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SARS-CoV-2 seroepidemiology among tertiary students and health workers at the Korle-Bu community in Accra, Ghana

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Abstract

Background: The COVID-19 pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has had an unprecedented impact on nations worldwide. Insight into a population's immunity level is key to implementing effective control measures. In Ghana, despite mass exposure to the virus, vaccination coverage is still far below expectation, and to date, very few data exist on anti-SARS-CoV-2 immunity in the Ghanaian population

Objective: This study determined the prevalence of antibodies (IgM and IgG) in both COVID-19 vaccinated and unvaccinated individuals at the Korle Bu Polyclinic and a cross-section of students of the School of Biomedical and Allied Health Sciences in Accra, Ghana.

Methods: A cross-sectional study including 207 participants was conducted. Sera were obtained and tested for SARS-CoV-2 specific IgG/IgM antibodies, while oropharyngeal swabs from IgM-reactive individuals were tested for SARS-CoV-2 RNA by RT-PCR. Our study population comprised 207 individuals of which 70 were vaccinated and 137 were unvaccinated.

Results: The total seropositivity in the population studied was 67.6% (n = 140/207). The IgG seroprevalence was 60.9% (n = 126/207). Evidence of seroconversion was observed in more of the vaccinated individuals (72.9%, n = 51/70) than in individuals who were not vaccinated (54.7%, n = 75/137). Thirteen (18.6%) of the vaccinated individuals were IgM reactive, while 19 (27.1%) were IgG unreactive. Seropositivity in healthcare workers was 63.2% (n = 12/19), which was consistent with that observed for the entire study population. About 20% (n = 9/46) of the individuals who tested positive for SARS-CoV-2-specific IgM had detectable SARS-CoV-2 by nucleic acid testing.

Conclusion: The results from this study show evidence of breakthrough infections and suggest a high exposure of the study population to SARS-CoV-2, which might underscore a high prevalence of asymptomatic COVID-19 in Ghana despite the low hospitalisation rate recorded at the time of sampling. This study also reaffirms the need for booster vaccination, reinforcement of COVID-19 control measures, and the need of broader serological studies in Ghana.

Keywords: COVID-19 vaccination, immunity, breakthrough infections, Ghana

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INTRODUCTION

Respiratory virus outbreaks and pandemics, such as those caused by coronaviruses, including the Severe Acute Respiratory Syndrome (SARS-CoV), the

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Middle East respiratory syndrome, and the new Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) have major impacts worldwide [1]. Every continent was affected by the devastating effects of the coronavirus disease 2019 (COVID-19) pandemic caused by SARS-CoV-2. Currently, available figures indicate that more than 766 million cases have been recorded, with at least 6.9 million deaths worldwide as of 17th May 2023 [2].

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Online first publication





According to reports, approximately 80% of COVID-19 cases are mild or asymptomatic, 15% are moderate, and 5% are severe in nature [3]. Observations have shown that not all individuals develop detectable antibodies after exposure or vaccination. In fact, how individuals respond to SARS-CoV-2 exposure is not well understood. However, host genetic differences may influence an individual's response following exposure or vaccination [4,5]. The time of blood collection also affects the outcome of serological studies, as antibody titers induced by vaccination have been shown to wane relatively fast [6].

In Ghana, the first case of SARS-CoV-2 was reported on 12 March 2020 [7]. More than 3 years into the pandemic, there have been 171,657 confirmed cases, 170,161 recoveries and about 1,462 COVID-19-related deaths in the country [8]. The Greater Accra Region (Accra), the capital of Ghana and the Ashanti Region are the two main epicentres of the COVID cases in the country. According to the projected population for May 2020 by the Statistical Service of Ghana [9], the Greater Accra region is the second most densely populated (next to the Ashanti region) of the 16 administrative regions in Ghana but accounts for about 56% of all recorded cases in the country [8]. It is noteworthy that in the first four months following the first case detection in Ghana, most of the cases detected were asymptomatic – a condition that might have implications for the control of the disease as these asymptomatic cases would potentially be the main drivers of the outbreak. However, Ghana's response to the pandemic was robust. An enhanced contact tracing with screening was instituted from March 31st, 2020 to April 27, 2020 [10]. This advanced form of surveillance involved testing samples from contacts or residents within a 1-2 km radius of a confirmed case based on population density and social interaction within an identified setting. This approach invariably enhanced early case detection, isolation, and control of the disease and, thus, significantly contributed to the detection of a high proportion (93%) of asymptomatic cases detected in the country as of April 2020 [11].

Despite the development of effective vaccines against SARS-CoV-2, inequitable vaccine distribution and hence low or poor vaccination coverage, especially in resourcelimited settings [12,13], as well as the continuous emergence of viral variants, have increased public health concerns. Our understanding of population susceptibility to SARS-CoV-2 infection and immunity among healthcare workers and students is limited. Serological surveys carried out in various areas reveal varying degrees of immunity in various populations, including healthcare workers (HCWs) and persons who access the healthcare environment [14, 15]. Importantly, a large number of HCWs have been involved in the various aspects of COVID-19 management since the first case was reported in the country. However, the prevalence of SARS-CoV-2 seropositivity among Ghanaian HCWs and in the country's general population remains to be described.

Meaningful combat of the COVID-19 pandemic requires an adequate and timely understanding of exposure outcomes and population immunity, as well as of the genetic diversity circulating in the population. Epidemiological surveillance of SARS-CoV-2 protective antibodies offers useful insight into the effectiveness of control measures and aids in preparedness against future outbreaks [16]. In Ghana, the vaccination rollout started in March 2021, and as of 9th December 2022, the total doses of COVID-19 vaccines administered stood at 21,400,539. The vaccines administered include AstraZeneca (the most administered), Pfizer-BioNTech, Johnson & Johnson, Moderna, and Sputnik-V (the least administered). Of the number that had been vaccinated, 12,155,754 individuals (53.2% of the targeted 22.9 million people and 38.3% of the Ghanaian population) had received at least one dose. Some 2,639,160 people had received the first booster, while the number of fully vaccinated individuals was 9,097,749, which constitutes 39.8% of the targeted 22.9 million and 28.7% of the total population of Ghana [17]. It is important to note that at the time of this study, the zeal for COVID-19 testing had gone down drastically following the initiation of vaccination in Ghana. Until now, data on seroprevalence estimates and immunity among healthcare workers and students is hardly available, especially after vaccination against SARS-CoV-2.

This study investigated the SARS-CoV-2 seropositivity from a set of vaccinated and unvaccinated adults who might have been exposed to the virus, irrespective of clinical presentation, during the months of August and September 2021. During this period, the Delta variant of concern (VOC; Pango lineage B.1.617.2.X) was the dominant SARS-CoV-2 variant in circulation globally, while the Omicron variant (subvariant BA.1) was under monitoring.

MATERIALS AND METHODS

Study site

The study was carried out at the Korle Bu Polyclinic and the University of Ghana (UG) School of Biomedical and Allied Health Sciences (SBAHS) Hostel and areas around the Korle Bu Teaching Hospital. The Korle Bu Polyclinic is a 42-bed facility that offers primary healthcare, especially to the Korle Bu and Korle Gonno communities in Accra, its environs, and the city as a whole. It was established primarily to serve as a service delivery facility in the catchment area but has grown over the years into a sub-BMC under the Korle Bu Teaching Hospital (KBTH). It has been accredited as a training facility for Family Physicians for both West Africa and Ghana College of Physicians since 2003. The SBAHS Hostel is a site close to the KBTH and houses students of SBAHS, UG.

Study selection

A cross-sectional study design was used. All individuals who were 18 years and above with access to the study site and willing to undergo one blood draw and oropharyngeal swabbing were eligible to participate. This involved HCWs of the study health facility, members of the Korle Bu community accessing healthcare at the Polyclinic, and students of the School of Biomedical and Allied Health Sciences. Specifically, participants included persons: (1) with confirmed (self-reported) history of COVID-19 infection, (2) who had or had not undergone vaccination, and (3) who got exposed to SARS-CoV-2 but did not develop symptomatic COVID-19 disease. Of those eligible, individuals with current symptoms consistent with COVID-19 infection and with a history of lung disease and/or severe cardiovascular disease, immunodeficiency, and/or those who had undergone transplantation were excluded.

Sampling and data collection procedures

A convenient sampling method was employed. This nonprobability sampling technique allows participant selection by virtue of convenient accessibility and proximity to the researcher. Sampling occurred between August and September 2021. A semi-structured questionnaire was administered to consenting participants to obtain their socio-demographic and clinical information. About 3 mL of venous blood was collected using the BD Vacutainer serum-separating collection system into tubes. Oropharyngeal swab samples were collected by trained personnel and stored in a 2 mL viral transport medium under aseptic conditions. For serology, the blood samples were transported in a cold box to the Virology Unit, Department of Medical Microbiology, University of Ghana Medical School (UGMS). Within 2 hours after collection, the tubes were centrifuged at 13000 rpm for 15 min to harvest sera, which were aliquoted into cryovials and stored at -80 °C to be used for serology. Swab specimens of SARS-CoV-2 seropositive subjects were transported to the Noguchi Memorial Institute for Medical Research of the University of Ghana for PCR assay.

Anti-SARS-CoV-2 IgM/IgG antibody detection

Seroreactivity was assessed by testing for SARS-CoV-2-specific immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies in serum. This was done by use of the COVID-19 IgG/IgM Rapid Test kit (Qingdao Hightop Biotech Co., Ltd), which is a lateral flow immunochromatographic assay designed to test whole blood, serum, or plasma for the qualitative detection of SARS-CoV-2 IgG/IgM specific antibodies. The test was performed in accordance with the manufacturer's instructions. 10 µl of thawed serum samples were transferred to the test cassette. Two drops (about 50 µl) of test buffer were then added to the serum in the test cassette and incubated at room temperature for 15-20 minutes. The test cassettes were observed for the appearance of three bands corresponding to the internal control, anti-SARS-CoV-2 IgM and anti-SARS-CoV-2 IgG. The test result was considered valid if the internal control band appeared in not more than 20 minutes; otherwise, it was invalid. Serum samples collected prior to the emergence of SARS-CoV-2 in December 2019 were included as negative controls for the seroprevalence de-termination of SARS-CoV-2 antibodies. The kit performance was evaluated by the

manufacturer as follows: IgG sensitivity of 93% and specificity of 97.5%, and IgM sensitivity of 82% and specificity of 96%.

Data analysis

Continuous data were described as mean and standard deviation (mean \pm SD) where appropriate, and categorical variables as percentages. Total seroprevalence was determined by pooling IgM and IgG positive samples and was expressed as the proportion of the total number studied. Percentage seroprevalence by age grouping was calculated as the total seropositivity within an age group divided by the total number of individuals sampled within the same age group. Analysis was also done for variables such as 'sex', 'age', 'age group', and 'vaccination status.' The Chi-square tests and Fisher's exact test (categorical variables) were performed to examine differences between specific groups. Logistic regression analysis was performed to examine the association (odds ratio, 95% confidence interval (CI)) between an individual's vaccination/exposure status and seroconversion. All data analyses were performed using IBM Statistical Package for Social Sciences (SPSS) Statistics for Windows, version 26 (IBM Corp., Armonk. N.Y., USA). The level of accepted statistical significance was p < 0.05.

RESULTS

This study included 207 individuals. The number comprised 19 HCWs, 68 medical laboratory science students, and 120 healthcare seekers. The ages of the participants ranged from 18 to 84 years. There were more females (n = 127, 61.4%) than males (n=80, 38.6%). The median age of the participants was 31 years. More than half (56.0%) of the participants were single, most of whom were below 30 years old. The majority (n = 198, > 95%) had undergone formal education, with at least 55% having had tertiary-level education. By occupation, the participants included government employees (which included HCWs), artisans or self-employed, and students who were mostly unemployed.

There was no record of travel outside Ghana among the participants studied. Seventy (33.8%) of participants had been vaccinated against SARS-CoV-2 (Table 1). More than half (n = 43; 26 with two vaccinations of the AstraZeneca vaccine and 17 with one vaccination of the Johnson & Johnson formulation) were fully vaccinated, and the remaining were only partially vaccinated. Most (63%) of the vaccinated participants were females. Anti-SARS-CoV-2 seropositivity in the study population was 67.6% (n = 140/207). More females (62.4%) than males showed anti-SARS-CoV-2 seropositivity, likely due to the higher proportion of females than males in the study population (Table 2(a) and (b)). Seroreactivity among the participants who were either vaccinated or non-vaccinated in the entire study population and among the vaccinated subpopulation alone are shown in Figure 1. Forty-five (45) (21.7%) participants of the study population indicated

Characteristics	n (%)	Median (IQR)
Demographic characteristics		
Age (years)		21 (12, 24)
<30	100 (48.3%)	31 (18-84)
30 - 60	76 (36.7%)	
> 60	31 (15.0%)	
Gender		
Male	81 (39.1%)	
Female	126 (60.9%)	
Marital status		
Single	116 (56.0%)	
Married	68 (32.9%)	
Widow	19 (9.2%)	
Separated	3 (1.4%)	
Divorced	1 (0.9%)	
Education (Highest level)		
Tertiary	115 (55.6%)	
Secondary/Technical/Vocational	63 (30.4%)	
Primary	20 (9.7%)	
No school	9 (4.3%)	
Occupation		
Health care workers	19 (9.2%)	
Other Govt. workers	36 (17.4%)	
Traders	47 (22.7%)	
Artisans	15 (7.2%)	
Unemployed	89 (43.0%)	
Retired	1 (0.5%)	
SARS-CoV-2 infection & COVID-19-related	ed characteristics	
Perceived/confirmed infection		
Yes	46 (22.2%)	
No	161 (77.8%)	
COVID-19 confirmation by PCR		
Yes	11 (23.9%)	
No	35 (76.1%)	
Vaccinated		
Yes	70 (66.2%)	
No	137 (33.8%)	
Antibody reactivity among the 70 vaccinees		
IgG reactive	51 (72.9%)	
IgM reactive	13 (18.6%)	
Probable source of transmission $(n = 45)$		
Healthcare environment	18 (40.0%)	
Home environment	3 (6.7%)	
Social event	2 (4.4%)	
Community spread	11 (24.4%)	
Workplace	6 (13.3%)	
Travel (within Ghana)	5 (11.1%)	

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knowledge or perception of having been infected with or been exposed to SARS-CoV-2 (Table 1). Eleven of those had confirmed the infection by RT-PCR testing. Of the 45, 18 (40%) indicated the healthcare environment as the probable place or source of infection. Others indicated contact with COVID-19-confirmed patients as the means of infection. More than 80% (38/45) of those who indicated having been infected said, they experienced some symptoms of COVID-19. The most common symptoms noted were cough (65.8%, n = 25), fever (5.3%, n = 2), chills (55.3%, n = 21), loss of taste and smell (57.9%, n =22) and shortness of breath (18.4%, n = 7). These figures are not additive, since participants commonly indicated more than one symptom; and only 8 out of the 38 (21.1%)symptomatic individuals indicated only one symptom involving fever, chills or cough.

Of the 38 symptomatic participants, 31 (81.6%) were IgG reactive, 18 (47.4%) IgM reactive, and 11 (28.9%) were both IgG and IgM reactive. In other words, 20 (52.6%) reacted to IgG alone, 7 (18.4%) reacted to IgM alone and 11 (28.9) reacted to both IgG and IgM. Thirty-two (84.2%) of the symptomatic individuals recovered naturally, while 6 (15.8%) were hospitalised due to critical disease and were treated. Five out of the six hospitalised individuals had not

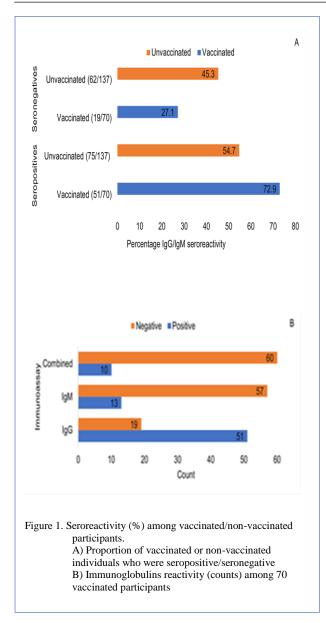
been vaccinated, while the remaining had an incomplete vaccination course. Regarding vaccination, AstraZeneca and Johnson and Johnson vaccines were among the most administered vaccines in the Ghanaian population, with 49 of the 70 vaccinated participants having received AstraZeneca and the remaining 21 participants having received the Johnson and Johnson vaccine type. Twenty-six of the AstraZeneca-vaccinated individuals had taken both vaccinations; 23 had taken only the first vaccination. In all, a higher level of IgG seropositivity (51,72.9%) was compared to vaccinated participants (Figure 1a) than was obtained for the unvaccinated individuals (54.7%). Among the vaccinated sub-populations, 18.6% (n = 13/70) were IgM reactive (Figure 1b), an indication of either failed or weak/unprotective seroconversion to vaccination and active breakthrough SARS-CoV-2 infection, respectively. In general, the least of the vaccinated population were below 40 years, and symptomatic infection was mainly among participants above 40 years. The proportion of individuals positive for who tested SARS-CoV-2-specific immunoglobulins was further categorised by age grouping of the entire study population (Figure 2A), as well as by the sexes (Figure 2B and 2C). Nearly half (n=97, 46.9%) of the participants were of the younger age (20 - 29 years) group. Generally, seropositivity appeared to decrease with

A: Seroreactivi	ty among the study populatio	n.		
	ing among the stady population	IgM		Total
		Non-reactive	Reactive	
IgG	Non-reactive	67	14	81
	Reactive	92	34	126
Total		159	48	207
B: Seroreactivi	ty among healthcare workers			
		IgM		Total
		Non-reactive	Reactive	
IgG	Non-reactive	5	2	7
	Reactive	9	3	12
Total		14	5	19

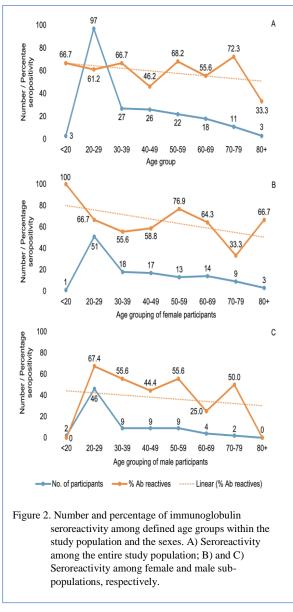
Characteristics		Serosta	tus (n)	Seropositivity (%)	p-value	OR	95% CI
		Negative	Positive				
Sex (N=207)	Female	38	88	69.8	0.4	0.77	0.43 to 1.40
	Male	29	52	64.2			
Vaccinated (N=207)	No	51	86	62.8	0.04	2	1.04 to 3.86
	Yes	16	54	77.1			

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increasing age (Figure 2a) independent of sex (Figures 2b and 2c). A total of 46 anti-SARS-CoV-2 IgM antibody reactive samples were subjected to nucleic acid testing by RT-PCR. Ten of these were from vaccinated individuals. Thirty-six (78.3%) were found negative, 19.6% (n = 9) were positive for the SARS-CoV-2 virus, and 2.2% (n = 1) was positive only for the E-gene, which depicts the presence of a coronavirus but not specifically SARS-CoV-2. Four of the nine (44.4%) PCR-positive results were from vaccinated individuals. Statistical analyses performed to examine the possible association of some participant characteristics with SARS-CoV-2 infection, and seroconversion revealed some interesting findings. A logistic regression analysis (Table 3) showed no association between sex and seroconversion (p = 0.397). As regards vaccination, there was a significant association (p = 0.04) between vaccination status and the



production of detectable antibodies against SARS-CoV-2 (Table 3).

DISCUSSION

Generally, serological testing is a good procedure for determining previous or present infection of SARS-CoV-2 [18] because, like most infections, it leads to immunity characterised by the production of viral-specific antibodies. However, observations from several studies also suggest that not all individuals produce detectable antibodies after exposure or vaccination [19,20]. In this study, 60.9% (n = 98) out of 161 of the participants who indicated no knowledge of previous exposure or infection with SARS-CoV-2 showed IgG reactivity and 10 ($6\cdot2\%$) showed IgM but no IgG reactivity. These results align with previous

studies indicating that a greater proportion of SARS-CoV-2-infected individuals are asymptomatic [21] and that about 10-30% of the asymptomatic individuals have the ability to transmit infection to other persons in close contact. Asymptomatic infections of SARS-CoV-2 thus represent an important concern in the spread of the virus during the COVID-19 pandemic [22,23].

It is also important to note that antibody non-reactivity is not conclusive of non-exposure. This is because some individuals may not produce antibodies at all after exposure or have antibody titers that decline fast after infection or vaccination [24]. The clinical presentation after SARS-CoV-2 exposure varies from person to person and from population to population, which underscores the differential susceptibility and immune response among exposed individuals. Notably, other factors besides immunodeficiency, such as the waning of natural and hybrid immunity [25] or the evolution and emergence of new viral variants, are responsible for the decline of antibody levels over time and/or immune evasion. Other host intrinsic factors can also influence the immune response to infection as well as the efficacy and effectiveness of COVID-19 vaccines [4,26]. It is conceivable that asymptomatic individuals did not perceive infection or exposure to the COVID-19 virus, although later laboratory investigation proved otherwise.

Characteristically, SARS-CoV-2 has evolved over time through the accumulation of mutations with fitness advantage, with different lineages replacing each other as the pandemic continued. Notably, the study was conducted when the earlier variants, Alpha and Delta VOC, decreased in circulation while the Omicron subvariants emerged. Studies have pointed to the symptomatology of the Omicron VOC being different from those of previous variants [27]; however, symptoms had not been fully described at the time of the study. However, the Alpha and Delta variants reached high global prevalence just as the Omicron, the Omicron VOC, which rapidly replaced the Delta, appeared to be far more successful due to its superior transmissibility and potential for escape of immunity elicited by vaccination and/or natural infection [28]. Thus, evidence surrounding SARS-CoV-2 evolutionary dynamics and immune response might explain immune reactivity and symptoms reports observed in this study.

The dynamics of antibody production among the vaccinated participants is also worthy of note. Generally, vaccines are meant to result in an immune response evidenced by antibody (IgG) production [29,30]. The detection of IgM in vaccinated individuals (13 IgM seropositives out of 70, 18.6%) is most likely evidence of active breakthrough infection. The absence of IgG antibody detection in 27.1% of vaccinated individuals indicates non-protection. This implies that among some individuals, even two vaccination doses do not elicit protective immune protection against the virus. This is in line with previous studies, which showed that vaccines confer protection against severe disease and

death but do not prevent breakthrough infections [31]. These variations in outcomes of exposure point to the need to consider inter-individual differences and viral factors when designing interventions against SARS-CoV-2 infection among individuals and populations [32,33].

When further tested by nucleic acid detection, not all IgG and IgM reactive samples were found positive by RT-PCR. The discordance between IgG /IgM seroreactivity and nucleic acid detection is understandable. The presence of IgG does not correlate with viral presence in the host. Also, levels of IgM, which indicate active infection, decrease by weeks five to seven after the onset of symptoms [34,35]. This partly explains why serology must be done in conjunction with RT-PCR before confirming a COVID-19 diagnosis. Even for RT-PCR testing, the result, to some extent, depends on the type and integrity of the specimen. For instance, in a study of 205 patients from China with confirmed COVID-19 infection, RT-PCR positivity was highest in bronchoalveolar lavage specimens (93%), followed by sputum (72%), nasal swab (63%) and pharyngeal swab (32%) [36-38]. This suggests that the type of sample may also affect the RT-PCR positivity. Of note, 10 out of the 46 IgM-positive samples selected for RT-PCR testing were from vaccinated individuals. RT-PCR assay confirmed nine positive cases of the 46 samples tested; 3 of the 9 were vaccinated individuals. This evidence of infection in vaccinated individuals underscores the possibility of breakthrough infection even after antibody production, which is likely due to the waning of antibody titers produced by vaccination/infection over time [39].

This study has some limitations. Participants were often unwilling to allow nasal swab collection, which, together with the oral swab, could produce a more reliable outcome of the viral testing, probably due to the discomfort of the sampling procedure. This might have resulted in an underestimation of the positivity rate of the RT-PCR assay. It is conceivable that a larger number of samples would have enhanced the study findings. We were also limited in our serological testing capacity, as neutralising virus titer measurement, which requires more specialised assays with real or pseudovirus, would have informed better on the protective capacity of the observed humoral responses [40].

The use of a variety of ELISA antigens (nucleoprotein, receptor binding domain, full spike protein) would allow us to better understand the polyclonal antibody response in our cohort and inform better on previous infection status based on nucleoprotein positivity. In our future clinical investigations, we would include infection status for other infectious diseases, as the present study could not properly address these due to the limited availability of clinical records. Given the tremendous impact of COVID-19 on society in general and healthcare systems in particular, a more elaborate, prospective, statistically-powered study on anti-SARS-CoV-2 immune responses in Ghanaians is warranted.

Conclusion

This study provides insight into the population exposure and seroprevalence of SARS-CoV-2 at a tertiary hospital in Accra, Ghana. Seroprevalence levels observed in the study population may suggest considerable protection of seroreactive individuals, irrespective of whether the antibody protection was gained via natural infection or through vaccination [35]. However, re-infection observed in vaccinated individuals may suggest that breakthrough infections have occurred in the vaccinated Ghanaian population. Thus, adherence to safety precautions remains key in the control of the COVID-19 disease. Further, a study involving host genetics, social behaviour, comorbidities, and the impact of hybrid immunity (vaccination + infection) in the context of COVID-19 may enhance our understanding of SARS-CoV-2 infection outcomes in various individuals and populations in different parts of the world.

DECLARATIONS

Ethical consideration

NIN-T participated in the conceptualisation. NIN-T, COMA, and EO developed the methodology. NIN-T, COM-A, and AY carried out the formal analysis. COM-A, AAKK, and YYA conducted the investigation. AB, NIN-T, and MS provided the resources. COMA and AY performed the data curation. NIN-T and CM undertook the writing of the original draft. AB, MS, and EDA handled the writing, review, and editing. NIN-T and EO provided supervision, and NIN-T managed the project administration.

Consent to publish

All authors agreed on the content of the final paper.

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Competing Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Author contributions

EEA was involved in the generation and editing of data for the article. AIB designed the study and drafted the manuscript. BM and AAA contributed to the editing and interpretation of data.

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Availability of data

Data is available upon request to the corresponding author.

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