BMJ Open

Epidemiology of SARS-CoV-2 in Healthcare Workers following the First Wave of the COVID-19 Pandemic

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-051415
Article Type:	Original research
Date Submitted by the Author:	18-Mar-2021
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Keywords:	COVID-19, EPIDEMIOLOGY, Infection control < INFECTIOUS DISEASES, Diagnostic microbiology < INFECTIOUS DISEASES

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Epidemiology of SARS-CoV-2 in Healthcare Workers following the First Wave of the COVID-19 Pandemic

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Keywords:

- COVID-19
- SARS-CoV-2
- Healthcare worker epidemiology
- Anti-nucleocapsid IgG

Word Count: 2,354

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Abstract

Objective
Our study aimed to measure seroprevalence of SARS-CoV-2 specific IgG antibodies, using the Abbott anti-nucleocapsid IgG CMIA assay, in five pre-specified HCW subgroups following the first wave of the COVID-19 pandemic.

Setting
An 800-bed tertiary level teaching hospital in the south of Ireland.

Participants
Serum was collected for anti-SARS-CoV-2 nucleocapsid IgG using the Abbott ARCHITECT SARS-CoV-2 IgG CMIA® qualitative assay, as per the manufacturer's specifications.

The groups were as follows:

1. HCWs who had RT-PCR confirmed COVID-19 infection (>1 month post positive RT-PCR)
2. HCWs identified as close contacts of persons with COVID-19 infection and who subsequently developed symptoms (RT-PCR not detected on swab)
3. HCWs identified as close contacts of COVID-19 cases and who remained asymptomatic (not screened by RT-PCR)
4. HCWs not included in the above groups working in areas determined as high risk clinical areas
5. HCWs not included in the above groups working in areas determined as low risk clinical areas

Results
6 of 404 (1.49%) of HCWs not previously diagnosed with SARS-CoV-2 infection (groups 2-5) were seropositive for SARS-CoV-2 at time of recruitment in to the study.

Out of the 99 participants in Group 1, 72 had detectable IgG to SARS-CoV-2 on laboratory testing (72.73%). Antibody positivity correlated with shorter length of time between RT-PCR positivity and antibody testing.

C_q value on RT-PCR was not found to be correlated with antibody positivity.

Conclusions
Seroprevalence of antibodies in participants who had not previously tested RT-PCR positive was low compared to similar studies.

Strengths and Limitations of this Study

- We successfully recruited the numbers that we had aimed for in each of the pre-specified groups
- This was a single centre study in an area of relatively low prevalence
- Enrolment began eight weeks after peak regional prevalence and therefore IgG antibodies may have become undetectable in a proportion of participants
- Recruitment of groups 3-5 was by self-selection and therefore was not a true random sample of these groups

Introduction

Healthcare workers (HCWs) at the frontline treating patients with suspected or confirmed coronavirus disease-2019 (COVID-19) have been heavily impacted by the pandemic. Due to potential occupational exposures, HCWs are at higher risk of infection from patients or from other HCWs than the general population. In a study published in July 2020, there was an estimated hazard ratio of 3.40 for COVID-19 infection in HCWs compared to risk of infection in the general population[1]. Indeed, as of November 2020 in the Republic of Ireland, the health protection and surveillance centre put the number of HCW infections at 10,976 accounting for 16.6% of total infections[2]

The first case of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection was reported in Ireland on February 29th 2020 relating to travel. On March 5th, a patient was diagnosed with SARS-CoV-2 infection who had been ventilated in the intensive care unit of Cork University Hospital (CUH) with atypical pneumonia despite having no epidemiological link to a known case or area of high prevalence. This was the first documented community acquisition of SARS-CoV-2 in the Republic of Ireland and was an indication of potential widespread community transmission[3]. From this date additional infection prevention measures were instituted in CUH including testing and contact tracing of all symptomatic patients and staff, changes in hospital operations, and provision of personal protective equipment (PPE).

Seroprevalence studies can provide relevant information on the proportion of a population who have experienced a recent or past infection. Monitoring the prevalence of infection among HCWs is useful for assessing the level of exposure and identifying high-risk areas.

There have been a number of studies that have attempted to characterise the immunological response to COVID-19. Median time to seroconversion appears to be 9-12 days following onset of symptoms depending on the antibody measured, with up to 100% developing antibodies by day 21[4]. It has also been shown that sensitivity of assays measuring the anti-nucleocapsid antibodies begin to decline from 60 days following PCR positivity[5]. However correlation between seropositivity or antibody levels and protection against reinfection remains to be fully determined[6,7].

The aim of this study was to investigate seroprevalence of SARS-CoV-2 specific IgG antibodies, using the Abbott anti-nucleocapsid IgG CMIA assay, in five pre-specified HCW subgroups following the first surge of the pandemic in a region of relative low prevalence of COVID-19 infection.

Methods

Study Design and Participants

This study was undertaken over a six week period from 27 May 2020 – 07 July 2020 in CUH [Cork University Hospital] an 800 bed university teaching hospital. CUH is the tertiary referral centre in the South West of Ireland; servicing a population of 1.1 million people. The study was designed to recruit 100 HCWs from five prespecified subgroups as outlined below:

HCW Subgroups:

1. HCWs who had RT-PCR confirmed COVID-19 infection (>1 month post positive RT-PCR)
2. HCWs identified as close contacts of persons with COVID-19 infection and who subsequently developed symptoms (RT-PCR not detected on swab)
3. HCWs identified as close contacts of COVID-19 cases and who remained asymptomatic (not screened by RT-PCR)
4. HCWs not included in the above groups working in areas determined as high risk clinical areas
5. HCWs not included in the above groups working in areas determined as low risk clinical areas

Basic demographic data was collected by means of a self-administered questionnaire (Appendix 1).

HCWs from groups 1 (confirmed RT-PCR positive) and 2 (identified as a close contact of confirmed case with SARS-CoV-2 not detected by RT-PCR when symptomatic) were contacted by the occupational health department. As there were fewer than 100 HCWs with RT-PCR confirmed COVID-19 in CUH, HCWs with RT-PCR confirmed COVID-19 from affiliated regional centres were invited to participate.

HCWs from group 3-5 were recruited by open invitation and group allocation was confirmed by recruiting investigators.

Inclusion Criteria

HCWs aged 18 years or over working in CUH or affiliated centers in the region were eligible to participate. HCWs were defined as those who deliver care and services to patients, either directly as physicians or nurses, healthcare. attendants, or other support staff (porters, administrative officers, cleaning, maintenance, etc.).

Exclusion Criteria

HCWs who tested positive by RT-PCR for SARS-CoV-2 within 30 days of recruitment to the study or reporting symptoms of COVID-19 at time of recruitment were deemed ineligible to participate. However there were no diagnosed infections among staff in our institution in the 30 days prior to enrolment.

Patient and public involvement

Patients and public were not involved in the design of this study, however feedback was enlisted on the sampling procedures and appropriateness of sampling modalities that the researchers used as part of the study (venepuncture for antinucleocapsid antigen as well as saliva and point of care testing used in the validation of other testing modalities not included in this paper).

Laboratory procedures:

Serological testing
Serum was collected for anti-SARS-CoV-2 nucleocapsid IgG using the Abbott ARCHITECT SARS-CoV-2 IgG CMIA® qualitative assay, as per the manufacturer's specifications.

qRT-PCR for SARS-CoV-2
HCWs from group 1 and 2 who had close contact to a case of COVID-19 infection and developed symptoms had a combined nasopharyngeal and oropharyngeal swab undertaken as part of clinical care. Laboratory confirmation of SARS-CoV-2 infection was performed using the MagNA Pure 24/MagNA Pure LC (Roche diagnostics) extraction system and Realstar® (Altona Diagnostics, Hamburg, Germany) or EURORealTime (EUROIMMUN, Lübeck, Germany) SARS-CoV-2 qRT-PCR kits, as per the manufacturer's instructions. Target detection was reported on a LightCycler® 480 Instrument II (Roche) if the quantification cycle (C_q) value was <40. In the absence of assay standardisation with RNA copy number controls, the C_q value was used as a relative quantitative indication of viral load.

Ethical Considerations
Informed consent was obtained from HCWs using the document contained in the appendix. The Clinical Research Ethics Committee of the Cork Teaching Hospitals (CREC) granted ethics approval for this study (ECM 4 (a) 16/06/2020).

Statistical analysis
SPSS 26.0 and GraphPad Prism 8 was used for statistical analysis. Chi-square test was used to compare categorical variables. Independent samples T test was used to compare means of independent scale variables where frequencies were normally distributed and Mann-Whitney U test was used to compare continuous variables where frequencies were non-normally distributed. Results were deemed to be significant if $P < 0.05$.

Results

Sample Characteristics

Of 4,500 staff employed directly in CUH, 503 HCWs were recruited to the study. Baseline demographics of participants are outlined in Table 1.

The age range of participants was 20-65 years (IQR 30-47 years), 77% female. There were no significant between-group differences in age profiles. Nurses were the most represented professional group (41.7%) followed by doctors (35.0%).

Overall level of co-morbidity was low across the groups with 58.8% of the study population reporting no known/current medical issues. There were a significantly greater number of ex-smokers among participants in Group 1 compared to other groups ($P < 0.001$) and a significantly greater number of current smokers in Group 2 ($P = 0.021$). There was no significant between-group difference for any of the other comorbidities listed.

Of the participants, 187 (187/503, 37.2%) worked in high-risk settings. These were deemed to be areas in which HCWs were having daily contact with patients with confirmed or suspected COVID-19 infection during the peak of the local epidemic.

469 (469/503, 93.2%) of the participants were working in the institution, CUH, in which the study was conducted with 34 participants (all from group 1) recruited from affiliated institutions within the South/Southwest Hospital Group.

Seroprevalence

Overall 78 of 503 (15.5%) HCWs who participated in the study were seropositive for SARS-CoV-2 at time of recruitment in to the study. Table 2 presents serology results by HCW group.

Out of the 99 participants in Group 1, 72 had detectable IgG to SARS-CoV-2 on laboratory testing (72.73%). Longitudinal IgG detection from date of positive RT-PCR is displayed in Figure 1. The mean period of time from RT-PCR positivity to IgG testing was significantly shorter in the IgG positive group, with a mean of 69.3 days compared to 77.0 days in those who were antibody negative ($P = 0.025$). There was no correlation noted between antibody seropositivity and age ($P = 0.63$), gender ($P = 0.416$) or presence of one or more comorbidities ($P = 0.935$).

Only 1 of 99 HCWs with RT-PCR confirmed COVID-19 required hospitalisation for management of infection with the vast majority experiencing mild symptoms.

RT-PCR C_q values were available for 69 of the participants in Group 1. This included 57 participants who were IgG positive and 12 who were IgG negative. There was no correlation found between RT-PCR C_q values and SARS-CoV-2 IgG detection ($P = 0.943$).

Overall seroprevalence was low among Groups 2-5, with IgG antibodies detected in only 6 out of 404 participants (1.49%). Prevalence was comparable between the four

groups with IgG antibodies detected in 2 participants in Group 2 (1.9%), 1 in Group 3 (1.1%), 1 in Group 4 (1.0%) and 2 in Group 5 (1.9%).

Discussion

Of 99 HCWs with RT-PCR confirmed SARS-CoV-2 infection. 73% (72) had detectable anti-nucleocapsid IgG antibodies to SARS-CoV-2. A single factor, time interval from positive RT-PCR was associated with antibody detection. This is consistent with much of the wider literature in indicating that anti-nucleocapsid IgG antibodies to SARS-CoV-2 begin to decline from day 60 following positive PCR, particularly in individuals with mild or asymptomatic primary infection[7–9].

We report a seroprevalence of SARS-CoV-2 IgG in HCWs in our institution not previously diagnosed with COVID-19 by RT-PCR of 1.49%. The national Irish population seroprevalence study (SCOPI) conducted over the same period estimated seroprevalence in the general population at 1.7%[10], although this sample would have included a small proportion of participants with previously had positive RT-PCR tests. Regionally, HCW infections represented 23% of total infections during the first wave. This was a smaller percentage than the figure seen nationally of 32.1% and would indicate that there was a lower proportion of HCW infected in Cork[11].

Seroprevalence in HCWs without previously diagnosed COVID-19 study is lower than in the majority of published international studies that report seroprevalence among HCWs not previously diagnosed with COVID-19 (Groups 2-5) of anywhere between 1.6% and 9.0%[12–17].

In the US, a study of a multistate hospital network reported 6% seropositivity in 3,248 HCWs across thirteen geographically diverse institutions. Notably, 69% of those who were antibody-positive did not have a prior diagnosis of COVID-19 infection (Self et al., 2020). A study of 46,117 HCWs in the greater New York City area across 52 sites revealed a 13.7% total seropositivity to SARS-CoV-2 specific IgG antibodies. 10.3% of individuals who had previously tested RT-PCR negative as well as 9% of those who were never tested were noted to have antibodies[18]. In Madrid, a large tertiary-level institution reported a seroprevalence of 11.2% in a random sample of HCWs at the peak of the first wave in Europe (28th March – 9th April 2020). Of this cohort, 40.0% had not had previously diagnosed COVID-19 infection[12]. However, one smaller scale study of 316 HCWs in Essen in Germany found just 5 (1.6%) were seropositive, none of whom had previously tested positive[14].

This was particularly surprising given that rate of asymptomatic infection in COVID-19 is thought to be about 15%[19]. Only 6 out of 105 participants (5.7%) in our study with laboratory evidence of SARS-CoV-2 infection were not diagnosed at time of infection. This was despite guidelines applicable early in the pandemic which dictated that only symptomatic individuals be tested for COVID-19

There are a number of factors that may have contributed to the low seroprevalence of SARS-CoV-2 IgG in the previously undiagnosed cohort.

The number of patients assessed or hospitalised with COVID-19 (n=150) at our institution was comparatively low during the first wave of the pandemic and therefore staff may have been exposed to a lower number of COVID-19 patients than in other institutions. The regional prevalence was also comparatively low with a total of 1,700

cases reported in Cork as of August 2020 with a peak incidence of 104 cases per 100,000 on 27 March 2020[11].

At no stage during the surge was there an interruption in personal-protective equipment (PPE) supply in our institution and high standards of infection prevention and control were employed throughout. At all times the guideline-recommended PPE was available to staff for the assessment of COVID-19 confirmed and suspected patients[20].

Public transport usage by CUH staff is comparatively low and there is no tram or commuter rail service serving the hospital. This would potentially reduce overall exposure of staff to tightly congregated environments. There is some data to suggest that use of public transport is positively correlated with antibody positivity[21].

Easily accessible RT-PCR testing and recommendation for quarantine of symptomatic staff members was implemented locally from identification of our first case of COVID-19 on March 5th 2020. This enabled diagnosis of the vast majority of symptomatic infections from the outset with isolation of these cases minimising risk of onward transmission to patients or other HCWs.

As well as within hospitals, similar targeted epidemiological studies would undoubtedly be useful in high-risk high-prevalence settings such as universities, schools and other healthcare institutions to gain a better understanding of patterns of transmission.

Limitations of this study include that it was a single centre study undertaken in an area of relative low prevalence of COVID-19. Enrolment began eight weeks after peak regional prevalence and therefore IgG antibodies may have become undetectable in a proportion of participants[22]. The assay used in the study, Abbott Architect SARS-CoV-2 IgG CMIA, is a qualitative assay so therefore we were unable to quantify antibody levels in participants. Recruitment of groups 3-5 was by self-selection and therefore was not a true random sample of these groups.

Conclusion

In the face of the ongoing pandemic, it is crucial to protect frontline HCWs from infection with COVID-19. Hospital-wide antibody screening for antibodies to SARS-CoV-2 can profile transmission dynamics and inform infection control policies. It is essential we learn from our experience from the initial surge in the healthcare setting and maintain continued vigilance to protect vulnerable patients and HCWs from infection. With rollout of effective vaccination on the horizon, studies such as this may inform optimal strategy and who to target for immunisation in the context of potentially limited initial supplies.

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Conflict of Interests Statement

The authors have no conflicts of interest to declare.

Funding

This research received no funding or grant from any funding agency in the commercial, public or not-for-profit treatment.

Author Contributions Section

Dr EF; Drafted paper, helped organise logistics of sample collection
Dr AW; Organised and oversaw sample collection for groups 2-5. Edited and signed off on paper
Dr RB; Edited and drafted sections of the paper pertaining to microbiological assays
Dr KC; Sample collection, paper edits
Dr CE; Sample collection, paper edits
Dr PF; Sample collection, paper edits
Dr CF; Sample collection, paper edits
Dr EH; Sample collection, paper edits
Dr GK; Enlisted Groups 1 and 2 for participation, paper edits
Dr SL; Sample collection, paper edits
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Dr EM; Sample collection, paper edits
Dr DO'S; Sample collection, paper edits
Dr GO'S; Enlisted Groups 1 and 2 for participation, paper edits
Professor JE; Edits to paper
DS; Validated and performed the Abbott assay for all these samples
CD; validated all the SARS-CoV-2 assays listed and personally performed many of the assays from March and April
JB; Personally performed many of the assays from March and April
Professor MP; Finalised aspects of paper pertaining to microbiology
Professor JG; Finalised aspects of paper pertaining to occupational health
Dr JMcS; Substantial edits and input in all sections of paper
Professor LF; Substantial edits and input in all sections of paper
Dr SO'R; Substantial edits and input in all sections of paper
Professor MH; Edited and helped finalise paper
Dr AJ; Edited and helped finalise paper
Dr CS; Substantial edits and input to all sections. Finalised paper

Tables

Characteristic	Total n = 503	Group 1[a] n = 99	Group 2[b] n = 106	Group 3[c] n = 91	Group 4[d] n = 100	Group 5[e] n = 107
Gender						
Male	115 (22.9)	24 (24.2)	20 (18.9)	26 (28.6)	29 (29.0)	16 (15.0)
Female	388 (77.1)	75 (75.8)	86 (81.1)	65 (71.4)	71 (71.0)	91 (85.0)
Age						
Range in years	20-65	20-65	22-64	21-61	20-56	21-62
Interquartile range	29.5-47.0	31.0-	30.0-46.0	28.8-48.0	28.0-42.0	30.0-47.0
20-29 years	125 (24.9)	49.0	25 (23.6)	24 (26.4)	32 (32.0)	24 (22.4)
30-39 years	164 (32.6)	20 (20.2)	41 (38.7)	29 (31.9)	33 (33.0)	34 (31.8)
40-49 years	122 (24.3)	27 (27.3)	24 (22.6)	19 (20.9)	23 (23.0)	27 (25.2)
50-59 years	80 (15.9)	30 (30.3)	14 (13.2)	17 (18.7)	12 (12.0)	21 (19.6)
60-69 years	9 (1.8)	16 (16.2)	1 (0.9)	1 (1.1)	0 (0.0)	1 (0.9)
		6 (6.1)				
Occupation						
Medical	176 (35.0)	18 (18.2)	29 (27.4)	38 (41.8)	55 (55.0)	36 (33.6)
Nursing	210 (41.7)	43 (43.4)	55 (51.9)	32 (35.2)	29 (29.0)	51 (47.7)
Healthcare assistant	27 (5.4)	11 (11.1)	7 (6.6)	3 (3.3)	4 (4.0)	2 (1.9)
Physiotherapy	15 (3.0)	5 (5.1)	1 (0.9)	5 (5.5)	3 (3.0)	1 (0.9)
Pharmacy	17 (3.4)	6 (6.1)	6 (5.7)	4 (3.8)	1 (1.0)	0 (0.0)
Other allied health professional	11 (2.2)	3 (3.0)	2 (1.9)	3 (3.3)	0 (0.0)	3 (2.8)
Administrative	12 (2.4)	4 (4.0)	1 (0.9)	1 (1.1)	0 (0.0)	6 (5.6)
Auxiliary staff	23 (4.6)	9 (9.1)	2 (1.9)	3 (3.3)	6 (6.0)	3 (2.8)
Other/not documented	12 (2.2)	0 (0.0)	3 (2.8)	2 (2.2)	2 (2.0)	5 (4.7)
Comorbidity						
Smoker	29 (5.8)	3 (3.0)	13 (12.3)	5 (5.5)	5 (5.0)	3 (2.8)
Ex-smoker	81 (16.1)	32 (32.3)	14 (13.2)	11 (12.1)	15 (15.0)	9 (8.4)
Hypertension	30 (6.0)	8 (8.1)	5 (4.7)	5 (5.5)	5 (5.0)	7 (6.5)
COPD[a]	5 (1.0)	1 (1.0)	3 (2.8)	0 (0.0)	1 (1.0)	0 (0.0)
Asthma	70 (13.9)	14 (14.1)	14 (13.2)	8 (8.8)	17 (17.0)	17 (15.9)
Diabetes mellitus	10 (2.0)	0 (0.0)	4 (3.8)	1 (1.1)	2 (2.0)	3 (2.8)
Heart disease	4 (0.8)	0 (0.0)	0 (0.0)	2 (2.2)	1 (1.0)	1 (0.9)
Other metabolic conditions	22 (4.4)	1 (1.0)	8 (7.5)	2 (2.2)	6 (6.0)	5 (4.7)
Chronic kidney disease	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)
Chronic liver disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Immunosuppressed	9 (1.8)	0 (0.0)	4 (3.8)	0 (0.0)	1 (1.0)	4 (3.7)
Blood disorder	5 (1.0)	0 (0.0)	2 (1.9)	0 (0.0)	1 (1.0)	2 (1.9)
Active cancer diagnosis	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)
Neurological condition	7 (1.4)	1 (1.0)	2 (1.9)	2 (2.2)	1 (1.0)	1 (0.9)
None of the above	296 (58.8)	52 (52.5)	61 (57.5)	62 (68.1)	55 (55.0)	66 (61.7)
Risk profile by area of work						
High risk	187 (37.2)	10 (10.1)	43 (40.6)	34 (37.4)	100 (100)	0 (0.0)
Low risk	316 (62.8)	89 (89.9)	63 (59.4)	57 (62.6)	0 (0.0)	107 (100)
Institution						
Cork University Hospital	469 (93.2)	65 (65.7)	106 (100)	91 (100)	100 (100)	107 (100)
Other institution	34 (6.8)	34 (34.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Table 1: Participant demographics and comorbidities. Data are presented as n (% of total displayed at top of individual columns) unless otherwise stated

[a] RT-PCR confirmed COVID-19 infection (>1 month post positive RT-PCR)
[b] Close contacts of persons with COVID-19 infection and who subsequently developed symptoms (RT-PCR not detected on swab)
[c] Close contacts of COVID-19 cases and who remained asymptomatic
[d] HCWs working in areas determined as high risk clinical areas
[e] HCWs working in areas determined as low risk clinical areas
[f] Chronic obstructive pulmonary disease

Study Group	Total	IgG positive
Group 1[a]	99	72 (72.73)
Group 2[b]	106	2 (1.9)
Group 3[c]	91	1 (1.1)
Group 4[d]	100	1 (1.0)
Group 5[e]	107	2 (1.9)
Total	503	78 (15.5)

Table 2: SARS-CoV-2 IgG seropositivity by study group. Data are presented as n (%), or total in first column.

[a] RT-PCR confirmed COVID-19 infection (>1 month post positive RT-PCR)
[b] Close contacts of persons with COVID-19 infection and who subsequently developed symptoms (RT-PCR not detected on swab)
[c] Close contacts of COVID-19 cases and who remained asymptomatic
[d] HCWs working in areas determined as high risk clinical areas
[e] HCWs working in areas determined as low risk clinical areas

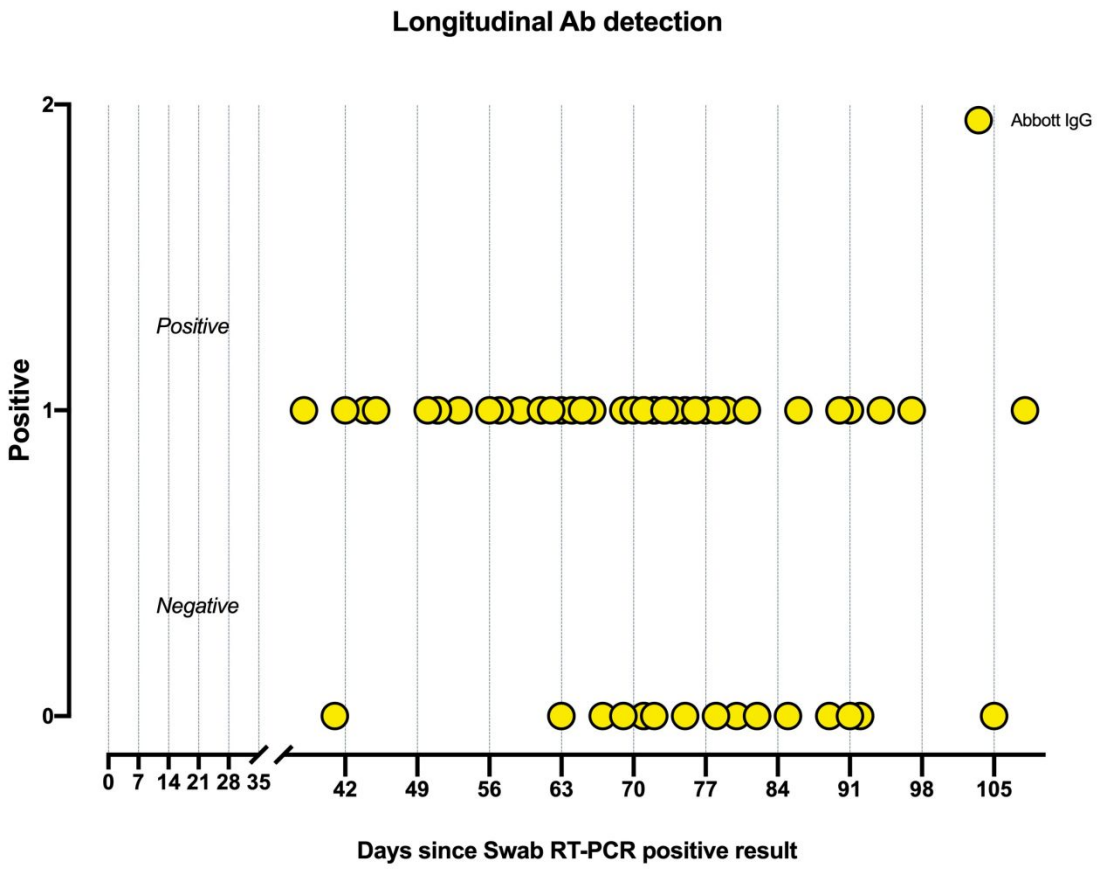
Figure Legend

Figure 1: Group 1 longitudinal SARS-CoV-2 IgG detection since date of positive RT-PCR. n=99

Acknowledgements

I'd like to acknowledge and thank the HRB Clinical Research Facility Cork for the resources and effort contributed towards this study. In particular Jennifer Connolly, Niamh Kelly, Maeve Kelsey and Lisa McSweeney

Figure



Study Title: Prevalence of SARS-CoV-2 in Healthcare workers in the early stages of the pandemic

Appendix 1

Demographic data

Participant study Code (to be filled in by researchers): _____
Date: _____

Age _____

Gender_____

Healthcare occupation_____

Healthcare location e.g. ED, ward_____

COVID-19 contact risk_____

Weight_____

Height_____

Participant co-morbidities; please tick

I have already had to stay overnight in a hospital because of COVID-19	**Yes** ☐	**No** ☐
I am a smoker	**Yes** ☐	**No** ☐
I am an ex-smoker	**Yes** ☐	**No** ☐
I have high blood pressure	**Yes** ☐	**No** ☐
I have COPD/emphysema/bronchitis	**Yes** ☐	**No** ☐
I have asthma	**Yes** ☐	**No** ☐
I have diabetes	**Yes** ☐	**No** ☐
I have heart disease (for example: angina/previous heart attack/stents/heart bypass surgery/heart failure)	**Yes** ☐	**No** ☐
I have other metabolic conditions apart from diabetes (such as thyroid disease)	**Yes** ☐	**No** ☐
I have Chronic Kidney Disease	**Yes** ☐	**No** ☐
I have Chronic Liver Disease	**Yes** ☐	**No** ☐
I have immunosupression (from medications like chemotherapy or biological agents, or from infection)	**Yes** ☐	**No** ☐
I have a blood disorder (such as Leukaemia, Haemophilia etc)	**Yes** ☐	**No** ☐
I have an active cancer diagnosis	**Yes** ☐	**No** ☐
I have a Neurological condition (such as Epilepsy or Stroke)	**Yes** ☐	**No** ☐
I don't have any of the above risk factors or medical conditions	**Yes** ☐	**No** ☐

| Name (Block Capitals) | Participant Signature | Date

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	6-7
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6-7
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8-9
		(b) Indicate number of participants with missing data for each variable of interest	8-9
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	8-9
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	*8-9*
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-9
		(*b*) Report category boundaries when continuous variables were categorized	8-9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8-9
Discussion			
Key results	18	Summarise key results with reference to study objectives	10-11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10-11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Seroprevalence of SARS-CoV-2 Antibodies in Healthcare Workers following the First Wave of the COVID-19 Pandemic in a Tertiary Level Hospital in the South of Ireland

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-051415.R1
Article Type:	Original research
Date Submitted by the Author:	19-Apr-2021
Complete List of Authors:	Faller, Eamonn; Cork University Hospital Wyse, ADRIANNE; Cork University Hospital Barry, Rachel; Cork University Hospital Conlon, Kevin; Cork University Hospital Everard, Cormac; Cork University Hospital Finnegan, Paula; Cork University Hospital Foran, Claire; Cork University Hospital Herlihy, Emer; Cork University Hospital Kerr, Gerry; Cork University Hospital Lapthorne, Susan; Cork University Hospital McGreal-Bellone, Aimee; Cork University Hospital Morrissey, Edmond; Cork University Hospital O'Sullivan, Deirdre; Cork University Hospital O'Sullivan, Grainne; Cork University Hospital Eustace, Joseph; University College Cork; Cork University Hospital Spillane, Declan; University College Cork; Cork University Hospital Dempsey, Catherine; University College Cork; Cork University Hospital Benson, John; University College Cork; Cork University Hospital Prentice, Mike; University College Cork; Cork University Hospital Gallagher, John; Cork University Hospital Group, Occupational Health MacSharry, J.; University College Cork Fanning, L.J.; University College Cork, Department of Medicine O'Riordan, Stephen; Cork University Hospital Horgan, Mary; University College Cork; Cork University Hospital Jackson, Arthur; Cork University Hospital Sadlier, Corinna; Cork University Hospital
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Diagnostics, Immunology (including allergy), Occupational and environmental medicine
Keywords:	EPIDEMIOLOGY, Infection control < INFECTIOUS DISEASES, Diagnostic microbiology < INFECTIOUS DISEASES, COVID-19

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Seroprevalence of SARS-CoV-2 Antibodies in Healthcare Workers following the First Wave of the COVID-19 Pandemic in a Tertiary Level Hospital in the South of Ireland

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Keywords:

- COVID-19
- SARS-CoV-2
- Healthcare worker epidemiology
- Anti-nucleocapsid IgG

Word Count: 2,494

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Abstract

Objective
This study investigated seroprevalence of SARS-CoV-2 specific IgG antibodies, using the Abbott anti-nucleocapsid IgG CMIA assay, in five pre-specified healthcare worker (HCW) subgroups following the first wave of the COVID-19 pandemic.

Setting
An 800-bed tertiary level teaching hospital in the south of Ireland.

Participants
Serum was collected for anti-SARS-CoV-2 nucleocapsid IgG using the Abbott ARCHITECT SARS-CoV-2 IgG CMIA® qualitative assay, as per the manufacturer's specifications.

The groups were as follows:

1. HCWs who had real time polymerase-chain-reaction (RT-PCR) confirmed COVID-19 infection (>1 month post positive RT-PCR)
1. HCWs identified as close contacts of persons with COVID-19 infection and who subsequently developed symptoms (virus not detected by RT-PCR on oro/nasopharyngeal swab)
2. HCWs identified as close contacts of COVID-19 cases and who remained asymptomatic (not screened by RT-PCR)
3. HCWs not included in the above groups working in areas determined as high risk clinical areas
4. HCWs not included in the above groups working in areas determined as low risk clinical areas

Results
6 of 404 (1.49%) HCWs not previously diagnosed with SARS-CoV-2 infection (groups 2-5) were seropositive for SARS-CoV-2 at time of recruitment in to the study.

Out of the 99 participants in Group 1, 72 had detectable IgG to SARS-CoV-2 on laboratory testing (72.73%). Antibody positivity correlated with shorter length of time between RT-PCR positivity and antibody testing.

C_q value on RT-PCR was not found to be correlated with antibody positivity.

Conclusions
Seroprevalence of SARS-CoV-2 antibodies in HCWs who had not previously tested RT-PCR positive for COVID-19 was low compared to similar studies.

Strengths and Limitations of this Study

- We successfully recruited the numbers that we had aimed for in each of the pre-specified groups
- This was a single centre study in an area of relatively low SARS-CoV-2 prevalence
- Enrolment began eight weeks after peak regional prevalence and therefore IgG antibodies may have become undetectable in a proportion of participants
- Recruitment of groups 3-5 was by self-selection and therefore was not a true random sample of these groups
- C_q values were only available for 69 of the 99 participants who were RT-PCR positive including only 12 of whom were IgG negative. It is therefore difficult to draw any firm conclusion as regards correlation between C_q value and antibody positivity

Introduction

Healthcare workers (HCWs) at the frontline treating patients with suspected or confirmed coronavirus disease-2019 (COVID-19) have been heavily impacted by the pandemic. Due to potential occupational exposures, HCWs are at higher risk of infection from patients or from other HCWs than the general population. In a study published in July 2020, there was an estimated hazard ratio of 3.40 for COVID-19 infection in HCWs compared to risk of infection in the general population[1]. Indeed, as of November 2020 in the Republic of Ireland, the Health Protection and Surveillance Centre (HPSC) put the number of HCW infections at 10,976 accounting for 16.6% of total infections[2].

The first case of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection was reported in Ireland on February 29th 2020 relating to travel. On March 5th, a patient was diagnosed with SARS-CoV-2 infection who had been ventilated in the intensive care unit of Cork University Hospital (CUH) with atypical pneumonia despite having no epidemiological link to a known case or area of high prevalence. This was the first documented community acquisition of SARS-CoV-2 in the Republic of Ireland and was an indication of potential widespread community transmission[3]. From this date additional infection prevention measures were instituted in CUH including testing and contact tracing of all symptomatic patients and staff, changes in hospital operations, and provision of personal protective equipment (PPE).

Seroprevalence studies can provide relevant information on the proportion of a population who have experienced a recent or past infection. Monitoring the prevalence of infection among HCWs is useful for assessing the level of exposure and identifying high-risk areas.

There have been a number of studies that have attempted to characterise the immunological response to COVID-19. Median time to seroconversion is estimated at 9-12 days following onset of symptoms depending on the antibody measured, with up to 100% developing antibodies by day 21[4]. Sensitivity of assays measuring the anti-nucleocapsid antibodies have been shown to decline from 60 days following PCR positivity[5]. However correlation between seropositivity or antibody levels and protection against reinfection remains to be fully determined[6,7].

The aim of this study was to investigate seroprevalence of SARS-CoV-2 specific IgG antibodies, using the Abbott anti-nucleocapsid IgG chemiluminescent microparticle immunoassay (CMIA), in five pre-specified HCW subgroups following the first surge of the pandemic in a region of relative low prevalence of COVID-19 infection.

Methods

Study Design and Participants

This study was undertaken over a six week period from the 27th May 2020 - 07th July 2020 in CUH, an 800 bed university teaching hospital. CUH is the tertiary referral centre in the South West of Ireland serving a population of 1.1 million people. The study was designed to recruit 100 HCWs from five prespecified subgroups as outlined below:

HCW Subgroups:

1. HCWs who had RT-PCR confirmed COVID-19 infection (>1 month post positive RT-PCR)
2. HCWs identified as close contacts of persons with COVID-19 infection and who subsequently developed symptoms (virus not detected by RT-PCR on oro/nasopharyngeal swab)
3. HCWs identified as close contacts of COVID-19 cases and who remained asymptomatic (not screened by RT-PCR)
4. HCWs not included in the above groups working in areas determined as high risk clinical areas
5. HCWs not included in the above groups working in areas determined as low risk clinical areas

Basic demographic data including age, gender, occupation, comorbid illness was collected by means of a self-administered questionnaire (Appendix 1).

HCWs from groups 1 (previous confirmed RT-PCR COVID-19 infection) and group 2 (close contact of COVID-19 case with virus not detected by RT-PCR on oro/nasopharyngeal swab when symptomatic) were contacted by the occupational health department. As there were fewer than 100 HCWs with RT-PCR confirmed COVID-19 in CUH, HCWs with RT-PCR confirmed COVID-19 from affiliated regional centres were invited to participate.

HCWs from group 3-5 were recruited by open invitation and group allocation was confirmed by recruiting investigators.

Inclusion Criteria

HCWs aged 18 years or over, fluent in English working in CUH or affiliated centers in the region were eligible to participate. HCWs were defined as those who deliver care and services to patients, either directly as physicians or nurses, healthcare. attendants, or other support staff (porters, administrative officers, cleaning, maintenance, etc.).

Exclusion Criteria

HCWs who tested positive by RT-PCR for SARS-CoV-2 within 30 days of recruitment to the study or reporting symptoms of COVID-19 at time of recruitment were deemed ineligible to participate. However there were no diagnosed infections among staff in our institution in the 30 days prior to enrolment.

Patient and public involvement

Patients and public were not involved in the design of this study, however feedback was enlisted on the sampling procedures and appropriateness of sampling modalities that the researchers used as part of the study (venepuncture for antinucleocapsid antigen as well as saliva and point of care testing used in the validation of other testing modalities not included in this paper).

Laboratory procedures:

Serological testing
Serum was collected for anti-SARS-CoV-2 nucleocapsid IgG using the Abbott ARCHITECT SARS-CoV-2 IgG CMIA® qualitative assay, as per the manufacturer's specifications.

qRT-PCR for SARS-CoV-2
HCWs from group 1 and group 2 who had close contact to a case of COVID-19 infection and developed symptoms had a combined oro/nasopharyngeal swab undertaken as part of clinical care. Laboratory confirmation of SARS-CoV-2 infection was performed using the MagNA Pure 24/MagNA Pure LC (Roche diagnostics) extraction system and Realstar® (Altona Diagnostics, Hamburg, Germany) or EURORealTime (EUROIMMUN, Lübeck, Germany) SARS-CoV-2 qRT-PCR kits, as per the manufacturer's instructions. Target detection was reported on a LightCycler® 480 Instrument II (Roche) if the quantification cycle (C_q) value was <40. In the absence of assay standardisation with RNA copy number controls, the C_q value was used as a relative quantitative indication of viral load.

Ethical Considerations
Written informed consent was obtained from HCWs using the document contained in the appendix. The Clinical Research Ethics Committee of the Cork Teaching Hospitals (CREC) granted ethics approval for this study (ECM 4 (a) 16/06/2020).

Statistical analysis
SPSS 26.0 and GraphPad Prism 8 was used for statistical analysis. Chi-square test was used to compare categorical variables. Independent samples T test was used to compare means of independent scale variables where frequencies were normally distributed and Mann-Whitney U test was used to compare continuous variables where frequencies were non-normally distributed. Results were deemed to be significant if $P < 0.05$.

Results

Sample Characteristics

Of 4,500 staff employed directly in CUH, 503 HCWs were recruited to the study. Baseline demographics of participants are outlined in Table 1.

The age range of participants was 20-65 years (IQR 30-47 years), 77% female. There were no significant between-group differences in age profiles. Nurses were the most represented professional group (41.7%) followed by doctors (35.0%).

Overall level of co-morbidity was low across the groups with 58.8% of the study population reporting no known/current medical issues. There were a significantly greater number of ex-smokers among participants in group 1 compared to other groups ($P < 0.001$) and a significantly greater number of current smokers in group 2 ($P = 0.021$). There was no significant between-group difference for any of the other comorbidities listed.

Of the participants, 187 (187/503, 37.2%) worked in high-risk settings. These were deemed to be areas in which HCWs were having daily contact with patients with confirmed or suspected COVID-19 infection during the peak of the local epidemic.

469 (469/503, 93.2%) of the participants were working in CUH, the institution in which the study was conducted with 34 participants (all from group 1) recruited from affiliated institutions within the South/Southwest Hospital Group.

Seroprevalence

Overall 78 of 503 (15.5%) HCWs who participated in the study were seropositive for SARS-CoV-2 at time of recruitment into the study. Table 2 presents serology results by HCW group.

Out of the 99 participants in group 1, 72 had detectable IgG to SARS-CoV-2 on laboratory testing (72.73%). Longitudinal IgG detection from date of positive RT-PCR is displayed in Figure 1. The mean period of time from RT-PCR positivity to IgG testing was significantly shorter in the IgG positive group, with a mean of 69.3 days compared to 77.0 days in those who were antibody negative ($P = 0.025$). There was no correlation noted between antibody seropositivity and age ($P = 0.63$), gender ($P = 0.416$) or presence of one or more comorbidities ($P = 0.935$).

Only 1 of 99 HCWs with RT-PCR confirmed COVID-19 required hospitalisation for management of infection with the vast majority experiencing mild symptoms.

RT-PCR C_q values were available for 69 of the participants in group 1. This included 57 participants who were IgG positive and 12 who were IgG negative. There was no correlation found between RT-PCR C_q values and SARS-CoV-2 IgG detection ($P = 0.943$).

Overall seroprevalence was low among groups 2-5, with IgG antibodies detected in only 6 out of 404 participants (1.49%). Prevalence was comparable between the four

groups with IgG antibodies detected in 2 participants in group 2 (1.9%), 1 in group 3 (1.1%), 1 in group 4 (1.0%) and 2 in group 5 (1.9%).

Discussion

Of 99 HCWs with RT-PCR confirmed SARS-CoV-2 infection 73% (72) had detectable anti-nucleocapsid IgG antibodies to SARS-CoV-2. A single factor, time interval from positive RT-PCR was associated with antibody detection. This is consistent with much of the wider literature in indicating that anti-nucleocapsid IgG antibodies to SARS-CoV-2 begin to decline from day 60 following positive PCR, particularly in individuals with mild or asymptomatic primary infection[7–9]. Although certain studies suggest a much higher sensitivity using this assay[10], our data would suggest that sensitivity drops over time potentially limiting usefulness of this assay over the longer term.

We report a seroprevalence of SARS-CoV-2 IgG in HCWs in our institution not previously diagnosed with COVID-19 by RT-PCR of 1.49%. The national Irish population seroprevalence study (SCOPI) conducted over the same period estimated overall seroprevalence in the general population at 1.7%[11], with regional differences between urban Dublin (3.1%) and rural Sligo (0.6%). In Cork and Kerry, the two main counties served by our hospital, HCW infections represented 23% of total infections during the first wave. This was a smaller percentage than the figure seen nationally of 32.1% and would indicate that there was a lower proportion of HCW infected in Cork[12].

Seroprevalence in HCWs without previously diagnosed COVID-19 is lower than in the majority of published international studies that report seroprevalence among HCWs not previously diagnosed with COVID-19 (groups 2-5) of anywhere between 1.6% and 9.0%[13–18].

In the USA, a study of a multistate hospital network reported 6% seropositivity in 3,248 HCWs across thirteen geographically diverse institutions. Notably, 69% of those who were antibody-positive did not have a prior diagnosis of COVID-19 infection (Self et al., 2020). A study of 46,117 HCWs in the greater New York City area across 52 sites revealed a 13.7% total seropositivity to SARS-CoV-2 specific IgG antibodies. 10.3% of individuals who had previously tested RT-PCR negative as well as 9% of those who were never tested were noted to have antibodies[19]. In Madrid, a large tertiary-level institution reported a seroprevalence of 11.2% in a random sample of HCWs at the peak of the first wave in Europe (28th March – 9th April 2020). Of this cohort, 40.0% had not had previously diagnosed COVID-19 infection[13]. However, one smaller scale study of 316 HCWs in Essen in Germany found just 5 (1.6%) were seropositive, none of whom had previously tested positive[15].

This was particularly surprising given that rate of asymptomatic infection in COVID-19 is thought to be about 15%[20]. Only 6 out of 105 participants (5.7%) in our study with laboratory evidence of SARS-CoV-2 infection were not diagnosed at time of infection. This was despite guidelines applicable early in the pandemic which dictated that only symptomatic individuals be tested for COVID-19.

There are a number of factors that may have contributed to the low seroprevalence of SARS-CoV-2 IgG in the previously undiagnosed cohort.

The number of patients assessed or hospitalised with COVID-19 (n=150) at our institution was comparatively low during the first wave of the pandemic and therefore staff may have been exposed to a lower number of COVID-19 patients than in other institutions. The regional prevalence was also comparatively low with a total of 1,700 cases reported in Cork as of August 2020 with a peak incidence of 104 cases per 100,000 on 27 March 2020[12].

At no stage during the surge was there an interruption in personal-protective equipment (PPE) supply in our institution and high standards of infection prevention and control were employed throughout. At all times the guideline-recommended PPE was available to staff for the assessment of COVID-19 confirmed and suspected patients[21].

Public transport usage by CUH staff is comparatively low and there is no tram or commuter rail service serving the hospital. This would potentially reduce overall exposure of staff to tightly congregated environments. There is some data to suggest that use of public transport is positively correlated with antibody positivity[22].

Easily accessible RT-PCR testing and recommendation for quarantine of symptomatic staff members was implemented locally from identification of our first case of COVID-19 on March 5th 2020. This enabled diagnosis of the vast majority of symptomatic infections from the outset with isolation of these cases minimising risk of onward transmission to patients or other HCWs.

Given antibody positivity was only 73% in group 1, it is possible that some individuals in groups 2-5 may have been infected but have had undetectable antibodies at time of sampling. This would result in a slight underestimate of previously infected individuals in these groups.

As well as within hospitals, similar targeted epidemiological studies would undoubtedly be useful in high-risk high-prevalence settings such as universities, schools and other healthcare institutions to gain a better understanding of patterns of transmission.

Limitations of this study include that it was a single centre study undertaken in an area of relative low prevalence of COVID-19. Enrolment began eight weeks after peak regional prevalence and therefore IgG antibodies may have become undetectable in a proportion of participants[23]. The assay used in the study, Abbott Architect SARS-CoV-2 IgG CMIA, is a qualitative assay so therefore we were unable to quantify antibody levels in participants. Recruitment of groups 3-5 was by self-selection and therefore was not a true random sample of these groups. Data regarding C_q was only available for 69 participants of whom only 12 were IgG negative. Therefore numbers would not be sufficient to draw a firm conclusion as to the lack of correlation between viral load and subsequent IgG positivity.

Conclusion

In the face of the ongoing COVID-19 pandemic, it is important to define the epidemiology of infection in the healthcare setting. Hospital-wide screening for antibodies to SARS-CoV-2 can profile transmission dynamics and inform infection control and prevention policies. With rollout of effective vaccination on the horizon, studies such as this may inform recommendations for prioritisation of immunisation in the context of potentially limited initial supplies.

It is essential that learning from experience of the initial surge of COVID-19 in the healthcare setting informs future practice and response to optimally protect HCWs and vulnerable patients.

Conflict of Interests Statement

The authors have no conflicts of interest to declare.

Funding

This research received no funding or grant from any funding agency in the commercial, public or not-for-profit treatment. The study was supported by Cork University Hospital, affiliated institutions in the hospital group and University College Cork.

Data Availability Statement

Data are available upon reasonable request. The authors are happy to share data with a data repository if paper is accepted for publication.

Author Contributions Section

Dr EF; Study concept and design, protocol development. Drafted paper, helped organise logistics of sample collection
Dr AW; Organised and oversaw sample collection for groups 2-5. Edited and signed off on paper
Dr RB; Edited and drafted sections of the paper pertaining to microbiological assays
Dr KC; Sample collection, paper edits
Dr CE; Sample collection, paper edits
Dr PF; Sample collection, paper edits
Dr CF; Sample collection, paper edits
Dr EH; Sample collection, paper edits
Dr GK; Enlisted Groups 1 and 2 for participation, paper edits
Dr SL; Sample collection, paper edits
Dr AM; Sample collection, paper edits
Dr EM; Sample collection, paper edits
Dr DO'S; Sample collection, paper edits
Dr GO'S; Enlisted Groups 1 and 2 for participation, paper edits
Professor JE; Edits to paper
DS; Validated and performed the Abbott assay for all these samples
CD; validated all the SARS-CoV-2 assays listed and personally performed many of the assays from March and April
JB; Personally performed many of the assays from March and April
Professor MP; Study concept and design, protocol development. Finalised aspects of paper pertaining to microbiology
Professor JG; Study concept and design, protocol development. Finalised aspects of paper pertaining to occupational health
Dr JMcS; Study concept and design, protocol development, substantial edits and input in all sections of paper
Professor LF; Study concept and design, protocol development, substantial input in all sections of paper
Dr SO'R; Study concept and design, protocol development, substantial edits and input in all sections of paper
Professor MH; Edited and helped finalise paper
Dr AJ; Edited and helped finalise paper
Dr CS; Study concept and design, protocol development and substantial edits and input to all sections. Finalised paper

All authors approved the final manuscript.

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Tables

Characteristic	Total n = 503	Group 1[a] n = 99	Group 2[b] n = 106	Group 3[c] n = 91	Group 4[d] n = 100	Group 5[e] n = 107
Gender						
Male	115 (22.9)	24 (24.2)	20 (18.9)	26 (28.6)	29 (29.0)	16 (15.0)
Female	388 (77.1)	75 (75.8)	86 (81.1)	65 (71.4)	71 (71.0)	91 (85.0)
Age						
Range in years	20-65	20-65	22-64	21-61	20-56	21-62
Interquartile range	29.5-47.0	31.0-	30.0-46.0	28.8-48.0	28.0-42.0	30.0-47.0
20-29 years	125 (24.9)	49.0	25 (23.6)	24 (26.4)	32 (32.0)	24 (22.4)
30-39 years	164 (32.6)	20 (20.2)	41 (38.7)	29 (31.9)	33 (33.0)	34 (31.8)
40-49 years	122 (24.3)	27 (27.3)	24 (22.6)	19 (20.9)	23 (23.0)	27 (25.2)
50-59 years	80 (15.9)	30 (30.3)	14 (13.2)	17 (18.7)	12 (12.0)	21 (19.6)
60-69 years	9 (1.8)	16 (16.2)	1 (0.9)	1 (1.1)	0 (0.0)	1 (0.9)
		6 (6.1)				
Occupation						
Medical	176 (35.0)	18 (18.2)	29 (27.4)	38 (41.8)	55 (55.0)	36 (33.6)
Nursing	210 (41.7)	43 (43.4)	55 (51.9)	32 (35.2)	29 (29.0)	51 (47.7)
Healthcare assistant	27 (5.4)	11 (11.1)	7 (6.6)	3 (3.3)	4 (4.0)	2 (1.9)
Physiotherapy	15 (3.0)	5 (5.1)	1 (0.9)	5 (5.5)	3 (3.0)	1 (0.9)
Pharmacy	17 (3.4)	6 (6.1)	6 (5.7)	4 (3.8)	1 (1.0)	0 (0.0)
Other allied health professional	11 (2.2)	3 (3.0)	2 (1.9)	3 (3.3)	0 (0.0)	3 (2.8)
Administrative	12 (2.4)	4 (4.0)	1 (0.9)	1 (1.1)	0 (0.0)	6 (5.6)
Auxiliary staff	23 (4.6)	9 (9.1)	2 (1.9)	3 (3.3)	6 (6.0)	3 (2.8)
Other/not documented	12 (2.2)	0 (0.0)	3 (2.8)	2 (2.2)	2 (2.0)	5 (4.7)
Comorbidity						
Smoker	29 (5.8)	3 (3.0)	13 (12.3)	5 (5.5)	5 (5.0)	3 (2.8)
Ex-smoker	81 (16.1)	32 (32.3)	14 (13.2)	11 (12.1)	15 (15.0)	9 (8.4)
Hypertension	30 (6.0)	8 (8.1)	5 (4.7)	5 (5.5)	5 (5.0)	7 (6.5)
COPD[a]	5 (1.0)	1 (1.0)	3 (2.8)	0 (0.0)	1 (1.0)	0 (0.0)
Asthma	70 (13.9)	14 (14.1)	14 (13.2)	8 (8.8)	17 (17.0)	17 (15.9)
Diabetes mellitus	10 (2.0)	0 (0.0)	4 (3.8)	1 (1.1)	2 (2.0)	3 (2.8)
Heart disease	4 (0.8)	0 (0.0)	0 (0.0)	2 (2.2)	1 (1.0)	1 (0.9)
Other metabolic conditions	22 (4.4)	1 (1.0)	8 (7.5)	2 (2.2)	6 (6.0)	5 (4.7)
Chronic kidney disease	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)
Chronic liver disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Immunosuppressed	9 (1.8)	0 (0.0)	4 (3.8)	0 (0.0)	1 (1.0)	4 (3.7)
Blood disorder	5 (1.0)	0 (0.0)	2 (1.9)	0 (0.0)	1 (1.0)	2 (1.9)
Active cancer diagnosis	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)
Neurological condition	7 (1.4)	1 (1.0)	2 (1.9)	2 (2.2)	1 (1.0)	1 (0.9)
None of the above	296 (58.8)	52 (52.5)	61 (57.5)	62 (68.1)	55 (55.0)	66 (61.7)
Risk profile by area of work						
High risk	187 (37.2)	10 (10.1)	43 (40.6)	34 (37.4)	100 (100)	0 (0.0)
Low risk	316 (62.8)	89 (89.9)	63 (59.4)	57 (62.6)	0 (0.0)	107 (100)
Institution						
Cork University Hospital	469 (93.2)	65 (65.7)	106 (100)	91 (100)	100 (100)	107 (100)
Other institution	34 (6.8)	34 (34.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Table 1: Participant demographics and comorbidities. Data are presented as n (% of total displayed at top of individual columns) unless otherwise stated

[a] RT-PCR confirmed COVID-19 infection (>1 month post positive RT-PCR)
[b] Close contacts of persons with COVID-19 infection and who subsequently developed symptoms (RT-PCR not detected on swab)
[c] Close contacts of COVID-19 cases and who remained asymptomatic
[d] HCWs working in areas determined as high risk clinical areas
[e] HCWs working in areas determined as low risk clinical areas
[f] Chronic obstructive pulmonary disease

Study Group	Total	IgG positive
Group 1[a]	99	72 (72.73)
Group 2[b]	106	2 (1.9)
Group 3[c]	91	1 (1.1)
Group 4[d]	100	1 (1.0)
Group 5[e]	107	2 (1.9)
Total	503	78 (15.5)

Table 2: SARS-CoV-2 IgG seropositivity by study group. Data are presented as n (%), or total in first column.

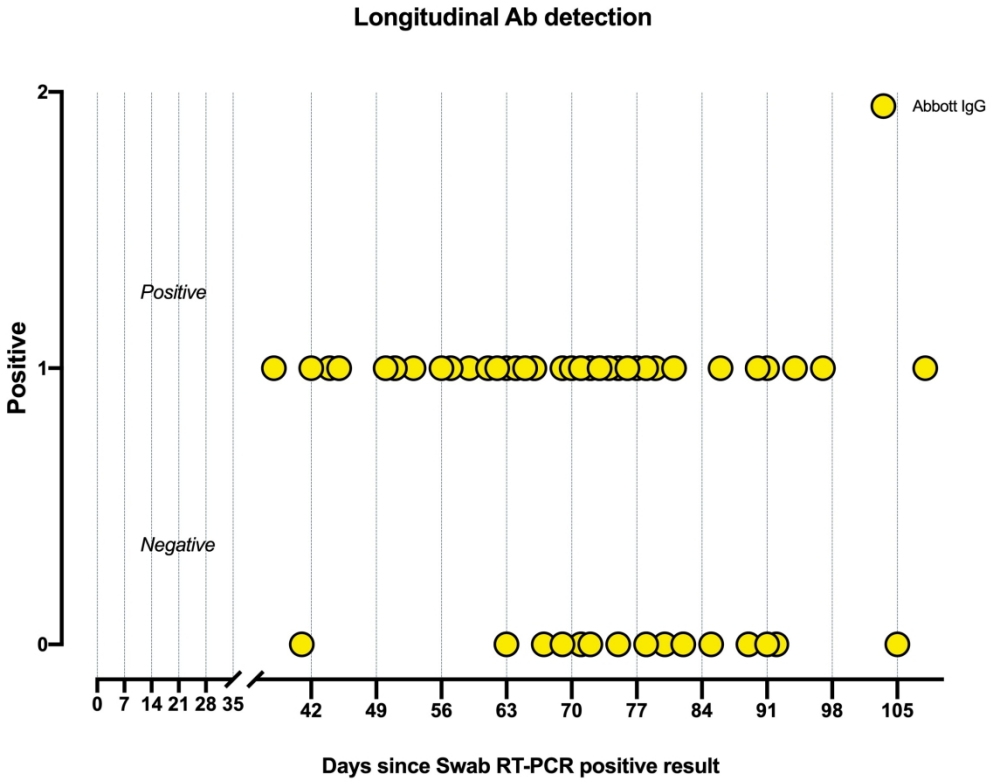
[a] RT-PCR confirmed COVID-19 infection (>1 month post positive RT-PCR)
[b] Close contacts of persons with COVID-19 infection and who subsequently developed symptoms (RT-PCR not detected on swab)
[c] Close contacts of COVID-19 cases and who remained asymptomatic
[d] HCWs working in areas determined as high risk clinical areas
[e] HCWs working in areas determined as low risk clinical areas

Figure Legend

Figure 1: Group 1 longitudinal SARS-CoV-2 IgG detection since date of positive RT-PCR. n=99

Acknowledgements

We would like to acknowledge and thank the staff of CUH and affiliated hospitals in the South/Southwest hospital group who participated in this study. We would also like to thank the Health Research Board (HRB) Clinical Research Facility, Cork for the resources and effort contributed towards this study. In particular Jennifer Connolly, Niamh Kelly, Maeve Kelsey and Lisa McSweeney.



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Study Title: Prevalence of SARS-CoV-2 in Healthcare workers in the early stages of the pandemic

Appendix 1

Demographic data

Participant study Code (to be filled in by researchers): _____
Date: _____

Age _____

Gender_____

Healthcare occupation_____

Healthcare location e.g. ED, ward_____

COVID-19 contact risk_____

Weight_____

Height_____

Participant co-morbidities; please tick

I have already had to stay overnight in a hospital because of COVID-19	**Yes** ☐	**No** ☐
I am a smoker	**Yes** ☐	**No** ☐
I am an ex-smoker	**Yes** ☐	**No** ☐
I have high blood pressure	**Yes** ☐	**No** ☐
I have COPD/emphysema/bronchitis	**Yes** ☐	**No** ☐
I have asthma	**Yes** ☐	**No** ☐
I have diabetes	**Yes** ☐	**No** ☐
I have heart disease (for example: angina/previous heart attack/stents/heart bypass surgery/heart failure)	**Yes** ☐	**No** ☐
I have other metabolic conditions apart from diabetes (such as thyroid disease)	**Yes** ☐	**No** ☐
I have Chronic Kidney Disease	**Yes** ☐	**No** ☐
I have Chronic Liver Disease	**Yes** ☐	**No** ☐
I have immunosupression (from medications like chemotherapy or biological agents, or from infection)	**Yes** ☐	**No** ☐
I have a blood disorder (such as Leukaemia, Haemophilia etc)	**Yes** ☐	**No** ☐
I have an active cancer diagnosis	**Yes** ☐	**No** ☐
I have a Neurological condition (such as Epilepsy or Stroke)	**Yes** ☐	**No** ☐
I don't have any of the above risk factors or medical conditions	**Yes** ☐	**No** ☐

| Name (Block Capitals) | Participant Signature | Date

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	6-7
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6-7
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8-9
		(b) Indicate number of participants with missing data for each variable of interest	8-9
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	8-9
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	*8-9*
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-9
		(*b*) Report category boundaries when continuous variables were categorized	8-9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8-9
Discussion			
Key results	18	Summarise key results with reference to study objectives	10-11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10-11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

A Seroprevalence Study of SARS-CoV-2 Antibodies in Healthcare Workers following the First Wave of the COVID-19 Pandemic in a Tertiary Level Hospital in the South of Ireland

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-051415.R2
Article Type:	Original research
Date Submitted by the Author:	07-May-2021
Complete List of Authors:	Faller, Eamonn; Cork University Hospital Wyse, ADRIANNE; Cork University Hospital Barry, Rachel; Cork University Hospital Conlon, Kevin; Cork University Hospital Everard, Cormac; Cork University Hospital Finnegan, Paula; Cork University Hospital Foran, Claire; Cork University Hospital Herlihy, Emer; Cork University Hospital Kerr, Gerry; Cork University Hospital Lapthorne, Susan; Cork University Hospital McGreal-Bellone, Aimee; Cork University Hospital Morrissey, Edmond; Cork University Hospital O'Sullivan, Deirdre; Cork University Hospital O'Sullivan, Grainne; Cork University Hospital Eustace, Joseph; University College Cork; Cork University Hospital Spillane, Declan; University College Cork; Cork University Hospital Dempsey, Catherine; University College Cork; Cork University Hospital Benson, John; University College Cork; Cork University Hospital Prentice, Mike; University College Cork; Cork University Hospital Gallagher, John; Cork University Hospital Group, Occupational Health MacSharry, J.; University College Cork Fanning, L.J.; University College Cork, Department of Medicine O'Riordan, Stephen; Cork University Hospital Horgan, Mary; University College Cork; Cork University Hospital Sadlier, Corinna; Cork University Hospital
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Diagnostics, Immunology (including allergy), Occupational and environmental medicine
Keywords:	EPIDEMIOLOGY, Infection control < INFECTIOUS DISEASES, Diagnostic microbiology < INFECTIOUS DISEASES, COVID-19

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A Seroprevalence Study of SARS-CoV-2 Antibodies in Healthcare Workers following the First Wave of the COVID-19 Pandemic in a Tertiary Level Hospital in the South of Ireland

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Keywords:

- COVID-19
- SARS-CoV-2
- Healthcare worker epidemiology
- Anti-nucleocapsid IgG

Word Count: 2,533

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Abstract

Objective
This study investigated seroprevalence of SARS-CoV-2 specific IgG antibodies, using the Abbott anti-nucleocapsid IgG CMIA assay, in five pre-specified healthcare worker (HCW) subgroups following the first wave of the COVID-19 pandemic.

Setting
An 800-bed tertiary level teaching hospital in the south of Ireland.

Participants
Serum was collected for anti-SARS-CoV-2 nucleocapsid IgG using the Abbott ARCHITECT SARS-CoV-2 IgG CMIA® qualitative assay, as per the manufacturer's specifications.

The groups were as follows:

1. HCWs who had real time polymerase-chain-reaction (RT-PCR) confirmed COVID-19 infection (>1 month post positive RT-PCR)
1. HCWs identified as close contacts of persons with COVID-19 infection and who subsequently developed symptoms (virus not detected by RT-PCR on oro/nasopharyngeal swab)
2. HCWs identified as close contacts of COVID-19 cases and who remained asymptomatic (not screened by RT-PCR)
3. HCWs not included in the above groups working in areas determined as high risk clinical areas
4. HCWs not included in the above groups working in areas determined as low risk clinical areas

Results
6 of 404 (1.49%) HCWs not previously diagnosed with SARS-CoV-2 infection (groups 2-5) were seropositive for SARS-CoV-2 at time of recruitment into the study.

Out of the 99 participants in Group 1, 72 had detectable IgG to SARS-CoV-2 on laboratory testing (73%). Antibody positivity correlated with shorter length of time between RT-PCR positivity and antibody testing.

C_q value on RT-PCR was not found to be correlated with antibody positivity.

Conclusions
Seroprevalence of SARS-CoV-2 antibodies in HCWs who had not previously tested RT-PCR positive for COVID-19 was low compared to similar studies.

Strengths and Limitations of this Study

- We successfully recruited the numbers that we had aimed for in each of the pre-specified groups
- This was a single centre study in an area of relatively low SARS-CoV-2 prevalence
- Enrolment began eight weeks after peak regional prevalence and therefore IgG antibodies may have become undetectable in a proportion of participants
- Recruitment of groups 3-5 was by self-selection and therefore was not a true random sample of these groups
- C_q values were only available for 69 of the 99 participants who were RT-PCR positive including only 12 of whom were IgG negative. It is therefore difficult to draw any firm conclusion as regards correlation between C_q value and antibody positivity

Introduction

Healthcare workers (HCWs) at the frontline treating patients with suspected or confirmed coronavirus disease-2019 (COVID-19) have been heavily impacted by the pandemic. Due to potential occupational exposures, HCWs are at higher risk of infection from patients or from other HCWs than the general population. In a study published in July 2020, there was an estimated hazard ratio of 3.40 for COVID-19 infection in HCWs compared to risk of infection in the general population[1]. Indeed, as of November 2020 in the Republic of Ireland, the Health Protection and Surveillance Centre (HPSC) put the number of HCW infections at 10,976 accounting for 16.6% of total infections[2].

The first case of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection was reported in Ireland on February 29th 2020 relating to travel. On March 5th, a patient was diagnosed with SARS-CoV-2 infection who had been ventilated in the intensive care unit of Cork University Hospital (CUH) with atypical pneumonia despite having no epidemiological link to a known case or area of high prevalence. This was the first documented community acquisition of SARS-CoV-2 in the Republic of Ireland and was an indication of potential widespread community transmission[3]. From this date additional infection prevention measures were instituted in CUH including testing and contact tracing of all symptomatic patients and staff, changes in hospital operations, and provision of personal protective equipment (PPE).

Seroprevalence studies can provide relevant information on the proportion of a population who have experienced a recent or past infection. Monitoring the prevalence of infection among HCWs is useful for assessing the level of exposure and identifying high-risk areas.

There have been a number of studies that have attempted to characterise the immunological response to COVID-19. Median time to seroconversion is estimated at 9-12 days following onset of symptoms depending on the antibody measured, with up to 100% developing antibodies by day 21[4]. Sensitivity of assays measuring the anti-nucleocapsid antibodies have been shown to decline from 60 days following PCR positivity[5]. However correlation between seropositivity or antibody levels and protection against reinfection remains to be fully determined[6,7].

The aim of this study was to investigate seroprevalence of SARS-CoV-2 specific IgG antibodies, using the Abbott anti-nucleocapsid IgG chemiluminescent microparticle immunoassay (CMIA), in five pre-specified HCW subgroups following the first surge of the pandemic in a region of relative low prevalence of COVID-19 infection.

Methods

Study Design and Participants

This study was undertaken over a six week period from the 27th May 2020 - 07th July 2020 in CUH, an 800 bed university teaching hospital. CUH is the tertiary referral centre in the South West of Ireland serving a population of 1.1 million people. The study was designed to recruit 100 HCWs from five prespecified subgroups as outlined below:

HCW Subgroups:

1. HCWs who had RT-PCR confirmed COVID-19 infection (>1 month post positive RT-PCR)
2. HCWs identified as close contacts of persons with COVID-19 infection and who subsequently developed symptoms (virus not detected by RT-PCR on oro/nasopharyngeal swab)
3. HCWs identified as close contacts of COVID-19 cases and who remained asymptomatic (not screened by RT-PCR)
4. HCWs not included in the above groups working in areas determined as high risk clinical areas
5. HCWs not included in the above groups working in areas determined as low risk clinical areas

Basic demographic data including age, gender, occupation, comorbid illness was collected by means of a self-administered questionnaire (Appendix 1).

HCWs from groups 1 (previous confirmed RT-PCR COVID-19 infection) and group 2 (close contact of COVID-19 case with virus not detected by RT-PCR on oro/nasopharyngeal swab when symptomatic) were contacted by the occupational health department. As there were fewer than 100 HCWs with RT-PCR confirmed COVID-19 in CUH, HCWs with RT-PCR confirmed COVID-19 from affiliated regional centres were invited to participate.

HCWs from group 3-5 were recruited by open invitation and group allocation was confirmed by recruiting investigators.

Inclusion Criteria

HCWs aged 18 years or over, fluent in English working in CUH or affiliated centers in the region were eligible to participate. HCWs were defined as those who deliver care and services to patients, either directly as physicians or nurses, healthcare. attendants, or other support staff (porters, administrative officers, cleaning, maintenance, etc.).

Exclusion Criteria

HCWs who tested positive by RT-PCR for SARS-CoV-2 within 30 days of recruitment to the study or reporting symptoms of COVID-19 at time of recruitment were deemed ineligible to participate. However there were no diagnosed infections among staff in our institution in the 30 days prior to enrolment.

Patient and public involvement

Patients and public were not involved in the design of this study, however feedback was enlisted on the sampling procedures and appropriateness of sampling modalities that the researchers used as part of the study (venepuncture for antinucleocapsid antigen as well as saliva and point of care testing used in the validation of other testing modalities not included in this paper).

Laboratory procedures:

Serological testing

Serum was collected for anti-SARS-CoV-2 nucleocapsid IgG using the Abbott ARCHITECT SARS-CoV-2 IgG CMIA® qualitative assay, as per the manufacturer's specifications. The Abbott Elisa Kit (Abbott Diagnostics ®) uses a nucleocapsid protein as the antigen and report a 100% concordance (95% CI 95.89-100) with their RT-PCR positive panel >14 days after symptom onset and 99.6% negative on their historical pre-COVID-19 controls (95% CI 98.98-99.89)[8]

qRT-PCR for SARS-CoV-2

HCWs from group 1 and group 2 who had close contact to a case of COVID-19 infection and developed symptoms had a combined oro/nasopharyngeal swab undertaken as part of clinical care. Laboratory confirmation of SARS-CoV-2 infection was performed using the MagNA Pure 24/MagNA Pure LC (Roche diagnostics) extraction system and Realstar® (Altona Diagnostics, Hamburg, Germany) or EURORealTime (EUROIMMUN, Lübeck, Germany) SARS-CoV-2 qRT-PCR kits, as per the manufacturer's instructions. Target detection was reported on a LightCycler® 480 Instrument II (Roche) if the quantification cycle (C_q) value was <40. In the absence of assay standardisation with RNA copy number controls, the C_q value was used as a relative quantitative indication of viral load.

Ethical Considerations

Written informed consent was obtained from HCWs using the document contained in the appendix. The Clinical Research Ethics Committee of the Cork Teaching Hospitals (CREC) granted ethics approval for this study (ECM 4 (a) 16/06/2020).

Statistical analysis

SPSS 26.0 and GraphPad Prism 8 was used for statistical analysis. Chi-square test was used to compare categorical variables. Independent samples T test was used to compare means of independent scale variables where frequencies were normally distributed and Mann-Whitney U test was used to compare continuous variables where frequencies were non-normally distributed. Results were deemed to be significant if $P < 0.05$.

Results

Sample Characteristics

Of 4,500 staff employed directly in CUH, 503 HCWs were recruited to the study. Baseline demographics of participants are outlined in Table 1.

The age range of participants was 20-65 years (IQR 30-47 years), 77% female. There were no significant between-group differences in age profiles. Nurses were the most represented professional group (41.7%) followed by doctors (35.0%).

Overall level of co-morbidity was low across the groups with 58.8% of the study population reporting no known/current medical issues. There were a significantly greater number of ex-smokers among participants in group 1 compared to other groups ($P < 0.001$) and a significantly greater number of current smokers in group 2 ($P = 0.021$). There was no significant between-group difference for any of the other comorbidities listed.

Of the participants, 187 (187/503, 37.2%) worked in high-risk settings. These were deemed to be areas in which HCWs were having daily contact with patients with confirmed or suspected COVID-19 infection during the peak of the local epidemic.

469 (469/503, 93.2%) of the participants were working in CUH, the institution in which the study was conducted with 34 participants (all from group 1) recruited from affiliated institutions within the South/Southwest Hospital Group.

Seroprevalence

Overall 78 of 503 (15.5%) HCWs who participated in the study were seropositive for SARS-CoV-2 at time of recruitment into the study. Table 2 presents serology results by HCW group.

Out of the 99 participants in group 1, 72 had detectable IgG to SARS-CoV-2 on laboratory testing (73%). Longitudinal IgG detection from date of positive RT-PCR is displayed in Figure 1. The mean period of time from RT-PCR positivity to IgG testing was significantly shorter in the IgG positive group, with a mean of 69.3 days compared to 77.0 days in those who were antibody negative ($P = 0.025$). There was no correlation noted between antibody seropositivity and age ($P = 0.63$), gender ($P = 0.416$) or presence of one or more comorbidities ($P = 0.935$).

Only 1 of 99 HCWs with RT-PCR confirmed COVID-19 required hospitalisation for management of infection with the vast majority experiencing mild symptoms.

RT-PCR C_q values were available for 69 of the participants in group 1. This included 57 participants who were IgG positive and 12 who were IgG negative. There was no correlation found between RT-PCR C_q values and SARS-CoV-2 IgG detection ($P = 0.943$).

Overall seroprevalence was low among groups 2-5, with IgG antibodies detected in only 6 out of 404 participants (1.49%). Prevalence was comparable between the four

groups with IgG antibodies detected in 2 participants in group 2 (1.9%), 1 in group 3 (1.1%), 1 in group 4 (1.0%) and 2 in group 5 (1.9%).

Discussion

Of 99 HCWs with RT-PCR confirmed SARS-CoV-2 infection 73% (72) had detectable anti-nucleocapsid IgG antibodies to SARS-CoV-2. A single factor, time interval from positive RT-PCR was associated with antibody detection. This is consistent with much of the wider literature in indicating that anti-nucleocapsid IgG antibodies to SARS-CoV-2 begin to decline from day 60 following positive PCR, particularly in individuals with mild or asymptomatic primary infection[7,9,10]. Although a higher sensitivity has been reported for this assay[11], our data indicates that sensitivity drops over time potentially limiting usefulness of this assay over the longer term.

We report a seroprevalence of SARS-CoV-2 IgG in HCWs in our institution not previously diagnosed with COVID-19 by RT-PCR of 1.49%. The national Irish population seroprevalence study (SCOPI) conducted over the same period estimated overall seroprevalence in the general population at 1.7%[12], with regional differences between urban Dublin (3.1%) and rural Sligo (0.6%). In Cork and Kerry, the two main counties served by our hospital, HCW infections represented 23% of total infections during the first wave. This was a smaller percentage than the figure seen nationally of 32.1% and would indicate that there was a lower proportion of HCW infected in Cork[13].

Seroprevalence in HCWs without previously diagnosed COVID-19 is lower than in the majority of published international studies that report seroprevalence among HCWs not previously diagnosed with COVID-19 (groups 2-5) of anywhere between 1.6% and 9.0%[14–19].

In the USA, a study of a multistate hospital network reported 6% seropositivity in 3,248 HCWs across thirteen geographically diverse institutions. Notably, 69% of those who were antibody-positive did not have a prior diagnosis of COVID-19 infection (Self et al., 2020). A study of 46,117 HCWs in the greater New York City area across 52 sites revealed a 13.7% total seropositivity to SARS-CoV-2 specific IgG antibodies. 10.3% of individuals who had previously tested RT-PCR negative as well as 9% of those who were never tested were noted to have antibodies[20]. In Madrid, a large tertiary-level institution reported a seroprevalence of 11.2% in a random sample of HCWs at the peak of the first wave in Europe (28th March – 9th April 2020). Of this cohort, 40.0% had not had previously diagnosed COVID-19 infection[14]. However, one smaller scale study of 316 HCWs in Essen in Germany found just 5 (1.6%) were seropositive, none of whom had previously tested positive[16].

This was particularly surprising given that rate of asymptomatic infection in COVID-19 is thought to be about 15%[21]. Only 6 out of 105 participants (5.7%) in our study with laboratory evidence of SARS-CoV-2 infection were not diagnosed at time of infection. This was despite guidelines applicable early in the pandemic which dictated that only symptomatic individuals be tested for COVID-19.

There are a number of factors that may have contributed to the low seroprevalence of SARS-CoV-2 IgG in the previously undiagnosed cohort.

The number of patients assessed or hospitalised with COVID-19 (n=150) at our institution was comparatively low during the first wave of the pandemic and therefore staff may have been exposed to a lower number of COVID-19 patients than in other institutions. The regional prevalence was also comparatively low with a total of 1,700 cases reported in Cork as of August 2020 with a peak incidence of 104 cases per 100,000 on 27 March 2020[13].

At no stage during the surge was there an interruption in personal-protective equipment (PPE) supply in our institution and high standards of infection prevention and control were employed throughout. At all times the guideline-recommended PPE was available to staff for the assessment of COVID-19 confirmed and suspected patients[22].

Public transport usage by CUH staff is comparatively low and there is no tram or commuter rail service serving the hospital. This would potentially reduce overall exposure of staff to tightly congregated environments. There is some data to suggest that use of public transport is positively correlated with antibody positivity[23].

Easily accessible RT-PCR testing and recommendation for quarantine of symptomatic staff members was implemented locally from identification of our first case of COVID-19 on March 5th 2020. This enabled diagnosis of the vast majority of symptomatic infections from the outset with isolation of these cases minimising risk of onward transmission to patients or other HCWs.

Given antibody positivity was only 73% in group 1, it is possible that HCWs in groups 2-5 were infected but have had undetectable antibodies at time of sampling. This would result in a potential underestimate of previously infected individuals in these groups.

As well as within hospitals, similar targeted epidemiological studies would undoubtedly be useful in high-risk high-prevalence settings such as universities, schools and other healthcare institutions to gain a better understanding of patterns of transmission.

Limitations of this study include that it was a single centre study undertaken in an area of relative low prevalence of COVID-19. Enrolment began eight weeks after peak regional prevalence and therefore IgG antibodies may have become undetectable in a proportion of participants[24]. The assay used in the study, Abbott Architect SARS-CoV-2 IgG CMIA, is a qualitative assay so therefore we were unable to quantify antibody levels in participants. Recruitment of groups 3-5 was by self-selection and therefore was not a true random sample of these groups. Data regarding C_q was only available for 69 participants of whom only 12 were IgG negative. Therefore numbers would not be sufficient to draw a firm conclusion as to the lack of correlation between viral load and subsequent IgG positivity.

Conclusion

In the face of the ongoing COVID-19 pandemic, it is important to define the epidemiology of infection in the healthcare setting. Hospital-wide screening for antibodies to SARS-CoV-2 can profile transmission dynamics and inform infection control and prevention policies. With rollout of effective vaccination on the horizon, studies such as this may inform recommendations for prioritisation of immunisation in the context of potentially limited initial supplies.

It is essential that learning from experience of the initial surge of COVID-19 in the healthcare setting informs future practice and response to optimally protect HCWs and vulnerable patients.

Conflict of Interests Statement

The authors have no conflicts of interest to declare.

Funding

This research received no funding or grant from any funding agency in the commercial, public or not-for-profit treatment. The study was supported by Cork University Hospital, affiliated institutions in the hospital group and University College Cork.

Data Availability Statement

Data are available upon reasonable request. The authors are happy to share data with a data repository if paper is accepted for publication.

Author Contributions Section

Dr EF; Study concept and design, protocol development. Drafted paper, helped organise logistics of sample collection
Dr AW; Organised and oversaw sample collection for groups 2-5. Edited and signed off on paper
Dr RB; Edited and drafted sections of the paper pertaining to microbiological assays
Dr KC; Sample collection, paper edits
Dr CE; Sample collection, paper edits
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Dr GK; Enlisted Groups 1 and 2 for participation, paper edits
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Professor JE; Edits to paper
DS; Validated and performed the Abbott assay for all these samples
CD; validated all the SARS-CoV-2 assays listed and personally performed many of the assays from March and April
JB; Personally performed many of the assays from March and April
Professor MP; Study concept and design, protocol development. Finalised aspects of paper pertaining to microbiology
Professor JG; Study concept and design, protocol development. Finalised aspects of paper pertaining to occupational health
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Professor MH; Edited and helped finalise paper
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All authors approved the final manuscript.

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Tables

Characteristic	Total n = 503	Group 1[a] n = 99	Group 2[b] n = 106	Group 3[c] n = 91	Group 4[d] n = 100	Group 5[e] n = 107
Gender						
Male	115 (22.9)	24 (24.2)	20 (18.9)	26 (28.6)	29 (29.0)	16 (15.0)
Female	388 (77.1)	75 (75.8)	86 (81.1)	65 (71.4)	71 (71.0)	91 (85.0)
Age						
Range in years	20-65	20-65	22-64	21-61	20-56	21-62
Interquartile range	29.5-47.0	31.0-	30.0-46.0	28.8-48.0	28.0-42.0	30.0-47.0
20-29 years	125 (24.9)	49.0	25 (23.6)	24 (26.4)	32 (32.0)	24 (22.4)
30-39 years	164 (32.6)	20 (20.2)	41 (38.7)	29 (31.9)	33 (33.0)	34 (31.8)
40-49 years	122 (24.3)	27 (27.3)	24 (22.6)	19 (20.9)	23 (23.0)	27 (25.2)
50-59 years	80 (15.9)	30 (30.3)	14 (13.2)	17 (18.7)	12 (12.0)	21 (19.6)
60-69 years	9 (1.8)	16 (16.2)	1 (0.9)	1 (1.1)	0 (0.0)	1 (0.9)
		6 (6.1)				
Occupation						
Medical	176 (35.0)	18 (18.2)	29 (27.4)	38 (41.8)	55 (55.0)	36 (33.6)
Nursing	210 (41.7)	43 (43.4)	55 (51.9)	32 (35.2)	29 (29.0)	51 (47.7)
Healthcare assistant	27 (5.4)	11 (11.1)	7 (6.6)	3 (3.3)	4 (4.0)	2 (1.9)
Physiotherapy	15 (3.0)	5 (5.1)	1 (0.9)	5 (5.5)	3 (3.0)	1 (0.9)
Pharmacy	17 (3.4)	6 (6.1)	6 (5.7)	4 (3.8)	1 (1.0)	0 (0.0)
Other allied health professional	11 (2.2)	3 (3.0)	2 (1.9)	3 (3.3)	0 (0.0)	3 (2.8)
Administrative	12 (2.4)	4 (4.0)	1 (0.9)	1 (1.1)	0 (0.0)	6 (5.6)
Auxiliary staff	23 (4.6)	9 (9.1)	2 (1.9)	3 (3.3)	6 (6.0)	3 (2.8)
Other/not documented	12 (2.2)	0 (0.0)	3 (2.8)	2 (2.2)	2 (2.0)	5 (4.7)
Comorbidity						
Smoker	29 (5.8)	3 (3.0)	13 (12.3)	5 (5.5)	5 (5.0)	3 (2.8)
Ex-smoker	81 (16.1)	32 (32.3)	14 (13.2)	11 (12.1)	15 (15.0)	9 (8.4)
Hypertension	30 (6.0)	8 (8.1)	5 (4.7)	5 (5.5)	5 (5.0)	7 (6.5)
COPD[a]	5 (1.0)	1 (1.0)	3 (2.8)	0 (0.0)	1 (1.0)	0 (0.0)
Asthma	70 (13.9)	14 (14.1)	14 (13.2)	8 (8.8)	17 (17.0)	17 (15.9)
Diabetes mellitus	10 (2.0)	0 (0.0)	4 (3.8)	1 (1.1)	2 (2.0)	3 (2.8)
Heart disease	4 (0.8)	0 (0.0)	0 (0.0)	2 (2.2)	1 (1.0)	1 (0.9)
Other metabolic conditions	22 (4.4)	1 (1.0)	8 (7.5)	2 (2.2)	6 (6.0)	5 (4.7)
Chronic kidney disease	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)
Chronic liver disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Immunosuppressed	9 (1.8)	0 (0.0)	4 (3.8)	0 (0.0)	1 (1.0)	4 (3.7)
Blood disorder	5 (1.0)	0 (0.0)	2 (1.9)	0 (0.0)	1 (1.0)	2 (1.9)
Active cancer diagnosis	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)
Neurological condition	7 (1.4)	1 (1.0)	2 (1.9)	2 (2.2)	1 (1.0)	1 (0.9)
None of the above	296 (58.8)	52 (52.5)	61 (57.5)	62 (68.1)	55 (55.0)	66 (61.7)
Risk profile by area of work						
High risk	187 (37.2)	10 (10.1)	43 (40.6)	34 (37.4)	100 (100)	0 (0.0)
Low risk	316 (62.8)	89 (89.9)	63 (59.4)	57 (62.6)	0 (0.0)	107 (100)
Institution						
Cork University Hospital	469 (93.2)	65 (65.7)	106 (100)	91 (100)	100 (100)	107 (100)
Other institution	34 (6.8)	34 (34.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Table 1: Participant demographics and comorbidities. Data are presented as n (% of total displayed at top of individual columns) unless otherwise stated

[a] RT-PCR confirmed COVID-19 infection (>1 month post positive RT-PCR)
[b] Close contacts of persons with COVID-19 infection and who subsequently developed symptoms (virus not detected by RT-PCR on oro/nasopharyngeal swab)
[c] Close contacts of COVID-19 cases and who remained asymptomatic
[d] HCWs working in areas determined as high risk clinical areas
[e] HCWs working in areas determined as low risk clinical areas
[f] Chronic obstructive pulmonary disease

Study Group	Total	IgG positive
Group 1[a]	99	72 (72.7)
Group 2[b]	106	2 (1.9)
Group 3[c]	91	1 (1.1)
Group 4[d]	100	1 (1.0)
Group 5[e]	107	2 (1.9)
Total	503	78 (15.5)

Table 2: SARS-CoV-2 IgG seropositivity by study group. Data are presented as n (%), or total in first column.

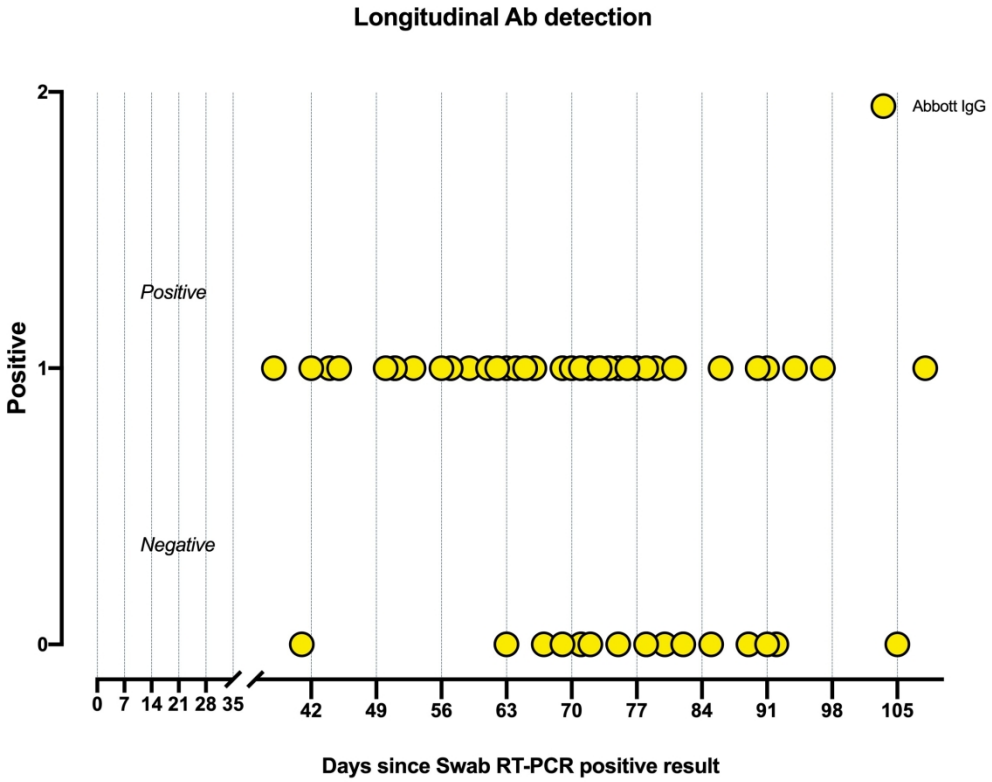
[a] RT-PCR confirmed COVID-19 infection (>1 month post positive RT-PCR)
[b] Close contacts of persons with COVID-19 infection and who subsequently developed symptoms (virus not detected by RT-PCR on oro/nasopharyngeal swab)
[c] Close contacts of COVID-19 cases and who remained asymptomatic
[d] HCWs working in areas determined as high risk clinical areas
[e] HCWs working in areas determined as low risk clinical areas

Figure Legend

Figure 1: Group 1 longitudinal SARS-CoV-2 IgG detection since date of positive RT-PCR. n=99

Acknowledgements

We would like to acknowledge and thank the staff of CUH and affiliated hospitals in the South/Southwest hospital group who participated in this study. We would also like to thank the Health Research Board (HRB) Clinical Research Facility, Cork for the resources and effort contributed towards this study. In particular Jennifer Connolly, Niamh Kelly, Maeve Kelsey and Lisa McSweeney.



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Study Title: Prevalence of SARS-CoV-2 in Healthcare workers in the early stages of the pandemic

Appendix 1

Demographic data

Participant study Code (to be filled in by researchers): _____
Date: _____

Age _____

Gender_____

Healthcare occupation_____

Healthcare location e.g. ED, ward_____

COVID-19 contact risk_____

Weight_____

Height_____

Participant co-morbidities; please tick

I have already had to stay overnight in a hospital because of COVID-19	**Yes** ☐	**No** ☐
I am a smoker	**Yes** ☐	**No** ☐
I am an ex-smoker	**Yes** ☐	**No** ☐
I have high blood pressure	**Yes** ☐	**No** ☐
I have COPD/emphysema/bronchitis	**Yes** ☐	**No** ☐
I have asthma	**Yes** ☐	**No** ☐
I have diabetes	**Yes** ☐	**No** ☐
I have heart disease (for example: angina/previous heart attack/stents/heart bypass surgery/heart failure)	**Yes** ☐	**No** ☐
I have other metabolic conditions apart from diabetes (such as thyroid disease)	**Yes** ☐	**No** ☐
I have Chronic Kidney Disease	**Yes** ☐	**No** ☐
I have Chronic Liver Disease	**Yes** ☐	**No** ☐
I have immunosupression (from medications like chemotherapy or biological agents, or from infection)	**Yes** ☐	**No** ☐
I have a blood disorder (such as Leukaemia, Haemophilia etc)	**Yes** ☐	**No** ☐
I have an active cancer diagnosis	**Yes** ☐	**No** ☐
I have a Neurological condition (such as Epilepsy or Stroke)	**Yes** ☐	**No** ☐
I don't have any of the above risk factors or medical conditions	**Yes** ☐	**No** ☐

| Name (Block Capitals) | Participant Signature | Date

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	Not applicable
Study size	10	Explain how the study size was arrived at	Not applicable
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	6-7
		(*c*) Explain how missing data were addressed	8
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods	Not applicable

taking account of sampling strategy	
(*e*) Describe any sensitivity analyses	Not applicable

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6-7
		(b) Give reasons for non-participation at each stage	Not applicable
		(c) Consider use of a flow diagram	Not applicable
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8-9
		(b) Indicate number of participants with missing data for each variable of interest	8-9
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	8-9
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	Not applicable
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	*8-9*
		Cross-sectional study—Report numbers of outcome events or summary measures	Not applicable
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-9
		(*b*) Report category boundaries when continuous variables were categorized	8-9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8-9
Discussion			
Key results	18	Summarise key results with reference to study objectives	10-11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10-11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.