Uncertainty and sensitivity analysis of the basic reproduction number of diphtheria: A case study of Rohingya refugee camp in Bangladesh, November-December 2017

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Background. Rohingya refugee camp in Cox's Bazar, Bangladesh experienced a large-scale diphtheria epidemic in 2017. The background information of previously immune fraction among refugees cannot be explicitly estimated, and thus, we conducted an uncertainty analysis of the basic reproduction number, R_0. Methods. A renewal process model was devised to estimate the R_0 and ascertainment rate of cases, and loss of susceptible individuals was modeled as the depletion due to initially immune fraction and also to natural infections during the epidemic. To account for the uncertainty of initially immune fraction, we employed a Latin Hypercube sampling (LHS) method. As part of sensitivity analysis, partial rank correlation coefficient (PRCC) was computed between every single pair of parameters. Results. R_0 ranged from 3.6 to 12.9 with the median estimate at 5.8. Residuals of R_0 showed a negative correlation with the residuals of the ascertainment rate after improvement of the case definition (Spearman's rank correlation = -0.50). Discussion. Estimated R_0 was consistent with published estimate from endemic data, indicating that the vaccination coverage of 83% has to be satisfied to prevent the epidemic by means of mass vaccination. LHS appeared to be particularly useful in the setting of refugee camp in which the background health status is hardly quantified.

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Abstract

Background

Rohingya refugee camp in Cox's Bazar, Bangladesh experienced a large-scale diphtheria epidemic in 2017. The background information of previously immune fraction among refugees cannot be explicitly estimated, and thus, we conducted an uncertainty analysis of the basic reproduction number, R_0.

Methods

A renewal process model was devised to estimate the R_0 and ascertainment rate of cases, and loss of susceptible individuals was modeled as the depletion due to initially immune fraction and also to natural infections during the epidemic. To account for the uncertainty of initially immune fraction, we employed a Latin Hypercube sampling (LHS) method. As part of sensitivity analysis, partial rank correlation coefficient (PRCC) was computed between every single pair of parameters.

Results

R_0 ranged from 3.6 to 12.9 with the median estimate at 5.8. Residuals of R_0 showed a negative correlation with the residuals of the ascertainment rate after improvement of the case definition (Spearman's rank correlation = -0.50).

Discussion

Estimated R_0 was consistent with published estimate from endemic data, indicating that the vaccination coverage of 83% has to be satisfied to prevent the epidemic by means of mass vaccination. LHS appeared to be particularly useful in the setting of refugee camp in which the background health status is hardly quantified.

Introduction

Diphtheria, a bacterial disease caused by *Corynebacterium diphtheriae*, is one of vaccine preventable diseases. Symptomatic patients initially complain sore throat and fever, and if exacerbated, the airway is blocked leading to a barking cough or the so-called “croup”, and a grey or white patch is sometimes developed in the throat or any other part of the respiratory tract. Due to widespread use of Diphtheria-Tetanus-Pertussis (DTP) vaccine for the long time across the world, the incidence has steadily declined over time, and thus, diphtheria has been perceived as almost a disease of pre-vaccination era. Nevertheless, sporadic cases and even epidemics of the disease have been yet reported especially in politically unstable areas, and many cases have been considered as arising from susceptible pocket of the vulnerable population (Rusmil et al., 2015; Hosseinpoor et al., 2016; Sangal et al., 2017).

The year 2017 was undoubtedly an epidemic year of diphtheria involving outbreaks in multiple refugee camps including those in Yemen and Bangladesh (World Health Organization (WHO), 2017a). Of these, a Rohingya refugee camp in Bangladesh, which is temporarily located in Cox’s Bazar, experienced a large-scale diphtheria epidemic. As of 26 December 2017, the cumulative number of 2,526 cases including 27 deaths have been reported (WHO, 2017a). To cut continued chains of transmission, emergency vaccination has been conducted among children since 12 December 2017, achieving the overall coverage greater than 90% by the end of 2017. Due to vaccination effort and other countermeasures including contact tracing and hospital admission of cases, the epidemic has been considered to be gradually brought under control and the incidence started to decline in the end of December 2017 (WHO, 2017a).

Considering that diphtheria has become a rare disease in industrialized countries, epidemiological information on model parameters that govern the transmission dynamics has become very limited, and thus, it is valuable to assess how transmissible diphtheria would be through the analysis of the recent outbreak data. The basic reproduction number, R_0, is interpreted as the average number of secondary cases that are produced by a single primary case in a fully susceptible population, acting as the critical measure of the transmissibility. To date, an explicit epidemiological estimate of R_0 for diphtheria has been reported only by Anderson and May (1982): using a static modeling approach to age-dependent incidence data with an assumption of the endemic equilibrium, R_0 was estimated as 6.6 in Pennsylvania, 1910s and 6.4 in Virginia and New York from 1934-47. Subsequently, a few additional modeling studies of diphtheria took place (Kolibo, 2001; Sornbundit, 2017; Torrea, 2017), but none of them offered an empirical estimate of R_0.

Here we analyze the epidemiological dataset of diphtheria in Rohingya refugee camp, 2017, aiming to estimate R_0 in this particular epidemic setting. Given that the epidemic occurred among refugees, we explicitly account for uncertainties associated with unknown background information including the fraction of previously immune individuals and ascertainment rate of cases.

Materials & Methods

Epidemiological data

The latest epidemic curve was extracted from the report of the World Health Organization (WHO) Regional Office for South East Asia (SEARO) (WHO, 2017a). Figure 1 shows the latest available epidemic curve. As of 26 December 2017, a total of 2,526 cases have been diagnosed. Cases consist of (i) confirmed cases: cases

reported as positive for *C. diphtheria*e by multiplex assay, (ii) probable cases: cases with upper respiratory tract illness with laryngitis or nasopharyngitis or tonsillitis AND sore throat or difficulty swallowing and an adherent membrane (pseudomembrane) OR gross cervical lymphadenopathy, and (iii) suspected cases: any case with a clinical suspicion of diphtheria including cases that are unclassified due to missing values (WHO, 2017b). Such case definition had not been fully formulated by 11 December 2017, but the definition was improved on and after 12 December (WHO, 2017c). For this reason, cases reported by 11 December are considered to have been perhaps over-ascertained compared with cases that were reported later under improved case definition. Mass child vaccination started on 12 December and the vaccination coverage greater than 90% was achieved by 30 December. Assuming that vaccine-induced immunity requires at least 7-14 days to become effective, it is likely that the following analysis of the epidemiological dataset by 22 December was not considerably influenced by emergency vaccination.

Modeling methods

Let i_t be the number of new cases on day t. g_τ represents the distribution of the serial interval. We assume that secondary transmission does not take place before illness onset. According to a classical study by Stocks (1930) in the United Kingdom (UK), the time interval from first to second diphtheria cases in the household revealed a bimodal shape. Following Klinkenberg and Nishiura (2011), the first peak corresponds to an independent infection in the community and the second peak reflects within-household transmission. As the mode of second peak was observed on day 5, we assumed that the mean serial interval was 5 days, and we imposed an assumption that the coefficient of variation (CV) of the serial interval distribution was

50% (Nishiura, personal communications) and later varied it from 25% to 75% as part of the sensitivity analysis.

The renewal process to describe the time-dependent incidence i_t on day t is

$$i_t = R_0 s_t \sum_{\tau=1}^{t-1} i_{t-\tau} g_\tau , \quad (1)$$

where s_t represents the fraction of susceptible individuals on day t. It should be noted that the incidence i_t includes both symptomatic and asymptomatic cases. Let c_t be the reported number of cases on calendar day t. Supposing that only the fraction α_t among the total number of infections are diagnosed and reported, c_t satisfies

$$i_t = \frac{c_t}{\alpha_t} , \quad (2)$$

where α_t is modeled as a function of t. Because the case definition was improved from 12 December 2017 onward, the ascertainment rate likely varied around that time. Namely, we set $\alpha_t = a_1$ for time by 11 December and a_2 on 12 December and later.

We model the fraction susceptible s_t on day t in the following way. Let v represent the previously immunized fraction so that only fraction (1-v) of the population is susceptible at the beginning of the epidemic. In addition to the previously immune fraction, s_t decreases when natural infection takes place. Suppose that the total population size was N, s_t is written as

$$s_t = 1 - v - \frac{\sum_{y=1}^{t-1} \frac{c_y}{\alpha_y}}{N} . \quad (3)$$

We assume that N is equal to the population size of epidemic site in Rohingya refugee camp as 579,384 persons (Banerji & Ahmed, 2017). Accordingly, the renewal equation is written as

$$E(c_t;R_0,\nu,a_1,a_2)=R_0\left(1-\nu-\frac{\sum_{y=1}^{t-1}\frac{c_y}{\alpha_y}}{N}\right)\sum_{\tau=1}^{t-1}c_{t-\tau}g_\tau\,. \quad (4)$$

We assume that c_t follows a Poisson distribution. The likelihood to estimate θ consisting of the parameters R_0, v and α_t is derived as

$$L(\theta;\mathbf{c_T})=\prod_{t=1}^{T}\left(\frac{E(c_t)^{c_t}\exp(-E(c_t))}{c_t!}\right), \quad (5)$$

where T is the latest time of observation (i.e., 22 December in our case study) and $\mathbf{c_T}=(c_1,c_2,\ldots,c_T)$. The dataset of last 5 days (i.e. from 23-27 December) was discarded as the number of cases may be biased by the reporting delay.

Uncertainty and sensitivity analyses

While we specified unknown parameters as R_0, v and α_t, it is expected that R_0 is correlated with initially immune fraction v and also α_t. Thus, it is vital to quantify R_0 while accounting for the uncertainty of other model parameters. Uncertainty in parameter values can be addressed by randomly sampling the uncertain parameter value from probability distributions (Gilbert et al., 2014). Here we use the Latin Hypercube sampling (LHS) method (Sanchez & Blower, 1997) in which a symmetric triangular distribution of v was assumed to be in the range from 0.0 to 0.7; the health survey of Rohingya population indicated that overall 30.8% of children had received no vaccinations (Guzek et al, 2017) and we expect that the actual coverage is nearby the mid-point of the range. As part of sensitivity analyses, we computed partial rank correlation coefficient (PRCC) between every single pair of parameters. To do so, we (i) rank transformed LHS of input parameters and output parameter samples, (ii) computed two linear regression models using the samples, (iii) computed correlation coefficient between the two residuals, and (iv) subsequently calculated PRCC.

Ethical considerations

The present study analyzed data that is publicly available. As such, the datasets used in our study were de-identified and fully anonymized in advance, and the analysis of publicly available data without identity information does not require ethical approval.

Results

Figure 2 shows univariate distributions of estimated parameters R_0 and α_t based on Latin hypercube sampling (n=1000). a_1 reflects ascertainment by 11 December 2017, while a_2 shows the same on and after 12 December. R_0 took the minimum and maximum estimates at 3.6 and 12.9, respectively, with the median estimate at 5.8. The distribution was skewed to the right with the mode at 5.6. Excluding lower and upper tails, 950 samples (95%) of R_0 were in the range of 3.9 to 10.5. Distributions of a_1 and a_2 were also right skewed. a_1 ranged from 0.02 to 5.00 with the median 0.91, while α_2 ranged from 0.005 to 0.014 with the median 0.007. Lower and upper 95% tolerance intervals of a_1 and a_2 were (0.22, 1.18) and (0.005, 0.012), respectively.

Figure 3 shows the distributions of two estimated parameters in two dimensional spaces and also the comparison between observed and predicted epidemic curve. As can be expected from equation (4), R_0 and v were positively correlated given an epidemic curve. Namely, if v was greater, R_0 should have been greater so that an identical epidemic curve can be observed. The relationship between R_0 and a_1 was an interesting hyperbola, because α_1 contained the value of 1 within its range. The value of a_1 at around 1.0 was considered as plausible, because the time period corresponded to the initial growth phase of the epidemic before introduction of improved case definition, and the value greater than 1.0 could reflect the efflux of reported cases that can partly be attributed to over-ascertainment and inclusion of

non-diphtheria cases in the dataset. On the contrary, the relationship between R_0 and a_2 was a positive linear pattern. While the ascertainment might have been lowered due to more strict case definition, the small estimate of a_2 can also indicate that substantial fraction of undiagnosed individuals existed and the susceptible fraction was then gradually depleted in the population. While the model is kept simple with four unknown parameters, the predicted epidemic curve overall captured the observed pattern.

Estimated PRCC is shown in Figure 4. Again, residuals of R_0 and those of v are positively correlated (Spearman's rank correlation coefficient=0.78). It is interesting that the residuals of R_0 and those of a_1 were both evenly distributed around the value of zero, and thus, R_0 was not sensitive to the value of a_1 (Spearman's rank correlation coefficient <0.005). On the other hand, residuals of R_0 showed negative correlation with the residuals of a_2 (Spearman's rank correlation coefficient = -0.50). This dependency is anticipated, because R_0 would influence how many susceptibles to be depleted to curb the epidemic curve and that is regulated by the value of a_2. Residuals of a_1 and those of a_2 were not strongly correlated (Spearman's rank correlation coefficient =0.02).

We also varied the CV of the serial interval distribution from 25% to 75%. When the CV was 25%, the median and mode of R_0 from Latin hypercube sampling were 6.6 and 7.9, respectively. When the CV was 75%, the median and mode of R_0 were estimated to be 4.9 and 4.2, respectively. Namely, the estimate was sensitive to increased variance of the serial interval distribution.

Discussion

The present study estimated R_0 of diphtheria in the Rohingya refugee camp, explicitly accounting for case ascertainment and previously immune fraction. Since previously immune fraction v of the refugee population was not precisely known, uncertainty analysis of R_0 was conducted with an input parameter assumption for v employing the Latin Hypercube sampling method. R_0 ranged from 3.6 to 12.9 with the median estimate at 5.8. To our knowledge, the present study is the first to statistically estimate R_0 of diphtheria from an epidemic data.

Estimated median R_0 was broadly consistent with the value ranging from 6 to 7 as indicated by Anderson and May (1982) based on a static model for endemic data that uses the age-dependent incidence in the UK. We have shown that the frequently quoted estimate agrees well with dynamically estimated R_0 from the refugee camp in the present day. To control diphtheria by means of mass vaccination, the coverage greater than 83% must be satisfied. Since our study focused on uncertainty and sensitivity analyses, the exact estimate of R_0 cannot be pointed out. However, the possible distribution of R_0 given uncertain information of the distribution of v was obtained. While the mode of distribution for R_0 was seen at around 5.6, the validity of representative value depends on the validity of our underlying assumption that the vaccination coverage in the beginning of an epidemic was most likely at 35%, which was not supported by any published evidence of this refugee population. Nevertheless, the demographic health survey data of the Rohingya population in Myanmar indicated a close value from 40-50% as the coverage of DTP (Ministry of Health and Sports, 2017). It is remarkable that ascertainment rates were jointly estimated only by using the epidemiological case data and the population size.

What we have shown in the present study is that when we have an access to not only the initial growth rate of the epidemic but also the incidence data around the time at which peak incidence is observed, R_0 and susceptible fraction can potentially be jointly quantified. Even without explicit estimate of the initially immune fraction, we have shown that an indication of the possible value of R_0 can be obtained through uncertainty analysis. LHS appeared to be particularly useful in the setting of refugee camp in which the background health status is not well quantified (Helton & Davis, 2002; Nishiura et al., 2017). LHS can offer probabilistic distribution of the outcome measure, R_0 in our case, and this method appeared to be particularly useful when one or more uncertain input information exist (Elderd et al., 2006; Coelho et al., 2008; Samsuzzoha et al., 2013; Gilbert et al., 2014). While Bayesian modeling has replaced LHS to some extent of uncertainty analysis as it can also offer posterior distributions of even uncertain parameters (Elderd et al., 2006; Coelho et al., 2008), there could be an issue of identifiability when two or more parameters are evidently correlated, e.g. as anticipated between R_0 and v in our model (4). In such an instance, we cannot be sure if the limited epidemic data with the Bayesian estimation method can offer identifiable distributions for all parameters, and then LHS can remain to act as a useful tool for uncertainty analysis.

Several limitations must be noted. First, our model rested on a homogeneous mixing assumption. No heterogeneous patterns of transmission including contact patterns and age-dependency were taken into account due to shortage of information. Second, for similar reasons, no spatial information was explicitly incorporated into the model. Third, a little more realistic features of refugee population, such as the impact of migration on the epidemic were unfortunately discarded in the present study. Similarly, one could investigate how overcrowding and malnutrition in the deprived

population would help enhance the spread of diphtheria, given sufficient data backup from epidemiological investigations.

While these features need to be explicitly quantified in the future, we believe that our study adds an important piece of evidence to the literature on diphtheria. The transmissibility of diphtheria in the refugee population was estimated to be consistent with that in an endemic setting and mass vaccination must satisfy at least the coverage of 83% to halt the major epidemic of diphtheria.

Conclusions

The present study estimated R_0 of diphtheria in the Rohingya refugee camp, explicitly accounting for case ascertainment and previously immune fraction. Since previously immune fraction v of the refugee population was not precisely known, uncertainty analysis of R_0 was conducted with an input parameter assumption for v employing the Latin Hypercube sampling. R_0 ranged from 3.6 to 12.9 with the median estimate at 5.8. LHS can offer probabilistic distribution of the outcome measure, and this method appeared to be particularly useful in the setting of refugee camp in which the background health status is hardly quantified.

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Figures

Figure 1. Daily incidence of diphtheria cases in Rohingya refugee camp, 2017

Daily number of new cases as extracted from the latest open data (WHO, 2017a). The vertical axis represents the total of confirmed, probable and suspected cases. By 11 December 2017, the count represents suspected cases. On and after 12 December 2017, the case definition was improved, and probable cases replaced the majority.

Figure 2. Estimated values of the basic reproduction number and case ascertainment rate

Univariate probability distribution of the basic reproduction number, a_1 by 11 December and a_2 from 12 December from Latin Hypercube sampling (n = 1,000). During the Latin Hypercube sampling, the vaccination coverage, v, has a symmetric triangular distribution ranging from 0.0 to 0.7.

Figure 3. Estimated correlations in each pair of estimated parameters, and comparison between observed and predicted epidemic curves

Three panels except for right lower panel represent two-dimensional plot of estimated parameters. During the Latin Hypercube sampling (n = 1,000), the vaccination coverage, v, has a symmetric triangular distribution ranging from 0.0 to 0.7. Lower right panel is the comparison between observed and predicted epidemic curves. Bars constituting the epidemic curve show the observed data, while dark dots indicate predicted epidemic curve from Latin Hypercube sampling (n = 1,000).

Figure 4. Sensitivity analysis: Partial rank scatterplots

Partial ranks for each pair of parameters. Scatter plots were generated from Latin Hypercube sampling with the sample size of 1,000. Residuals of two parameters were plotted to determine the monotonicity between the two.

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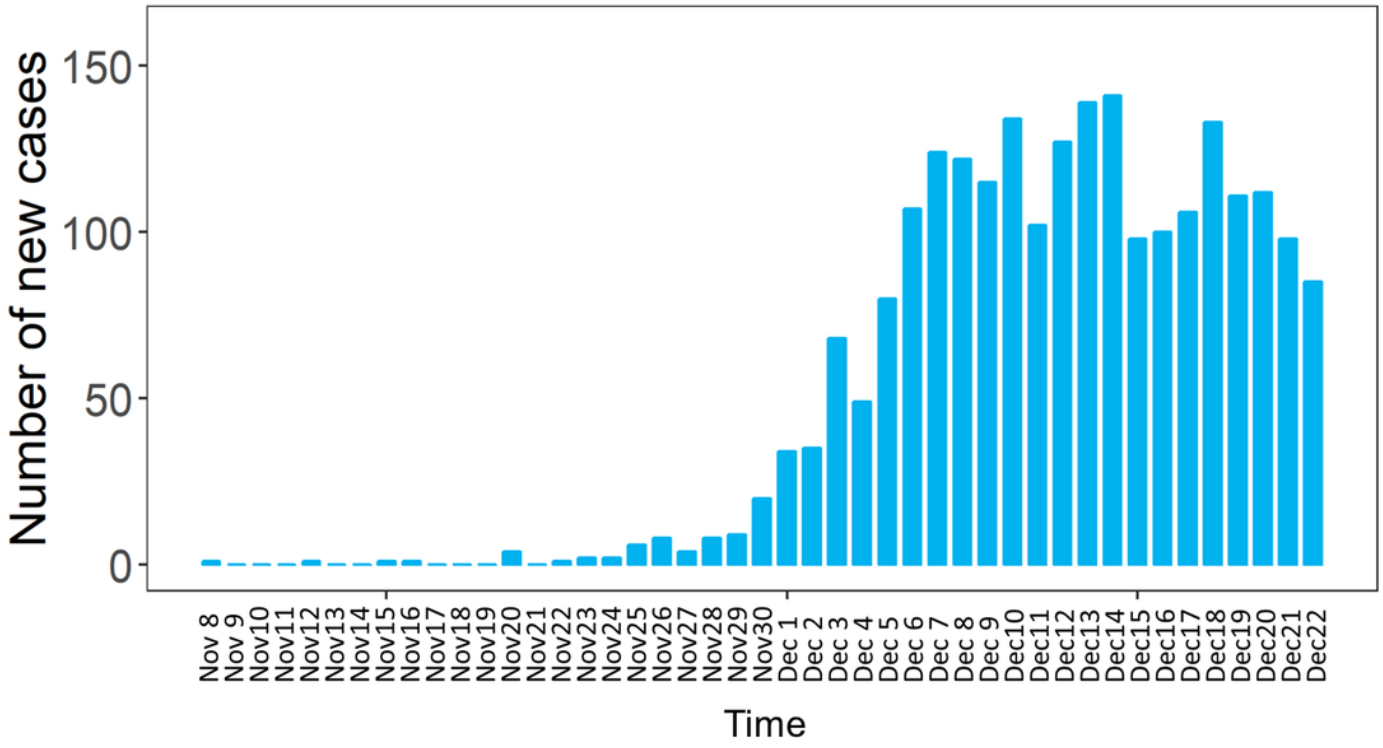

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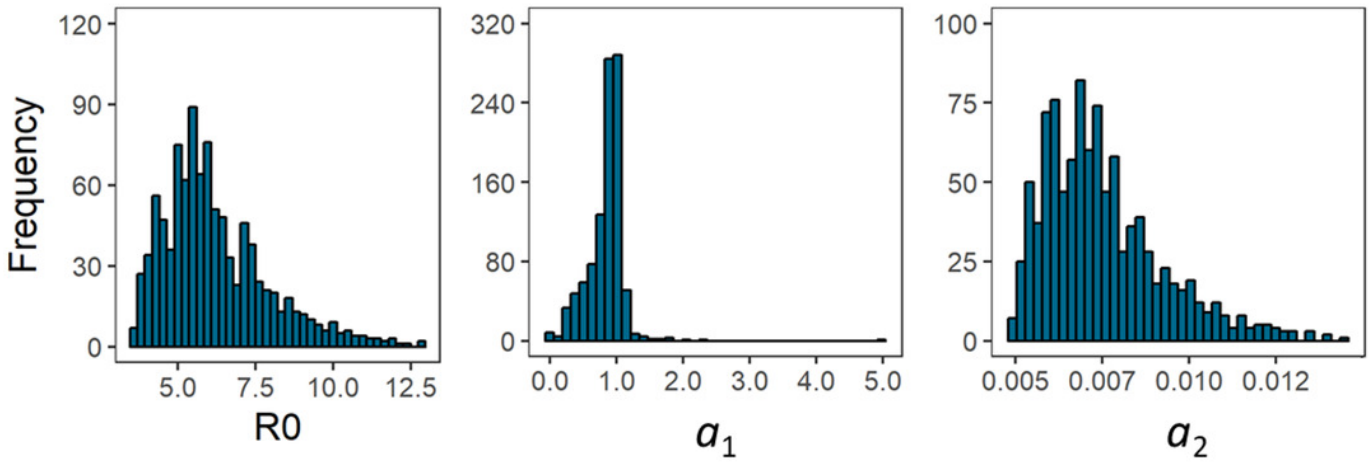

Figure 3

Estimated correlations in each pair of estimated parameters, and comparison between observed and predicted epidemic curves

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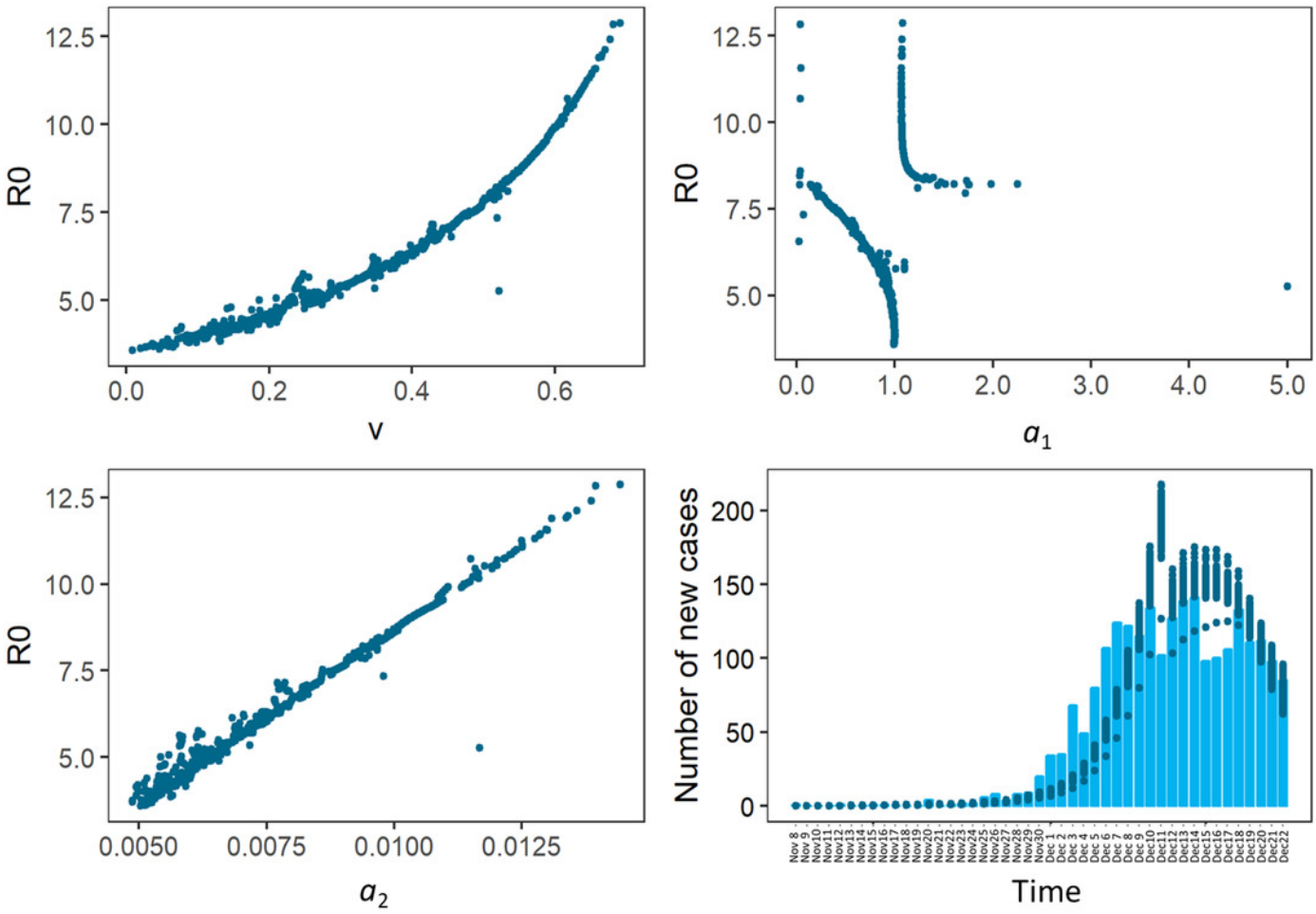

Figure 4

Sensitivity analysis: Partial rank scatterplots

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