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(Summary of Dissertation)

博士の専攻分野の名称 博士（医学）　　氏 名
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Statistical modeling to estimate the protective effect of case isolation and reconstruct transmission dynamics during the 2014 Ebola virus disease epidemic

（2014年エボラウイルス病流行における個体情報を基にした感染者隔離の有効性評価）

【Background and Objectives】

The 2014 Ebola virus disease (EVD) epidemic caused more than 28,000 cases and 11,000 deaths internationally. The epidemic mainly affected West African countries, spreading initially from Guinea, then to Liberia and Sierra Leone. A minor outbreak also occurred in Nigeria. Multi-country epidemics led to an announcement of the public health emergency of international concern (PHEIC) and the transmission routes were contributed by human-to-human infections. Patients developed symptoms such as fever, vomiting or diarrhea, acting as infectious sources and transmitting the viruses to others by contact with bodily fluids. The mainstream of intervention was case isolation and contact tracing because vaccines were not available for the general public. This work aims to devise a statistical model to estimate the impact of case isolation using observational data. The model was applied to two countries, Nigeria and Sierra Leone. Empirically observed data from both countries did not offer a full spectrum of the epidemiological datasets for all individuals. Thus, a modeling framework was designed to reconstruct transmission and to analyze the dynamics in detail. Due to different methods of data reconstruction, the studies in two countries are presented separately in Chapters 1 and 2. The former was based on a dataset containing relatively less missing information whereas the latter required a more complicated approach due to larger parts of missing pieces.

【Materials and Methods】

This work was based on two local outbreaks in Nigeria and Sierra Leone that involved 20 and 49 cases respectively, of which 20 and 44 were hospitalized. In particular, transmission trees that provide information on sources of infection and time events such as dates of symptom onset and hospitalization of each individual were analyzed. However, there were only partially observed details while some missing pieces require reconstruction. Missing dates were imputed using distributions of various intervals between time events. For example, an incubation period with the mean of 9 days was used to evaluate the timing of symptom onset from observation of exposure. Subsequently, a statistical model that quantifies the protective effect of case isolation as a reduction in secondary transmission rate was developed. Accordingly, the reproduction number representing infected cases per individual is reduced and the serial interval representing time lag of symptom onsets between primary and secondary cases is shortened. The modeling was combined with Bayesian statistical approaches to estimate parameters and to assess missing links in the transmission trees simultaneously. Two statistical methods, maximum likelihood estimation (MLE) and Markov chain Monte Carlo (MCMC), were adopted in the estimation. Furthermore, a sensitivity analysis was performed by considering different model assumptions and statistical methods. Alternative scenarios on the reproduction number, protective effect of unknown hospitalized cases and proposal distribution in MCMC were evaluated.

【Results】

The time from symptom onset to hospitalization follows Weibull distributions in both outbreaks. The mean values were 4.0 and 5.0 days and SD were 2.3 and 2.5 days for the data from Nigeria and Sierra Leone respectively. The key time events of all individuals were probabilistically reconstructed by various time lags. The best-fitted models were found to be employing geometrically distributed secondary case numbers in both outbreaks while the serial intervals follow gamma and Weibull distribution for the data from Nigeria and Sierra Leone. The transmission dynamics were represented using mean and 95% credible interval (CI) of the corresponding posterior distributions of parameters. The protective effect of case isolation was 39.7% (95%CI: 2.4%-82.1%) and 23.9% (95%CI: 1.1%-69.5%) in the outbreaks in Nigeria and Sierra Leone, respectively. Most of the individual protective effect was similar to others sharing the same missing information patterns. Each missing link was represented by a list of possible candidates, which identified one and three most likely cases in two outbreaks respectively. The modeling demonstrated consequences in the absence of case isolation. The reproduction numbers at the beginning of two outbreaks were 10.0 (95%CI: 3.0-18.5) and 3.0 (95%CI: 1.2-9.1) respectively, which declined exponentially with the rates of 0.14 (95%CI: 0.07-0.23) and 0.019 (95%CI: 0.005-0.035) per day. The mean of unbiased serial intervals was 15.3 (95%CI: 14.2-16.6) and 12.6 (95%CI: 10.8-14.3) days. As the sensitivity analysis, the reproduction numbers were found to depend on the dynamical assumption in time (e.g. exponential decline). The protective effect of both known and unknown hospitalized cases was influenced by the variation. The serial intervals remained unchanged under alternative scenarios.

【Discussion】

The statistical modeling estimated the protective effect of case isolation during the 2014 EVD outbreaks in Nigeria and Sierra Leone using partially observed contract tracing data. The model captures the dynamical features of EVD transmission using two main components, the reproduction number and serial interval. The former indicates the outbreak magnitude and the latter shows the speed of generation replacement. The estimates of serial intervals coincide with other studies of the two-week interval. The intervals were shortened in two outbreaks as a consequence of successful control. On the other hand, the reproduction numbers in two outbreaks were significantly different due to the index case as a super-spreader in Nigeria, whereas there was no super-spreading event during the outbreak in Sierra Leone. However, the protective effect and final sizes indicated that the interventions were more successful in Nigeria. The unknown hospitalization of the outbreak in Sierra Leone gave another explanation to the controlling impact. Overall, the major factor that lowered the protective effect is infections that occurred during isolation including transmission in hospitals. In addition, traditional burials with a series of practices during ceremonies made the isolation less effective in the early phase before the EVD burial teams conducting safe burials. Nevertheless, the major limitation of this model is the assumption on infectiousness starting from the time of symptom onset, which valid for EVD but not broadly applicable to other infectious diseases.

【Conclusion】

The modeling approach explicitly estimated the protective effect of case isolation and reconstructed missing information of transmission among all individuals involved. The statistical model was formulated to demonstrate that the case isolation during two local outbreaks of the 2014 EVD in Nigeria and Sierra Leone effectively reduced reproduction number and shortened the serial interval. Due to such local containment efforts in preventing secondary transmissions, affected countries were able to avoid the 2014 EVD becoming a global pandemic.