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学 位 論 文 題 名

Epidemiological studies on effective reproductive number and asymptomatic infections of COVID-19

（COVID-19 の実効再生産数及び不顕性感染についての疫学的研究）

【Background and Objectives】Quantifying key parameters governing infectious dynamics of ongoing epidemics of coronavirus disease 2019 (COVID-19) is very important from the public health point of view. The effective reproduction number, R(t), and the relative transmissibility of asymptomatic cases are among them and have been focuses of many epidemiological studies done so far. R(t) reflects the epidemic dynamics based on readily available illness onset data and is useful for the planning and implementation of public health and social measures. However, COVID-19 infection events are generally not directly observable, and full datasets are rarely available. As a result, most studies have leveraged information on illness onset or the serial interval, or both, to estimate R(t). While the estimation of R(t) based on illness onset is conventional, accumulating evidence suggests that pre-symptomatic transmission contributes to the secondary transmission of COVID-19. Estimates of R(t) based on illness onset data seldom take into account pre-symptomatic transmission. In Section 1 of present study, I proposed a new method for computing the R(t) of COVID-19 and applied this method to the epidemic in Osaka prefecture from February to September 2020. Individuals with asymptomatic severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection can propagate the virus unknowingly and thus understanding viral transmissibility among asymptomatic individuals is critical for successful control of COVID-19. The epidemiological importance of asymptomatic individuals who would never develop illness, compared to those who eventually develop symptoms, has yet to be fully clarified. In Sections 2 and 3, I aimed to understand SARS-CoV-2 transmissibility in asymptomatic individuals using data from two distinct clusters in Japan and to assess whether symptomatology was associated with transmission of symptomatic vs. asymptomatic infections.

【Methods】 In Section 1, I employed a modified renewal equation based on the date of illness onset, leveraging the frequency of secondary transmission to capture pre-symptomatic transmission. Using a piecewise constant model with a 5-day time interval, I estimated R(t) as a function of the time of infection using the date of illness onset. To understand if R(t) estimates were associated with the important countermeasures implemented in Osaka prefecture, I compared the negative log likelihood values of all possible combinations of "event-based" models using step functions to approximate R(t). A Joinpoint segmented regression model was also used to assess whether a significant change in R(t) during each wave was associated with any of the start dates of key interventions. In Section 2, the very first cluster data in Tokyo and Kanagawa, Japan, were analyzed. Movement of all close contact was restricted for 14 days, and they underwent laboratory testing with polymerase chain reaction. Assuming that the number of secondary cases resulting from either primary symptomatic or asymptomatic cases independently followed negative binomial distributions, I estimated the relative reproduction numbers of an asymptomatic case compared with a symptomatic case. In Section 3, I

analyzed another first cluster that occurred among university students in Kyoto prefecture, Japan, using discrete and two-type branching process models as in Section 2. To explore the potential association between symptomatology and transmission of symptomatic vs. asymptomatic incident infections, I estimated the proportion of secondary symptomatic cases produced by primary symptomatic and asymptomatic cases. I also explored the impact of isolation on these estimates using the probability distribution function of the serial interval shortened by isolation.

【Results】 In Section 1, it was shown that based on estimated R(t) by the new method, the epidemic in Osaka came under control around 2 April during the first wave, and 26 July during the second wave. R(t) did not decline drastically following any single intervention. However, when multiple interventions were combined, the relative reductions in R(t) during the first and second waves were 70% and 51%, respectively. Although the second wave was brought under control without declaring a state of emergency, our model comparison indicated that relying on a single intervention would not be sufficient to reduce R(t) < 1. In Section 2, the reproduction number for symptomatic cases was estimated to be 1.2 (95% confidence interval (CI): 0.5-2.9). The relative infectiousness of asymptomatically infected cases was estimated to be 0.27 (95% CI: 0.03-0.81) of symptomatic cases. The reproduction number for a symptomatic primary case was estimated at 1.14 (95% CI: 0.61-2.09) in Section 3. The relative reproduction number for asymptomatic cases was estimated at 0.19 (95% CI: 0.03-0.66), indicating that asymptomatic primary cases did not result in sufficient numbers of secondary infections to maintain chains of transmission. There was no apparent tendency for symptomatic primary cases to preferentially produce symptomatic secondary cases.

【Discussion】 The method of estimation of R(t) proposed in Section 1 could accurately estimate R(t) using illness onset data. Compared with the procedure involving multiple inferential steps like non-parametric back-projection, the advantage of this method is the simplicity of the estimation procedure while accounting for a critical element of the natural history of COVID-19, i.e., pre-symptomatic transmission. The relative transmissibility of asymptomatic cases estimated in Section 3 was broadly consistent with the estimated value in Section 2. These results suggest that the transmissibility of asymptomatic cases is less than half that of symptomatic cases. It would be justified to implement contact tracing beginning with symptomatic cases, especially if testing capacity is limited.

【Conclusion】 The present study was successful in estimating the R(t) for COVID-19 over the course of the epidemic in Osaka prefecture from February to September 2020. The R(t) of COVID-19 did not decline following a single intervention event, and my results indicate that concerted efforts would be required to curb the COVID-19 epidemic. Using data from two distinct transmission networks during the early epidemic in Japan, I also successfully estimated the relative infectiousness of asymptomatically infected cases of SARS-CoV-2 to be 0.27 or 0.19. These results suggest that the relative transmissibility of asymptomatic cases is limited and contract tracing focusing on symptomatic index cases may be justified given limited testing capacity. The outcome of the COVID-19 or future pandemics would continue to rely on political leadership to swiftly design and implement combined interventions to reduce contacts broadly and appropriately.