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ORIGINAL ARTICLE

# Risk factors of SARS-CoV-2 seroprevalence among hospital employees in Italy: a single-centre study

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**Key words**
serology, SARS-CoV-2, healthcare worker.

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## Abstract

**Background:** The SARS-CoV-2 outbreak early in 2020 overwhelmed the Italian national health system, and hospitals were considered places at high risk of spreading the infection. We explored specific antibody seroprevalence of all employees at a single hospital in the epicentre of the outbreak, to identify areas of risk in nosocomial setting and to evaluate the usefulness of antibody testing.

**Aims:** Aim of this study was to explore SARS-CoV-2 seroprevalence in a single hospital workers cohort.

**Methods:** All hospital workers were invited to fill in a questionnaire and undergo a blood test for SARS-CoV-2 IgG, using two commercial tests (DiaSorin and Abbott). Seropositivity was determined overall and according to demographic and occupations characteristics, for both tests singly and combined.

**Results:** The study enrolled 1562 hospital workers (95% of the eligible population). Overall, 153 (9.8%) participants were positive for SARS-CoV-2 IgG on DiaSorin test, and 150 (9.6%) were positive on Abbott test; both tests were positive in 123 (7.9%) cases and at least one was positive in 180 (11.5%) cases. Factors associated with SARS-CoV-2 seropositivity included: being a smoker, working in emergency or medicine departments, being a healthcare practitioner, self-reporting a relative with COVID-19 or symptoms suggestive of COVID-19, and having undergone a nasopharyngeal swab test. The tests were accurate in discriminating infected cases, with an area under the receiver operating characteristic curve of 0.867 using manufacturer-suggested cut-offs and 0.929 using optimised cut-offs. For discriminating symptomatic subjects, this value was 0.915 using optimised cut-offs.

**Conclusions:** Seroprevalence for SARS-CoV-2 in this population of hospital workers was overall about 10%, with an excess prevalence in roles and departments associated with contacts with COVID-19 patients.

## Introduction

The novel coronavirus SARS-CoV-2 outbreak started, in Italy, on 20 February 2020, and northern Italy was severely affected, with more than 230 000 infected subjects as of 28 May 2020, and more than 33 000 deaths attributable to the infection.[1] However, official figures are thought to underestimate the real exposure at the population level, and according to the Italian Civil Protection, the actual infected cases may be 5–10 times higher (e.g. 1–2 million).[2] SARS-CoV-2 infection causes overt disease called COVID-19 (coronavirus disease 2019), but asymptomatic infections have been reported and, together with pre-symptomatic infections, are responsible for transmission of the infection in 15–50% of the cases, according to a recent meta-analysis.[3]

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The novel coronavirus outbreak is affecting not only the general population but also healthcare practitioners. Hospitals are risk spots for spreading the infection among inpatients,[4] due to hospital workers' multiple contacts with patients, impossibility of respecting social distancing[5–8] and virus contamination of hospital surfaces.[9] A recent study from a single hospital in Madrid found that, of all employees with known exposure or symptoms suggestive of infection, 38% was positive for SARS-CoV-2 genome in nasopharyngeal swabs, corresponding to 11.6% of all 6800 employees.[10]

Detection of viral genome in nasopharyngeal swabs permits the monitoring of active infection in hospital workers.[7,10] However, positive test results are transient (becoming negative as soon as the virus is cleared) and potentially inaccurate,[11] and do not allow the reliable tracking of safety of hospital pathways.[12] In contrast, serology is a promising epidemiologic tool to detect COVID-19 cases reliably[13,14] and to monitor infected people for a long time after viral contact.[14] The onset of IgG to SARS-CoV-2 antigens has been reported to occur 2–6 weeks after the start of infection.[13,14] However, the protective effects and diagnostic meaning of antibodies against different SARS-CoV-2 antigens are still poorly understood.[15] Furthermore, for some antibody tests, like point-of-care tests, there are quality concerns.[16] In contrast, serology is useful for detecting asymptomatic infections and thereby helps trace the spread of the disease. This information is needed to inform practices, especially in hospital, to understand risks and prevent future infections.[13]

This epidemiological study assessed SARS-CoV-2 seroprevalence in a well characterised population of hospital workers at a single hospital in northern Italy, and determined risk profiles for different healthcare practitioners and support staff. Furthermore, the study explored the diagnostic performance of two commercial serological tests that detect antibodies against different SARS-CoV-2 antigens, using manufacturer-suggested case-finding criteria as well as *ad hoc* cut-offs for seropositivity distinguishing infected from non-infected cases (nasopharyngeal swab test). Moreover, we tried to answer a question we were repeatedly asked: 'Why am I seronegative? I'm pretty sure I had COVID-19'. Therefore, we also defined *ad hoc* cut-offs for seropositivity to discriminate hospital workers with self-reported symptoms of COVID-19.

## Methods

### Study design, setting and population

This observational study was conducted at the Azienda Ospedaliera Ordine Mauriziano, a public, 450-bed hospital in northwestern Italy. During the first pandemic wave, between March and April 2020, up to half of the hospital beds were converted to COVID beds. The study protocol was submitted for evaluation on 21 April 2020, to the City Ethical Independent Committee, which granted approval on 29 April 2020 (approval #CS3/27, protocol 0042241).

All 1650 hospital employees (including administrative personnel, technicians and healthcare practitioners) were eligible and invited to participate by internal electronic mail. The letter they received contained a link to an electronic informed consent form. After reading and agreeing, they were requested to complete an electronic case report form (Google Forms; an English translation is presented as presented in the Supporting Information Form S1) and to have blood sampled within 2 days of each other (in either order). The case report form collected personal data (e.g. date of birth, gender, comorbidities), occupational information (e.g. position, department and tasks) and SARS-CoV-2 exposure information (e.g. possibility of direct contact with COVID-19 patients, use of personal protective equipment, COVID-19 symptoms and nasopharyngeal swab testing). More specifically, staff had to report if being appointed to high-intensity COVID wards (intensive and sub-intensive care units dedicated to COVID-19 patients), to low-intensity COVID wards (internal medicine wards dedicated to COVID-19 patients not requiring ventilation supports) or to 'clean' wards (admitting patients negative to SARS-CoV-2) or to other hospital facilities with no direct contact with COVID-19 patients.

Also, for staff members the usual rules for suspect case definition (positive symptoms or unprotected contact with known case) were applied , and they were triaged, isolated and swabbed accordingly: suspected cases underwent SARS-CoV-2 swab (depending in some time frames on swab availability) and isolated/managed at home if positive with no or mild COVID-19 symptoms, or hospitalised in COVID wards if positive with severe symptoms (or respiratory distress), according to World Health Organization (WHO) and National Health Systems protocols for the general population. For the study, all data were self-reported by the subjects. All staff members tested positive for SARS-CoV-2 were required to isolate at home or were admitted depending on their being asymptomatic/mildly symptomatic as opposite to severely COVID-19 symptomatic, in order to minimise intra-hospital virus spillover.

### Diagnostic procedures

One 9 mL blood sample was taken for serological assessment. Serum was freshly separated and stored at −20°C for a maximum of 2 days, until tested. Serological testing for specific SARS-CoV-2 IgG was done using two

commercial tests. The SARS-CoV-2 S1/S2 IgG test (Diasorin, Saluggia, Italy) is a chemiluminescence immunoassay for quantifying anti-spike 1 (S1) and anti-spike 2 (S2) IgG on the LIAISON XL automated analyser; according to the manufacturer, a titre <12 AU/mL is negative, from 12 to 15 is equivocal and >15 is positive; values below 3.8 are undetectable. The SARS-CoV-2 IgG assay (Abbott, Abbott Park, Illinois, USA) is a chemiluminescent microparticle immunoassay for quantifying anti-capsid IgG on the ARCHITECT iSystem analyser; according to the manufacturer, a titre <1.4 is negative and >1.4 is positive. Subjects who tested positive for SARS-CoV-2 IgG underwent a confirmatory nasopharyngeal swab polymerase chain reaction (PCR) test.

### Statistical analyses

Participants whose case report forms were lacking basic personal data (date of birth, gender, comorbidities) were excluded from analysis. Agreement between the two immunoassays was tested with Cohen's kappa coefficient ($\kappa$). To assess the impact of dependent variables on serological class, univariate analyses on $2 \times 2$ contingency tables were done to calculate odds ratios and 95% confidence interval (CI); *P*-values were calculated using the Chi-squared test. These analyses were done for each diagnostic test separately and for the two tests combined, in a conservative approach (positivity according to both assays, called 'AND' analysis) and in a more sensitive one (positivity according to at least one test, called 'OR' analysis).

To identify covariates associated with positive SARS-CoV-2 serology, multivariate stepwise logistic regression was done using those variables considered significant or borderline ($P < 0.10$) in univariate analyses. For this analysis, a $P < 0.05$ indicated significance. The magnitude of the impact of significant variables was expressed as odds ratios and 95% CI, and the relevance of prediction was reported as the area under the receiver operating characteristics curve and 95% CI.

Receiver operating characteristics (ROC) analyses were done to identify the best performing cut-off values for antibody tests. A first analysis identified the optimal cut-off for discriminating cases of COVID-19 with at least one previous positive or equivocal nasopharyngeal swab result (i.e. ability to discriminate infected from non-infected cases). A second analysis explored the best performing cut-off for discriminating self-reported cases with symptoms suggestive of COVID-19 (i.e. ability to discriminate symptomatic from asymptomatic subjects, even if not PCR confirmed). These new categorisations of serological data were used, together with the manufacturer-suggested cut-offs, to assess the diagnostic performance of the tests. The new cut-offs were also used in repeat univariate and multivariate analyses to identify demographic or occupational characteristics that are associated with newly defined seropositivity, in order to proceed to sensitivity analysis of the model.

Statistical analyses were carried out with MedCalc software, version 19.2.6 (MedCalc Software, Ostend, Belgium). A *P*-value of <0.05 was considered significant unless otherwise specified. The full anonymised data set is available as Supplemental data for authorised analyses.

## Results

### Study population

A total of 1607 hospital workers provided informed consent to participate in the study, but 45 cases failed to provide either a blood sample or the required personal data. Therefore, the study considered 1562 hospital workers (out of 1650 employees, i.e. 95% of the eligible population) who filled in the case report form between 7 and 18 May 2020, with a questionnaire completeness rate of 98%. The participants' median age was close to 50 years, and more than two-thirds were female (Table 1). Overweight or obesity was reported by 39.2%, a smoking habit by 22.4% and at least one comorbidity by 25.4%. Only 335 (21.5%) had been vaccinated for the flu. Most respondents were nurses or midwives (31.9%) and physicians (23.4%), but the study also included administrators, technicians and other employees. More than two-thirds (1114, 71.3%) of the participants were directly involved in patient care. Since 1 March 2020, 423 (27.1%) participants were directly involved in COVID-19 patient care, and an additional 193 provided services for COVID-19 patients; the remaining 60.6% worked in COVID-19-free areas. Personal protective equipment was used by most (1464, 93.7%) participants, and 864 (55.3%) had received formal training for such use. Finally, 334 (21.4%) participants self-reported previous symptoms suggestive of COVID-19, 879 (56.3%) had undergone a nasopharyngeal swab test before this study, and seven had been hospitalised for the disease; at the time of the study, all of these persons had recovered.

### Antibody seroprevalence

Blood samples were collected between 8 and 15 May 2020, and processed by 19 May 2020. According to manufacturer-supplied cut-offs for seroprevalence, on the DiaSorin test, 153 (9.8%) participants were positive for anti-S1 or anti-S2 IgG, while 24 (1.5%) were equivocal and 1385 (88.7%) were negative. On the Abbott test, 150 (9.6%) participants were positive for anti-capsid IgG and 1412 (90.4%) were negative. Altogether,

**Table 1** Characteristics of study population

| Variable | Value |
|---|---|
| Total study population, *n* | 1562 |
| Age, median (range) (years) | 49.9 (21.2–69.2) |
| Female gender, *n* (%) | 1070 (68.5) |
| Body mass index (95% CI) (kg/m$^2$) | 23.9 (15.6–43.0) |
| Overweight or obese, *n* (%) | 613 (39.2) |
| Smoker, *n* (%) | 350 (22.4) |
| Cigarettes, median (range) *n*/day | 10 (1–50) |
| Any comorbidity, *n* (%) | 397 (25.4) |
| Flu vaccination, *n* (%) | 335 (21.4) |
| Work contract, *n* (%) | |
| Full time | 1339 (85.7) |
| Part time | 86 (5.5) |
| Resident | 82 (5.2) |
| Other | 55 (3.5) |
| Work position, *n* (%) | |
| Nurse or midwife | 498 (31.9) |
| Physician | 366 (23.4) |
| Healthcare aide or social worker | 250 (16.0) |
| Administrator | 197 (12.6) |
| Technician | 178 (11.4) |
| Other | 73 (4.7) |
| Department | |
| Medicine | 483 (30.9) |
| Surgery | 424 (27.1) |
| Administration | 245 (15.7) |
| Imaging and services | 228 (14.6) |
| Emergency | 109 (7.0) |
| Maternity and infant | 73 (4.7) |
| COVID-19 patient care† | |
| No (COVID-19-free services or wards) | 946 (60.6) |
| High-intensity COVID-19 ward | 249 (15.9) |
| Services for COVID-19 patients | 193 (12.4) |
| Low-intensity COVID-19 ward | 174 (11.1) |
| PPE use, *n* (%) | 1464 (93.7) |
| Formal PPE training, *n* (%) | 864 (55.3) |
| Contact at COVID-19 risk at work | |
| No | 526 (33.7) |
| Yes | 1036 (66.3) |
| Household contact/relative with COVID-19, *n* (%) | |
| No | 1380 (88.3) |
| Yes | 112 (7.2) |
| Unsure | 70 (4.5) |
| Symptoms suggestive of COVID-19, *n* (%) | 334 (21.4) |
| Admitted for COVID-19, *n* (%) | 7 (0.4) |
| Nasopharyngeal swab test‡ | 879 (56.3) |
| Swab test result, *n* (%)§ | |
| Negative | 791 (90.0) |
| Positive | 71 (8.1) |
| Equivocal | 17 (1.9) |

†Since March 2020.‡For SARS-CoV-2 genome, prior to this study; data missing for six respondents.
§Percentage of respondents who had the test; in case of multiple tests, the worst test result is reported.
PPE, personal protective equipment.

123 (7.9%) participants had a positive result on both tests, while 180 (11.5%) were positive according to one test. Agreement between the two analytical tests was good, with $\kappa = 0.792$ (95% CI 0.739–0.844).

All subjects who were positive on a serological test ($n = 180$, 11.5%) underwent a successive nasopharyngeal swab PCR test. In 112 (62.2%) out of 180 cases swab tests resulted negative, in 61 (33.9%) cases resulted positive, in subjects with a known COVID-19 disease history, while in seven (3.9%) cases there was an unexpected positive result either after previous negativisation of swab tests (two (1.1%) cases) or as first swab (five (2.8%) cases, or 0.3% of all subjects tested). All but two new swab positivity cases were transient, and not confirmed at subsequent nasopharyngeal swabs, corresponding to 0.1% of the 1562 tested subjects.

Univariate analyses were done to examine associations between seropositivity and the participants' demographic and occupational characteristics (Table 2). Age greater than 50 years was associated with higher seropositivity according to both tests, while non-smokers had a lower odds of seropositivity than smokers on the Abbott test (and in the combined 'AND' and 'OR' analysis; Supporting Information Table S1). Both tests revealed significantly greater seropositivity among healthcare providers (namely, nurses, midwives, physicians, healthcare aides and social workers) than among other personnel, among emergency and medical department workers (than workers in other departments), in subjects directly involved in patient care, and among participants who were involved in COVID-19 patient care than those involved in other activities. Moreover, SARS-CoV-2 seropositivity was greater in participants who reported household contacts/relatives with (or suspected to have) COVID-19, especially if disease onset in the household contact/relative occurred after the study participant began to have symptoms suggestive of COVID-19 or was diagnosed with the disease. Finally, seropositivity was greater in cases with symptoms suggestive of COVID-19, in those who had undergone a nasopharyngeal swab test before this study, and in the seven cases hospitalised for COVID-19. Of the 791 persons who had a negative nasopharyngeal swab test, 741 (94%) and 734 (93%) were also negative on the Diasorin and Abbott tests, respectively. With one exception (smoking), all of these significant findings held true for both tests considered independently (Table 2) and when combined (Table S1), both when two tests had to be positive to define seropositivity ('AND' analysis) and when at least one test was sufficient to define seropositivity ('OR' analysis).

Since the time lag between active infection and the development of IgG, it was possible that some serology test results would be negative even in cases of PCR-confirmed infection. However, for the 238 study

**Table 2** Seropositivity for anti-SARS-CoV-2 IgG, by diagnostic test, using manufacturer-suggested cut-offs (significant associations are shown in bold)

| Characteristic | DiaSorin | | Abbott | |
|---|---|---|---|---|
| | *n* (%) | OR (95% CI) | *n* (%) | OR (95% CI) |
| Overall | 153 (9.8) | — | 150 (9.6) | — |
| Gender | | | | |
| Male (*n* = 492) | 54 (11.0) | Reference | 47 (9.6) | Reference |
| Female (*n* = 1070) | 99 (9.3) | 0.83 (0.58–1.17) | 103 (9.6) | 1.00 (0.70–1.45) |
| Age group | | | | |
| ≤50 years (*n* = 786) | **63 (8.1)** | **Reference** | **61 (7.9)** | **Reference** |
| >50 years (*n* = 776) | **90 (11.5)** | **1.46 (1.04–2.05)** | **89 (11.3)** | **1.50 (1.06–2.11)** |
| BMI group[†] | | | | |
| <30 kg/m$^2$ (*n* = 916) | 55 (9.0) | Reference | 50 (8.2) | Reference |
| ≥30 kg/m$^2$ (*n* = 613) | 93 (10.2) | 1.15 (0.81–1.63) | 96 (10.5) | 1.32 (0.92–1.89) |
| Smoker[‡] | | | | |
| No (*n* = 1209) | 30 (8.6) | Reference | **23 (6.6)** | **Reference** |
| Yes (*n* = 350) | 123 (10.2) | 1.21 (0.80–1.84) | **127 (10.5)** | **1.67 (1.05–2.65)** |
| Comorbidities | | | | |
| No (*n* = 1165) | 122 (10.5) | Reference | 120 (10.3) | Reference |
| Yes (*n* = 397) | 31 (7.8) | 0.72 (0.48–1.09) | 30 (7.6) | 0.71 (0.47–1.08) |
| Flu vaccination[‡] | | | | |
| No (*n* = 1224) | 122 (10.0) | Reference | 120 (9.8) | Reference |
| Yes (*n* = 335) | 30 (9.0) | 0.89 (0.58–1.35) | 29 (8.7) | 0.87 (0.57–1.33) |
| Work contract | | | | |
| Full time (*n* = 1339) | 130 (9.7) | Reference | 126 (9.4) | Reference |
| Other (*n* = 223) | 23 (10.3) | 1.07 (0.67–1.71) | 24 (10.8) | 1.16 (0.73–1.84) |
| Department | | | | |
| Other (*n* = 970) | **59 (6.1)** | **Reference** | **52 (5.4)** | **Reference** |
| Emergency or Medicine (*n* = 592) | **94 (15.9)** | **2.91 (2.07–4.11)** | **98 (16.6)** | **3.50 (2.46–4.99)** |
| Involved in patient care[¶] | | | | |
| No (*n* = 448) | **24 (5.4)** | **Reference** | **19 (4.2)** | **Reference** |
| Yes (*n* = 1114) | **129 (11.6)** | **2.62 (1.71–4.03)** | **131 (11.8)** | **3.13 (1.98–4.95)** |
| COVID-19 patient care | | | | |
| Other (*n* = 1139) | **98 (8.6)** | **Reference** | **93 (8.2)** | **Reference** |
| COVID-19 wards (*n* = 423) | **55 (13.0)** | **1.59 (1.12–2.26)** | **57 (13.5)** | **1.75 (1.23–2.49)** |
| PPE use | | | | |
| Any (*n* = 1464) | 143 (9.8) | Reference | 141 (9.6) | Reference |
| None (*n* = 98) | 10 (10.2) | 1.05 (0.53–2.06) | 9 (9.2) | 0.95 (0.47–1.92) |
| PPE training[††] | | | | |
| Yes (*n* = 864) | 84 (9.7) | Reference | 86 (10.0) | Reference |
| No (*n* = 589) | 58 (9.8) | 1.01 (0.71–1.44) | 54 (9.2) | 0.91 (0.64–1.31 |
| Exposure to COVID-19 at work through colleagues or patients | | | | |
| No (*n* = 526) | 44 (8.4) | Reference | 42 (8.0) | Reference |
| Yes (*n* = 1036) | 109 (10.5) | 1.29 (0.89–1.86) | 108 (10.4) | 1.34 (0.92–1.95) |
| Household contacts/relatives with COVID-19 | | | | |
| No (*n* = 1380) | **119 (8.6)** | **Reference** | **116 (8.4)** | **Reference** |
| Yes or unsure (*n* = 182) | **34 (18.7)** | **2.43 (1.60–3.70)** | **34 (18.7)** | **2.50 (1.65–3.80)** |
| When relatives were infected[‡‡] | | | | |
| Before (*n* = 111) | **13 (11.7)** | **Reference** | **16 (14.4)** | **Reference** |
| After (*n* = 24) | **16 (66.7)** | **15.1 (5.40–42.1)** | **16 (66.7)** | **11.9 (4.37–32.3)** |
| Symptoms suggestive of COVID-19 | | | | |
| No (*n* = 1228) | **77 (6.3)** | **Reference** | **70 (5.7)** | **Reference** |
| Yes (*n* = 334) | **76 (22.8)** | **4.40 (3.12–6.21)** | **80 (24.0)** | **5.21 (3.68–7.38)** |
| Nasopharyngeal swab test[§§] | | | | |
| No (*n* = 677) | **29 (4.3)** | **Reference** | **20 (3.0)** | **Reference** |
| Yes (*n* = 879) | **124 (14.1)** | **3.67 (2.42–5.57)** | **130 (14.8)** | **5.70 (3.52–9.24)** |
| Swab test result | | | | |
| Negative (*n* = 791) | **50 (6.3)** | **Reference** | **57 (7.2)** | **Reference** |
| Positive or equivocal (*n* = 88) | **74 (84.1)** | **78.3 (41.3–148)** | **73 (83.0)** | **62.7 (33.8–116)** |

**Table 2** *Continued*

| Characteristic | DiaSorin | | Abbott | |
|---|---|---|---|---|
| | *n* (%) | OR (95% CI) | *n* (%) | OR (95% CI) |
| Hospitalised for COVID-19[¶¶] | | | | |
| No (*n* = 1552) | **149 (9.6)** | **Reference** | **146 (9.4)** | **Reference** |
| Yes (*n* = 7) | **4 (57.1)** | **12.6 (2.78–56.6)** | **4 (57.1)** | **12.8 (2.85–57.9)** |

[†]Missing data for 33 (2.1%) cases.
[‡]Missing data for three (0.2%) cases.
[¶]Yes, nurses, midwives, physicians, healthcare aides and social workers; no, administrators and technicians.
[††]Missing data for nine (0.6%) cases.
[‡‡]Relatives affected before or after the interviewed, in 47 cases the interviewed did not report symptoms while the relative became positive.
[§§]Missing data for six (0.4%) cases.
[¶¶]Missing data for three (0.2%) cases.BMI, body mass index; CI, confidence interval; OR, odds ratio; PPE, personal protective equipment.

subjects who had a nasopharyngeal swab test <15 days before the serology test, no significant association to serological status was observed, and also the time between last swab and serology tests was not significantly different (Table S2).

According to multivariate logistic regression, covariates independently associated with seropositivity were, for both tests independently or combined, working in a high-risk department (i.e. emergency and medicine), reporting a household contact or relative with confirmed or suspected COVID-19, reporting symptoms suggestive of COVID-19 and having undergone a nasopharyngeal swab test (Table 3). A smoking habit was significantly associated with seropositivity on the Abbott test and in the 'AND' analysis (both diagnostic tests), while having comorbidity significantly associated with seropositivity on the DiaSorin test and in the 'OR' analysis (at least one test positive).

## Diagnostic performance

The diagnostic performance of the tests, alone and combined, was determined using the manufacturer-suggested cut-offs and two *ad hoc* ROC-generated cut-offs (Table 4). According to manufacturer-suggested cut-offs, for participants with a positive or equivocal result of

**Table 3** Covariates independently associated with seropositivity, by diagnostic test, according to stepwise multivariate logistic regression and area under the receiver operating characteristic (ROC) curve

| Test (cases, *n*) | Overall *P*-value | Variables retained | Variable *P*-value | Odds ratio (95% CI) | AUROC (95% CI) |
|---|---|---|---|---|---|
| DiaSorin (1528) | <0.0001 | Comorbidity | 0.020 | 0.60 (0.39–0.92) | 0.755 (0.732–0.776) |
| | | Department | 0.0001 | 2.12 (1.47–3.06) | |
| | | Household contacts/relatives with COVID-19 | 0.0008 | 2.16 (1.38–3.40) | |
| | | Symptoms suggestive of COVID-19 | <0.0001 | 3.48 (2.43–5.00) | |
| | | Nasopharyngeal swab test | <0.0001 | 2.53 (1.62–3.96) | |
| Abbott (1525) | <0.0001 | Smoker | 0.009 | 0.52 (0.32–0.85) | 0.795 (0.773–0.815) |
| | | Department | <0.0001 | 2.60 (1.78–3.83) | |
| | | Household contacts/relatives with COVID-19 | 0.0003 | 2.38 (1.49–3.77) | |
| | | Symptoms suggestive of COVID-19 | <0.0001 | 3.96 (2.73–5.73) | |
| | | Nasopharyngeal swab test | <0.0001 | 3.92 (2.32–6.64) | |
| DiaSorin AND Abbott (1525) | <0.0001 | Smoker | 0.005 | 0.45 (0.26–0.79) | 0.814 (0.793–0.833) |
| | | Department | <0.0001 | 2.47 (1.62–3.78) | |
| | | Household contacts/relatives with COVID-19 | 0.004 | 2.10 (1.26–3.49) | |
| | | Symptoms suggestive of COVID-19 | <0.0001 | 4.66 (3.11–6.99) | |
| | | Nasopharyngeal swab test | <0.0001 | 4.74 (2.53–8.89) | |
| DiaSorin OR Abbott (1496) | <0.0001 | Comorbidity | 0.018 | 0.60 (0.40–0.92) | 0.760 (0.737–0.781) |
| | | Department | <0.0001 | 2.43 (1.71–3.47) | |
| | | Household contacts/relatives with COVID-19 | <0.0001 | 2.56 (1.67–3.93) | |
| | | Symptoms suggestive of COVID-19 | <0.0001 | 3.32 (2.34–4.72) | |
| | | Nasopharyngeal swab test | <0.0001 | 2.45 (1.61–3.75) | |

AUROC, area under the ROC curve; CI, confidence interval.

nasopharyngeal swab testing, the sensitivity was above 80% and the specificity above 90% for both diagnostic tests considered independently or combined in the 'OR' analysis. ROC analysis of the data set, using the same case definition, generated substantially different cut-offs, namely ≥7.6 for the DiaSorin test (instead of ≥15) and >0.3 for the Abbott test (instead of >1.4). Recalculation of the diagnostic performance showed sensitivity values above 90% for all test combinations; however, the specificity values did not uniformly improve. Finally, ROC analysis of the data set, using a case definition of self-reporting symptoms suggestive of COVID-19, generated a third set of cut-off values and measures of diagnostic performance.

These new cut-offs were then used in repeat univariate analyses to identify demographic or occupational characteristics that associated with seropositivity (Tables 5, S3). These results were only slightly different from those obtained using the manufacturer-suggested cut-offs.

Multivariate logistic regression of covariates independently associated with seroprevalence gave similar results irrespective of the different cut-off values considered. Covariates associated with seropositivity on any single test at any cut-off value were: working in a high-risk department (emergency or medicine), reporting a household contact/relative with suspected or known COVID-19 and having undergone a SARS-CoV-2 nasopharyngeal swab test. In the combined 'AND' analysis, also being a smoker and being involved in patient care (nurses, midwives, physicians, healthcare aides, social workers) were significantly and independently associated with seropositivity rates (Table S4).

## Discussion

This study recorded an approximately 10% seroprevalence of anti-SARS-CoV-2 antibodies among employees of a large hospital in northern Italy. This result reflects almost universal coverage of all hospital employees, who were screened on two diagnostic tests detecting different IgG.

Employees involved in patient care (i.e. nurses, midwives, physicians and healthcare aides) were at least two times more likely to have been exposed to the virus than those with technical or administrative duties (Diasorin test, odds ratio = 2.62; Abbott test, odds ratio = 3.13). Moreover, employees of the emergency and medicine departments were approximately three times more at risk of the infection (Diasorin test, odds ratio = 2.91; Abbott test, odds ratio = 3.50). More than half of the study population had had a nasopharyngeal swab test before this study, and we observed an almost perfect overlap of serology results, with an accuracy of PCR predicting serology exceeding 90%. However, when exploring tests performance with different cut-off values, more sensitive to suggestive COVID-19 symptoms, we were not able to catch reliably much larger proportion of subjects.

Serological testing yielded only marginal number of asymptomatic subjects actively infectious, as shown by positive nasopharyngeal swabs (0.1% of all subjects tested).

The 10% seropositivity rate is similar to the rate of positive nasopharyngeal swab tests in a Spanish hospital study (available in preprint form[10]). It is also similar to

**Table 4** Diagnostic performance of tests and their combinations, according to manufacturer-suggested and receiver operating characteristics-determined cut-offs

| Test | Cut-off value | Sensitivity (95% CI) | Specificity (95% CI) | LH+ (95% CI) | LH− (95% CI) | AUC (95% CI) |
|---|---|---|---|---|---|---|
| Original cut-offs | | | | | | |
| DiaSorin | >15 | 84.1% (74.8–91.0) | 93.7% (91.8–95.3) | 13.3 (10.0–17.7) | 0.17 (0.11–0.28) | 0.889 (0.866–0.909) |
| Abbott | >1.4 | 83.0% (73.4–90.1) | 92.8% (90.8–94.5) | 11.5 (8.8–15.0) | 0.18 (0.12–0.29) | 0.879 (0.855–0.900) |
| 'AND' | AND | 78.4% (68.4–86.5) | 94.9% (93.2–96.4) | 15.4 (11.2–21.4) | 0.23 (0.15–0.34) | 0.867 (0.842–0.889) |
| 'OR' | OR | 88.6% (80.1–94.4) | 91.5% (89.4–93.4) | 10.5 (8.2–13.3) | 0.12 (0.07–0.22) | 0.901 (0.879–0.920) |
| Cut-offs for infected versus not infected | | | | | | |
| DiaSorin | ≥7.6 | 93.2% (85.7–97.5) | 88.2% (85.8–97.5) | 7.9 (6.5–9.7) | 0.08 (0.04–0.17) | 0.907 (0.886–0.925) |
| Abbott | >0.3 | 92.0% (84.3–96.7) | 90.8% (88.5–92.7) | 10.0 (7.9–12.5) | 0.09 (0.04–0.18) | 0.914 (0.894–0.932) |
| 'AND' | AND | 92.0 (84.3–96.7) | 93.7% (91.8–95.3) | 14.6 (11.1–19.2) | 0.09 (0.04–0.17) | 0.929 (0.910–0.945) |
| 'OR' | OR | 93.2% (85.7–97.5) | 85.3% (82.7–87.7) | 6.4 (5.3–7.6) | 0.08 (0.04–0.17) | 0.893 (0.870–0.912) |
| Cut-offs for symptomatic *vs.* asymptomatic | | | | | | |
| DiaSorin | >12.2 | 88.6% (80.1–94.4) | 92.3% (90.2–94.1) | 11.5 (8.9–14.8) | 0.12 (0.07–0.22) | 0.905 (0.883–0.923) |
| Abbott | ≥0.2 | 92.0% (84.3–96.7) | 89.0% (86.6–91.1) | 8.4 (6.8–10.3) | 0.09 (0.04–0.18) | 0.905 (0.884–0.924) |
| 'AND' | AND | 88.6% (80.1–94.4) | 94.4% (92.6–95.9) | 15.9 (11.8–21.4) | 0.12 (0.07–0.22) | 0.915 (0.895–0.933) |
| 'OR' | OR | 92.0% (84.3–96.7) | 86.9% (84.3–89.1) | 7.0 (5.8–8.5) | 0.09 (0.05–0.19) | 0.894 (0.872–0.914) |

'AND', seropositivity when both tests were positive; AUC, area under the receiver operating characteristics curve; CI, confidence interval; LH+, positive likelihood ratio; LH−, negative likelihood ratio; 'OR', seropositivity when at least one test was positive.

**Table 5** Overall and subgroup SARS-CoV-2 IgG positivity, based on DiaSorin and Abbott tests; results are based on receiver operating characteristics analysis-generated cut-off values for positivity tailored to detection of affected cases or self-reported COVID-19 symptoms (cases with a significant *P*-value are shown in bold)

| Characteristic | DiaSorin (≥7.6)† | | Abbott (>0.3)† | | DiaSorin (>12.2)‡ | | Abbott (≥0.2)‡ | |
|---|---|---|---|---|---|---|---|---|
| | *n* (%) | OR (95% CI) | *n* (%) | OR (95% CI) | *n* (%) | OR (95% CI) | *n* (%) | OR (95% CI) |
| Overall | 234 (15.0) | — | 197 (12.6) | — | 171 (10.9) | — | 219 (14.0) | — |
| Age group | | | | | | | | |
| ≤50 years (*n* = 786) | **132 (16.8)** | **Reference** | **114 (14.5)** | **Reference** | **101 (12.8)** | **Reference** | **125 (15.9)** | **Reference** |
| >50 years (*n* = 776) | **102 (13.1)** | **0.75 (0.57–0.99)** | **83 (10.7)** | **0.71 (0.52–0.96)** | **70 (9.0)** | **0.67 (0.49–0.93)** | **94 (12.1)** | **0.73 (0.55–0.97)** |
| Smoker§ | | | | | | | | |
| No (*n* = 1209) | 187 (15.5) | Reference | 161 (13.3) | Reference | 137 (11.3) | Reference | 180 (14.9) | Reference |
| Yes (*n* = 350) | 47 (13.4) | 0.85 (0.60–1.20) | 36 (10.3) | 0.75 (0.51–1.09) | 34 (9.7) | 0.84 (0.57–1.25) | 39 (11.1) | 0.72 (0.50–1.04) |
| Involved in patient care¶ | | | | | | | | |
| No (*n* = 448) | **44 (9.8)** | **Reference** | **34 (7.6)** | **Reference** | **28 (6.2)** | **Reference** | **40 (8.9)** | **Reference** |
| Yes (*n* = 1114) | **190 (17.1)** | **1.89 (1.33–2.67)** | **163 (14.6)** | **2.09 (1.42–3.07)** | **143 (12.8)** | **2.21 (1.45–3.37)** | **179 (16.1)** | **1.95 (1.40–2.80)** |
| Department | | | | | | | | |
| Other (*n* = 970) | **110 (11.3)** | **Reference** | **79 (8.1)** | **Reference** | **69 (7.1)** | **Reference** | **95 (9.8)** | **Reference** |
| Emergency or Medicine (*n* = 592) | **124 (20.9)** | **2.07 (1.57–2.74)** | **118 (19.9)** | **2.81 (2.07–3.81)** | **102 (17.2)** | **2.72 (1.97–3.76)** | **124 (20.9)** | **2.44 (1.83–3.26)** |
| COVID-19 patient care | | | | | | | | |
| Other (*n* = 1139) | **156 (13.7)** | **Reference** | **130 (11.4)** | **Reference** | **111 (9.7)** | **Reference** | 149 (13.1) | Reference |
| COVID-19 wards (*n* = 423) | **78 (18.4)** | **1.43 (1.06–1.92)** | **67 (15.8)** | **1.46 (1.06–2.01)** | **60 (14.2)** | **1.53 (1.09–2.14)** | 70 (16.5) | 1.32 (0.97–1.79) |
| Household contacts/relatives with COVID-19 | | | | | | | | |
| No (*n* = 1380) | **184 (13.3)** | **Reference** | **158 (11.4)** | **Reference** | **132 (9.6)** | **Reference** | **177 (12.8)** | **Reference** |
| Yes or unsure (*n* = 182) | **50 (27.5)** | **2.46 (1.72–3.53)** | **39 (21.4)** | **2.11 (1.43–3.12)** | **39 (21.4)** | **2.58 (1.73–3.84)** | **42 (23.1)** | **2.04 (1.40–2.98)** |
| Nasopharyngeal swab test†† | | | | | | | | |
| No (*n* = 677) | **59 (8.7)** | **Reference** | **43 (6.4)** | **Reference** | **32 (4.7)** | **Reference** | **51 (7.5)** | **Reference** |
| Yes (*n* = 879) | **175 (19.9)** | **2.60 (1.90–3.57)** | **154 (17.5)** | **3.13 (2.20–4.46)** | **139 (15.8)** | **3.79 (2.54–5.64)** | **168 (19.1)** | **2.90 (2.08–4.04)** |

†Cut-off value generated for optimal discrimination of infected/non-infected cases.

‡Cut-off value generated for optimal discrimination of symptomatic/ asymptomatic subjects.

§Missing data for three cases (0.2%).

¶Yes, nurses, midwives, physicians, healthcare aides and social workers; no, administrators and technicians.

††Missing data for six (0.4%) cases.

OR, odds ratio.

the prevalence of active infection in our sample, where 71 of 879 subjects who had a swab test were positive and 17 were equivocal. Our results are also similar to those of a recent multicentre study done in a neighbouring Italian region (available in preprint form[17]), where overall 11% of hospital workers were positive and 2% were equivocal on the Diasorin test (using the same test, we observed 9.8% and 1.5% respectively) and similar proportions of subjects were not directly involved in patient care (34.5% in our study, roughly 40% in a previous study[17]). The Spanish study tested 30.6% of all hospital employees[10] and the Italian study did not report coverage, while we were able to test SARS-CoV-2 serology virtually in all employees (1562 of 1650, 94.7%). Therefore, our results can be considered to give a realistic picture of SARS-CoV-2 seroprevalence.

Seroprevalence in some employee categories significantly exceeded the average, and was higher among subjects directly involved in patient care, in COVID-19 patient care and in emergency or medicine department activities. Instead, employees involved in care pathways for services (i.e. imaging, laboratory), surgery (i.e. general and specialty surgery wards) and administration were relatively safe from exposure. The excess seroprevalence in the emergency and medicine departments can be explained by the intrinsic greater difficulty to protect employees from infection during patients' first contact with the hospital (i.e. emergency department) or where patients are transferred from other hospitals and nursing home (i.e. medicine department). Better safety and care pathways, with stricter triage and more frequent swab testing at admission, should be implemented to reduce the risk of infection in these departments. Moreover, the observed seroprevalence in staff members with no direct COVID cases interactions (4–5%) is likely to reflect the background seroprevalence in the area, even if some population-based series in northern Italy reported much higher seroprevalence at the end of the second pandemic wave.[18,19]

It should be noted that the use of personal protective equipment (PPE) only limited, but not completely prevented, SARS-CoV-2 infections. It should be kept in mind that in earliest days only surgical mask use was prescribed, according to WHO statements,[20] but since mid-March 2020 PPE use was differentiated between COVID wards (where the use of double gloves, waterproof gowns, eye protection, boots and filtering face piece-2 (FFP2) or FFP3 masks was prescribed according to the eventual aerosol generating procedure) and non-COVID/administrative areas (where only the use of surgical masks together with hygiene and distancing rules were prescribed).

Many serological tests have been developed to detect anti-SARS-CoV-2 antibodies. We opted to use two high-throughput serological platforms, DiaSorin and Abbott, because they test antibodies to different viral epitopes and are marketed as being highly accurate. Although these tests measure only IgG, we avoided using point-of-care tests that detect IgM because they are only qualitative and are subjected to larger pre-test variability.[16,21] Moreover, using two diagnostic methods reduces the risk of relying too much on a single diagnostic modality. Given that they test different IgG, we combined the results using both a conservative approach (considering cases positive in both tests) and a sensitive approach (considering cases with at least one positive test result). Nonetheless, these approaches did not increase the rate of overall positivity beyond 11.5%. Therefore, it seems that the epidemiological impact of SARS-CoV-2 serology is limited, as it identified only 85 of the 334 symptomatic subjects, and missed 10 of the 88 PCR-confirmed or equivocal cases (data for the 'OR' analysis).

Possible explanations for the low seroprevalence are a low infection rate and a limited sensitivity of serological tests outside the setting of known COVID-19 cases or hard-hit regions. At present, there is no evidence to support serological testing of the general population or to grant 'immunity passports', and probably these tests should be used only in research protocols, as already suggested.[21] Since 2020 SARS-CoV-2 outbreak worldwide is partly fostered by infections transmitted by asymptomatic and pre-symptomatic subjects,[22,23] there is great need for a tool to monitor infections in hospitals, to best protect employees and other patients during virus outbreaks. At present, SARS-CoV-2 serology, based on our results, is unable to track these cases reliably and timely. A completely opposite read-out of data is that one should expect that the systematic use of adequate PPEs should have lowered even more the seroprevalence among hospital staff members, and therefore the 10% could be seen as a moderately high seroprevalence. The exact background population seroprevalence is not clear, but it is likely to be very close to the seroprevalence reported in our cohort.[18,19]

Different cut-off values for serology were tested to explain why PCR- or serology-based tests are negative in many persons who self-reported symptoms of COVID-19. However, the results were similar to those using manufacturer-supplied thresholds for positivity. One reason could be that the reported symptoms were not specific, and only sometimes were due to COVID-19. Another explanation, based on the expected ~40% of asymptomatic or mildly symptomatic cases,[3,7,22] could be that the serological tests are not sensitive enough. A third explanation could be that immune response differs between asymptomatic and symptomatic cases, and that serological tests are not calibrated to detect the

differences. Finally, our ROC-defined cut-offs to best detect subjects who self-reported COVID-19 symptoms may be ineffective in best identifying asymptomatic infections.

The prevalence of cases with PCR-confirmed SARS-CoV-2 infection was around 5% (88 of 1562) overall or 10% (88 of 879) of all subjects who had the test. This subset of subjects was used as internal reference for affected cases. However, using either the manufacturers' or our ROC-generated cut-off values, we found both cases with confirmed disease and negative serology (67 of 879, 7.6%) and cases with negative swabs and positive serology (10 of 879, 1.1%). The former can be explained in part by the latency to develop IgG (although our analysis of the time between swab and serological tests failed to find differences). The latter cases, which are rare, can be explained as false-negative swab results or false-positive serology results, although we do not know which are most likely.

The robustness of our results was indirectly confirmed by the observation that univariate and multivariate analyses associated the likelihood of seropositivity for SARS-CoV-2 to factors linked to higher risks of infection and were not influenced by variations in the cut-off values. Factors associated with higher seroprevalence were: being involved in COVID-19 patient care or in any patient care, or working in departments with higher number of infected healthcare practitioners (as opposed to having technical or administrative roles).

A limitation of the present study, regarding the assessment of diagnostic performance, is the lack of a reference method for comparison. Moreover, because the development of IgG requires a few weeks,[13,14] we may have missed some cases exposed to the virus. If we consider that COVID-19 peaked in northern Italy between mid-March and the end of April, we had high chances to detect all true-positive cases with a 2- to 4-week minimal follow up. Another limitation is that all personal data are referred by each employee, and therefore they may be affected by recall biases.

## Conclusion

This analysis of SARS-CoV-2 serology in a well characterised hospital employee population in northern Italy showed that one in 10 workers was exposed to the virus during the pandemic. The workers most at risk were those usually involved in patient care and those assigned to departments where COVID-19 cases were likely to present. Serology tests are valuable epidemiological tools that can help to ameliorate the safety of clinical pathways for possible subsequent SARS-CoV-2 pandemic waves and for future pandemics. However, serology seems to add little to a clinical diagnosis based on symptoms and on the detection of viral genome in nasopharyngeal swabs of suspected cases.

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## Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's web-site:

**Table S1** Seropositivity for anti-SARS-CoV-2 IgG, by diagnostic test, using manufacturer-suggested cut-offs. Significant associations are shown in bold.
**Table S2** Proportion of cases with previous last SARS-CoV-2 swab less than 15 days before serology and time in days between last swab and serology, calculation in the 879 subjects undergone SARS-CoV-2 PCR on swabs.
**Table S3** Overall and subgroup SARS-CoV-2 IgG positivity, based on DiaSorin test, Abbott test, and combination (concomitant positivity – 'AND' – or positivity at either test – 'OR'); results are based on ROC analysis-generated cut-off values for positivity tailored to detection of affected cases or self-reported COVID-19 symptoms. Results are reported as number of positive cases, percentage, *P*-value for comparison, odds ratios (OR) with 95% confidence interval (95% CI). In bold are highlighted cases with significant *P*-value.
**Table S4** Multivariate analysis results; stepwise logistic regression including variables significant/borderline significant at univariate was carried out for each seropositivity definition according to new cut-off values identified: DiaSorin (≥7.6 or >12.2), Abbott (>0.3 or ≥0.2), combination with both test positive ('AND') or with either one being positive ('OR') for calling a case positive, according to models based on disease or on symptoms.
**Form S1** Questionnaire for self-assessment for healthcare workers in SARS-CoV-2 study.