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Correlation between times to SARS-CoV-2 symptom onset and secondary transmission undermines epidemic control efforts

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ABSTRACT

Severe acute respiratory coronavirus 2 (SARS-CoV-2) infections have been associated with substantial pre-symptomatic transmission, which occurs when the generation interval—the time between infection of an individual with a pathogen and transmission of the pathogen to another individual—is shorter than the incubation period—the time between infection and symptom onset. We collected a dataset of 257 SARS-CoV-2 transmission pairs in Japan during 2020 and jointly estimated the mean incubation period of infectors (4.8 days, 95 % CrI: 4.4–5.1 days), mean generation interval to when they infect others (4.3 days, 95 % credible interval [CrI]: 4.0–4.7 days), and the correlation (Kendall's tau: 0.5, 95 % CrI: 0.4–0.6) between these two epidemiological parameters. Our finding of a positive correlation and mean generation interval shorter than the mean infector incubation period indicates ample infectiousness before symptom onset and suggests that reliance on isolation of symptomatic COVID-19 cases as a focal point of control efforts is insufficient to address the challenges posed by SARS-CoV-2 transmission dynamics.

1. Introduction

The generation interval and incubation period of an infectious disease are key epidemiological parameters used to inform outbreak response. The former represents the time between when a given host (an infector) is infected with a pathogen and when they transmit that pathogen to another host (an infectee). In contrast, the incubation period represents the time between infection and development of symptoms, and can provide some indication of how long an infection may remain unnoticed in an individual. For emerging diseases, estimates of the incubation period are used to determine quarantine periods (Lauer et al., 2020; Linton et al., 2020; Nishiura et al., 2009) while estimates of the generation interval indicate the speed of epidemic growth. Together, they can provide insight into the intrinsic dynamics of infection and characterize the effectiveness of public health interventions on control of pathogen spread.

At the beginning of the coronavirus 2019 (COVID-19) pandemic, estimates of the mean incubation period of severe acute respiratory disease coronavirus 2 (SARS-CoV-2)—the pathogen causing COVID-19—were rapidly produced (Backer et al., 2020; Lauer et al., 2020; Li et al., 2020; Linton et al., 2020) and estimates of the mean serial interval, which is the time between symptom onset in an infector and symptom onset in a person they infect, quickly followed (Ferretti et al., 2020; Ganyani et al., 2020; Nishiura et al., 2020b; Tindale et al., 2020). However, due to difficulty in ascertaining exposure times of cases and directionality of transmission between epidemiologically linked cases, few attempts were made to estimate the generation interval, with the serial interval (time from onset of symptoms for infector to onset of symptoms for infectee) often used as a proxy for the generation interval when estimating epidemiological quantities (Deng et al., 2020; Ferretti et al., 2020; Ganyani et al., 2020; Li et al., 2021; Tindale et al., 2020). Unfortunately, use of the serial interval as a proxy for the generation time can lead to biased estimates of other epidemiological parameters—such as the effective reproduction number, which represents the average number of persons infected by a single infector in the presence of interventions—due to factors such as differences in their variances, the presence of asymptomatic infections, and the ability for the serial interval to have negative values—i.e. infectee symptom onset preceding infector symptom onset (Ganyani et al., 2020; Griffin et al., 2020; Knight and Mishra, 2020; Park et al., 2021; Torneri et al., 2021).

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The average length of the generation interval for a pathogen depends on many factors; for example, the ratio of infected to susceptible persons among contacts, or the behavior of infected persons (Nishiura, 2010). Actions such as self-isolation after symptom onset can shorten generation intervals by limiting the opportunity for infected individuals to infect others during their early symptomatic period. However, if an infected person can transmit the pathogen before symptom onset, then isolation of symptomatic persons alone is insufficient to control the spread (Fraser et al., 2004). For pathogens such as SARS-CoV-2, interventions targeting nonsymptomatic cases is vital due to the existence of asymptomatic and presymptomatic transmission (D. He et al., 2020; Lovell-Read et al., 2021; Nakajo and Nishiura, 2021; Tindale et al., 2020).

Frequently, estimates of the generation interval of SARS-CoV-2 have been derived from the serial interval and formulated following an implicit assumption that the incubation period and generation interval are independent (Lehtinen et al., 2021). However, correlation between the generation interval and incubation period of SARS-CoV-2 was shown to be biologically plausible, as evidenced by occurrence of the peak viral load of SARS-CoV-2 around the time of symptom onset (X. He et al., 2020). Studies early in the pandemic that considered such a correlation did not attempt to directly estimate it (Bushman et al., 2021), though a recent study based on transmission pairs with infectors who had symptom onset on or prior to January 17, 2020 found a correlation of 0.75 (Sender et al., 2022). Serial interval-based generation interval estimation also lacks consideration for asymptomatic infectors (Gandhi et al., 2020; Mizumoto et al., 2020; Nakajo and Nishiura, 2021), and cannot assess whether generation intervals for asymptomatic infectors would be similar to or different from those of their symptomatic counterparts.

In this study, we provide direct evidence of the correlation between the incubation period and generation interval of SARS-CoV-2 through joint bivariate estimation of the two parameters using transmission pairs identified in Japan in 2020. We also assessed whether either interval or their correlation varied based on demographic and epidemiological characteristics, as well as estimated the mean generation interval from a group of transmission pairs with asymptomatic infectors.

2. Results

2.1. Characteristics of transmission pairs

Information on timing of exposure and onset for infectors as well as contact between infectors and infectees was obtained for 286 transmission pairs of confirmed cases reported in Japan during 2020, of which 257 pairs had symptom onset available for the infector. For the other 29 pairs the infectors were asymptomatic at time of report. Of the 257 pairs with symptomatic infectors, 49 (19.2 %) had single dates reported for both infector exposure and contact between infector and infectee. Among the remaining 208 pairs with coarse dates of exposure, after cleaning the data (see Supplementary Methods) the median of the range of possible dates of exposure for infectors was 3 days (IQR: 0–11

Table 1
Characteristics of COVID-19 transmission pairs in Japan, 2020.

Subgroup	Role	Characteristics	Coarse dates of exposure† (%)	Single dates of exposure‡ (%)	Asymptomatic infectors (%)
		All	257 pairs	49 pairs	29 pairs
Age	Infector	Under 30 years	65 (25.3 %)	11 (22.4 %)	6 (20.7 %)
		30–59 years	129 (50.2 %)	32 (65.3 %)	15 (51.7 %)
		60 + years	57 (22.2 %)	6 (12.2 %)	7 (24.1 %)
		Not reported	6 (2.3 %)	–	1 (3.4 %)
	Infectee	Under 30 years	69 (26.8 %)	17 (34.7 %)	9 (31.0 %)
		30–59 years	114 (44.4 %)	19 (38.8 %)	10 (34.5 %)
		60 + years	67 (26.1 %)	13 (26.5 %)	9 (31.0 %)
		Not reported	7 (2.7 %)	–	1 (3.4 %)
Sex	Infector	Female	79 (30.7 %)	17 (34.7 %)	12 (41.4 %)
		Male	177 (68.9 %)	32 (65.3 %)	16 (55.2 %)
		Not reported	1 (0.4 %)	–	1 (3.4 %)
	Infectee	Female	131 (51.0 %)	22 (44.9 %)	16 (55.2 %)
		Male	125 (48.6 %)	27 (55.1 %)	12 (41.4 %)
		Not reported	1 (0.4 %)	–	1 (3.4 %)
Transmission setting	Infector	Household	4 (1.6 %)	0 (0.0 %)	0 (0.0 %)
		Social	153 (59.5 %)	48 (98.0 %)	25 (86.2 %)
		Community	100 (38.9 %)	1 (2.0 %)	4 (13.8 %)
	Infectee	Household	109 (42.4 %)	2 (4.1 %)	11 (37.9 %)
		Social interaction	113 (44.0 %)	38 (77.6 %)	15 (51.7 %)
		Community	35 (13.6 %)	9 (18.4 %)	3 (10.3 %)
Epidemic wave		Wave 1	86 (33.5 %)	14 (28.6 %)	2 (6.9 %)
		Wave 2	95 (37.0 %)	16 (32.7 %)	13 (44.8 %)
		Wave 3	76 (29.6 %)	19 (38.8 %)	14 (48.3 %)
Basis for selection		Cluster	138 (53.7 %)	29 (59.2 %)	24 (82.8 %)
		Contact pattern	54 (21.0 %)	19 (38.8 %)	4 (13.8 %)
		Domestic travel	43 (16.7 %)	1 (2.0 %)	1 (3.4 %)
		Import	22 (8.6 %)	–	–
Region§		Hokkaido & Tohoku	35 (13.6 %)	6 (12.2 %)	2 (6.9 %)
		Kanto	31 (12.1 %)	4 (8.2 %)	0 (0.0 %)
		Chubu	73 (28.4 %)	12 (24.5 %)	11 (37.9 %)
		Kinki	38 (14.8 %)	6 (12.2 %)	3 (10.3 %)
		Chugoku & Shikoku	34 (13.2 %)	6 (12.2 %)	6 (20.7 %)
		Kyushu & Okinawa	46 (17.9 %)	15 (30.6 %)	7 (24.1 %)

†Dataset using intervals of exposure and/or contact between infector and infectee; only includes infectors with reported symptom onset; includes pairs with exact dates of exposure and contact. ‡Subset of the coarse dates of exposure dataset that is limited to pairs where infector exposure and infector-infectee contact were limited to a single date. "Hokkaido & Tohoku" includes Hokkaido, Aomori, Iwate, Miyagi, Akita, Yamagata, and Fukushima prefectures. "Kanto" includes Ibaraki, Tochigi, Gunma, Saitama, Chiba, Tokyo, and Kanagawa prefectures. "Chubu" includes Niigata, Toyama, Ishikawa, Fukui, Yamanashi, Nagano, Gifu, Shizuoka, and Aichi prefectures. "Kinki" includes Mie, Shiga, Kyoto, Osaka, Hyogo, Nara, and Wakayama prefectures. "Chugoku & Shikoku" include Tottori, Shimane, Hiroshima, Yamaguchi, Tokushima, Kagawa, Ehime, and Kochi prefectures. "Kyushu & Okinawa" include Fukuoka, Saga, Nagasaki, Kumamoto, Oita, Miyazaki, Kagoshima, and Okinawa prefectures.

days), and the median of the range of possible dates of contact between infector and infectee was 5 days (IQR: 0–10 days). Characteristics of the pairs in each dataset are shown in Table 1, while S1 Fig. provides insight into the relationship between the empirical generation intervals, serial intervals, and incubation periods associated with these cases.

For the dataset of 257 pairs with symptomatic infectors, most infectors (50.2 %) and infectees (44.4 %) were between 30 and 59 years of age. There were fewer female infectors (30.7 %) detected compared to female infectees (51.0 %). Age and sex distributions of infectors and infectees are shown in S2 Fig. Pairs were relatively evenly distributed between the three pandemic waves that occurred in 2020. Most pairs (53.7 %) were linked to a cluster—an aggregation of cases with a common exposure, while other pairs were identified by having contact patterns indicative of directionality of transmission (21.0 %), the infector had travel to another prefecture before onset (16.7 %), or the infector was an imported case or otherwise linked to an imported case (8.6 %). Given that it was easier to determine the directionality of transmission within pairs and obtain information on timing of exposure if the infector was linked to a cluster or had travel history, our dataset includes only a handful of infectors (1.6 %) with household exposure. In contrast, nearly half (42.4 %) of infectees were household/family members of their infectors. The single-date (49 pairs) and asymptomatic infector (29 pairs) datasets were similarly structured in terms of age and sex, though only one asymptomatic infector was detected during the first wave.

2.2. Joint estimates of the generation interval and incubation period

The jointly estimated mean generation interval ranged between 3.7 and 5.1 days, depending on the dataset used in estimation, with the mean for the overall dataset estimated at 4.3 days (95 % CrI: 4.0–4.7 days) (Table 2). The estimated generation interval for the dataset of asymptomatic infectors was longer than for the overall dataset, at 4.6 days (3.9–5.5 days), resulting in a ratio of asymptomatic-to-symptomatic generation intervals of 1.1 The jointly estimated mean incubation period was consistently longer than the generation interval, ranging from 4.4 to 5.7 days, and estimated at 4.8 days (95 % CrI: 4.4–5.1 days) for the overall dataset, providing evidence of presymptomatic transmission. The prior and posterior distributions of the generation interval and incubation period are shown in S3 Fig, and the

Table 2
Joint estimates of the generation interval and incubation period of COVID-19 cases by subgroup.

				Generation interval			Incubation period			
Category	Subgroups	N	Copula	Distribution	Mean (95% CrI)	SD (95% CrI)	Distribution	Mean (95% CrI)	SD (95% CrI)	Kendall's tau (95% CrI)
Exact data	All cases	49	Clayton	Weibull	4.38 (3.88, 4.98)	2.10 (1.70, 2.79)	Lognormal	4.91 (4.34, 5.60)	2.66 (2.18, 3.33)	0.61 (0.46, 0.68)
All data*	All cases	257	Clayton	Weibull	4.34 (3.98, 4.74)	2.31 (2.00, 2.81)	Lognormal	4.75 (4.42, 5.11)	2.57 (2.25, 2.98)	0.54 (0.44, 0.63)
Infector age	Under 30 years	65	Clayton	Lognormal	4.51 (3.95, 5.13)	2.15 (1.68, 2.89)	Lognormal	4.67 (4.06, 5.36)	2.60 (2.12, 3.27)	0.50 (0.23, 0.65)
	30–59 years	129	Gumbel	Gamma	4.43 (3.97, 4.94)	2.43 (2.01, 3.00)	Lognormal	5.10 (4.63, 5.62)	2.87 (2.45, 3.44)	0.60 (0.48, 0.68)
	60 + years	57	Gumbel	Gamma	4.58 (3.87, 5.37)	2.68 (1.98, 3.68)	Lognormal	4.59 (3.91, 5.37)	2.89 (2.31, 3.74)	0.50 (0.28, 0.65)
Infectee age	Under 30 years	69	Clayton	Gamma	4.57 (4.02, 5.20)	2.39 (1.90, 3.18)	Lognormal	4.72 (4.15, 5.38)	2.62 (2.15, 3.26)	0.56 (0.37, 0.68)
	30–59 years	114	Gumbel	Weibull	4.66 (4.13, 5.22)	2.59 (2.07, 3.25)	Lognormal	5.26 (4.72, 5.85)	3.12 (2.62, 3.78)	0.58 (0.47, 0.68)
	60 + years	67	Gumbel	Lognormal	4.10 (3.48, 4.83)	2.08 (1.49, 3.01)	Lognormal	4.45 (3.84, 5.15)	2.59 (2.10, 3.32)	0.42 (0.14, 0.61)
Infector sex	Female	79	Gumbel	Gamma	3.72 (3.20, 4.35)	2.09 (1.57, 2.92)	Lognormal	4.38 (3.82, 5.02)	2.59 (2.10, 3.26)	0.54 (0.36, 0.66)
	Male	177	Clayton	Weibull	4.71 (4.29, 5.20)	2.36 (2.00, 2.90)	Lognormal	5.00 (4.60, 5.46)	2.73 (2.35, 3.22)	0.52 (0.39, 0.63)
Infectee sex	Female	131	Clayton	Gamma	4.35 (3.82, 4.95)	2.50 (1.99, 3.28)	Lognormal	4.65 (4.20, 5.16)	2.60 (2.20, 3.15)	0.50 (0.33, 0.64)
	Male	125	Gumbel	Gamma	4.50 (4.05, 4.99)	2.28 (1.88, 2.87)	Lognormal	4.96 (4.48, 5.52)	2.88 (2.43, 3.48)	0.55 (0.43, 0.65)
Epidemic wave	Wave 1	109	Gumbel	Weibull	4.38 (3.74, 5.01)	1.99 (1.59, 2.58)	Lognormal	4.75 (4.21, 5.36)	2.93 (2.46, 3.63)	0.53 (0.31, 0.67)
	Wave 2	113	Clayton	Gamma	4.50 (4.04, 5.03)	2.50 (2.09, 3.13)	Lognormal	4.85 (4.39, 5.38)	2.55 (2.16, 3.07)	0.58 (0.47, 0.67)
	Wave 3	35	Gaussian	Gamma	4.52 (3.81, 5.32)	2.39 (1.74, 3.43)	Lognormal	4.98 (4.19, 5.87)	3.01 (2.38, 3.93)	0.57 (0.36, 0.68)
Transmission setting	Household	86	Gumbel	Weibull	5.09 (4.46, 5.77)	2.82 (2.25, 3.59)	Lognormal	5.13 (4.53, 5.79)	2.87 (2.38, 3.55)	0.55 (0.38, 0.67)
	Social contact	95	Gumbel	Weibull	3.84 (3.42, 4.33)	1.74 (1.38, 2.32)	Lognormal	4.53 (4.02, 5.12)	2.68 (2.22, 3.34)	0.55 (0.40, 0.66)
	Community	76	Clayton	Gamma	4.45 (3.87, 5.11)	2.36 (1.85, 3.20)	Lognormal	5.00 (4.40, 5.69)	2.93 (2.42, 3.68)	0.48 (0.29, 0.63)
Basis for selection	Cluster	138	Gumbel	Gamma	4.08 (3.62, 4.60)	2.17 (1.73, 2.81)	Lognormal	4.55 (4.14, 5.02)	2.50 (2.13, 2.99)	0.46 (0.29, 0.60)
	Contact pattern	54	Clayton	Weibull	4.62 (4.03, 5.30)	2.31 (1.82, 3.11)	Lognormal	5.12 (4.45, 5.90)	3.07 (2.48, 3.92)	0.59 (0.42, 0.68)
	Domestic travel	43	Clayton	Gamma	4.84 (4.12, 5.64)	2.64 (2.01, 3.62)	Lognormal	5.01 (4.22, 5.92)	3.02 (2.40, 3.93)	0.47 (0.23, 0.64)
	Import	22	Gaussian	Weibull	4.83 (3.91, 5.78)	2.33 (1.62, 3.50)	Lognormal	5.65 (4.60, 6.77)	3.49 (2.73, 4.55)	0.64 (0.37, 0.69)
Asymptomatic infectors		29	–	Gamma	4.62 (3.78, 5.61)	2.45 (1.78 3.59)	–	–	–	–

* Includes the 49 cases with exact dates of exposure (for infectors) and contact (between infector and infectee). The 257 pairs all include symptomatic infectors. CrI: credible interval. Wave 1 began 16 January 2020, wave 2 is assumed to have begun 1 June 2020, and wave 3 is assumed to have begun 1 October 2020.

contour plots of the jointly estimated generation interval and incubation period are shown in Fig. 1.

The generation interval and incubation period were positively correlated, with Kendall's tau ranging between 0.4 and 0.6 and estimated at 0.5 (95 % CrI: 0.4–0.6) for the overall dataset (Table 2). For the dataset with single dates of reported exposure and contact, the generation interval was estimated at 4.4 days (95 % CrI: 3.9–5.0 days) while the mean incubation period was estimated at 4.9 days (95 % CrI: 4.4–5.6 days). Kendall's tau was slightly higher than for the overall dataset, at 0.6 (95 % CrI: 0.5–0.7). Fig. 2 shows the estimated values for all subgroups.

The mean generation interval did not vary substantially between subgroups but was shortest for female infectors, at 3.7 days (95 % CrI: 3.2–4.4 days). It was also shorter for the second wave of the epidemic (3.8 days, 95 % CrI: 3.4–4.3 days) compared to the first wave (5.1 days, 95 % CrI: 4.5–5.8 days) (Kenah et al., 2008). However, the generation interval for the third wave was longer than that of the second wave—nearly as long as that of the first wave—at 4.5 days (95 % CrI: 3.9–5.1 days). Estimates of the incubation period varied less between subgroups, although the mean incubation period for pairs linked to importation from other countries (mostly from the first wave) was a bit longer than the overall estimate, at 5.7 days (95 % CrI: 4.6–6.8 days).

The Clayton copula—which emphasizes lower tail dependence—was the most frequently selected copula, although the Gumbel and Gaussian copulas were also selected for some subgroups. The Gumbel copula emphasizes upper tail dependence while the Gaussian copula does not consider tail dependence. The independence copula was never selected (Table 2). For the overall dataset, where the Clayton copula was selected, the lower tail dependence was 0.7 (95 % CrI: 0.6–0.8), indicating that infectors with an extremely short incubation period would be likely to quickly transmit the virus given contact with a susceptible person (see Supporting Materials). For the generation interval, the Weibull distribution was most often selected, although the gamma and lognormal distributions were selected for some subgroups. The lognormal distribution was the only distribution selected across all joint estimates of the incubation period. It is typically the best fit for respiratory disease incubation period data (Lessler et al., 2015) including COVID-19 data (McAloon et al., 2020).

2.3. Correlation, presymptomatic transmission, and control measures

We found that 63.2 % (95 % CI: 62.9–63.5 %) of pairs experienced presymptomatic transmission, defined as the generation interval being shorter than the incubation period, by simulating 10,000 transmission pairs from our fitted estimates of the generation interval, incubation period, and Kendall's tau (Table 2). Using the fitted estimates of the generation interval and the incubation period, we further varied Kendall's tau and show that as Kendall's tau approached zero (independence) the proportion of presymptomatic transmission reached a lower boundary of 54.2 % (95 % CI: 54.0–54.6 %). Conversely, as Kendall's tau approached 1 (complete dependence), the proportion of presymptomatic transmission increased to nearly 100 % (Fig. 3a), and the difference between symptom onset and transmission became so small that the two events mostly occurred on the same day (within 24 h, Fig. 3b), with only a small portion of presymptomatic transmission occurring outside of one day before or after symptom onset, and no symptomatic transmission occurring.

The average difference between the generation interval and incubation period across all data subsets and subgroups was 0.4 days, indicating a mean time from onset of symptoms to transmission of −0.4 days. The probability density function of the time from onset of symptoms to transmission fitted with a normal distribution based on simulated data with Kendall's tau varied between 0.2, 0.5, and 0.9, is shown in Fig. 3c. The mean was centered at −0.4 days, and lower correlation resulted in a larger standard deviation.

Using the same simulated dataset, Kendall's tau was varied against the fraction of transmission reduced by case isolation. Increasing Kendall's tau indicated greater difficulty in controlling transmission via isolation alone given the same level of reduction in transmission due to rapid isolation φ (Fig. 4). Given a basic reproduction number R_0 of 2.2 or 2.9 (Riou and Althaus, 2020), the effective R_0 (denoted R_0^E) failed to reduce below the epidemic threshold of 1 (Fig. 4b and c). Moreover, as Kendall's tau approaches 1 and the proportion of presymptomatic transmission (with a mean time from onset of symptoms to transmission of approximately 0) approaches 100 %, control through isolation alone becomes impossible, and there is no difference between R_0 and R_0^E. When case isolation does not occur promptly following onset (lower φ) the dependence between the generation interval and incubation period has less impact on the reduction of R_0^E. Improving the speed of case isolation following symptom onset (higher φ) will have the greatest

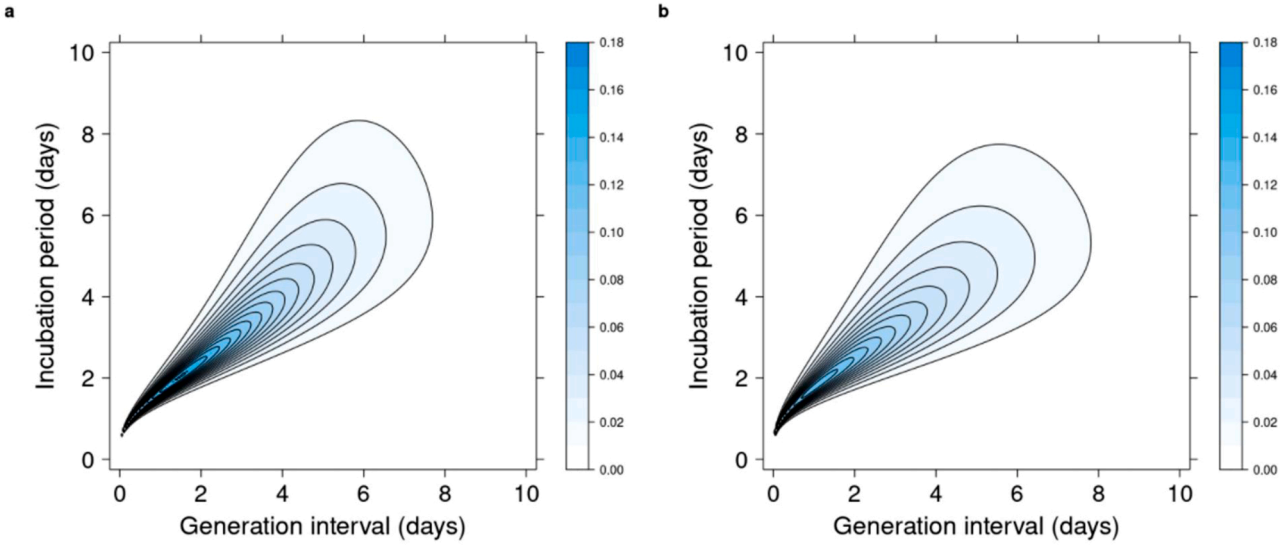

Fig. 1. Joint distribution of the generation interval and incubation period. Contour plots of the fitted distributions. For both a (the dataset of 49 transmission pairs with single dates of reported exposure) and b (the dataset of 257 transmission pairs that also includes pairs with more coarsely reported possible dates of exposure and contact) a Clayton copula with a Weibull marginal for the generation interval and lognormal marginal for the incubation period distribution was selected.

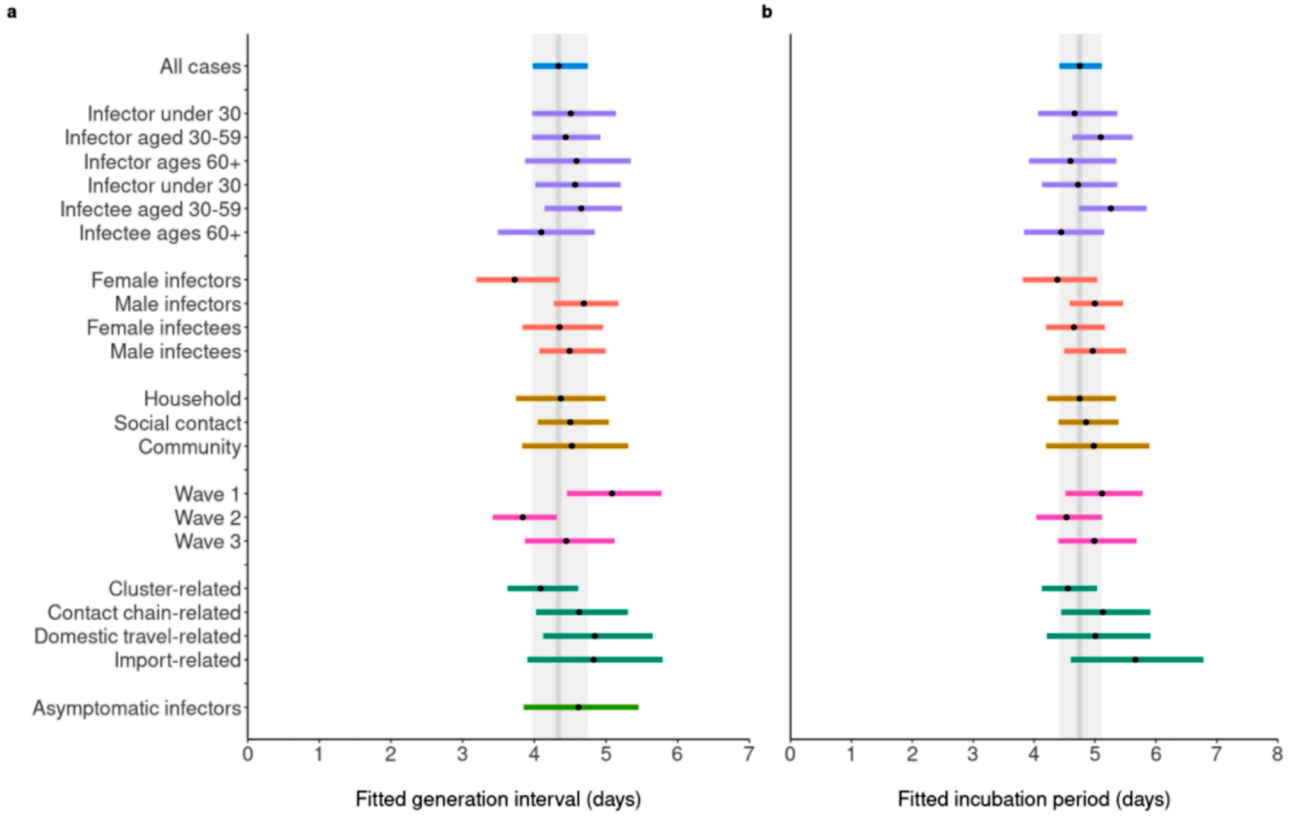

Fig. 2. Joint estimates of the generation interval and incubation period by stratum for COVID-19 transmission pairs from Japan. The joint distribution using best-fit Gaussian, Gumbel, or Clayton copula combined with gamma, lognormal, or Weibull distributions for the a, generation interval and b, incubation period are presented for the dataset of 257 transmission pairs that also includes pairs with more coarsely reported possible dates of exposure and contact. The points are point estimates for the means of each stratum, while the colored bars indicate the 95 % credible intervals. The gray bars show the overall point estimate and 95 % CrI for all cases in the background. The estimate for asymptomatic infectors was fitted to the generation interval alone, as infector incubation period could not be estimated.

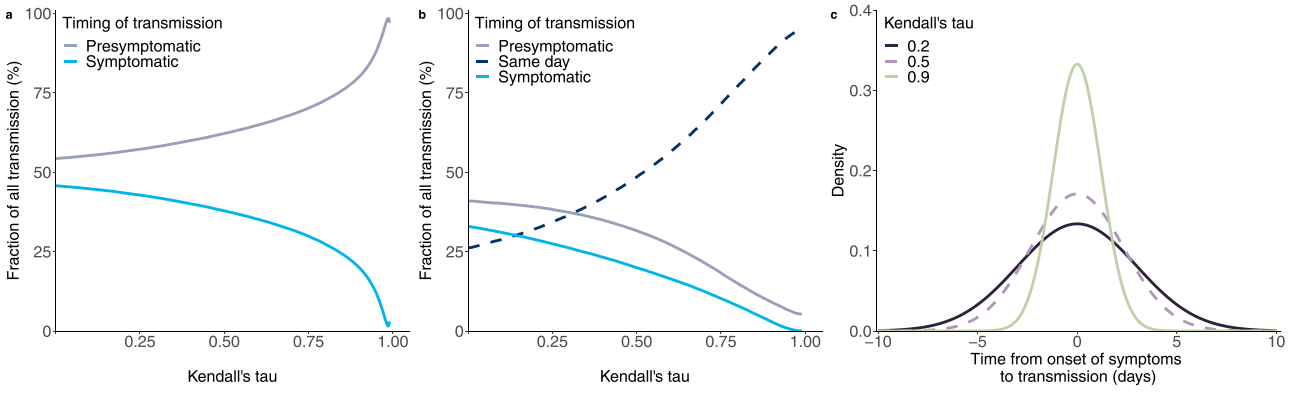

Fig. 3. Increased correlation leads to a predominance of presymptomatic transmission. From estimates made by simulating the generation interval (GI) and incubation period (IP) for 10,000 pairs using the fitted Clayton copula with Weibull (GI) and lognormal (IP) marginals: a, the proportion of transmission that was symptomatic or presymptomatic for various values of Kendall's tau; b, the proportion of transmission that was symptomatic, presymptomatic, or occurred on the same day (GI-IP $\in [-1, 1]$) for various values of Kendall's tau; c, the time from onset of symptoms to transmission (TOST), defined as GI-IP, fitted with a normal distribution.

impact on R_0^E, particularly for lower levels of correlation.

3. Discussion

The generation interval underpins many infectious disease models (Cori et al., 2013; Gostic et al., 2020), and here we provide insight into the generation interval of COVID-19 over time and across different characteristics of transmission pairs, providing one of the most comprehensive characterizations of the generation interval of wild-type SARS-CoV-2 to date. In addition, we quantitatively measured the relationship between the generation interval and incubation period of COVID-19, the lack of which was identified as a limiting factor in previous studies (Kremer et al., 2020; Lehtinen et al., 2021; Tindale et al., 2020). From transmission pairs identified using publicly available data reported in Japan during 2020 we found a positive correlation between the generation interval and incubation period with a Kendall's tau ranging from 0.4 to 0.6. The mean generation interval was consistently shorter than the mean incubation period when jointly estimated, with

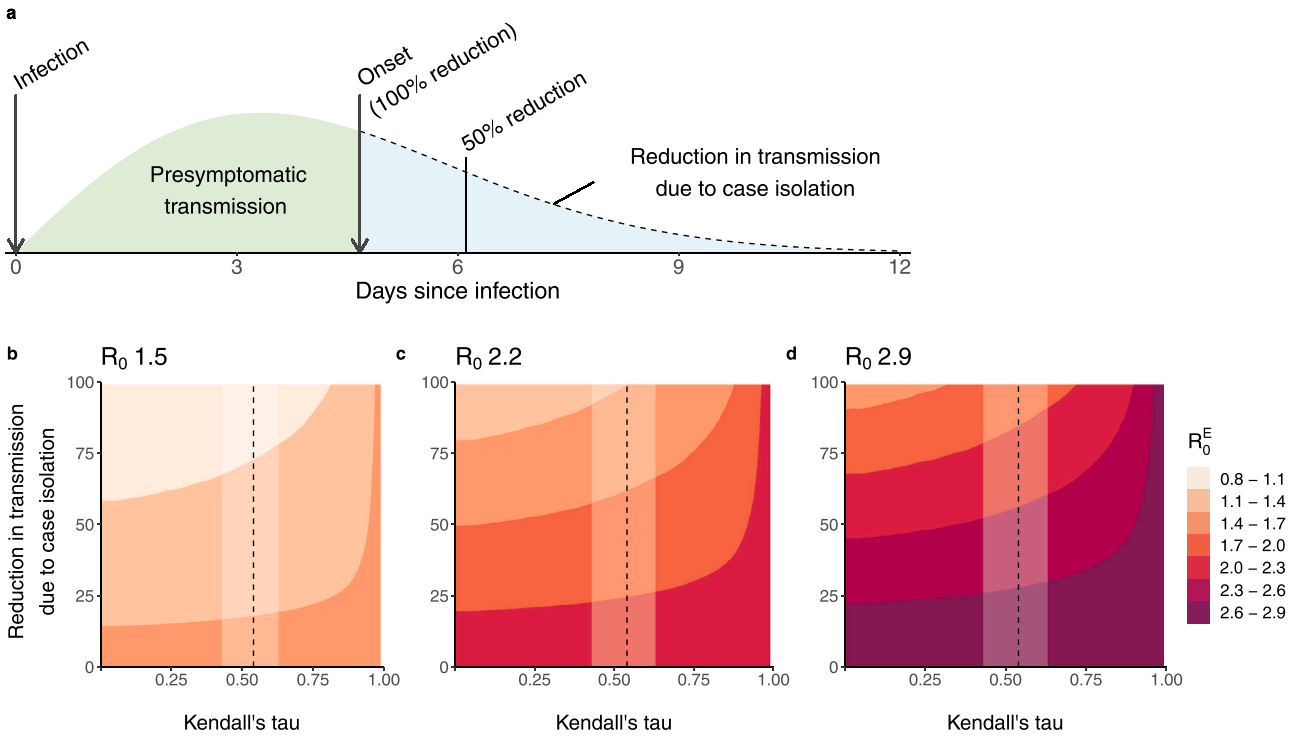

Fig. 4. Effect of stronger correlation between the generation interval and incubation period on effectiveness of isolation. The top figure, a, shows the fitted generation interval probability distribution function (4.2 days). The arrow dividing the green and blue sections indicates onset at 4.7 days (the mean incubation period). If case isolation occurs at onset this is equivalent to a 100 % reduction in possible transmission for symptomatic cases. Figures b, c, and d, show the effective basic reproduction number (R_0^E) as a function of this reduction in transmission as well as the level of correlation between the generation interval and incubation period. The dashed line is the point estimate of Kendall's tau obtained in this study, while the shaded white rectangle shows its 95 % credible interval. We assume baseline R_0 of b, 1.5, c, 2.2, and d, 2.9. As the generation interval and incubation period approach independence (Kendall's tau→1) case isolation will become ineffective—shown by the unchanging effective R_0 (R_0^E)—as transmission will either be presymptomatic or occur nearly at the same time as symptom onset.

the former ranging between 3.7 and 5.1 days and the latter between 4.4 and 5.7 days, indicating constant presence of presymptomatic transmission.

The means of the jointly estimated generation interval and incubation period for wild-type SARS-CoV-2 infections are in line with those reported elsewhere (Ferretti et al., 2020; Ganyani et al., 2020; Li et al., 2021; Tindale et al., 2020), with the mean generation interval shown for all transmission pairs with symptomatic infectors in this study—4.3 days—falling in the range of 2.8–7.5 days previously reported (see S1 Table and S4 Fig). The positive correlation between the generation interval and incubation period supports evidence shown in virological studies (X. He et al., 2020) that for symptomatic cases onset is tied to infectiousness. Our estimates are derived from a time and situation where most individuals were aware of the pandemic and mitigation measures were implemented. Individuals who became symptomatic after infection may have been likely to isolate soon after symptom onset, and contacts of cases were encouraged to quarantine, reducing opportunities for onward transmission among individuals with longer incubation periods (who were more likely to have been identified as cases and had their contacts traced prior to symptom onset compared to individuals with shorter incubation periods), thereby driving infector incubation period and generation interval estimates downwards. In the absence of public awareness of the virus and implementation of widespread public health and social measures, generation interval and infector incubation period estimates may be longer and the correlation between the two parameters may be even higher that what was demonstrated by this study (Sender et al., 2022). However, the key factor when considering onward transmission is whether the mean generation interval is shorter or longer than the infector incubation period, as this dictates the proportion of presymptomatic transmission. As shown in Fig. 3, a slightly shorter generation interval that is highly correlated with the infector incubation period is indicative of a great deal of presymptomatic transmission, with much of it occurring within 24 h before or after symptom onset.

The mean generation interval estimated from asymptomatic infectors (4.6 days, 95 % CrI: 3.8, 5.6 days) was longer than the jointly estimated generation interval using symptomatic infectors, indicating that the generation interval for asymptomatic infectors may be less influenced (shortened) by symptom-based public health and social measures—potentially leading to an underestimation of R_0 using estimates from symptomatic pairs (Park et al., 2020, Sender et al., 2022). Although evidence has indicated that asymptomatic COVID-19 cases are less infectious than symptomatic cases (Nakajo and Nishiura, 2021), asymptomatic cases nonetheless play a notable role in epidemic dynamics (Ferretti et al., 2020).

The proportion of presymptomatic transmission among symptomatic cases estimated in this study, 63.2 %, is higher than estimates reported by published studies using data from early in the pandemic (Ferretti et al., 2020; X. He et al., 2020; Sender et al., 2022), but is similar to other estimates (Ganyani et al., 2020; Hart et al., 2021; Tindale et al., 2020). Among those pairs with presymptomatic transmission, 33.5 % had transmission occurring within (either prior to or after) one day of infector symptom onset, and 49.1 % within two days of infector symptom onset. Combining estimates of asymptomatic transmission—in the range of 18–30 % (Mizumoto et al., 2020; Nishiura et al., 2020a)—with the estimate of presymptomatic transmission shared here, the proportion of nonsymptomatic transmission could feasibly reach 90 %. Thus, interventions such as physical distancing that do not depend on detection of potential infectors while they are not showing symptoms, enhanced surveillance to detect nonsymptomatic cases, and contact tracing to identify exposed individuals while their infected contacts are not symptomatic are crucial for COVID-19 control (Ferretti et al., 2020;

Fraser et al., 2004; Lovell-Read et al., 2021).

Data collection for this study focused on high certainty of directionality of transmission based on publicly announced epidemiological data. In contrast to most other countries, Japan applied backward contact tracing methods from the beginning of the pandemic in an effort to prevent large clusters of cases (Oshitani, 2020), making it an apt setting for obtaining transmission pair data. This is because links between cases—and particularly those related to clusters—were more likely to have been detected compared to countries where backward contact tracing was not conducted. As well, using backward contact tracing can increase the chance of identifying additional cases and individuals with longer incubation periods due to enhanced awareness of exposure status and vigilance for identifying symptoms and testing.

Nonetheless, backward contact tracing may not always be sufficient to detect all cases, as the timing of COVID-19 testing also plays an important role in case ascertainment (Long et al., 2021). Infected persons who were epidemiologically linked to COVID-19 cases but did not become symptomatic after initially testing negative for SARS-CoV-2 may have been missed as cases. In addition, Japan did not promote widespread community SAR-CoV-2 testing during the data collection period, and this perhaps limited the number of unlinked cases that may have otherwise been detected and retrospectively linked to other cases during that time period. As well, public health jurisdiction reporting practices changed over time, with details generally becoming more sparse once daily incidence became high enough to wear contact tracing capacity thin, and also towards the end of the year as concerns grew around infection-related stigmatization (Yoshioka and Maeda, 2020). Though not available for this study, sequencing data in combination with epidemiological data could help disentangle the directionality of transmission and may be helpful for future studies.

The shorter mean generation interval during the second and third waves of the pandemic in Japan compared to the first wave may in part reflect the increase in prevalence of infection, as intensified competition between infectious individuals when encountering susceptible contacts can lead to contraction of the generation interval (Ali et al., 2020; Kenah et al., 2008; Nishiura, 2010). Shorter generation intervals were also noted in the United Kingdom during September–November 2020, when there was a rise in the number of new cases (Hart et al., 2021). However, our results indicate that increases in incidence do not perforce lead to a contraction of the generation interval.

During the first epidemic wave, a nationwide state of emergency was declared. However, during the second wave and the 2020 half of the third wave, no such preventative measures were introduced. Conversely, campaigns intending to restart the Japanese economy following the difficulties caused by the first wave of COVID-19 were developed and implemented. In particular, the Go To Travel campaign, which offered discounts on travel inside Japan, was a fixture of the second and third waves (S5 Fig). The campaign began just before the peak of the second wave and was associated with an increase in COVID-19 cases reporting inter-prefecture travel (Anzai and Nishiura, 2021). Of pairs identified for the second wave, only 20.0 % of infectors were reported before the start of the Go To Travel campaign. Although we did not find that pairs where the infector had domestic travel experienced longer generation intervals (Fig. 2), travel effectively left-censors the generation interval between an infector who traveled and an infectee who did not travel with them.

Most identified transmission pairs had contact in the household or in settings related to social behavior, such as eating at restaurants, visiting nightlife, singing karaoke, attending sports events, listening to live music, visiting gyms, or meeting with friends, relatives, acquaintances, etc. (Table 1). These types of social contact settings have also been associated with SARS-CoV-2 transmission in other countries (Leclerc et al., 2020). In Japan, settings for social contact first are the first among those requested to be restricted by prefectural and local governments when control measures or a state of emergency were deemed necessary to reduce case incidence (Cabinet Secretariat of Japan, 2021). However, such emergency measures were not implemented during the second or third wave portions of 2020. Similar interventions focused on limiting social contact were implemented in other parts of the world (Imai et al., 2020), though other countries had a greater focus on reducing formalized community contact, such as by moving schools and workplaces online (Brauner et al., 2021; Liu et al., 2020).

The ongoing waves with different SARS-CoV-2 variants gaining predominance remains a unique challenge for pandemic control. Recent variants are understood to have shorter generation intervals than wild-type SARS-CoV-2 beyond the shortening that already occurred as a result of public health and social measures, leading to increased speed of transmission as has been seen during Omicron waves (Park et al., 2022; Sender et al., 2022). Whether the correlation between the generation interval and incubation period would be weaker or stronger than has been presented here remains to be seen. However the estimates of correlation and of the generation interval and incubation period we share and our estimate of the generation interval of asymptomatic infectors provide unique insights into SARS-CoV-2 transmission characteristics, and inform decision-making around public health and social measures, such as support for isolation of individuals regardless of symptom status, due to the significant proportion of transmission that occurs before and around time of symptom onset.

4. Materials and methods

4.1. Ethics oversight

This study was approved by the Medical Ethics Board of the Graduate School of Medicine at Kyoto University (R2676). It uses data published online by public health jurisdictions in Japan.

4.2. Study population and setting

We compiled a dataset of COVID-19 transmission pairs using openly published case data from reporting jurisdictions (prefectures and cities) in Japan, focusing on detecting pairs for whom directionality of transmission could be determined with some degree of certainty. Cases were limited to those reported during the calendar year 2020. Jurisdiction reporting practices changed over time, with details generally becoming sparser over time, as concerns grew around infection-related stigmatization (Yoshioka and Maeda, 2020), as well as in prefectures with large case loads.

Among the information publicly shared by the prefectures were links between cases and links to common exposures (e.g., a medical facility, event, or restaurant). However, clear statements as to who was the infector between linked cases or within clusters were generally not published. As well, dates of contact between cases and details of the type of link between cases were often only reported in detail if deemed to be important for public health action, limiting the number of cases for whom detailed epidemiological information related to their linkages were available. Therefore, assumptions about directionality of transmission were largely at the discretion of the authors, and in consequence we used the following bases for identifying linked cases as directional transmission pairs: 1) linkage of the infector (but not infectee) to a cluster; 2) the dates of contact, type of contact, and onset dates reported for linked cases provided some insight into directionality of transmission; 3) the infector or index case of an identified transmission chain traveled to a location with increased/increasing transmission prior to onset; or 4) the infector or index case of a chain was presumed to have been infected while traveling abroad. Households with >2 cases and links between cases in clusters where directionality of transmission and timings of contact could not be clearly identified were not selected (Britton and Tomba, 2019).

We included pairs with infectors who had multiple possible exposures (their exposure period takes the lower and upper bounds of all possible exposures) but excluded possible pairs where potential infectees had multiple possible infectors, and it is possible that infectees with

multiple potential infectors would have different contact patterns (and possibly be associated with shorter generation intervals) compared to infectees that had only one potential infector identified, as a susceptible person is likely to become infected more quickly if they are surrounded by multiple possible sources of infection (Kenah et al., 2008; Nishiura, 2010). Further details regarding ascertainment of transmission pairs are available in the Supporting materials.

Exposures were defined in relation to travel, contact with a confirmed case, or link to a cluster/common exposure. Reports of symptom onset in Japan were not restricted to any particular symptom, such as fever, but may have been reported as beginning with any of a variety of symptoms associated with SARS-CoV-2 infection such as fever, cough, fatigue, or runny nose.

4.3. Data stratification

The dataset including coarsely reported dates of exposure and contact were divided into subgroups to assess whether the generation interval, incubation period, or correlation between the two parameters would vary by subpopulation. Age (reported in deciles) was divided into three groups: cases under 30 years of age, cases 30–59 years of age, and cases 60 + years of age. Sex was reported as female or male. Separate age and sex subgroups were established for infectors and infectees. Type of contact between infector and infectee was divided into three categories: household contact, social contact-based interaction, and core community interaction. These divisions were made with public health interventions in mind. For example, social contact-based interaction includes types of contact that may not have occurred when local control measures were advised or a state of emergency was declared (Cabinet Secretariat of Japan, 2021).

Generally, public health control measures in Japan promoted during 2020 focused on reducing the number of individuals who had physi contact in a given day, as well as reducing scenarios where the "Three C's"—closed spaces, crowded places, and close-contact settings—were present (Oshitani, 2020). Interventions in Japan included limiting the total number of people who can visit facilities and venues, limiting restaurant hours, encouraging staying home, and at times discouraging cross-prefecture travel. Our definition of core community interaction, in contrast, focuses more on contact that occurs in schools, workplaces for general business, essential workplaces (medical facilities, care facilities, government services, etc.), and unknown sources of infection (community infection). Although these settings assigned to the core community interaction category may also be targeted by public health measures, they are perhaps less acutely affected by government decrees and social sentiment compared to settings more closely related to social interaction (Cabinet Secretariat of Japan, 2021).

Japan experienced three waves of COVID-19 during 2020, with the third wave extending into 2021 (S5 Fig). The first wave began with the first reported case, confirmed to be positive for SARS-CoV-2 on 16 January 2020. The second wave we set to begin on 1 June, which is around the center of the bottom of the trough between the first and second waves. The third wave we set to begin on 1 October, which likewise is around the center of the bottom of the trough between the second and third waves. Assignment to a given wave for each pair was determined by infector report date. Lastly, to check for differences given our basis for selecting transmission pairs we also stratified the dataset according to whether directionality was determined with respect to 1) importation from abroad, 2) linkage of the infector (but not infectee) to a cluster, 3) domestic travel by the infector to a location with increasing transmission, or 4) the timing and type of contact between cases in transmission chains.

4.4. Statistical analyses

Descriptive analyses and visualization were performed using R 4.1.0 (R Development Core Team, 2019). Bayesian parameter estimation was implemented in Stan using the cmdstanr interface to CmdStan 2.26.1 (Stan Development Team, 2021). Data and code are available at https://github.com/nlinton/covid19_generationinterval.

To assess correlation between the generation interval and incubation period of the infector we constructed a joint probability distribution by use of copulas—multivariate cumulative distribution functions (Klinkenberg and Nishiura, 2011; Sklar, 1959). The copulas we assessed included the Gaussian (normal), Clayton, Gumbel, and independence copulas. They are described in detail in the Supporting Materials. Timing of pathogen transmission and symptom onset were estimated using interval censoring methods derived from Reich et al. (2009) and adapted from previously published work (Linton et al., 2020; Nishiura et al., 2020b). For all parameters, posterior point estimates are given by the 50th percentiles of the converged Markov chain Monte Carlo (MCMC) chains from 100,000 iterations, and the best combination of copula and parametric distributions were selected using weights from a Bayesian mixture model (see Supporting Materials).

To consider the effect of correlation between the generation interval and incubation period on transmission, we simulated 10,000 pairs from the best-fit model of the jointly estimated generation interval and incubation period for all possible values of Kendall's tau from 0 to 1. For each simulated pair, we determined whether transmission was presymptomatic based on whether the incubation period was greater than the generation interval, and thereby calculated the proportion of presymptomatic transmission p for the 10,000 pairs for each value of Kendall's tau. We then considered that symptomatic transmission could result in a decrease in transmission as defined by the basic reproduction number R_0—the average number of infectees generated by a single infector. We calculated the effective R_0 as $R_0^E = \varphi R_0 + (1-\varphi)(1-\varepsilon)R_0$, where φ is the proportion of presymptomatic transmission and ε is the percent reduction in transmission due to rapid isolation among symptomatic cases, considering $R_0 = 2.2$ (Li et al., 2020; Riou and Althaus, 2020) and varied this by $\pm$ 0.7, also considering $R_0 = 1.5$ and $R_0 = 2.9$.

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Credit authorship contribution statement

Conceptualization: NML, ARA, HN, Data collection: NML, Methodology: NML, ARA, HN, Validation: NML, Formal analysis: NML, HN, Writing- Original draft: NML, Writing – Review & Editing: NML, ARA, HN, Supervision: HN.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.epidem.2022.100655.

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