmission models (with Susceptible, Exposed, Infected, Recovered compartments) have been published that aimed to estimate epidemiological parameters, and to forecast the evolution of the epidemic [7–10]. Most models, and especially the ones early in the outbreak, were fitted on reported cumulative national data. Doing so, they did not account for the transmission heterogeneity of this outbreak and the serial correlation induced by the accumulation of data. However, in the course of the outbreak, others highlighted the importance of the spatial and temporal heterogeneity of the outbreak, questioning assumptions made by early models [11]. A study by King et al. [12] illustrated through simulations that deterministic models, fitted on cumulative incidence data, lead to substantial underestimation of the uncertainty in estimates and forecasts. In addition, fitting of the models was often done not taking into account the serial correlation. The clustered pattern of transmission could be attributed to variability in transmission settings (e.g. healthcare facilities, households, burials) [13], behaviour (e.g. expressions of mistrust) and control measures (e.g. contact tracing and monitoring and establishment of a treatment centre). However, there is still a lack of insight in the relative contribution of each factor to the transmission pattern [14].

A good understanding of the outbreak transmission may support an efficient allocation of resources at national and at district level. With our study, we aimed to develop a model that would overcome previously identified model limitations, including the not-used district level data and the assumption of homogenous transmission across districts. Our two-stage model is based on publicly available data that might improve the information for operational decisions to control the epidemic. The first stage is the use of a growth model that addresses the spatio-temporal correlation; the second stage is the use of a compartmental model—whenever deemed appropriate—that provides a district-specific estimation of the effective reproduction number—a composite dynamic estimate of the evolution of the outbreak—and its uncertainty. In addition, we performed a sensitivity analysis to study the effect of the model assumptions on the parameter estimates.
Methods

Data sources

Data on cases and deaths. We used publicly available district-level data on cumulative cases and deaths, reported from 30 December 2013 until 8 July 2015 through situational reports by the Ministries of Health of Guinea [15], Liberia [16] and Sierra Leone [17,18]. The data were collected and reported to the national authorities by the Ebola treatment units and diagnostic testing facilities in the three countries, following national guidelines and/or WHO case definitions [19].

Data were reported every two to three days, and more recently on a daily basis. The data sources provided no detailed information about the used case definition. Data for Liberia and Guinea were the reported total cumulative number of (suspected, probably and confirmed) cases and deaths, while for Sierra Leone, we calculated the sum of the reported suspected, probable and confirmed cases. This allowed us to calculate for each district the new cases and new deaths between two reporting intervals. The models were fitted to these new cases and new deaths over the corresponding time intervals and not to the cumulative data. The observed number of new cases and deaths were depicted by taking these new cases and new deaths and dividing them by the number of days the time intervals span.

A presentation of how the cases were reported can be found in S4 Fig. The reporting scheme for deaths was similar, but the dates at which reporting occurred is not necessarily the same.

Data on control measures. Publicly available situation reports of response measures were used to assess the intensity of interventions [20,21] (https://data.hdx.rwlabs.org/dataset?q=ebola). The publicly available data regarding interventions provided little detail and was not regular over time or over the entire outbreak region. Due to the complexity of response measures and limited availability of data, we used the presence of triage centres, holding or community care centres and Ebola Treatment Units (ETUs) as a surrogate marker of response activities.

Models

Growth model. To compare growth patterns over time among districts, we used a flexible spatiotemporal growth rate model across all districts. This model allowed the estimation of the district-specific expected number of new cases per week, the district-specific time trend, the district-specific growth rate and the spatial distribution of the growth rate within the three countries. In addition, to investigate the effect of implemented intervention measures on the estimated growth rates, for each district a Pearson’s Chi-square test was used. Doing so, we tested, for different time lags, the association between positive and negative growth rates and the absence or presence of aforementioned intervention measures. We used Integrated Nested Laplace Approximation [22] as a more flexible estimation method and alternative for the more computationally intensive Markov chain Monte Carlo (MCMC). We made a growth rate distribution heat map as a method to visualise the weekly change for each district-specific rate of infection with an overlay of intervention measures.

Compartmental model. Further, district-specific SEIR compartmental models were fitted to the number of newly reported cases and deaths (see S1 File for more details). We applied this model to data of several districts to address within-district disease evolution over time. In this paper we show the obtained results for a selection of rural and urban districts: Forecariah (Guinea), Conakry (Guinea), Western Area Urban (Sierra Leone), and Grand Cape Mount (Liberia). This selection was based on events of interest during the course of the outbreak e.g. sudden increase in cases. We were, however, also restricted by inconsistencies in the data as
pointed out as a limitation of the model in the discussion. For each of these four districts the effective reproduction number, $Re(t)$, was estimated over time. The SEIR model incorporates disease-related mortality by making the distinction between survivors and non-survivors. It also takes into account an underreporting factor for cases and deaths. Goodness of fit was assessed visually.

We assessed retrospectively the quality of three-week long predictions made at 4 different time points, for the selected districts and we compared these predictions with the actual observed number of cases and deaths.

Assumptions and sensitivity analysis. For the compartmental models, we used prior estimates of the incubation period for EVD (9-4 days), the duration of infectiousness for survivors (16-4 days) and deceased (7-5 days) [23]. The reproductive number was modelled with a piecewise constant interval of 21 days. The remaining parameters are estimated via an MCMC approach. The MCMC procedure, which we made publicly available, was performed in R 3.1.1 using the Laplaces-Demon package [24,25].

Furthermore, due to reclassification of suspected cases over time, the cumulative data expected to increase monotonically over time, decreased at certain time points. It was thus necessary to monotonize the data. The algorithm that was used to do so is described in S1 File.

Lastly, we assessed the sensitivity of our results to the model assumptions by performing a sensitivity analysis. We investigated the estimability of the fixed parameters mentioned in the previous paragraph, the effect of the number of exposed individuals at time 0, transmission through contacts with bodies of dead people, and protective immunity by asymptomatic infections. We compared the models with Deviance Information Criterion (DIC).

More details about the models and estimation methods, as well as results from the sensitivity analysis can be found in the S1 File. Our compiled data and code are made available for reproducibility purpose.

Results

Results of the growth rate model are shown in the heat map in Fig 1. Comparing the growth rates in the different districts (rows), it was clear that the outbreak did not evolve uniformly over districts. Pearson’s Chi-square test for decrease in growth rate after implementation of control measures, for different time lags, did not reveal any insights (results not shown). A map of the geographical distribution of the estimated growth rates can be found in S3 Fig.

Results of the SEIR models for the four selected districts are presented in Figs 2–4. The observed and estimated number of new and cumulative cases and deaths are shown in Fig 2. From this figure, we observe that the model fits both the number of cases and the number of deaths relatively well. Also at the level of the cumulative numbers model and data show a reasonable fit.

The estimated effective reproduction numbers over time are shown in Fig 3. Re(t) ranges from below unity to up to 3.5. Furthermore, estimates are below one for all four districts in the last time period. However, the 95% credible intervals indicate substantial variability.

Results of the short-term predictions are presented in Fig 4 for Western Area Urban. Note that the credible intervals do not contain all data points. Hence, even within a 3-week forecast period, the models are not always able to capture all the trends.

The results of the sensitivity analysis (S1 File) show that the fixed parameters in our model are not estimable from the data. Further, taking into account the transmission from dead bodies does not improve model fit. We do, however, see an improvement when including an increasing (from 10 to 40%) proportion of asymptomatic cases (S4 Table).
Discussion

The results of our study strengthen the evidence of a strong temporal and spatial variability of the EVD transmission at a subnational level in the affected regions of Guinea, Sierra Leone and Liberia. The variable transmission dynamics are a major challenge for the implementation of intervention measures and the mobilisation of resources among districts. This complexity highlights the importance of constant monitoring and the usefulness of quantitative tools, thereby taking full account of the uncertainty, to inform the response.

Our growth model quantifies spatiotemporal transmission patterns at a sub-national level, which cannot be derived from visual inspection of incidence curves and maps alone. The
visualisation of the growth rates with a two dimensional (time and space) heatmap, is useful for decision makers to make evidence based informed decisions on resource allocation. On the other hand, our compartmental model allows the calculation of a quantitative measure of transmission, Re(t), that can be used to compare and communicate about differences in outbreak dynamics between districts and over time.

The combined model illustrates how district-level data can be used to gain a quantitative insight in the complex outbreak dynamics. Both models show how the trend varies widely among the districts and changes quickly in time and space (Figs 1 and 3). While our estimates of Re(t) are within the range of published estimates, most of the published estimates were derived from country-level data and do not provide the granularity we provide at time-dependent district level. The wide range of Re(t) between near 0 and 3.5 illustrates the need to complement national with district data driven models, to support public health action.

We further show that it is difficult to generate accurate predictions. Forecast results should be interpreted with caution, as control measures and behavioural changes cannot be sufficiently quantified with the publicly available data. Also, there are still gaps in our basic knowledge about the disease spread that could potentially explain outliers, departing from modelling approaches. We think here, for example, of the three last reported cases in Liberia; one from
suspected sexual transmission months after the source case recovered from disease [26], and most recently two connected cases without any recognised link to outbreak chains.

One of the limitations of our model is the assumption of constant underreporting. Previous studies have also assumed a proportion of underreporting [13]. Knowledge about the level and changes in underreporting over time would improve the estimates of transmission dynamics. Unfortunately we do not have data to assess the magnitude or the variability of underreporting. Also, inconsistent reporting with undocumented backlogging and the absence of dates of disease onset may affect the accuracy of the estimates and need to be taken into consideration when interpreting the results [27]. Furthermore, the district-specific SEIR model is a mathematical model assuming a deterministic disease process. As a consequence, the second phase of our approach was deemed inappropriate for some districts, because the data didn’t seem to follow any consistent pattern, presumably due to the aforementioned inconsistencies in detection and reporting and the sporadic introduction of cases.

EVD can be transmitted through contact with dead bodies; therefore, a model accounting for this transmission was included in the sensitivity analysis. However, this model did not improve the fit to the data. Most likely, the extent to which dead bodies versus cases contribute to transmission is indistinguishable with this model and requires more information and a fully stochastic modelling approach on disaggregated data, which is not publicly available.

Since there is evidence suggesting the presence of asymptomatic Ebola infections [28], we looked at the effect of accounting for protective immunity by asymptomatic infection. We observed that the model fit improved with increasing proportion of asymptomatic cases, suggesting that our data do not reject the hypothetical occurrence of asymptomatic cases. Asymptomatic cases could partially explain why the epidemic did not reach the expected incidence as predicted by models ignoring them. This again highlights the need for serological studies in order to clarify the role of asymptomatic infection.

While our sensitivity analysis assesses the influence of unknown parameters, it cannot substitute for non-public data. The growth rate and compartmental models can be run in real time using our published code and dataset, and can be improved by organizations that have additional data available or to explore adaptations to the models and parameters. In the end, different modelling approaches bring different insights and will improve our ability to effectively
support public health action. We recommend that minimal datasets and standards for data processing, including de-identification, and data sharing will be developed for future multi-country outbreaks, especially Public Health Events of International Concern under the International Health Regulations. The importance of this has also been retained as a conclusion in a recent research paper on this topic [29].

Our two-stage modelling approach, built with the most detailed publicly available data, provides time-dependent district-specific quantitative measures of growth and transmission. We hope that such tool, in addition to other approaches, can complement public health action against such devastating events as the West-African Ebola epidemic.
Supporting Information

S1 Fig. Cumulative cases per district and implemented intervention measures. A light dot indicates that a triage, holding centre or CCC is in place and a dark dot indicates that an ETU or ETU and CCC are in place.

S2 Fig. Cumulative deaths per district and implemented intervention measures. A light dot indicates that a triage, holding centre or CCC is in place and a dark dot indicates that an ETU or ETU and CCC are in place.

S3 Fig. Estimated growth rate per district and implemented intervention measures during week 21 and 40 of 2014 and week 8 and 26 of 2015. ‘1’ triage, holding centre or CCC is in place; ‘2’ ETU or ETU plus CCC is in place.

S4 Fig. Flow diagram for the SEIR model with distinction between cases that survive and fatal cases.

S5 Fig. Schematic representation of reporting of case notifications.

S1 File. Supplementary file.

S1 Table. Prior distributions.

S2 Table. Parameter estimates with 95% posterior confidence intervals. Note that for Conakry a $U(0, 100)$ prior for $E(0)$ was used.

S3 Table. Parameter estimates sensitivity analysis. Fixed values are indicated in bold, blue values indicate model differences compared to the final model 1.

S4 Table. Parameter estimates sensitivity analysis. Fixed values are indicated in bold, blue values indicate changes compared to the final model 1.

Acknowledgments

The authors further acknowledge Valeria Pelosi, for contribution in data collection and Yvan Hutin, for editorial support. The computational resources and services used in this work were provided by the VSC (Flemish Supercomputer Center), funded by the Hercules Foundation and the Flemish Government–department EWI.

Author Contributions

Analyzed the data: ES CF TK TH FVR NH. Wrote the paper: ES ER BS CQ NH DP. Data collection: MT. Data interpretation: ES ER BS CF CQ WVB NH DP. Literature search: TG.
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