Scientific Research Publishing

Advances in Microbiology, 2025, 15(8), 444-467
https://www.scirp.org/journal/aim
ISSN Online: 2165-3410
ISSN Print: 2165-3402

Characterization of Respiratory Bacterial Co-Infection among Patients with COVID-19 in Ghana

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How to cite this paper: Asante-Poku, A., Addae, E.N., Osei-Wusu, S., Osman, A.H., Bonsu, C., Yussif, M., Darkwah, S. and Sampane-Donkor, E. (2025) Characterization of Respiratory Bacterial Co-Infection among Patients with COVID-19 in Ghana. *Advances in Microbiology*, **15**, 444-467.
https://doi.org/10.4236/aim.2025.158029

Received: July 18, 2025
Accepted: August 25, 2025
Published: August 28, 2025

Abstract

The COVID-19 pandemic significantly challenged Ghana's healthcare system, exacerbated by a rise in bacterial co-infections in patients. The rising prevalence of antibiotic consumption in this setting is driving antimicrobial resistance, as documented in recent studies from Ghana. Individuals infected with the virus have a higher prevalence of bacterial simultaneous and sequential co-infections and present a greater prevalence of drug-resistant bacteria compared to non-infected individuals. This study aimed to investigate the prevalence of respiratory bacterial co-infections among COVID-19 patients and assess their antibiotic resistance profiles to improve bacterial infection care. A cross-sectional analysis was conducted involving 216 COVID-19 patients and 92 RT-PCR negative controls from major testing centres in Greater Accra. Utilizing microbial culture techniques to examine nasopharyngeal and oropharyngeal samples alongside statistical analysis of clinical and demographic data, findings were categorized based on COVID-19 test results, demographics, clinical characteristics, and duration of hospital stay. The results indicated higher COVID-19 positivity rates among males, younger age groups (19 - 38 years), and inpatients, with these patients also exhibiting a significant proportion of bacterial carriage. Although co-infection rates were similar in patients with reported infections like HIV, malaria, diabetes, and hypertension, COVID-19 patients had much higher levels of antibiotic-resistant bacteria. This underscores the urgent need for enhanced antibiotic stewardship to tackle rising antimicrobial resistance, particularly among vulnerable populations. Overall, the study strengthens understanding of the link between respiratory infections and antibiotic resistance, advocating for integrated One Health approaches to improve public health outcomes.

Keywords

COVID-19, Antimicrobial Resistance, Respiratory Infections, Bacterial Co-Infection, Nasopharyngeal Carriage, Oropharyngeal Microbiota, Ghana, Comorbidities

1. Introduction

COVID-19, is a viral infection that targets the upper respiratory system and manifests as a range of respiratory symptoms [1] [2]. This infection ranges from asymptomatic to symptomatic cases that result in various respiratory conditions such as pneumonia, acute exacerbations of Chronic Obstructive Pulmonary Disease (COPD), and bronchiolitis, while patients with underlying respiratory conditions are prone to the severe form of the viral infection [3]. The symptoms of the infection range from flu-like symptoms, such as fever, cough, body aches, and fatigue, to broader spectrum symptoms such as loss of taste or smell, chest congestion, shortness of breath, and pneumonia [4]. The main infectious agent responsible for COVID-19 is Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) [5], an enveloped RNA beta coronavirus phylogenetically related to previously characterized SARS-CoV-1 [6] [7]. In January 2020, the World Health Organization (WHO) announced the COVID-19 outbreak as a global public health emergency [8], and its profound effect led to its official classification as a pandemic in March 2020 [9] [10].

As of May 2023, a global analysis demonstrated that over 765 million individuals were confirmed to be infected with COVID-19 worldwide, with over 50 million fatalities attributed to the virus [9] [10]. A subsequent analysis a year later also indicated a staggering surge, with the number of infected cases increasing to over 183 million cases [9]. Given the significant number of asymptomatic cases observed during the peak of the pandemic, the global rise in this viral infectious agent may have been underestimated [11] [12]. The disproportionate distribution of healthcare facilities and services worldwide has led to challenges in measuring the severity of the pandemic, particularly in developing countries such as Ghana. The burden of morbidity and mortality of this viral infection is not only localized to the respiratory system but is also associated with liver disease and other internal tissue damage [13]. The extent of the virus's impact on transitioning from respiratory asymptomatic patients to other internal organs remains to be fully elucidated [14]. The association between severe COVID-19 and comorbidities, such as hypertension, cancer, and diabetes, has been reported [15]. The drastic effects of COVID-19 infection are further exacerbated by the possibility of bacterial infections within the respiratory system [16] [17]. An individual infected with COVID-19 is subjected to compromised immunity, potentiating the pathogenicity of "supposed normal flora" colonizing the respiratory system. The interplay between the viral-infected immune system and the widespread availability of bacterial patho-

gens can exacerbate the clinical threat of infection [16]-[18].

Respiratory infections are induced by many species; still, bacteria constitute a major contribution to the worldwide illness burden, representing a prevalent risk for respiratory comorbidities in individuals infected with COVID-19.

The bacteria that are commonly responsible for respiratory infections include: *Streptococcus pneumoniae*, *Mycobacterium* spp., *Achromobacter* spp., *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, and *Staphylococcus aureus* [19]-[25]. However, many of these identified bacteria usually colonize the nasopharynx and oropharynx of individuals. In certain conditions, such as a compromised immune system or underlying condition, they can invade and become pathogenic to the host [23] [26].

The array of colonized bacteria capable of instigating respiratory infections is not the only concern; there is a rising concern regarding the surge in antibiotic resistance among these pathogens. A significant number of these bacteria have acquired resistance to a wide range of antibiotics and are now evolving towards pan-drug resistance, displaying insensitivity to multiple drugs. This complicates the treatment of invasive infections caused by these bacteria [27] [28]. These high antibiotic resistances of respiratory bacterial pathogens may significantly contribute to the mortality and morbidity rates associated with respiratory infections among COVID-19 patients.

The COVID-19 pandemic has had a profound impact on Ghana, a Low- and Middle-Income Country (LMIC) in West Africa. The country confirmed its first two cases of COVID-19 in March 2020 [29] and rapidly peaked at over 171,889 confirmed cases by April 2024. Key measures implemented to combat the pandemic, such as lockdowns, have led to substantial economic downturns in Ghana and other LMICs. In Ghana, the effect of the pandemic ranged from socioeconomic impact to disruptions in the education system, as well as significant pressure on the healthcare systems [30] [31]. Like other LMIC settings, Ghanaians are exposed to many factors that predispose individuals to bacterial infections during the pandemic. Factors such as extended hospital stays, pre-existing medical conditions, treatment environments, and natural bacterial circulation may contribute to the coexistence of COVID-19 and bacterial carriage [32]-[35]. Recent reviews have highlighted the disparity in bacterial infections among COVID-19 patients, revealing an increased risk of bacterial superinfections. Additionally, the proportion of COVID-19 patients with co-infections varies widely, ranging from no co-infections to 100% in those who succumbed to the disease [36] [37].

The frequent use of antibiotics in this context [38] heightens the risk of antimicrobial resistance and the rising prevalence of antibiotic consumption and resistance in recent studies in Ghana [38]-[41], underscoring the urgent need for the surveillance of antibiotic resistance among these "at-risk populations" to facilitate appropriate medications in case of an infection. Therefore, this study provides an evaluation of the bacterial carriage (nasopharynx and oropharynx) and their respective AMR among COVID-19 patients in Ghana to ease the management of bacte-

rial infections in these patients.

2. Method

2.1. Study Design, Sites, and Sampling

This cross-sectional study took place at three COVID-19 detection sites located in the Greater Accra region: the Ghana Infectious Disease Centre (GIDC), the University of Ghana Hospital in Legon, and the Noguchi Memorial Institute for Medical Research (NMIMR) COVID-19 testing centre. The sites were chosen in the Greater Accra Area because of its dense population and the highest number of positive COVID-19 cases reported in Ghana. Sample processing was performed at the Department of Bacteriology at NMIMR.

2.2. Study Participants

This study enrolled participants between the ages of 10 - 85 years, who tested RT-PCR positive for COVID-19, based on the WHO guidelines for testing COVID-19, and were enrolled at GIDC, the University of Ghana Hospital, and NMIMR between December 2021 and March 2022. In addition to the positive cases, a few individuals who tested negative for COVID-19 were also enrolled in the study.

2.3. Sample Size Determination

The minimum sample size was determined as previously described [41] as follows:

$$n = \frac{z^2 \times p(1-p)}{m^2}$$

where n = minimum sample size, z = 95% confidence level (standard value of 1.96), m = 5% margin of error (standard value of 0.05), p = the estimate of the proportion of confirmed COVID-19 cases among suspected cases and their close contact was 9.9%. or 0.099 respectively (https://ghs.gov.gh/covid-19/).

$$n = \frac{1.96^2 \times 0.099\ (1-0.099)}{0.05^2} = 137.07$$

Therefore, a minimum sample size of 137 was determined. However, it was increased to 308 to enhance the statistical power of the study.

2.4. Data and Sample Collection

Before sample collection, participants provided informed consent through either by signing or writing. Clinical and demographic information was gathered using structured questionnaires. Following standard clinical procedures, nasopharyngeal (NPS) and oropharyngeal (OPS) swabs were simultaneously obtained and placed in sterile tubes with Viral Transport Media (VTM) for COVID-19 testing to identify respiratory bacteria. The swabs were placed in a commercially prepared VTM containing antimicrobials to preserve bacterial viability and were transported to the laboratory within 6 hours for immediate culture.

2.5. Bacterial Culture and Identification

Aliquots from each sample were cultured on blood agar (CM0055) and MacConkey (CM0007) following the manufacturer's guidelines for 24 to 48 h at 37˚C. Additionally, 5% CO_2 was added to blood agar cultures to produce a microaerophilic environment for fastidious organisms. Where Macroscopic growth was observed, Gram staining was carried and a loopful of bacterial colonies was sub-cultured on blood agar plates to produce pure colonies. The morphological features of the cultures were observed and recorded. Pure bacterial isolates were identified at the species level using matrix-assisted laser desorption/ionization mass spectrometry (MALDI TOF MS) following the manufacturer's guidelines.

2.6. Antibiotic Sensitivity Testing

Antimicrobial susceptibility testing of bacterial isolates was conducted following standard procedures, using the Kirby-Bauer disk diffusion method. The results were interpreted following the protocols outlined by the Clinical and Laboratory Standards Institute (CLSI) [42]-[44]. *Escherichia coli ATCC 25922* was used as the control strain. The disks of antibiotics used were, penicillin (PEN – µg), ampicillin (AMP – 10 µg), cloxacillin (COX – 5 µg), erythromycin (ERY – 5 µg), tetracycline (TET – 30 µg), vancomycin (VAN – 30 µg), cotrimoxazole (trimethoprim-sulfamethoxazole) (COT – 25 µg), cefuroxime (CRX – 10 µg), gentamicin (GEN – 10 µg), ciprofloxacin (CIP – 5 µg), augmentin (amoxicillin-calvulanate) (AUG – 30 µg), meropenem (MEM – 10 µg), chloramphenicol (CHL – 10 µg), ceftriaxone (CTR – 30 µg), cefotaxime (CTX – 30 µg), and amikacin (AMK – 30 µg).

The suspension of pure bacterial colonies was adjusted to a McFarland standard of 0.5. The suspension was then uniformly swabbed on Mueller-Hinton agar to ensure semi-confluent growth. Antibiotic discs were applied to the seeded plates using antibiotic dispensers, followed by an incubation period of 37˚C for 18 - 24 hours. Subsequently, the zones of inhibition surrounding the antimicrobial discs were measured using digital Vernier calipers.

2.7. Statistical Analysis

Statistical analyses were performed using GraphPad Prism version 10.0. Descriptive statistics were performed to investigate the association between demographic factors, and clinical characteristics at admission (symptoms reported, microbiome identified, disease severity, co-infection status, duration of hospital admission, treatment outcomes, and drug resistance. Categorical variables were reported as frequencies and percentages. Continuous variables are reported as means and Standard Deviations (SD) or medians and Interquartile Ranges (IQRs). Data were normalized using D'Agostino and Pearson normality, along with the Shapiro-Wilk test, to determine the significance and normality of the data. Statistically significant results (p-value < 0.05) were considered for further analysis. Differences between groups were compared using Student's t-test or the Mann-Whitney U test, while

ANOVA and Kruskal-Wallis were used for groups with more than two variables (depending on the normality of the data) for continuous variables and chi-square (χ^2) or Fisher's exact test for categorical variables.

3. Results

Table 1 categorizes data based on clients' COVID-19 test results, considering demographic factors, clinical characteristics, including reported symptoms, identified microbiome, disease severity, co-infection status, duration of hospital admission, treatment outcomes, and drug resistance. A total of 308 clients were tested during the specified period. Of the participants, 216 (70.1%) tested positive, while 92 (29.9%) tested negative for COVID-19 (Table 1). The study enrolled 92 RT-PCR-negative individuals as controls, which constitutes a smaller proportion relative to the RT-PCR-positive cohort. The controls were included as a reference group to identify distinguishing features without necessitating 1:1 matching. Based on the available demographic breakdown, there is no evidence that the control group was age- or sex-matched to the COVID-19-positive group. The absence of matching may introduce selection bias, particularly since infection rates varied notably by age and sex. This limits the comparability between groups and could confound any associations observed.

Among the percentages, males comprised the largest group with a total of 191 (62.0%), of which 65.3% tested positive. In contrast, females accounted for a total of 117 (38.0%), with 34.7% testing positive. The highest total count within the age groups is observed in those aged 30 - 39, comprising 32.5%, followed closely by the 20 - 29 age group at 32.1%. Conversely, the age groups 10 - 19 and 70 - 79 represent the lowest counts. The age group 20 - 29 exhibited the highest incidence of COVID-19 positive tests, followed by the 30 - 39 age group, while the 70 - 79 age group recorded the lowest incidence. Individuals aged 10 to 19 tested positive.

The analysis indicates that while the percentage of outpatient admissions was higher (58.8%) compared to inpatient admissions (41.2%), the rate of positive confirmations was greater among inpatients than outpatients. The duration of hospital stays for admitted patients demonstrated a decline, with 50.9% staying for 2 weeks and only 0.5% for 7 weeks among those who tested positive for COVID-19. In contrast, the duration for patients without COVID-19 ranged from 2 to 3 weeks, comprising 93.5% and 6.5%, respectively. The data distribution indicated that the percentage of individuals with COVID-19 was higher for co-infection (6.5%) and multiple infection (20.8%) compared to those without COVID-19, despite the absence of multiple infections in those who tested negative. Regarding case categories, the majority of individuals without COVID-19 presented with mild cases (93.5%) and a smaller proportion exhibited moderate cases (6.5%). The highest percentages of positive tests were observed in individuals with moderate (56.0%), mild (37.5%), and severe (6.5%) conditions. The treatment outcome indicated a recovery rate of 98.1% and a mortality rate of 1.9%.

Table 1. Demographic characteristics of enrolled participants.

Demographics	Total 308 (100%)	COVID 216 (70.1%)	No-COVID 92 (29.9%)	Sig
Sex				
Female	117 (38.0%)	75 (34.7%)	42 (45.7%)	0.006
Male	191 (62.0%)	141 (65.3%)	50 (54.3%)	
Age group				
10 - 19	3 (1.0%)	3 (1.4%)	0	0.653
20 - 29	99 (32.1%)	71 (32.9%)	28 (30.4%)	
30 - 39	100 (32.5%)	68 (31.5%)	32 (34.8%)	
40 - 49	62 (20.1%)	41 (19.0%)	21 (22.8%)	
50 - 59	30 (9.7%)	25 (11.6%)	5 (5.4%)	
60 - 69	11 (3.6%)	6 (2.7%)	5 (5.4%)	
70 - 79	3 (1.0%)	2 (0.9%)	1 (1.1%)	
COVID strain				
Delta	47 (15.3%)	44 (20.4%)	3 (3.3%)	0.000
Omicron	261 (84.7%)	172 (79.6%)	89 (96.7%)	
Hosp status				
Outpatient	181 (58.8%)	95 (44.0%)	86 (93.5%)	0.000
Inpatient	127 (41.2%)	121 (56.0%)	6 (6.5%)	
Hosp duration				
2 weeks	196 (63.6%)	110 (50.9%)	86 (93.5%)	0.000
3 weeks	72 (23.4%)	66 (30.6%)	6 (6.5%)	
4 weeks	5 (1.6%)	5 (2.3%)	0 (0.0%)	
5 weeks	20 (6.5%)	20 (9.3%)	0 (0.0%)	
6 weeks	14 (4.5%)	14 (6.5%)	0 (0.0%)	
7 weeks	1 (0.3%)	1 (0.5%)	0 (0.0%)	
Category case				
Mild	167 (54.2%)	81 (37.5%)	86 (93.5%)	0.000
Moderate	127 (41.2%)	121 (56.0%)	6 (6.5%)	
Severe	14 (4.5%)	14 (6.5%)	0 (0.0%)	
Treatment outcome				
Died	4 (1.3%)	4 (1.9%)	0 (0.0%)	0.008
Recovered	304 (98.7%)	212 (98.1%)	92 (100%)	
Morbidity				
No co-infection	246 (79.9%)	157 (72.7%)	89 (96.7%)	0.000
Co-infection	17 (5.5%)	14 (6.5%)	3 (3.3%)	
Multiple-infection	45 (14.5%)	45 (20.8%)	0 (0.0%)	

3.1. Differences among the Groups

Descriptive statistics for the three case categories as shown in Figure 1 revealed the following: Mild cases had a Standard Deviation (SD) of 11.73 and a mean of 13.5 (range: 1.19 - 25.81); Moderate cases had an SD of 16.47 and a mean of 20.2 (range: 2.88 - 37.45); Severe cases exhibited an SD of 1.86 and a mean of 2.33 (range: 0.38 - 4.29), with a 95% Confidence Interval (CI). The moderate case exhibited the highest average and a broader dispersion in comparison to mild and severe cases. The Analysis of Variance (ANOVA) test indicated that R-squared = 0.3209, $F(2, 15) = 3.544$, $p = 0.055$, suggesting no statistically significant difference among the three categories.

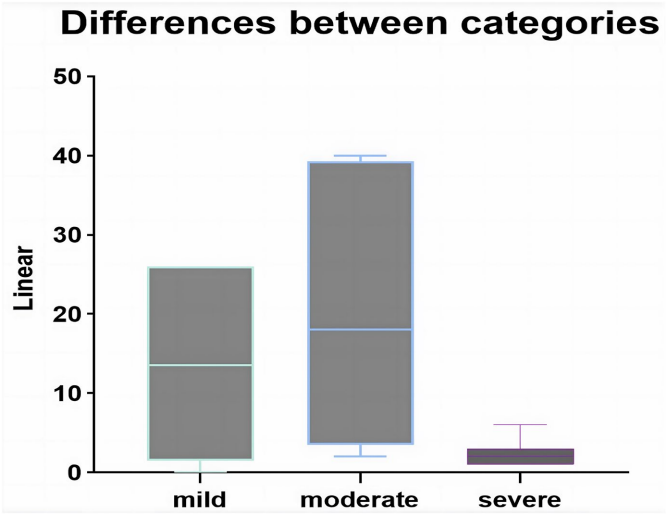

Figure 1. Box plot representing the severity of COVID-19 cases ranging from mild, moderate, to severe cases.

Morbidity was assessed through various indicators, including other infections that may influence case severity and management. The reported infections included HIV 42 (39.3%), Diabetes 48 (44.9%), Malaria 3 (2.8%), and Hypertension 14 (13.1%) (Figure 2).

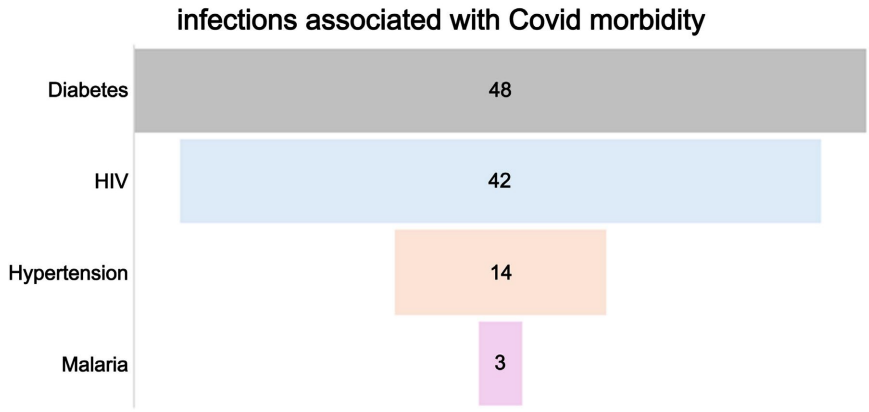

Figure 2. Co-infections associated with COVID morbidity.

To further determine whether there was a significant difference between the three levels of morbidity classifications based on Mono infections, co-infection and multiple infection. Descriptive statistics among the three kinds of morbidities as shown in Figure 3 indicated that those without co-infection had SD = 21.1, Mean = 26.2 (4.01 - 48.32), those with co-infection had SD = 1.97 mean = 2.33 (0.27 - 4.397) and those with multiple infections showed SD = 6.98, Mean = 7.5 (0.18 - 14.82), with 95% CI. From the descriptive statistics, those with a mono infection had the highest on average and wider dispersion compared to those with multiple infections and the least was those with co-infection. An Analysis of Variance (ANOVA) test was conducted to determine whether there were differences in variance between the groups. The analysis showed that R-squared = 0.4309, $F(2, 15) = 5.678$, and $p < 0.05$, indicating statistically significant difference between the three categories of infections. A post-hoc analysis was performed to determine the differences between the three groups using Tukey adjustment for pairwise comparison. The test of multiple comparison yielded a mean difference = 23.83, $t(15) = 3.203$, adjusted $p = 0.018$ between those with mono-infection and co-infection, which showed that there was a statistically significant difference between those without co-infection and those with co-infection. Comparison between mono-infection and multiple infections also showed mean difference =18.67, $t(15) = 2.509$, adjusted $p = 0.048$, which indicates that there was a statistically significant difference between those without co-infection and those with multiple infections. However, no statistically significant difference was observed between those with co-infection and those with multiple infections $t(15) = 0.6943$, $p = 0.498$).

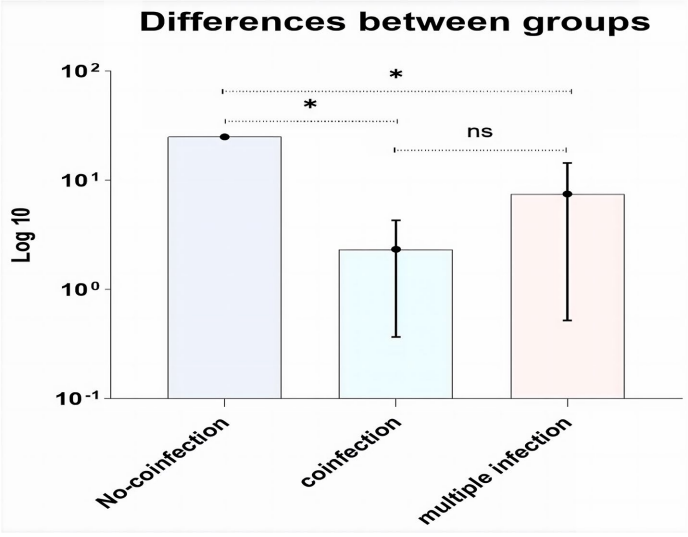

Figure 3. Comorbidities among categories.

Figure 3 shows a plot representing the types of morbidities identified for those with COVID-19, ranging from single infection, and co-infection to multiple infections. Co-infection in this context refers to simultaneous isolation of multiple pathogens, that is SARS-CoV-2 and bacterial species within 48 - 72 hours of presenta-

tion, indicating concurrent infection at the onset of disease. In contrast, multiple infections refer to sequential identification of different microbial isolates at distinct time points during hospitalization or recovery, reflecting evolving or superimposed infections over time.

Table 2. Various symptoms and conditions among COVID-19 patients and the negative counterparts.

Symptoms	All Patients		COVID positive		No-COVID negative		Sig
	n	%	n	%	n	%	
Asymptomatic	185	32.2%	98	20.5%	87	88.8%	0.000
Sore throat	63	11.0%	59	12.4%	4	4.1%	0.000
Fever	57	9.9%	56	11.7%	1	1.0%	0.000
Bronchitis	36	6.3%	33	6.9%	3	3.1%	0.003
Body aches	35	6.1%	35	7.3%	0	0.0%	0.000
Vomiting	35	6.1%	35	7.3%	0	0.0%	0.000
Headache	30	5.2%	27	5.7%	3	3.1%	0.012
Fatigue	27	4.7%	27	5.7%	0	0.0%	0.000
Cough	25	4.3%	25	5.2%	0	0.0%	0.001
Diarrhea	27	4.7%	27	5.7%	0	0.0%	0.002
Nausea	20	3.5%	20	4.2%	0	0.0%	0.003
Congestion	18	3.1%	18	3.8%	0	0.0%	0.004
Red eyes	6	1.0%	6	1.3%	0	0.0%	0.106
Abdominal pain	5	0.9%	5	1.0%	0	0.0%	0.141
General maise	3	0.5%	3	0.6%	0	0.0%	0.256
Expectorate	3	0.5%	3	0.6%	0	0.0%	0.256
Total	**575**	**100.0%**	**477**	**100.0%**	**98**	**100.0%**	

We assessed various symptoms and conditions reported during a hospital visit, presented as frequency and percentage for individuals with COVID-19 in comparison to those without. Notable disparities in symptoms and other reported conditions were observed between individuals with COVID-19 and those who tested negative (Table 2). Excluding Asymptomatic, which showed a significant percentage (88.8%) in individuals without COVID-19, the other symptoms and conditions revealed statistically significant differences between positive and negative test results. Individuals testing negative for COVID-19 displayed a narrow spectrum of symptoms, including sore throat (4.1%), fever (1.0%), bronchitis (3.1%), and headache (3.1%). The figures are lower than those observed in individuals who tested positive. Individuals who tested positive demonstrated increased percentages for all symptoms observed during the diagnostic phase. Sore throat was the most prevalent symptom, accounting for 12.4%, followed by fever at 11.7%. Body ache and vomiting were observed in 7.3% of cases, whereas bron-

chitis was recorded in 6.9%. Headache, fatigue, diarrhea, and cough each represented 5.7%, while red eyes, abdominal pain, and general malaise were the least frequently reported symptoms. The elevated prevalence of asymptomatic cases (20.5%) can be ascribed to multiple factors, notably the age group with the highest proportion.

3.2. Measure of Association (Symptoms Reported)

This study evaluated the correlation between symptoms reported during hospital visits and COVID-19 infection to determine a potential relationship. Significance measures were assessed based on the assumptions associated with the statistical tests and the established significance level. The Pearson chi-square test revealed a significant statistical association between throat conditions and COVID-19, with results indicating $\chi^2(1, N = 308) = 20.917$, $p < 0.000$, and Cramer's V = 0.261. This indicates a statistically significant correlation between throat conditions and COVID-19 infection. The odds ratio of 8.268 indicates that individuals who tested positive for COVID-19 are 8.3 times more likely to report a sore throat compared to those who tested negative. The occurrence of fever showed statistical significance, $\chi^2(1, N = 308) = 26.394$, $p = 0.000$, Cramer's V = 0.293, suggesting a notable association between fever and COVID-19 infection. Estimates for the odds ratio (31.850) suggest that individuals who tested positive for COVID-19 are 31.9 times more likely to present with fever than those without the infection. A statistically significant association exists between Bronchitis and COVID-19 infection, $\chi^2(1, N = 308) = 9.026$, $p = 0.003$, Cramer's V = 0.234. Estimates for an odds ratio of 5.350 indicate that individuals who tested positive for COVID-19 were 5.40 times more likely to have bronchitis compared to those without COVID-19. The relationship between body aches and COVID-19 infection was statistically significant, $\chi^2(1, N = 308) = 16.819$, $p = 0.000$, Cramer's V = 0.171. Estimates indicate a ratio of 0.663, suggesting that individuals who tested positive for COVID-19 were 0.67 times more likely to experience body aches compared to those without the infection. Vomiting exhibited a statistically significant correlation with COVID-19 infection, $\chi^2(1, N = 308) = 16.819$, $p = 0.000$, Cramer's V = 0.234. Estimates indicate a ratio of 0.663, suggesting that individuals who tested positive for COVID-19 are 0.67 times more likely to experience vomiting compared to those without the infection. Headache demonstrated a statistically significant correlation with COVID-19 infection, $\chi^2(1, N = 308) = 6.316$, $p = 0.012$, Cramer's V = 0.143. Estimates for the ratio of 4.261 indicate that individuals who tested positive for COVID-19 are 4.3 times more likely to experience headaches compared to those without the infection. Fatigue demonstrated a statistically significant correlation with COVID-19 infection, $\chi^2(1, N = 308) = 12.605$, $p = 0.000$, Cramer's V = 0.202. The ratio is 0.673. The presence of cough demonstrated a statistically significant correlation with COVID-19 infection, $\chi^2(1, N = 308) = 11.589$, $p = 0.001$, Cramer's V = 0.194. The association between diarrhoea and COVID-19 infection was significant, with $\chi^2(1, N = 308) = 12.605$, $p = 0.002$, Cramer's V = 0.202. Nausea also exhib-

ited a statistically significant association with COVID-19 infection, $\chi^2(1, N = 308) = 9.110$, $p = 0.003$, Cramer's $V = 0.172$. These findings indicate a statistically significant relationship between these symptoms and COVID-19 infection.

3.3. Prevalence of Organism Identification

In general, the proportion of microbiome organisms identified for those with COVID-19 was higher in terms of number and kind of organisms. Out of 37 micro-organism signatures identified, 8 signatures were identified with a cumulative count [25] for client without COVID-19. Apart from *Staphylococcus sciuri,* which was absent for those COVID-19 positive clients all the 36 organisms were identified and with higher count compared to those without COVID-19 (**Table 3**). proportion of *Rothia mucilaginosa* (32.2%), *Rothia aeria* (9.1%), *Staphylococcus aureus* (7.4%), *Streptococcus Parasanguinis* (5.8%) and *Klebsiella* species (5.0%) yielded statistically significance. The rest of the organisms, however, did not yield statistically significance for further analysis. Measure of association between organism identification and COVID-19 infection was performed to determine if there was relationship between them. Measures of significance were assessed based on the assumptions surrounding statistical test and significant level. From the analysis below, the relationship between *Rothia mucilaginosa* growth and COVID-19 infection was statistically significance, $\chi^2(1, N = 308) = 44.49$, $p < 0.000$, Cramer's $V = 0.380$; indicating that there was a statistically significant association between *Rothia mucilaginosa* growth and COVID-19 infection. Estimates for odd ratio (0.600) showed that those tested positive for COVID-19 infection are 0.6 more likely to have *Rothia mucilaginosa* organism growth compared to those without COVID-19 infection. The relationship between *Rothia aeria* presence and COVID-19 infection was statistically significance, $\chi^2(1, N = 308) = 7.73$, $p = 0.005$, Cramer's $V = 0.158$; indicating that there was a statistically significant association between *Rothia aeria* growth and COVID-19 infection. Estimates for odd ratio (10.320) showed that those tested positive for COVID-19 infection are 10.3 more likely to have *Rothia aeria* organism presence compared to those without COVID-19 infection. *Staphylococcus aureus* presence and COVID-19 infection showed statistical significance, $\chi^2(1, N = 308) = 5.85$, $p = 0.016$, Cramer's $V = 0.138$; indicating that there was a statistically significant association between *Staphylococcus aureus* growth and COVID-19 infection. Estimates for Odd ratio = 8.273 showed that those tested positive for COVID-19 infection are 8.3 more likely to have *Staphylococcus aureus* organism presence compared to those without COVID-19 infection. *Streptococcus Parasanguinis* was statistically significance, $\chi^2(1, N = 308) = 6.25$, $p = 0.012$, Cramer's $V = 0.142$; indicating that there was a statistically significant association between *Streptococcus Parasanguinis* growth and COVID-19 infection. Estimates for Odd ratio = 0.687 showed that those tested positive for COVID-19 infection are 0.7 risk to have *Streptococcus Parasanguinis* organism presence compared to those without COVID-19 infection. *Klebsiella species* was

statistically significance, $\chi^2(1, N = 308) = 5.318$, p = 0.021, Cramer's V = 0.131; indicated that there was a statistically significant association between *Klebsiella* species growth and COVID-19 infection. Estimates for Odd ratio = 0.689 showed that those tested positive for COVID-19 infection are at 0.7 risk to have *Klebsiella* species organism growth compared to those without COVID-19 infection. However, a multivariable logistic regression to adjust for age, sex, inpatient status, and comorbidities was not feasible due to incomplete data on these covariates. Therefore, the observed associations between specific bacterial organisms and COVID-19 infection should be interpreted as unadjusted and may be influenced by residual confounding.

Table 3. Prevalence of organism identification.

Organism	All patients		COVID-19		No infection		Sig
	n	%	N	%	n	%	
Streptococcus_salivarius	17	6.4%	12	5.0%	5	20.0%	0.959
Rothia mucilaginosa	78	29.2%	78	32.2%	0	0.0%	0.000
Strepto parasanguinis	14	5.2%	14	5.8%	0	0.0%	0.012
Staphylococcus aureus	19	7.1%	18	7.4%	1	4.0%	0.016
Rothia aeria	23	8.6%	22	9.1%	1	4.0%	0.005
E. coli	22	8.2%	18	7.4%	4	16.0%	0.214
Staphylo-epidermidis	21	7.9%	15	6.2%	6	24.0%	0.893
Staphylo_cohnii	18	6.7%	12	5.0%	6	24.0%	0.741
Strepto_sanguinis	3	1.1%	3	1.2%	0	0.0%	0.256
Klebsiella sp	12	4.5%	12	5.0%	0	0.0%	0.021
Staphylo_hominis	2	0.7%	2	0.8%	0	0.0%	0.354
Strepto_oralis	3	1.1%	2	0.8%	1	4.0%	0.895
Pseudo_fluorescens	3	1.1%	3	1.2%	0	0.0%	0.256
Pseudo_synxantha	2	0.7%	2	0.8%	0	0.0%	0.354
Strepto_cristatus	2	0.7%	2	0.8%	0	0.0%	0.354
Neisseria sub flava	2	0.7%	2	0.8%	0	0.0%	0.354
Arthrobacter woulwensis	1	0.4%	1	0.4%	0	0.0%	0.513
Strepto_vestibularis	1	0.4%	1	0.4%	0	0.0%	0.513
Staphylo_warneri	2	0.7%	2	0.8%	0	0.0%	0.354
Pseudo_aeruginosa	2	0.7%	2	0.8%	0	0.0%	0.354
Kocuria kristinae	1	0.4%	1	0.4%	0	0.0%	0.513
Bacillus pumilus	1	0.4%	1	0.4%	0	0.0%	0.513
Bacillusmegaterium	1	0.4%	1	0.4%	0	0.0%	0.513
Strepto_pneumoniae	1	0.4%	1	0.4%	0	0.0%	0.513
Neisseria sicca	2	0.7%	2	0.8%	0	0.0%	0.354
Micrococcus luteus	2	0.7%	2	0.8%	0	0.0%	0.354

Continued

Strepto_peroris	1	0.4%	1	0.4%	0	0.0%	0.513
Staphylo_sciuri	1	0.4%	0	0.0%	1	4.0%	0.125
Staphylo_haemolytics	1	0.4%	1	0.4%	0	0.0%	0.513
Staphylo_pasteuri	1	0.4%	1	0.4%	0	0.0%	0.513
Abiotrophic defectiva	1	0.4%	1	0.4%	0	0.0%	0.513
Pseudo_tolaasii	2	0.7%	2	0.8%	0	0.0%	0.354
Pseudo_azotoformans	1	0.4%	1	0.4%	0	0.0%	0.513
Staphylo_auricularis	1	0.4%	1	0.4%	0	0.0%	0.513
Pseudo_plecoglossicida	1	0.4%	1	0.4%	0	0.0%	0.513
Enterobacter sp	1	0.4%	1	0.4%	0	0.0%	0.513
Pseudo_rhodesiae	1	0.4%	1	0.4%	0	0.0%	0.513
Total	**267**	**100%**	**242**	**100%**	**25**	**100%**	

3.4. Drug Resistance among All Patients vs. COVID Patients

Positive COVID-19 patients exhibit higher levels of drug resistance relative to those who tested negative in this dataset. A total of 384 counts were recorded for the entire dataset from the drug distribution (Table 4). The total of 334 cases pertains to individuals with COVID-19. Among these, Ciprofloxacin was the predominant antibiotic associated with resistance, accounting for 103 cases (30.8%). This was followed by Penicillin with 84 cases (25.1%), Erythromycin with 51 cases (15.3%), and Ampicillin with 45 cases (13.5%). The remaining antibiotics each represented less than 5.0% of the resistance cases.

Table 4. Aggregate data recorded during AST (drug resistance) testing that showed different levels of drug resistance.

Drugs	*All Patients*		*COVID Patients*	
CIP	105	27.3%	103	30.8%
ERY	64	16.7%	51	15.3%
MEM	15	3.9%	14	4.2%
PEN	101	26.3%	84	25.1%
AMP	49	12.8%	45	13.5%
TET	25	6.5%	16	4.8%
VAN	8	2.1%	4	1.2%
CTR	8	2.1%	8	2.4%
GEN	1	0.3%	1	0.3%
AUG	3	0.8%	3	0.9%
CRX	5	1.3%	5	1.5%
Total	384	100	334	100

Drug resistances were categorized into three levels based on the magnitude and classification of the identified drugs. In a state where one type is identified, it is classified as single resistance; when multiple types are identified, it is classified as multiple drug resistance; and when no resistance is identified, it is classified as no resistance. Figure 4 illustrates the representation of the three groups identified in the AST (drug resistance) data. Descriptive statistics indicated that the no resistance case had a Standard Deviation (SD) of 7.731 and a mean of 7.167 (range: 0.9464 - 15.28). The single resistance case exhibited an SD of 11.2 and a mean of 13.67 (range: 1.91 - 25.42), while the multiple resistance case demonstrated an SD of 15.6 and a mean of 15.17 (range: 1.205 - 31.54). An Analysis of Variance (ANOVA) was conducted to assess the differences among the three groups. R-squared = 0.2315, $F(2, 10) = 1.506$, $p = 0.275$, indicating no statistically significant difference among the three categories.

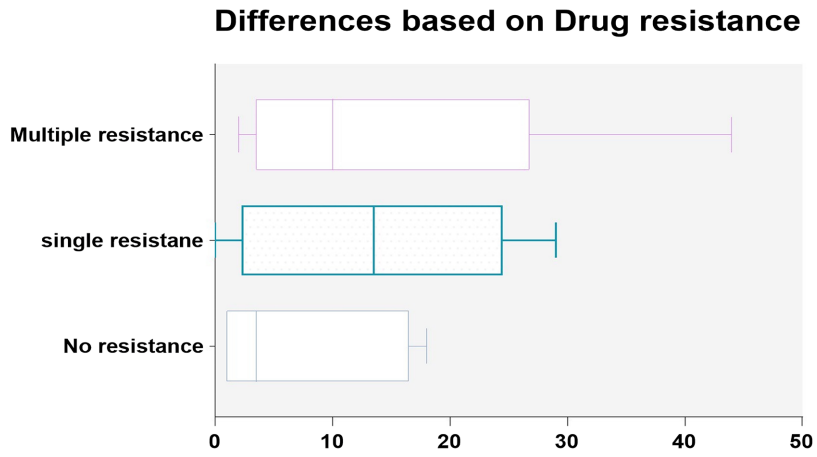

Figure 4. Differences in drug resistance levels.

Comparisons were made among age groups concerning co-infection, case severity, and drug resistance (Figure 5). Co-infection and length of hospital stay. Descriptive statistics for the three levels of co-morbidity by age group revealed that mono-infection had a Standard Deviation (SD) of 21.11 and a mean of 26.2 (range: 4.01 - 48.32). Co-infection exhibited an SD of 1.966 and a mean of 2.33 (range: 0.2697 - 4.397), while multiple infections showed an SD of 6.979 and a mean of 7.5 (range: 0.18 - 14.82), with a 95% Confidence Interval (CI). Mono-infection exhibited the highest average and broader dispersion in comparison to co-infection and multiple infection. The Analysis of Variance (ANOVA) test indicated that R-squared = 0.4309, $F(2, 15) = 5.678$, $p = 0.015$, demonstrating a statistically significant difference among at least two groups. The multiple comparisons test indicated a mean difference of 23.83, $t(15) = 3.203$, and an adjusted p-value of 0.018, demonstrating a statistically significant difference between individuals with mono-infection and those with co-infection. The comparison between mono-infection and multiple infections revealed a mean difference of 18.67, $t(15) = 2.509$, and an adjusted p-value of 0.048, indicating a statistically significant difference between

individuals without co-infection and those with multiple infections. A statistically significant difference was not found between individuals with co-infection and those with multiple infections, t(15) = 0.6943, p = 0.498. Co-morbidity associated with hospital duration revealed that mono-infection had a standard deviation of 42.24 and a mean of 26.2 (range: 18.2 - 70.5). Co-infection exhibited a standard deviation of 2.066 and a mean of 2.33 (range: 0.1656 - 4.501), while multiple infections showed a standard deviation of 8.503 and a mean of 7.5 (range: 1.423 - 16.42), with a 95% confidence interval. Analysis of Variance (ANOVA) indicated R-squared = 0.1685, F(2, 15) = 1.52, p = 0.25, suggesting no statistically significant difference among the groups. Furthermore, variations in case severity and length of stay did not achieve statistical significance (R-squared = 0.09802, F(2, 15) = 0.815, p = 0.461).

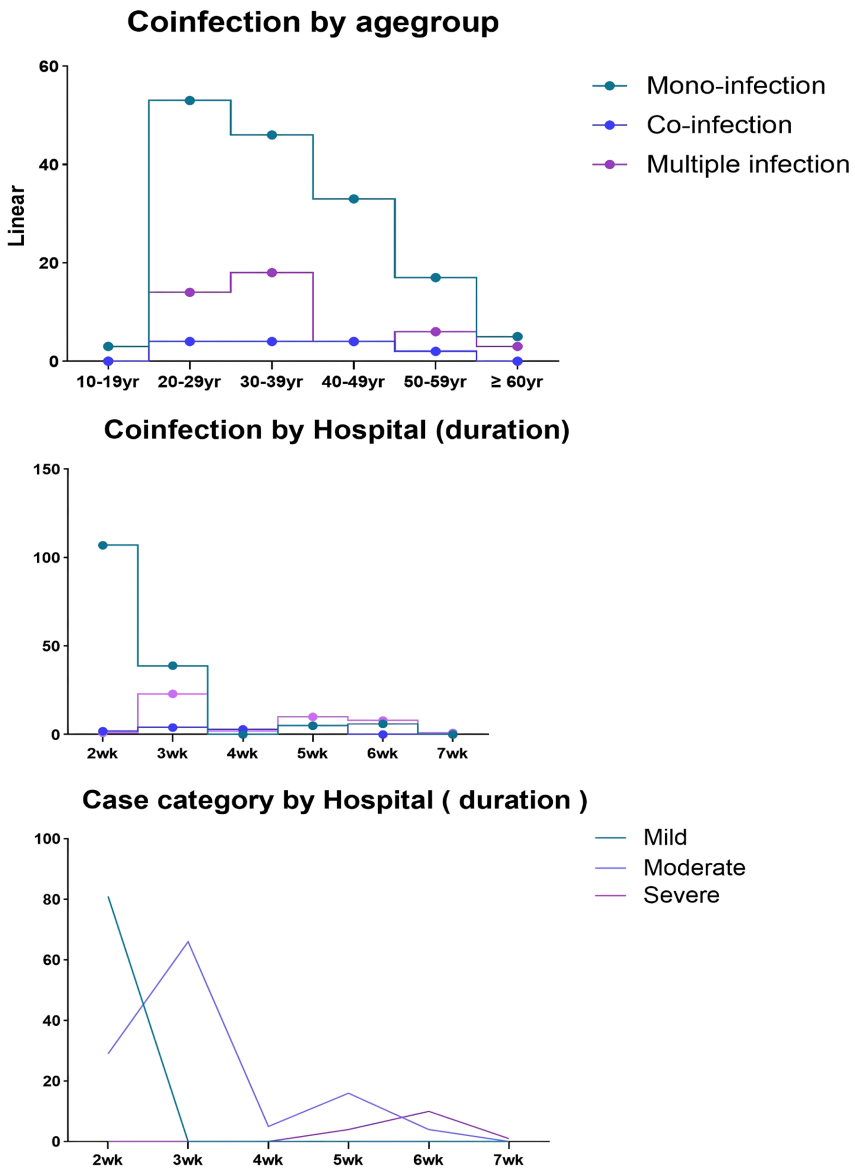

Figure 5. Age groups, VRS co-infection, case severity, and drug resistance.

The study indicates a decline in the magnitude of infections across age groups at a specific point. Mono-infection with COVID-19 was most prevalent in the 20 to 29 age group and decreased in individuals aged 60 and older. The prevalence of multiple infections was highest in the age group of 30 to 39, followed by a sharp decline in subsequent age groups. In contrast, individuals with co-infection exhibited a stable count until a decrease began in the age group of 50 to 59, continuing into the 60 and above category. The data indicated a significant reduction in hospital stay duration after the second week, although the changes observed in weeks five and six were minimal. In week 2, COVID-19 was the predominant case; however, week 3 saw a rising trend in multiple infections. In assessing the severity of COVID-19 infection concerning hospital admission, it can be inferred that mild cases experience a significant decline from week 2 to week 3. Moderate cases increase from week 2 to week 3, then decrease sharply by week 4, followed by fluctuations in week 6. The severity of COVID-19 infection typically emerges between weeks 4 and 7, potentially due to opportunistic infections and comorbidities.

4. Discussion

In our study, we observed a higher prevalence of COVID-19 among male patients (65.3%) compared to female patients (34.7%). We also found that male patients had higher hospitalization rates than female patients. Specifically, 56.0% of COVID-19 positive male patients were inpatients, while only 6.5% of COVID-19 positive female patients were inpatients. These key findings reiterate previous research, both in Ghana and other parts of the world [45]-[49], which identified male gender as a risk factor for COVID-19 infection. The factors contributing to this gender disparity are not well understood. Numerous authors argue that biological differences, comorbidities, and health behaviours may play a role. Men experience more life-threatening conditions like chronic lung diseases, hypertension, cardiovascular diseases, and type-2 diabetes [46] [50]. A study on sex and risk of severe outcomes in COVID-19 revealed that males displayed an increased vulnerability to viral pneumonia, acute kidney injury, sepsis, acute respiratory insufficiency, and acute respiratory distress syndrome, a pattern that persisted even after adjustments were made in the models [46]. However, the direct correlation of these factors with men as risk factors is yet to be firmly established.

In our study, we observed a disproportionate trend in the hospitalization rates of patients across different age groups. Specifically, we found that younger adults in the age group 20 - 29 had a higher incidence of mono-infection (only COVID-19) and were more likely to be hospitalized. In contrast, middle-aged adults in the age group 30 - 39 showed a peak in multiple infections and had higher hospitalization rates. As the age increased, the trend of hospitalization varied, with older adults (50 - 59 and above) showing a decline in hospitalization rates. Participants in the age groups (20 - 29) and (30 - 39) predominated our study population and had the highest prevalence of COVID-19 (mono-infections) with increased multiple infections. This could be due to increased social interactions and less strin-

gent adherence to public health guidelines during peak transmission periods.

SARS-CoV-2 infection can impact various organs in the body, leading to a wide range of symptoms in patients. In comparison to the patients who tested negative for COVID-19, COVID-19-positive patients reported higher percentages of symptoms such as sore throat (12.4%), fever (11.7%), body aches (7.3%), and bronchitis (6.9%). Similar trends of the disease symptoms have been previously reported in Ghana [48] and are also sporadically reported in other parts of the world [51] [52]. Interestingly, we did not observe a significant association of COVID-19 with fatigue, cough, and dyspnea, which have been largely reported to be major symptoms of COVID [51] [53] [54]. A recent systematic review in Ghana reported COVID-19 vaccine administration to range from 17.5% to 82.6% [55]. This favourable vaccination campaign might be a contributing factor in minimizing the symptoms reported.

Among the pool of patients, the Omicron variant of the COVID-19 infection predominated, accounting for about 84.7% of cases, while 15.3% were attributed to the Delta variant. These findings align with César Fernández-de-las-Peña's [53], who, in their systematic review, found the Omicron variant as the highest. However, our findings varied from Morang'a *et al.* [49], who found the Delta variant to be predominant (32%) in 2021, during the early stages of the COVID-19 pandemic in Ghana. We found that most COVID-19 positive patients had moderate cases (56.0%), followed by mild cases (37.5%) and severe cases (6.5%). Our finding is like Akrong *et al.* [56], where most COVID-19 patients responded well to standard management and were categorized as having moderate severity, while a smaller proportion (21% of patients) became critically ill or passed away. The 6.5% severe cases in our study could be attributed to other conditions, such as diabetes and hypertension, that were noted among some of the patients in our study population. Notably, the study period coincided with the dominance of the Omicron variant, which is known to cause milder clinical presentations compared to earlier variants. In addition, the study was conducted exclusively in urban health facilities, which may limit how relevant or applicable the findings are to rural or peri-urban populations with different healthcare access and population characteristics.

Our study revealed that COVID-19 positive patients had a significantly higher rate of co-infections (6.5%) and multiple infections (20.8%) compared to those without COVID-19. The amount of co-infection reported in our study is significantly lower than the 22.2% bacterial co-infection reported among COVID patients in Brazil [57]. Our finding reiterates that individuals with COVID-19 are more susceptible to additional infections, likely due to the weakened immune system caused by the primary COVID-19 infection. This is consistent with our observation that COVID-19 positive patients had longer hospital stays, with 50.9% staying for 2 weeks. The patients' weakened immune system and nosocomial infections [58] might be a significant contributing factor in the longer hospital stay. The presence of co-infections and multiple infections can complicate the clinical management and treatment of COVID-19 patients, requiring healthcare providers to

be vigilant in monitoring and addressing these additional infections to improve patient outcomes.

The dynamics of the human microbiome play a crucial role in regulating the host's immune system. Previous studies suggested that SARS-CoV-2 infection causes significant changes in the microbiota of the respiratory tract and gut [59]-[61], but Xu *et al.* [62] found that gut microbiota remained relatively stable in their cohort study comprising healthy and COVID-19 patients. Our study revealed significant association of COVID-19 positivity with the presence of organisms such as *Rothia mucilaginosa*, *Rothia aeria*, *Staphylococcus aureus*, *Streptococcus parasanguinis*, and *Klebsiella* spp. Broad-spectrum antibiotic therapy and medications during COVID-19 infection may alter the microbiome. This dysbiosis and alteration of microbiota shift the paradigm of the microbial population, leading to reduced diversity and an increased population of certain species [63]. Our observation that *Rothia mucilaginosa* is high among COVID-19 positive patients differs from the findings of Merenstein *et al.* [64], who found *Rothia mucilaginosa* to be predominant in the oral microbiota of their healthy control group, who had not taken antibiotics three months before sampling. Our findings are consistent with data from the United States, where *Rothia* spp. and *Streptococcus* were associated with hospitalization of COVID-19 patients [65].

The study results indicate that COVID-19-positive patients exhibited higher levels of antibiotic resistance compared to negative patients. Specifically, significant differences were found for ciprofloxacin, erythromycin, and penicillin, with p-values of 0.000 for each. The higher levels of antibiotic resistance in COVID-19 positive patients could be attributed to several factors, including the overuse or misuse of antibiotics during the pandemic, the impact of the virus on the immune system, and the presence of co-infections. Feehan *et al.* [66] found that antibiotic sales were positively associated with COVID-19 cases globally during 2020-2022. This association points out the importance of enhancing antibiotic stewardship practices to address the rising issue of antibiotic resistance in the context of the COVID-19 pandemic [66].

Funding

The study was supported by a grant from the Noguchi Memorial Institute for Medical Research. This work was carried out under the institute's research program.

Ethical Compliance

All procedures conducted in studies involving human participants adhered to the ethical standards set forth by the institutional and/or national research committee, as well as the 1964 Helsinki Declaration and its subsequent amendments or equivalent ethical guidelines.

Conflicts of Interest

The authors declare that they have no affiliations with or involvement in any or-

ganization or entity with any financial interest in the subject matter or materials discussed in this manuscript.

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