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Clinical characteristics and humoral immune response in healthcare workers with COVID-19 in a teaching hospital in Belgium

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SUMMARY

Background: Healthcare workers (HCWs) are at high risk of acquiring COVID-19 and could play a role in nosocomial transmission. Since 4th February 2020, Belgian Health authorities reported more than 90,568 cases, of which 8.3% were HCWs. Data on clinical characteristics, sources of infection and humoral immune response of HCWs with COVID-19 remain scarce.

Aim: To analyse the clinical characteristics, humoral immune response, sources of contamination, and outcomes among HCWs with COVID-19.

Methods: This retrospective study included 176 HCWs with laboratory-confirmed COVID-19 in a teaching hospital in Belgium. Between 1st March and 31st May 2020, all HCWs with symptoms suspected of COVID-19 were tested by reverse transcription polymerase chain reaction on a nasopharyngeal swab. Serological testing was performed between 55 and 137 days after the onset of symptoms.

Findings: Median age was 40.8 years and 75% were female. Median delay between onset of symptoms and diagnosis was 4.39 days. Most frequent symptoms were cough and headache (both 75%). Fever accounted for 68.7%. Most represented professions were nurses (42%). HCWs were mainly infected by patient contact (32.9%); 7.6% required hospitalization and 1.7% were admitted to the intensive care unit. Unfortunately, one HCW died (0.5%). Total antibodies were positive in 109/126 (86.5%).

Conclusions: Clinical presentation of COVID-19 in HCWs does not differ from the general population. However, outcomes were more favourable with a mortality rate lower than that reported in Belgian COVID-19 patients in general (16%). The main source of infection was the hospital setting. Our positive antibodies rate was high but lower than previously reported.

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Introduction

In December 2019, a new coronavirus responsible for severe acute respiratory syndrome (SARS-CoV-2) appeared in Wuhan, China [1]. The disease, later named COVID-19, has now spread worldwide. The World Health Organization (WHO) declared a pandemic on 11th March 2020 [2]. Healthcare workers (HCWs) are at increased risk of being exposed to SARS-CoV-2 and could potentially have a role in hospital transmission. Currently, the extent of SARS-CoV-2 transmission and risk factors associated with infection in healthcare settings are unclear. On 5th June 2020, the International Council of Nurses (ICN) showed that, on average, 6% of all confirmed cases of COVID-19 were among HCWs. The figures released by the ICN were based on data from just 30 countries. If that proportion were to be repeated globally, the 3.5 million confirmed cases of COVID-19 around the world would yield a figure of 210,000 for the number of infected HCWs [3]. Bandyopadhyay et al. reported that the total number of HCWs deaths as of 8th May 2020 was 1413 [4], representing 0.5% of the 270,426 COVID-19 deaths worldwide. This also suggests that for every 100 HCWs who were infected, one died. At the end of August, more than 800,000 deaths had been recorded worldwide. The first case of SARS-CoV-2 infection in Belgium was reported on 30th March 2020. Since then, the Institute of Public Health in Belgium (Sciensano) has reported over 90,568 cases, of which 30th March and 31st May 2020, in a large teaching hospital (7757 employees, Cliniques Universitaires Saint-Luc (CUSL) in Brussels, Belgium). Ethical approval for this study (Ethical Committee no. CEHF 2020/06AVR/201) was provided by the Institutional Review Board (CEBH of the Universite´ catholique de Louvain (UCLouvain), Brussels, Belgium), that provided a waiver for de-identified and anonymous analysis.

Materials and methods

This was a retrospective study performed between 1st March and 31st May 2020, in a large teaching hospital (7757 employees), Cliniques Universitaires Saint-Luc (CUSL) in Brussels, Belgium. HCWs working in non-COVID wards; the final group was HCWs working in COVID-19 dedicated wards. These are fully automated quantitative chemiluminescent immunoassays (CLIA) using magnetic microbeads.
coated with SARS-CoV-2 recombinant antigen labelled with ABEI, a non-enzyme small molecule with a special molecular formula that enhances stability in acid and alkaline solutions. The thresholds of positivity for these automated immunoassays are 1.0 AU/mL for IgM and IgG. The sensitivity and specificity are reported to be 64.5% and 100%, respectively [7]. Of note, diagnostic sensitivity is said to increase over time, reaching 95.5% (95% confidence interval (CI) = 84.9–99.2) between 15 and 25 days after symptom onset [7].

Statistical analysis

We collected data on an Excel sheet. We used GraphPad Prism version 8 to performed analysis. Continuous variables were expressed as means with standard deviations and categorical variables were expressed as counts and percentages. Categorical variables were analysed using chi-squared test or Fisher’s exact test. Differences between means or medians were compared using unpaired Student’s t-test or Mann–Whitney U-test, according to the distribution. All tests were two-sided, with significance set at the 0.05 probability level.

Results

A total of 176 HCWs with laboratory-confirmed COVID-19 were included in this study. Table I summarizes their demographic and clinical characteristics. The median age of the HCWs was 40.8 years (24–64) and 75% were female. Median

Table I

| Healthcare workers, N (%) | P |
|---------------------------|---|
| Overall (N = 176)         |   |
| COVID units (N = 53)      |   |
| Non-COVID units (N = 81)  |   |
| Other departments (N = 42) |   |
| Woman                     |   |
| 132 (75%)                 | 0.0009 |
| Age — median              |   |
| 40.8                      |   |
| Profession                 |   |
| Physician                  | <0.001 |
| 29 (16.4%)                 |   |
| Nurse<                      |   |
| 74 (42%)                   |   |
| Paramedics                 |   |
| 21 (11.9%)                 |   |
| Other, no direct patient contact |   |
| 52 (29.5%)                 |   |
| Symptoms                   |   |
| Cough                      |   |
| 133 (75.5%)                |   |
| Headache                   |   |
| 132 (75%)                  |   |
| ENT symptoms<               |   |
| 126 (71.5%)                |   |
| Fever<                     |   |
| 121 (68.7%)                |   |
| Myalgia                    |   |
| 115 (65.3%)                |   |
| Fatigue                    |   |
| 93 (52.8%)                 |   |
| Shortness of breath        |   |
| 66 (37.5%)                 |   |
| Gastrointestinal symptoms< |   |
| 54 (30.6%)                 |   |
| Ageusia or anosmia         |   |
| 40 (22.7%)                 |   |
| Outcomes                   |   |
| Hospitalization            |   |
| 13 (7.3%)                  |   |
| ICU                        |   |
| 3 (1.7%)                   |   |
| Death                      |   |
| 1 (0.5%)                   |   |
| Probable source of contamination |   |
| Hospital, health care setting |   |
| 58 (32.9%)                 |   |
| Private sphere             |   |
| 47 (26.7%)                 |   |
| Hospital, no health care setting |   |
| 40 (22.7%)                 |   |
| Unknown                    |   |
| 23 (13%)                   |   |
| Multiple sources           |   |
| 8 (4.5%)                   |   |
| Time between onset of symptoms and diagnosis — median (range) |   |
| 4.39 (0–18)                |   |

NS, non-significant.

< ENT symptoms include sore throat, and/or runny nose.

< Gastrointestinal symptoms include diarrhoea, and/or nausea, vomiting, abdominal pain.

< Fever is defined as a temperature of >38°C or the presence of solemn chills.

d Six assistant nurses and two physiotherapists.

e One ophthalmologist technician, five assistant nurses, one audiologist, four physiotherapists, and one radiology technologist.

f One priest.

g One administrative nurse assistant and one cleaner.

h Two administrative nurse assistants, two social workers, one dietician, and four psychologists.

i Thirteen administrative workers, five administrative nurses, four cleaners, three pharmacists, four childcare workers, seven secretaries, one waitress, one general technician, one social worker, and two laboratory technicians.
delay between symptom onset and diagnosis was 4.39 days (range 0–18).

The most frequent symptoms were cough and headache (both 75%), followed by sore throat/rhinorrhoea (71.5%). Fever, myalgia, and fatigue accounted for 68.7%, 65.3% and 52.8%, respectively. Other symptoms were shortness of breath (37.5%), gastrointestinal symptoms, mostly diarrhoea (30.6%), and ageusia/anosmia (22.7%).

Among the 176 cases, 30.1% worked in a COVID-dedicated ward, 46% worked in non-COVID ward and 23.8% in other departments (Table I). The most represented professions were nurses (42%) followed by non-paramedic workers (29.5%); physicians and paramedics accounted for 16.4% and 11.9%, respectively. One priest was considered a paramedic as he had close contact with patients.

A proportion of 32.9% of HCWs were infected through patient contact. Private and co-workers contact accounted for 26.7% and 22.7% of infections, respectively. Multiple sources of contamination were identified in 4.5% of cases, and a source of infection was not identified in 13% of cases. HCWs from COVID-dedicated units were mainly infected by contact with a patient (35/53, 66%) while contamination by a co-worker was the principal source of infection for HCWs from other departments of the hospital (18/42, 42.8%). For the HCWs from non-COVID wards, private contact was most common (30.8%), with infection from patient contact coming second (27.1%). The hospital setting accounted for 55.6% of all sources of infection in all HCWs. HCWs of the COVID unit were at greater risk than others of being infected in healthcare settings (P<0.001). No differences were observed between different categories of HCWs concerning infection outside the healthcare setting.

Figure 1 summarizes the timeline of HCW testing by RT-PCR between 1st March and 31st May 2020. 1st March and the days after 18th May are hidden from the graph to ensure a better visibility (no tests were performed on healthcare workers during these periods). Arrow represents the date (4th April) when universal masking was made mandatory inside the hospital.

Figure 1. Reverse transcription polymerase chain reaction tests performed on healthcare workers between 1st March and 31st May 2020. 1st March and the days after 18th May are hidden from the graph to ensure a better visibility (no tests were performed on healthcare workers during these periods). Arrow represents the date (4th April) when universal masking was made mandatory inside the hospital.

The outcomes of the infected HCWs were favourable in most cases. However, 13 (7.3%) required hospitalization; three (1.7%) required intensive care and invasive mechanical ventilation; two patients required extracorporeal oxygenation, and one patient unfortunately died (0.5%) (Table II). The median age of the hospitalized HCWs was 52 years (range 26–64), and 12 (92.3%) had at least one comorbidity.

Total antibodies were positive in 109/126 (86.5%) of HCWs with laboratory confirmed COVID-19. Of the 17/126 (13.5%) who were antibody-negative, 13/17 (76.5%) were tested at more than 3 months, three (17.6%) between two and three months, and one at less than two months following infection. Conversely, for the 109 total antibodies positive, 87/109 (80%)
| Patient | Age | Sex | Comorbidity                      | Severity of disease | Treatment | Symptoms at admission | LOS | ICU Intubation | ECMO | Serology (Roche) | Serology (IgG) (AU/mL) |
|---------|-----|-----|----------------------------------|---------------------|-----------|----------------------|-----|----------------|------|-----------------|------------------------|
| 1       | 53  | F   | Asthma                           | Moderate            | HCQ 5 days| Diarrhoea Dry cough  | 10  | /              | /    | /               | +                      |
| 2       | 58  | F   | Hypertension                     | Severe              | HCQ 5 days| Cough                 | 11  | /              | /    | /               | + 23.5                 |
| 3       | 50  | M   | Hypercholesterolemia             | Critical            | AZM 5 days| Cough Diarrhoea Fatigue | 78  | Yes            | Yes  | Yes             | + 114.5                |
| 4       | 64  | F   | Hypertension Type 2 diabetes     | Severe              | AZM 3 days| Anosmia/ageusia       | 12  | /              | /    | +               | Not done               |
| 5       | 56  | F   | Type 2 diabetes                  | Moderate            | /         | Anosmia/ageusia       | 7   | /              | /    | +               | /                      |
| 6       | 47  | M   | Type 2 diabetes Obesity          | Severe              | AZM 3 days| Cough Diarrhoea       | 14  | /              | /    | +               | 27.4                   |
| 7       | 55  | F   | None                             | Moderate            | HCQ 5 days|                      | 4   | /              | /    | +               | 20.9                   |

(continued on next page)
| Patient | Age | Sex | Comorbidity                              | Severity of disease | Treatment       | Symptoms at admission | LOS | ICU Intubation | ECMO | Serology (Roche) | Serology (IgG) (AU/mL) |
|---------|-----|-----|------------------------------------------|--------------------|-----------------|-----------------------|-----|----------------|------|-----------------|------------------------|
| 8       | 26  | F   | Pregnancy (29 weeks) Gestational diabetes | Severe             | HCQ 5 days CS 5 days | Cough Dyspnea Fatigue Fever Headache Rhinorrhea | 12 days | /              | /    | /         | + 54.3                |
| 9       | 51  | F   | Chronic neutropenia                      | Critical           | HCQ 5 days CS 5 days | Cough Dyspnea Fatigue Fever Headache Myalgia | 15 days (10 days in ICU) Death Yes Yes / | +   | 4             | /                      |
| 10      | 52  | F   | Chronic kidney disease (KDIGO III)       | Severe             | HCQ 5 days AZM 3 days CS 3 days | Anosmia/ageusia Cough 8 days Fever Dyspnea Myalgia | /     | /              | /    | /         | + 52.4                |
| 11      | 54  | M   | Hypertension Hypercholesterolemia Obstructive sleep apnea syndrome | Critical           | HCQ 5 days AZM 3 days CS 3 days Tocilizumab | Cough Dyspnea Fatigue Fever Headache Myalgia | 80 days (62 days in ICU) Yes Yes / | +   | 64.9          | /                      |
| 12      | 57  | F   | Asthma Hypertension                      | Moderate            | HCQ 5 days       | Diarrhoea Dyspnea Fatigue Fever | 5 days | /              | /    | /         | + 6.9                 |
| 13      | 57  | M   | Metabolic syndrome                       | Severe             | HCQ 5 days       | Cough Dyspnea Fatigue Fever Headache Myalgia Rhinorrhea | 9 days | /              | /    | /         | /                     |

AZM, azithromycin; CS, Corticosteroids; ECMO, extracorporeal membrane oxygenation; HCQ, hydroxychloroquine; ICU, intensive care unit; LOS, length of stay.
had been tested after 3 months and 22 (20%) between two and three months.

One hundred and two (102/109, 93.6%) were IgM-negative and 69/109 (63.3%) were IgG-positive. Of the 69/109 IgG positive HCWs, 51 (74%) were tested beyond three months and 18 (26%) between two and three months. In those with IgG negative (40/109), four (10%) were tested between two and three months and the others (36/40, 90%) beyond three months. Ageusia and or anosmia were the most predictive symptoms for positive antibodies, with, 28/29 HCWs with these symptoms was in part due to the movement of HCWs from one facility to another.

The outcome of COVID-19 was good, as many of the HCWs presented with mild disease. Thirteen of 176 patients required hospitalization (7.4%) of whom six had severe, and three critical, illness. The median age of hospitalized HCWs was 12 years higher than those who were not hospitalized, and all but one had comorbidities. The mortality in our cohort was lower than reported in COVID-19 patients in general in Belgium (16%) [5]. Sahu et al. [12] analysed the incidence of severe or critical disease and deaths among the affected HCWs. The incidence of severe or critical disease was nearly three times lower compared with all positive COVID-19 patients (9.9% vs 29.4%), and the mortality among HCWs was seven times lower (0.3% vs 2.3%). These observations may be explained by the younger age of HCWs, who are also less likely to have comorbidities [14]. Indeed, the median age of HCWs with COVID-19 was 52 years compared with 71 years in all COVID-19 hospitalized patients in Belgium [5]. A US study showed only 6% of HCWs were aged >65 years but 37% of the deaths occurred among this age group [8]. The one HCW who died in our series was aged of 51 years and had chronic neutropenia.

Concerning humoral immune response, total antibodies were positive in 109/126 (86.5%) of HCWs and of the 109 total antibodies positive, 69/109 (63.3%) were IgG positive. A large study in Spain [13] reported a seroprevalence close to 90% after 14 days after a positive PCR test, which is consistent with a recent study concluding that SARS-CoV-2 IgG antibodies are detected in more than 90% of infected people two weeks after symptom onset [16] and the recently reported 99% of antibody response among confirmed COVID-19 cases [17]. Our results seem to be lower than those reported by other authors [15–17]. This can be partially explained by the fact that we performed serological testing for the majority of the time more than three months after the onset of symptoms (80%). Indeed, rapid decrease of anti-SARS-CoV-2 antibodies in persons with mild COVID-19 have been described [18,19]. Long et al. found that the IgG levels in 93.3% (28/30) of the asymptomatic patients and 96.8% (30/31) of the symptomatic patients declined during the early convalescent phase. The median percentage of decrease was 71.1% (range, 32.8–88.8%) for IgG levels in the asymptomatic patients, whereas the median percentage of decrease was 76.2% (range, 10.9–96.2%) in the symptomatic patients [19]. Another explanation could be related to the performance of the assays used for serological testing [18]. Soleimani et al. reported the performances of a fully automated chemiluminescent immunoassay (CLIA) on 276 serum samples using the MAGLUMI 800 platform. All COVID-19-free samples had Ab levels below the cut-off values. Hence, the diagnostic specificity was estimated at 100% (95% CI = 96.3–100.0; positive predictive value = 100%). By the 18th day from the onset of symptoms, they reached an optimal diagnostic sensitivity (more than 95.0%) In fact, the diagnostic sensitivity increased over time and between 15 and 25 days after symptoms onset, reached 95.5% (95% CI = 84.9–99.2) [7]. However a recent study of humoral immune response to SARS-CoV-2 in Iceland by Gudbjartsson et al. using two pan-immunoglobulin (pan-Ig) assays found that over 1797 persons who had recovered from SARS-CoV-2 infection, 1107 of the 1215 who were tested (91.1%) were seropositive and antiviral

**Discussion**

We describe here the clinical characteristics and humoral immune response, as well as sources of infection and outcomes in a cohort of HCWs with laboratory confirmed COVID-19 in our teaching hospital. The clinical presentation was quite similar to other recent studies [8–10]. The United States Department of Health and Human Services (DHHS) reported a study of 4707 HCWs in whom 78% of the HCWs had cough, 68% fever, 66% myalgia, 65% headache, 50% sore throat/rhinorrhea, 41% shortness of breath, 32% diarrhoea, and 16% loss of ageusia or anosmia [8]. These findings are in line with Chinese (110 HCWs) and Dutch (86 HCWs) studies [9,10]. Symptoms in HCWs do not differ with those seen in the general population; according to a meta-analysis by Hu et al., fever, cough, fatigue, dyspnea were present in 85.6%, 65.7%, 42.4%, and 21.4% respectively [11]. In our series sore throat/rhinorrhea and headache was more common than in others series (71% and 75%, respectively).

Regarding the source of infection, HCWs in our study were mainly infected through patient contact (32.9%). Private and co-worker contact accounted for 26.7% and 22.7%, respectively. Overall, 55.6% of infections were attributed to contact in healthcare settings, and HCWs working in a COVID unit were at greater risk (<0.0001). Likewise, Burrer et al. [8] found that exposure in a healthcare setting accounted for 55% of the cases, household setting 27%, community setting 13% and multiple exposure settings 5%. Lai et al. [9] in a study of 110 Chinese HCWs with COVID-19 reported that 65 (59.1%) infections were attributed to contact with patients, 12 (10.9%) to contact with colleagues, and 14 (12.7%) to contact with family or friends.

In our study HCWs from a COVID-dedicated ward were mainly infected by patient contact (66%) while contamination by a co-worker was the principal source of infection for HCWs from other departments of the hospital (42.8%). For the HCWs from non-COVID wards, private sphere seems to be the first source of contamination (30.8%), with contamination by patient contact coming second (27.1%). In a recent meta-analysis [12], data on the specialty of HCWs and the area of the hospital where they were exposed were not available in most of the studies. Only Wang et al. [13] had reported that among the affected HCWs, 77.5% worked on general wards, 17.5% in the emergency department and 5% in the intensive care unit. It is important to note that some HCWs worked in both COVID-dedicated wards and non-COVID wards. Indeed, McMichael et al. [14] described the incidence of COVID-19 among HCWs working in long-term care facilities, and showed that the temporal and geographical transmission of the disease was in part due to the movement of HCWs from one facility to another.
antibody titers increased during 2 months after diagnosis by quantitative PCR and remained on a plateau for 4 months [20].

This study has several limitations. First, it is a retrospective single-centre study, albeit conducted in a large teaching hospital with over 7000 employees. Second, testing and surveys were based on self-reported symptoms, which could have led to an over-reporting of specific symptoms. Third, there is a lack of knowledge of the underlying health conditions of all HCWs. Another limitation is that it was not possible to follow the kinetics of antibodies as levels were measured at a single time-point. Finally, we do not know the total number of employees who worked in the dedicated or non-dedicated COVID wards, which prevented us establishing the actual rates of infection amongst HCWs working in different types of ward. The source of infection was determined on the basis of self-reported data by HCWs, which may not have been accurate; in particular HCWs working in dedicated COVID wards may have over-estimated the likelihood that they acquired their infection from patients.

Despite these limitations, we provide here an excellent and relatively complete point of view of HCWs with laboratory-confirmed COVID-19.

In conclusion, the clinical presentation of COVID-19 in HCWs does not differ from the general population. However, outcomes were more favourable with a mortality rate (1.7%) lower than that reported in Belgian COVID-19 patients in general (16%). This can be explained by the younger age of HCWs who probably also have fewer comorbidities. The main source of infection was in healthcare settings (55.6%). This underlines the importance of having clear protective procedures and also the fact of giving personal protective equipment of quality to HCWs. Our positive antibodies rate was high, but lower than in some other reports. Whether antibodies in HCWs confer protection against reinfection remains unclear [20].

Conflict of interest statement
All authors report no conflicts of interest relevant to this article.

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