Nosocomial COVID-19 Incidence and Secondary Attack Rates among Patients of Tertiary Care Center, Zurich, Switzerland

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Of 1,118 patients with COVID-19 at a university hospital in Switzerland during October 2020–June 2021, we found 83 (7.4%) had probable or definite healthcare-associated COVID-19. After in-hospital exposure, we estimated secondary attack rate at 23.3%. Transmission was associated with longer contact times and with lower cycle threshold values among index patients.

Since the beginning of the COVID-19 pandemic, hospitals have introduced infection prevention and control (IPC) measures to protect inpatients from SARS-CoV-2. Despite these precautions, healthcare-associated COVID-19 has affected a notable proportion of hospitalized patients (*1*–*3*). During the second and third waves of COVID-19 in Switzerland, an increasing number of patients with presymptomatic or asymptomatic COVID-19 exposed hospital roommates to SARS-CoV-2. We estimated the secondary attack rate (SAR) after exposure in a hospital in Zurich and identified risk factors for SARS-CoV-2 transmission.

The Study

University Hospital Zurich, a 900-bed tertiary care center, implemented intensified standard precaution measures during the COVID-19 pandemic (Appendix, https://wwwnc.cdc.gov/EID/article/28/10/22-0321-App1.pdf). We included in our analysis all patients with COVID-19 admitted during the second and third COVID-19 waves, weeks 40 of 2020 through 25 of 2021; a small percentage were also included in a study investigating transmission to healthcare workers (*4*). We stratified COVID-19 sources as community-associated, healthcare-associated (definite and probable), or indeterminate according to European Centre for Disease Prevention and Control criteria (*5*). We defined index patients as those who, during the 48 hours before onset of signs and symptoms or a positive SARS-CoV-2 test, had contact with an exposed patient. We defined exposed patients as those sharing a room with an index patient for ≥6 hours in an intermediate care unit (IMC) or intensive care unit (ICU) (*1*), any time on the general ward, or when the index patient underwent an aerosol-generating procedure (*2*). We initiated droplet isolation precaution measures for exposed patients and tested them upon symptom onset or, beginning week 47 of 2020, systematically at 2, 5, and 10 days after exposure. We contacted discharged patients by phone and offered testing in the outpatient clinic. Patients with up-to-date vaccination or known COVID-19 during the previous 6 months were considered unexposed.

We assessed transmission pathways between patients by in-depth reviews of symptom onset and dynamics of cycle threshold (Ct) values. If sequencing results were available, evidence of transmission was defined as ≤1 single-nucleotide polymorphism (SNP). Exposed patients with >1 SNP difference from the index patient were excluded from the main analysis, but patients without sequencing data were included. For association with SARS-CoV-2 transmission, we assessed index patient age, sex, aerosol generating

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procedures, and Ct values from first positive PCR test, duration of contact between an index patient and exposed patient, ward type, and pandemic week.

Routine SARS-CoV-2 PCR testing was conducted in 3 laboratories and whole-genome sequencing performed according to nCoV-2019 sequencing protocol v3 (LoCost) V.3 (https://www.protocols.io/view/ncov-2019-sequencing-protocol-v3-locost-bp2l6n-26rgqe/v3) (Appendix 2). To estimate SAR, we calculated cumulative incidence using the Kaplan-Meier estimator. We assessed risk factors for transmission in univariate and multivariable logistic regression models. We conducted sensitivity analyses on patients with ≥10 days clinical or laboratory follow-up (Appendix Table 1), on all patients irrespective of phylogenetic results (Appendix Table 2), and on patients with phylogenetically proven transmission (Appendix Table 3). We conducted analyses using Stata statistical software release 16 (StataCorp LLC, https://www.stata.com) and R version 4.0.2 (https://cran.r-project.org/bin/windows/base). The Zurich Cantonal Ethics Commission waived formal ethics evaluation because our analysis was part of an outbreak investigation for quality control and infection prevention (Req 2021-00560).

Of 1,118 patients with COVID-19, a total of 1,012 (90.5%) cases were community-associated, 40 (3.6%) probable healthcare-associated, 43 (3.8%) definite healthcare-associated, and 23 (2.1%) indeterminate (Figure 1). In total, we found 127 index patients for 303 exposed patients. Phylogenetic data supported transmission in 14/23 pairs of index–exposed patients with epidemiologic links for whom we had available data (Appendix Figure 1). In addition, we confirmed 4 transmissions indirectly by data from transmission chains (Figure 2). We excluded 5 exposed patients from the analysis because of >1 SNP difference between index and exposed patient. Among exposed patients in the analysis, 42/298 (14.1%) tested positive for SARS-CoV-2 and 179/298 (69.9%) had a follow-up time <10 days. Cumulative incidence for COVID-19 as an estimator of the SAR was 23.3% (95% CI 16%–30%) (Appendix Figure 2). Clusters were small, with only 2 multigeneration transmissions (Figure 2). We found links to identified index patients for 26 (65%) patients with probable and 15 (34.9%) patients with definite healthcare-associated COVID-19.

We performed univariable and multivariable analyses to explore factors associated with transmission of SARS-CoV-2 from patients to roommates (Table). We found similar results for 2 of the 3 sensitivity analyses (Appendix Tables 2, 3). However, in analysis of patients with a follow-up ≥10 days (Appendix Table 1), exposure on IMC/ICUs and higher number of weeks into the COVID-19 pandemic were associated with a lower risk for transmission, likely because of greater physical distance between immobile patients on the IMC/ICU and increased IPC standards.

In a mostly unvaccinated population in which most infections were caused by pre-Alpha variant SARS-CoV-2 (6), we found that 7.4% of all COVID-19 patients had probable or definite healthcare-associated COVID-19. This finding is comparable to that from the second wave in Brazil (8.6%) (*7*) but lower than that from the first wave in the United Kingdom (9%–15%) (*2*,*3*). We were able to link only half of the healthcare-associated cases in our hospital to an identified index patient. Despite all the IPC measures in place, high population incidence probably contributed to an increased risk for healthcare-associated transmissions from other patients but also from visitors and HCWs.

We identified ≈11% of all COVID-19 patients as index patients and estimated a 23% SAR in exposed

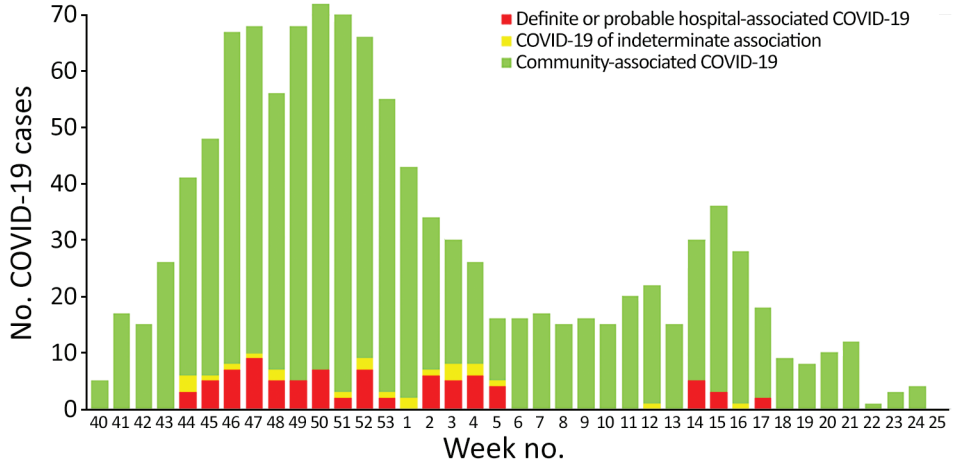

Figure 1. Incidence of admitted patients with positive SARS-CoV-2-PCR per week, including categorization hospital-associated versus community-associated, temporal trend of incidence of SARS-CoV-2 positive patients from week 40 of 2020 through week 25 of 2021. Incident cases were stratified according to European Centre for Disease Prevention and Control definitions of healthcare-associated COVID-19.

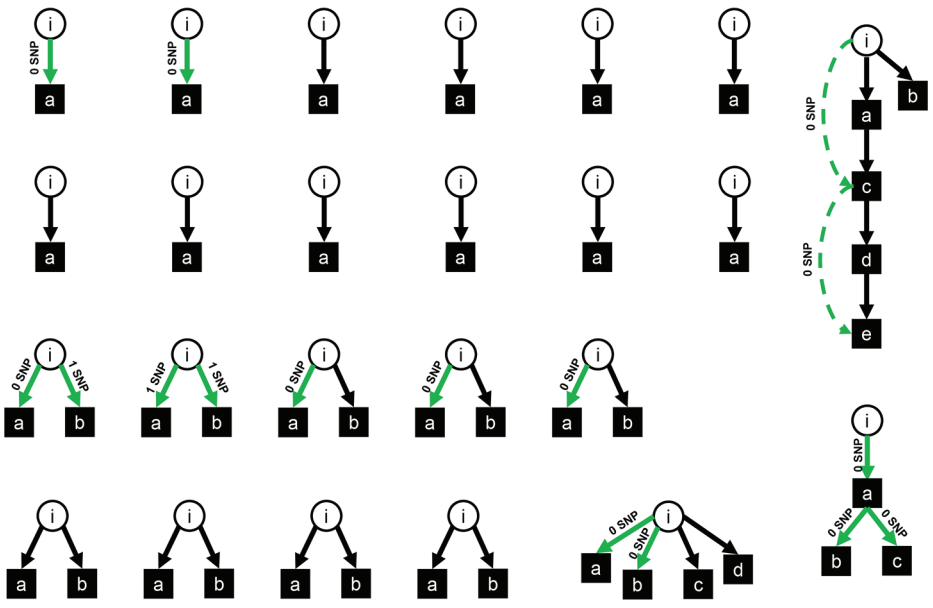

Figure 2. Transmission clusters of patients after exclusion of 5 exposed patients in whom phylogenetic data did not support transmission. Circles are index patients, squares are infected contact patients. Green arrows represent phylogenetically confirmed transmissions, with the labels "0 SNP" and "1 SNP" indicating 0 or 1 SNP difference between index and exposed patient. Green dashed arrows represent phylogenetic proof of second-generation transmission. Black arrows represent assumed transmissions without phylogenetic proof. i, index patient; a–d, exposed.

patients. From the 23 epidemiologically linked pairs with available phylogenetic data, transmission was endorsed in only 18, suggesting that the overall index-to-contact patient transmission rate may have been overestimated. SARs among hospital roommates in a study from a tertiary care center in Iowa, USA, was 21.6% (*8*); from a tertiary care center in New York, New York, USA, 18.9% (*9*); and from a hospital in Boston, Massachusetts, USA, 39% (*10*). These SAR numbers are comparable to those in households (*11*), implying either that distancing and masking are of limited effectiveness for preventing transmission while sharing accommodations (supporting an aerosol transmission pathway between patients) (*13*) or that adherence to distancing and masking were low. Unsurprisingly, as also demonstrated elsewhere (*8*,*10*), the 2 parameters most strongly associated with SARS-CoV-2 were longer contact time between index and exposed patients and low Ct values (i.e., high viral loads) among index patients; Ct values <21 were shown to be associated with transmission.

Among limitations in our study, phylogenetic results were available for only half of the patients, laboratory follow-up with inpatients was only 10 days, and discharged patients were often not available for further follow-up. We also limited contact time on IMC/ICUs to >6 hours, which might have excluded relevant contacts, and we might have missed superinfection. Finally, we were unable to model potential drivers for transmission, such as patient nonadherence to IPC-measures, distance between index and exposed patients, or respiratory signs or symptoms of index patients.

Table. Univariable and multivariable analysis of factors associated with SARS-CoV-2 transmission to exposed patients in a hospital in Zurich, Switzerland, October 2020–June 2021*

Exposure	Exposed patients positive for SARS-CoV-2, n = 42	Exposed patients not testing for SARS-CoV-2, n = 256	OR (95%CI) Univariable analysis	OR (95%CI) Multivariable analysis
Contact time of index and exposed patient in hours, median (IQR)	54 (28–96)	17 (8–29)	1.03 (1.02–1.03)	1.02 (1.01–1.03)
Ct value of index patient in units, median (IQR)	19 (18–26)	28 (19–33)	0.91 (0.87–0.96)	0.93 (0.87–0.98)
AGP in index patient, mean (SD)	0.26 (0.44)	0.25 (0.43)	1.04 (0.50–2.19)	NA
Exposure on IMC/ICU, mean (SD)	0.14 (0.35)	0.31 (0.46)	0.37 (0.15–0.92)	0.70 (0.27–1.87)
Male sex of index patient, mean (SD)	0.55 (0.50)	0.52 (0.50)	1.08 (0.56–2.09)	NA
Age of index patient, y, median (IQR)	71 (58–77)	72 (58–78)	1.00 (0.98–1.02	NA
Exposure before mandatory patient masking at bed place, mean (SD)	0.09 (0.28)	0.11 (0.32)	1.41 (0.50–3.96	NA
Calendar week into second and third waves, median (IQR)	13 (9–17)	13 (8–18)	0.96 (0.91–1.01)	0.95 (0.90–1.01)

*AGP, aerosol-generating procedures; Ct, cycle threshold; IQR, interquartile range; IMC, intermediate care units; ICU, intensive care units; NA, not available; OR, odds ratio.

Conclusions

High viral loads among index patients and prolonged contact time in shared hospital rooms play critical roles in healthcare-associated SARS-CoV2-transmission. Although based on data from a time when pre-Alpha and Alpha variants circulated in a nonvaccinated population, our findings might be relevant in the context of more recently emerged and future variants of concern (*13*,*14*) and waning immunity (*15*). The findings in our study and other studies of substantial SARs in hospitals support early adoption strategies to prevent healthcare-associated transmission during times of high population COVID-19 incidence. Those strategies include identifying contagious patients early (e.g., by performing systematic and repetitive SARS-CoV-2 testing), improving mask-wearing adherence in patients, and frequently replacing air in shared patient rooms.

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A.W., S.K.R., and W.Z. designed the study. V.K., M.Za., I.N., P.W.S., M.V., V.S., T.S., and D.S. acquired the data, and A.W., M. Ze., and P.W.S. performed statistical analysis. V.K., M.Za., E.P., and S.S. performed laboratory analyses. A.W., V.K., M.Za., M. Ze., and W.Z. analyzed and interpreted the data. A.W. and V.K. drafted the manuscript, and M.Za., M. Ze., I.N., P.W.S., M.V., V.S., T.S., S.S., E.P., D.S., M.H., S.K.R., and W.Z. provided critical review of the manuscript for intellectual content.

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Dr. Wolfensberger is an infectious disease physician and hospital epidemiologist at the University Hospital Zürich. Her primary research interests include outbreak investigations and hospital-acquired pneumonia.

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Appendix

Intensified Standard Precautions during the COVID-19 Pandemic

For HCW:

- Systematic use of surgical masks.
- Wearing protective eyewear when approaching patients not wearing masks.
- Using FFP2 masks during aerosol-generating procedures (AGP).

For patients: Wearing face masks whenever leaving the bed and, from week 45 in 2020, also when staff or visitors were approaching the bed.

In patient rooms:

- Curtains between beds were requested to be kept closed.
- Windows opened regularly in nonventilated rooms after week 47.
- Aerosol-generating procedures other than nebulization in multibed rooms were minimized but not prohibited.

Laboratory Testing and Phylogenetic Analysis

SARS-CoV-2 polymerase chain reaction (PCR) testing was conducted in three different laboratories using either Roche cobas SARS-CoV-2 IVD test (Roche Diagnostics, Mannheim, Germany), Thermofisher Scientific SARS-CoV-2- IVD test (Thermofisher Scientific, Basel, Switzerland), GeneXpert Xpress SARS-CoV-2 (Cepheid, CA, USA), or two in-house RT-PCR assays as described by Corman et al. and Tastanova et al. (*1*,*2*).

SARS-CoV-2 whole-genome sequencing was performed on all available samples according to the nCoV-2019 sequencing protocol v3 (LoCost) V.3 (https://www.protocols.io/view/ncov-2019-sequencing-protocol-v3-locost-bh42j8ye). SARS-CoV-2 consensus sequences were generated by iteratively aligning reads using SmaltAlign (https://github.com/medvir/SmaltAlign), and sequences were uploaded to GISAID. The sequence lineages were obtained using the PANGOLIN package version v1.2.66 (*3*). Background sequences which represent the most frequent lineages during the investigated time interval in the Zurich region were downloaded from GISAID (*4*) and implemented in the phylogenetic analysis. Multiple sequence alignment was done with MAFFT v7.271 (*5*), followed by phylogenetic analysis using RAxML (*6*).

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Appendix Table 1. Sensitivity analysis S1 including only patients with follow-up of ≥10 days (all patients except those with proven nontransmission), univariable and multivariable analyses of factors associated with SARS-CoV-2 transmission to exposed patients

Exposure	Exposed patients positive for SARS-CoV-2, n = 42	Exposed patients not positive for SARS-CoV-2, n = 77	OR univariable analysis (95% CI)	p value	OR multivariable analysis (95% CI)	p value
Exposure time in hours, median (IQR)	53 (28–96)	17 (11–25)	1.02 (1.01–1.03)	<.001	1.02 (1.00–1.03)	.007
Ct value of index patient in units, median (IQR)	19 (18–26)	27 (20–33)	0.92 (0.87–0.98)	.006	0.93 (0.87–1.00	.039
AGP in index patient, mean (SD)	0.26 (0.45)	0.26 (0.44)	1.01 (0.42–2.38)	.979	NA	NA
Exposure on IMC/ICU, mean (SD)	0.14 (0.35)	0.52 (0.50)	0.15 (0.06–0.41)	.001	0.25 (0.09–0.72)	.011
Male gender of index patient, mean (SD)	0.55 (0.50)	0.62 (0.48)	0.73 (0.34–1.57)	.421	NA	NA
Age of index patient in years, median (IQR)	71 (58–77)	72 (62–78)	0.99 (0.96–1.01)	.627	NA	NA
Exposure before mandatory patient masking at bedplace, mean (SD)	0.12 (0.33)	0.09 (0.29)	1.35 (0.40–4.56)	.511	NA	NA
Calendar week into 2nd and 3rd wave, median (IQR)	13 (9–17)	17 (12–18)	0.92 (0.87–0.98)	.010	0.92 (0.86–1.00)	.045

*Ct, cycle threshold; OR, odds ratio; IQR, interquartile range; IMC, intermediate care unit; ICU, intensive care unit; NA, not available.

Appendix Table 2. Sensitivity analysis S2 including all patients irrespective of phylogenetic result, univariable and multivariable analyses of factors associated with SARS-CoV-2 transmission to exposed patients

Exposure	Exposed patients positive for SARS-CoV-2, n = 47	Exposed patients not positive for SARS-CoV-2, n = 256	OR univariable analysis (95% CI)	p value	OR multivariable analysis (95% CI)	p value
Exposure time in hours, median (IQR)	57 (28–96)	17 (8–29)	1.03 (1.02–1.04)	<.001	1.02 (1.02–1.03)	<.001
Ct value of index patient in units, median (IQR)	20 (18–26)	28 (20–33)	0.91 (0.87–0.96)	<.001	0.93 (0.88–0.98)	.010
AGP in index patient, mean (SD)	0.26 (0.44)	0.25 (0.43)	1.03 (0.50–2.10)	.938	NA	NA
Exposure on IMC/ICU, mean (SD)	0.17 (0.38)	0.31 (0.46)	0.45 (0.20–1.01)	.032	0.88 (0.36–2.12)	
Male gender of index patient, mean (SD)	0.55 (0.50)	0.52 (0.50)	1.13 (0.60–2.11)	.707	NA	NA
Age of index patient in years, median (IQR)	71 (58–78)	72 (58–77)	1.00 (0.98–1.02)	.810	NA	NA
Exposure before mandatory patient masking at bedplace, mean (SD)	0.09 (0.28)	0.11 (0.31)	1.27 (0.45–3.52)	.652	NA	NA
Calendar week into 2nd and 3rd wave, median (IQR)	12 (8–17)	15 (9–18)	0.95 (0.90–0.99)	.022	0.94 (0.89–1.00)	.050

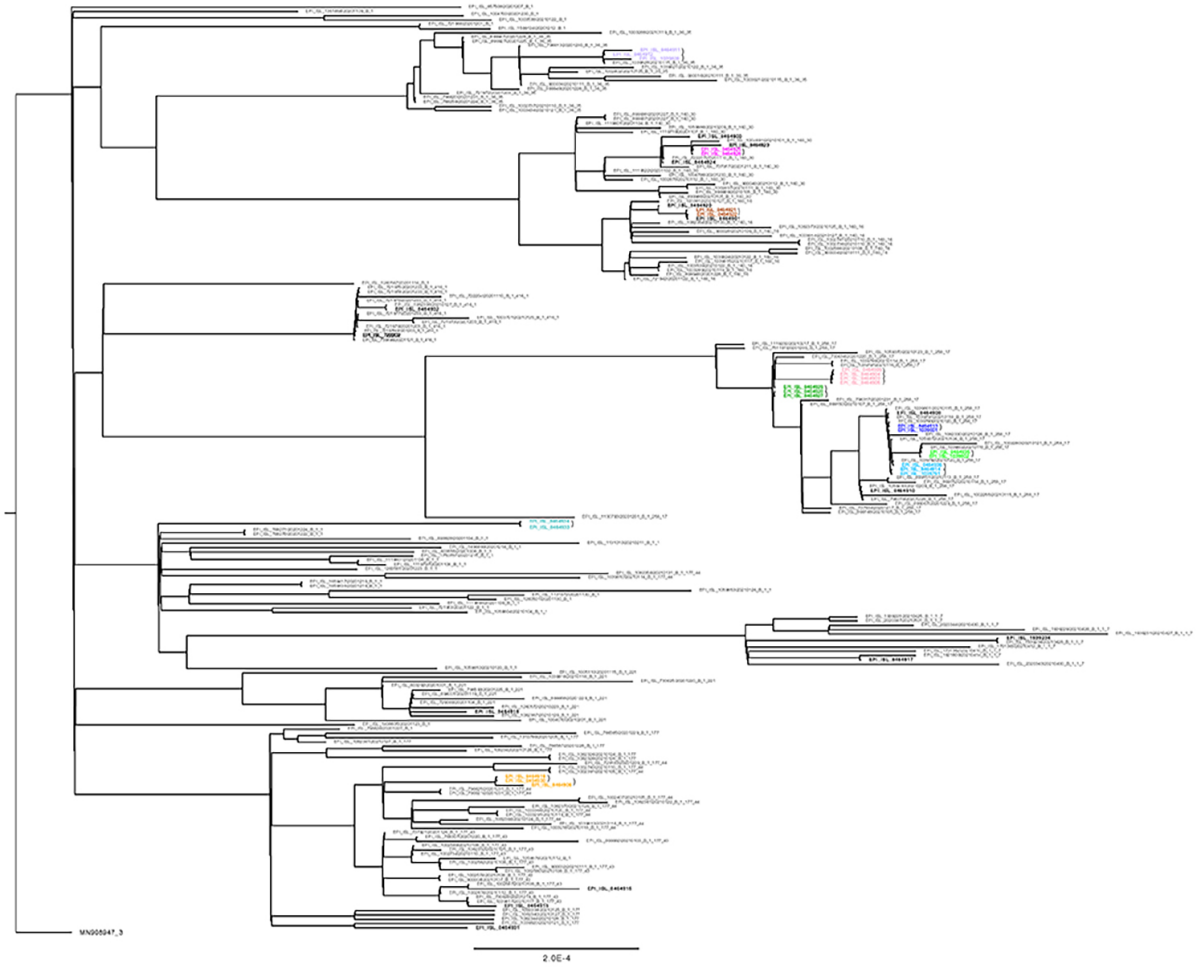
*Ct, cycle threshold; OR, odds ratio; IQR, interquartile range; IMC, intermediate care unit; ICU, intensive care unit; NA, not available.

Appendix Table 3. Sensitivity analysis S3 including only patients with phylogenetically proven transmission, univariable and multivariable analyses of factors associated with SARS-CoV-2 transmission to exposed patients

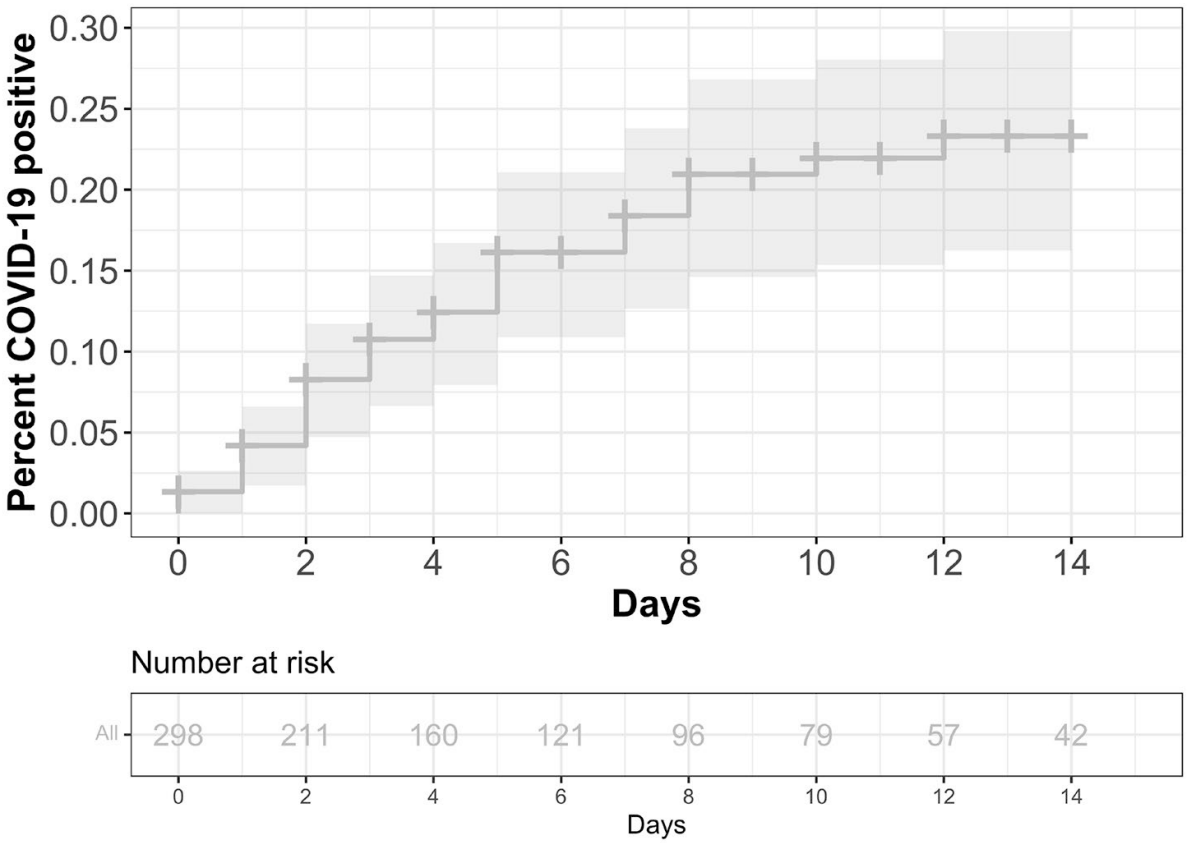
Exposure	Exposed patients positive for SARS-CoV-2, n = 18	Exposed patients not positive for SARS-CoV-2, n = 256	OR univariable analysis (95% CI)	p value	OR multivariable analysis (95% CI)	p value
Exposure time in hours, median (IQR)	53 (22-82)	17 (8–29)	1.02 (1.01–1.03)	<.001	1.02 (1.01–1.03)	.004
C_t value of index patient in units, median (IQR)	19 (18–20)	28 (20–33)	0.83 (0.76–0.92)	<.001	0.83 (0.75–0.93)	.001
AGP in index patient, mean (SD)	0.11 (0.32)	0.25 (0.42)	0.38 (0.08–1.7)	.199	NA	NA

Exposure	Exposed patients positive for SARS-CoV-2, n = 18	Exposed patients not positive for SARS-CoV-2, n = 256	OR univariable analysis (95% CI)	p value	OR multivariable analysis (95% CI)	p value
Exposure on IMC/ICU, mean (SD)	0.17 (0.38)	0.31 (0.46)	0.44 (0.12–1.56)	.032	NA	NA
Male gender of index patient, mean (SD)	0.56 (0.51)	0.52 (0.50)	1.08 (0.56–2.09)	.811	NA	NA
Age of index patient in years, median (IQR)	70 (58–80)	72 (58–78)	1.00 (0.98–1.03)	.792	NA	NA
Exposure before mandatory patient masking at bedplace, mean (SD)	0.09 (0.28)	0.00 (0.00)	NA	NA	NA	NA
Calendar week into 2nd and 3rd waves, median (IQR)	13 (11–17)	15 (9–18)	0.97 (0.90–1.04)	.330	NA	NA

*C_t, cycle threshold; OR, odds ratio; IQR, interquartile range; IMC, intermediate care unit; ICU, intensive care unit; NA, not available.



Appendix Figure 1. Phylogenetic analysis of SARS-CoV-2 isolates from 41 patients and 1 healthcare worker, and SARS-CoV-2 background sequences downloaded from GISAID. Patient isolates are indicated using GISAID accession IDs, colors, and parentheses indicate supported transmission clusters.



Appendix Figure 2. Cumulative incidence of COVID-19 in exposed patients. X-axis indicates days since last exposure to index case, y-axis indicates percentage of exposed patients who tested positive for SARS-CoV-2, grey-shaded area corresponds to 95% CIs. Bottom graph shows number of patients at risk per day of follow-up after exposure.