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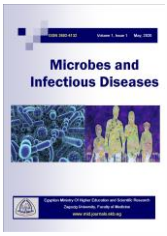

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Original article

Changes in antibiotic resistance before and during the COVID-19 pandemic: Laboratory surveillance study in a single Indonesian tertiary hospital

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ABSTRACT

Background: Antibiotic resistance is related to inappropriate empiric antibiotics, particularly during the COVID-19 pandemic. Limited information about changes in antibiotic resistance before and during the pandemic in Indonesia. This study aimed to describe changes in the prevalence of antibiotic resistance among patients with proven bacterial infections before and during the COVID-19 pandemic. **Methods:** A retrospective surveillance study was carried out to review culture and antibiotic susceptibility data among hospitalized patients diagnosed with sepsis and COVID-19 according to the ICD-10. In this context, the predefined periods were 1 January–31 December 2019 and 1 March 2020–31 December 2021. The result was the percentage of resistance to selected antibiotics among the study population, stratified by gram-bacterial isolates type, with the evaluation of changes in antibiotic resistance over time. **Results:** In this study, 596 adult patients were diagnosed with sepsis (before COVID-19), and 2786 were diagnosed with confirmed COVID-19 (during COVID-19). The rate of culture growth in patients with sepsis and COVID-19, with values of 51.6% and 29.2%, respectively. Gram-negative bacterial isolates were predominantly found in all observation periods, 41.2% - 47.3% of the adult middle-aged group. Changes in antibiotic resistance against Gram-negative bacteria were observed during COVID-19 (peak phase, above 20%) compared to the early phase. **Conclusions:** This study revealed that changes in antibiotic resistance before and during the COVID-19 pandemic affected both Gram-negative and Gram-positive bacteria. Therefore, implementing surveillance systems and antimicrobial stewardship programs are recommended for combatting antibiotic resistance.

Introduction

Antibiotic resistance (AR) is recognized as a public health threat and has received great attention due to its significant impact on mortality and increased economic burdens. The incidence is driven by inappropriate use of empiric antibiotics, which often occur in severe or critical situations, such as sepsis.[1] This life-threatening condition is associated with a dysregulated immune response to infection and leads to organ dysfunction. In 2020, the World Health Organization (WHO) reported that approximately 20% of global deaths were due to sepsis.[2] Subsequently, a new rapidly spreading respiratory disease, namely, COVID-19, was

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declared a global pandemic disease caused by severe acute respiratory coronavirus 2 (SARS-CoV-2).[3] Similar to sepsis, COVID-19 also results in a dysregulated immune response and organ dysfunction. Several factors have contributed to the use of antibiotics for treating COVID-19. These include (1) rapid progression of the disease, (2) limited information on disease management, and (3) difficulties in differentiating between COVID-19 and bacterial pneumonia.[4–8] Moreover, both sepsis and COVID-19 patients require long-term hospitalization and increasing the risk of hospital-acquired infections.[9,10] This suggests that the complex factor of sepsis and COVID-19 may contribute to the development of antibiotic resistance. To access the development of AR, surveillance of antibiotics has been identified as one of the strategy pillars for combatting resistance by the WHO. This strategy is essential for identifying local antibiotic situations and providing evidence for the development of empirical guideline therapies. Consequently, continuous monitoring is crucial, particularly in severe or critical situations, such as sepsis and COVID-19. This will help in clinician decision-making management to prevent inappropriate antibiotic use. Previous studies have reported the prevalence of antibiotic resistance during the COVID-19 pandemic.[11,12] However, limited information about antibiotic resistance changes among bacterial isolates before and during the pandemic, particularly in Indonesia. Therefore, a laboratory-based surveillance study was conducted at a single tertiary hospital, Dr. Hasan Sadikin Hospital (RSHS), to describe the changes in the prevalence of antibiotic resistance among bacterial isolates during the following time frames: (a) before the COVID-19 pandemic (2019), (b) early (2020), and (c) the peak phase (2021).

Materials and Methods

Study Design

A retrospective descriptive study was conducted to review the medical records of hospitalized patients diagnosed with sepsis and COVID-19 according to the International Classification of Disease 10th Revision (ICD-10). The predefined periods were 1 January–31 December 2019 and 1 March 2020–31 December 2021, while the study was conducted at a tertiary hospital, RSHS. This hospital is the main province hospital in the western part of Java Island, with a maximum capacity of 1000 bed inpatients. It acted as a referral hospital, but later during the pandemic, the status changed to a primary referral COVID-19 hospital.

The medical records were obtained and extracted from the hospital information system (Sistem Informasi Rumah Sakit Dr. Hasan Sadikin, Bandung, Indonesia) following the standard operating procedure. Subsequently, this list was merged with culture and antibiotic susceptibility test data from a laboratory information system (HCLAB Micro, Sysmex, Asia Pacific). Merged data were screened for population eligibility, and medical records were manually searched to select patients according to the inclusion and exclusion criteria. Baseline demographic data, including age, sex, type of ward, clinical outcome, bacterial species, and antibiotic susceptibility, were also collected as recommended from WHO Global Antimicrobial Resistance and Use Surveillance System (GLASS).[13]

Time Frame Before the Pandemic: Sepsis Population

The medical records of hospitalized patients diagnosed with sepsis according to the ICD-10 codes A40-A41.9 between 1 January and 31 December 2019 were identified, screened, and merged with culture data. The diagnosis of sepsis followed the Sepsis-3 consensus.[14] Merged data were retrospectively hand-searched to identify the inclusion/exclusion criteria. The inclusion criteria were as follows: (1) adult patients aged 18 years or older, (2) admitted to intensive or non-intensive wards, and (3) who submitted any clinical specimens (blood, sputum, or urine) during hospital admission for culture. The exclusion criteria were as follows: (1) had conditions, including HIV, malignancy, use of immunosuppressant drugs[15–17], or autoimmune diseases (systemic lupus erythematosus, rheumatoid arthritis)[18]; and (2) had commensal bacteria, namely, *Viridans group streptococci*, *Micrococcus* sp., and *Bacillus* sp., as well as fungi.[11,12,19]

Time Frame During the Pandemic: COVID-19 Population

Similar to the sepsis population, the medical records of hospitalized patients diagnosed with COVID-19 according to the ICD-10 code U70.1 between 1 March 2020 and 31 December 2021 were identified, screened, and merged with culture data. The diagnosis of COVID-19 followed the Indonesian Guideline of COVID-19.[20]

Subsequently, merged data were manually searched to identify the inclusion/exclusion criteria. The similar inclusion criteria were applied as time frame before the pandemic. The exclusion criteria were (1) patients who were rehospitalized during the same period and (2) patients with commensal bacteria, namely, *Viridans group streptococci*, *Micrococcus* sp., *Bacillus* sp., and fungi growing on clinical specimens.[11,12,19] Among the COVID-19 population, a specific time frame was applied and categorized into three periods according to demographic distribution by the Indonesian Ministry of Health [20,21]: (1) the early phase, 1 March–30 November 2020; (2) the peak phase, 1 December 2020–30 June 2021; and (3) the late phase, 1 July–31 December 2021.

Cumulative Antibiotic Resistance Report

The clinical specimen collection procedure for the study population followed the hospital laboratory protocol and WHO recommendations.[19] Bacterial identification and antibiotic susceptibility testing (AST) were performed using an automatic microbiology analyzer (Vitek2 Compact, Biomerieux, France). The protocol followed the WHO and Clinical and Laboratory Standards Institute (CLSI) guidelines.[19,22] To fulfill the surveillance report according to the WHO recommendation, the dedicated software WHONET 5.6 (WHO Collaborating Centre for Surveillance of Antimicrobial Resistance, Boston, USA) was used to produce the cumulative reports of organisms and ASTs. This includes the surveillance rules according to the WHO GLASS.[13,22] The antibiotics reported in this study were selected based on the American Thoracic Society Guidelines for Pneumonia and CLSI Guidelines for Gram-negative (GNB) and Gram-positive bacteria (GPB).[23,24] The antibiotics used for GPB were ampicillin/sulbactam, ceftriaxone, ciprofloxacin, gentamicin, oxacillin, and vancomycin. Moreover, the antibiotics used for GNB were amikacin, ampicillin/sulbactam, aztreonam, cefepime, ceftriaxone, ceftazidime, ciprofloxacin, gentamicin, and meropenem. In this study, antibiotics with intermediate results were interpreted as resistant. The selected antibiotic resistance percentage was considered high when it was equal to or greater than 20%.[25]

Data Analysis

The data were entered into Microsoft Excel 2013 (Microsoft Corp.) and merged using the statistical software STATA 12.0 (Stata, Texas, USA). The characteristic data were categorized into age groups according to Peng et al.[26] The type of ward was categorized into intensive and nonintensive, while clinical outcome was classified into surviving and nonsurviving. The prevalence of resistance to selected antibiotics among the study population was defined as the percentage of bacteria tested, stratified by gram-bacteria type and time (before, during the early, and peak phases of COVID-19) with changes over time. Patient characteristics and cumulative antibiotic resistance results were summarized as frequencies and percentages using STATA 12.0 and WHONET 5.6.

Ethical approval and consent to participate

This study was conducted under the Declaration of Helsinki, and the study protocol was approved by the Ethics Committee of Dr. Hasan Sadikin General Hospital (LB.02.01/X.6.5/94/2022). Informed consent was not required to obtain data from the hospital or laboratory information system. Therefore, the ethics committee waived the need for written patient consent and participation in this study.

RESULTS

Population characteristics

During the study, 596 adult patients were identified as having sepsis (before the pandemic), and 2786 were confirmed to have COVID-19 (during the pandemic). In the sepsis population, 77.7% (463 specimens) were submitted for culture, while only 26.3% (732 specimens) were submitted for culture in the COVID-19 population. The percentage of positive bacterial cultures in the sepsis population was greater than that in the COVID-19 population, with values of 51.6% and 29.2%, respectively. GNB isolates were predominantly found during the observation period (**Figure 1**). Overall, 41.2% - 47.3% of the adult patients were in the middle-aged group. In contrast, the occupancy of intensive care for patients with positive bacterial cultures was low during the COVID-19 pandemic, at 12.6%, 19.2%, and 23.6% in the early, peak, and late phases, respectively. This also corresponded with the survival rate among this population, ranging from 82.4% - 95.8%, which was categorized as surviving and discharged from hospitalization (**Table 1**).

Bacterial identification profiles

GNB were predominantly observed before and during the COVID-19 pandemic. Critical priority bacteria, including *Klebsiella pneumoniae*

(31.7%, 531 out of 1673 GNB isolates), *Acinetobacter baumanii* (20.3%, 340 out of 1673 GNB isolates), and *Pseudomonas aeruginosa* (10.8%, 180 out of 1673 GNB isolates), were commonly identified among both populations as the etiology of infection. Environmentally related GNB, such as *Stenotrophomonas maltophilia* and *Burkholderia cepacia*, were more commonly found during the COVID-19 pandemic than during the previous period. Moreover, coagulase-negative Staphylococci (48.5%, 161 out of 331 GPB isolates) were the predominant bacteria among both populations. *Streptococcus* sp. was more commonly identified during the COVID-19 pandemic than during the previous period. In general, there were no changes in the distribution of bacterial pathogens before or during the COVID-19 pandemic, particularly in GNB, the most common pathogen in hospital settings (**Figure 2**).

Changes in Antibiotic Resistance

Based on the results, there were changes in antibiotic resistance against GNB based on the time frame before and during COVID-19 (**Table 2**). Before the pandemic, there was high-range resistance among GNB isolates (above 20%), except for amikacin (16.7%). In the early phase of COVID-19, the percentage of bacterial isolates with antibiotic resistance decreased compared with that in the previous period, particularly for primary empirical pneumonia treatment. This effect was detected for cephalosporin (35.4-68.1% vs 27.8-43.8%), beta-lactam combinations (36.8-68.7% vs 26.8-52.5%), fluoroquinolone (58.3% vs 28.9%) and monobactam (63.2% vs 20.4%). Subsequently, elevated resistance to beta-lactam combinations (28.6-56.8% vs 26.8-52.5%), antipseudomonal cephalosporins (ceftazidime, 34.7% vs 26.8%; cefepime, 27.8% vs 30.6%), fluoroquinolone (38.9% vs 41.9%), monobactam (20.4% vs 29.9%) and carbapenem (26.4% vs 27.1%) was detected among GNB strains during the peak phase compared to the early phase. In the late phase, high resistance against GNB was observed, particularly to restricted intravenous broad-spectrum antibiotics such as ceftazidime, cefepime, piperacillin-tazobactam, amikacin, and meropenem. The lowest prevalence of extended-spectrum beta-lactamases (ESBLs) among GNB occurred in the early phase of COVID-19 (20.4%). Moreover, increasing carbapenem resistance among GNB strains was recorded throughout the study period, ranging between 22.9% and 47.2%.

In the GPB, the greatest changes in antibiotic resistance were found in the late phase of COVID-19 (above 70%), except for vancomycin (0%) (**Table 3**). The resistance of GNB to fluoroquinolone (ciprofloxacin) ranged from 56.8% to 87.5% before and during the COVID-19 pandemic. Furthermore, increased resistance to oxacillin, a surrogate marker for methicillin-resistant staphylococci, particularly coagulase-negative staphylococci, was observed during the peak and late phases of COVID-19, with values of 70.8% and 100%, respectively. Vancomycin resistance against GPB was low, ranging between 0% and 1.1%.

Table 1. Patient Characteristics Based on Submitted Specimens.

Variable	Before COVID-19 n=239		During COVID-19 n=214					
			Early Phase n=78		Peak Phase n=119		Late Phase n=17	
	n	%	n	%	n	%	n	%
Age Group								
Young Age	6	2.5	5	6.4	12	10.1	2	11.8
Adult	48	20.1	17	21.8	19	15.9	0	0.0
Middle Age	113	47.3	35	44.8	65	54.6	7	41.2
Old Age	72	30.1	21	27.0	23	19.4	8	47.0
Ward Type								
Intensive	132	55.2	15	19.2	15	12.6	4	23.5
Nonintensive	107	44.8	63	80.8	104	87.4	13	76.5
Clinical Outcome								
Surviving	94	39.3	71	91.0	114	95.8	14	82.4
Nonsurviving	145	60.7	7	9.0	5	4.2	3	17.6

Notes: n, number of patients based on the submitted specimen; %, percentage; young age, 18-25 years; adult, 26-44 years; middle-aged, 45-59 years; old age, 60 years; before the pandemic, 1 January–31 December 2019; early phase, 1 March–30 November 2020; peak phase, 1 December 2020–30 June 2021; late phase, 1 July–31 December 2021.

Table 2. Percent antibiotic resistance of GNB before and during COVID-19 pandemic.

Antibiotic Class	Antibiotic Agent	Before COVID-19		During COVID-19					
		2019		2020		2021			
				Early Phase		Peak Phase		Late Phase	
		n= 144		n= 232		n= 1096		n= 201	
		n	%R	n	%R	n	%R	n	%R
Beta-lactam combination	Ampicillin-Sulbactam	144	68.7	232	52.5	1096	56.8	201	37.5
	Piperacillin-Tazobactam	144	36.8	232	26.8	1096	28.6	201	43.4
Cephalosporin	Ceftriaxone	144	68.1	232	43.8	1096	43.1	201	36.6
	Ceftazidime	144	48.6	232	34.7	1096	36.8	201	39.6
	Cefepime	144	35.4	232	27.8	1096	30.6	201	49.1
Monobactam	Aztreonam	144	63.2	232	20.4	1096	29.9	201	52.9
Fluoroquinolone	Ciprofloxacin	144	58.3	232	38.9	1096	41.9	201	37.7
Aminoglycoside	Amikacin	144	16.7	232	9.7	1096	15.5	201	77.4
	Gentamicin	144	42.4	232	31.9	1096	34.9	201	41.5
Folate pathway antagonist	Trimethoprim-sulfamethoxazole	144	55.6	232	22.1	1096	35.0	201	55.6
Carbapenem	Meropenem	144	22.9	232	26.4	1096	27.1	201	47.2

Notes: n, number of isolates tested for a certain antibiotic; %R, percentage of antibiotic resistance; before the pandemic, 1 January–31 December 2019; early phase, 1 March–30 November 2020; peak phase, 1 December 2020–30 June 2021; late phase, 1 July–31 December 2021.

Table 3. Percent antibiotic resistance of GPB before and during the COVID-19 pandemic.

Antibiotic Class	Antibiotic Agent	Before COVID-19		During COVID-19					
		2019		2020		2021			
				Early Phase		Peak Phase		Late Phase	
		n= 95		n= 59		n= 136		n=42	
		n	%R	n	%R	n	%R	n	%R
Beta-lactam combination	Ampicillin-Sulbactam	95	60.0	59	61.1	136	64.5	42	100
Fluoroquinolone	Ciprofloxacin	95	56.8	59	70.6	136	77.4	42	87.5
Cephalosporin	Ceftriaxone	95	63.2	59	30.0	136	42.5	42	72.7
Folate pathway antagonist	Trimethoprim-sulfamethoxazole	95	43.2	59	46.7	136	37.5	42	85.7
Penicillin	Oxacillin	95	65.3	59	64.3	136	70.8	42	100
Aminoglycoside	Gentamicin	95	38.9	59	31.2	136	35.7	42	85.7
Glycopeptide	Vancomycin	95	1.1	59	0.0	136	0.0	42	0.0

Notes: n, number of isolates tested for a certain antibiotic; %R, percentage of antibiotic resistance; before the pandemic, 1 January–31 December 2019; early phase, 1 March–30 November 2020; peak phase, 1 December 2020–30 June 2021; late phase, 1 July–31 December 2021

Figure 1. Study flowchart. Notes: ($), number of submitted cultures from any clinical suspicion, including blood, urine, sputum; (*), multiple isolates can be identified among submitted specimens.

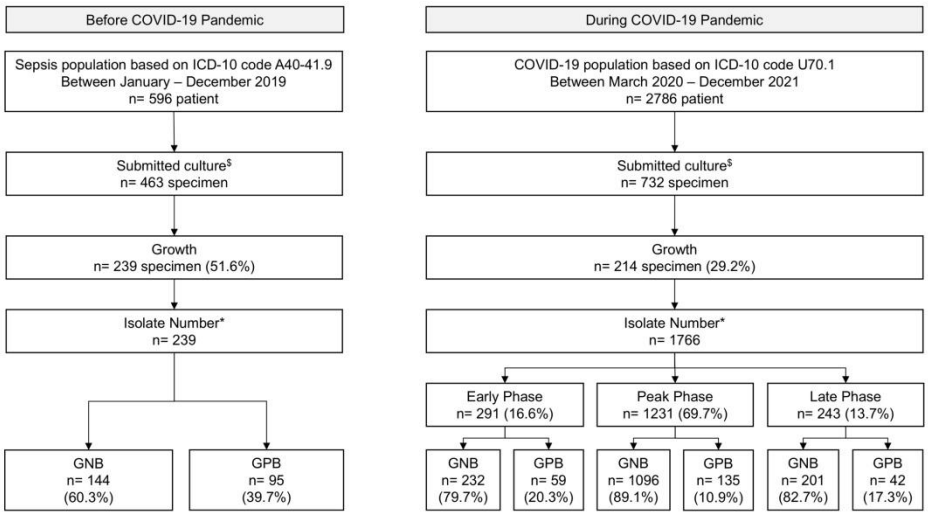
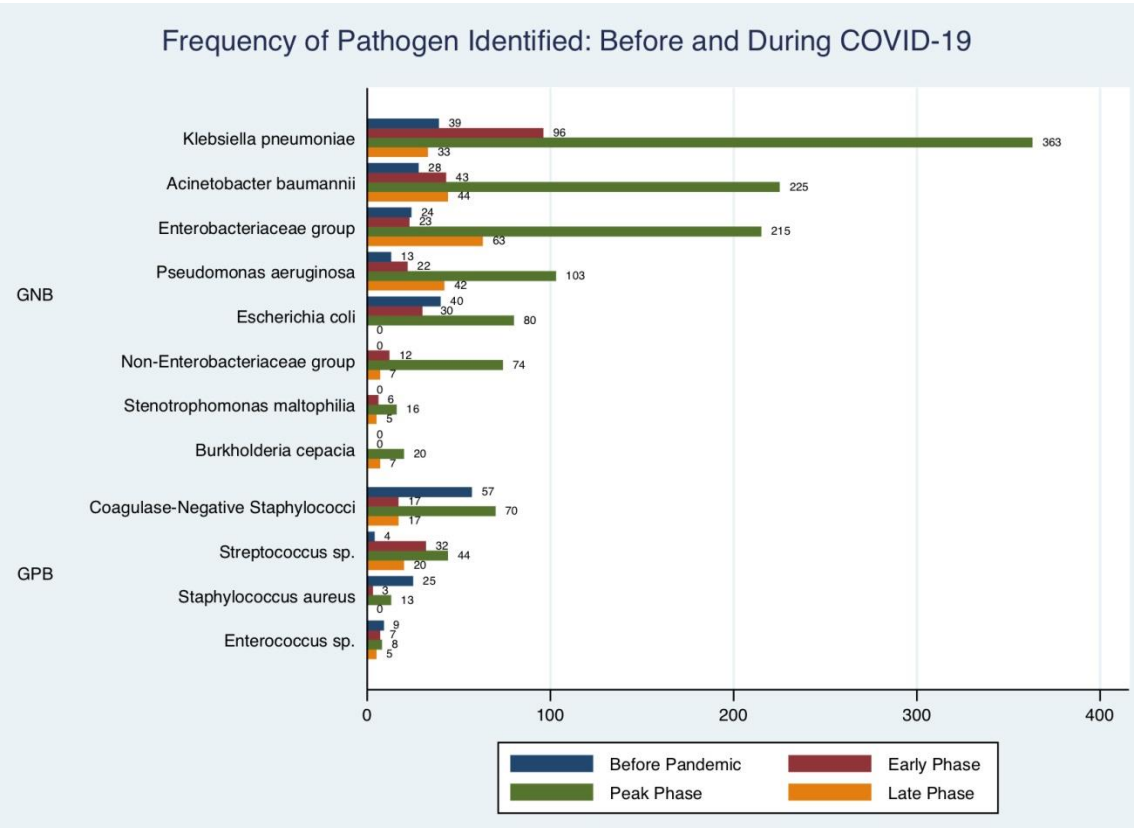


Figure 2. Bacterial distribution. Notes: before the pandemic, 1 January–31 December 2019; early phase, 1 March–30 November 2020; peak phase, 1 December 2020–30 June 2021; late phase, 1 July–31 December 2021; x-axis, number of isolates identified; y-axis, organism identified stratified by Gram type.



Discussion

The COVID-19 pandemic has sparked global concern and raised awareness about antibiotic resistance. This study revealed changes in antibiotic resistance before and during the COVID-19 pandemic. These changes can be influenced by several factors, including health regulation, antibiotic usage, health workers, and hospital equipment, as reported previously.[9] In the early phase of COVID-19, the lowest prevalence of antibiotic resistance was observed against several GNB isolates compared to other phases. During this phase, several health regulations were established, including social restrictions, self-awareness, hand hygiene, and the use of medical masks. These regulations were deemed effective for reducing the transmission of infection and mitigating the spread of multidrug-resistant organisms, particularly in the hospital setting. [10,27] As the pandemic progressed, national or international guidelines for COVID-19 were published, recommending the use of antibiotics for patient management.[28,29] The empirical use of antibiotics has impacted and driven increasing resistance, as observed in the peak and late phases. However, this is unavoidable since COVID-19 is a risk factor for the development of healthcare-associated infections (HAIs) and multidrug-resistant (MDR) pathogens. Prolonged hospital stays and increased usage of equipment also contributed to the development of HAIs. These complex factors collectively contribute to the development of multidrug-resistant bacteria, which leads to treatment failure and increased mortality.[11] However, issues with HAI were already present before the pandemic, as observed in the sepsis population. Both populations in this study showed a similar frequency of bacteria identified across all periods, with GNB, including *Klebsiella pneumoniae, Acinetobacter baumanii, Escherichia coli, and Pseudomonas aeruginosa*, as the critical priority of hospital-associated pathogens.[30] Environmental related GNB, such as *Stenotrophomonas maltophilia* and *Burkholderia cepacia*, were also detected. The GPB, Coagulase-negative staphylococci, also become important bacteria isolates identified in both population, since this group act as reservoirs genes facilitating MRSA infection.[31,32]

Although limited information was provided for this surveillance study, the age group of patients for both populations was recorded. The occurrence of bacterial isolates was likely in the middle-aged and older groups among the sepsis and COVID-19 populations. The aging of the immune response, or immunosenescence, is the dysregulated state of an aged immune system, including short-lived memory responses, a defective response to new antigens, a greater disposition of autoimmunity, and the development of chronic low-grade systemic inflammation. As described in a previous study [33], both sepsis and COVID-19 resulted in severe inflammation associated with the activation and proliferation of lymphocytes, including cytotoxic T and natural killer cells. This reaction is related to the general immune response to viral infection or to neutrophil activation and recruitment during bacterial infection. Subsequently, with the secretion of antibodies or cytokines/lymphokines (interferon), the immune system eliminates the infected cell and performs viral clearance.[33] Immunosenescence enhances the severe dysregulation of immune responses, leading to a severe hyperinflammatory state. This state also facilitates the type of bacteria, as reported in a previous study. Based on previous study results, more severe responses were observed in GNB sepsis patients than in GPB sepsis patients because lipopolysaccharide may induce alterations in complement protein levels.[34] Moreover, in this age group, an impaired immune response contributes to the development of antibiotic resistance. This hypothesis has been shown in a previous study indicating that a synergism between the immune response and antibiotic drug concentrations reduces the development of resistance to the pathogen. For example, in situations where resistance has not yet developed at the beginning of the treatment period, an immune response helps to eradicate and minimize the chance of creating a resistant pathogen. Correspondingly, an impaired immune response creates selective pressure and leads to the development of resistant pathogens.[35–37]

This study also revealed rapid changes in the resistance to meropenem and oxacillin, which serve as surrogate markers for carbapenem-resistant GNB and methicillin-resistant GPB, respectively. As reported previously, there has been an increase in MDR pathogens, including carbapenem-resistant *Acinetobacter baumanii* (CRAB), ESBL-producing *Enterobacterales*, carbapenem-resistant *Enterobacterales* (CRE), MDR *Pseudomonas* sp. and methicillin-resistant *Staphylococci*.[9,34] The surge in COVID-19 admissions, many of which require mechanical ventilation, suggests the

occurrence of MDR outbreaks. Furthermore, the lack of up-to-date guidance, shortage of personnel-protective equipment, lack of infection prevention due to increased workload, and decreased time for patient care caused by healthcare personnel shortages have contributed to rapid changes in resistance. Previous studies also reported the time lag between antibiotic use and the increase in the number of resistant pathogens among hospitalized patients. Data obtained across all pathogens (GNB or GPB) showed that the development of antibiotic resistance tends to occur over 0 to 6 months following exposure to antibiotics.[38] Therefore, the data agreed with the rapid changes in antibiotic resistance before and during the COVID-19 pandemic.

There are several limitations of the study. First, the potential for selection bias for both populations was unavoidable due to the use of a laboratory-based surveillance approach.[17] The clinical-symptom diagnosis approach was adapted and used as part of laboratory surveillance based on a previous study to minimize selection bias.[39] However, the selection of a culture based on clinician decisions may still introduce bias to this study. Second, due to the limited information available, antibiotic resistance was not stratified into other categories, including disease severity, type of infection (community or hospital-onset), hospital equipment use such as mechanical ventilation, and urinary catheterization. Third, this study was designed as a surveillance report; hence, statistical analysis to measure the effect of changes in antibiotic resistance could not be performed.

Conclusion

In conclusion, this study revealed changes in antibiotic resistance before and during the COVID-19 pandemic for both GNB and GPB. High antibiotic use and age-related immune response (immunosenescence) may contribute to these rapid changes. This underscores the need for strengthened recommendations in combatting HAIs and MDR pathogens. These recommendations included (1) having a sustainable antibiotic resistance and antibiotic usage surveillance system at the local (hospital) and national levels (country), (2) continuous monitoring for prevention infection programs, together with antimicrobial stewardship programs in the hospital, and (3) enhancing knowledge and skills among healthcare personnel about HAI and MDR pathogens, as well as treatment options.

List of abbreviations

World Health Organization (WHO); severe acute respiratory coronavirus 2 (SARS-CoV-2); Dr. Hasan Sadikin Hospital (RSHS); International Classification of Disease 10th Revision (ICD-10); antibiotic susceptibility testing (AST); Clinical and Laboratory Standards Institute (CLSI); Global Antimicrobial Resistance and Use Surveillance System (GLASS); Gram-negative bacteria (GNB); Gram-positive bacteria (GPB); healthcare-associated infections (HAI); multi-drug resistance (MDR); carbapenem-resistant *Acinetobacter baumanii* (CRAB); carbapenem-resistant *Enterobacterales* (CRE)

Declaration of interests and Funding information

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Authors' contributions

All the authors have made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted.

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