

Analysis of Asymptomatic and Presymptomatic Transmission in SARS-CoV-2 Outbreak, Germany, 2020

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We determined secondary attack rates (SAR) among close contacts of 59 asymptomatic and symptomatic coronavirus disease case-patients by presymptomatic and symptomatic exposure. We observed no transmission from asymptomatic case-patients and highest SAR through presymptomatic exposure. Rapid quarantine of close contacts with or without symptoms is needed to prevent presymptomatic transmission.

During the ongoing coronavirus disease (COVID-19) pandemic, worldwide, >85 million severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections had been reported as of January 7, 2021 (<https://covid19.who.int>). Although it was clear from the beginning of the pandemic that symptomatic transmission of SARS-CoV-2 occurs, presymptomatic transmission has also been described (1–6). Furthermore, transmission from asymptomatic cases was deemed possible on the basis of findings that viral load of asymptomatic cases was similar to that of symptomatic cases (7). Understanding how transmission occurs from asymptomatic cases and from symptomatic cases in their presymptomatic and symptomatic phase, as well as the frequency of transmission, is essential for public health management. We assessed asymptomatic, presymptomatic, and symptomatic transmission during an outbreak investigation of 59 COVID-19 cases by determining secondary attack rates (SAR) according to the

respective exposure periods. In addition, we estimated key parameters such as serial interval and incubation period.

The Study

On February 29, 2020, a COVID-19 case was notified to the local public health authority (LPHA) of a rural district in southern Germany without previously observed community transmission. During the infectious period, the case-patient had attended several carnival events in the district. The LPHA immediately initiated contact tracing, identifying all close contacts; they were quarantined and tested irrespective of symptoms. By the end of March 2020, a cluster of 59 cases had been identified through successive contact tracing activities.

We interviewed the case-patients of the cluster by phone regarding symptoms developed during SARS-CoV-2 infection; potential source cases or events; and household contacts (HCs) and close nonhousehold or other contacts (OCs) in their infectious period (Appendix, <https://wwwnc.cdc.gov/EID/article/27/4/20-4576-App1.pdf>). We obtained an empirical distribution of the serial interval from the average over all possible transmission trees of the cluster. We obtained generation time and incubation period by averaging over the estimates as described by Reich et al. (8) (Appendix).

To estimate SAR and relative risks (RRs) we conducted a retrospective cohort study, including all HCs and OCs as recalled by the case-patients that met inclusion criteria (Appendix). We calculated pooled SAR of HCs and OCs for 2 outcomes, laboratory confirmation (SAR_{lab}) and development of respiratory symptoms (SAR_{res}) in the following groups: HCs and OCs of asymptomatic case-patients who never experienced symptoms; HCs and OCs of

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Table 1. Demographics of coronavirus disease case-patients and their contacts in a district in southern Germany*

Case type	No. (%) asymptomatic	No. (%) symptomatic			Total
		Phase not specified or both†	Presymptomatic phase only	Symptomatic phase only	
Case-patients					
Total	7 (13.2)	46 (86.8)	NA	NA	53 (100)
Female	3 (11.5)	23 (88.5)	NA	NA	26 (100)
Male	4 (14.8)	23 (85.2)	NA	NA	27 (100)
Median age	36 (IQR 6–68)	40 (IQR 29–50)	NA	NA	39.5 (IQR 29–50)‡
Contact persons by type of exposure					
HC	7 (16.7)	35 (83.3)	NA	NA	42 (100)
OC	52 (24.5)	48 (22.6)	81 (38.2)	31 (14.6)	212 (100)

*HC, household contact; IQR, interquartile range; NA, not applicable; OC, nonhousehold or other contact.

†The phase in which the contact occurred was not specified, or contact occurred in both phases.

‡Three of 53 cases were children <15 y of age.

symptomatic case-patients in which the phase with contact could not be specified by the case-patient or with contact in both phases; OCs of symptomatic case-patients with contact only in the presymptomatic phase; and OCs of symptomatic case-patients with contact only in the symptomatic phase.

We were able to contact 53/59 (90%) case-patients. Three case-patients were children <15 years of age (Table 1). Forty-six (87%) were symptomatic, and 7 (13%) were asymptomatic (Appendix Figure 1). The

cluster resulted in 144 possible transmission trees, which span over 5 generations (Figure). No secondary transmission resulted from asymptomatic cases. We determined a median serial interval of 3.0 (IQR 1.0–6.0) days and a median incubation period of 4.3 (IQR 2.5–6.5) days (Appendix Table 1).

In total, 42 HCs and 212 OCs were included in the cohort study (Table 1). The overall SAR_{lab} was 13% (4/32) for HCs and 14% (20/148) for OCs. The overall SAR_{res} was 29% (12/42) for HCs and 17% (29/170)

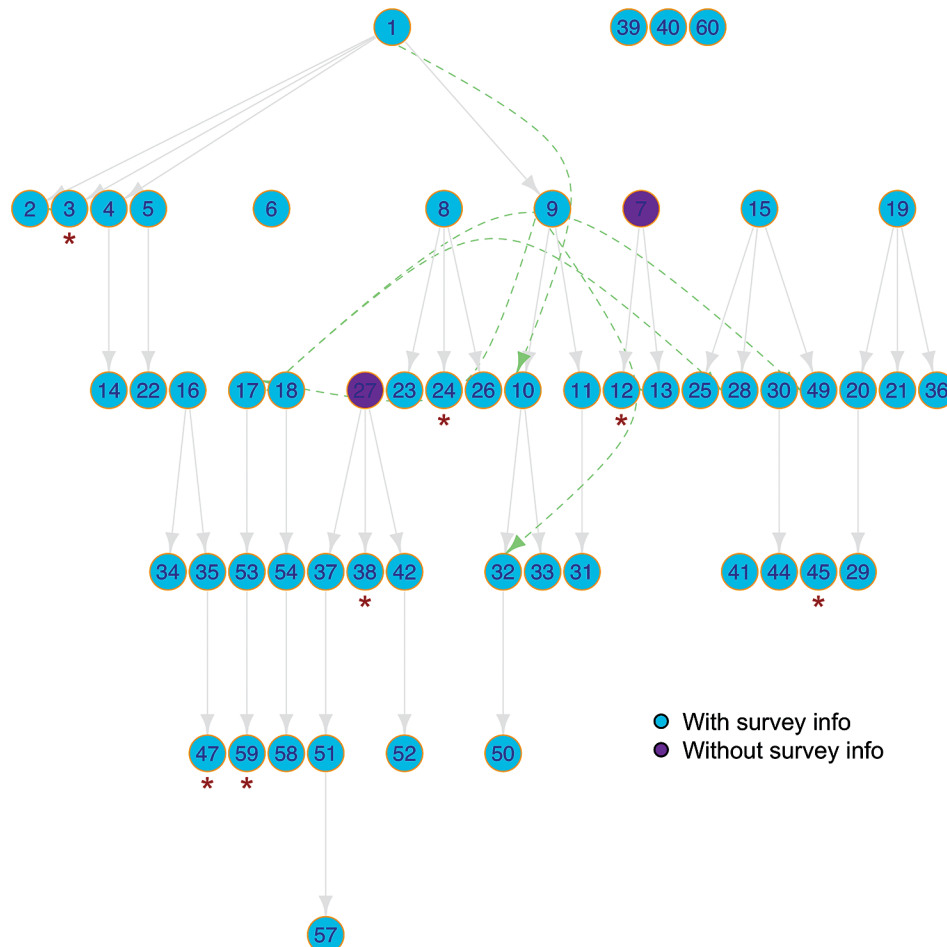


Figure. Transmission tree of the investigated cluster of coronavirus disease that evolved in a district in southern Germany. Cases 39, 40, and 60 participated in the survey but were not included in the analysis because we had no information on source case. Cases 7 and 27 did not participate in the survey and thus, no information on source case was available. Dashed lines represent source case–infectee pairs in which the infectee reported >1 possible source case; solid lines represent source case–infectee pairs in which only 1 source case was mapped to the infectee. Asterisks (*) indicate asymptomatic cases. Implausible transmissions (e.g., ID 6) were omitted.

Table 2. Secondary attack rates among contacts of coronavirus disease case-patients in a district in southern Germany*

Clinical symptoms of source case	No. contacts tested positive or experienced respiratory symptoms	Total no. contacts	SAR, %	RR (95% CI)
Household contacts SAR_{lab}				
Asymptomatic	0	4	0	Reference
Symptomatic, phase not specified or both†	4	28	14.3	0.8 (0.09–∞)
Total	4	32	12.5	
Household contacts SAR_{res}				
Asymptomatic	0	7	0	Reference
Symptomatic, phase not specified or both	12	35	34.3	3.4 (0.56–∞)
Total	12	42	28.6	
Other contacts SAR_{lab}				
Asymptomatic cases	0	22	0	Reference
Symptomatic, phase not specified or both	3	25	12.0	3.4 (0.36–∞)
Symptomatic, presymptomatic phase only	15	72	20.8	6.5 (1.1–∞)
Symptomatic, symptomatic phase only	2	29	6.9	1.8 (0.14–∞)
Total	20	148	13.5	
Other contacts SAR_{res}				
Asymptomatic cases	2	52	3.8	Reference
Symptomatic, phase not specified or both	4	22	18.2	4.7 (0.68–52)
Symptomatic, presymptomatic phase only	22	67	32.8	8.5 (2.1–75)
Symptomatic, symptomatic phase only	1	29	3.5	0.90 (0.02–17)
Total	29	170	17.1	

*RR relative risk; SAR, secondary attack rate; SAR_{lab} secondary attack rate for laboratory-confirmed SARS-CoV-2-positive contact persons; SAR_{res}, secondary attack rate for contact persons who experienced respiratory symptoms after contact.

†The phase in which the contact occurred was not specified, or contact occurred in both phases.

for OCs (Table 2). We did not identify any HC who tested positive or experienced respiratory symptoms after contact with asymptomatic case-patients. Neither SAR_{lab} nor SAR_{res} of HCs of symptomatic case-patients were significantly higher compared with HCs of asymptomatic cases (SAR_{lab} $p = 1.0$; SAR_{res} $p = 0.23$). We observed no laboratory-confirmed SARS-CoV-2 transmission from asymptomatic case-patients to any of the 22 OCs (Table 2; Appendix Figure 2). SAR_{lab} was highest for OCs with contact during the case-patients' presymptomatic phases (21%; 15/72) yielding a RR of 6.5 (95% CI 1.1–∞) when compared with contacts of asymptomatic case-patients. Adjusting for case-patients' age, sex, and number of contact persons showed no substantial changes in the magnitude of estimates (data not shown). Presymptomatic transmission accounted for $\geq 75\%$ of all transmissions to OCs in the cohort (Appendix).

Conclusions

In this cluster of COVID-19 cases, little to no transmission occurred from asymptomatic case-patients. Presymptomatic transmission was more frequent than symptomatic transmission. The serial interval was short; very short intervals occurred.

The fact that we did not detect any laboratory-confirmed SARS-CoV-2 transmission from asymptomatic case-patients is in line with multiple studies (9–11). However, Oran et al. have speculated that asymptomatic cases contribute to the rapid progression of the pandemic (12). Some studies may be prone to misclassify

presymptomatic cases as asymptomatic, leading to heterogeneous reporting of SAR of asymptomatic cases, because of different case definitions or differential duration of follow-up. In our study we used a very sensitive case definition for symptomatic cases that did not require specific symptoms (e.g. fever) to be present. Also, timing of our study would have enabled detection of late onset of symptoms, which gives us confidence in our classification of exposure groups.

The 75% of SARS-CoV-2 transmissions in our cohort from case-patients in their presymptomatic phase exceeds reported transmission rates from other investigations (1,13,14). Possible reasons are the prior evidence that infectiousness peaks around the date of symptom onset, declining thereafter (15), and that case-patients probably reduced social contacts themselves once they experienced symptoms or when ordered to self-isolate. A large proportion of cases with presymptomatic transmission in our cluster is further supported by the median serial interval of 3 days.

Of note are the consequences for public health management: first, the need for early detection of COVID-19 cases and for initiation of contact tracing as soon as possible to quarantine close contacts, particularly because short serial intervals may lead to further transmission chains. Second, suspect case-patients or persons with any respiratory illness should immediately self-isolate and inform their contacts met in the presymptomatic and symptomatic phases.

A limitation of our study is that evidence was obtained from a single outbreak and might not be

applicable to other settings. We used only information as recalled by the case-patients, which is imperfect and may introduce errors or bias. Because we used development of respiratory symptoms as a proxy for possible SARS-CoV-2 infections among contacts, and because incidence of respiratory illnesses was still high in this winter timeframe, SAR_{res} may be overestimated. However, this possible source of misclassification should be nondifferential between groups. We excluded many HCs because of uncertainties about the potential simultaneous introduction of SARS-CoV-2 in the household, which may have led to an underestimation of SAR among HCs. In the transmission tree, we had to omit various source case-infectee pairs because case-patients' recalled symptom onset differed substantially from surveillance data and was not plausible (Appendix). Finally, although community transmission of SARS-CoV-2 was deemed unlikely in the affected district at the time, we cannot rule out that some cases acquired infections from other sources.

In conclusion, our study suggests that asymptomatic cases are unlikely to contribute substantially to the spread of SARS-CoV-2. COVID-19 cases should be detected and managed early to quarantine close contacts immediately and prevent presymptomatic transmissions.

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Appendix

Methods

Cluster Definition

Our cluster consisted of all severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) laboratory-confirmed cases living in one district, who were identified by contact tracing activities of the local public health authority (LPHA) following notification of the index case.

Case Survey

Using a comprehensive and standardized questionnaire, a team of scientists from the Robert Koch Institute interviewed all cases belonging to the cluster. We conducted the phone interviews \approx 6 weeks after the last date of symptom onset of any of the cases to ascertain correct classification of asymptomatic and symptomatic clinical presentation.

Information on Possible Exposure

With respect to SARS-CoV-2 exposure, we asked each case to provide information regarding possible source cases for their SARS-CoV-2 infection (i.e., case-patients by whom they suspected they had been infected), about their travel history (outside their home district \leq 14 days before infection) and whether and which of the district's carnival events they had attended during February 23–26, 2020 (carnival season).

Definition of Asymptomatic and Symptomatic Cases

We defined a case with laboratory-confirmed SARS-CoV-2 infection as symptomatic if he or she recalled at least one of the following symptoms in the 14 days after the last close contact with a case: cough, sore throat, common cold (blocked/runny nose), fever (38.5°C or higher), chills, shortness of breath, pneumonia, headache, back pain, muscle pain, joint pain, loss

of appetite/weight, nausea, vomiting, diarrhea, conjunctivitis, rash, swollen lymph nodes, fatigue, anosmia (loss of smell), or ageusia (loss of taste).

Definition of the Symptom Onset and the Infectious Period

If cases were symptomatic, we defined symptom onset as the first day on which any of the above-listed symptoms had occurred; we did neither document which symptoms were present on the day of symptom onset and which were not, nor did we ask when a specific symptom started or how long it lasted. For cases displaying flu-like symptoms on a day before their most probable exposure, we defined an alternative date of symptom onset as the first date of contact to their most probable source case or most likely exposure (e.g., carnival events). The rationale for this correction was that the influenza season was still not over and no community transmission of SARS-CoV-2 was reported in the district until the carnival weekend.

Based on the reported or assumed (alternative) date of symptom onset of the cases of the cluster, we defined the infectious period for symptomatic cases from 2 days before until 10 days after the date of symptom onset, in accordance with RKI guidelines (https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/Kontaktperson/Management.html). For asymptomatic cases we assumed that the infectious period started 2 days after and ended 14 days after the presumed infectious encounter with their source case. In the event that there was contact to the source case on several days, we defined the first contact day as the day of the infectious encounter if the source case was a household member and the median date between first and last contact day if the source case was not a household member.

Transmission Tree and Plausibility Checks

We constructed all plausible transmission trees of the cluster based on the cases' information on their possible source cases. To do so, we applied plausibility checks; source case–infectee pairs were regarded implausible when it was not possible to identify a directionality, e.g., if dates of symptom onset and possible exposures were on the same day or interaction took place outside the estimated infectious period.

Determination of Serial Interval, Generation Time and Incubation Period

For each transmission tree, we obtained an empirical distribution of the serial interval (time from symptom onset of the source case to symptom onset in their infectee) based on the date of symptom onset in all resulting source case–infectee pairs. This distribution was then

averaged over all possible trees. Furthermore, because possible exposures were specified as time periods, we used the double-interval-censored approach developed by Reich et al. (1) to estimate both the generation time (time from infection of the source case to infection of its infectee) distribution and the incubation period (time from infection to symptom onset) distribution for each tree as Weibull distribution. The estimated distributions for each tree were then combined as follows: for each tree, we sampled 100 parameter instances from the asymptotic multivariate normal distribution for the 2 Weibull parameters. For each parameter combination, we drew 1 instance from the Weibull distribution. The resulting sample of $100 \times$ no. of trees values then constitutes a sample of the generation time distribution and incubation period distribution, which takes both estimation uncertainty and uncertainty of who infected whom and when into account.

Cohort Study among Contact Persons

The study population of the cohort study consisted of all household (HC) and close non-household or other contact persons (OC) whom the cases of our cluster could recall in the interviews and who met the inclusion criteria. We defined a close contact person as a person with >15 minutes face-to-face contact within a maximum distance of 2 m to the case. We did not conduct interviews with the cohort of HC and OC directly.

Inclusion criteria for our cohort analysis were the following: first, we included only HC and OC of those cases, for which it was clear who the primary case in households or other group settings was. Second, we included HC and OC of only those cases in which there was no ambiguity regarding the date of symptom onset (≤ 2 days difference to the case information in the German surveillance system) (2). Third, we included only those HC and OC for whom the interviewed case could provide information about the contact period, if a SARS-CoV-2 test result was available, and if the HC/OC experienced respiratory symptoms after contact with them.

We calculated relative risks (RR) of OC/HC of symptomatic cases for whom the phase could not be specified or with contact in both phases; OC of symptomatic cases with contact only in the presymptomatic phase; and OC of symptomatic cases with contact only in the symptomatic phase by using OC/HC of asymptomatic cases as reference. For this, we used exact Poisson regression and considered $p < 0.05$ as statistically significant.

Software

We entered data from the questionnaires into a database using EpiData version 3.1 (EpiData Association, <http://www.epidata.dk>). The subsequent analyses were performed with STATA version 15.0 (StataCorp, <https://www.stata.com>) and R version 3.6.1 (R Foundation for Statistical Computing, <https://www.R-project.org>).

Ethics

This outbreak investigation was conducted as part of the authoritative official tasks of the LPHA of the district supported by the RKI upon official request in accordance to §4 of the German Protection against Infection Act. Therefore, this investigation was exempt from institutional review.

Results

Cohort Study

Among laboratory-confirmed OC, most (75%; 15/20) had contact with their source case only during the presymptomatic period of the case; 10% (2/20) of laboratory-confirmed OC had contact with their source case only in the symptomatic period of the case. For 15% (3/20), contact could not be specified by the symptomatic case, in which phase of the infectious period the contact took place, or contact took place in both phases.

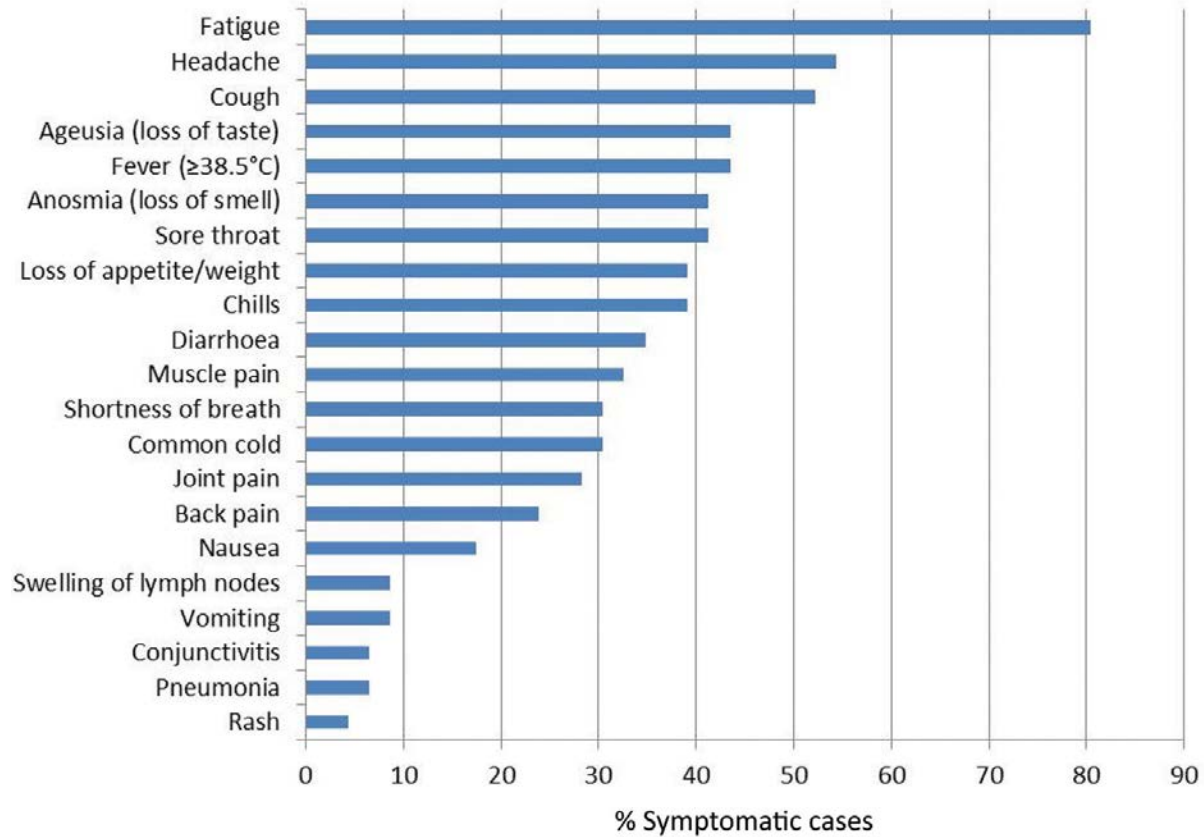
Among OC with respiratory symptoms, the proportion that had contact only in the presymptomatic period of their source case was similar (76%; 22/29). Furthermore, 3% (1/29) of OC experienced symptoms after contact with the source case only in their symptomatic period and 14% (4/29) if the symptomatic period could not be specified or if contact occurred in both phases. In this study, 7% (2/29) of OC from asymptomatic cases later became symptomatic.

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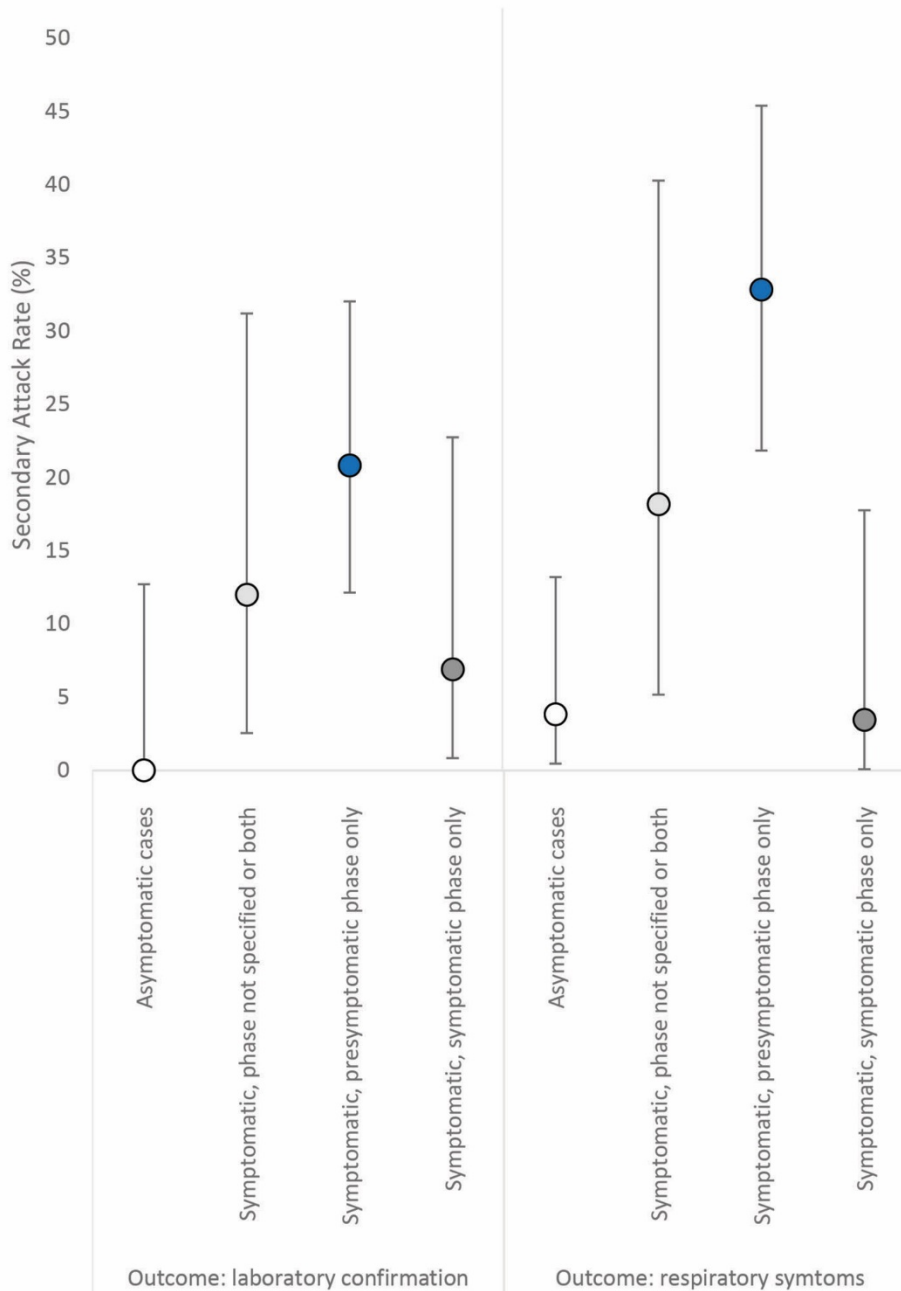
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Appendix Table. Distributions of the calculated serial interval, incubation period and generation time as inferred from the 53 COVID-19 cases of the cluster in a district in Southern Germany.

Time	Quantiles							Mean
	1%	5%	25%	50%	75%	95%	99%	
Serial interval, d	-2.0	-1.0	1.0	3.0	6.0	15.0	22.0	4.5
Generation time, d	0.1	0.3	1.7	3.6	6.6	13.1	21.6	4.9
Incubation period, d	0.3	0.8	2.5	4.3	6.5	10.6	14.3	4.8



Appendix Figure 1. Reported symptoms among symptomatic cases from the COVID-19 cluster in a district in Southern Germany (n = 46).



Appendix Figure 2. Secondary attack rates (SAR) among non-household/other contacts in the COVID-19 cluster in a district in southern Germany. SAR for the outcomes of laboratory-confirmed COVID-19 and the development of respiratory symptoms in contacts of cases belonging to the cluster are shown for each group of the infectious phase/clinical presentation of the case. Bars represent 95% CI. White dot represents SAR among contacts from asymptomatic cases; light gray, SAR among contacts from symptomatic cases where phase was not specified or contact in both phases; blue, SAR among contacts from symptomatic cases with contact in presymptomatic phase only; dark grey, SAR among contacts from symptomatic cases with contact in symptomatic phase only.