RESEARCH ARTICLE

Discrepancy between frequent occurrence of COVID-19-like symptoms and low seroconversion rates among healthcare workers

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Abstract

During the first wave of the pandemic, we compared the occurrence of subjectively experienced COVID-19-like symptoms and true severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) seroconversion rates among medical personnel in general practices. This cross-sectional study determined the SARS-CoV-2-specific immunoglobulin G (IgG) antibody status of medical staff from 100 outpatient practices in Germany. Study cohort characteristics and COVID-19-like symptoms were obtained by questionnaires. The initial screening for SARS-CoV-2-recognizing antibodies was performed using a commercial chemiluminescence microparticle immunoassay. Positive results were controlled with another approved test. Samples with discrepant results were subjected to a third IgG-binding assay and a neutralization test. A total of 861 participants were included, 1.7% ($n = 15$) of whom tested positive for SARS-CoV-specific IgG in the initial screening test. In 46.6% ($n = 7$) of positive cases, test results were confirmed by an independent test. In the eight samples with discrepant results, neither spike-specific antibodies nor in vitro neutralizing capacity were detectable, resulting in a genuine seroprevalence rate of 0.8%. 794 participants completed the questionnaire. Intriguingly, a total of 53.7% ($n = 426$) of them stated episodes of COVID-19-like symptoms. Except for smell and taste dysfunction, there were no significant differences between the groups with and without laboratory-confirmed SARS-CoV-2 seroconversion. Our results demonstrated that only 0.8% of participants acquired SARS-CoV-2 even though 53.7% of participants reportedly experienced COVID-19-like symptoms. Thus, even among

medical staff, self-diagnosis based on subjectively experienced symptoms does not have a relevant predictive value.

KEYWORDS
antibodies, COVID-19, general practice, infection rate, SARS-CoV-2, seroconversion rates

1 | INTRODUCTION

In situations such as the ongoing coronavirus disease (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), medical personnel and staff in general practices (GPs) in particular are in close contact with patients who spread the virus. While personal protective equipment (PPE) is broadly available in Germany now, many colleagues had to work with insufficient PPE or even without PPE during the first phase of the pandemic.[1] Data from a seroprevalence study comprising 3186 blood donors aged between 18 and 65 years in the German federal states North Rhine-Westphalia (NRW), Lower Saxony, and Hesse showed a low seroprevalence of 0.91% between March and June 2020.[2] A study from the United States and the United Kingdom (March/April 2020) demonstrated that healthcare workers (HCWs) were significantly more likely (~3.4-fold) to become infected with SARS-CoV-2 compared with the general population.[3] Worldwide, the data on the seroprevalence of SARS-CoV-2 in HCW differ significantly with an overall seroprevalence of 8.7% (North America 12.7%, Europe 8.5%).[4] In studies among HCWs in the northern metropolitan region of Barcelona, Spain (10.3%)[5] and in Sweden (19.1%),[6] the seroprevalence was even higher. In contrast, studies among clinic personnel from Germany showed significantly lower values with a seroprevalence between 1% and 4.36%.[7-9]

However, until now—at least to our knowledge—data on infection rates among medical staff in the outpatient sector are limited.

Almost all SARS-CoV-2-infected individuals develop at least one type of specific immunoglobulin (Ig) such as IgM, IgA or IgG, which remain detectable in most symptomatic patients for a 6-month period.[10-15] Given the phylogenetic relationship as well as the genetic and antigenetic similarity between human coronaviruses (hCoV), a certain cross-reactivity between the immune response triggered by seasonal hCoVs and SARS-CoV-2 may occur. A straightforward solution to solve potential specificity issues is the implementation of a two- or multi-layered testing strategy based on an initial screening test followed by one or more validation tests.

The course of COVID-19 is highly variable, ranging from asymptomatic to mild and moderate to severe as well as critical cases.[16] Since COVID-19 symptoms are highly nonspecific, according to the *Cochrane COVID-19 Diagnostic Test Accuracy Group* neither the presence nor the absence of a particular symptom can be considered a COVID-19 disease. In this context, anosmia or ageusia could be a red flag and fever or cough could also be symptoms that should trigger early testing for SARS-CoV-2.[17] So far, to our knowledge, there are few data from the outpatient sector examining whether SARS-CoV-2-specific diagnostics are also essential for healthcare professionals or whether an individual

assessment based on subjective reports of experiencing symptoms is sufficient.

2 | METHODS

2.1 | Subjects

Hundred registered GP participated in the study. The network is supra-regional, with practices being evenly distributed throughout NRW, Germany. In total, 861 doctors and medical staff members took part in the study and provided blood samples for the antibody determination. Of the 861 study participants, 87.1% (n = 750) were female. The questionnaire was completed by 92.2% (n = 794) of participants. Most participants were medical assistants (73.8%, n = 586), while 26.2% (n = 208) were medical doctors. The mean age of participants was 42.6 years (17–80 years); 34.4% (n = 273) were 50 years or older. For more details, see Table 1.

2.2 | Procedure

Study participants received the required material for blood sampling and the questionnaires by mail or by the laboratory's courier service. Blood samples were drawn in June 2020 by the practice staff and

TABLE 1 Description of the characteristics of the total cohort (n = 794) and the cohort with a positive confirmatory test

Properties in cohort	Total cohort, n = 794		Positive confirmatory test using DiaSorin Liaison (CMIA), n = 7	
	n	(%)	n	(%)
Medical assistants	586	(73.8)	5	(71.4)
Medical doctors	208	(26.2)	2	(28.6)
Age in years				
<50	521	(65.6)	3	(42.9)
≥50	273	(34.4)	4	(57.1)
50–59	176	(22.2)	1	(14.3)
60–69	90	(11.3)	3	(42.8)
≥70	7	(0.9)	0	(0)

Note: Describes the characteristics of the total cohort (n = 794) and the subgroup (n = 7) with a positive confirmatory test using DiaSorin Liaison (CMIA).

collected and analyzed by the laboratory "*Labor im Westen*". Since three recruited practices were on vacation at the time, their serum samples were collected and analyzed in July 2020.

The initial SARS-CoV-2 IgG screening was conducted using the approved Abbott SARS-CoV-2 IgG CMIA (Abbott). The test detects IgG by recognizing the N protein of SARS-CoV-2. According to the manufacturer, the specificity is 99.63% and the sensitivity is reported as 96.77% at ≥14 days postinfection.

Samples returning a positive SARS-CoV-2 IgG CMIA result were subjected to a second validation test using the approved Liaison SARS-CoV-2 S1/S2 IgG (CMIA; DiaSorin). According to the manufacturer, the diagnostic specificity and the sensitivity are 98.9% and 97.4%, respectively, at ≥15 days postinfection. Discordant results were subjected to a third analysis using the EUROIMMUN Anti-SARS-CoV-2 enzyme-linked immunosorbent assay (ELISA) (Lübeck) for which the manufacturer indicates a specificity and sensitivity of 99.6% and 94.4%, respectively, at ≥10 days postinfection. Both tests use the spike (S) protein as the target antigen. Additionally, samples with discrepant results were further tested for the presence of neutralizing antibodies using an automated SARS-CoV-2 neutralization assay based on an in-cell ELISA.[18]

Each participant received a questionnaire collecting information on COVID-19-like symptoms as well as on previous testing for a SARS-CoV-2 infection such as a swab-based real-time quantitative polymerase chain reaction assay (RT-qPCR). In this regard, an evaluation of the performance of local swab sample collections found an accuracy exceeding 90% of cases.[19] Some questions were identical to the previous corona questionnaire of the Heinz-Nixdorf Recall Study and the NAKO (National Cohort) Health Study.[20]

2.3 | Statistical analyses

All analyses were performed using IBM SPSS Statistics for Windows, Version 27 (Armonk: IBM Corp.). To compare subjects who tested positive and subjects who tested negative using the CMIA, DiaSorin Liaison test, the nonparametric Mann–Whitney U test was employed, as the values of the CMIA in S/CO (Abbott) are not normally distributed (Kolmogorov–Smirnov test; $p = 0.034$). Cross-tabulations were applied to compare the symptoms reported between March and June 2020 of those who tested positive and negative for COVID-19-specific antibodies. Since the expected cell frequencies were less than 5 due to the small sample size of those testing positive for COVID-19, Fisher's exact test was calculated, and two-sided p values were reported. The Bonferroni correction was applied to exclude multiple testing, resulting in an adjusted $\alpha = 0.00385$.

The primary data that support the findings of this study are available from the corresponding author upon reasonable request. We adhered to the principles of the Declaration of Helsinki. All participants received written information leaflets and provided signed informed consent forms. Ethical approval was obtained from the Ethics Committee of the Medical Faculty of the University of Duisburg-Essen (reference number: 20-9339-BO, date of approval: 05/20/2020). The study was entered in the German registry for clinical studies (DRKS00021788, 07/14/2020).

3 | RESULTS

3.1 | Antibody determination

Fifteen of the 861 participants (1.7%) had a positive screening test result according to the approved Abbott test. In 7 (46.6%) samples, the test result was validated using the DiaSorin Liaison SARS-CoV-2 S1/S2 IgG CMIA test. In the eight samples with discrepant results, SARS-CoV-2-specific antibodies recognizing the S protein were also undetectable by the EUROIMMUN Anti-SARS-CoV-2 ELISA. Accordingly, a neutralization test did not show neutralizing capacities of these sera against SARS-CoV-2. For more details, see Table 2.

The subjects with negative results in the validation test had significantly lower scores (median = 2.05, mean = 2.07, SD = 0.359) in the initial test (Abbott) than the subjects with positive results (median = 5.11, mean = 5.51, SD = 1.670) in the validation test (U = 0.000, Z = −3.243, p < 0.001). For more details, see Figure 1.

3.2 | COVID-19-like symptoms among medical personnel between February and July 2020

Several hundred (n = 794) participants completed the questionnaire, of whom 53.7% (n = 426) stated episodes of COVID-19-like symptoms in early 2020. Among those without SARS-CoV-2 IgG antibodies (n = 787), 420 study participants (53.4%) reported at least one symptom that could have been attributed to a SARS-CoV-2 infection. The most common symptoms were headache (32.0%; n = 252), fatigue (27.6%; n = 217), sore throat (26.8%; n = 211), and cough (23.0%; n = 181). For further details, see Figure 2.

Among the seven participants who tested positive in all tests, two were medical doctors and five were medical assistants aged between 27 and 67 years (mean age 48.9 years). Six of the seven study participants (85.7%) had experienced at least one COVID-19 symptom between 1 February and 13 July 2020. The majority of the seven participants reported one to three symptoms, while one participant reported as many as eleven symptoms. The most common symptoms included: recent loss of taste (42.9%; n = 3), recent loss of smell (42.9%; n = 3), and nasal congestion (42.9%; n = 3). For more details, see Figure 2.

The percentage of participants with positive test results and of those with negative test results did not differ significantly with regard to the following symptoms: fatigue (p = 1.000), respiratory problems (p = 0.408), diarrhea (p = 0.583), fever (p = 0.180), body ache (p = 0.336), sore throat (p = 1.000), cough (p = 0.664), headache (p = 1.000), nasal congestion (p = 0.137), chills (p = 0.379), and nausea (p = 0.430). However, significant differences between the two groups were found for the symptoms smell dysfunction/recent loss of smell (p < 0.000) and taste dysfunction/recent loss of taste (p < 0.000).

TABLE 2 Results of the IgG antibody determination for SARS-CoV-2 as well as the neutralization test in the total cohort and in the cohort with an initially positive antibody test

n = 846	CMIA in S/CO (Abbott) <1.4	CMIA (DiaSorin) –	ELISA (EUROIMMUN) –	Neutralization test icELISA SARS-CoV-2 –
1	8.62	Positive	–	–
2	6.31	Positive	–	–
3	5.46	Positive	–	–
4	5.11	Positive	–	–
5	5.07	Positive	–	–
6	4.99	Positive	–	–
7	2.98	Positive	–	–
8	2.74	Negative	Negative	Negative
9	2.31	Negative	Negative	Negative
10	2.07	Negative	Negative	Negative
11	2.05	Negative	Negative	Negative
12	2.05	Negative	Negative	Negative
13	2.04	Negative	Negative	Negative
14	1.79	Negative	Negative	Negative
15	1.51	Negative	Negative	Negative

Note: Describes the results of the antibody determination for SARS-CoV-2 and the result of the neutralization test. First the CMIA from Abbott was applied and afterwards a second test with Liaison SARS-CoV-2 S1/S2 IgG (CMIA; DiaSorin) was used to validate the results. Discordant results were subjected to further analysis using the EUROIMMUN Anti-SARS-CoV-2 ELISA (Lübeck, Germany) on the one hand and an automated SARS-CoV-2 neutralization test based on an in-cell ELISA on the other hand.

Abbreviations: ELISA, enzyme-linked immunoassay; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
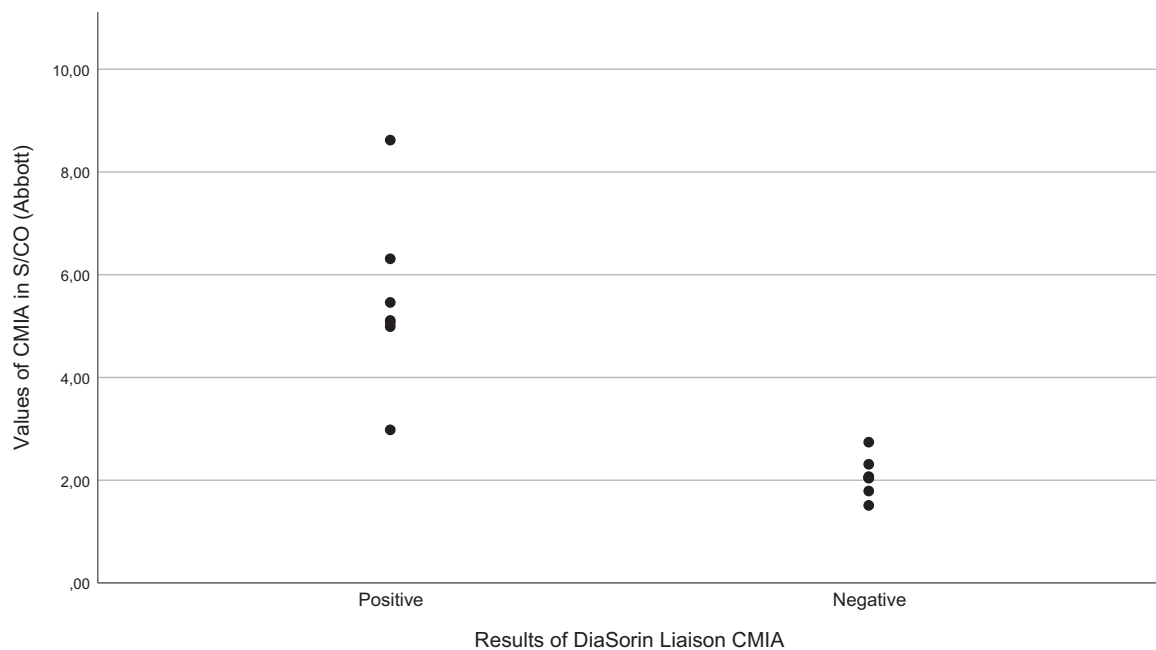

FIGURE 1 Scatter plot of the values of the Abbott SARS-CoV-2 IgG CMIA and the results of the confirmatory test using DiaSorin Liaison (CMIA). IgG, immunoglobulin G; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

FIGURE 2 Comparison of COVID-19 symptoms reported during the observational period of HCWs who tested positive (n = 7) and negative (n = 787) in %. ***p < 0.000. describes the COVID-19-like symptoms of HCWs who tested positive (n = 7) and negative between February and July, 2020. HCW, healthcare worker
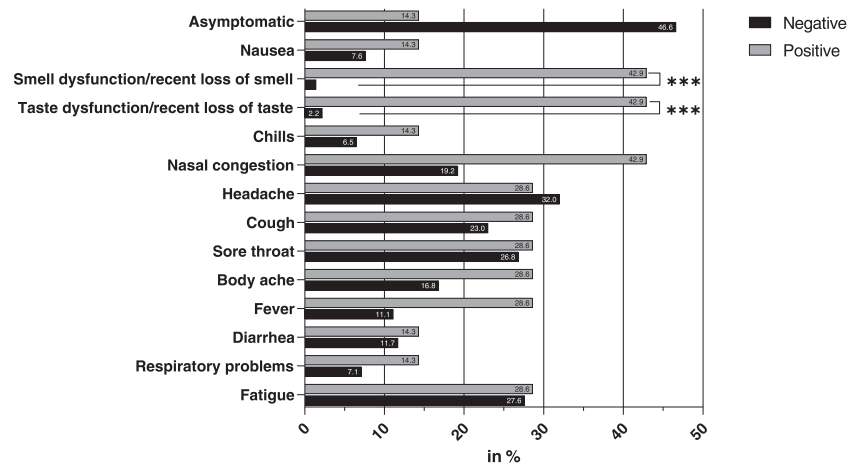
3.3 | Frequency of a previous RT-qPCR

Of the 794 participants who completed the questionnaire, 789 (99.4%) provided information concerning previous swab-based virus recognition tests (RT-qPCR). In total, 166 (21.0%) participants had been tested for the presence of SARS-CoV-2 since February 2020, including tests for participants without symptoms. The majority of the cohort had not been tested with a RT-qPCR for the presence of SARS-CoV-2, irrespective of the presence or absence of COVID-19 symptoms.

Of the seven participants with a positive confirmatory test in the aforementioned serology, three previously had an RT-qPCR. All three tests returned positive results. These three subjects gave the following reasons for having the throat swab: typical COVID-19 symptoms and contact with a patient with laboratory-confirmed COVID-19 within 14 days before the test.

4 | DISCUSSION

Due to their repeated contact with people infected with SARS-CoV-2, medical staff members have an increased risk of SARS-CoV-2 exposure.[3] Therefore, we assessed the occurrence of COVID-19-like symptoms and SARS-CoV-2 seroconversion rates among medical personnel in GPs during the first wave of the pandemic in 2020. Surprisingly, the present study revealed a low seroprevalence of SARS-Cov-2 among GP personnel during the first infection wave. The screening test to determine the antibody status recognizing the SARS-CoV-2 N protein showed a positivity rate of 1.7%. Considering the results of three subsequent tests, two of which recognize the SARS-CoV-2 S antigen and one that detects neutralizing capacities, an even lower overall seroprevalence of 0.8% was identified. Similar results were found in other seroprevalence studies among clinic staff in Europe, with seroprevalence rates between 1.6% and 7.4%.[21–23] To our knowledge, only one other study focusing on the outpatient sector has been conducted in Germany so far, namely a seroprevalence study among 151 employees of a primary care facility (medical care center, MVZ) with eight locations in Bavaria. Here, a

higher seroprevalence rate of 2.4% was reported, but it must be noted that a confirmatory test was not part of the study protocol.[24] With a total of 100 practices across NRW and given the different types of practices included (single practice, group practice, MVZ), and the verification of the test results for SARS-CoV-2 IgG antibodies with two validation tests (DiaSorin Liaison SARS-CoV-2 IgG Assay, EUROIMMUN Anti-SARS-CoV-2 ELISA) as well as a neutralization test, we feel that our study constitutes a reliable source of information. Given the global shortage of protective equipment in the early phase of the pandemic[1] and the fact that staff in GPs in particular are the first point of contact for patients, it is rather surprising that the seroprevalence rate remained so low. Thus, it can be concluded that the recommended nonpharmacological intervention strategies (e.g., establishment of test centers for swab collections, prior telephone contact with the practices in case of COVID-19 symptoms, obtaining a medical certificate only via telephone contact, washing hands more frequently etc.) were effective and successful.

Additionally, this study revealed a discrepancy between the subjective experience that apparently felt like COVID-19 in contrast to real SARS-CoV-2 infections. Interestingly, more than half of the respondents reported at least one symptom that was compatible with COVID-19, while only a minority showed seroconversion. In our study, only the symptoms smell and taste dysfunction differed significantly; other symptoms such as sore throat, headache, and fatigue did not differ significantly and were similarly common in both the group with and the group without SARS-CoV-2 seroconversion. Although we found a significant difference only in the symptoms smell and taste dysfunction, these symptoms do not appear to be exclusive to COVID-19, as 1.4% and 2.2% of those without seroconversion mentioned them.

Furthermore, it is noteworthy that many practice personnel reported episodes of symptoms compatible with COVID-19 but only a fraction of them were tested by RT-qPCR. In the initial phase of the pandemic, the SARS-CoV-2 test capacities were limited and the Robert Koch-Institute recommended a test only if typical symptoms were present, upon returning from defined risk areas, or after contact with a confirmed COVID-19 case.[25] A very important issue here is that the misconception of having had a SARS-CoV-2 infection caused

not only anxiety and stress, but also led to false assumptions regarding acquired immunity. This could result in neglect of the use of protective measures, vaccination hesitancy, and finally an increased risk of infections. Extensive education and testing as early as possible would be desirable to counteract this uncertainty.

In summary, even among medical staff, self-diagnosis based on subjectively experienced symptoms lacks predictive value. Accordingly, early and broad testing is indispensable due to the unspecific nature of COVID-19 symptoms.

4.1 | Strengths, limitations, and perspectives

GPs are an essential part of the German healthcare system and until now the data on infection rates among medical staff in the outpatient sector are scarce. This study is one of the first to provide detailed data on SARS-CoV-2 infection rates among medical staff in GPs. One of the strengths of the study is certainly that the test results for SARS-CoV-2 IgG antibodies were verified with two validation tests as well as with a neutralization test. A study by Cervia et al.[26] showed that systemic IgG antibody production depends on the severity of the disease. Antibody responses appear to be less sustained following asymptomatic infections and/or in patients who experience only mild symptoms.[26] Thus, it cannot be completely ruled out that the humoral immune response in some participants, in particular following asymptomatic or very mild COVID-19 course, waned to a point where SARS-CoV-2-specific antibodies were below the level of detection. In this regard, however, other studies argue in favor of more sustained IgG responses especially after symptomatic COVID-19 infection.[12]

In view of the overall sample size, one limitation is the small number of subjects with a positive test result, which limits the applicability of statements about the participants with a positive test result. Larger study populations are required for further analyses.

5 | CONCLUSIONS

The present study shows that COVID-19 infection rates among medical staff in GPs in NRW in Germany remained low during the first wave of the pandemic. Furthermore, an individual assessment based on experienced symptoms has no or very little predictive value even among medical staff.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Dorothea Dehnen: developed the study idea and concept, collected data, performed statistical analysis and data interpretation, prepared the manuscript and revised it in communication with the co-authors. **Katja Dehnen**: performed statistical data analysis and data interpretation, prepared and revised the manuscript. **Mirko Trilling**: performed and supervised the validation and the neutralization test, supported data interpretation, reviewed the manuscript. **Melanie Fiedler**: developed the study idea, supported data interpretation, supervised the validation and the neutralization test, reviewed the manuscript. **Julia Drexler** and **Marcel Goralski**: supported the data collection. **Vu Thuy Khanh Le-Trilling** and **Lara Schöler**: performed and supervised the validation and the neutralization test, reviewed the manuscript. **Karl-Heinz Jöckel**: supported the development of the study concept, supported statistical analysis, reviewed the manuscript. **Martina Heßbrügge**: supervised the project, reviewed the manuscript. All authors contributed to the article and approved the submitted version.

ETHICS STATEMENT

Ethical approval was obtained from the Ethics Committee of the Medical Faculty of the University of Duisburg-Essen (reference number: 20-9339-BO, date of approval: 05/20/2020). All participants received written information leaflets and provided signed informed consent forms.

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