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＜ Research Data ＞

Trends in the incidence of symptomatic COVID-19 during the first endemic wave in the Japanese population

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Abstract

Object: First coronavirus disease 2019 (COVID-19) endemic wave in Japan was almost stabilized in late May in 2020, without strong physical distancing interventions. Our objective was to analyze temporal trends in the incidence of symptomatic COVID-19 during this phase in Osaka Prefecture (population of 8.8 million).

Methods: We calculated 7-day moving averages of the date-of-onset-based number of symptomatic COVID-19 cases using anonymous data posted on the official website of the Osaka Prefectural Government between February 27 and May 23 in subjects whose route of transmission was known (linked case) or unknown (unlinked case). Joinpoint regression analysis was performed. Daily percent change (DPC) in the incidence and dates of significant change ("joinpoint") were identified in the Joinpoint regression analysis.

Results: The maximum daily number of symptomatic COVID-19 cases was 72 on April 3. From March 12 to April 2, the incidence of unlinked cases significantly increased (DPC: +14.8%). Then, the incidence rapidly decreased until late May with accelerating downward trend between April 12 and 17 (DPC%: -15.8%). The temporal change in linked cases was almost synchronized to that of unlinked cases with 6-7 days' delay.

Conclusions: The peak incidence of unlinked COVID-19 cases in the first endemic wave in Osaka was observed at April 2, 2020. The temporal trend was synchronically followed by that of linked cases with 6-7 days' delay.

keywords: COVID-19, incidence, unlinked case, Japanese, joinpoint regression analysis

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I. Introduction

Japan (120 million population) experienced sporadic cases of coronavirus disease 2019 (COVID-19) mainly in Hokkaido, Tokyo, Osaka and some local areas in February 2020. Then, the first endemic wave occurred from mid-March [1]. During the same period, the government Expert Meeting was urging people to avoid crowded and confined spaces to prevent spread of the virus [2]. In addition, the Japanese Government stated emergency on outbreaks in April 7[3], which was made based on the Act on Special Measures for Pandemic Influenza and New Infectious Diseases. Surprisingly, the number of daily reported cases rapidly declined starting on April 10[1], without strong physical distancing interventions such as closures of workplace, shutdown of public transportation and restrictions on movement (lockdowns). The number of daily reported cases in the late May decreased to 50[4] which was approximately one twelfth of the peak incidence in the first endemic wave on April 9. The cumulative incidence by May 27 in Japan was 16,651 [4], which was much lower than the respective incidence in the UK (265,231), Italy (230,555), Germany (179,364), France (142,704), China (84,544) and the US (1,634,010) [5],

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even though many of these countries conducted multiple physical distancing interventions [6].

In the first endemic wave, Japanese COVID-19 patients without known exposure had longer time of symptom onset to the diagnosis than those with known exposure [7]. We assume this finding might influence difference in temporal trends in the incidence of symptomatic COVID-19 cases between the two groups. Thus, we analyzed the temporal trends in the incidence of symptomatic COVID-19 during this phase in Osaka Prefecture, which has a population of 8.8 million with a density of 4700/km2, in classifying linked and unlinked cases.

II. Methods

1. Definition of a case of COVID-19

A confirmed COVID-19 case was defined according to the definition of a case issued in a guideline of the Infection Control Act [8]. In the study period, a physician diagnosed a symptomatic patient as COVID-19-positive if the patient tested positive on reverse transcription-polymerase chain reaction (PCR) [9] or loop-mediated isothermal amplification (LAMP)[10] in a sample obtained by a naso-pharyngeal swab or sputum from the patient. Physicians are mandatorily required to submit notification of positive cases to the public health center (PHC) that has jurisdiction over his/her medical institution based on the Infection Control Act.

The Department of Health of the Osaka Prefectural Government (DHOPG) collects all incident reports from the 18 PHCs located in Osaka Prefecture, and publicizes the daily anonymous personal data on the official website of the Osaka Prefectural Government (OPG) [11]. We used this publicized data in this study.

2. Study subjects and data items

There were 1,780 confirmed COVID-19 cases diagnosed between February 27 and May 23, which include the first endemic wave of COVID-19 in Osaka. Among these, we excluded 22 cases imported from overseas, 324 cases clustered in 4 rock-music halls, 6 hospitals and one faculty of a university, and 172 cases either with asymptomatic COVID-19 or in which the date of onset was unknown. The remaining 1,262 symptomatic cases were analyzed in this study (Figure 1).

When a Japanese PHC received an incident report from a physician, the PHC immediately investigates the index case's behavior during the 14-day period before the date of onset to identify the route of transmission. At the same time, the PHC performs contact tracing of the index case to identify persons with whom the index case was in close contact between 2 days before the date of onset and the

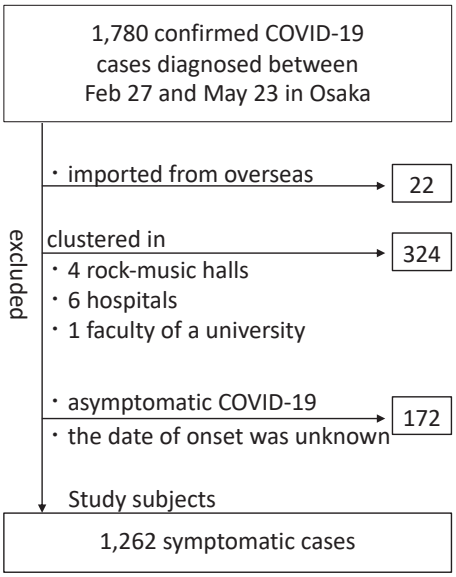

Figure 1 Recruitment of study subjects in the first endemic wave of COVID-19 in Osaka, 2020

date of the beginning of isolation in hospital admission or hotel stay [12]. The asymptomatic persons with whom the index case was in close contact are required to stay at home for 14 days from the date of last contact with the index case with active health monitoring by the PHC. We used data on index cases whose route of transmission is known (linked case) or unknown (unlinked case) in this study.

3. Analysis

To give an overview of the trend in symptomatic COVID-19 cases until the first endemic wave was stabilized in Osaka, 7-day moving averages of the date-of onset-based number of cases were calculated in both linked and unlinked subjects.

Then, to identify days when there was a statistically significant change in the slope of the temporal trend in the incidence of symptomatic COVID-19, we applied the joinpoint regression model [13] by using the Joinpoint Regression Program, version 4.8.0.1[14]. We computed the estimated slopes describing the 5-day moving average daily percent change (DPC%) in the incidence in date-of-onset per 100,000 person-days. In this computation, we added one dummy case in all the date of the incident number to avoid exaggeration of the temporal changes. Permutation test was performed to identify days when a statistically significant change had occurred ($p<0.05$).

III. Results

1. Overview

We saw a small peak (n=9) in the daily number of symp-

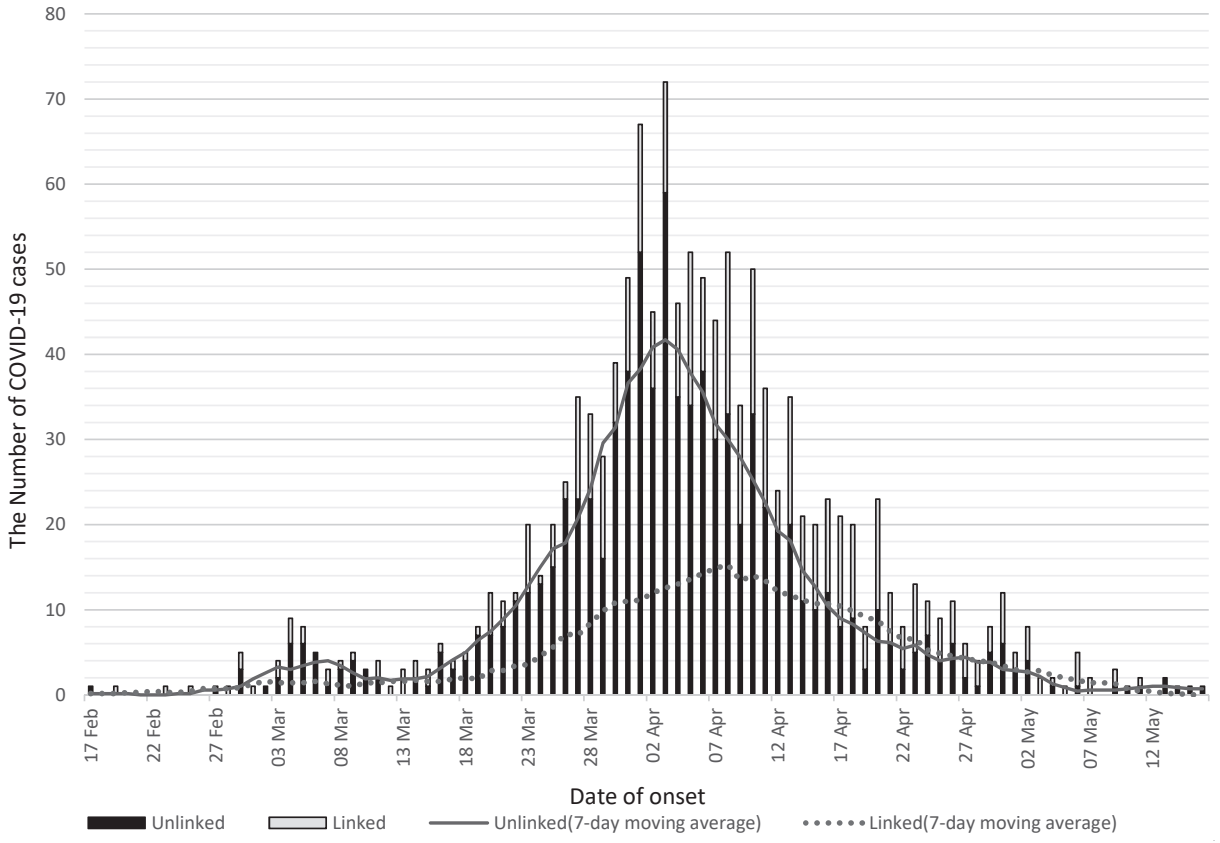

Figure 2 Seven-day moving averages of the date-of onset-based number of COVID-19 cases in linked and unlinked symptomatic subjects in Osaka between February 17 and May 16 in 2020.

tomatic COVID-19 cases on March 4, which was followed by a rapid increase with a peak (n=72) on April 3 (Figure 2). Then, it decreased to zero to 5 patients per day on May 7 and thereafter.

The trend in the 7-day moving average of the incidence of unlinked cases was characterized by a triangular shape, reaching a peak on April 2. The seven-day moving average in linked cases increased from March 20 to April 8. It seemed to decrease to zero to three patients per day on May 10 and thereafter (Figure 2).

2. Joinpoint analysis

Figure 3A shows trends in the incidence of symptomatic COVID-19 among unlinked cases in Osaka between February 29 and May 21 in 2020. There were five joinpoints on March 5, March 12, April 2, April 12 and April 17, with statistically significant changes. A conspicuous upward trend (DPC: +14.8%, for 21 days) continued from March 12 to April 2, and was followed by three significant downward segments (DPC: -7.5%, -15.8% and -6.5 %) divided by two joinpoints (April 12 and April 17).

Among the linked cases, a significant upward trend with a DPC of +15.7% started on March 19, which was 7 days after the beginning of the conspicuous upward trend in the unlinked cases (Figure 3B). This upward trend ended on April 8, which was 6 days after the date of the peak incidence in the unlinked cases. The downward trend continued to May 21, with a DPC% that ranged from -4.6 to -8.0% (Figure 3B).

VI. Disucussion

The DHOPG identified 48 COVID-19-positive cases who were part of clusters at four rock-music concerts held between February 15 and 24 in the Osaka metropolitan area [11]. The presence of a small unlinked wave at the beginning of March indicates that these clusters had limited impact on subsequent community transmission among Osaka citizens. At the time, Osaka citizens received no official announcement on refrain from going to the "three Cs" ("closed spaces with poor ventilation"; "crowded places with many people nearby"; "close contact settings in a loud voice") such as night clubs, karaoke clubs and fitness centers from the central nor local governments. Therefore, COVID-19 positive individuals infected in the four rock music concerts might have negative behavior to go to these other three

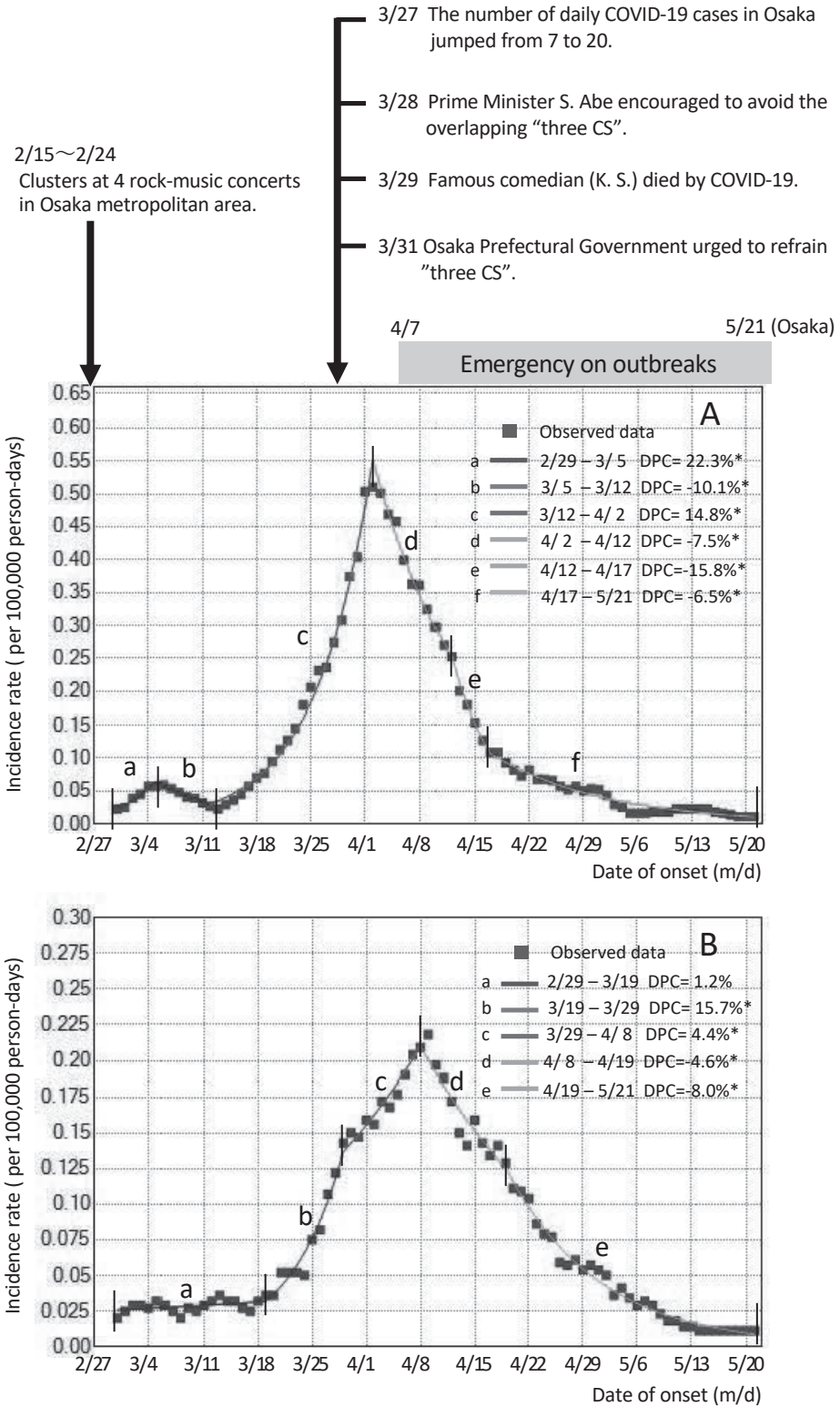

Figure 3 Joinpoint analysis of the symptomatic COVID-19 incidence rate per 100,000 person-days in Osaka between February 29 and May 21 in 2020. (A) is incidence rate of unlinked case, (B) is incidence of linked case. Daily percent change (DPC) was estimated by using the Joinpoint Regression Program version 4.8.10. * Statistical significance was set at p-vale < 0.05.

Cs although these places were opened in part at the time. A previous online survey of Japanese citizens conducted at the end of March showed that approximately 85 percent were practicing social distancing measures recommended by the Japanese government and 86 percent were performing frequent handwashing [15]. Participants of this survey responded that the most important event influencing these preferable actions was the infection aboard the Diamond Princess cruise ship [15] that was quarantined at Yokohama Port in early February. We suppose this report implies that the majority of Osaka citizens had already had social distancing measures and performing handwashing behaviors by mid-March, which might be partially attributed to reduce the risk of unlinked community transmission from these clusters.

Japan, including Osaka, experienced the first endemic wave of COVID-19 from mid-March to early May. As a whole genome sequencing network analysis of the virus that was predominant in clusters at this time demonstrated that the viruses were related to the virus in the outbreak in Europe [16], the primary virus in the first endemic wave was probably imported from Europe, before the Japanese government restricted European travelers from entering Japan in mid-March.

The number of daily unlinked symptomatic cases in Osaka started to drastically decrease on April 3. This suggests that the magnitude of COVID-19 transmission rapidly decreased around March 28, on the basis of the assumption of one incubation period interval [17]. At this time, i) the Osaka Prefectural Government requested the citizens' cooperation to stay at home on the weekend of March 21 and 22; ii) the Osaka prefectural government announced that the number of daily COVID-19 cases in Osaka jumped from 7 to 20 on March 27; iii) Prime Minister S. Abe encouraged the Japanese public to avoid the overlapping three Cs on March 28; iv) a famous Japanese comedian (K.S.) died by COVID-19 with severe dyspnea on March 29 and v) the Osaka prefectural government urged the public to refrain from going to the "three Cs" such as night clubs, karaoke clubs and fitness centers on March 31. We speculate that these events and messages possibly influenced some Osaka citizens to refrain from engaging in high-risk behaviors with regard to COVID-19 transmission in late March. In addition, the Japanese social custom of being quiet in public spaces, and the Japanese language which is characterized by soft pronunciation of both vowels and consonants may have contributed to the low risk of droplet infection even in close-contact settings.

The declining trend in the daily number of unlinked symptomatic COVID-19 cases was accelerated between April 12 and April 19. We think that this change was attributed to Prime Minister Abe's statement of emergency on outbreaks issued on April 7[3], which was made based on the Act on Special Measures for Pandemic Influenza and New Infectious Disease. Osaka citizens probably maintained self-restraint to avoid the "three Cs" more strictly, which led to the accelerated downward trend that occurred after one incubation interval from the time of the statement (April 7 to 12).

On the other hand, the joinpoint analysis showed that the change in daily number of linked symptomatic cases was synchronized with the temporal trends in unlinked cases with an interval of almost one incubation period (6 to 7 days). This finding was possibly due to the situation that many linked cases were detected by contact tracing of the index unlinked cases by the local PHC.

Osaka had 268 COVID-19 cases clustered in 6 hospitals between April 17 and May 8[11]. However, the downward trend in the DPC% in late April was not changed until late May. This phenomenon indicates that these clusters had a limited impact on the spread of the virus among Osaka citizens, possibly in part by self-restraint behaviors to protect against the virus.

One strength of this study is that all the incident data were obtained from the 8.8 million Osaka residents through the preventive action based on the Infection Control Act. Trained public health nurses in local PHC offices ask all confirmed COVID-19-positive individuals about their behaviors to explore the route of transmission. Moreover, as we excluded asymptomatic cases, the significant trends we found would have low influence from detection bias due to patients' accessibility to physicians or patients receiving PCR testing.

Limitations of this study were: in the study period, we had lower COVID-19 PCR test availability than other developed countries [mean number of PCR tests per day in the second week of April in Osaka was 380[11]]. Therefore, the incidence rate was probably underestimated. However, since such underestimation might occur during the observation period equally, it would not have an influential detection bias in the temporal trends nor joinpoints we found.

In conclusion, we showed that the first symptomatic COVID-19 endemic wave in Osaka ended at around 60 days with a peak daily incidence of less than 100. The peak incidence of unlinked COVID-19 cases in the first endemic wave in Osaka was observed at April 2, 2020. The temporal trend was synchronically followed by that of linked cases with 6-7 days' delay.

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Conflict of Interest

The authors declare no conflict of interest.

Ethical approval

All the anonymous data we used in this study was obtained from the official website of the Osaka Prefectural Government. Therefore, this descriptive epidemiologic study does not need approval of an institutional review board on ethical issue.

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＜資料＞

日本人（大阪府）における新型コロナウイルス流行第１波時期の症候性罹患数のトレンド分析

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抄録

目的：日本における新型コロナウイルス感染症（COVID-19）流行の第１波は，国民に対する強制的な行動制限を実施することなく2020年５月後半には一旦下火となった．本研究では大阪府人口（880万人）における同期の有症状となったCOVID-19罹患数の継時的トレンドの特徴を明らかにする．

方法：2020年２月27日から５月23日の間に大阪府内で発生届のあった，診断時有症状のCOVID-19罹患者の，発症日および感染ルートが不明か否かの情報を，大阪府健康医療部が公開する府ホームページから入手した．これを用いて発症日で見た罹患数の７日間移動平均を算出した．また，罹患者を感染ルート不明者と判明者に２分し，ジョインポイント回帰分析法を用いてそれぞれの発症日で見た罹患数のトレンドを分析し，当時の社会情勢や行政の取り組みの影響を検討した．

結果：第１波における罹患数のピークは４月３日（72人）であった．感染ルート不明罹患数の３月12日から４月２日までのannual percent change（DPC）は+14.8％と顕著な増加を示し，それ以後急速に減少し始め（DPC:-7.5％），特に，緊急事態宣言が出された４月７日から５日後の４月12日から５日間はDPCが-15.8％と，減少率が加速していた．一方，感染ルート判明者の罹患数のトレンドは，概ね６日から７日遅れて感染ルート不明罹患数のトレンドに同調していた．

結論：大阪府のCOVID-19流行第１波における感染ルート不明者の罹患数のピークは４月２日であった．感染ルート判明者の罹患数の継時的変化のパターンは，感染ルート不明者のそれに６-７日遅れで同調していた．

キーワード：新型コロナウイルス感染症，罹患，感染ルート不明者，日本，ジョインポイント分析