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Changes in Antibiotic Resistance Patterns Before and During the COVID-19 Pandemic in Hospitalized Children at Dr. Mohammad Hoesin General Hospital, Palembang, Indonesia

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ABSTRACT

Introduction: The coronavirus disease (COVID-19) pandemic has influenced antibiotic usage patterns due to overlapping clinical symptoms between viral and bacterial infections. This may lead to inappropriate antibiotic prescriptions, thereby increasing antimicrobial resistance. This study examined antibiotic resistance patterns in hospitalized children before and during the COVID-19 pandemic, highlighting their clinical and epidemiological significance.

Methods: This was a retrospective cross-sectional study using secondary data from the Central Laboratory Installation at Dr. Mohammad Hoesin General Hospital, Palembang, Indonesia. All patients aged 1 month to 18 years old with blood cultures and antibiotic sensitivity test results were included. The data were analyzed using Chi-square and linear regression in Microsoft Excel and the International Business Machines Corporation (IBM) Statistical Package for the Social Sciences (SPSS) version 26.0 for Windows.

Results: The proportion of Gram-positive bacterial isolates increased from 66% before the pandemic to 75% during the pandemic. The proportion of multidrug-resistant (MDR) isolates rose from 71.7% to 74.3%. Methicillin-resistant *Staphylococcus aureus* (MRSA) isolates rose from 20.6% to 25.8%. The proportion of extended-spectrum beta-lactamase (ESBL) isolates increased from 81.8% to 88.9%. All *Enterobacteriaceae* isolates were carbapenem-resistant *Enterobacteriaceae* (CRE). Significant resistance changes were observed in *S. aureus* to oxacillin.

Conclusion: There was a change in antibiotic resistance patterns during the pandemic. These findings are crucial for antibiotic stewardship and clinical policy-making.

Highlights:
1. Antibiotic resistance patterns before and during COVID-19 have changed.
2. There was an increase in MDR, MRSA, ESBL, and CRE isolates.

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Introduction

Coronavirus disease (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has had a profound impact on global health, including changes in the pattern of antibiotic use. Due to overlapping clinical symptoms between COVID-19 and bacterial infections, the administration of empirical antibiotics increased significantly, even though antibiotics are ineffective against viruses.[1,2] Although a virus causes COVID-19, antibiotics were frequently administered empirically due to difficulties in differentiating viral from bacterial pneumonia during early clinical assessment. Moreover, concerns about bacterial coinfections, especially in severe cases, led to broader antibiotic use.

This increase was evident in various healthcare settings. A study in China reported that 66.1% of pediatric inpatients in 2019 received multiple antibiotics.[3] Similarly, at Dr. Mohammad Hoesin General Hospital, Palembang, Indonesia, antibiotic use among pediatric inpatients increased during the early months of the pandemic, despite a decline in the number of hospital admissions.[4] This was likely due to stricter hospital admission criteria, which only treated moderate to severe cases in person, often necessitating antibiotic therapy.

Symptoms of COVID-19, such as cough, fever, and respiratory distress, often mimic those of bacterial pneumonia or tuberculosis (TB), which can lead to challenges in diagnosis and contribute to the overuse of antibiotics.[5] In some cases, bacterial coinfections or secondary infections can occur, especially in critically ill or ventilated patients.[6,7] However, several studies have shown a mismatch between the high rates of antibiotic prescribing and the relatively low prevalence of confirmed bacterial infections in COVID-19 patients.[8,9] The rise in antibiotic use has implications for antimicrobial resistance (AMR), a significant public health concern. Antimicrobial resistance occurs when microbes evolve and no longer respond to treatment, leading to persistent infections and increased transmission risks.[10] Several factors, including irrational antibiotic prescribing, inadequate antimicrobial stewardship, and insufficient surveillance systems, exacerbate the problem.[11]

Children are especially vulnerable due to their developing immune systems and increased exposure to invasive procedures during hospitalization. Over the past two decades, multidrug-resistant organisms (MDROs) such as Methicillin-resistant *Staphylococcus aureus* (MRSA), extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae*, and carbapenem-resistant *Enterobacteriaceae* (CRE) have been increasingly reported in pediatric populations.[12–14] Public health measures during the pandemic, such as lockdowns and telemedicine, also influenced hospital admission patterns, typically resulting in fewer but more severe pediatric cases being treated.[15,16] These factors may have contributed to shifts in antimicrobial resistance trends in hospital settings. This study aimed to investigate the changes in antibiotic resistance patterns in hospitalized children at Dr. Mohammad Hoesin General Hospital, Palembang, Indonesia, before and during the COVID-19 pandemic.

Methods

This retrospective cross-sectional study utilized secondary data collected from the Central Laboratory Installation at Dr. Mohammad Hoesin General Hospital, Palembang, Indonesia. All pediatric patients aged 1 month to 18 years old who underwent blood culture and had antibiotic susceptibility testing (AST) results during the pre-pandemic period (1 October 2018-31 March 2020) and the COVID-19 pandemic period (1 April 2020-30 September 2021) were included.

Blood cultures were performed using standard microbiological procedures. Positive cultures were identified, and antibiotic susceptibility testing was performed using the Kirby-Bauer disk diffusion method, following the guidelines of the Clinical and Laboratory Standards Institute (CLSI).[17] Culture and sensitivity tests were conducted on media such as blood agar and MacConkey agar, using standardized antibiotic disks.

This study included data on bacterial species isolated from blood specimens, their resistance profiles, patient demographics (age and sex), and hospital location (intensive vs. non-intensive care unit/ICU). Given that all isolates were obtained from hospitalized patients, the possibility of nosocomial infection was considered, although definitive classification could not be made due to data limitations. Data were entered and processed using Microsoft Excel and analyzed using the International Business Machines Corporation (IBM) Statistical Package for the Social Sciences (SPSS) version 26.0 for Windows.[18,19] The normality of the data distribution was assessed before conducting the comparative analysis. The Chi-square test was used to analyze differences in bacterial isolate distribution between the two time periods.[20] Linear regression analysis was applied to examine trends in resistance patterns of *S. aureus, Escherichia coli,* and *Klebsiella pneumoniae* isolates between the period before and during the COVID-19 pandemic.

Results

A positive bacterial culture was obtained from 523 of 2,102 (24.8%) blood samples before the pandemic and 404 of 1,478 (27.3%) during the pandemic. In the pandemic period, the majority of patients were aged >1 to 18 years old (283 cases, 70%), and male patients were more common, totaling 248 cases (61.4%). The data are presented in Table 1.

Table 1. Demographic characteristics of hospitalized children with positive blood culture results for bacteria

Patient Demographics	Before Pandemic n (%)	During Pandemic n (%)
Age		
>1 month-1 year old	206 (39.4)	121 (30)
1-18 years old	317 (60.6)	283 (70)
Sex		
Male	303 (57.9)	248 (61.4)
Female	220 (42.1)	156 (38.6)

Source: Research data, processed

Based on Table 2, there was an increase in the number of isolates of Gram-positive bacteria between before the pandemic (66%) and during the pandemic (75%). The statistical test results revealed significant differences in the frequency of bacterial isolates before and during the pandemic ($p<0.05$).

Table 2. Differences in the frequency of bacterial isolates in hospitalized children

Period	Gram-Based Bacteria Type	n	%	p-value
Before pandemic	Gram positive	345	66	0.003
	Gram negative	178	34	
During pandemic	Gram positive	303	75	
	Gram negative	101	25	

Source: Research data, processed

Before the pandemic, most bacterial isolates were obtained from non-ICU settings, with 426 isolates (81.5%), with Gram-positive bacteria holding the highest proportion in both the ICU (70.1%) and non-ICU settings (65%). Coagulase-negative *staphylococci*/CoNS (56.4%) were the most prevalent bacteria during that period. The distribution of bacterial isolates during the pandemic also showed the same pattern.

Table 3. Frequency distribution of blood specimen bacterial isolates in hospitalized children

Bacterial Isolates	Intensive Care Unit (n%)	Non-Intensive Care Unit (n%)	Total (n%)
Gram Positive			
Coagulase-negative *Staphylococci*	56 (57.7%)	239 (56.1%)	295 (56.4%)
Staphylococcus aureus	7 (7.2%)	27 (6.3%)	34 (6.5%)
Streptococcus spp.	2 (2.1%)	7 (1.6%)	9 (1.7%)
Enterococcus spp.	3 (3.1%)	4 (0.9%)	7 (1.3%)
Gram Negative			
Klebsiella pneumoniae	12 (12.4%)	38 (8.9%)	50 (9.6%)
Acinetobacter spp.	6 (6.2%)	35 (8.2%)	41 (7.8%)
Escherichia coli	2 (2.1%)	24 (5.6%)	26 (5%)
Sphingomonas paucimobilis	1 (1%)	19 (4.5%)	20 (3.8%)
Pseudomonas spp.	2 (2.1%)	11 (2.6%)	13 (2.5%)
Enterobacter spp.	0	7 (1.6%)	7 (1.3%)
Salmonella spp.	1 (1%)	4 (0.9%)	5 (1%)
Other Gram-negative bacteria	5 (5.2%)	11 (2.6%)	16 (3.1%)

Source: Research data, processed

A total of 351 bacterial isolates (86.9%) came from the non-ICU. Gram-positive bacteria held the highest proportion in the ICU, with the highest overall distribution during the pandemic being CoNS (65.3%). Data on the frequency distribution of blood specimen bacterial isolates can be seen in Table 3 and Table 4.

Figure 1 illustrates the differences in the frequency of bacterial isolates based on antibiotic resistance patterns among hospitalized children. Of all the bacterial isolates, 372 (71.7%) before the pandemic and 300 (74.3%) during the pandemic were multidrug-resistant (MDR). The highest distribution was observed in the non-ICU setting. *Escherichia coli* and *K. pneumoniae* isolates that produced ESBL were found in as many as 36 isolates (81.8%) before the pandemic and 16 (88.9%) during the pandemic. The isolates in both periods originated from non-ICU settings. Furthermore, all isolates of MRSA were found in non-ICU in both periods. A total of 2 isolates (100%) of *Enterococcus spp.* from non-ICU were vancomycin-resistant *Enterococcus* (VRE). *Enterococcus spp.* isolates were all susceptible to vancomycin during the pandemic.

Table 4. Frequency distribution of blood specimen bacterial isolates in hospitalized children

Bacterial Isolates	Intensive Care Unit (n%)	Non-Intensive Care Unit (n%)	Total (n%)
Gram Positive			
Coagulase-negative *Staphylococci*	35 (66%)	229 (65.2%)	264 (65.3%)
Staphylococcus aureus	0	28 (8%)	28 (6.9%)
Enterococcus spp.	3 (5.7%)	4 (0.9%)	7 (1.7%)
Streptococcus spp.	0	3 (1.1%)	3 (0.7%)
Staphylococcus pseudintermedius	0	1 (0.3%)	1 (0.2%)
Gram Negative			
Acinetobacter spp.	5 (9.4%)	19 (5.4%)	24 (5.9%)
Escherichia coli	3 (5.7%)	17 (4.8%)	20 (5%)
Klebsiella pneumoniae	1 (1.9%)	16 (4.6%)	17 (4.2%)
Enterobacter spp.	0	8 (2.3%)	8 (2%)
Pseudomonas spp.	2 (3.8%)	5 (1.4%)	7 (1.7%)
Sphingomonas paucimobilis	0	4 (1.1%)	4 (1%)
Salmonella spp.	0	3 (0.9%)	3 (0.7%)
Other Gram-negative bacteria	4 (7.5%)	14 (4%)	18 (4.5%)

Source: Research data, processed

A total of 15 out of 90 *Enterobacteriaceae* isolates before the pandemic were CRE, with the highest distribution coming from non-ICU settings, specifically 12 isolates (80%). During the pandemic, most CRE isolates originated from non-ICU, with as many as five isolates reported. The *Enterobacteriaceae* family bacteria found in this study included *K. pneumoniae, E. coli, Enterobacter spp., Salmonella spp.*, and other Gram-negative bacteria. This study also showed an increase in MDR bacterial isolates before the pandemic (71.7%) and during the pandemic (74.3%).

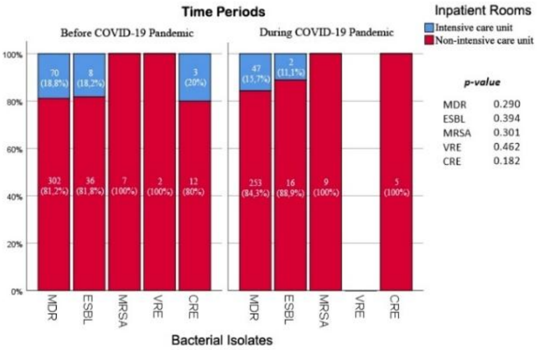

Figure 1. Differences in the frequency of bacterial isolates based on antibiotic resistance patterns in hospitalized children

Methicillin-resistant *S. aureus* isolates also increased before the pandemic (20.6%) and during the pandemic (25.8%). In contrast, other bacterial isolates showed a decrease in distribution. However, the statistical test results showed no significant difference in bacterial isolates based on antibiotic resistance patterns before and during the COVID-19 pandemic (p>0.05).

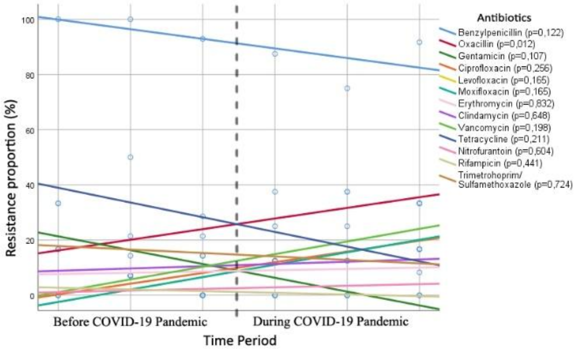

Figure 2. Trends in patterns of resistance of *Staphylococcus aureus isolates* to antibiotics in hospitalized children

Staphylococcus aureus isolates had a high level of resistance to benzylpenicillin before (97.1%) and during (85.7%) the pandemic. The statistical test revealed an increase in the antibiotic resistance pattern of *S. aureus* isolates to the antibiotic oxacillin by 11.5% (p<0.05). Before the COVID-19 pandemic, *E. coli* isolates showed a high level of resistance to ampicillin (88.5%), cefazolin (81.8%), and ampicillin/sulbactam (69.2%). *Escherichia coli* isolates also showed a relatively high level of bacterial resistance to cefazolin (100%), ampicillin (95%), ciprofloxacin (75%), and trimethoprim/sulfamethoxazole (75%) during the pandemic. The data showed no significant change in the pattern of *E. coli* resistance before and during the COVID-19 pandemic (p>0.05).

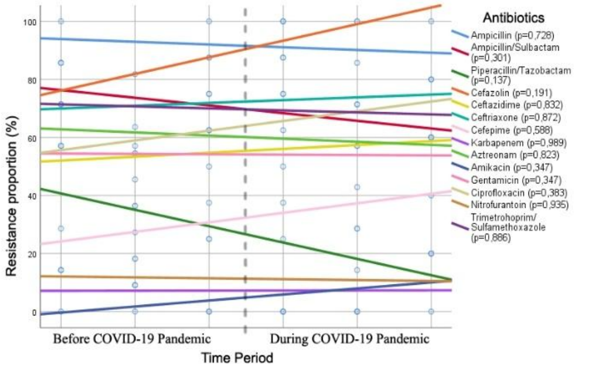

Figure 3. Trends in patterns of resistance of *Escherichia coli* isolates to antibiotics in hospitalized children

Klebsiella pneumoniae isolates exhibited a high level of resistance to ampicillin (98%), cefazolin (93.6%), and ampicillin-sulbactam (82%) prior to the pandemic. During the pandemic, *K. pneumoniae* isolates also showed resistance to ampicillin (100%), cefazolin (100%), and ampicillin/sulbactam (58.8%). The statistical test results showed no significant change in the resistance pattern of *K. pneumoniae* to all antibiotics tested before and during the COVID-19 pandemic (p>0.05).

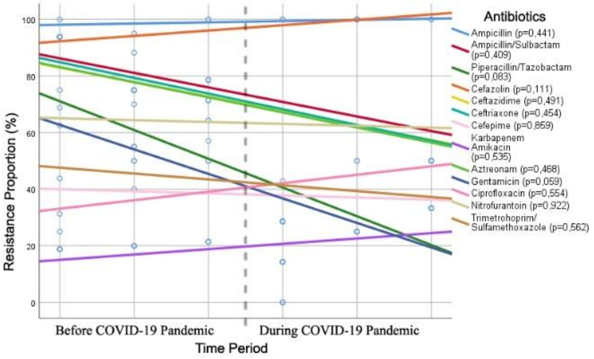

Figure 4. Trends in patterns of resistance of *Klebsiella pneumoniae* isolates to antibiotics in hospitalized children

Discussion

The increase in Gram-positive isolates, particularly CoNS and MRSA, can be attributed to hospital-related factors, such as the increased use of intravascular devices, prolonged hospital stays, and empirical antibiotic use, due to the overlap of COVID-19 symptoms with those of bacterial infections. The predominance of Gram-positive isolates in non-ICU settings also supports the likelihood of nosocomial transmission, particularly in patients with disrupted skin barriers or immune suppression. Although CoNS are often considered contaminants, their high prevalence in this study suggests they may act as true pathogens in vulnerable pediatric populations.

This study revealed a significant increase in the frequency of Gram-positive bacterial isolates among hospitalized children at Dr. Mohammad Hoesin General Hospital, Palembang, Indonesia, before and during the pandemic ($p<0.05$), which was most commonly found in non-ICU. These results align with a study conducted by Wang, *et al*. (2021), which found that most pediatric patients in East China between 2015 and 2018 were treated in non-ICU settings, and Gram-positive bacteria held the highest proportion, with CoNS being the primary isolate.[21] In addition, *S. aureus* was also recognized as a common etiological agent of bloodstream infections.[22] This study is also similar to a study by Indrasari, *et al*. (2022).[23] Saini, *et al*. (2021) showed that *Acinetobacter baumannii* was the dominant Gram-negative bacterium isolated during the COVID-19 pandemic compared to the pre-pandemic period. *Klebsiella pneumoniae*, followed by *Acinetobacter spp., E. coli*, and *Pseudomonas aeruginosa,* were frequently isolated in blood cultures.[24]

This study revealed an increase in MDR and MRSA isolates before (71.7%) and during the pandemic (74.3%). The excessive use of broad-spectrum antibiotics and the relatively lax management of MDR bacteria, which was focused on COVID-19 treatment, may have contributed to the increased prevalence of MDR bacteria.[25] The increase in MRSA isolates between the two periods (from 20.6% to 25.8%) is consistent with the study of Indrasari, *et al*. (2022), who also reported a rise in MRSA during the pandemic in hospitalized patients in Dr. Soetomo General Hospital, Surabaya, Indonesia.[23] This rise is suspected to be due to nosocomial infections, where MRSA is a common bacterial co-infection and a cause of mortality in influenza patients.[26] However, it remains challenging to distinguish whether these were hospital-acquired (nosocomial) or community-acquired infections due to the absence of clinical and epidemiological metadata, such as timing of onset, previous hospitalization, or source tracing. Thus, the findings must be interpreted with caution.

Despite these increases, statistical tests revealed no significant differences in the prevalence of bacterial isolates based on antibiotic resistance patterns before and during the pandemic ($p>0.05$). This finding aligns with a study conducted by Langford, *et al*. (2023), which concluded that there was no significant correlation between the resistance rates of Gram-positive bacteria (MRSA and VRE) or Gram-negative bacteria (ESBL and CRE) and the COVID-19 pandemic.[27] This study also revealed a significantly increased resistance of *S. aureus* to oxacillin during the pandemic ($p<0.05$). This result is supported by the findings of Sulayyim, *et al*. (2022), which reported higher oxacillin resistance in *S. aureus* isolates during COVID-19.[28] Fu, *et al*. (2021) also noted that the prevalence of *S. aureus* resistance to penicillin was high, with approximately 35% of isolates in pediatric inpatients in China being resistant to oxacillin.[29]

Most *S. aureus* isolates express the mecA gene, which encodes resistance to beta-lactam antibiotics. This bacterium, a skin commensal, frequently causes nosocomial infections, particularly in association with intravenous catheters and prosthetic devices. Resistance can increase due to factors such as prolonged use of invasive devices, extended hospital stays, or underlying comorbidities.[30] Pediatric hospitalization rates have been significantly lower than adult rates during the COVID-19 pandemic. Children generally present with milder symptoms, contributing to a decrease in hospital admissions.[31] A study in Denmark found a reduction in pediatric hospitalizations for infectious diseases during 2020 compared to 2018 and 2019.[15] This may be explained by parental reluctance to visit hospitals due to concerns about infection or to avoid overburdening the healthcare system.[15]

As a result, only children with more severe symptoms tended to be hospitalized during the pandemic, often requiring antibiotic therapy. This change in hospitalization patterns could influence bacterial resistance trends in pediatric patients. Moreover, increased infection prevention measures, such as hand hygiene and the use of personal protective equipment (PPE), may have impacted the types and frequency of bacterial transmission within hospitals. Therefore, enhanced microbiological surveillance, comprehensive clinical data collection, and strengthened antimicrobial stewardship are crucial, especially during times of health system strain, such as a pandemic.

Strengths and Limitations

The strength of this study lies in its finding of significant changes in antibiotic resistance patterns in children, thereby providing a strong basis for further action in clinical management and health policy. The limitation of this study was that it lacked information on the status of old or new patients, the diagnosis of each patient, whether they were infected with COVID-19 or not, and the length of hospitalization. As a result, it was challenging to distinguish between nosocomial infections, infections with other diseases, and COVID-19 infections as the cause of the infection. This study did not include the history of previous antibiotic medication. Furthermore, even when the infection was the same, the antibiotics employed may differ. These limitations also restricted the ability to perform more nuanced subgroup analyses by age categories or infection transmission patterns, which could have provided more profound insight into resistance patterns.

Conclusion

Antibiotic resistance patterns in hospitalized children changed during the COVID-19 pandemic, with an increase in MDR, MRSA, ESBL, and CRE isolates. These findings underscore the importance of enhanced antibiotic use and infection control, particularly during health emergencies.

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Conflict of Interest

The authors declared there is no conflict of interest.

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Ethical Clearance

This study had received ethical clearance from the Ethics Committee for Medical and Health Research, Universitas Sriwijaya, Palembang (No. 123/2022) on 07/09/2022.

Authors' Contributions

Designed the study and drafted the manuscript: WK, YA, and AK. Collected data and performed background literature review: WK, YA, and AK. Performed statistical analysis: WK. Supervised results and discussion: YA and AK. All authors reviewed and approved the final version of the manuscript.

Data Availability

N/A.

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