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## 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 坂本 洋平

### 学位論文題名

Studies on transmission dynamics of viral infectious disease by using mathematical model

(数理モデルを用いたウイルス感染症の感染動態に関する研究)

**【Background】** Mathematical models of infectious diseases are mathematical systems that mathematically represent and analyze the dynamics of infectious diseases in a population. Stability analysis was discussed and quantitative validity was gradually assured, and mathematical models of infectious diseases came to play an essential role in infectious disease epidemiology. When constructing and analyzing mathematical models for individual infectious diseases, it is necessary to clarify the transmission characteristics by considering factors such as the biological nature of the disease, clinical perspectives, human behavior, and individual heterogeneity. Implementation of the models will be delayed, and it will lead to the inability to spread infection if models are developed from scratch for a wide range of infectious diseases. Therefore, it is crucial to establish methodologies for each infectious disease with similar elements and adapt them quickly when an epidemic occurs. When using a mathematical model for viral infections, it is necessary to construct a model that considers factors such as "drug treatment," "diagnosis," "surveillance," "transmission route," and "vaccine" to estimate the number of potentially infected people and assess risk. This study will formulate two viral infections (Yellow fever and Cytomegalovirus (CMV)) with different characteristics and quantitatively evaluate their epidemic dynamics and risks.

**【Methods】** In Chapter 1, to estimate the risk of yellow fever among travelers, we analyzed both the confirmed cases in Brazil and imported cases reported abroad (Chile, Argentina, Netherlands, Switzerland, France, the United Kingdom, Romania and Germany) from May 2017 to May 2018. A statistical model was employed to capture the risk of importing yellow fever by returning international travelers from Brazil. We estimated the relative risk of importation among travelers by the extent of wealth measured by GDP per capita and the relative risk obtained by random assignment of travelers' destination within Brazil by the relative population size. In Chapter 2, the seroepidemiological datasets (i.e. the prevalence of anti-CMV IgG antibodies) for pregnant women collected from five cord blood banks in Sapporo, Tokyo, Osaka/Kyoto, Okayama and Fukuoka from 1996 to 2009 were utilized to quantify the time-dependent transmission dynamics of CMV infection in Japan. By employing a mathematical model and using the maternal age distribution of childbirths from the Vital Statistics of Japan, we computed the seroprevalence among the pregnant Japanese women as a function of time.

**【Results】** In Chapter 1, travelers from wealthier fraction of countries were  $a = 2.3$  (95% CI: 0.7, 8.6) times more likely to be infected with yellow fever compared with countries below median GDP per capita. Upper-half wealthier countries had 2.1 to 3.4 times greater risk of importation than remainders. Even among countries with lower half of GDP per capita, the risk of importation was 2.5

to 2.8 times greater than assuming that the risk of travelers' infection within Brazil is determined by the regional population size. In Chapter 2, From a total of 22,100 samples, 16,191 were revealed to be positive, with the sample proportion positive estimated at 73.3% (95% CI: 72.7, 73.8). By linearly regressing the sample proportion by year, the seropositive fraction has decreased every year by 0.7% ( $p < 0.001$ ). From 1980–2009, the median age of infection was elevated from 10.0 to 19.7 years old. A decreasing trend was observed for the force of infection, i.e., the rate at which susceptible individuals are infected, which decreased from 0.04 to 0.03 (/year) over the period from 1996 to 2009. While the total number of births has steadily declined in Japan over time, the estimated number of live births at risk of CMV infection has increased over time. Comparing the time-dependent patterns of the estimated force of infection against the different geographic locations of the cord blood banks in Japan, while a time-dependent decline was evident in Hokkaido and Fukuoka, the rate of decrease in the force of infection was slower in Tokyo.

**【Discussion】** In Chapter 1, we have shown that countries with wealthier GDP per capita appeared to be more often infected. It also indicates that travelers' local destination and behavior at high risk of infection are likely to act as a key determinant of the heterogeneous risk of importing case. In addition, we found that even non-wealthy countries were at 2.5–2.8 times greater risk of importing yellow fever case as compared with a common modeling assumption that the destination-specific risk of infection is proportional to the relative population size of the destination to the entire country. Apart from the future tasks for finer estimation of the risk of infection among travelers, we believe that our study successfully quantified the relative risk of infection by GDP per capita and also compared with the risk that rests on population-size specific assumption of travelers' destination. In Chapter 2, we indicated that the force of infection for CMV has declined over time in Japan by using blood samples from pregnant women only. Our data reveal that in 2009 in Japan, at least 0.3 million women may have been at risk of contracting a CMV infection during the perinatal period. Moreover, about 2,726 congenital CMV infections were expected to have occurred in 2009. The average age at infection has already reached the child bearing age, and it must be noted that the age at infection can be elevated even more, reaching close to 30 years old which is the ongoing mean age at child delivery.

**【Conclusion】** In Chapter 1, travelers from wealthier countries were at elevated risk of yellow fever, allowing us to speculate that travelers' local destination and behavior at high risk of infection are likely to act as a key determinant of the heterogeneous risk of importation. It is advised to inform travelers over the ongoing geographic foci of transmission, and if it appears unavoidable to visit tourist destination that has the history of producing imported cases, travelers must be strongly advised to receive vaccination in advance. In Chapter 2, Data from the seroprevalence survey among pregnant women were analyzed as a function of time, and seropositivity among pregnant women was calculated by year. By fitting the computed probability to the observed seropositive data, we have shown that the observed decline in the proportion of CMV-positive pregnant women mirrors the steadily declining force of infection over time. Due to the elevated age at infection, pregnant women are exposed to high risk of congenital CMV infections in Japan.