Letter to the Editor

Decline in antibody responses to SARS-CoV-2 post-vaccination poses a risk to health care workers

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Abbreviations

HCW, health care worker
IGG, immunoglobulin g
IGM, immunoglobulin m
IQR, interquartile range
LFIA, lateral flow immunoassay
POC, point-of-care
SAHPRA, South African Health Products Authority
SA-MRC, South African Medical Research Council
VOC, variant of concern

Dear Editor,

We read with interest the article published in this journal by Pezzati et al. on the use of rapid lateral flow assays to detect antibodies induced by vaccination against SARS-CoV-2 infection. The authors concluded that a number of rapid lateral flow assays were useful in a qualitative assessment of vaccine responses [1]. SARS-CoV-2 caused the global COVID-19 outbreak originating in the Wuhan Province of China in late 2019 [2]. The first case of COVID-19 in South Africa was reported on 5 March 2020 [3], and the World Health Organization (WHO) declared a global pandemic on 11 March 2020 [4]. As of 25 February 2022, South Africa had >3.6 million laboratory-confirmed COVID-19 cases [5]. South Africa experienced several waves of the pandemic, owing to infection with different SARS-CoV-2 variants of concern (VOC), namely the Wuhan B.1 lineage variant (infection peak between June - August 2020), the Beta variant (infection peak between November 2020 - February 2021), and the Delta variant (infection peak between May - September 2021). The Omicron variant was first identified in South Africa and Botswana in mid-November 2021 [6], just before participants were recruited into this study. Omicron rapidly became the dominant infective variant in South Africa.

Health care workers (HCWs) are at high risk of exposure to COVID-19. In February 2021, South Africa, through the Sisonke phase 3B trial, began vaccinating HCWs against COVID-19 with the Johnson & Johnson vaccine [7]. Other vaccines, including the Pfizer Comirnaty and Oxford/Astra-Zeneca were also subsequently approved by the South African Health Products Regulatory Authority (SAHPRA). These vaccines are effective in preventing severe disease and hospitalization, however mild to moderate infections still occur. In a recent report, ~8.5% of HCWs vaccinated in the Sisonke trial contracted SARS-CoV-2 post-vaccination, with over 43% of infections caused by the Omicron VOC [8]. Breakthrough infections in HCWs have been reported in other studies, with participants being either asymptomatic or with mild to moderate symptoms [9]. A number of reports show waning antibody levels in both previously infected and vaccinated individuals [10,11], although the rate of decline varies amongst individuals.

The humoral response to SARS-CoV-2 infection is not clearly defined, though it is reported that most infected individuals produce Immunoglobin M (IgM) antibodies from 4 days post-symptom onset which peak between day 14 and 21 before declining. Immunoglobin G (IgG) levels start to rise between 7 and 14 days, although it is unclear how long these IgG antibodies are sustained [12]. In individuals vaccinated with the BNT162b2 Pfizer vaccine, antibody levels peaked between 4 and 5 weeks after the initial dose and decreased thereafter. After the second vaccine dose, antibodies were detected in >90% of participants but, again, decreased over time, especially in older recipients [11]. Similar trends in waning antibody levels have also been observed with other COVID-19 vaccines, with rapid decline in antibody levels reported in patients with obesity, autoimmune diseases, and other chronic inflammatory conditions [13]. While antibodies are not the only indication of protection against COVID-19, the presence of antibodies does decrease the risk of infection [14].

A number of laboratory-based assays are able to detect antibodies against SARS-CoV-2. Lateral flow immunoassays (LFIA) are rapid tests where a patient specimen (either whole blood, serum, or plasma) is placed onto a cassette containing the analyte of interest. If the patient has developed antibodies to SARS-CoV-2, the IgM and/or IgG test lines will change color indicating a positive result. LFIAs can be used in remote sites or point-of-care (POC) settings, as they require no other laboratory equipment, and can be performed by less skilled personnel.

We aimed to assess the seroprevalence of IgM and IgG antibodies to the spike protein of SARS-CoV-2 in HCWs using the Orient Gene COVID-19 IgG/IgM Rapid Test Cassette which detects antibodies to the N-terminal of the spike protein (S1) of SARS-CoV-2 [15]. We recruited HCWs at or affiliated with the University of Pretoria in South Africa between November 2021 and March 2022. We asked participants to provide written informed consent, to answer some questions relating to COVID-19 vaccination status and prior infection, and drew blood samples from them. This study was approved by the Human Research Ethics Committee at the University of Pretoria (approval number 680/2021).

One drop of whole blood was placed onto the cassette with 2 drops of buffer. Those that reacted with either the IgG or IgM band or both were considered seropositive. Data were analyzed using GraphPad Prism 9.3.1 for Windows. The participant characteristics, previous SARS-CoV-2 infection, vaccine data, and seropositivity are summarized in Table 1. Of the 203 total participants, the median age was 35 years (IQR 27–50), 160 (78.8%) were female, and 38.4% reported previous COVID-19 infection. Of the total participants, 195 (96%) were

vaccinated, while 8 (4%) were unvaccinated. In total, 82.3% of the participants tested positive for antibodies to SARS-CoV-2.

Table 1. Study population characteristics.

			Overall	**Antibody Negative**	**Antibody Positive**
All participants, n (%)	Total		203	36 (17.7%)	167 (82.3%)
	Gender, n (%)	Female	160 (78.8%)	23 (63.9%)	137 (82%)
		Male	43 (26.9%)	13 (36.1%)	30 (18%)
	Age, median [IQR]		35 [27–50]	29 [24–42]	37 [28–50]
	Past COVID-19 infection, n (%)	COVID-19 positive	78 (38.4%)	4 (11.1%)	74 (44.3%)
		COVID-19 negative	125 (61.6%)	32 (88.9%)	93 (55.7%)
Vaccinated, n (%)	Total		195	33 (16.9%)	162 (83.1%)
	Gender, n (%)	Female	154 (79%)	20 (60.6%)	134 (82.7%)
		Male	41 (21%)	13 (39.4%)	28 (17.3%)
	Age, median [IQR]		35 [27–50]	29 [25–39]	38 [29–50]
	Vaccine type, n(%)	J&J	152 (77.9%)	33 (21.7%)	119 (78.3%)
		Pfizer	41 (21%)	0	41 (100%)
		Astra-Zeneca	2 (1%)	0	2 (100%)
	Past COVID-19 infection, n (%)	COVID-19 positive	71 (36.4%)	0	71 (100%)
		COVID-19 negative	122 (62.6%)	31 (25.4%)	91 (74.6%)
Unvaccinated, n (%)	Total		8	3 (37.5%)	5 (62.5%)
	Gender, n (%)	Female	6 (75%)	3 (50%)	3 (50%)
		Male	2 (25%)	0	2 (100%)
	Age, median [IQR]		32 [24–44]	42 [32–47]	30 [24–33]
	Past COVID-19 infection, n (%)	COVID-19 positive	5 (62.5%)	0	5 (100%)
		COVID-19 negative	3 (37.5%)	3 (100%	0

The vaccinated participants (195) had a median age of 35 years (IQR 27–50), 79% were female, and 83.1% of this group tested positive for SARS-CoV-2 antibodies. Antibodies were tested on average 41 weeks (IQR 34–44) post vaccination. Thirty-six percent (36%) of this group reported testing positive for COVID-19, with 67% of infections occurring at a median of 24 weeks (IQR 17–33) post-vaccination. All participants who had COVID-19 tested antibody positive. Of the vaccinated participants who did not report previous COVID-19 (122), 74.6% were antibody positive. The majority of the vaccinated participants received the Johnson & Johnson vaccine (77.9%), while fewer received Pfizer (21%) or Astra-Zeneca (1%). There were 8 unvaccinated participants of whom 6 were female. The median age was 32 years (IQR 24–44). Five participants reported prior COVID-19 infection and all had positive antibody tests. Those who had not had COVID-19 also did not test positive for antibodies.

Of interest, one vaccinated participant who tested positive for antibodies, reported testing positive for COVID-19 during the second, third, and fourth waves of the pandemic. This individual reported having an unspecified autoimmune disease. This suggests that the antibody-mediated defenses induced by vaccination with vaccines designed against the wild-type strain may offer suboptimal protection in certain autoimmune conditions.

These results show that 18% of healthcare workers tested in this study did not have detectable antibodies to SARS-CoV-2. All participants without prior vaccination or infection were sero-negative as were a quarter of those previously vaccinated but uninfected. Such HCWs should be prioritized for vaccination and booster doses due to their ongoing, and potentially high-risk, exposure to the pathogen.

We acknowledge that there are several limitations to this study. Firstly, the study population is a convenient sample of HCWs within a specific geographic location and may not be representative of the general population. Secondly, LFIAs are qualitative, and levels of antibodies cannot be determined. We aim to confirm these results with quantitative assays. Thirdly, most of these antibody tests were conducted several months after vaccination. It is therefore difficult to determine in seronegative participants if antibodies were induced initially at all, and whether they declined over time. In addition, we do not know whether the antibodies detected are protective against future infection, or whether antibodies induced by the vaccine are protective against different variants. Lastly, we only looked at antibodies against SARS-CoV-2, and did not assess their functionality or take immune responses induced by other immune cells (e.g. T cells) into consideration. We aim to explore these responses further in subsequent studies.

In conclusion, antibodies to SARS-CoV-2 can be induced by both prior infection and vaccination. All participants with previous COVID-19 were seropositive, irrespective of vaccination status. However, only 83.1% of the vaccinated participants with a history of COVID-19 and just 74.6% with no such history, were seropositive. This indicates that, while vaccination successfully induces antibodies to SARS-CoV-2 which persist several months after vaccination in 3 out of 4 participants, 25% are potentially unprotected. Regular antibody surveillance is important to assess the longevity of vaccine responses. Regular booster vaccination may be needed to increase antibody-mediated protection in certain individuals.

Declaration of interests

None.

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