学位論文内容の要旨

博士の専攻分野の名称　　博士（医　学）　　　　氏 名　　齋藤　涼平

学 位 論 文 題 名

Studies on quantitative assessment of countermeasures during a hepatitis A virus outbreak using renewal equation model

（再生方程式モデルによるA型肝炎のアウトブレイク対応策の定量的評価に関する研究）

【Background】

Hepatitis A is an acute infectious disease that frequently causes long-lasting fever, nausea, vomiting, diarrhea, abdominal pain, and strong fatigue, with or without jaundice. Hepatitis A is caused by hepatitis A virus (HAV) and infection of HAV is known to transmit via the fecal-oral route and the ingestion of contaminated food. Since transmission of HAV can occur by direct mucous-to-mucous contact, there is a transition among men who have sex with men (MSM) as a route of transmission of HAV. It has been recognized that MSM sex tourism across multiple countries is a pathway to new outbreaks, and there have been many outbreaks of hepatitis A among MSM. In 2018, Japan experienced a major outbreak, mainly in young men. Recent sporadic cases have occurred among MSM in previous decades, and we can assume that another outbreak occurred in 2018. In this outbreak a particularly substantial increase in disease incidence was observed in Tokyo and Osaka and it was brought under control in about 6 months. Based on the data of confirmed infections in Japan from 2006 to 2019, it can be inferred that the infected individuals in the outbreaks were mainly males, especially in the MSM population, while females did not play the role of infection host and were mainly infected by environmental factors. A campaign was conducted among MSM to reduce the transmission of hepatitis A and our purpose in this study was to evaluate the effectiveness of the intervention by quantitatively assessing the efficacy of this campaign.

【Methods】

In the Japanese law of Infection Control, hepatitis A is a class 4 notifiable disease and reported within 24 hours of confirmatory diagnosis. The countermeasures against HAV outbreak from 2017 to 2018 were conducted among MSM especially from February 13 to May 5 in 2018: for instance, 1,000 pamphlets were widely distributed on February 29 and an online article were uploaded on March 30, which recorded over 120,000 accesses. Environmental transmission with seasonal variation was described as the linear combination of some trigonometric function with different period. The number of cases newly infected via human-to-human transmission is calculated as convolution of the number of the people infected in the past and the generation time multiplied average secondary cases per one case. Moreover, we assumed that when the first countermeasure was implemented the reproduction number changed. Similarly, when the second countermeasure was conducted at time, the reproduction number changed. This modeling is under assumption that the reproduction number is partly constant and changes at the timing of countermeasures. By taking the sum of environmentally and human-to-human transmitted cases and convoluting it with the incubation period, we obtained the expected number of cases with illness onset. These models are like integral equations called renewal equations, which describe reproduction process of some sort of population. In actual calculations, the model is discretized into a unit time of one week. We assumed that the observed incidence data followed a Poisson distribution with the expected value of the illness onset, and we obtained the likelihood function. Because parameters can vary with the serial interval, which is assumed to be known in the present study, it is vital to examine how these parameters changes corresponding with the

serial parameters. Then we also estimated these parameters for each situation in which the ratio of the standard deviation to the mean (i.e., the coefficient of variation, CV) of the serial interval takes different value as a sensitivity analysis. This study analyzed publicly available data. The datasets used in our study were de-identified and fully anonymized in advance. The analysis of publicly available data without identity information does not require ethical approval.

【Results】

At first, we specified hyperparameter and the amount of data used in parameter estimation. We can compare goodness of different model by calculation of Akaike Information Criterion (AIC). We tested 9 patterns of model. As a result, the minimum AIC was observed when we adopted simple trigonometric function to describe environmental transmission. Moreover, the human-to-human transmission epidemic was estimated to begin in the 35th week in 2017. Estimated number decomposed into environmental transmission and human-to-human transmission is compared with the observed data, which shows that the human-to-human transmission peaked out when the second countermeasure was implemented. The reproduction number before the interventions, was estimated to range from 2.6 to 3.1, and constant environmental transmission always yielded a greater reproduction number estimate compared with the other cases. The relative risk of transmission at the time of the first countermeasure, which involved the dissemination of pamphlets by non-governmental organizations associated with MSM, ranged from 0.59 to 0.87. Using the 2017 data with trigonometric-function-like environmental transmission, the first decline rate of reproduction number was estimated at 0.72 (95% CI: 0.39-1.04). At the time of the second countermeasure, which used online web articles, the additional relative impact was estimated to range from 0.36 to 0.43. Using the 2017 data with trigonometric function, the second decline rate of reproduction number was estimated at 0.39 (95% CI: 0.27-0.52). Thus, the reproduction number was 0.28 times the baseline; accordingly, the reproduction number fell below one, and the incidence started to decline. It should also be noted that the upper bound of the CI for the reproduction number fell below one following the second countermeasure. We also conducted the same analyses about the alternative model, in which we assumed that the reproduction number declines exponentially. Applying the alternative model with time-dependent effect of interventions to 2015-2017 data, trigonometric function was best-fit, and baseline reproduction number was estimated at 2.00. The two parameters which corresponds with decline rate of reproduction number were estimated to be 0.96 and 1.03, respectively. The AIC value of this model was 1183.6 which was greater than the original model with 1040.4 AIC. A sensitivity analysis was carried out. We examined how sensitive the parameters were to variation in the CV of the serial interval. Except for very small CV values, which would perhaps be unrealistic, the relative risk of transmission remained stable as CV varied. Thus, the estimated impact of the examined campaigns in terms of preventing hepatitis A transmission was shown to be robust to variation in the generation time, which remained uncertain in our model.

【Conclusions】

During this epidemic, preventive campaigns were conducted to avoid further transmission in the MSM population. Our study evaluated the effectiveness of these campaigns. Development of a mathematical model and estimation of the parameters using surveillance data captured the epidemic dynamics, quantifying the seasonal variation in environmental transmission. In this study, we objectively shown that the reproduction number abruptly declined following the two examined campaign periods. This finding suggests that publishing online articles may potentially have widespread impact enough to change risky behaviors. Given our study results, it would be valuable to survey the MSM population to investigate which types of input and messages were influential in promoting their behavioral changes.