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Original article

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The protective effect of SARS-COV-2 antibodies in Scottish healthcare workers.

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Abstract

Background: Healthcare workers (HCW) are believed to be at increased risk of SARS-CoV-2 infection. It is not known to what extent the natural production of antibodies to SARS-CoV-2 is protective against re-infection.

Methods: A prospective observational study of HCW's in Scotland (UK) from May to September 2020. The Siemens SARS-CoV-2 total antibody assay was used to establish seroprevalence in this cohort. Controls, matched for age and sex to the general local population, were studied for comparison. New infections (up to 2/12/2020) post antibody testing were recorded to determine if the presence of SARS-CoV-2 antibodies protect against re-infection.

Results: A total of 2063 health and social care workers were recruited for this study. At enrolment 300 HCW had a positive antibody test (14.5%). 11/231 control sera tested positive (4.8%). HCW therefore had an increased likelihood of a positive test (Odds ratio 3.4 95% CI 1.85-6.16, $p<0.0001$). Dentists were most likely to test positive. 97.3% of patients who had previously tested positive for SARS-CoV-2 by RT-PCR had positive antibodies. 18.7% had an asymptomatic infection. There were 38 new infections with SARS-CoV-2 in HCW who were previously antibody negative and one symptomatic RT-PCR positive re-infection. The presence of antibodies was therefore associated with an 85% reduced risk of re-infection with SARS-CoV-2 (HR 0.15, 95% CI 0.06 to 0.35, $p=0.026$).

Conclusion: HCW were three times more likely to test positive for SARS-CoV-2 than the general population. Almost all infected individuals developed an antibody response which was 85% effective in protecting against re-infection with SARS-CoV-2.

Background

Healthcare workers (HCWs) are known to be at increased risk of symptomatic infection with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)[1,2]. HCWs accounted for 21% of SARS cases during the outbreak in 2002[3] and high rates of symptomatic infections have been reported across Europe during the present pandemic, including in the UK[4]. Measures taken to mitigate this increased risk include adequate personal protective equipment (PPE)[5], infection prevention and control (IPC) procedures within healthcare environments and staff testing. Across the UK, testing for healthcare and other key workers with symptoms has been widely available since April 2020[6].

A key challenge in containing the spread of SARS-CoV-2 has been the potential for asymptomatic or atypical infection[7]. Even in the case of symptomatic individuals reverse transcriptase polymerase chain reaction (RT-PCR) on nasopharyngeal, oropharyngeal or combined upper airway swabs has a reported sensitivity of 70-90% and consequently will underestimate the number of infected individuals[8]. Therefore, the extent of infections in HCWs in different parts of the world remain largely unknown.

Serological testing can be used to determine the incidence and prevalence of SARS-CoV-2 infection[9]. Identifying the extent of healthcare worker infections and the proportion of undetected infections is important to inform IPC measures during future waves of the pandemic.

An antibody response is expected after infection with SARS-CoV-2 but the rate of antibody development has not been extensively reported. Little is known about the protective effect of natural immunity and no studies have been published which demonstrate how protective natural antibodies are against re-infection with SARS-CoV-2.

In this study, we investigated the seroprevalence of SARS-CoV-2 antibodies in a large population of Scottish HCWs. We also investigate if the presence of antibodies protects against re-infection with the virus.

Methods

We conducted a prospective observational study recruiting HCWs employed within the National Health Service in Tayside (NHS Tayside). NHS Tayside is an NHS board in the East of Scotland that is responsible for delivering healthcare for over 400,000 people and employs around 14,000 staff.

Healthcare staff were invited to participate in the study via advertisements, including email newsletters and posted adverts on the staff intranet page. Recruitment took place during a single study visit at Ninewells Hospital, which is the health board's largest teaching hospital. Recruitment took place between 28th May 2020 and the 2nd September 2020. Electronic results were followed up until the 2nd December 2020 to record new laboratory confirmed infections. All participants gave written informed consent to participate. The study was approved by the West of Scotland Research Ethics committee, approval number 20/WS/0078.

The inclusion criteria were: Employment as a health or social care worker and age over 16 years. Participants were excluded if they had any contraindication to venepuncture, and symptoms consistent with current SARS-CoV-2 infection at the time of enrolment or had tested positive for SARS-CoV-2 in the preceding 14 days.

At the study visit, participants completed a questionnaire on demographics, previous symptoms, employment role, hours of work, contact with patients with COVID-19 infection and whether they had previously tested positive for SARS-CoV-2. Blood samples were taken for measurement of SARS-CoV-2 antibodies in serum.

SARS-CoV-2 antibody detection

The Siemens SARS-CoV-2 total antibody assay was used in this study. This is a one stop bridging chemiluminescent immunoassay (CLIA) method that detects antibodies against the receptor-binding domain (RBD) of the SARS-CoV-2 spike (S1) protein. The assay is performed on the Siemens Atellica 1300 platform. Validation of this assay was approved by the NHS Scotland national laboratories programme quality group and was then further validated against other commercial antibody platforms in a previous study and found to have 95-100% sensitivity while titres remained constant beyond 81 days following a positive PCR test result[10].

Population control subjects

A random selection of blood samples taken at NHS Tayside General Practice Surgeries were tested covering the same time period as the HCW study cohort. Samples were age and sex matched to the Scottish population demographics to provide a representative sample of the local population to determine the background prevalence of SARS-CoV-2. Serum samples were run on the same Siemens analyser described above.

Follow-up

All individuals in Scotland have a unique identifier number (community health index) that links to their healthcare records. Using these identifiers, participants antibody data was linked to results of symptomatic testing for SARS-CoV-2 at regional and national laboratories. Immediate testing for healthcare workers displaying symptoms is available in the study region, ensuring all symptomatic SARS-CoV-2 infections would be captured during follow-up up until 02/12/2020.

Statistical analysis

Data was analysed using IBM SPSS v25 and GraphPad Prism 8.1.2. Chi-squared and Fisher's test were used as appropriate to compare proportions between groups. Logistic regression was used to derive the odds ratio values for the reported symptom analysis. Kaplan-Meier survival analysis with follow-

up from date of antibody testing until 02/12/2020 was used with groups compared using the log-rank (Mantel-Cox) test. A p-value <0.05 was considered statistically significant for all analyses.

Results

A total of 2063 health and social care workers were recruited for this study. The participants were predominantly female (81.7%) and 95.5% were white. The median age of participants was 46 years. Table 1 presents the demographic characteristics of the study participants and their healthcare roles.

Seroprevalence of SARS-CoV-2 antibodies

In our study, 300 HCWs had a positive antibody test directed against SARS-CoV-2 spike protein. This represents a seroprevalence of 14.5%. 11 out of 231 control sera tested positive (4.8%) which was consistent with the broader Scottish surveillance data reported by Health protection Scotland (214 positive tests out of 4751, 4.5%). Compared to both sets of population controls, HCWs had 3.6 times greater odds of a positive test (Odds ratio 3.4 95% CI 1.85-6.16, p<0.0001 compared to local controls) and (OR 3.6, 95% CI 2.99-4.32, p<0.001 compared to Scotland wide controls).

Table 1 shows the seroprevalence rate amongst subgroups in our study characterised demographic, job role and area of work. Male gender was more frequently associated with detected antibodies (18.5% vs 13.7%, p=0.02). Some job roles were significantly associated with a higher rate of SARS-CoV-2 antibody detection. Healthcare workers in dentistry were the most frequently associated with detected antibodies (26%), followed by health care assistants (HCAs) (23.3%) and hospital porters (22.2%), p<0.0001 when comparing across groups. Figure 1 displays the rates of antibody prevalence amongst the HCW by profession.

Healthcare staff who worked in areas of the hospital that treated suspected or confirmed cases of COVID-19 were more frequently associated with detected antibodies (17.4% vs. 13.5%, p=0.03). Staff who worked in critical care and the intensive care unit were not more frequently associated with detected antibodies (16% vs. 14.4%, p=0.61).

Prior positive test results and symptomatic infections

797 study participants had a SARS-COV-2 RT-PCR swab prior to enrolment into the study and therefore prior to antibody measurement. 111 of these were positive for SARS-CoV-2 prior to enrolment. 97.3% (108/111) of participants with positive RT-PCR had detectable antibodies. 10.9% of participants with a negative PCR test prior to enrolment had detectable antibody levels. In those who never had a RT-PCR test 8.9% of them had detectable antibodies. Figure 2 displays the proportion of PCR positive and PCR negative participants with detected antibodies.

45.4% (n=936) of the HCWs recruited believed they had COVID-19 but only 25.1% (n=235) of these HCWs had detectable antibodies. Conversely, 18.7% (n=56) of those who had antibodies detected did not believe they ever had COVID-19 and were completely asymptomatic.

5.1% (n=56) of Asymptomatic participants had detectable antibodies compared to 25.6% (n=243) of symptomatic recruits who had detectable antibodies. When compared with the general population individuals who did not have a symptomatic illness during the period of the study did not have an increased frequency of SARS-CoV-2 antibodies (OR 1.20 95% CI 0.30-4.83, p=0.26).

Anosmia was the self-reported symptom that was most likely to correspond with detected antibodies (OR 12.3, 95% CI [9.3-16.3], p <0.001) but was only reported in 5.8% of HCWs at any time (Table 2). A combination of cough, fever and anosmia was only reported at a frequency of 2.6% but when present was associated with a 10-fold increase in odds of detectable antibody (OR 9.7, 95% CI

[6.4-14.7], p <0.001). The absence of any cough, fever and anosmia was associated with an 82% chance of not having detectable antibodies (OR 0.18, 95% CI [0.14-0.24], p <0.001).

Infection rate and antibody protection during second wave of infections

In the three months following the end of the recruitment period, there were 39 new symptomatic infections with SARS-CoV-2. 38/39 of these infections were in HCWs who did not have prior antibodies to SARS-CoV-2.

There was only one re-infection (1/300 or 0.33%) with SARS-CoV-2. This re-infection was in a symptomatic HCW who tested RT-PCR positive 76 days after having detectable antibodies in their serum.

From the first recorded PCR positive infection in this cohort to the end of follow-up period was 261 days and from the first positive antibody test to the end of the follow-up period was 188 days. Figure 3 shows an analysis of time from antibody testing to development of PCR confirmed symptomatic SARS-CoV-2 infection. This demonstrates that having antibodies to SARS-CoV-2 at baseline is highly protective against re-infection (hazard ratio 0.15, 95% CI 0.06 to 0.35, p=0.026 over a follow-up period of up to 6 months.

Discussion

In this observational study of health and social care workers the SARS-COV-2 seroprevalence rate was 14.5%. Importantly, the presence of antibodies was associated with clear protection against subsequent infection. This is important for our future understanding of risk for healthcare workers and the general population.

At the time of writing Health Protection Scotland (HPS) is leading a surveillance study for COVID-19 in Scotland on behalf of the Scottish Government[11]. Present data from this study demonstrates a comparative seroprevalence of 4.5%. Our data suggest therefore that health and social care workers are greater than 3 times more likely to be positive for spike protein antibodies and therefore likely to have been infected SARS-CoV-2.

Other HCWs seroprevalence studies conducted in the rest of the UK also reported higher seropositivity when compared to the general population with seroprevalence rates of 24.4%[12], 25.4%[13] and 10.7%[14].

Our study was notable for the inclusion of dentistry staff, who had the highest seroprevalence rate at 26%. This was well above the average seroprevalence rate of 14.5% amongst our HCWs although this higher rate should be interpreted with some caution given the lower number of dentistry staff enrolled (table 1). Dentistry staff are expected to be a higher risk group given their focus of work is more likely to be aerosol generating and with close exposure to potentially infected mucosal surfaces[15]. Health care assistants, including such staff at nursing homes, had the second highest prevalence at 23%. The caring roles of these workers necessitate close patient contact and their increased risk was also reported in a recent Swedish study[16].

In other published HCW studies[12], domestic or housekeeping staff had the highest seroprevalence of antibodies. This was not evident in our study where domestic staff had a below average seroprevalence rate of 13.1%. Other groups who had a seroprevalence rate above average were hospital porters and doctors. Doctors and porters are typically exposed to multiple patients in different working areas. By comparison nurses typically care for up to 6 patients in a defined area

during their working day. The variability in work location in a particular time period could be a factor in the increased infection rate we observed.

In our study, HCWs who worked in COVID-19 areas of the hospital had a slightly higher seroprevalence than those workers who did not. This finding is consistent with other studies, including HCW studies conducted in major urban areas where the community burden of COVID-19 was a significant source of exposure[17]. Working in COVID-19 areas of the hospital is one way to define high risk exposure. Nevertheless, the majority of SARS-CoV-2 infections detected in this study occurred in staff who were not working directly with COVID-19 patients, and even so, this group still had a significantly higher prevalence of SARS-CoV-2 antibodies than the general population. While a seroprevalence study cannot establish the source of infection this strongly suggests transmission between healthcare staff within non-clinical environments since many staff roles that did not involve direct contact with patients were still associated with an increased rate of antibody positivity. Therefore, while much media attention has focused on the importance of PPE for front line staff, this data emphasises the importance of IPC measures in non-clinical areas within healthcare environments such as hospitals. The relative success of measures to protect high-risk frontline staff is illustrated by the low rate of antibody detection in critical care staff. All staff working in critical care areas wore PPE in accordance with Health Protection Scotland guidance on working in aerosol generating procedures[18] .We found no significant increased risk of infection for these staff. In the recently published study from Birmingham, UK[12] staff in intensive care had a significantly lower risk of seropositivity.

We asked our study participants to report if they thought they had COVID-19 and list the symptoms they experienced. We describe that only one in four participants who thought they had contracted COVID-19 demonstrated serological evidence of infection. The heightened suspicion of infection is justified amongst HCWs, but perceived infection does not correlate well with actual infection. This has some potentially important implications when considering the issue of chronic symptoms in individuals who believe they have had COVID-19 infection[19]. However, we demonstrated in this study that certain symptoms are significantly more predictive of infection with SARS-CoV-2. Anosmia represented twelve-fold increased odds with having serologic evidence of infection. This particular symptom was also shown to be strongly predictive in similar analysis performed in other European studies[16,20].

Our study demonstrates that approximately one fifth (18.7%) of seropositive HCWs were completely asymptomatic. This is consistent with studies that only recruited asymptomatic HCWs[12] and represents that a significant proportion of the healthcare workforce will attend work without knowing that they may potentially transmit the infection to their colleagues.

After the end of the recruitment period we followed our study participants for up to 6 months from antibody positivity and up to 10 months from first PCR confirmed SARS-CoV-2 infection. Winter 2020 coincided with the second wave of SARS-CoV-2 infections in Scotland and we had 39 new infections amongst our HCW during this period. One of these infections (0.33% of total study group) was a symptomatic re-infection in a HCW who had previously developed an antibody response from a previous infection. To our knowledge this is the first reported case of laboratory confirmed re-infection after the development and confirmed presence of natural antibodies.

97.4% of new infections were in HCWs who did not have previous antibodies, in our study the presence of a natural antibody response was therefore 85% protective against re-infection with SARS-CoV-2 over a period of 6 months (May to December 2020).

Our results on antibody protection fits within the range of efficacy of vaccine mediated immunity reported in the recently published SARS-CoV-2 vaccine trials[21,22]. These results may have implications for the roll out of vaccine programmes, since healthcare workers are often prioritised, but our

results suggest HCWs with prior infection may be at low risk of future infection and may therefore be considered a lower priority.

This study has potential limitations, including potentially that individuals more likely to believe they have had a SARS-CoV-2 like illness would be more likely to volunteer for such a study. Nevertheless, we were successful in enrolling participants who had never experienced a symptomatic infection and demonstrate an increased seroprevalence even amongst this group. We enrolled patients up to September 2020 and therefore potentially up to 4-5 months post-infection. This raises the possibility of antibodies waning over time[23]. This seems unlikely as a prior study found no evidence of waning of the Siemens assay over 4 months[10], while a similar Total spike protein antibody assay showed no waning over time in a study from Iceland[24]. Other studies have reported increased infection rate in the BAME population[25,26,27], we were unable to investigate this as NHS Tayside has a workforce which is 97% white. The patient population was representative of NHS Scotland staff. In 2019, the median age of staff employed across NHS Scotland was 46 years, 77.4% of NHS Scotland employees were female. 9% were doctors, 0.4% dental staff, 42.6% nursing staff, 8.4% allied health professionals and 18.1% administrative staff. Our sample include 11.5% doctors, 29.2% nurses, 11.6% AHPs, and 19.6% administrative staff. Our median age was 46 and 81.7% of our cohort were female.

CONCLUSION

Our study suggests that HCWs are at increased risk of infection with SARS-COV-2 compared with the general population. Our study suggests a differential risk amongst hospital staff and a high proportion of undetected symptomatic and asymptomatic infections. This will help to inform targeted IPC strategies during future epidemics. We report a single re-infection in a HCW who had developed natural antibodies and we estimate the natural antibody response is 85% protective against re-infection.

LIST OF ABREVIATIONS

HCW: Healthcare Worker.

RT-PCR: Real time polymerase chain reaction.

NHS: National Health Service.

PPE: Personal protective equipment.

IPC: Infection prevention and control.

CLIA: Chemiluminescent immunoassay.

RBD: Receptor binding domain.

AHP: Allied health professional.

HPS: Health protection Scotland.

DECLARATIONS

Ethics Approval: West of Scotland Research Ethics committee, approval number 20/WS/0078.

Consent for publication: Our manuscript contains no person identifiable information.

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Availability of data and materials: Data and materials can be made available upon reasonable request and in keeping with our ethics and data protection protocols.

Patient and public involvement statement: Patients or the public were not involved in the design, or conduct, or reporting or dissemination plans of our research.

CONFLICTS OF INTEREST SUMMARY

JDC reports grants and personal fees from GlaxoSmithKline, Boehringer-Ingelheim, Astrazeneca, Pfizer, Bayer Healthcare, Grifols, Napp, Insmed and Zambon outside the submitted work; All other authors report no conflicts of interest.

CONTRIBUTORS

Study design and conduct: SG, DC, BP, JG, EF, JDC

Data collection: HAL, SG, DC, RS, NG, CS, EH, JK, EF, JDC

Laboratory work: DC, YHG, JK, BM, GH, TP, RS, EF

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Reviewed the manuscript and approval the final version: all authors

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Tables

Characteristic	Number (% of Total)	Number of Ab positive	Seroprevalence	P value
Gender:				0.02
Male	378 (18.3%)	70	18.5%	
Female	1685 (81.7%)	230	13.7%	
Age Group:				0.5
18-30	290 (14.1%)	46	15.9%	
31-40	403 (19.5%)	60	14.9%	
41-50	536 (26.0%)	76	14.2%	
51-60	637 (30.9%)	97	15.2%	
60+	196 (9.5%)	21	10.7%	
Ethnicity:				0.86
White European	1964 (95.5%)	285	14.5%	
Other White	16 (0.8%)	2	12.5%	
South Asian	36 (1.7%)	8	22.2%	
Chinese	10 (0.5%)	1	10.0%	
Black	8 (0.4%)	2	25.0%	
Arab	5 (0.2%)	1	20.0%	
Traveller	2 (0.1%)	0	0.0%	
Other Ethnic	16 (0.8%)	1	6.3%	
Role:				<0.001
Doctor	237 (11.5%)	50	21.1%	
Nurse	601 (29.2%)	80	13.3%	
AHP	239 (11.6%)	25	10.5%	
Pharmacy staff	69 (3.4%)	9	13.0%	
HCA	172 (8.4%)	40	23.3%	
Student	25 (1.2%)	4	16.0%	
Domestic	84 (4.1%)	11	13.1%	
Admin	403 (19.6%)	49	21.1%	
Porter	27 (1.3%)	6	22.2%	
Other	151 (7.3%)	13	8.6%	
Dentistry	50 (2.4%)	13	26.0%	
Area:				0.024
COVID	552 (26.8%)	96	17.4%	
Non-COVID	1511 (73.2%)	204	13.5%	
Critical Care:				0.61
Yes	131 (6.3%)	21	16.0%	
No	1931 (93.7%)	279	14.4%	

Table 1:Demographic characteristics and seroprevalence of study participants including roles and areas of work. AHP= Allied health professional, HCA= Healthcare assistant. Other role includes: Lab technician, health scientist, maintenance, laundry, medical physics, other technician, patient transport, chaplaincy, volunteers. Chi-squared and Fisher's exact test used to determine statistical significance ($p<0.05$ = statistically significant (black font colour).

Symptoms	Frequency	OR	P value	95% CI	
Fatigue	15.4%	4.5	0.0001	3.458	5.912
Headache	12.3%	3.6	0.0001	2.809	4.653
Cough	11.8%	2.1	0.0001	1.619	2.67
Myalgia	11.7%	3.8	0.0001	2.931	4.856
Fever	10.0%	2.5	0.0001	1.74	2.901
Sore throat	9.8%	1.4	0.009	1.092	1.86
Dyspnoea	9.2%	2.4	0.0001	1.825	3.076
Runny nose	5.9%	1.2	0.378	0.835	1.61
Anosmia	5.8%	12.3	0.0001	9.306	16.348
Other	5.0%	3.5	0.001	2.615	4.705
Diarrhoea	3.1%	2.5	0.0001	1.773	3.66
Cough+Fever+Anosmia (CFA)	2.6%	9.7	0.0001	6.433	14.738
Absence of CFA	13.1%	0.2	0.001	0.136	0.239

Table 2: Frequency of reported symptoms and Odds ratio (OR) of each symptom corresponding to a detectable antibody against SARS-COV-2. CFA= combination of cough, fever and anosmia being reported. CI= 95% confidence interval. See appendix for list of other symptoms reports.

Figure Legends

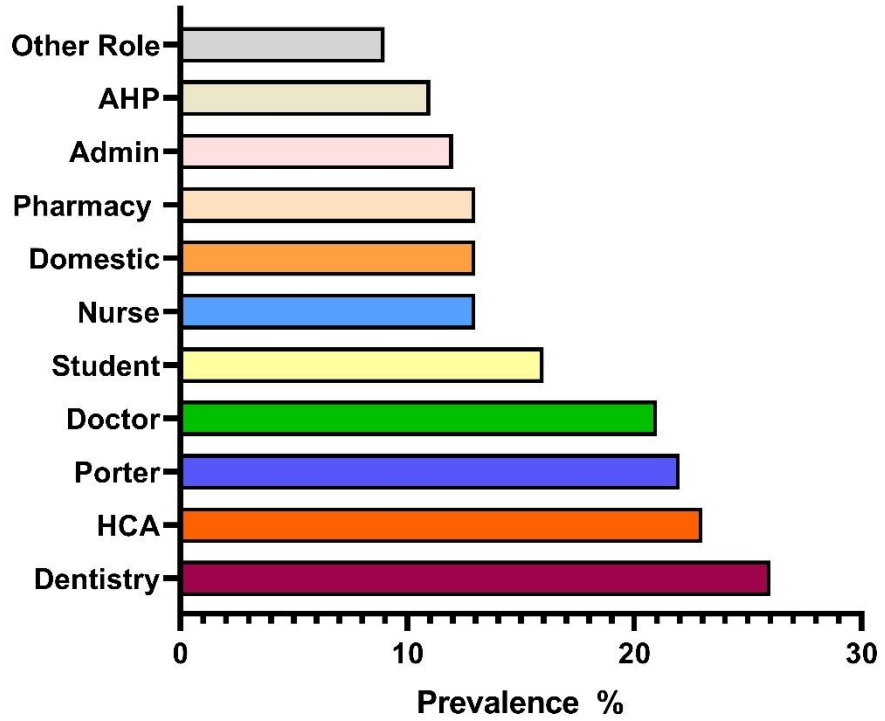

Figure 1: Percentage prevalence of SARS-COV-2 antibody amongst different HCW roles. Staff working in dentistry had the highest prevalence of infection.

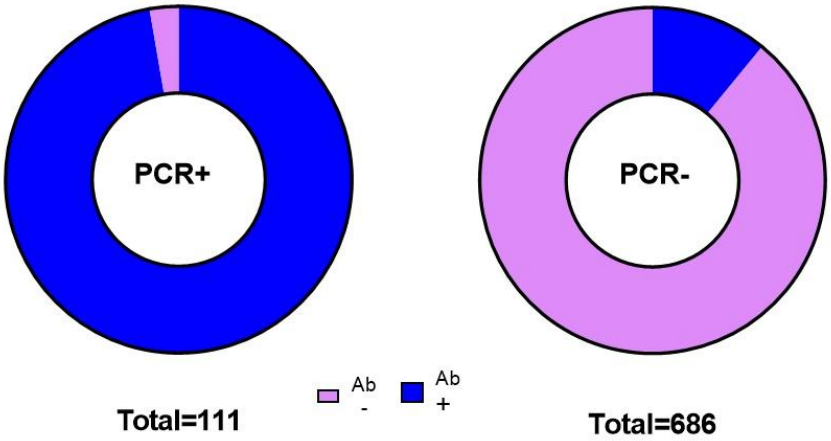

Figure 2: Proportion of antibody detection according to PCR status. 97.3% of PCR- positive individuals had detectable antibodies. 10.9% of PCR negative participants had detectable antibodies.

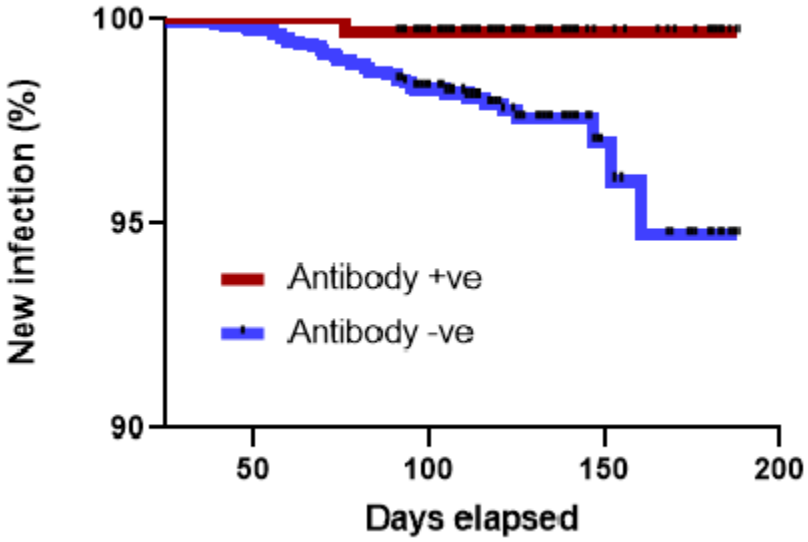

Figure 3 Survival curve showing protective effect of pre-existing antibodies to developing new SARS-CoV-2 infections. Those who had previously detected antibodies to SARS-CoV-2 were protected against re-infection.