



Factors associated with time lag between symptom onset and reporting in the first epidemic wave of COVID-19 in Osaka, Japan

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ABSTRACT

Objectives: Longer reporting lags after symptom onset reportedly exert a substantial impact on onward transmission, increasing outbreak probability. Our study investigated the risk factors associated with reporting lag.

Methods: Using active epidemiological surveillance data for all symptomatic cases reported in Osaka Prefecture during the first wave of the coronavirus disease 2019 (COVID-19) epidemic (February 1–May 13, 2020), multi-variable regression analyses were implemented to estimate the effects of exposure variables on reporting lag, by controlling for potential confounders.

Results: Cases in their 30s showed a longer reporting lag than cases ≥ 80 years old. Cases who lived in areas with a high COVID-19 incidence demonstrated a longer reporting lag. Cases with a history of visiting a nightlife district also showed longer reporting lag than cases without such a history. Healthcare workers and cases with immunodeficiency both displayed shorter reporting lags than others.

Conclusion: Identifying newly infected cases as soon as possible and increased testing capacity for all age groups, and for individuals with a history of visiting high infection-risk areas, represented important measures in shortening reporting lags in the first wave period. The evidence from this study may provide lessons for controlling future emerging diseases.

1. Introduction

In December 2019, an outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections occurred in Wuhan, Hubei Province, China (Chen et al., 2020; Huang et al., 2020; Zhu et al., 2020), and spread across China and around the world. The World Health Organization declared the coronavirus disease 2019 (COVID-19) outbreak as a global pandemic on March 11, 2020 (Cucinotta and Vanelli, 2020). In Japan, the first case was confirmed on January 15, 2020. By the end of January 2020, 13 cases had been reported (MHLW, 2020a), including one case in Osaka Prefecture. On February 1, 2020, COVID-19 was added as a designated infectious disease under the Infectious Diseases Control Law in Japan, and doctors were required to report diagnosed COVID-19 cases to the public health center in their jurisdiction. Active epidemiological investigations have been underway since then. In the early phase of the first epidemic wave of COVID-19 in Osaka, lasting from February 17 to March 8, 2020, clusters relating to live entertainment events were reported in Osaka, resulting in 41 positive cases (Osaka Institute of Public Health et al., 2020). Containment of music event clusters in livehouses was achieved by detailed epidemiological investiga-

tions of cases and their contacts. Using analyses of early cases in Japan, the Japanese Ministry of Health, Labour, and Welfare (MHLW) found that most transmissions occurred through a small proportion of cases, often leading to clusters (i.e. superspreading events) (Nishiura et al., 2020). The MHLW therefore prioritized cluster investigation and backward contact tracing approaches to reduce the risk of transmissions (Jindai et al., 2020), and established the COVID-19 Cluster Response Taskforce on February 25, 2020 (Oshitani, 2020).

Well-implemented, fast, and effective contact tracing could offer important benefits in controlling and preventing outbreaks (Davis et al., 2021; Endo et al., 2021; Hellewell et al., 2020; Keeling et al., 2020; Kretzschmar et al., 2021). With regard to the effectiveness of contact tracing, a shorter 'reporting lag' – representing the time lag between symptom onset and a positive diagnosis/report – has a substantial impact in reducing onward transmissions (Baker et al., 2021; Hellewell et al., 2020; Kretzschmar et al., 2021, 2020). A longer lag contributes to a reduced probability of outbreak containment and an increased effective reproduction number. In Japan, a negative association between longer reporting lag and doubling time was reported using empirical data (Ogata and Tanaka, 2021). Keeping the reporting lag short plays an important role in preventing the transmission of diseases, and

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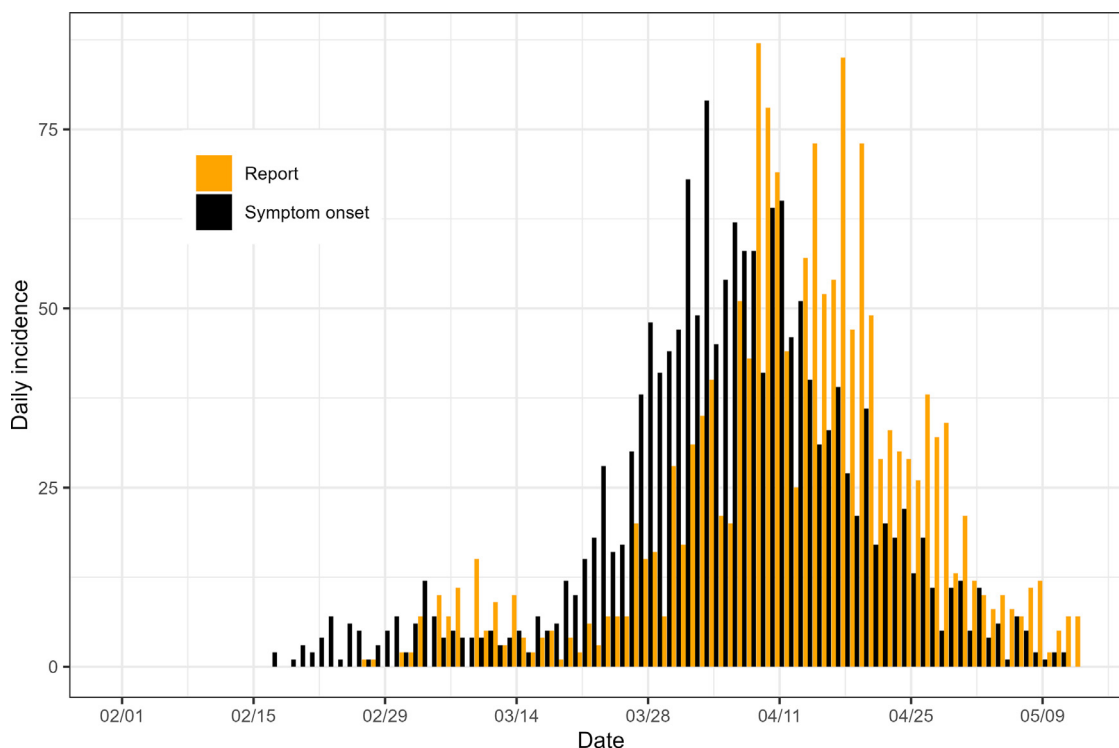


Figure 1. Epidemic curves between February 1 and May 13, 2020 for the study population by date of symptom onset (black) and reporting (orange)

therefore identifying and understanding factors that influence reporting lag is crucial.

Cobre et al. (2020) investigated risk factors associated with delays in diagnosis, and found that male sex and living in low social development index areas (i.e. relating to economic, health, and educational levels) were risk factors for delays. In Japan, Ogata and Tanaka (2020) reported that cases with an unknown transmission link (i.e. the source from whom the individual had been infected) were associated with a longer reporting lag. However, the sample size used for data analysis was limited, since their study examined only a very early stage of the first wave in Japan. In addition, those results might have been influenced by regional situations, because measures enacted against this unprecedented pandemic varied among regions and countries from the beginning of the pandemic.

Our study was therefore conducted to investigate risk factors associated with reporting lag, using active epidemiological surveillance data from all symptomatic cases reported in Osaka Prefecture during the first wave of the COVID-19 epidemic (February 1–May 13, 2020). Another objective of this study was to gain an overview of experiences from Osaka Prefecture, and to provide evidence to support the control of future emerging diseases.

2. Methods

A cross-sectional study was conducted to identify risk factors for increased lag time between date of symptom onset and reporting.

2.1. Data source

Between February 1 and May 13, 2020, 1765 positive PCR tests for SARS-CoV-2 were reported in Osaka Prefecture. For these reported cases, positive epidemiological surveillance was conducted by the public health centers in Osaka Prefecture, and detailed information was collected. Among these cases, 1657 had information available on symptom onset date, 96 were asymptomatic, and 12 were unable to provide a date

of symptom onset. The 1657 cases for whom date of symptom onset was available were used for this analysis.

The following factors were analyzed: date of symptom onset; date of report; age; sex; transmission link; residential area; history of visiting a nightlife district; employment as a healthcare worker; severe case; underlying disease (diabetes, heart disease, hypertension, immunodeficiency, kidney disease, cancer, or asthma); number of newly infected cases in Osaka on the reporting date; total number of PCR tests for SARS-CoV-2 per day; and number of days since February 1, 2020 (the date on which the first case was reported in Osaka). Visiting a nightlife district, such as using host/hostess clubs, restaurants, and bars – i.e. closed environments and/or places where meals are consumed – is considered to be high-infection-risk behavior (Takaya et al., 2020; Liu et al., 2020; Nishiura et al., 2020). Daytime visits to these venues were also included, because some places are open during the day. Severity was defined at the time of reporting, and a severe condition was defined as requiring the use of critical care beds or any of an intensive care unit, ventilator, or extracorporeal membrane oxygenation (Osaka Prefecture, 2020).

Residential area information was missing for 24 cases from the study population of 1,657 cases. These 24 cases were therefore excluded from analyses.

2.2. Statistical analysis

2.2.1. Descriptive epidemiology

Mean, median, and interquartile ranges for reporting lag were calculated, and stratified by categories for the following factors: age (< 10, 10s, 20s, 30s, 40s, 50s, 60s, 70s, and ≥ 80 years); transmission link (known/unknown); incidence rate in residential area (incidence rate levels 1–4, see below); history of visiting a nightlife district (yes/no); healthcare worker (yes/no); severe case (yes/no); and underlying disease conditions (yes/no). The incidence rate was calculated for each municipality as the number of positive PCR tests for the study period divided by the population. Interquartile ranges for incidence rate were assigned as four levels (low, middle, high, severe). The percentiles for the incidence rate per 100,000 were: 0th percentile, 4.92; 25th percentile,

9.26; 50th percentile, 16.00; 75th percentile, 19.11; 100th percentile, 30.47.

2.2.2. Risk factor analysis for time between date of symptom onset and reporting

To estimate the effects of factors (exposures) on reporting lag, multivariable regression models were built for each exposure variable to control for confounding effects, using generalized linear models. The following factors were set as exposure variables in the model that may have influenced reporting lag, and were considered biologically plausible: a) age; b) sex; c) transmission link; d) incidence rate in residential area; e) history of visiting a nightlife district; f) healthcare worker; g) severe case; h) underlying diabetes, heart disease, hypertension, immunodeficiency, kidney disease, cancer, or asthma; i) number of newly infected cases in Osaka; j) total number of PCR tests for SARS-CoV-2 per day on the reporting date; and k) number of days since February 1, 2020. The reporting lag was set as an outcome variable and it was assumed that a gamma distribution would be followed, referring to Akaike's information criterion (AIC) values (Cobre et al., 2021) when fitted to Gaussian, Poisson, gamma, Weibull, and log-normal distributions (i.e. the AIC was lowest when fitting a gamma distribution). The calculated AICs are shown in Supplementary Table 1. Correlation coefficients among independent variables were calculated to check for multicollinearity (Dohoo et al., 2014). Covariates included in the model to control for confounding effects were selected based on the backdoor criteria (Morgan and Winship, 2015) by drawing causal diagrams using DAGitty (Textor, 2020) (Supplementary Figure 1).

3. Results

3.1. Descriptive epidemiology

The median reporting lag for the target population (1657 cases with information on date of symptom onset) was 8 days (mean: 8.6 days; interquartile range: 6–8 days). Reporting lag stratified by each factor is shown in Table 1. Age-dependent mean reporting lag was longest for individuals in their 30s (9.1 days) and shortest for individuals in their 10s (7.1 days). The reporting lags for individuals with unknown transmission link, living in a high-incidence-rate area for COVID-19, or with a history of visiting a nightlife district were longer than that for individuals without those factors. Healthcare workers, severe cases, and cases with an underlying comorbidity of heart disease, hypertension, immunodeficiency, kidney disease, or cancer showed shorter reporting lags compared with individuals without those factors. No significant differences were observed for the underlying disease condition of diabetes or for sex. Epidemic curves by date of symptom onset and by date of reporting for the study population (1657 symptomatic cases) are shown in Figure 1.

3.2. Risk factors for time between symptom onset and reporting

The estimated effects of exposures are shown in Table 2. No pairs of independent variables showed correlation coefficients > 0.9. The reporting lag for individuals in their 30s was 1.13 (95% CI 1.02–1.25) times longer than that for individuals ≥ 80 years. The reporting lag for those with a known transmission link was 0.84 (95% CI 0.81–0.90) times shorter than that for those with an unknown transmission link. Cases who lived in a high-COVID-19 incidence rate area showed a longer reporting lag (adjusted relative reporting lag 1.12; 95% CI 1.01–1.24) than cases who lived in an area with a low incidence rate. Cases who had a history of visiting a nightlife district showed a longer reporting lag (adjusted relative reporting lag 1.18; 95% CI 1.09–1.29) than cases who did not. Healthcare workers (adjusted relative reporting lag 0.79; 95% CI 0.73–0.85) and cases with immunodeficiency (adjusted relative reporting lag 0.70; 95% CI 0.55–0.90) had shorter reporting lags

Table 1
Reporting lag stratified by investigated factors

Factor	Reporting lag			n
	Median	Mean	Interquartile range	
Age (years)				
≥ 80	7	8.1	5–11	138
70s	8	8.5	5–11	165
60s	8	8.3	5–11	156
50s	8	8.6	6–11	250
40s	8	8.5	5–11	280
30s	8	9.1	6–11	269
20s	8	8.7	6–11	342
10s	7	7.1	5–9	32
< 10	6	7.4	4–8	25
Sex				
Female	8	8.6	5–11	738
Male	8	8.6	6–11	919
Transmission link				
Unknown	9	9.4	6–12	794
Known	7	7.8	5–10	863
Residential area incidence rate ^a				
Low	7	7.9	5–10	106
Middle	8	8.2	5–10	237
High	7	8.4	6–10	237
Severe	8	8.8	6–11	1053
Visiting a nightlife district ^b				
No	8	8.4	5–11	1487
Yes	9	10.1	7–12	170
Healthcare worker				
No	8	8.8	6–11	1460
Yes	7	7.2	5–9	197
Severe case				
No	8	8.6	6–11	1535
Yes	7	7.9	5–10	122
Diabetes				
No	8	8.6	5–11	1530
Yes	8	8.7	6–11	127
Heart disease				
No	8	8.6	6–11	1579
Yes	7	7.6	4–9	78
Hypertonia				
No	8	8.6	6–11	1626
Yes	7	7.3	4–9	31
Immunodeficiency				
No	8	8.6	6–11	1640
Yes	5	6.1	3–7	17
Kidney disease				
No	8	8.6	6–11	1625
Yes	6	7.1	4–10	32
Cancer				
No	8	8.6	6–11	1615
Yes	7	7.8	4–10	42
Asthma				
No	8	8.5	6–11	1606
Yes	8	9.6	5.5–14	51

^a Incidence rate was calculated for each municipality, and interquartile levels for incidence rate were assigned as low, middle, high, or severe. ^b History of visiting a nightlife district.

than individuals without those factors. The number of cases newly reported as positive PCR tests was negatively associated with reporting lag (adjusted relative reporting lag, 0.998; 95% CI 0.997–0.999). The full results for models, including covariates adjusted in the models, are shown in Supplementary Table 2 (i.e. the results for exposure variables only are shown in Table 2).

4. Discussion

For this study, the reporting lag was described using active epidemiological surveillance data for all symptomatic cases reported in Osaka Prefecture during the first wave of the COVID-19 epidemic (February 1–May 13, 2020). Factors associated with reporting lag were also quantitatively assessed in the first wave of the COVID-19 epidemic in Osaka,

Table 2
Estimated effects of exposures on time between symptom onset and report: results from multivariable analyses

Factor	Relative reporting lag ^a (adjusted reporting lag for reference, days)	95% CI – lower	95% CI – upper	p-value	n
Age (years)					1657
≥ 80	Reference (8.10)	(7.45)	(8.84)		
70s	1.05	0.93	1.17	0.448	
60s	1.03	0.92	1.16	0.628	
50s	1.07	0.96	1.18	0.243	
40s	1.05	0.95	1.17	0.331	
30s	1.13	1.02	1.25	0.025	
20s	1.08	0.97	1.19	0.153	
10s	0.88	0.72	1.07	0.186	
< 10	0.91	0.73	1.14	0.389	
Sex					1657
Female	(8.59)	(8.28)	(8.91)		
Male	1.00	0.95	1.05	0.937	
Transmission link					1633
Unknown	Reference (8.50)	(5.80)	(8.75)		
Known	0.84	0.81	0.90	< 0.001	
Residential area incidence rate ^b					1633
Low	Reference (7.38)	(6.46)	(8.46)		
Middle	1.04	0.92	1.17	0.510	
High	1.05	0.94	1.19	0.372	
Severe	1.12	1.01	1.24	0.036	
Visiting a nightlife district ^c					1633
No	Reference (7.51)	(6.57)	(8.60)		
Yes	1.18	1.09	1.29	< 0.001	
Healthcare worker					1633
No	Reference (7.51)	(6.58)	(8.59)		
Yes	0.79	0.73	0.85	< 0.001	
Severe case					1657
No	Reference (8.30)	(7.57)	(9.14)		
Yes	0.92	0.84	1.02	0.119	
Diabetes					1657
No	Reference (8.05)	(7.35)	(8.83)		
Yes	1.04	0.94	1.15	0.425	
Heart disease					1657
No	Reference (8.28)	(7.56)	(9.08)		
Yes	0.89	0.79	1.01	0.061	
Hypertonia					1657
No	Reference (8.17)	(7.48)	(8.94)		
Yes	0.86	0.72	1.04	0.105	
Immunodeficiency					1657
No	Reference (8.13)	(7.45)	(8.90)		
Yes	0.70	0.55	0.90	0.004	
Kidney disease					1657
No	Reference (7.37)	(6.06)	(9.08)		
Yes	0.83	0.70	1.01	0.051	
Cancer					1657
No	Reference (7.37)	(6.06)	(9.09)		
Yes	0.93	0.79	1.09	0.348	
Asthma					1657
No	Reference (7.37)	(6.06)	(9.08)		
Yes	1.11	0.97	1.29	0.136	
Number of newly reported cases ^d					1657
Intercept	Reference (7.60)	(6.66)	(8.69)		
Slope	0.998	0.997	0.999	0.001	
Total number of PCR tests for SARS-CoV-2 ^e					1657
Intercept	(7.96)	(6.84)	(9.27)		
Slope	1.0001	0.9998	1.0003	0.518	
Number of days since February 1, 2020 ^f					1657
Intercept	Reference (7.80)	(6.80)	(8.95)		
Slope	1.0013	0.9995	1.0030	0.178	

^a Reporting lag: time between symptom onset and report. ^b Interquartile levels of incidence rate were assigned as low, middle, high, or severe. ^c History of visiting a nightlife district. ^d Number of newly reported cases as positive PCR tests in Osaka on the date that a case was reported. ^e Total number of PCR tests for SARS-CoV-2 in Osaka per day on the date a case was reported. ^f February 1, 2020 was the date on which the first COVID-19 case was reported in Osaka.

Japan in order to provide an overview of our experiences. Cases in their 30s had a longer reporting lag than cases ≥ 80 years old. Cases who lived in an area with a high COVID-19 incidence rate had a longer reporting lag than cases who lived in an area with a low incidence rate. Cases who had a history of visiting a nightlife district had a longer re-

porting lag than cases who did not. The limited contact tracing and testing capacity could be one reason for a longer reporting lag. In the first wave of the COVID-19 epidemic in Japan, the limited capacity for testing meant that testing was prioritized for elderly and high-risk populations (e.g. individuals with comorbidities) (MHLW, 2020b). The lim-

ited capacity for contact tracing and testing might also have contributed to the longer time lag between symptom onset and testing for populations with high COVID-19 incidence, such as people in their 30s (16% of all cases observed), those in high-incidence residential areas, and those who visited nightlife districts. Our results revealed that cases for whom the transmission link was known had a shorter reporting lag than those for whom the transmission link was unknown. Generally, transmission links were detected by contact tracing. Since efficient contact tracing (including shorter reporting lag) acts to reduce COVID-19 transmissions (Baker et al., 2021; Hellewell et al., 2020; Kretzschmar et al., 2021, 2020), our study revealed that finding transmission links by contact tracing in Osaka Prefecture contributed to the control of the COVID-19 epidemic in Osaka. To shorten the reporting lag, our results suggested the following as crucial goals: a) identifying newly infected cases (regarding time, place, and person) as soon as possible by testing and contact tracing; b) increasing testing capacity for all age groups (specifically for those in their 30s) and for those with a history of visiting high-infection-risk areas (nightlife districts) or living in a high-incidence-rate residential area.

Healthcare workers and cases with immunodeficiency had shorter reporting lags than cases without those factors. Although not statistically significant, cases with other comorbidities of the heart and kidney also tended to show a shorter reporting lag ($p < 0.1$). Infected healthcare workers were quickly identified as not transmitting the virus to others. Cases with immunodeficiency, heart, or kidney diseases, which represent high-risk factors for COVID-19 (Dessie and Zewotir, 2021; Williamson et al., 2020), were detected in a shorter time after symptom onset than others, indicating that high-risk groups were efficiently tested to avoid serious outcomes.

The number of newly reported cases was negatively associated with reporting lag. This result might indicate that detecting positive cases by contact tracing, which resulted in an increased number of reported cases, contributed to reducing reporting lag during the study period.

The results of this study must be viewed in consideration of several limitations. First, the estimated effects for reporting lag were not adjusted by possible confounders, such as accessibility of medical facilities and public health centers, or educational or income status. Second, underlying comorbidities other than immunodeficiency did not show significant results. The small sample sizes of groups with such comorbidities might have contributed to these results (diabetes, $n = 134$ cases; heart disease, $n = 84$; hypertension, $n = 31$; immunodeficiency, $n = 17$; kidney disease, $n = 33$; cancer, $n = 44$; asthma, $n = 54$). Third, our study did not assess how transmission settings (such as household, office, or welfare facility) influenced reporting lag among cases in which the transmission source was known. Finally, because the study period represented the very early phase of the pandemic, the laboratory testing system was not well prepared and the number of PCR tests was limited. The MHLW indicated that elderly individuals and those with an underlying comorbidity should consult public health centers earlier (MHLW, 2020b). Healthcare workers, hospitalized patients, the elderly, and workers in facilities for the elderly had higher priority for testing, based on decisions by public health centers. The capacity for testing varied among regions (according to expert opinions from the director of the regional public health center), and might have affected the incidence rates used for analysis.

In conclusion, risk factors associated with reporting lag in the early phase of the COVID-19 pandemic were quantitatively identified. Challenges that should be addressed to further minimize reporting lag were also found. The evidence from this study may provide lessons for controlling emerging diseases in Japan in the future.

Author contributions

TM: conceptualization, formal analysis, funding acquisition, investigation, methodology, visualization, writing – original draft; KK: data curation, investigation, methodology, validation, writing – review and

editing; NI: investigation, interpretation, supervision, validation, writing – review and editing; KM: investigation, interpretation, supervision, validation, writing – review and editing

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Conflicts of interest

None

Ethical approval

This study was approved by the ethics committee of Osaka Institute of Public Health (application no. 2107-05-2). Personally identifiable information was not included in the dataset analyzed.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.ijregi.2022.06.002](https://doi.org/10.1016/j.ijregi.2022.06.002).

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