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The impact of the COVID-19 pandemic on antimicrobial resistance at Dr. Soetomo Academic Hospital of Surabaya

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***Abstract*---**The coronavirus disease-2019 pandemic promote antibiotic resistance in bacteria due to overuse of antibiotics, and inhibit the spread of antibiotic-resistant bacteria due to numerous transmission control methods. The research is observational analytic with retrospective approach, aims to compare microorganism profile data, prevalence of multidrug-resistant microorganisms, and susceptibility patterns in patients treated at Dr. Soetomo Surabaya Hospital before and during the pandemic. The most species isolated before the pandemic: E. coli, K. pneumoniae, P. aeruginosa, S. aureus, A. baumannii, and Candida spp. The prevalence of multidrug resistant microorganisms before the pandemic: MRSA 28.4%, VRSA 3.57%, VRE 15.41%, ESBL 49.5% and carbapenem resistant 20.56%. The most species isolated during the pandemic: K. pneumoniae, E. coli, Candida spp, P. aeruginosa, A. baumannii, and S. aureus. Prevalence of multidrug resistant microorganisms during the pandemic: MRSA 29.3%, VRSA 1.5%, VRE 21.05%, ESBL 48.82% and carbapenem resistant 25.97%. The microorganism profiles are different before and during the pandemic, significant decrease in the prevalence of E. coli and S. aureus, significant increase in Candida spp. and carbapenem-resistant Enterobacteriaceae, particularly E. coli, E. cloacae, and Citrobacter spp, and significant alterations of susceptibility patterns

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in S. aureus, K. pneumoniae, E. coli, A. baumannii, and P. aeruginosa.

***Keywords*---**antimicrobial, resistance, carbapenem resistant, susceptibility pattern.

Introduction

Antibiotic resistance is global health issue because it have a variety of negative consequences that lower the quality of healthcare (Hsu, 2020; Neill, 2014). The coronavirus disease-2019 (COVID-19) pandemic has caused various problems related to the use of antibiotics (Murray, 2020; North et al., 2020). As result of the rising number of COVID-19 patients being admitted to hospitals, antibiotic therapy is being used more frequently to avoid secondary infections (Garcia-Vidal et al., 2020; Knight et al., 2021; Lai et al., 2020). Based on an examination of data on COVID-19 cases, largely from Asia, it was discovered that more than 70% of COVID-19 patients had received antibiotic therapy, with just 10% of those suffering from subsequent bacterial infections (Zhou et al., 2020). Patients with COVID-19 who were hospitalized in several countries were found to be administered various antibiotics as part of their treatment (van Duin et al., 2020). Antibiotics used as empirical therapy in COVID-19 patients are broad spectrum antibiotics, and it is thought that their usage during pandemic could raise the risk of antibiotic resistance (Hirabayashi et al., 2021; Hsu, 2020; Huttner et al., 2020). Antibiotics are prohibited in moderate cases of COVID-19, but they are recommended in severe cases of COVID-19 and in patients who are at risk of secondary infection from bacteria that can cause mortality (Clancy et al., 2020; Clancy & Nguyen, 2020; Vickers et al., 2019).

The ambiguous clinical symptoms of COVID-19 infection, as well as the urgency if the patient is in severe condition, are factors that enhance the usage of antibiotics in COVID-19 patients. Other variables that may contribute to antibiotic abuse include accusations concerning medications that may be successful in treating COVID-19, such as the use of teicoplanin, azithromycin, and hydroxychloroquine. Supported by frantic headlines in the media and speeches from politicians claiming the efficacy of these medications in COVID-19 therapy. Telephone consultations have increased during the pandemic to prevent transmission. This telephone consultation has also resulted in an increase in antibiotic prescriptions that are inappropriate (Di Gennaro et al., 2020).

Antibiotic use to treat or prevent secondary bacterial infections in COVID-19 patients, as well as possible COVID-19 treatments, will raise antibiotic concentrations in sewage treatment systems and the final disposal environment. Increased use of soap and cleaners in hospitals and the environment can also lead to a rise in the content of antibiotic compounds in waste. Increased concentrations of antibiotic compounds in this waste will result in selective pressure, increasing microorganism resistance to antibiotics (Murray, 2020). Various measures, such as alertness when making direct contact, droplets, and aerosols, are being taken to avoid the spread of COVID-19 infection to medical professionals who treat patients. Antibiotic-resistant microorganisms can be prevented by increasing hygiene and sterilizing practices. COVID-19 prevention can also help to curb the spread of antibiotic-resistant bacteria both locally and worldwide (Murray, 2020).

The COVID-19 pandemic has caused changes in the population, including social isolation, mask use, isolation, and reduced domestic and international travel, all of which have restricted the spread of antibiotic-resistant organisms and resistance genes (van Duin et al., 2020). *Enterococcus faecalis/faecium, Staphylococcus aureus, Klebsiella pneumoniae, E. coli, Acinetobacter baumaniii, Pseudomonas aeruginosa*, and *Enterobacter* are among the bacteria that are multi-resistant to antibiotics, according to the World Health Organization. Because these bacteria has variety of resistance mechanisms, it will be difficult to treat an infection.

Materials and Methods

This is analytical observational study with retrospective approach, aims to understanding the microorganism profile, prevalence of multidrug resistant organism (MDRO), and antibiotic sensitivity tests from various clinical samples sent toward the Dr. Soetomo clinical microbiology laboratory, which includes urine, blood, fluid, pus, and sputum samples. From January 1 through December 31, 2020. The sample was determined by total sampling, with the following inclusion criteria: a) the culture results were identified in the Microbiology Unit of Dr. Soetomo Surabaya Hospital (DSSH), using the BD Phoenix™ automated identification and susceptibility testing system, the Vitex® 2 system, and manual identification; b) the isolates analyzed were the first isolates per patient per period (before the pandemic: 1 January 2019 - 14 March 2020, during the pandemic; 15 March 2020 - 31 December 2020). The first isolate is chosen, taking into consideration the patient's diagnosis as well as the pathogenicity and virulence of the isolated pathogen; c) The isolates were obtained from patient specimens treated at DSSH. The exclusion criteria were culture results from specimens sent for the purpose of screening for MRSA.

Results and Discussions

Results

Prior to the pandemic (2019) 8760 isolates were collected, while 3434 isolates were obtained during the pandemic (2020). Male patients' specimens were found in greater abundance than female patients' specimens both before and during the pandemic. However, during the pandemic, male specimen senders increased from 52.8% isolates to 56.1% isolates, about 4.7% rise ($p = 0.001$). Before the pandemic, the majority of isolates originated from sputum specimens (31.9%), urine specimens (25.4%), and wound specimens (20.9%). During the pandemic, the most common specimens were sputum (40.0%), blood specimens (23.3%), and wound specimens (17.4%). Sputum and blood cultures have been sent more frequently during the pandemic, while the rest of the specimens shrank. There was a significant difference in the distribution of isolates based on the type of patient specimen before and during the pandemic ($p < 0.001$).

Wards at DSSH is grouped into pediatrics, medical, surgical, obstetric, emergency (IRD), intensive care (ICU, ROI, NICU, RES), and outpatients. Medical ward includes internal medicine, neurology, dermatology, and respiratory. The surgical ward includes surgery, ophthalmology, and ENT. Before the pandemic the most isolates were from medical (40.8% of the total isolates), surgical (25.3% of the total isolates) and IRD (11.8%), while during the pandemic the most isolates came from medical (30.6% of the total isolates), intensive care (27.4%) and surgical (19.5%). During the pandemic, the relative frequency of isolates from the intensive care increased compared to before the pandemic, from 9.5% to 27.4%. Statistical analysis using chi square obtained $p < 0.001$, thus there is a significant difference in the distribution of isolates based on the origin of the patient's ward before and during the pandemic.

Microscopic analysis revealed that the frequency of fungal isolates increased from 5.4% to 8.2% ($p < 0.05$) during the pandemic, while gram-negative bacteria isolates declined by 4.1% and gram-positive bacteria isolates increased by 1.2%. Prior to the pandemic, the most isolated species were *E. coli* (15.68%), *K. pneumoniae* (13.40%),.*P. aeruginosa* (7.07%), *S. aureus* (6.91%), *A. baumannii* (5.98%) and Candida spp. (5.22%). Meanwhile, during the pandemic the most isolated species were *K. pneumoniae* (14.39%), *E. coli* (13.16%), Candida spp (7.83%), *P. aeruginosa* (7.34%), *A. baumannii* (5.97%) and *S. aureus* (5.77%) During the pandemic there was a significant increase in the relative frequency of Candida spp species, which rose from 5.22% before the pandemic, to 7.83% during the pandemic ($p < 0.05$). This increase at the same time increased the order of Candida spp from the sixth rank before the pandemic to the third rank during the pandemic. Other species whose relative frequency increased compared to before the pandemic were *K. pneumoniae* (13.40% to 14.39%, with $p > 0.05$), and *P. aeruginosa* (from 7.07% to 7.34%, with $p > 0.05$). During the pandemic there was a decrease in the relative frequency of *E. coli* species (15.68% to 13.16%, $p < 0.05$) and *S. aureus* (6.91% to 5.77%, $p < 0.05$). Thus, there is a significant decrease in the prevalence of *E. coli* and *S. aureus* during the pandemic.

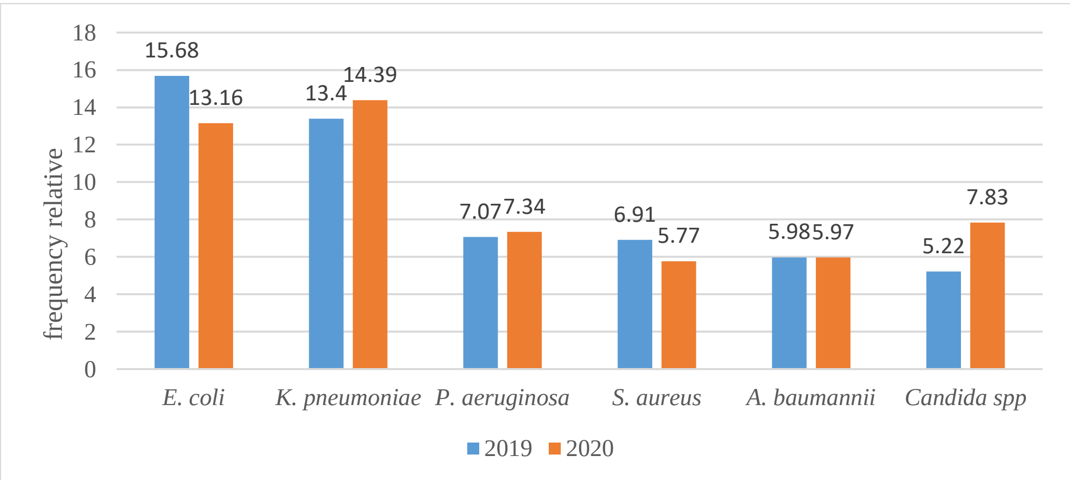

Figure 1. Comparison of the prevalence of the six most isolated species

Methilcillin resistant S. aureus (MRSA) and Vancomycin resistant S. aureus (VRSA)

S. aureus before the pandemic were 605 isolates (6.91%), during the pandemic there were 198 isolates (5.77%). The MRSA prevalence before the pandemic was 28.4%, while during the pandemic was 29.3%, that was increase of 1.1% (p = 0.816). During the pandemic there was increase in the MRSA prevalence from specimens pediatric, medical and intensive care ward. Meanwhile, specimens from the surgical ward, IRD, and obstetrics had decreased. The prevalence of VRSA before the pandemic was 3.5%, while during the pandemic it was 1.5%, so that decrease of 2% (p > 0.05).

Vancomycin resistant Enterococcus (VRE)

Enterococcus isolates obtained from all specimens before the pandemic were 357 isolates (4.08%), while during the pandemic were 76 isolates (2.21%). The Enterococcus isolates included *Enterococcus faecalis, Enterococcus faecium* and Enterococcus spp. Before and during the pandemic, Enterococcus isolates were dominated by *Enterococcus faecalis*, which accounted for 80% and 78.95%, respectively, of the total Enterococcus isolates.Before the pandemic, the prevalence of VRE was 15.41%, while during the pandemic it was 21.05%, there was an increase in VRE of 5.64%. The wards with the most VRE isolates before the pandemic was the medical ward (50.91%), while during the pandemic the intensive care ward (25.00%), and medical ward (18.75%). As shown on Table 2, there was no difference in the susceptibility of Enterococcus antibiotics between before and during the pandemic. Treatment options for infections caused by *E. faecalis* before and during the pandemic are ampicillin, vancomycin, teicoplanin, nitrofurantoin (urine only).

Table 1
Differences in *S. aureus* susceptibility patterns

Antibiotic	Before Pandemic % S (N)	During Pandemic % S (N)	p
Gentamycin	73,78 (595)	75,26 (194)	p= 0,683
Ampicilllin Clavulanat	72,35 (586)	75,14 (185)	p= 0,458
Ampicilllin	0,7% (567)	0,0% (172)	p= 0,269
Trimethoprim-Sulfamethoxazole	80,40 (597)	80,73 (192)	p= 0,921
Tetracyclin	40,44 (586)	50,26 (195)	p= 0,016
Chloramphenicol	60,65 (526)	59,16 (191)	p= 0,720
Erythromycin	84,58 (577)	82,45 (188)	p= 0,489
Clindamycin	83,42 (567)	79,78 (183)	p= 0,259
Quinopristin-dalfopristin	92,67 (559)	92,86 (168)	p= 0,933
Ciprofloxacin	69,93 (582)	74,35 (191)	p= 0,243
Levofloxacin	67,98 (253)	72,22 (54)	p= 0,542
Vancomycin	93,16 (599)	87,37 (198)	p= 0,010
Linezolid	96,82 (597)	97,42 (194)	p= 0,669
Teicoplanin	92,66 (586)	84,74 (190)	p= 0,001
Rifampycin	94,77 (574)	95,68 (185)	p= 0,625

Notes :
%S: percentage of isolates susceptible to the tested antibiotics
N: total number of tested isolates p <0,05 significant

Table 2
Comparison of Enterococcus susceptibility patterns

Antibiotics	Before pandemic % S (N)	During pandemic % S (N)	p
Gentamycin	1,7 (353)	0,0 (76)	p=0,252
Ampicilllin	88,70 (301)	85,51 (69)	p=0,459
Penicillin	45,90 (268)	29,41 (17)*	p=0,185
Trimethoprim-Sulfamethoxazole	1,2 (338)	0,0 (75)	p=0,344
Trimethoprime	5,7 (122)	0,0 (61)	p=0,056
Tetracyclin	17,81 (219)	17,07 (41)	p=0,910
Chloramphenicol	43,75 (160)	36,99 (73)	p=0,331
Erythromycin	15,73 (286)	21,43 (42)	p=0,353
Ciprofloxacin	20,30 (202)	21,57 (51)	p=0,841
Levofloxacin	29,84 (248)	33,33 (15)*	p=0,774
Vancomycin	83,63 (342)	75,68 (74)	p=0,105
llinezolid	35,8 (338)	44,59 (74)	p=0,157
Teicoplanin	84,83 (290)	86,30 (73)	p=0,752
Nitrofurantoin#	72,0 (246)	71,1 (38)	p=0,909

Note:
%S: percentage of isolates susceptible to antibiotics tested against total isolates
*: total number of isolates less than 30
#: only from urine specimen
p <0,05 significant

Extended-spectrum beta-lactamases (ESBL)

Before the pandemic, 3018 isolates of ESBL-producing bacteria were obtained (34.45%). The bacteria capable of producing ESBL included 1174 isolates of *K. pneumoniae* (13.40%), 1374 isolates of *E. coli* (15.68%), 66 isolates of *E. aerogenes* (0.75%), 294 isolates of *E. cloacae* (3.36%) and 110 other Enterobacteriaceae bacteria (1.26%). The other Enterobacteriaceae bacteria included Klebsiella spp 65 isolates (0.74%), Enterobacter spp 4 isolates (0.05%), *Kluyvera ascorbata* (26 isolates), *E. fergusonii* (1 isolate), *E. vulveneris* (1 isolate), *E. hermanii* (1 isolate), *Klyuvera intermedia* (2 isolates), *Cedecea lapagei* (2 isolates), *Cedecea reteri* (1 isolate), *Hafnia alfei* (3 isolates). Routella ornithinolytica (1 isolate), *Pleisomonas shigelloides* (2 isolates), *Pluralibacter gergoviae* (1 isolate).

During the pandemic, 1106 ESBL-producing bacteria were found (32.21%). The ESBL-producing bacteria included *K. pneumoniae* 494 isolates (14.39%), *E. coli* 452 isolates (13.16%), *E. aerogenes* 18 isolates (0.52%), *E. cloacae* 98 isolates (2.85%) and several other Enterobacteriaceae groups as many as 44 isolates (1.23%), which included Klebsiella spp (36 isolates), Enterobacter spp (1 isolate), *Hafnia alvei* (1 isolate), *Cedecea lapagei* (1 isolate), *Klyuvera ascorbata* (3 isolates), *Kluyvera intermedia* (1 isolate), *E. vulneris* (1 isolate). There was an increase in ESBL-producing bacteria from the intensive care unit, especially *K. pneumoniae*, *E. coli*, and *E. cloacae* species. There is also an increase in the pediatric ward, but only in *E. coli* species).

Carbapenem resistant

Prior to pandemic, there were 524 isolates of *A. baumannii* (5.98%) and during the pandemic, 205 isolates of *A. baumannii* were isolated (6%). Before the pandemic, 203 (38.74%) of 524 isolates *A. baumanni* were resistant to carbapenems. Meanwhile, during the pandemic, 91 isolates (44.39%) were resistant to carbapenem, from 205 isolates of *A. baumannii*. Thus, during the pandemic there was an increase in the prevalence of CRAB (Carbapenem Resistant *A. baumannii*) by 5.25% compared to before the pandemic. Prior to pandemic *Pseudomonas aeruginosa* were 619 isolates (7.07%), about 143 isolates (23.10%) among them were resistant to carbapenems. Meanwhile, during the pandemic, *P. aeruginosa* were 252 isolates (7.34%), about 59 isolates (24.41%) were resistant to carbapenem. Thus during the pandemic there was an increase in CRPA (Carbapenem Resistant *P. aeruginosa*) of 0.31% compared to before the pandemic. The prevalence of carbapenem resistant varied significantly before and during the pandemic. *E. cloacae* species and Citrobacter spp. both had a significant rise in carbapenem resistant. In *E. coli* species, there was a significant decline in carbapenem resistant. During the pandemic there was significant decrease susceptibility of *A. baumannii* and *P. aeruginosa* to amikacin.

Table 3
Comparison of the percentage of ESBL-producing bacteria

Species	before pandemic					during pandemic					P
	Non ESBL	ESBL			Total	Non ESBL	ESBL			Total	
	N	N	%*	%**		N	N	%*	%**		
K. pneumoniae	629	545	46,42	36,55	1174	307	187	37,85	34,63	494	P=0,002
E. coli	578	796	57,93	53,39	1374	160	292	64,60	54,07	452	P=0,014
E. aerogenes	53	13	19,70	0,87	66	15	3	16,67	0,56	18	P=0,961
E. cloacae	195	99	33,67	6,64	294	57	41	41,84	7,59	98	P=0,181
Other Enterobacteriaceae	72	38	34,54	2,54	110	27	17	38,63	3,15	44	P=0,769
Total	1527	1491	49,40	100	3018	566	540	48,82	100	1106	P=0,752

Note:
*: frequency relative to the total of the same species in the same period
**: frequency relative to total ESBL earners in a period

Table 4
Comparison of susceptibility patterns of ESBL-producing bacteria

Antibiotic	*K. pneumoniae*			*E. coli*			Enterobacter spp		
	before %S (N)	during %S (N)	P	before %S (N)	during %S (N)	P	before %S (N)	during %S (N)	P
Amikacin	92,83 (1171)	94,88 (488)	p=0,125	98,10 (1368)	96,67 (451)	p=0,077	96,2 (364)	98,3 (116)	p=0,268
Gentamycin	68,07 (1168)	73,91 (483)	p=0,019	71,40 (1367)	62,39 (444)	p<0,001	75,3 (364)	72,1 (111)	p=0,498
Aztreonam	52,05 (1168)	61,59 (492)	p<0,001	40,26 (1371)	34,67 (450)	p=0,035	58,4 (361)	52,6 (116)	p=0,267
Amoxicillin-Clavulanate	57,49 (1169)	67,21 (491)	p<0,001	42,01 (1364)	57,08 (452)	p<0,001	0,3 (362)	0,0 (117)	p=0,569
Ampicilllin	0,60 (1166)	0,0 (488)	p=0,086	8,92 (1356)	7,40 (446)	p=0,318	0,3 (360)	0,0 (117)	p=0,568
Ampicillin-Sulbactam	45,71 (1155)	56,12 (490)	p<0,001	24,74 (1362)	34,51 (452)	p<0,001	0,8 (363)	0,0 (116)	p=0,326
Piperacillin	37,08 (1122)	45,99 (474)	p=0,001	11,60 (1319)	12,90 (442)	p=0,467	47,6 (353)	46,5 (114)	p=0,838
PiperacillinTazobactam	77,31 (1168)	77,91 (489)	p=0,789	84,89 (1357)	83,85 (452)	p=0,594	75,2 (359)	79,5 (117)	p=0,345
Cefoxitin	72,19 (169)	61,22 (49)	p=0,141	77,05 (122)	81,25 (32)	p=0,610	12,2 (49)	14,3 (14)*	p=0,840
Cefazolin	45,22 (1108)	57,14 (455)	p<0,001	26,85 (1192)	19,43 (386)	p=0,003	0,6 (357)	0,0 (116)	p=0,419
Ceftazidime	52,60 (1171)	62,07 (493)	p<0,001	41,55 (1372)	35,03 (451)	p=0,014	67,8 (363)	59,5 (116)	p=0,102
Cefepime	49,48 (1154)	61,27 (488)	p<0,001	39,74 (1359)	33,70 (451)	p=0,022	57,9 (359)	58,6 (116)	p=0,897
Cefotaxime	52,73 (1172)	61,84 (490)	p=0,001	40,51 (1370)	34,67 (450)	p=0,027	59,3 (364)	61,2 (116)	p=0,721
Ceftriaxone	52,19 (1142)	60,94 (489)	p=0,001	38,58 (1335)	33,48 (442)	p=0,055	55,3 (351)	55,6 (117)	p=0,957
Cefoperazone-Sulbactam	75,11 (1161)	76,72 (451)	p=0,499	78,54 (1356)	79,90 (398)	p=0,559	77,2 (356)	78,4 (97)	p=0,818
Trimethoprim-Sulfamethoxazole	56,92 (1170)	64,27 (487)	p=0,006	36,22 (1361)	34,23 (447)	p=0,445	72,3 (364)	75,0 (116)	p=0,562
Tetracyclin	56,13 (1126)	61,54 (481)	p=0,044	26,08 (1315)	29,08 (447)	p=0,216	71,2 (351)	63,8 (116)	p=0,132
Tigecycline	56,33 (1019)	41,46 (398)	p<0,001	81,26 (1099)	73,51 (336)	p=0,002	61,8 (301)	37,9 (87)	p<0,001
Chloramphenicol	64,19 (997)	70,45 (440)	p=0,021	61,48 (732)	58,99 (278)	p=0,470	62,2 (299)	56,3 (103)	p=0,291
Ciprofloxacin	67,57 (1150)	59,25 (346)	p=0,004	39,60 (1341)	22,53 (364)	p<0,001	78,0 (355)	48,1 (81)	p<0,001
Levofloxacin	79,12 (1159)	75,38 (325)	p=0,149	40,47 (1364)	24,23 (359)	p<0,001	87,0 (361)	65,2 (69)	p<0,001
Moxifloxacin	65,25 (1108)	74,31 (471)	p<0,001	38,16 (1305)	33,41 (440)	p=0,074	74,9 (342)	70,2 (114)	p=0,326
Fosfomycin	72,56 (554)	61,42 (127)	p=0,013	90,80 (685)	88,72 (133)	p=0,455	78,0 (355)	48,1 (81)	p<0,001
Ertapenem	12/12			16/17					
Imipenem	82,04	80,21	p=0,386	89,25	83,07	p=0,001	74,4	63,5	p=0,024

	(1125)	(480)		(1321)	(443)		(348)	(115)	
Meropenem	87,94 (1161)	83,16 (487)	p=0,010	92,38 (1364)	89,58 (451)	p=0,062	90,2 (358)	91,3 (115)	p=0,731
Colistin	2/2			2/6	0,0 (1)				
Nitrofurantoin	11,64 (189)	11,76 (51)	p=0,980	89,7 (377)	88,1 (59)	p=0,724	21,2 (66)	0,0 (18)*	p=0,032

Note:
%S : percentage of isolates susceptible to the tested antibiotics
N : total number of isolates tested for antibiotics
p <0,05 significant

Table 5
Comparison of bacteria potentially resistant to carbapenem

Spesies	Before pandemic					During pandemic					p
	Non-carbapenem resisten	Carbapenem Resisten			Total	Non-carbapenem resisten	Carbapenem Resisten			Total	
	N	N	%*	%**	N	N	N	%*	%**	N	
K. pneumoniae	947	227	19,34	23,47	1174	384	110	22,27	24,55	494	p=0,173
A. baumannii	321	203	38,74	20,99	524	114	91	44,39	20,31	205	p=0,162
E. coli	1199	175	12,74	18,10	1374	368	84	18,58	18,75	452	p=0,002
P. aeruginosa	476	143	23,10	14,79	619	193	59	23,41	13,17	252	p=0,921
E. cloacae	235	59	20,07	6,10	294	68	30	30,61	6,70	98	p=0,043
E. aerogenes	29	37	56,06	3,83	66	4	14	77,78	3,13	18	p=0,094
Klebsiella spp	46	19	29,23	1,96	65	20	16	44,44	3,57	36	p=0,124
Pseudomonas spp	61	19	23,75	1,96	80	18	10	35,71	2,23	28	p=0,219
Serratia spp	45	16	26,23	1,65	61	13	3	18,75	0,67	16	p=0,537
Proteus mirabilis	131	14	9,66	1,45	145	31	5	13,89	1,12	36	p=0,458
Citrobacter spp	58	10	14,71	1,03	68	13	12	48,00	2,68	25	p=0,002
Enterobacteriaceae (others)	30	10	26,83	1,14	41	4	4	50,00	0,89	8	p=0,193
Acinetobacter spp	37	10	21,28	1,03	47	13	4	23,53	0,89	17	p=0,847
P. stuartii	41	9	18,00	0,93	50	11	2	15,38	0,45	13	p=0,825
M. *morganii*	45	8	15,09	0,83	53	14	3	17,66	0,67	17	p=0,801
Providencia spp	11	5	31,25	0,52	16	3	1	25,00	0,22	4	p=0,714
Proteus vulgaris	20	2	9,09	0,21	22	5	0	0,0	0,0	5	p=0,484
Enterobacter spp	4	0	0,0	0,0	4	1	0	0,0	0,0	1	
Total	3736	967	20,56	100	4703	1277	448	25,97	100	1725	p<0,001

Note
*: frequency relative to the total of the same species in the same period
**: relative frequency to total carbapenem-resistant bacteria

Fungi

Fungal prevalence increased by 2.79% (p 0.05) from 472 fungal isolates (5.3%) before the pandemic to 281 fungal isolates (8.18%) during pandemic. During the pandemic there was significant increase in the prevalence of *C. dubliniensis* species from the medical ward, *C. albicans* from the combined ward and emergency room, and significant decrease in the prevalence of *C. glabrata* from the medical ward and *C. tropicalis* from the intensive care unit. The susceptibility of fungus to antifungals during the pandemic is not significantly different than the susceptibility patterns before the pandemic).

Discussion

The specimens received by the DSSH clinical microbiology laboratory decreased during the pandemic. The decreased bed occupancy rate at the start of the pandemic was the cause of the reduced number of specimens. DSSH occupancy rate before the start of the pandemic was 83%, compared to 90% before the pandemic (Hakim et al., 2021). Various additional health services, such as the Kedung Cowek Field Hospital, have been opened by the government to treat COVID-19 patients with mild to moderate symptoms during the pandemic. Patients with mild to moderate symptoms of COVID-19 are treated at DSSH. Sputum (31.87%), urine (25.4%), wounds (20.89%), and blood were the most frequently analyzed specimens before to the pandemic (17.83%). Sputum (39.98%), blood (23.01%), wounds (17.36%), and urine were the most frequently analyzed specimens during the pandemic (16.34%). The number of isolates produced from blood increased by 5.18% during the pandemic compared to before it. This is comparable to a Sepulveda study, which discovered that during the pandemic, blood cultures were more in demand in New York by 34.8%, particularly among patients with COVID-19 (Sepulveda et al., 2020).

Sepulveda discovered that COVID-19 patients had significantly lower rates of bacteremia than people without the virus. Blood cultures from COVID-19 patients more typically reveal skin commensal microorganisms. According to the DSSH data, the majority of the species obtained from blood cultures during the pandemic were Staphylococus coagulase negative. When compared to before the pandemic, the number of isolates of *K. pneumoniae* and *E. coli* from blood was lower during the epidemic. Meanwhile, blood levels of *A. baumannii* (4.61% and 4.81%) and *P. aeruginosa* (2.88% and 3.03%) were similar to those before the pandemic. Before the pandemic, the most isolates were obtained from the medical ward (40.75%), surgical (25.25%), and IRD (11.79%). Meanwhile, during the pandemic, most of the isolates came from the medical ward (30.63%), intensive care (27.37%), and surgical (19.51%). Thus, there was a significant increase in intensive care of 17.88% compared to before the pandemic which was only 9.49% of all isolates. This is due to increase in the bed occupancy rate from intensive care during the pandemic (Noor et al., 2019).

Table 6
Comparison of susceptibility patterns of *A. baumannii* and *P. aeruginosa*

Antibiotic	*A.baumannii*	*P. aeruginosa*				
	before pandemic %S (N)	during pandemic %S (N)	p	before pandemc %S (N)	during pandemic %S (N)	p
Amikacin	68,5 (521)	59,4 (202)	p=0,020	88,7 (611)	93,3 (252)	p= 0,043
Gentamycin	39,3 (519)	38,4 (198)	p=0,821	70,0 (607)	71,5 (246)	p= 0,658
Aztreonam	0,0 (513)	1,0 (203)	p=0,024	47,6 (609)	48,4 (250)	p= 0,835
Amoxicillin-Clavulanate	0,0 (518)	0,5 (204)	p=0,111	0,3 (612)	0,0 (252)	p= 0,364
Ampicilllin	0,2 (510)	0,0 (201)	p=0,530	0,0 (604)	0,0 (251)	
Ampicillin-Sulbactam	60,3 (522)	56,6 (205)	p=0,353	0,2 (606)	0,0 (252)	p= 0,519
Piperacillin	40,7 (509)	40,5 (200)	p=0,967	77,0 (579)	77.6 (241)	p= 0,861
Piperacillin-Tazobactam	49,8 (520)	48,5 (204)	p=0,757	80,9 (608)	80,7 (249)	p= 0,947
Cefoxitin	2,6 (76)	2,7 (37)	p=0,982	0,0 (55)	0,0 (21)	
Cefazolin	0,6 (518)	0,0 (202)	p=0,278	0,2 (611)	0,0 (248)	p= 0,524
Ceftazidime	47,3(522)	44,1 (204)	p=0,437	72,1 (609)	73,1 (249)	p= 0,765
Cefepime	44,1 (519)	43,9 (198)	p=0,965	66,8 (590)	65,5 (249)	p= 0,712
Cefotaxime	26,5 (517)	23,6 (203)	p=0,430	1,5 (610)	0,4 (252)	p= 0,179
Ceftriaxone	4,8 (504)	4,5 (201)	p=0,872	22,5 (595)	24,0(250)	p= 0,641
Cefoperazone-Sulbactam	67,6 (516)	60,8 (171)	p=0,103	80,6 (608)	80,8 (234)	p= 0,954
Trimethoprim-Sulfamethoxazole	68,6 (523)	70,6 (204)	p=0,610	1,3 (605)	1,2 (250)	p= 0,885
Tetracyclin	46,2 (156)	45,8 (24)*	p=0,977	0,7 (595)	0,8 (248)	p= 0,833
Tigecycline	48,9 (444)	33,5 (158)	p=0,001	5,1 (507)	2,0 (205)	p= 0,056
Chloramphenicol	1,6 (504)	2,0 (199)	p=0,697	0,9 (584)	0,8 (251)	p= 0,931
Ciprofloxacin	45,2 (520)	46,8 (201)	p=0,704	64,3 (588)	69,1(246)	p= 0,181
Levofloxacin	47,1 (518)	48,8 (203)	p=0,687	64,7 (607)	66,5 (248)	p= 0,618
Moxifloxacin	57,14 (56)			48,9 (45)	100 (1)*	p=0,312
Fosfomycin	7,9 (38)	25,0 (4)*	p=0,268	56,4 (55)	0,0 (6)*	p= 0,009
Imipenem	61,9 (506)	56,5 (200)	p=0,190	78,5 (576)	77,7 (247)	p= 0,814
Meropenem	61,9 (515)	55,8 (199)	p=0,131	85,1 (605)	88,4 (251)	p= 0,201
Colistin	100 (15)*	100 (1)*		6,7 (30)	0,0 (30)	p= 0,453

Nitrofurantoin	1,3 (75)	0,0 (17)*	p=0,632	2,9 (104)	7,7 (26)*	p= 0,254

Note:
%S : percentage of isolates susceptible to the tested antibiotics
N : total isolates tested
p <0,05 significant

The number of fungal isolates increased during the pandemic by 2.79 % in compared to before it. Similar to a study by Seagle, which discovered that COVID-19 patients who are hospitalized for extended periods of time are at high risk of infection due to the use of corticosteroids, an immune system imbalance, and a significant demand for ventilator use, this is presumed to be due to a link between COVID-19 and fungal infection as well as the use of anti-inflammatory steroids (Seagle et al., 2022). Before the pandemic, there were 605 *S. aureus* isolates (6.91%), while there were 198 isolates during the pandemic (5.77%). This finding is comparable to that of Hirabayashi et al, who found that the isotation rate of S. aureus decreased during the pandemic. Several preventive measures taken during the pandemic to reduce COVID-19 transmission, such as hand washing, using hand sanitizers, wearing gloves, and avoiding close contact, are thought to be responsible for the decline in *S. aureus* isolates (Hirabayashi et al., 2021). The decline in *S. pneumoniae* and *H. influenzae* isolation rates is likely being attributed to the use of masks as well as various government recommendations to reduce COVID-19 transmission, such as maintaining distance from others, avoiding crowds, reducing mobilization, and completing online education.

MRSA prevalence increased by 2.66% from 25.12% to 27.78% during the pandemic. VRSA prevalence decreased by 1.95% during the pandemic from 3.47% to 1.52%, from before the pandemic. This condition is similar to the findings of Polly (Polly et al., 2020). which stated that in Brazil during the pandemic there was an increase in MRSA. It is suspected that the increase in MRSA in this study occurred because MRSA is the most common bacterial co-infection and the cause of death in influenza patients (Sepulveda et al., 2020). Most MRSA isolates before the pandemic and during the pandemic were obtained from wound, blood and sputum specimens. However, during the pandemic there was an increase in the relative frequency of MRSA isolated from blood (24.34% to 30.91%) and from sputum (17.76% to 21.82%). These results are consistent with the Westblade study which stated that MRSA is associated with co-infection in COVID-19 patients.

During the pandemic there was statistically significant increase in the sensitivity of *S. aureus* to tetracycline. However, the increase in sensitivity is still below 70%, so tetracyclines cannot be used as empirical therapy even though there has been a significant increase in sensitivity compared to before the pandemic. During the pandemic there was also an increase in the sensitivity of *S. aureus* to ciprofloxacin and levofloxacin, but the increase was not statistically significant, although the increase increased to more than 70% of isolates sensitive to ciprofloxacin and levofloxacin. During the pandemic there was also decrease in the sensitivity of *S. aureus* to vancomycin and teicoplanin, with statistical analysis, $p < 0.05$. Thus, during the pandemic there was a significant decrease in the sensitivity of *S. aureus* to vancomycin and teicoplanin. However, the percentage of concentrated *S. aureus* isolates to vancomycin and teicoplanin was still more than 70%.

Enterococcus isolates made up 357 of the total isolates before the pandemic (4.08%) and 76 of the total during the pandemic (2.21%). As a result, there was 2.59% decrease in the relative frequency of Enterococcus isolates during the pandemic compared to before the pandemic. However, the decrease in the relative frequency of Enterococcus isolates coincided with the increased prevalence of VRE during the pandemic, from 15.41% to 21.05%, or an increase of 5.64% ($p = 0.301$). According to the Riordan study, which found no appreciable differences between VRE prevalence before and during the pandemic, comparable conditions were discovered throughout Europe (O'Riordan et al., 2022). In comparison to before the pandemic, the relative frequency of E. coli ESBL and E. cloacae ESBL increased during the epidemic. Meanwhile, compared to before the pandemic, the relative frequency of *K. pneumoniae* ESBL and *E. aerogenes* ESBL declined during the epidemic.

The prevalence of carbapenem resistance increased by 5.41% during the pandemic compared to before the pandemic ($p < 0.05$). Polly et al. found comparable results in their research, Carbapenem resistance was primarily discovered in intensive care and medical wards, as well as in sputum and blood samples. This is thought to be linked to the prevalence of co-infections in COVID-19 patients, particularly those who spend a lengthy period in the isolation ward, ICU, on broad-spectrum antibiotics, and on a ventilator (Westblade et al., 2021). The bias produced by the culture of taking specimens and sending cultures when patient has been hospitalized for a long time, has undergone antibiotic medication, and is in severe condition can also contribute to the high occurrence of carbapenem resistance (Huttner et al., 2020). The PPRA Committee closely monitors the use of carbapenem antibiotics, ensuring that each class of carbapenem is only used as definitive therapy after culture results and conformity to the patient's clinical situation. The DSSH has seen an upsurge in carbapenem-resistant bacteria. This is type A referral hospital that receives patients from various locations, and these recommended patients have already had antibiotic medication before being referred.

Conclusion

The microorganism profiles are different before and during the pandemic, significant decrease in the prevalence of *E. coli* and *S. aureus*, significant increase in Candida spp. and carbapenem-resistant Enterobacteriaceae, particularly *E. coli, E. cloacae*, and Citrobacter spp, and significant alterations of susceptibility patterns in *S. aureus, K. pneumoniae, E. coli, A. baumannii,* and *P. aeruginosa*.

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