Prevalence of Antimicrobial Resistance of *ESKAPE* Pathogens before and during Pandemic COVID-19 Pandemic in a University Affiliated Hospital in Tangerang, Indonesia

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Abstract

Introduction: Antimicrobial resistance is the most important health problems currently. Antibiotic prophylaxis to prevent bacterial co-infections in hospitalized COVID-19 patients, and lack of surveillance were associated with antimicrobial resistance. *ESKAPE* pathogens consisting of *E. faecium*, *S. aureus*, *K. pneumoniae*, *A. baumanii*, *P. aeruginosa* and *Enterobacter* spp. are associated with healthcare-associated infections. **Patients and Methods:** This descriptive, retrospective, longitudinal study aims to describe the resistance rates of bloodstream infection due to *ESKAPE* pathogens from patients admitted in Siloam Hospital Karawaci, before and during COVID-19 pandemic (January 1st, 2019 until December 31st, 2022). Out of 296 *ESKAPE* pathogens collected from blood samples, *S. aureus* was the most frequent species, followed by *K. pneumoniae*, *A. baumannii*, *P. aeruginosa*, *Enterobacter* spp., and *E. faecium*. **Results:** Resistance rates of *E. faecium* were alarmingly high from 2019 until 2021, but in 2022 no sample was found. Resistance rates of *S. aureus* and MRSA decreased from 2019 until 2021 and then increased again in 2022 while for *K. pneumoniae* it peaked in 2020 and reached the lowest in 2022. Resistance pattern of *A. baumanii* was not favorable from 2019 until 2021, but decreased dramatically in 2022. Resistance pattern of *P. aeruginosa* was quite variable in 2021 and 2022 while for *Enterobacter* spp. it was variable in 2020 to 2022. **Conclusion:** The COVID-19 pandemic affected the antimicrobial resistance pattern of *ESKAPE* pathogens in Banten province, Indonesia. Resistance rates increased as the pandemic peaked in 2020 to 2021, and decreased as the pandemic resolves in 2022.

1. Introduction

One of the most important health problems currently is antimicrobial resistance [1]. The emergence of the COVID-19 pandemic could seriously impact the development of antibiotic resistance worldwide. Antibiotic use has further increased in the time of COVID-19 pandemic. Many COVID-19 treatment guidelines have incorporated antibiotic prophylaxis to prevent bacterial co-infections in hospitalized COVID-19 patients [1]. In the midst of chaotic COVID-19 pandemic, the inappropriate use of antibiotic and the lack of attention to surveillance could worsen the situation of antimicrobial resistance [2] [3]. The increased prevalence of resistant bacterial infections such as methicillin-resistant *Staphylococcus aureus* (MRSA) in the previous severe acute respiratory syndrome (SARS) epidemic in 2003 was an example that situation could deteriorate further due to healthcare-associated infections by multidrug-resistant microorganisms [1]. A review stated that every year more than two million infections associated with antimicrobial resistance, causing 29,000 deaths occur in the United States, with costs more than 4.7 billion US Dollars [3].

The *ESKAPE* pathogens consisting of *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumanii*, *Pseudomonas aeruginosa* and *Enterobacter* spp. were designated as priority status by World Health Organization in 2017 as these organisms has the capability to escape the bactericidal action of antibiotics [4]. The *ESKAPE* pathogens are major etiology of healthcare-associated infections around the world, which cause serious and usually fatal human infections [3]. The data before and after COVID-19 pandemic are necessary to assess the impact of the pandemic on antimicrobial resistance [1]. This study aims to describe the rates of bloodstream infection due to *ESKAPE* pathogens and their resistance pattern in Siloam Hospital Karawaci, the teaching hospital for Faculty of Medicine, Pelita Harapan University before and after COVID-19 pandemic, from the year 2019 to 2022.

2. Materials and Methods

2.1. Design and Setting

The descriptive, retrospective, longitudinal study assesses the rates of bloodstream infection due to *ESKAPE* pathogens and their resistance pattern. Samples were collected from blood of patients admitted in Siloam Hospital Karawaci, Banten Province, Indonesia, from the January 1st, 2019 until December 31st, 2022. This is the teaching hospital for Faculty of Medicine, Pelita Harapan University. This hospital did not care for COVID-19 patients during the pandemic.

Bacterial cultures and antibiotic resistance were performed using an automated VITEK® system (Bio-Mérieux) [5]. Resistance to antibiotics was evaluated based on the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and the Clinical and Laboratory Standard Institute (CLSI) and the definition of multidrug resistance (MDR) was according to the European Centre for Disease Prevention and Control (ECDC). MDR bacteria are bacteria with resistance to more than 1 antibiotics in more than 3 different classes [6].

2.2. Data Analysis

The data of antibiotic susceptibility tests were collected to determine the absolute number of resistant and its rate out of the total number of tests performed on the species in that year. Analysis and plot of the result were created using Microsoft Excel 2016 software (Microsoft Corp., Redmond, WA, USA).

3. Results

3.1. Bacterial Species According to Calendar Years

Out of the 296 *ESKAPE* pathogens from blood samples obtained, *S. aureus* was the most frequent species (37.8%), followed by *K. pneumoniae* (31.4%), *A. baumannii* (13.9%), *P. aeruginosa* (8.8%), *Enterobacter* spp. (5.1%), and *E. faecium* (3.0%). In 2019 and 2022 *S. aureus* was the most frequent species (45.6% and 45.7%), and in 2020 and 2021 *K. pneumoniae* was the most frequent species (36.4% and 30.0%), while least frequent species in 2019, 2020, 2022 was *E. faecium* (1.9%, 2.6%, 0.0%) and in 2021 was *Enterobacter* spp. (4.3%) (**Figure 1**).
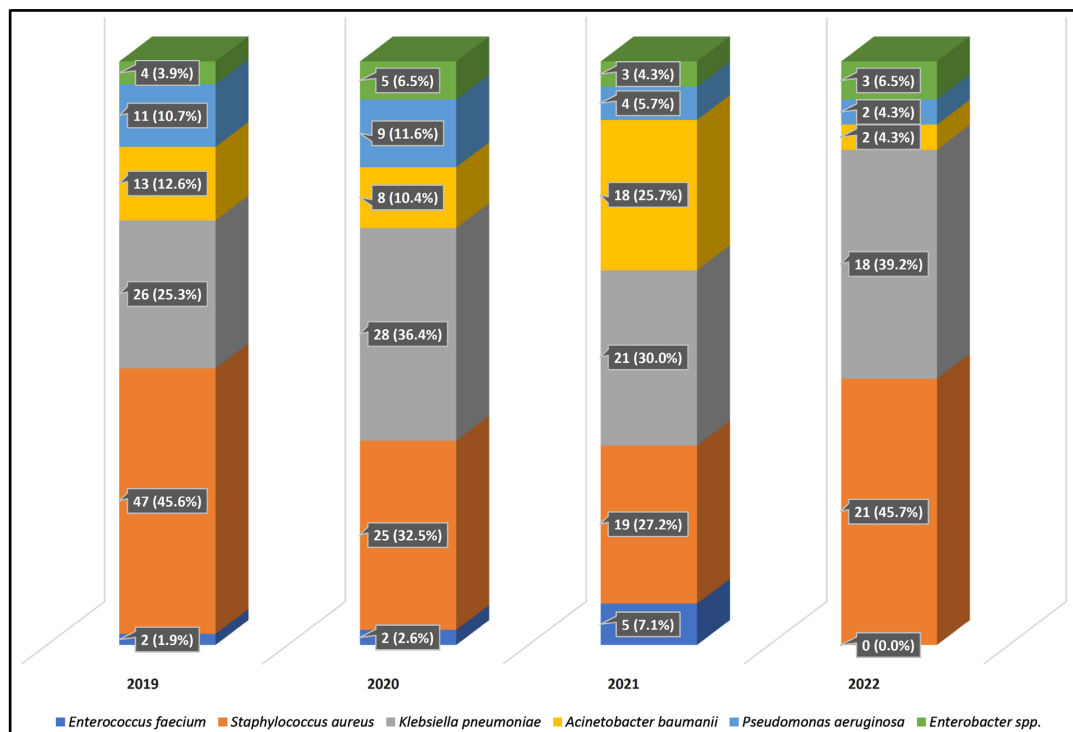

Figure 1. Distribution of *ESKAPE* pathogens from 2019-2022.

## 3.2. Resistance Patterns per Pathogen According to Calendar Years

In the case of *E. faecium*, the resistance rates against penicillin-beta lactamase inhibitor, aminoglycoside, and trimethoprim sulfamethoxazole were high and increased from 2019 until 2021 (50.0% - 80.0%). The resistance rates against quinolone were also high but they increased from 2019 (50.0%) to 2020 (100.0%), then decreased in 2021 (80.0%). The resistance rates against nitrofurantoin and tigecycline were 0.0% from 2019 to 2021. The vancomycin resistance was only noted in 2020 (50.0%). In 2022, no sample of *E. faecium* was found (**Figure 2(a)**).

For *Staphylococcus aureus*, the resistance rates against penicillin-beta lactamase inhibitor, 3rd generation cephalosporin, quinolone, aminoglycoside, trimethoprim sulfamethoxazole, fosfomycin decreased from 2019 (12.8% - 3.4%) until 2021 (0.0%) and then increased again in 2022 although lower than 2019 (9.5% - 14.3%). The resistance rates of MRSA were similar against penicillin-beta lactamase inhibitor during the four-year study. As for imipenem and meropenem, the highest resistance rates occurred in 2021, and the lowest were in 2022. Resistance against ertapenem was the highest although the rates decreased from 2020 until 2022 (68.0% - 28.6%). For tigecycline the resistance rates quite similar throughout 2019 until 2022 4.0% - 6.0%) (**Figure 2(b)**).

The resistance rates for *K. pneumoniae* against penicillin-beta lactamase inhibitor, 3rd generation cephalosporin, quinolone, aminoglycoside, trimethoprim sulfamethoxazole, meropenem and ertapenem peaked from 2019 to 2020, then decreased in 2021 and reached the lowest in 2022. Resistance against imipenem and tigecycline were quite similar throughout 2019 until 2022 (3.6% - 5.6% and 9.5% - 15.4%). Resistance against fosfomycin decreased from 2019 until 2022 (15.4% - 0.0%) (**Figure 2(c)**).

Resistance pattern of *A. baumanii* was not favorable for most antimicrobials from 2019 until 2021, as the rates were above 50.0%, with the exception of tigecycline. The resistance rates peaked from 2019 to 2020, then decreased in 2021, and reached 0.0% in 2022 in most antimicrobials. Resistance rates against ertapenem were decreasing from 2019 until 2022, but it was still high (50.0%) (**Figure 2(d)**).

In the case of *P. aeruginosa*, the resistance pattern was quite variable. The resistance rates against piperacillin/tazobactam increased from 2019 to 2020 and then decreased to 0.0% in 2021 and 2022. The resistance rates against ceftriaxone could only reach 50.0% in 2021, but they were very high in other year (88.9% - 100.0%). The resistance rates against aminoglycoside and quinolone decreased from 2019 until 2021 and reaching as low as 0.0% in 2022. The resistance against imipenem and meropenem decreased from 2019 until 2022, reaching as low as 0.0%. On the other hand, the resistance against ertapenem was increased from 2019 until 2022, reaching 100.0%. Against tigecycline, the resistance rates were even worrying, reaching 100.0% except in 2020 (88.9%) (**Figure 2(e)**).
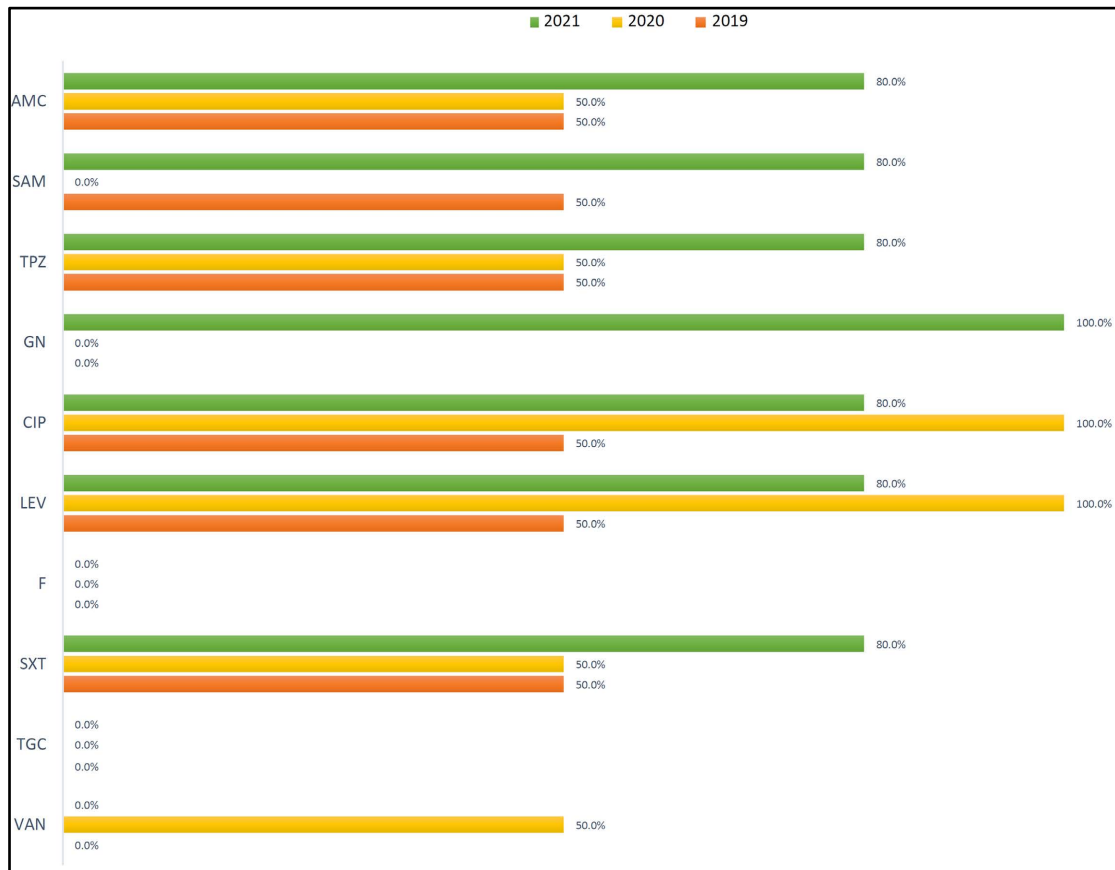
(a)
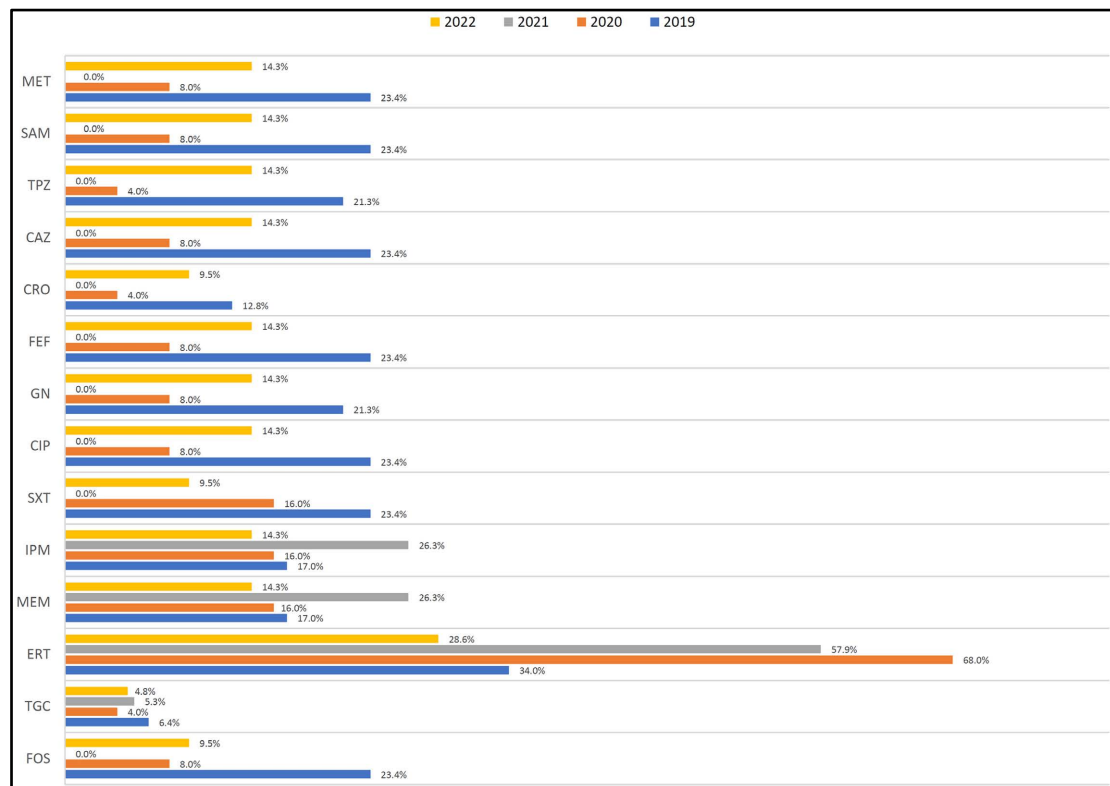
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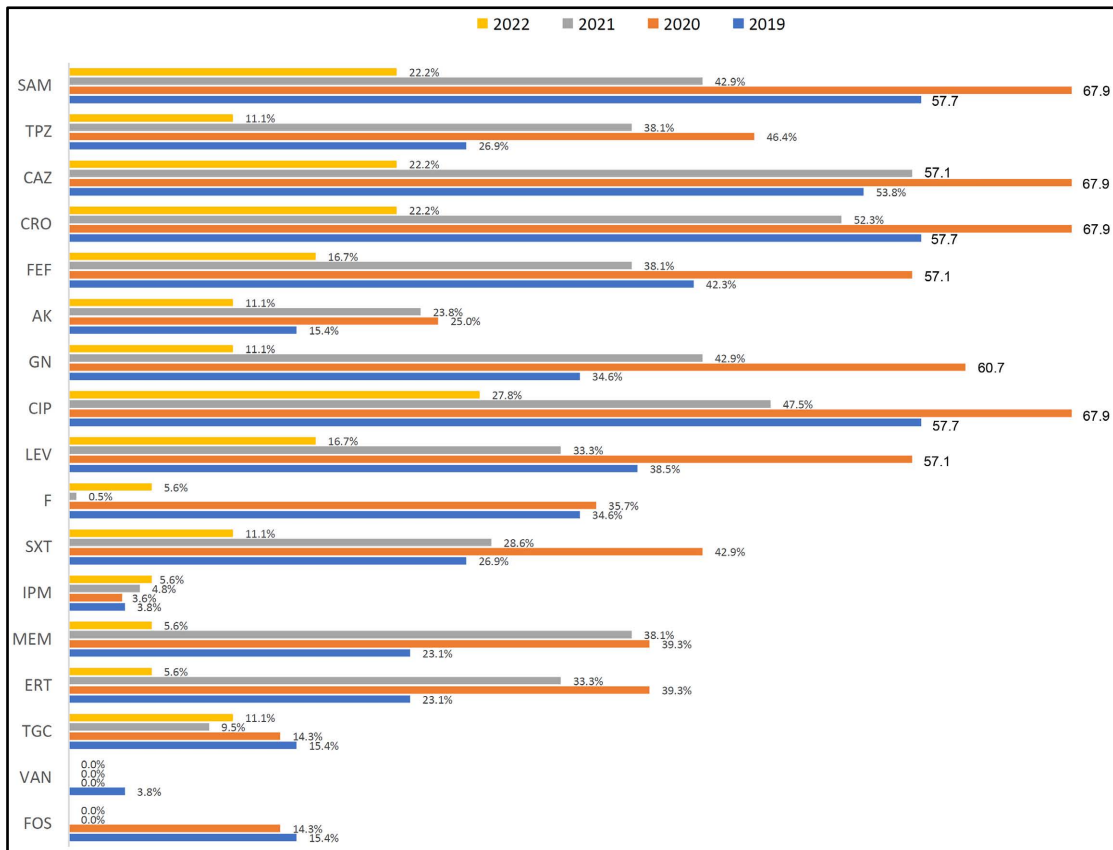
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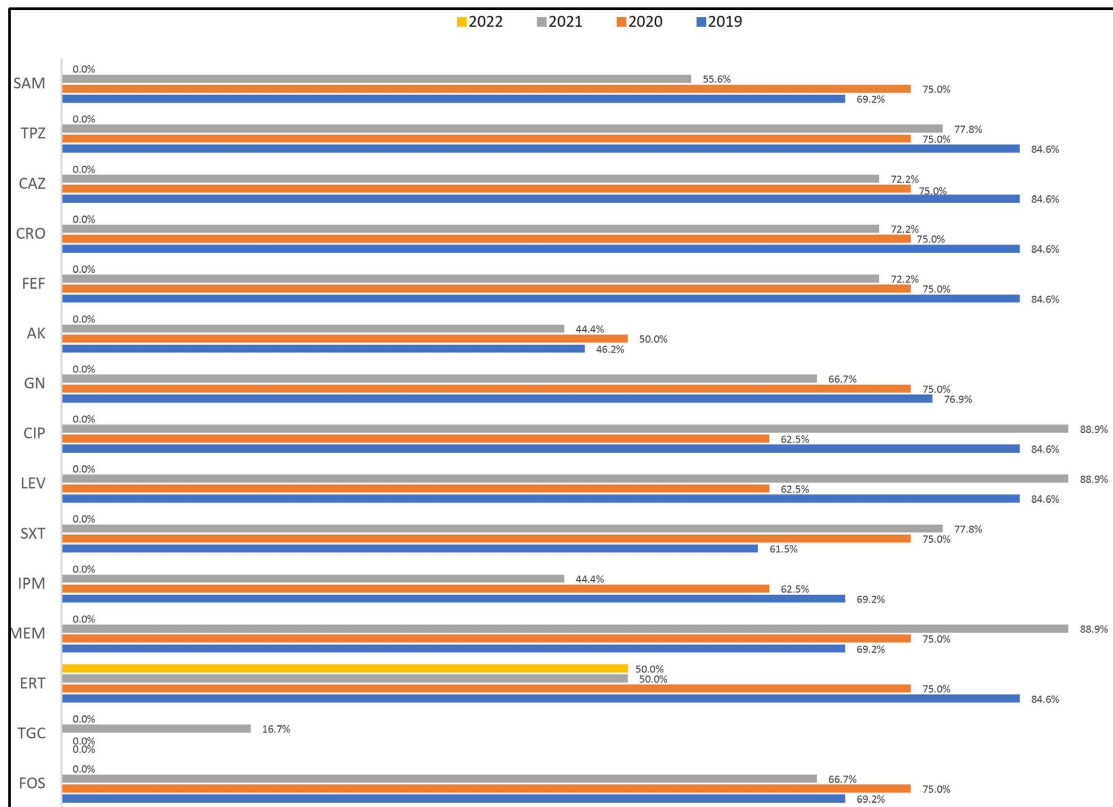
(d)
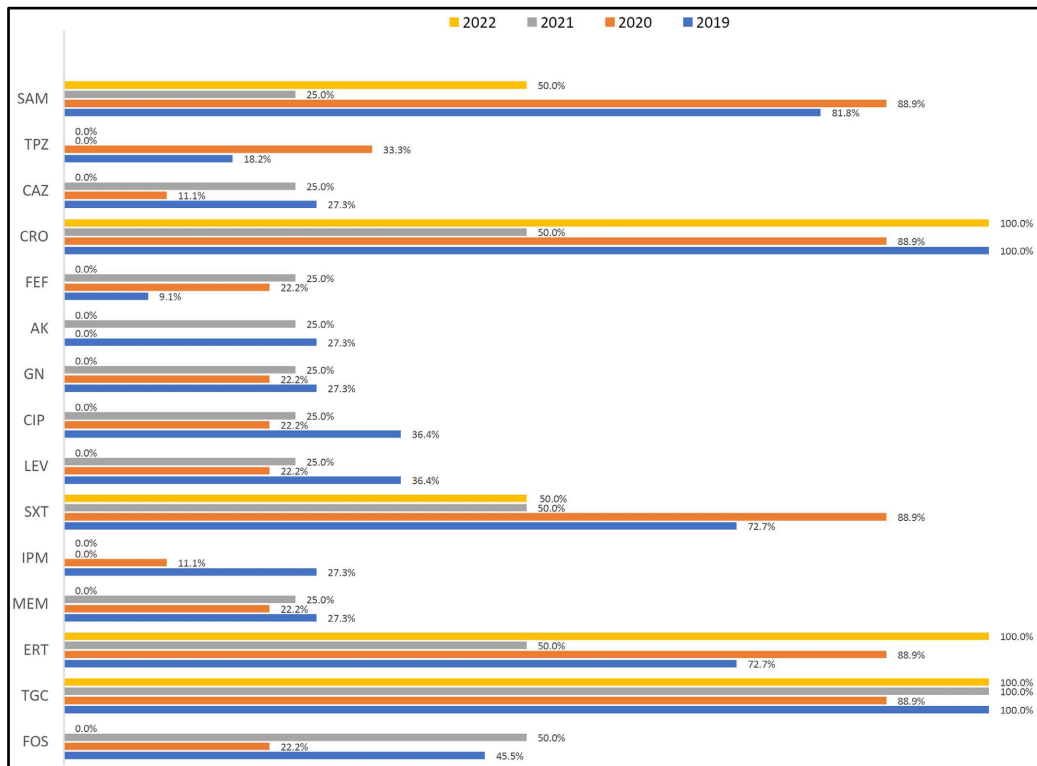
(e)
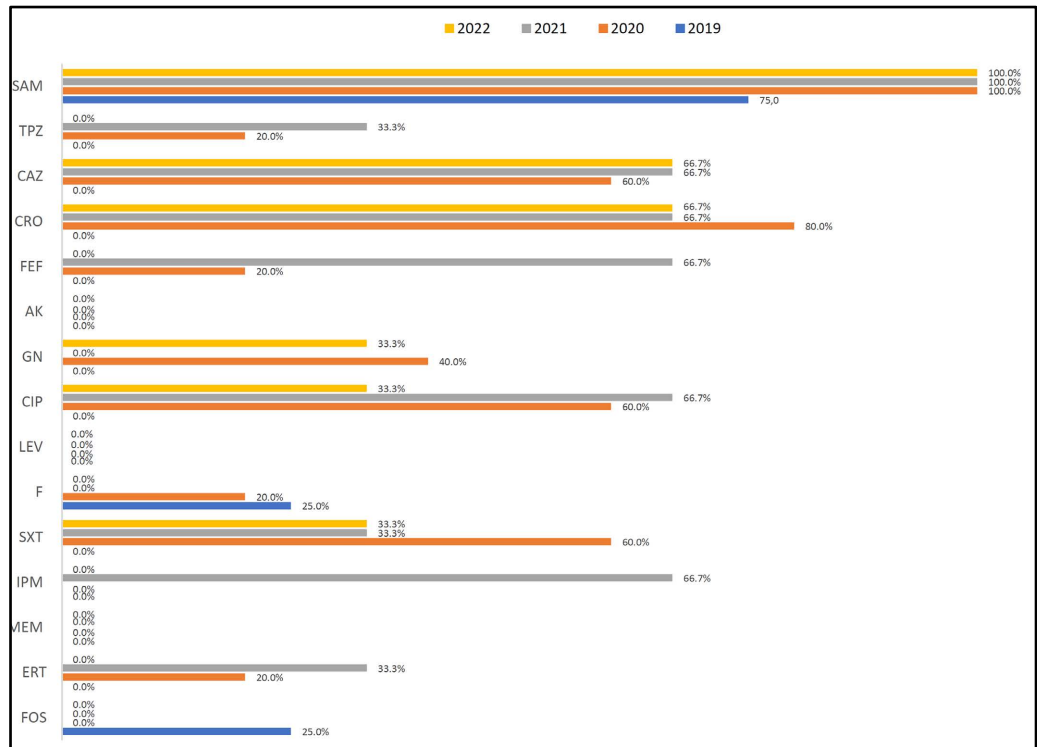
(f)

Figure 2. Resistance pattern of each *ESKAPE* pathogens against antibiotics from 2019-2022. (a). Resistance pattern of *E. faecium* against antibiotics. (b). Resistance pattern of *S. aureus* against antibiotics. (c). Resistance pattern of *K. pneumoniae* against antibiotics. (d). Resistance pattern of *A. baumanii* against antibiotics. (e). Resistance pattern of *P. aeruginosa* against antibiotics. (f). Resistance pattern of *Enterobacter* spp. against antibiotics.

Resistance pattern of *Enterobacter* spp. against ampicillin sulbactam increased from 75.0% in 2019, reaching 100.0% in 2020 until 2022. Against ceftazidime the rates increased dramatically from 2019 to 2020 (0.0% to 60.0%), reaching to 66.7% in 2021 and 2022. Against ceftriaxone and trimethoprim sulfamethoxazole, the rates also increased dramatically from 2019 to 2020, then decreased in 2021 and 2022. The resistance against ciprofloxacin increased from 2020 and 2021, then decreased in 2022. The resistance against levofloxacin, amikacin, meropenem, and fosfomycin were 0.0% in the four-year study (**Figure 2(f)**).

3.3. Multidrug Resistance Patterns per Pathogen According to Calendar Years

S. aureus and *K. pneumoniae* showed similar pattern as the MDR rates decreased from 2019 until 2021 and then increased again in 2022, although the rate in 2022 did not exceed the rate in 2019. *A. baumanii* showed substantial decrease in rate of MDR from 2019 until 2022, while *P. aeruginosa* had similar rate of MDR in 2019 and 2020, and then decreased substantially in 2021 and 2022. *E. faecium* and *Enterobacter* spp. showed great variability of MDR rate throughout 2019 until 2022 (**Figure 3**).
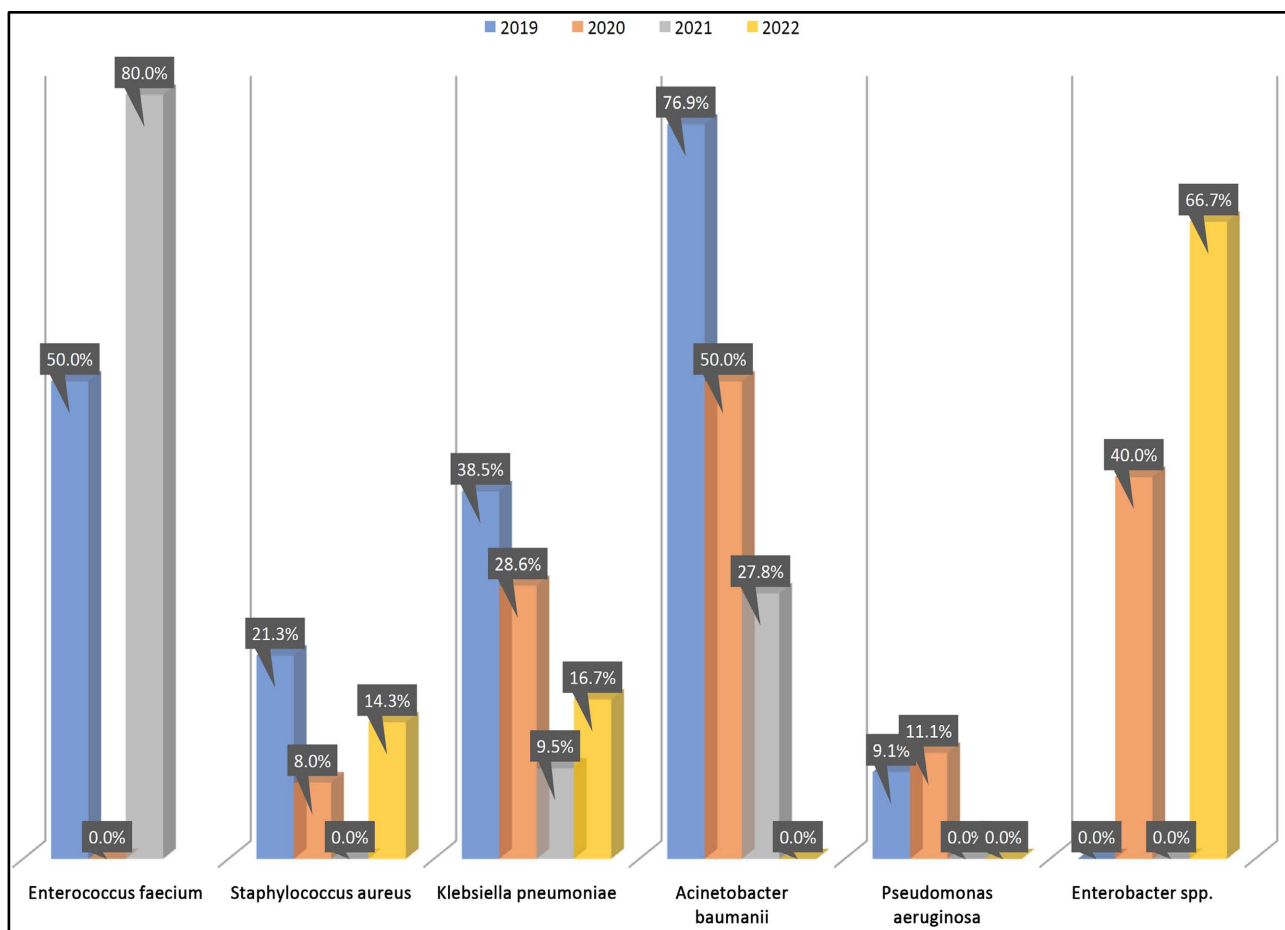

Figure 3. Pattern of multidrug resistance of each *ESKAPE* pathogens from 2019-2022.

4. Discussion

Caglione *et al.* in a study on *ESKAPE* pathogens in Italy from 2015 to 2019 found that *K. pneumoniae* was the most frequent species (31.1%), followed by *P. aeruginosa* (19.8%), *S. aureus* (18.6%), *Enterobacter* spp. (13.4%), *A. baumannii* (13.2%), and *E. faecium* (3.8%) [7]. El-Kady *et al.* in a study in Saudi Arabia from January 2019 to December 2020 found that *K. pneumoniae* was the most frequent species (47.4%), followed by *P. aeruginosa* (29.2%), *Enterobacter* spp. (14.0%), and *A. baumannii* (9.4%) [8]. Azimi *et al.* in a study from May 2016 to March 2017 found that *A. baumannii* was the most frequent species (44%), followed by *S. aureus* (39%), *E. coli* (30%), *K. pneumoniae* (32%), *Enterococcus* spp. (22%), *Enterobacter* spp. (21%), and *P. aeruginosa* (20%) [9]. The results of this study were different, as that *S. aureus* was the most frequent species (37.8%), followed by *K. pneumoniae* (31.4%), *A. baumannii* (13.9%), *P. aeruginosa* (8.8%), *Enterobacter* spp. (5.1%), and *E. faecium* (3.0%). In 2019 and 2022 *S. aureus* was the most frequent species (45.6% and 45.7%), but in 2020 and 2021 *K. pneumoniae* was the most frequent species (36.4% and 30.0%). Although the results between these studies were different, by *S. aureus* and *K. pneumoniae* were the dominant species among *ESKAPE* pathogens before and after the COVID-19 pandemic.

In the case of *Enterococcus faecium*, the resistance rates against penicillin-beta lactamase inhibitor, aminoglycoside, quinolone, and trimethoprim sulfamethoxazole were high (50.0% - 100.0%). On the other hand, the rate of vancomycin resistant *Enterococcus faecium* in this study was 11.1%, lower than studies by Jahansepas *et al.* [10] and Azimi *et al.* [9] (17.0% - 22.0%). One important note was the low rate of *E. faecium* in this study (3.0%).

This study found in the group of *Staphylococcus aureus*, the resistance rates against penicillin-beta lactamase inhibitor, 3rd generation cephalosporin, quinolone, aminoglycoside, trimethoprim sulfamethoxazole, fosfomycin decreased from 2019 (12.8% - 23.4%) until 2021 (0.0%) and then increased again in 2022 although lower than 2019 (9.5% - 14.3%). These figures were lower than the resistance rates found in a study by Bitew *et al.* that were ranging from 20.0% - 66.7% [11]. Resistance rates of MRSA in a study by Scaglione ranged from 23.2% in 2015 to 19.7% in 2019 [7]. This resistance rates were similar with this study (0.0% - 23.4%) and they were decreasing during the four-year study. Bitew *et al.* also stated that the MDR prevalence rate of *S. aureus* was 66.7%, which is higher than the rate of MDR in this study (13.4%).

In this study, the resistance rates for *K. pneumoniae* against penicillin-beta lactamase inhibitor, 3rd generation cephalosporin, quinolone, aminoglycoside, trimethoprim sulfamethoxazole, meropenem and ertapenem peaked from 2019 to 2020 reaching above 50.0%, then decreased in 2021. The resistance rate was the lowest in 2022, ranging 5% - 20%. The resistance rates for 3rd generation cephalosporin, quinolone, aminoglycoside in this study were lower compared to a study by Scaglione *et al.* (74.9% - 91.4%) [7], but higher than the study by

El-Kady *et al.* in 2019-2021 (21.6% - 42.3%) [8], but in 2022 the rates were comparable. El-Kady also found that the MDR rate of *K. pneumoniae* of 21.4%, which is comparable to this study (24.7%)

Musyoki *et al.* showed the rate of MDR *A. baumannii* was 85%, and amikacin were the most effective antibiotics [12]. A study in Morocco in 2019 found that co-trimoxazole was the most effective antibiotics against *A. baumannii* [13]. Scaglione *et al.* showed that the resistance rate to carbapenems was in the 2015-2019 was 74.4% [7]. In this study, resistance pattern of *A. baumanii* was not favorable for most antimicrobials during the first three years of the study, as the rates were above 50.0%, with the exception of tigecycline. The resistance rates peaked from 2019 to 2020, then decreased in 2021, and reached 0.0% in 2022 in most antimicrobials. *A. baumanii* also showed substantial decrease in rate of MDR from 2019 until 2022 (76.9%, 50.0%, 27.8%, 0.0% respectively). In 2022 there were only two samples of *A. baumanii*, which decreased from previous years (13 samples, 8 samples, and 18 samples in 2019, 2020, 2021). It is surprising that the samples of *A. baumanii* decreased drastically in 2022. One study expresses the concern on the challenging clinical problem of *A. baumanii* as the number of active antibiotics was limited, such as carbapenems and tigecycline [7]. In this study, only tigecycline were highly active against *A. baumanii* and thus could be used in managing infection.

Azimi *et al.* [9] reported that 20% of *P. aeruginosa* was MDR, and Cabral *et al.* reported MDR rate of *P. aeruginosa* was 10.7% [14]. In this study, the rates of MDR *P. aeruginosa* were lower, ranging from 0.0% - 11.1% during 2019-2022. Lari *et al.* reported high rate of resistance to all antibiotics except colistin [15]. Farhan *et al.* found that imipenem was the most effective antibiotic [16]. In this study, the resistance rates against ceftriaxone, ertapenem, and tigecycline were very high (88.9% - 100.0%). The resistance rates against aminoglycoside, quinolone, imipenem and meropenem decreased from 2019 until 2021 was in accordance to the result of Farhan *et al.* (36.3% - 36.4%), and even reached to 0.0% in 2022.

Resistance pattern of *Enterobacter* spp. against amoxicillin clavulanic reached 100.0% in 2020-2022. Against ceftazidime, ceftriaxone, ciprofloxacinand trimethoprim sulfamethoxazole the rates increased dramatically from 2019 to 2020 then decreased in 2021 and 2022. The resistance against levofloxacin, amikacin, meropenem, and fosfomycin were 0.0% in the four-year study. El-Kadystated that in the past decade, there was an emergence of carbapenem-resistant *Enterobacteriaceae* [8], but in the present study this phenomenon did not occur. In the study above, the rate of MDR in *Enterobacter* spp. was 17.4%, with 0.0% resistance to amikacin. The result of the present study, the rate of MDR were 26.7% during the four-year study, which was higher than the study by El-Kady. One study stated that the MDR rate of *Enterobacter* spp. would not be considered an important problem as the *Enterobacter* spp. only account for low number of isolates, which is 5.1% in this study [7].

It is quite interesting to observe the extreme spectrums of antimicrobial resistance in the era of COVID-19 pandemic. On one end was the drastic increase of resistance to one antibiotic, while on the other end was the absence of resistance to others. There are many factors related to the increase and decrease of antimicrobial resistance in the era of COVID-19 pandemic. Factors related to the increase of antimicrobial resistance are mainly the antibiotic prophylaxis to prevent bacterial co-infections in hospitalized COVID-19 patients, the lack of attention to surveillance of antimicrobial resistance, healthcare facilities overcrowded with patients with COVID-19 patients. The increased number of nosocomial pathogens was also influenced by the increased number of intensive care patients and the use of mechanical ventilation [17]. Other factor that could play a role in the increase of antimicrobial resistance is the infection control measures such as hand and environment hygiene using soap and water, alcohol-based hand sanitizer, or other disinfectants. Before COVID-19 pandemic, this hygiene practice is one of the ways to decrease the development of antimicrobial resistance, but there is also some possibility that it also contributes to emergence of drug resistance [1].

Scaglione *et al.* stated that the reasons for dramatic increase of susceptible *P. aeruginosa* compared to other microorganisms in their study were difficult to explain, as it might be result of antimicrobial stewardship and infection control or this result occurred by chance due to the low number of samples analyzed [1]. This phenomenon also occurred in the case of a few samples of *Enterobacter* spp. in this study which resistance rates were low or even 0.0% for most antibiotics. In the case of other bacteria where there many samples, similar tendency also occurred. In the case *A. baumanii* and *P. aeruginosa*, the decrease of resistance rates to most antibiotics in 2022. The resistance pattern of *S. aureus* and *K. pneumoniae* were also lower in 2022 compared to before COVID-19 pandemic. The decrease of resistance rates could be explained by the development of COVID-19 pandemic. As the pandemic commenced in 2020, antibiotic prophylaxis was used in hospitalized COVID-19 patients to prevent bacterial co-infections. The pandemic reached its peak as delta variant dominated in 2021, and antibiotics were still used to treat COVID-19 patients. As the pandemic receded in 2022 when the severity and mortality to COVID-19 decreased, antibiotics use also declined. This decline of antibiotics use could influence the resistance rate of many pathogens including *A. baumanii*, *P. aeruginosa*, *S. aureus*, and *K. pneumoniae*. As for *E. faecium* the resistance pattern increased from 2019 to 2021, except for the 2022 as no samples were found.

There are several limitations in this study. First, there was no determination of drug resistance genes of *ESKAPE* pathogens using molecular methods in this study due to technical limitation in the hospital laboratory. Second, antibiotic resistance index could not be determined because clinical data was not available. Third, there were missing hospital laboratory database on the ESBL-producing organisms. Fourth, the limited number of sample size as this study only accounted for data of single hospital.

5. Conclusion

From this study, it is concluded that the COVID-19 pandemic has affected the antimicrobial resistance pattern of *ESKAPE* pathogens as one of the etiologies of healthcare-associated infections in Banten province, Indonesia. The resistance rates increased as antibiotic prophylaxis were used in hospitalized COVID-19 patients at the start of the pandemic in 2020 and 2021, along with the lack of attention to surveillance of antimicrobial resistance in the chaotic health situation. As the situation began to resolve in 2022, the resistance rates also decreased, with the exception of a few resistance rates against specific microorganisms.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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