学位論文内容の要旨
（Summary of dissertation）

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学 位 論 文 題 名

Estimation and application of epidemiological parameters of COVID-19
(新型コロナウイルス感染症における疫学パラメータの推定と応用)

Background and Objectives: Coronavirus disease 2019 (COVID-19) emerged as a human-to-human transmissible disease in late 2019, with its causal pathogen identified as severe acute respiratory disease coronavirus 2 (SARS-CoV-2) in January 2020. Identification of key characteristics of the natural history of SARS-CoV-2 infections was necessary for understanding transmission patterns of the newly emerged disease, as well as for investigating the likelihood that transmission would die out, as had happened with another coronavirus, severe acute respiratory disease (SARS), in 2005. Chapter 1 estimates the incubation period—the time between infection and illness onset—of COVID-19 cases reported in January–February 2020 in order to establish a recommended quarantine period. Time from illness onset to hospital admission, time from illness onset to death, and time from hospital admission to death—parameters which are useful for estimating understanding hospitalization and fatality rates—were also estimated. Next, Chapter 2 explores end-of-outbreak probabilities for clusters of COVID-19 cases Japan, which had adopted a cluster-based approach to COVID-19 response from February 2020. Lastly, Chapter 3 identifies transmission pairs in Japan and determines the correlation between joint estimates of the incubation period and generation interval—the time between infection of an individual with a pathogen and transmission of that pathogen to another individual—of COVID-19 to evaluate the effectiveness of case isolation on pathogen transmission.

Chapter 1: Incubation period and other epidemiological characteristics of 2019 novel coronavirus infections with right truncation: A statistical analysis of publicly available case data

Methods: The geographic spread of SARS-CoV-2 infections from the original epicenter of Wuhan, China, in early 2020 provided an opportunity to study the natural history of the recently emerged virus. Using publicly available event-date data from COVID-19 cases reported in January 2020 we investigated the incubation period and other time intervals that govern the epidemiological dynamics of SARS-CoV-2 infections. **Results:** The incubation period fell within the range of 2–14 days with 95% confidence and has a mean of around 5 days when approximated using the best-fit lognormal distribution. The mean time from illness onset to hospital admission (for treatment and/or isolation) was estimated at 3–4 days without truncation and at 5–9 days when right-truncated. **Discussion:** Based on the 95th percentile estimate of the incubation period, we recommended that the length of quarantine should be at least 14 days. The median time delay of 13 days from illness onset to death (17 days with right truncation) should be considered when estimating the COVID-19 case fatality risk.

Chapter 2: Localized end-of-outbreak determination for coronavirus disease 2019 (COVID-19): examples from clusters in Japan

Methods: End-of-outbreak declarations are an important component of outbreak response as they indicate that public health and social interventions may be relaxed or lapsed. We assessed end-of-outbreak probabilities for clusters of COVID-19 cases detected during the first wave of the pandemic in Japan. We computed a statistical model for

end-of-outbreak determination using the offspring distribution—the distribution of the number of secondary cases infected by each case—and serial interval—the time from illness onset in a given infected case to illness onset in a case they infect—that accounted for the reporting delay for new cases. Four clusters representing different social contexts and time points during the first wave of the epidemic were selected and their end-of-outbreak probabilities were evaluated.
Results: The speed of end-of-outbreak determination was most closely tied to outbreak size. Notably, accounting underascertainment of cases led to later end-of-outbreak determinations. In addition, end-of- outbreak determination was closely related to estimates of case dispersion k and the effective reproduction number R_e. Increasing local transmission ($R_e > 1$) leads to greater uncertainty in the probability estimates. **Discussion:** When public health measures are effective, lower R_e (less transmission on average) and larger k (lower risk of superspreading) will be in effect and end-of-outbreak determinations can be declared with greater confidence. The application of end-of-outbreak probabilities can help distinguish between local extinction and low levels of transmission, and communicating these end-of-outbreak probabilities can help inform public health decision-making with relation to the appropriate use of resources.
Chapter 3: Correlation between times to SARS-CoV-2 symptom onset and secondary transmission undermines epidemic control efforts.
Methods: We used publicly available case data from Japan to reconstruct networks of transmission for different prefectures in Japan and identify infector-infectee pairs where exposure dates and symptom onset for the infector as well as dates of contact between the infector and infectee were reported. From this data, we used doubly-interval censoring and copula methods to jointly estimate the generation interval and incubation period and obtain an estimate of correlation between the two epidemiological parameters. **Results:** We collected a dataset of 257 SARS-CoV-2 transmission pairs in Japan and jointly estimated the mean generation interval (3.7–5.1 days) and mean incubation period (4.4–5.7 days), taking into consideration sociodemographic and transmission characteristics. The generation interval and incubation period were positively correlated (Kendall's tau of 0.4–0.7). **Discussion:** Accounting for this dependence can improve the prediction of SARS-CoV-2 transmission in epidemic models as well as enhance evaluation of the effectiveness of public health interventions on disease control. However, as SARS-CoV-2 variants begin to dominate transmission in many countries, whether the correlation between the generation interval and incubation period would be weaker or stronger than has been presented here remains to be seen. Nonetheless, this study provides a basis for consideration of such correlation moving forward.
Conclusion: The COVID-19 pandemic has proven longer-lasting and more severe than most predicted in early 2020. Partially this is due to the large fraction of presymptomatic and asymptomatic transmission. Understanding of epidemiological parameters related to SARS-CoV-2 infection has been critical to the creation and fine-tuning of statistical models describing disease transmission, severity, and the impact of nonpharmaceutical interventions on control. The present dissertation has provided estimates for key epidemiological parameters of COVID-19 and provided guidance on a recommended quarantine period for COVID-19 cases at the beginning of the pandemic. In addition, shown the application of epidemiological parameters to end-of-outbreak estimation. Lastly, it has elucidated the role of presymptomatic transmission in transmission and evaluated the effectiveness of symptom-based case isolation given the level of correlation between the incubation period and generation interval. There is much work yet to be done to determine epidemiological parameters related to vaccination and SARS-CoV-2 variants, but the work presented here will continue to inform COVID-19 models moving forward.