Transmission Routes of Severe Acute Respiratory Syndrome Coronavirus 2 Among Healthcare Workers of a French University Hospital in Paris, France

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In this case-control study on 564 healthcare workers of a university hospital in Paris (France), contacts without protection with coronavirus disease 2019 (COVID-19) patients or with colleagues were associated with infection with severe acute respiratory syndrome coronavirus 2, whereas working in a COVID-dedicated unit and having children kept in childcare facilities were not.

Keywords. case-control study; COVID-19; determinants; healthcare workers; SARS-CoV-2.

Effective protection of healthcare workers (HCWs) against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) requires assessment of transmission routes in this at high-risk population, both inside and outside healthcare.

We previously published an observational multicenter cohort study on HCWs during the first French coronavirus disease 2019 (COVID-19) breakthrough [1]. Only 20% of HCWs infected with SARS-CoV-2 reported close contact with suspected or confirmed COVID-19 patients, and 78% were not regularly posted in COVID-19-dedicated units. In contrast, 54% declared frequent close contacts with colleagues without protection. However, we were unable to compare our cohort to a robust control group of HCWs not infected with SARS-CoV-2.

Diagnosis sensitivity of reverse-transcriptase polymerase chain reaction (rtPCR) on nasopharyngeal swab for COVID-19 is imperfect [2], and serological assessment was not available at this time. Immunoglobulin (Ig)G serological test has since been proven to be reliably associated with a COVID-19 past infection [3]. In this study, we present a case-control study that compared COVID-19-positive and COVID-19-negative HCWs regarding their occupational activity, symptoms, and in-hospital and out-of-hospital exposures to SARS-CoV-2.

MATERIAL AND METHODS

Patients and Design

This study was led among HCWs at a 2100-bed tertiary care university hospital (Assistance Publique-Hôpitaux de Paris Centre, Université de Paris) located in central Paris, France, employing 13 278 personnel. From February 24 to 10 April 2020, symptomatic staff were referred to dedicated onsite testing centers where trained medical staff collected a nasopharyngeal swab for SARS-CoV-2 rtPCR. The HCWs who tested positive were included as cases. For each confirmed case, we included a control symptomatic HCW tested on the same day, with a negative rtPCR and a negative serological assessment performed at least 1 month after symptoms onset. Immediately after testing, both cases and controls were questioned on their professional activity, symptoms, occupational exposures (eg, average daily number of close contacts with COVID-19 patients and without personal protective equipment [PPE], compliance to infection prevention protocols, contacts with colleagues during meal breaks, meetings, etc), and nonoccupational exposures to SARS-CoV-2 (eg, frequentation of public transports, contacts inside and outside the household) [1]. All schools and childcare facilities closed on March 12, 2020 in France, except for children of hospital staff, and a nationwide lockdown started on March 17, 2020. Lift of containment measures occurred on May 11, 2020.

Virology Methods

The SARS-CoV-2 rtPCR technique has been described elsewhere [1]. The SARS-CoV-2 serology was determined by...
the Abbott SARS-CoV-2 IgG assay, a chemiluminescent microparticle immunoassay for qualitative detection of IgG antibodies to SARS-CoV-2.

Statistical Analysis
Continuous variables are presented as median (interquartile range), and categorical variables are presented as number (percentage). Fisher exact tests were used for comparisons of qualitative variables, and Mann-Whitney tests were used for quantitative variables. All tests were 2-sided with a .05 value for significance. Factors associated with SARS-CoV-2 infection were assessed using multivariate logistic regression models. To account for the impact of lockdown on exposures, we considered 2 periods before and after March 22, 2020 (March 17, 2020 [date of national lockdown] + mean incubation period of 5 days). For each period, we first entered all exposures with a \( P < .40 \) in a multivariate model then used a backward stepwise selection procedure (removal criteria: \( P > .05 \)) to build the final model. Statistical analyses were performed using R-software (version 3.3.2; R Foundation for Statistical Computing, Vienna, Austria).

Patient Consent Statement
This study was approved by the Ethical Review Committee for publications of the Cochin University Hospital (number AAA-2020-08012). According to French policy, a nonopposition statement was obtained for all participants, meaning that all had received written detailed information on the objectives of the study and were free to request withdrawal of their data at any time.

RESULTS
Between February 24 and April 10, 2020, 1344 symptomatic HCWs were screened for SARS-CoV-2 by rtPCR on a nasopharyngeal swab. Among them, 373 had positive rtPCR results (28%), 336 (90%) completed the questionnaire, and were included as cases. Among 338 matched HCWs with negative rtPCR, 247 (73%) had a serological assessment, and 228 (92%) tested negative. This group of 228 HCWs with both negative rtPCR and serology constituted the control group.

Cases and controls were comparable in terms of age, sex, and professional category (Table 1). Cases presented more frequently with anosmia, ageusia, asthenia, fever, muscle pain, dyspnea, and headaches. Frequency of diarrhea, cough, or rhinorrhea did not differ between groups. Among cases, 3 were hospitalized and no death was reported.

Univariate and multivariate analyses are displayed in the Table 1. In brief, patient-facing activities and assignment to a COVID-19-dedicated unit were not associated with infection in both periods. Before lockdown, wearing a mask at all times outside home and limiting contacts with colleagues were independently protective. During lockdown, only close contacts with suspected or confirmed COVID-19 patients without PPE were independently associated with infection in HCWs. In both periods, contacts with children kept outside of the household were not associated with infection in HCWs.

DISCUSSION
Our results confirm that COVID-19 infection in HCWs is associated with risky behavior both inside and outside healthcare, as already shown by others [4, 5]. Most previous reports focused on occupational exposures [5] or did not use PCR testing or serologic assessment to formally confirm or exclude the diagnosis of COVID-19 [6, 7]. Other strengths of our study are the evaluation of multiple sources of infection, both inside and outside care, in particular contacts with children at home, and data collection through a direct investigator-to-respondent interview.

Our study took place during first wave of the pandemic, and occupational risk factors for COVID-19 were dominated by exposure to suspected or confirmed COVID-19 patients without PPE, as described elsewhere [5]. However, it is interesting to note that direct patient care in COVID-19-dedicated wards was not associated with infection in HCWs in our cohort. The PPE supplies were immediately and fully available in our center, which was not the case in all French healthcare settings. Compliance to protective measures may also have been higher among highly trained HCWs in dedicated units, as suggested by others [4, 5]. In a recent report, a large cohort study on 99 795 HCWs suggested that frontline HCWs may be at increased risk of COVID-19 compared with community individuals, especially in case of exposition to patients with inadequate PPE [6]. Our results also underline the role of transmission outside care, through exposure to colleagues without protection. Indeed, SARS-CoV-2 infectiousness starts up to 2 days before symptoms onset [8], thus strict compliance to universal masking and social distancing measures at hospital are critical to prevent SARS-CoV-2 transmissions from asymptomatic individuals.

Analysis of nonoccupational exposures suggest that wearing a mask outside the home may provide protection against COVID-19. In Hong Kong, a study suggested that the number of COVID-19 clusters were reduced when universal masking was recommended [9], and a study conducted in the United States concluded that mandatory mask wearing reduced daily COVID-19 growth rates [10]. However, to our knowledge, no study with high level of evidence has been published yet on that question. Of note, HCWs who reported to wear a mask outside home in our cohort (17%) were also probably more cautious regarding social activities and other suspected sources of SARS-CoV-2, which were not assessed in the questionnaire.

One important result is that HCWs who reported to have children kept outside the family home did not have a higher risk of COVID-19 infection, as suggested in our first report [1]. This question of SARS-CoV-2 transmission from children is highly
Table 1. Cases and Controls Comparisons Regarding Demography, Profession, Symptoms, and Occupational or Out-of-Hospital Exposures

| Variable                          | Overall (n = 564) | Controls (HCW−) (n = 228) | Cases (HCW+) (n = 336) | Prelockdown Period | Lockdown Period |
|-----------------------------------|-------------------|-----------------------------|------------------------|--------------------|-----------------|
| Median age (IQR), years           | 40 (31–53)        | 41 (33–52)                  | 40 (30–53)             | 1.00 [0.98–1.02]   | 0.99 [0.97–1.01] |
| Sex (female)                      | 448 (79)          | 183 (80)                    | 265 (79)               | 0.79 [0.44–1.39]   | 1.32 [0.63–2.72] |
| Professional Categorya             |                   |                             |                        |                    |                 |
| Physicians                        | 155 (28)          | 64 (28)                     | 91 (27)                | ref                | ref             |
| Paramedic staff (nurses, care assistants...) | 331 (59)          | 126 (55)                    | 205 (61)               | 0.98 [0.60–1.60]   | 1.49 [0.75–2.93] |
| Administrative staff (secretaries) | 56 (10)           | 28 (12)                     | 28 (8)                 | 0.85 [0.39–1.84]   | 0.56 [0.19–1.59] |
| Other employees (housekeepers...)  | 22 (4)            | 10 (4)                      | 12 (4)                 | 0.71 [0.21–2.42]   | 1.02 [0.26–4.44] |
| Symptoms                          |                   |                             |                        |                    |                 |
| Headaches                         | 420 (75)          | 158 (69)                    | 262 (78)               | 1.19 [0.70–2.02]   | 1.99 [1.01–3.98] |
| Asthenia                          | 405 (72)          | 133 (58)                    | 272 (81)               | 3.03 [1.78–5.22]   | 2.66 [1.40–5.08] |
| Fever (measured or reported)      | 369 (65)          | 123 (54)                    | 246 (73)               | 3.17 [1.93–5.26]   | 1.35 [0.73–2.47] |
| Cough                             | 363 (64)          | 136 (60)                    | 227 (68)               | 1.23 [0.75–1.99]   | 1.55 [0.85–2.83] |
| Muscle pain                       | 323 (57)          | 103 (45)                    | 220 (66)               | 2.11 [1.32–3.39]   | 2.46 [1.36–4.49] |
| Rhinorrhea                        | 284 (50)          | 113 (49)                    | 171 (51)               | 0.89 [0.55–1.37]   | 1.32 [0.74–2.38] |
| Anosmia                           | 244 (43)          | 15 (7)                      | 229 (68)               | 16.3 [8.45–34.0]   | 118 [29.1–1032]  |
| Ageusia                           | 233 (41)          | 18 (8)                      | 215 (64)               | 21.7 [10.5–49.5]   | 172 [75.0–44.7]  |
| Diarrhea                          | 197 (35)          | 68 (30)                     | 129 (38)               | 1.24 [0.77–2.02]   | 1.73 [0.92–3.34] |
| Dyspnea                           | 187 (33)          | 61 (27)                     | 126 (38)               | 1.69 [1.03–2.80]   | 1.53 [0.82–2.94] |
| Exposures                          |                    |                             |                        |                    |                 |
| In-hospital exposures             |                   |                             |                        |                    |                 |
| Exposure to patients              |                   |                             |                        |                    |                 |
| Occupational activities with direct patient facing | 388 (69)          | 154 (68)                    | 234 (70)               | 0.86 [0.53–1.40]   | 1.47 [0.76–2.82] |
| Regularly posted in a unit dedicated to COVID-19 patients | 123 (22)          | 48 (21)                     | 75 (22)                | 0.59 [0.28–1.25]   | 1.53 [0.82–2.88] |
| Had on average ≥1/day close contact with suspected or confirmed COVID-19 patients without PPE | 100 (18)          | 28 (12)                     | 72 (21)                | 1.22 [0.64–2.38]   | 3.85 [1.59–10.8] |
| Had on average ≥1/day close contact with suspected or confirmed COVID-19 patients with PPE | 204 (38)          | 93 (45)                     | 111 (34)               | 0.28 [0.16–0.51]   | 1.04 [0.56–1.92] |
| Exposure to Colleagues            |                   |                             |                        |                    |                 |
| Wears a medical mask always/most of the time at hospital | 372 (67)          | 163 (73)                    | 209 (63)               | 0.45 [0.28–0.72]   | 0.99 [0.34–2.63] |
| Spends on average >1 hour/day with colleagues without mask | 153 (31)          | 42 (24)                     | 111 (34)               | 2.77 [1.63–4.77]   | 0.52 [0.20–1.43] |
| Had on average >10 close contacts/day with colleagues without mask | 101 (18)          | 26 (12)                     | 75 (23)                | 2.80 [1.57–5.16]   | 2.58 [1.49–4.60] |
| Out-of-Hospital Exposure          |                   |                             |                        |                    |                 |
| Uses public transports            | 328 (58)          | 127 (56)                    | 201 (60)               | 0.92 [0.57–1.47]   | 1.86 [1.03–3.37] |
| Systematically wears a mask outside home | 96 (17)          | 50 (22)                     | 46 (14)                | 0.40 [0.19–0.83]   | 0.43 [0.21–0.85] |
| Systematically washes hands when back home | 509 (91)          | 210 (92)                    | 299 (90)               | 1.01 [0.47–2.13]   | 0.31 [0.03–1.46] |
| Leaves home on average ≥1 times a week | 495 (88)          | 205 (90)                    | 290 (86)               | 0.81 [0.33–1.88]   | 0.62 [0.25–1.42] |
Table 1. Continued

| Variable                                      | Overall | Control (HCW−) | Cases HCW+ in Multivariate Analysis OR [95% CI] | Cases HCW+ in Univariate Analysis OR [95% CI] |
|-----------------------------------------------|---------|----------------|-----------------------------------------------|-----------------------------------------------|
| Lives with ≥2 additional household members   | 28 (5)% | 73 (32)        | 0.88 [0.56–1.40]                               | 0.86 [0.44–1.67]                               |
| Lives with ≥1 child aged 0–4 years           | 15 (4)% | 11 (5)         | 0.86 [0.36–2.04]                               | 0.81 [0.36–1.94]                               |
| Lives with ≥1 child aged 5–15 years          | 25 (6)% | 12 (5)         | 1.05 [0.96–1.13]                               | 0.72 [0.60–8.93]                               |
| Lives with ≥1 adult aged ≥70 years            | 1%      | 1 (0)          | 0.55 [0.08–3.31]                               | 1.71 [1.03–2.84]                               |
| Has ≥1 child kept outside the household (school, nursery) |           |                |                                               |                                               |
| School                                       | 105 (3)%| 30 (13)        | 0.88 [0.56–1.40]                               | 0.86 [0.44–1.67]                               |
| Nursery                                      | 45 (2)% | 13 (6)         | 0.86 [0.36–2.04]                               | 0.81 [0.36–1.94]                               |
| Children kept in a facility with >5 other children | 31 (10)% | 10 (4)        | 1.34 [0.40–4.31]                               | 1.16 [0.42–3.72]                               |
| School attendance                             | 70 (19)%| 22 (9)         | 1.02 [0.66–1.57]                               | 1.62 [0.30–8.91]                               |

Bold text show OR [95% CI] for variables significantly associated with COVID-19 (HCW+) in a multivariable analysis. PPE, personal protective equipment; ref, reference.

Potential conflicts of interest.

All authors: No reported conflicts of interest.

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Author contributions.

A. C., J. L., O. L., and S. K. designed the study and drafted the paper. A. C., J. L., M. L.-V., F. R., O. L., and S. K. contributed to data analysis and interpretation. All authors critically revised the manuscript for important intellectual content and gave final approval for the version to be published. S. K. had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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