学位論文内容の要旨

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学 位 論 文 題 名

Evaluating the risk of dengue importation and the control effect during the 2014 dengue outbreak in Japan

(わが国におけるデング熱の輸入リスクと 2014 年流行時の制御効果の評価)

Background and Purposes:

Dengue fever is one of the most common mosquito-borne infectious diseases worldwide. Aedes aegypti and Aedes albopictus are known as the two main vector species of dengue virus (DENV), which are composed of four antigenically related serotypes. While the primary infection with one serotype is often self-limiting, the secondary infection with a different serotype is more likely to cause severe clinical symptoms (WHO, 2020). The time from infection to illness onset ranges from 3 to 14 days (Gubler, D. J., 1998). At present, there is no specific treatment for the dengue infections and all the medical care are aimed at providing supportive treatment (WHO, 2020). Thereby the most effective measures to reduce the morbidity and mortality of dengue virus disease are to avoid infection. Dengue infections are seen mostly in tropical and subtropical countries, but nonendemic areas in temperate regions are also at increased risk due to the expansion of the Aedes species habitation areas and a growing volume of international travel. Japan is not an endemic country for the dengue virus, but the country has experienced a steady increase in the number of imported cases in the past decades, mainly from South and Southeast Asia. In 2014, an autochthonous dengue outbreak involving a total of 160 cases was observed in Tokyo. Once the outbreak has been recognized, the government took drastic mosquito control measures targeting both adults and the larvae, and timely news was disseminated. The subsequent park closure was a complement to containing the outbreak. This unexpected outbreak indicated that Japan is at risk of dengue during summer seasons. In this context, we first evaluate the risk of DENV infection among Japanese travelers to Asian countries, thereby obtaining an actual estimate of the number of DENV infections among travelers in the Chapter 1; then we conduct a modeling study to explore the transmission dynamics, evaluating the effectiveness of control measures which were implemented in the 2014 dengue outbreak in Tokyo in the Chapter 2.

Chapter 1: Estimating the importation risk of dengue infections among Japanese travelers to South and Southeast Asian countries

[Materials and Methods] For eight destination countries (Indonesia, the Philippines, Thailand, India, Malaysia, Vietnam, Sri Lanka, and Singapore), we collected age-dependent seroepidemiological data by conducting a systematic review. We also retrieved the number of imported cases, who were notified to the Japanese government, as well as the total number of travelers to each destination from the year of 2006 to 2016. The catalytic model was used to describe the expected fraction of seropositive individuals by the age-independent force of infection. Assuming an identical infection risk between the Japanese travelers and the local population in the destinations, the expected number of dengue infections among Japanese travelers can be deduced. The likelihood function to estimate the force of infection and the reporting coverage of dengue infections can be obtained assuming that the observed number of imported cases follows a Poisson distribution and the seroprevalence data in each destination country follows Bernoulli sampling. The maximum likelihood technique gives the optimal estimation values of the country-specific force of infection and the reporting coverage of dengue infections among Japanese travelers. [Results] The Philippines, Sri Lanka and Indonesia were the three

countries with the highest force of infection. The reporting coverage of dengue appeared to range from 0.6% to 4.3% through all eight selected countries. The risk of infection per journey was calculated ranging from 0.02% to 0.44%. [Discussion] We found that the actual number of imported cases of DENV infection among Japanese travelers could be more than 20 times the notified number of imported cases. This finding may be attributed to the substantial proportion of asymptomatic and under-ascertained infections.

Chapter 2: Assessing the intervention effectiveness in the dengue outbreak in Tokyo, 2014

[Materials and Methods] The case information in this epidemic including the visiting history to the parks, biting experience and the date of illness onset is publicly available on the official website of Tokyo Metropolitan Government. According to the date of exposure to parks at risk, we categorized all cases into three groups. Firstly, we partitioned the entire generation time of dengue infection as incubation period and the waiting time of infection. Using the derived distribution of generation time, we devised a generation-dependent epidemiological model to discretize the entire epidemic as a limited number of generation processes (we assume the unobserved primary case to be the generation zero, all the cases infected by the primary case to be the generation one, and so on). A piecewise function over time was integrated into the abovementioned model to describe the effectiveness of interventions taken at two time points. For each group of cases, the likelihood function to estimate unknown parameters was designed based on the convolution relationship between exposure time and incubation period. The maximum likelihood estimation technique is used to obtain the optimal parameter values. For each scenario with generation numbers as two, three or four, we identified the best fitted model with the lowest AIC by varying the unobserved day of the primary infection. Finally, the effective reproduction number was calculated by the renewal equation. [Results] The mean incubation period was estimated as 5.8 days (95% CI: 5.5, 6.0). The mean generation time was estimated at 17.2 days, 16.1 days and 12.4 days for each scenario model with generation number to be two, three or four. The control measures including mosquito control and epidemic communication, which has been initiated from 28 August 2014, have reduced the transmission by 30%-70%. By estimating the effective reproduction number, we determined that the effect of these two measures was insufficient enough to lower the reproduction number to below the value of 1. However, once Yoyogi Park has been closed on 4 September, the value of the effective reproduction number began to fall below 1, and the associated relative reduction in the effective reproduction number was estimated as 20%–60%. [Discussion] In this modeling exercise, we cannot determine the exact generation number which occurred in the entire epidemic period, so three assumed generation numbers were considered independently and the according estimated parameters were analyzed. It seems natural that there was some interplay between the assumed generation numbers and the resulting estimates. However, regardless of the three different scenarios, the joint reduction effect of all interventions was estimated to be 44%-88% and the combined interventions were effective to control the outbreak.

Conclusion:

In Japan, the notified number of imported dengue cases truly represent the tip of iceberg that consists of substantial number of infected individuals, indicating a much higher importation risk than we directly see from observed datasets of confirmed cases. The 2014 dengue outbreak in Tokyo is thought to have represented the result of this increased risk. In this epidemic, all control measures that we explored including massive mosquito control, timely risk communication, and rigorous park closure appeared to be successful in interrupting the transmission chain. To avoid the next dengue outbreak in Japan, the epidemiological surveillance of imported cases and the routine monitoring of mosquitos especially in public green zone are considered to be essential.