Multidrug resistant bacterial infections in severely ill COVID-19 patients admitted in a national referral and teaching hospital, Kenya

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Abstract

**Background:** Bacterial infections are a common complication in patients with seasonal viral respiratory tract infections and are associated with poor prognosis, increased risk of ICU admission and 29-55% mortality. Yet, there is limited data on the burden of bacterial infections among COVID-19 patients in Africa, where underdeveloped healthcare systems are likely to play a pertinent role in the epidemiology of the COVID-19 pandemic. Here, we evaluated the etiologies, Antimicrobial Resistance profiles, risk factors, and outcomes of bacterial infections in severely ill COVID-19 patients admitted to in a tertiary national teaching and referral hospital in Kenya.

**Methods:** A descriptive cross-sectional study design on severely ill COVID-19 patients at Kenyatta National Hospital between October and December 2021 was adopted. A structured questionnaire and case report forms were used to collect patients’ sociodemographic, clinical presentation and outcomes respectively. Blood, nasal/oropharyngeal swabs and tracheal aspirate samples were collected based on the decision of the treating physician and transported to microbiology laboratory for immediate processing following the standard bacteriological procedures.

**Results:** At least one bacterial infection was found in 44.2% (53/120) patients sampled. A mortality rate of 31.7% (38/120) was found. The majority of pathogens were from upper respiratory tract (62.7%, 42/67), with gram-negative bacteria as the most dominant isolates (73.1%, 49/67). Male were about three times more likely to acquire bacterial infection than females (aOR = 2.61, 95% CI: 1.2 – 5.65, p = 0.015). Those aged between 25 to 40 years (aOR = 0.13, 95% CI: 0.02 – 0.6, p =0.009), vaccinated (aOR = 0.2, 95%CI: 0.05 – 0.83, p = 0.027) and admitted to the Infectious Disease Unit (IDU) ward (aOR = 3.27, 95%CI: 1.08 – 6.89, p=0.031), for those admitted for a short length of stay (0 -5 days) (aOR=14.28, 95% CI:3.25 - 62.76, p<0.001) were more likely to have a positive outcome. The majority of bacteria isolates (64.3%, 46/67) were multidrug-resistant (MDR), mostly attributable to gram negative bacteria (GNB) (69.6%, 32/46). The predominant MDR phenotypes were found in *Enterococcus cloacae* (42.9%, 3/7), *Klebsiella pneumonia* (25%, 4/16), and *Escherichia coli* (40%, 2/5) and mostly involved cefotaxime, ceftriaxone, gentamicin, ciprofloxacin, aztreonam and trimethoprim/sulfamethoxazole.

**Conclusion:** Our findings highlight a high prevalence of bacterial infections in hospitalized COVID-19 patients during the peak of the pandemic, with males more likely to be infected, while those in advanced age, not vaccinated, admitted to the critical care unit, and those with prolonged length of hospital stay showing a poor hospitalization outcome. The observed high multidrug-resistant infections are unacceptably high, emphasizing the need to monitor the effectiveness of the existing infection control strategies at KNH-IDU and adherence to antimicrobial stewardship in line with local and global AMR control action plans.

**Background**

Coronavirus Disease-2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a febrile respiratory illness that may progress to pneumonia and respiratory failure and poses a global public health challenge [1]. Over 545 million infections and over 6.3 million deaths[2] had occurred by the time we wrote this publication, and the mortality rate is disproportionately higher in elderly
patients [3] than in other age groups. Study reports show that secondary bacterial infections increase the severity of viral respiratory infections[4] and significantly contribute to increased morbidity and mortality [5][6][7].

As reported in influenza, viral-induced epithelial immune damage and immune downregulation favor bacterial infections or colonization [8], [9][10],[11]; however, the role of bacterial infections in the pathogenesis of SARS-CoV-2 is not well understood. Some study reports suggest that bacterial infections in COVID-19 are a minority, with prevalence ranging from 0- 6.9%, and require no antimicrobial prescription [12], [6], [13]; but other reports, especially from Asia show a significantly higher burden, with up to 95.65% prevalence [14] and 50%-83% mortality[15][16]. Community-onset of bacterial infections in COVID-19 is low [17], but most bacterial infections occur after hospital admission, especially in the intensive care unit (ICU) [18], [19].

According to Shafran et al (2021), bacterial infections are a common complication associated with worse outcomes in COVID-19 patients than influenza patients, and careful surveillance and prompt antibiotic treatment may benefit selected patients[20]. Yet, there is limited data on the burden of bacterial infections among COVID-19 patients in Africa, where poor sanitation, inadequate potable water, and underdeveloped healthcare systems [21][22] are likely to play a pertinent role in the epidemiology of the COVID-19 pandemic. Additionally, the prevalence of bacterial infections and microbiological etiologies in critically ill COVID-19 patients in many developing countries is poorly understood. Due to the frequent use of invasive devices, hospitalized critically ill COVID-19 patients are at high risk of nosocomial infections, mostly bacteremia and respiratory tract infections, within 10–15 days of admission[23].

Differentiating COVID-19 from bacterial pneumonia is difficult, as a result, COVID-19 patients are frequently prescribed broad-spectrum antibiotics, without laboratory-based evidence, as part of clinical care to treat and prevent bacterial infections [24][25]. In Wuhan, for instance, 95% of 191 COVID-19 patients in two hospitals were empirically treated with antibiotics[25][14]. Elsewhere, in a randomly sampled cohort of 1705 patients hospitalized with COVID-19 in 38 Michigan hospitals, 56.6% (27–84%) of the patients were prescribed empiric antibacterial therapy at admission despite low (3.5%) community-onset of bacterial infections[17]. The indiscriminate use of antibiotics in COVID-19 pandemics is likely to exacerbate the global antimicrobial resistance (AMR) menace, with profound implications for global health and the economy[26][27],[28]. A high prevalence of carbapenem-resistant bacterial infections in COVID-19 patients admitted to ICUs was reported in Iran[15] With an estimated 10 million deaths and 100 billion dollars in economic loss annually due to multidrug-resistant bacteria by 2050 [21], [22], [23], a better understanding of the local epidemiology of bacterial infections in COVID-19 can inform judicious antimicrobials use in line with the national policy for the prevention and containment of AMR[29] and global action plan on AMR[29].

Previous study findings show that gram-negative bacteria are the predominant cause of infections in COVID-19 patients [30][14][13][15], but most of these reports are from outside Africa, and bacterial etiologies and antimicrobial resistance are subject to geographical variation. It is imperative to evaluate the etiologies and AMR of bacterial infections in COVID-19 patients to inform policymakers on local empiric therapy design and prevention interventions that can mitigate AMR spread in line with national and global strategies. In this study, we evaluated the etiologies, AMR profiles, risk factors, and outcomes of bacterial infections in critically ill COVID-19 patients admitted to ICU in a single tertiary national teaching and referral hospital in Kenya.
Methods

Study area and study design, data collection, and outcomes

This study was done at Kenyatta National Hospital (KNH) at the Infectious Disease Unit (KNH-IDU), Kenya. A descriptive cross-sectional study design was conducted between October and December 2021. Through a purposive sampling technique, 120 RT-PCR confirmed severely ill COVID-19 patients were recruited. Patients’ legal representatives or their guardians who declined to give consent for their patients’ participation in this study were excluded.

A structured questionnaire and case report forms were used to collect patients’ sociodemographic and clinical presentation and outcomes respectively. Based on clinical presentation of the patient and the decision of the treating physician, blood, swabs (nasopharyngeal & oropharyngeal) and tracheal aspirate samples were collected following standard recommended procedures. Thereafter, samples were transported to the KNH microbiology laboratory in a cool box and processed immediately. Bacteriological isolation of bacteria isolates was done following the standard bacteriological procedures (CLSI, 2021). Briefly, Nasopharyngeal (NP) swabs, oropharyngeal (OP) swabs and Tracheal Aspirates were streaked onto sheep blood agar and MacConkey and incubated at 37°C overnight. Blood samples were collected directly into the sterile commercial blood culture broth which were loaded to the BACT/ALERT® VIRTUO 3D Microbial Detection Systems (bioMérieux, Marcy l'Etoile, France), and those flagged positive were sub-cultured onto chocolate blood agar (CBA), MacConkey and sheep blood agar and incubated at 37°C overnight at ambient air and at 5% CO₂. The recovered isolates were identified using Mass Spectrometry System matrix assisted laser desorption ionization-time of flight (VITEK MS MALDI-TOF) (BioMérieux, Marcy l'Etoile, France). *Escherichia coli* ATCC 8739 was used for Quality Control (QC).

Antimicrobial susceptibility testing was done using the VITEK 2 COMPACT system (bioMérieux, Marcy l'Etoile, France) in accordance with the CLSI (2021) guidelines[31]. *Staphylococcus aureus* ATCC 29213 (AST GP 580) and *Enterococcus faecalis* ATCC 29212 (AST GP 586) were used as the AST cards for the gram-positive bacteria (GPB). *Pseudomonas aeruginosa* ATCC 27853 (AST GN 83) and *Escherichia coli* ATCC 25922 (AST GN 83) were used as the AST cards for the gram-negative bacteria (GNB). For GNB, antibiotic panels tested were: amoxicillin/clavulanic acid (AMC), ampicillin/subbactam (SAM), piperacillin/tazobactam (TZP), cefotaxime (CTX), ceftazidime (CAZ), ceftriaxone (CRO), cefepime (FEP), aztreonam (ATM), meropenem (MEM), Amikacin (AMK), gentamicin (GEN), ciprofloxacin (CIP), trimethoprim/sulfamethoxazole (SXT) for gram negative organisms. Antibiotics tested for GPB were: Benzylpenicillin (BP), levofloxacin (LVX), erythromycin (ERY), linezolid (LZD), teicoplanin (TEC), vancomycin (VAN), tetracycline (TET), and tigecycline (TGC) were used for the gram positives according to the CLSI guidelines, 2021. Isolate resistant to three or more antibiotic classes were considered a multidrug-resistant Organisms (MDRs) [32]

Statistical analysis

All analyses were two-sided and conducted using STATA version 16. We tested the data for normality, described continuous data in means and medians, and categorical data in frequencies and presented them in tables and figures. Bivariate analysis was performed using logistic regression where crude odds ratio (cOR)
were calculated. Variables with $p \leq 0.2$ were subjected to a multivariate analysis where adjusted odds ratio (aOR) were calculated and significant variables identified. Level of statistical significance was evaluated at $p < 0.05$, at 95% Confidence Interval (95% CI). Factors found statistically significant are indicated in bold.

Results

Socio-demographic and clinical characteristics of COVID-19-positive patients admitted at KNH-IDU

We sampled 120 RT-PCR confirmed COVID-19 positive patients in this study. The majority of the patients were 60 years old and above (43, 35.8%), female (69, 57.5%), married (66.7, 80%), not vaccinated (98, 81.7%), had other co-morbidities (94, 78.3%), mainly presenting with Difficulties in Breathing (DIB) (60, 50%), admitted to the Critical Care Unit (CCU) (35, 29.2%), and were discharged (82, 68.3%) after a median length of stay (48, 40%), Table 1.
| Attributes                  | Frequency (N = 120) | Percent (%) |
|-----------------------------|---------------------|-------------|
| Age (years)                 |                     |             |
| Median (IQR)                | 49 (32–65)          |             |
| ≤24                         | 18                  | 15.0        |
| 25–40                       | 39                  | 32.5        |
| 45–59                       | 20                  | 16.7        |
| ≥60                         | 43                  | 35.8        |
| Gender                      |                     |             |
| Male                        | 51                  | 42.5        |
| Female                      | 69                  | 57.5        |
| Admission site              |                     |             |
| IDU isolation ward          | 85                  | 70.8        |
| IDU CCU                     | 35                  | 29.2        |
| Marital status              |                     |             |
| Single                      | 33                  | 27.5        |
| Married                     | 80                  | 66.7        |
| Separated/Divorced          | 7                   | 5.8         |
| Presenting complains        |                     |             |
| Cough                       | 50                  | 41.7        |
| Fever                       | 32                  | 26.7        |
| Chest pain                  | 14                  | 11.7        |
| Nausea                      | 25                  | 20.8        |
| Pneumonia                   | 33                  | 27.5        |
| Vomiting                    | 15                  | 12.5        |
| DIB                         | 60                  | 50.0        |
| Others                      | 12                  | 10.0        |

**IQR-Interquartile Range, IDU-Infectious Disease Unit, IDU-CCU-Infectious Disease Unit- Critical Care Unit, DIB-Difficult in Breathing, HIV/AIDS-Human Immunodeficiency Virus/ Acquired Immunodeficiency Syndrome, COVID-19-Coronavirus Disease-2019**
| Attributes                              | Frequency (N = 120) | Percent (%) |
|----------------------------------------|---------------------|-------------|
| Yes                                    | 94                  | 78.3        |
| No                                     | 26                  | 21.7        |
| Comorbidities present                  |                     |             |
| HIV/AIDS                               | 6                   | 6.4         |
| Cancer                                 | 16                  | 17          |
| Kidney disease                         | 15                  | 16          |
| Diabetes                               | 14                  | 14.9        |
| Hypertension                           | 11                  | 11.7        |
| Haematological disorders               | 7                   | 7.4         |
| Liver disease                          | 1                   | 1.1         |
| Vaccination status                     |                     |             |
| Yes                                    | 22                  | 18.3        |
| No                                     | 98                  | 81.7        |
| Hospitalization Outcome                |                     |             |
| Discharged                             | 82                  | 68.3        |
| Dead                                   | 38                  | 31.7        |
| Length of hospital stay (days)         |                     |             |
| Median (IQR)                           | 9(5–12)             |             |
| Short stay (0–5 days)                  | 34                  | 28.3        |
| Medium stay (6–10 days)                | 48                  | 40.0        |
| Long stay (≥ 10 days)                  | 38                  | 31.7        |

IQR-Interquartile Range, IDU-Infectious Disease Unit, IDU-CCU- Infectious Disease Unit- Critical Care Unit, DIB- Difficult in Breathing, HIV/AIDS- Human Immunodeficiency Virus/ Acquired Immunodeficiency Syndrome, COVID-19-Coronavirus Disease-2019

**Bacterial Infections And Their Etiologies Among Covid-19-positive Patients Admitted At Knh-Idu**

The prevalence of bacterial infection among the COVID-19 patients was 44.2% (53/120). The majority of them were upper respiratory tract infections/colonization (URTI/C) (62.7%, 42/67). A total of 67 (55.8%) bacteria were isolated, with gram-negative bacteria (GNB) as the most dominant pathogens (73.1%, 49/67), Fig. 1b.
Klebsiella pneumoniae (32.7%, 16/49) was the most prevalent, whereas Serratia marcescens (2%, 1/49) was the least common gram-negative bacterium. Among the gram-positive bacteria (GPB) isolates, Enterococcus faecium (55%, 10/18) was the predominant pathogen, while the least were Enterococcus faecalis and Staphylococcus sciuri, each accounting for 5.6% (1/18) of the isolates, Fig. 1c.

Although Enterobacter cloacae complex, Proteus mirabilis, Staphylococcus aureus, Staphylococcus sciuri, Enterococcus faecalis, Stenotrophomonas maltophilia, and Acinetobacter calcoaceticus were causing URTI/C, lower respiratory tract infections (LRTIs) or bacteremia caused by these organisms absent. Pseudomonas aeruginosa (30.8%, 4/13) and Acinetobacter baumanii (30.8%, 4/13) were the dominant cause of LRTIs, whereas Klebsiella pneumoniae was the most prevalent cause of GNB-associated bacteremia (42.9%, 3/7) and upper respiratory tract infection (URTIs) (23.8%, 10/42). Overall, E. faecium (41.7%, 5/12) was not associated with LRTIs but was the most common cause of bacteremia, Fig. 1a.

**Factors Associated With Bacterial Infection In Covid-19 Patients Admitted At Knh-idu**

The male patients were about three times more likely to acquire bacterial infection than their female counterparts (aOR = 2.61, 95% CI: 1.2–5.65, p = 0.015 ((Table 2)), and no other COVID-19 patients' sociodemographic and clinical characteristics were associated with the occurrence of bacterial infections (p > 0.05).
Table 2
Association between social demographics and bacterial infection in Covid-19 patients admitted at KNH-IDU

| Variable                  | Bacterial infection | cOR (95%CI) | p-value | aOR (95%CI) | p-value |
|---------------------------|---------------------|-------------|---------|-------------|---------|
|                           | Yes n (%)           | No n (%)    |         |             |         |
| Age                       |                     |             |         |             |         |
| <=24 days                 | 6(11.3)             | 12(17.9)    | 1.45(0.56–3.75) | 0.211 | 2.15(0.54–8.6) | 0.281 |
| 25–40 years               | 13(24.5)            | 19(28.4)    | 2.21(0.69–7.05) | 0.18  | 1.37(0.49–3.81) | 0.545 |
| 45–59 years               | 13(24.5)            | 17(25.4)    | 1.62(0.63–4.13) | 0.317 | 1.45(0.53–4.01) | 0.470 |
| >=60 years                | 21(39.6)            | 19(28.4)    | Ref     | Ref         |         |
| Gender                    |                     |             |         |             |         |
| Male                      | 30(56.6)            | 22(32.8)    | 2.67(1.27–5.6) | **0.010** | 2.61(1.2–5.65) | **0.015** |
| Female                    | 23(43.4)            | 45(67.2)    | Ref     | Ref         |         |
| Marital status            |                     |             |         |             |         |
| Single                    | 13(24.5)            | 25(37.3)    | 0.56(0.25–1.25) | 0.168 | 0.7(0.28–1.79) | 0.457 |
| Married                   | 40(75.5)            | 42(62.7)    | Ref     | Ref         |         |
| Admission site            |                     |             |         |             |         |
| IDU isolation ward        | 40(75.5)            | 46(68.7)    | 1.41(0.62–3.16) | 0.541 | - | - |
| IDU-CCU                   | 13(24.5)            | 21(31.3)    | Ref     |             |         |
| Presence of comorbidity   |                     |             |         |             |         |
| Yes                       | 39(73.6)            | 51(76.1)    | 0.87(0.38–2.0) | 0.833 | - | - |
| No                        | 14(26.4)            | 16(23.9)    | Ref     |             |         |
| Vaccination               |                     |             |         |             |         |
| Yes                       | 14(26.4)            | 14(20.9)    | 1.36(0.58–3.17) | 0.519 | - | - |
| No                        | 39(73.6)            | 53(79.1)    | Ref     |             |         |
| Hospitalization outcome   |                     |             |         |             |         |

**IDU-** Infectious Disease Unit, **IDU-CCU-** Infectious Disease Unit-Critical Care Unit, **cOR-** crude odds ratio, **aOR-** adjusted odds ratio, **statistically significant, Ref-** Reference, **CI-** Confidence Interval, **LOS-** Length of Stay
### Hospitalization Outcomes Of Covid-19 Patients Admitted To KNH-IDU

The COVID-19 patients likely to have a positive hospitalization outcome (discharged alive) were those: aged between 25 to 40 years (aOR = 0.13, 95% CI: 0.02–0.6, p = 0.009), vaccinated (AOR = 0.2, 95% CI: 0.05–0.83, p = 0.027) and admitted to the IDU ward (aOR = 3.27, 95% CI: 1.08–6.89, p = 0.031) for a short length of stay ((0–5 days) (aOR = 14.28, 95% CI:3.25–62.76, p < 0.001)), Table 3.

| Variable | Bacterial infection | cOR (95%CI) | p-value | aOR (95%CI) | p-value |
|----------|---------------------|-------------|---------|-------------|---------|
|          | Yes n (%)           | No n (%)    |         |             |         |
| Discharged | 37(69.8) | 45(67.2) | 1.13(0.52–2.46) | 0.757 | - |
| Dead     | 16(30.2) | 22(32.8) | Ref | - |
| LOS (days) | 15(28.3) | 20(29.9) | 0.46(0.19–1.1) | 0.082 | 0.58(0.21–1.61) | 0.296 |
| Medium stay (6–10) | 25(47.2) | 22(32.8) | 0.69(0.27–1.79) | 0.449 | 0.39(0.15–1.02) | 0.056 |
| Long stay (> 10) | 13(24.5) | 25(37.3) | Ref | Ref |

**IDU**: Infectious Disease Unit, **IDU-CCU**: Infectious Disease Unit-Critical Care Unit, **cOD**: crude odds ratio, **aOR**: adjusted odds ratio, ****: statistically significant, **Ref**: Reference, **CI**: Confidence Interval, **LOS**: Length of Stay
Table 3
Association between patient characteristics and hospitalization outcome among COVID-19 patients admitted at KNH-IDU.

| Variable            | Hospitalization outcomes | OR (95%CI) | p-value | aOR (95% CI) | p-value |
|---------------------|--------------------------|------------|---------|--------------|---------|
|                     | Discharged               | Died       |         |              |         |
| Age (years)         |                          |            |         |              |         |
| ≤ 24                | 11(13.4)                 | 7(18.4)    | 0.34(0.11–1.01) | 0.052  | 0.39(0.08–1.85) | 0.236  |
| 25–40               | 24(29.3)                 | 8(21.1)    | 0.86(0.28–2.68) | 0.796  | 0.13(0.02–0.60) | **0.009** |
| 45–59               | 24(29.3)                 | 6(15.8)    | 0.45(0.16–1.25) | 0.125  | 0.31(0.08–1.22) | 0.093  |
| ≥ 60                | 23(28)                   | 17(44.7)   | Ref     | Ref          |         |
| Gender              |                          |            |         |              |         |
| Male                | 34(41.5)                 | 18(47.4)   | 0.79(0.36–1.71) | 0.559  | -          | -      |
| Female              | 48(58.5)                 | 20(52.6)   | Ref     |              |         |
| Marital status      |                          |            |         |              |         |
| Single              | 25(30.5)                 | 13(34.2)   | 0.84(0.37–1.91) | 0.679  | -          | -      |
| Married             | 57(69.5)                 | 25(65.8)   | Ref     |              |         |
| Admission site      |                          |            |         |              |         |
| IDU ward            | 68(82.9)                 | 18(47.4)   | 5.4(2.29–12.73) | < **0.001** | 3.27(1.08–6.89) | **0.031** |
| IDU-CCU             | 14(17.1)                 | 20(52.6)   | Ref     | Ref          |         |
| Presence of comorbidity |                        |            |         |              |         |
| Yes                 | 58(70.7)                 | 32(84.2)   | 0.45(0.17–1.22) | 0.173  | 1.62(0.31–4.94) | 0.061  |
| No                  | 24(29.3)                 | 6(15.8)    | Ref     | Ref          |         |
| Covid-19 vaccination|                          |            |         |              |         |
| Yes                 | 22(26.8)                 | 6(15.8)    | 2.0(0.72–5.31) | 0.247  | 0.20(0.05–0.83) | **0.027** |
| No                  | 60(73.2)                 | 32(84.2)   | Ref     | Ref          |         |
| LOS (days)          |                          |            |         |              |         |
| Short (0–5)         | 11(13.4)                 | 24(63.2)   | 1.09(0.34–3.48) | 0.879  | 0.66(0.17–2.61) | 0.556  |

**IDU**- Infectious Disease Unit, **IDU-CCU**- Infectious Disease Unit-Critical Care Unit, **cOR**- crude odds ratio, **aOR**- adjusted odds ratio, **LOS** – length of stay, **statistically significant**
| Variable | Hospitalization outcomes | OR (95%CI) | p-value | aOR (95% CI) | p-value |
|----------|--------------------------|------------|---------|--------------|---------|
|          | Discharged n (%) | Died n (%) |         |              |         |
| Medium (6–10) | 39(47.6) | 8(21.1) | 11.64(3.77–35.91) | <0.001** | 14.28(3.25–62.76) | <0.001** |
| Long (>10) | 32(39) | 6(15.8) | Ref | Ref |         |

IDU- Infectious Disease Unit, IDU-CCU- Infectious Disease Unit-Critical Care Unit, cOD- crude odds ratio, aOR- adjusted odds ratio, LOS – length of stay, ** statistically significant

**Mdr Phenotypes Among The Isolates**

The majority of bacteria isolates (64.3%, 46/67) were multidrug-resistant (MDR), defined as resistance to three or more classes of antibiotics[33] (Table 6). Most of the MDR was attributable to GNB (69.6%, 32/46), and all isolates of Enterococcus cloacae complex (100%, 7/7), Klebsiella pneumonia (100%, 16/16), and Escherichia coli (100%, 5/5) were MDR.

The predominant MDR phenotypes were those observed in Enterococcus cloacae (42.9%, 3/7), Klebsiella pneumonia (25%, 4/16), and Escherichia coli (40%, 2/5) and mostly involved beta-lactamase inhibitors (AMC and SAM), cefotaxime, ceftriaxone, gentamicin, ciprofloxacin, aztreonam and trimethoprim/sulfamethoxazole. Among the GPB, MDR phenotypes were majorly associated with Enterococcus faecium and mostly involved Benzylpenicillin, erythromycin, levofloxacin, and tetracycline. Notably, erythromycin resistance was present in all GPB-MDR phenotypes (Table 6).
Table 6
MDR phenotypes among the isolates

| Bacteria Isolate                        | MDR phenotype                                             | Frequency (n) | Percentage (%) |
|-----------------------------------------|-----------------------------------------------------------|---------------|----------------|
| **Gram Negative Bacteria**              |                                                           |               |                |
| Enterococcus cloacae complex (N = 7)    | AMC/TZP/CTX/CAZ/CRO/FEP/ATM/MEM/GEN/CIP/SXT              | 1             | 14.3           |
|                                          | AMC/CTX/CRO/ATM/GEN/CIP/SXT                              | 1             | 14.3           |
|                                          | AMC/CTX/CAZ/CRO/ATM/GEN/SXT                              | 1             | 14.3           |
|                                          | AMC/TZP/CTX/CRO/ATM/GEN/SXT                              | 1             | 14.3           |
|                                          | AMC/CTX/CRO/ATM/GEN/SXT                                  | 3             | 42.9           |
| Enterococcus cloacae (N = 3)            | AMC/CTX/CAZ/CRO/ATM/GEN/SXT                              | 1             | 33.3           |
|                                          | AMC/TZP/CTX/CAZ/CRO/ATM                                  | 1             | 33.3           |
| Klebsiella pneumonia (N = 16)           | AMC/SAM/CTX/CAZ/CRO/ATM/GEN/CIP/SXT                      | 1             | 6.3            |
|                                          | AMC/SAM/CTX/CAZ/CRO/FEA/ATM/GEN/SXT                      | 1             | 6.3            |
|                                          | SAM/CTX/CAZ/CRO/FEA/ATM/GEN/SXT                          | 1             | 6.3            |
|                                          | SAM/CTX/CAZ/CRO/ATM/GEN/CIP/SXT                          | 1             | 6.3            |
|                                          | AMC/SAM/CTX/CAZ/CRO/ATM/CIP                              | 1             | 6.3            |
|                                          | AMC/SAM/CTX/CRO/ATM/GEN/SXT                              | 1             | 6.3            |
|                                          | SAM/CTX/CRO/ATM/GEN/SXT                                  | 1             | 6.3            |
|                                          | SAM/CTX/CAZ/CRO/ATM/GEN/SXT                              | 4             | 37.5           |
|                                          | CTX/CRO/ATM/GEN/SXT                                      | 1             | 6.3            |
|                                          | SAM/CTX/CRO/ATM/SXT                                      | 3             | 18.8           |
|                                          | SAM/CTX/ATM                                              | 1             | 6.3            |
| Escherichia coli (N = 5)                | AMC/SAM/TZP/CTX/CAZ/CRO/FEA/GEN/CIP                      | 1             | 20             |
|                                          | SAM/CTX/CAZ/CRO/GEN/CIP/SXT                              | 1             | 20             |
|                                          | SAM/CTX/CRO/GEN/CIP/SXT                                  | 2             | 40             |
|                                          | SAM/GEN/SXT                                              | 1             | 20             |
| Acinetobacter baumanii (N = 5)          | TZP/CTX/CAZ/CRO/FEA/GEN/CIP/SXT                          | 1             | 20             |

**AMC**- Amoxicillin/Clavulanate; **SAM**- ampicillin/sulbactam; **TZP**- piperacillin/tazobactam; **CTX**- cefotaxime; **CAZ**- ceftazidime; **CRO**- ceftriaxone; **FEP**- cefepime; **ATM**- aztreonam; **MEM**- meropenem; **AMK**- Amikacin; **GEN**- gentamicin; **CIP**- ciprofloxacin; **SXT**- trimethoprim/sulfamethoxazole, **BP**- Benzylpenicillin; **ERY**- erythromycin; **LVX**- levofloxacin; **LZD**- linezolid; **TEC**- teicoplanin; **VAN**- vancomycin; **TET**- tetracycline; **TGC**- tigecycline.
| Bacteria Isolate                  | MDR phenotype                             | Frequency (n) | Percentage (%) |
|----------------------------------|-------------------------------------------|---------------|----------------|
| Acinetobacter calcoaceticus (N = 1) | SAM/TZP/CTX/CAZ/CRO/FEB/GEN/AMK/GEN/CIP/SXT | 1             | 100            |
| Pseudomonas aeruginosa (N = 7)   | CTX/CAZ/CIP                               | 1             | 14.3           |
| **Gram Positive Bacteria**       |                                           |               |                |
| Enterococcus faecium (N = 10)    | BP/ERY/LVX/TET                            | 4             | 40             |
| Enterococcus faecalis (N = 1)    | ERY/LVX/TET                               | 1             | 100            |
| Staphylococcus aureus (N = 6)    | BP/OXA/ERY/SXT                            | 1             | 16.7           |
| **Total**                        |                                           | 46            | 68.7           |

**AMC**- Amoxicillin/Clavulanate; **SAM**- ampicillin/sulbactam; **TZP**- piperacillin/tazobactam; **CTX**- cefotaxime; **CAZ**- ceftazidime; **CRO**- ceftriaxone; **FEP**- cefepime; **ATM**- aztreonam; **MEM**- meropenem; **AMK**- Amikacin; **GEN**- gentamicin; **CIP**- ciprofloxacin; **SXT**- trimethoprim/sulfamethoxazole, **BP**- Benzylpenicillin; **ERY**- erythromycin; **LVX**- levofloxacin; **LZD**- linezolid; **TEC**- teicoplanin; **VAN**- vancomycin; **TET**- tetracycline; **TGC**- tigecycline.

**Discussion**

Previous studies have shown that bacterial infections are a common complication in patients with seasonal viral respiratory tract infections due to virus-induced epithelial damage and immune down-regulation [29][32][34][35][36][37] and are associated with poor prognosis, increased risk of ICU admission and 29–55% mortality[14][16][38]. We report a 44.2% (53/120) prevalence of bacterial infections among COVID-19 patients admitted to KNH-IDU was 44.2% (53/120), similar to 41.8% reported among severe and critically ill COVID-19 patients at Aga Khan University Hospital, Kenya [39]. However, our study's bacterial prevalence is higher than reported elsewhere in Wuhan, China (19%) [40] and Bahrain (25%) [40] but lower than in Jiangsu Province, China (91.8%)[40][14][14]. The discordance in these findings may suggest a geographical variation in bacterial etiologies occurrence and antimicrobial resistance. Since the prevalence of bacterial infections among COVID-19 patients before hospitalization is reportedly low ((≤ 3.5%)[41][42][43][47] the high prevalence in our study suggests nosocomial transmission and is consistent with other reports [18], [19][44].

In our study, gram-negative bacteria (GNB) were the most dominant pathogens, with *Klebsiella pneumoniae* as the most prevalent bacterium in COVID-19 patients, findings consistent with similar studies done in Kenya.
The predominance of \textit{K. pneumoniae} and GNB infections in COVID-19 patients is attributable to the microorganisms’ ability to acquire different resistance traits\cite{46} and to cause infections in patients with invasive devices and mechanical ventilation during hospitalization \cite{47}. The bacterial isolates profile was not a typical representation of the conventional community-acquired but rather nosocomial infections, suggesting low co-infections at the time of admission.

The prevalence of Gram-positive bacterial infection in our study population was 26.9%, with \textit{Enterococcus faecium} and \textit{Staphylococcus aureus} as the most common isolates; finding corroborating other studies among COVID-19\cite{20} \cite{39}, \cite{48}, \cite{49} and MERS patients\cite{50}, reflecting the pattern of infections in these pandemics. \textit{Pseudomonas aeruginosa} and \textit{Acinetobacter baumanii} were the dominant lower respiratory tract isolates, whereas \textit{Klebsiella pneumoniae} was the most prevalent cause of GNB-associated bloodstream infections. These bacteria are well-known nosocomial pathogens \cite{51} that cause ventilator-acquired pneumonia \cite{52} and are often multidrug-resistant organisms \cite{53}. \textit{Enterococcus faecium} was the most common cause of bacteremia in our study population. The bacterium is a rare but emerging upper and lower respiratory tract pathogen, causing sinuses, trachea, bronchi, lung and pleural infections, and may worsen the clinical outcome in patients with impaired immunity \cite{54}. Also, viral infection can alter the nasopharyngeal microbiota allowing bacteria in the nasopharynx to invade the lower respiratory tract and cause respiratory diseases and bacteremia\cite{55}.

We found that the male COVID-19 patients were significantly at risk of bacterial infection as compared to female patients, and this is consistent with other studies that found men to be at risk of having bacterial infections, consequently being severely ill and at increased risk of death\cite{46}\cite{56}\cite{57}. Patients admitted to the critical care unit (CCU) had a significantly higher risk of death, and the finding corroborates those of Patone et al. (2021)\cite{58} and Zali et al. (2020)\cite{59}. Prolonged length of hospital stay was significantly associated with increased patients mortality, similar to other study reports in Africa and Asia \cite{36}\cite{45}\cite{60}, where the finding was due to frequent use of mechanical ventilators, treatment involving the combination of steroids (e.g., dexamethasone) and other immune-modulatory agents (e.g., infliximab), especially in the elderly patients admitted to the critical care unit. Non-vaccinated COVID-19 were at increased risk of death compared with vaccinated ones, corroborating other study findings on the effectiveness of COVID-19 vaccines on hospitalization outcomes \cite{61}, \cite{62} \cite{63} and suggesting that the COVID-19 vaccines may attenuate disease severity among patients and reduce the risk of death thus the total benefits of vaccination exceed those estimated from the prevention of hospitalization alone. Elderly patients aged 60 years and above were also at increased risk of death compared with those aged between 25–40 years, similar to other study findings in COVID-19 across America and Asia \cite{46} \cite{49} \cite{64} \cite{65} and MERS patients\cite{66} \cite{67} \cite{68} whereby older age identified as an independent predictor of mortality in SARS and MERS pandemics. Age-dependent defects in T-cell and B-cell function and overproduction of type II cytokines could lead to a deficiency in the regulation of viral replication and prolonged inflammatory responses, possibly leading to poor outcomes \cite{68}.

Gram-negative bacteria (GNB) isolates were susceptible to Amikacin (AMK) but not Gentamicin (GEN), as opposed to Stephanini et al. (2020), who reported high resistance to amikacin among COVID-19 patients\cite{47}. Aminoglycosides contain a defensin-mediated antiviral activity that, through retrocyclins, boosts immunity against SARS-CoV-2\cite{69}. In this study, GNB resistant to beta-lactamase inhibitor-containing antibiotics, third-generation cephalosporins (cefotaxime and ceftriaxone), and fourth-generation cephalosporins, cefepime,
were isolated. All these antibiotics are used in severe pneumonia management, with a possibility of overprescription, hence limiting their efficacy [47]. *Acinetobacter calcoaceticus* was resistant to all antibiotic classes, a phenomenon also observed in Italy among COVID-19 patients[47] and also in the general population [[70][71]].

Gram-positive bacteria (GPB), except for one *S. aureus* isolate (17%), were resistant to erythromycin, an antibiotic with a similar spectrum of activity as Azithromycin, which was widely prescribed for COVID-19[72][73] management and overused as a repurposed drug in many African countries, possibly exerting a positive selection pressure hence the observed resistance in our study [72][73][74][34]. The rationale of increased prescription for antibiotics was to avert bacterial co-infections and to the fact that there has been no specific treatment for COVID-19. *Enterococcus faecalis* isolates showed 100% resistance to levofloxacin in the current study, corroborating other study findings that showed the ineffectiveness of fluoroquinolones in SARS-CoV-2 and MERS-CoV infections' management [47][75]. Consistent with Ayobami et al. (2022) and Huang et al. (2019)[76][77]. We found no vancomycin-resistant *E. faecalis* or *E. Faecium*. Therefore, the empirical cover for resistant Gram-positive pathogens (e.g., vancomycin) may not be warranted.

The majority of bacteria isolates (64.3%) were multidrug-resistant (MDR), attributable to GNB (69.6%), and this agrees with the findings of Saeed et al. (2021) [46], who reported a 65.8% MDR rate among the GNB in patients infected with SARS-CoV-2. In our study, the predominant MDR phenotypes were those observed in *Klebsiella pneumonia, Enterococcus cloacae complex*, and *Escherichia coli*, similar to those documented by Ramadan et al. (2020) in Egypt [45], were the pathogens carrying diverse antimicrobial resistance genes. Several studies, especially from the United States, Italy, and Germany, have reported increased bacterial infections with high multidrug-resistance rates during the COVID-19 pandemic [78][79][80]. Weak antimicrobial policies, allowing improper consumption of the World Health Organization (WHO) Watch and Reserve antibiotics category [30] and prolonged hospital stay [81], among other varying contextual factors as observed and documented in other LMICs[30][82], could be implicated in increasing resistance and are likely to exacerbate the antimicrobial resistance (AMR) menace[27][26][28]. The indiscriminate use of antibiotics in COVID-19 pandemics may promote the selection of resistant strains and is likely to exacerbate the antimicrobial resistance (AMR) menace[26] [27] [28]. High resistance of these pathogens insinuates a near-patient environmental source, indicating compromised hand hygiene besides non-adherence to device-related bundle care practices [30]. A possible additional cause of multidrug resistance is the wide use of biocidal agents for individual and environmental decontamination outside hospital settings because some biocides exposure can predispose resistance and heighten the risk of cross-resistance to many antibiotics, especially those that are effective in treating GNB [83]. We may have another pandemic of AMR on top of the COVID-19 pandemic, as reported in a recent report where AMR caused more than 30,000 deaths in Europe alone in the year 2020[79]. AMR has both health and economic blows, remarkably in low resource settings, where there is low availability and high costs of some of the laboratory tests routinely conducted in high-income countries to manage AMR [82]. We therefore highly recommend carrying out appropriate microbiological culture tests, testing for specific biomarkers, improved surveillance and antibiotic de-escalation in the spirit of supporting antibiotic stewardship. Antibiotics use should be highly discouraged not unless there is supported bacterial infection evidence or the presence of signs of haemodynamic instability.
Some limitations to our study is that, first, it was a monocentre study performed in a tertiary level hospital with potentially high dominance of MDR bacteria. Therefore, the AST profiles observed in our study may not be a representation of other hospitals, thus limiting the generalization of our findings. With this study, we aim to highlight the need for strengthening antimicrobial stewardship programmes especially during the COVID-19 pandemic. This study was also conducted at the peak of the COVID-19 wave when the infection rate was very high and the findings may allude that there was over-prescription of antibiotics at the time. In addition, most of the isolates were not from sterile sites, (respiratory tract specimens), and may be more of colonization which might be pathogenic when the immunity of the COVID-19 patients is compromised rather than true infection. Furthermore, it is well known that steroids (e.g. dexamethasone) and other immune-modulatory agents (e.g. infliximab) which may have been used in treating of COVID-19 patients, (though we did not manage to evaluate the impact of these agents in our study), have been known to predispose such patient to bacterial infections[40]. However, our study specifically focused on bacterial infections during hospitalization and assessed the risk factors of acquiring these infections among COVID-19 infected patients, and this may have underrated the incidence of fungal and other viral infections in COVID-19 infected patients unlike other studies, which described superinfections and co-infections in COVID-19 patients. In spite of these limitations, we put focus on a critical need to scale up and rally culture-based and rationalized antibiotic prescription practices in our IDU and the hospital at large. Our findings are imperative in outlining the role of antibiotic therapy and stewardship strategies in COVID-19 patients to attain optimal therapeutic outcomes in future waves and pandemics.

**Conclusion**

Our findings highlight a high prevalence of bacterial infections in hospitalized COVID-19 patients during the peak of the pandemic, with males more likely to be infected, while those in advanced age, not vaccinated, admitted to the critical care unit, and those with prolonged length of hospital stay showing a poor hospitalization outcome. The observed high multidrug-resistant infections are unacceptably high, emphasizing the need to monitor the effectiveness of the existing infection control strategies at KNH-IDU and adherence to antimicrobial stewardship in line with local and global AMR control action plans.

**Abbreviations**

COVID-19-Corona Virus 2019

SARS-COV-2- Severe Acute Respiratory Syndrome-Corona Virus 2

AMR-Antimicrobial Resistant

MDR-Multidrug Resistant

KNH-IDU-Kenyatta National Hospital –Infectious Disease Unit

IDU-CCU-Infectious Disease Unit-Critical Care Unit

ICU-Intensive Care Unit
GNB- Gram Negative Bacteria
GPB- Gram Positive Bacteria
ATCC- American Type Culture Collection
LRTI-Lower Respiratory Tract Infection
URTI-Upper Respiratory Tract Infections
BSI-Blood Stream Infections
NP/OP-Nasopharyngeal/ Oropharyngeal Swab

Declarations

Ethics approval and consent to participate

The study was approved by Kenyatta National Hospital-University of Nairobi Ethics Review committee (protocol Number: P236/04/21) and was performed in accordance with Helsinki declaration. Participant were required to give informed written consent through a close relative or legal representative. Parents and/or guardians gave permission on behalf of their children after the study was explained to them in English, or Swahili. Personal Identification Number (PIN) unique to each patient was assigned to all samples collected for anonymity and the information collected was confidential. There were no monetary gains for the study participants, and no penalties for those who declined to participate. Approval to carry out the study was sought from the hospital management (Ref: KNH/DLM/60/VOL.11/110) and National Commission for Science, Technology and Innovation (License No: NACOSTI/P/22/18891).

Consent for publication: Not applicable

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request

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**Figures**

(a) Types of bacterial infections

| Infection Type | Total Number |
|----------------|-------------|
| URTI/C         | 42          |
| LRTI           | 13          |
| Blood          | 12          |

(b) Spectrum of gram-negative bacteria

| Bacterial Species | Total Number |
|-------------------|--------------|
| *K. pneumoniae*   | 16           |
| *E. cloacae*      | 3            |
| *P. mirabilis*    | 3            |
| *E. coli*         | 5            |
| *A. baumannii*    | 5            |
| *A. calcoaceticus*| 1            |
| *S. marcescens*   | 1            |
| *S. aureus*       | 6            |
| *E. faecalis*     | 1            |
| *S. sciuri*       | 1            |

(c) Spectrum of gram-positive bacteria

| Bacterial Species | Total Number |
|-------------------|--------------|
| S. pneumoniae     | 33%          |
| S. aureus         | 6%           |
| E. faecalis       | 5%           |

**Figure 1**

Bacterial infections and their etiologies in COVID-19-positive patients admitted at KNH-IDU
COVID-19 - coronavirus disease-2019; URTIs/C - Upper respiratory tract infections/colonization; LRTIs - Lower respiratory tract infections; BSI - Blood stream infections

Figure 2

AMR profiles for gram-negative bacteria in COVID-19 patients to IDU at KNH

AMR - Antimicrobial resistant; AMC - Amoxicillin/Clavulanate; SAM - ampicillin/sulbactam; TZP - piperacillin/tazobactam; CTX - cefotaxime; CAZ - ceftazidime; CRO - ceftiraxone; FEP - cefepime; ATM - aztreonam; MEM - meropenem; AMK - Amikacin; GEN - gentamicin; CIP - ciprofloxacin; SXT - trimethoprim/sulfamethoxazole

Figure 3
AMR profiles for gram-positive bacteria in COVID-19 patients in KNH-IDU

AMR- Antimicrobial resistant; BP- Benzylpenicillin; ERY- erythromycin; LVX- levofloxacin; LZD- linezolid; TEC- teicoplanin; VAN-vancomycin; TET- tetracycline; TGC- tigecycline