Original Research Article

Assess Antibiotic Resistance During Covid-19 Pandemic in Saudi Arabia

Abstract: Owing to disparities in the intensity of the breakouts, state and federal regulations, accessible means, cultural elements, and social consciousness, the global reaction to the COVID-19 pandemic has been varied. The COVID-19 pandemic, on the other hand, has had an impact on all parts of society, notably efforts to combat antimicrobial resistance (AMR). The pandemic has highlighted that a greater burden on medical infrastructure can contribute to higher, often unnecessary antibiotic usage and a de-prioritization of antimicrobial stewardship and surveillance (AMS). The focus of this research is to see if there is a growth in antibiotic resistance during the covid-19 pandemic in the King Salman Hospital in Riyadh, Saudi Arabia, and to investigate the subcomponent that leads to antibiotic resistance. This is a comprehensive review of patients hospitalized at the King Salman Hospital in Riyadh, Saudi Arabia, who were admitted to the Intensive Care Unit (ICU) during the first wave of the covid-19 pandemic, which occurred between March and August 2020. An analysis of the case dataset was performed to determine the rise in antibiotic resistance and relate it to resistant cases before the pandemic (September 2019 to February 2020). Before and throughout the pandemic, fifteen kinds of bacteria were found, with K pneumonia being the most prevalent bacteria (49; 30.6 %), and Ac. Baum/haem being the most removable bacteria during the pandemic (74; 37.3%). Cephalosporin antibiotics, in notably cefotaxime/k.c and ceftazidime/k (100%), cefazolin (96.3%), ceftriaxone (96%), cefuroxime and ceftazidime (95%), cefotaxime ((94.7%). These antibiotics also had the same amount of resistance during the pandemic. In pre-covid-19 and during covid-19, these findings were congruent with the penicillin antibiotics class, ampicillin, and piperacillin (96.3 % and 92.1 %), accordingly. It is presently uncertain if COVID-19 patients would develop new or growing antibiotic resistance in locations with low historical prevalence, but this should be investigated in retrospective and future clinical and microbiology research.

Keywords: COVID-19, Pandemic, Antimicrobial Resistance, Antibiotic

1. Introduction

Given the disparity in the intensity of the breakouts, state and federal regulations, accessible means, cultural elements, and social consciousness, the global reaction to the COVID-19 pandemic has been varied. Numerous states, on the other hand, attempted to guarantee that their health-care systems could deal with a high-predicted percentage of acute cases, but a variety of strategies were

used, spanning from rigorous, mandated lockdowns to ambiguous and encouraging physical distancing advice [1; 2].

The COVID-19 pandemic, on the other hand, has had an impact on all parts of society, such as efforts to combat antimicrobial resistance (AMR). The pandemic has highlighted that a greater burden on medical infrastructure can contribute to higher, sometimes unnecessary antibiotic utilization and a de-prioritization of antimicrobial stewardship and surveillance (AMS) [3; 4; 5].

There has been a considerable use of broad-spectrum antibiotics in COVID-19 patients [6]. Although more information is needed, early information (discussed below) suggests that outpatient antibiotic usage has been reduced in several contexts. This could be owing to an absence of availability to healthcare because of lockdowns and physical distancing, or it could be owing to a reduction in the transmission of other pathogens in specific circumstances or a mix of the two. Yet, initially in the COVID-19 pandemic, treating the large percentage of hospitalized COVID-19 patients with antibiotics, boosted antibiotic consumption relative to the pre-pandemic timeframe [7; 8; 9].

Many states have provided information to the WHO demonstrating alarming percentages of antibiotic resistance [10; 11]. According to [5], 72 percent of COVID-19 patients who were admitted got antibiotics, although only 8% had superimposed bacterial or fungal co-infections. There is a clear correlation between covid-19 and antibiotic resistance, and experts should begin to investigate its implications in medical guidelines and legislation [12]. Because severely sick patients are always at risk of secondary infection, hospital practitioners provide antibiotics to them to prevent infection [13]. Bacterial/fungal coinfection is uncommon among COVID-19 patients. It only accounted for 8% of the research surveyed [5]. Although the minimal number of cases of coinfection with COVID-19, antibiotic usage is on the rise [14].

Almost all the characteristics connected to acute SARS-CoV-2 contamination, such as inherent illnesses, old age, collective accommodation, and placement in an assisted living home for the elderly, are also related to an elevated likelihood of multidrug-resistant pathogens [15; 16].

The focus of this research is to see if there is a growth in antibiotic resistance throughout the covid-19 pandemic in the King Salman Hospital in Riyadh, Saudi Arabia, and to investigate the contributing elements that lead to antibiotic resistance.

2. Method

This is a retrospective analysis of patients hospitalized at the King Salman Hospital in Riyadh, Saudi Arabia, who were hospitalized to the Intensive Care Unit (ICU) during the first wave of the covid-19 pandemic, which occurred between March and August 2020. An analysis of the case dataset was performed to determine the rise in antibiotic resistance and relate it to resistant cases

before the pandemic (September 2019 to February 2020). The hospital information system (HIS) included all the basic patient data, medical assessment, antibiotic kinds, microbiological sensitivity test needs, and findings. To generate the appropriate statistics, the data was input into SPSS V.20. The connections between the attributes were investigated using a chi-square test. When $p< 0.05$, the findings were deemed statistically substantial. The IRB committee of (H1RE-24-NOV20-01) granted ethical clearance.

3. Results and Discussion

Number of Hospital's Wards Asked for Microbiology Sensitive Test

According to the report, roughly 160 microbiological sensitivity tests were requested from 13 wards in the hospital before the pandemic, with the most coming from the ICU (58 requests). Throughout the pandemic, just seven wards in the hospital were sought for microbiology sensitivity tests, with a total of 126 requests made all through the research timeframe. The ICU, on the other hand, made 109 requests. Table (1) shows.

Table (1): Number of Microbiology Sensitive Tests Based on Hospital Ward

Hospital Ward	Pre-Covid-19 (Study Period)	During Covid-19 (Study Period)	Total
Surgical Ward (A1)	15	2	17
Surgical Ward (A2)	6	2	8
Medical Ward (B1)	11	3	14
Medical Ward (B2)	8	0	8
Medical Ward (C1)	10	0	10
Children and Maternity Ward (C2)	6	1	7
Sleeve Surgery (D1)	1	0	1
Day Surgery Unit (D2)	3	0	3
Emergency Room (ER)	19	7	26
Intensive Care Unit (ICU)	58	109	167
Neonate Intensive Care Unit (NICU)	13	0	13
Out-Patient Department (OPD)	9	2	11
Paediatric Intensive Care Unit (PICU)	1	0	1
Total	160	126	286

Numbers and Types of Detected Bacteria

Earlier and throughout the pandemic, fifteen kinds of bacteria were found, with K. pneumoniae being the most prevalent bacteria (49; 30.6%), and Ac. Baum/Haem being the most removable bacteria throughout the pandemic (74; 37.3%). K. pneumoniae, on the other hand, stayed one of the most common bacteria among patients throughout the pandemic (39; 31 %). E. Coli was among the

top tenacious pathogens before and throughout the pandemic (46, 28.8%; 16, 12.7%) accordingly. In the pandemic, pathogens like B. Cepacia Cplx, Citrobacter Farmeri, K. aerogens, K. ozaenae, and Stenotrophomonas Maltophilia were identified. Before the pandemic, these pathogens were not found in patients. C. freundii, C. koseri, E. cloacae, K. oxytoca, M. Morganii, and Providnice stuartii, on the other hand, were first discovered before the pandemic. Table (2) shows.

Table (2): Types and Numbers of Bacteria

Bacteria	Pre-Covid-19 (Study Period) (%)	During Covid-19 (Study Period) (%)	Total
A. baum	7 (4.4)	5 (5.6)	12
A. baum./calco	9 (5.6)	1 (0.8)	10
Ac. Baum/haem	18 (11.3)	47 (37.3)	65
B. Cepacia Cplx	0	1 (0.8)	1
C. freundii	1 (0.6)	0	1
C.koseri	1 (0.6)	0	1
Citrobacter Farmeri	0	1 (0.8)	1
E. cloacae	3 (1.9)	0	3
E. coli	46 (28.8)	16 (12.7)	62
E. faecalis	3 (1.9)	1 (0.8)	4
k pneumoniae	49 (30.6)	39 (31.0)	88
K. aerogens	0	1 (0.8)	1
K. oxytoca	1 (0.6)	0	1
K. ozaenae	0	2 (1.6)	2
M. Morganii	1 (0.6)	0	1
P. mirabillis	6 (3.8)	2 (1.6)	8
P.aeruginosa	7 (4.4)	6 (4.8)	13
Providnice stuartii	1 (0.6)	0	1
S. aureus	7 (4.4)	3 (2.4)	10
Stenotrophomonas Maltophilia	0	1 (0.8)	1
Total	160	126	286

Microbiology Sensitive Test

According to the full resistance or sensitivity results, Cephalosporin antibiotics, in notably cefotaxim/k.c and ceftazidime/k (100%), cefazolin (96.3%), ceftriaxone (96%), cefuroxime and ceftazidime (95%), cefotaxime ((94.7 percent). These antibiotics also had an identical amount of resistance throughout the pandemic. In pre-covid-19 and during covid-19, these findings were equivalent with the penicillin antibiotics class, ampicillin, and piperacillin (96.3 % and 92.1 %) accordingly. When contrasted to their resistance values preceding the pandemic, carbapenem antibiotics reported a marked rise in resistance (meropenem (40 %; 67 %), ertapenem (59.2 %; 86 percent), and imipenem (61.8 %; 90.7 %). The aminoglycoside antibiotics tobramycin, gentamicin, and amikacin (53.7 %, 81.1 %, 56.6 %, 65.5 %, 31.5 %, and 63.5 %, accordingly) are in the identical posi-

tion. In both timeframes, though, full sensitivity to linezolid, rifampin, and vancomycin was observed. More information is available in table (3).

Table (3): Microbiology Sensitive Test

Antibiotic Class	Antibiotic	Pre-COVID1					DURING covid-19				
		Resistance (R)/sensitivity (S)		total test	R%	S%	Resistance (R)/sensitivity (S)		total test	R%	S%
		R	S	total test	R%	S%	R	S	total test	R%	S%
Fluoroquinolones	Norfloxacin	19	6	25	76.0	24.0	6	3	9	66.7	33.3
	Levofloxacin	88	64	152	57.9	42.1	93	26	119	78.2	21.8
	Ciprofloxacin	103	48	151	68.2	31.8	101	19	120	84.2	15.8
Carbapenems	Meropenem	58	87	145	40.0	60.0	77	38	115	67.0	33.0
	Ertapenem	42	29	71	59.2	40.8	43	7	50	86.0	14.0
	Imipenem	47	29	76	61.8	38.2	68	7	75	90.7	9.3
Aminoglycosides	Tobramycin	22	19	41	53.7	46.3	60	14	74	81.1	18.9
	Gentamicin	82	63	145	56.6	43.4	76	40	116	65.5	34.5
	Amikacin	46	100	146	31.5	68.5	73	42	115	63.5	36.5
Penicillin	Piperacillin / Tazobactam	19	15	34	55.9	44.1	65	15	80	81.3	18.8
	Piperacillin	93	8	101	92.1	7.9	78	4	82	95.1	4.9
	Amoxacillin/k clav	87	27	114	76.3	23.7	53	16	69	76.8	23.2
	Oxacillin	1	1	2	50.0	50.0	1	2	3	33.3	66.7
	Ampicillin	129	5	134	96.3	3.7	73	4	77	94.8	5.2
Cephalosporins	cefazolin	79	3	82	96.3	3.7	40	3	43	93.0	7.0
	cefepime	139	11	150	92.7	7.3	108	9	117	92.3	7.7
	Cefoxitin	61	58	119	51.3	48.7	42	30	72	58.3	41.7
	cefotaxime	71	4	75	94.7	5.3	68	4	72	94.4	5.6
	cefotaxime/ K clavulanate	3	-	3	100.0	0.0	0	0	0	0	0
	Ceftriaxone	48	2	50	96.0	4.0	31		31	100.0	0.0
	Cephalothin	49	3	52	94.2	5.8	27	2	29	93.1	6.9
	Ceftazidime	115	6	121	95.0	5.0	100	7	107	93.5	6.5
	Ceftazidime/ K clavulanate	1		1	100.0	0.0	0	0	0	0	0
	Cefuroxime	116	6	122	95.1	4.9	66	3	69	95.7	4.3
Oxazolidinones	Linezolid	-	7	7	0.0	100.0	-	5	5	0.0	100.0
Polypeptides Polymyxins	Colistin	11	3	14	78.6	21.4	28		28	100.0	0.0
Macrolides	Clindamycin	1	1	2	50.0	50.0	1	2	3	33.3	66.7
Monobactams	Aztreonam	80	8	88	90.9	9.1	62	1	63	98.4	1.6
Phosphonic acid derivatives	Fosfomycin	11	63	74	14.9	85.1	8	39	47	17.0	83.0
Nitrofurantoins	Nitrofurantoin	33	29	62	53.2	46.8	20	13	33	60.6	39.4
Ansamycins	Rifampin	-	3	3	0.0	100.0	1	4	5	20.0	80.0

Glycopeptides and Lipoglycopeptides	Vancomycin	-	2	2	0.0	100.0		4	4	0.0	100.0
Glycylcyclines	Tigecycline	18	85	103	17.5	82.5	4	45	49	8.2	91.8
Tetracyclines	Tetracycline	60	30	90	66.7	33.3	56	18	74	75.7	24.3
Sulfonamides,	Trimethoprim / Sulfamethoxazole	106	40	146	72.6	27.4	87	30	117	74.4	25.6
Lincosamides	Clindamycin	1	1	2	50.0	50.0	1	2	3	33.3	66.7
Amphenicols	Chloramphenicol	0	1	1	0.0	100.0	1	4	5	20.0	80.0

Types of Bacterial Resistance

The most common resistant types of bacteria observed prior to the pandemic were Extended Spectrum β- Lactamase (ESBL), Multi-Drug Resistant (MDR) and Carbapenem-resistant Enterobacteriaceae (CRE) (61; 45; 17), respectively. On the other hand, the most dominant resistant types during the COVID-19 pandemic were Pan- Drug Resistant (PDR) (34), (ESBL) (27) and the (CRE) (23). Significant records prior to and during the pandemic were noted for Extended-Drug Resistant (XDR) and the Carbapenem/Multi-Drug Resistant (MDR-ESBL), respectively. Table (4).

Table (4): Types of Bacterial Resistant

Resistant type	Pre-covid-19 (study period)	during covid-19 (study period)	Total
CRE	17	23	40
ESBL	61	27	88
MDR	45	7	52
MDR-CRE	3	5	8
MDR-ESBL	13	12	25
MRSA	1	1	2
PDR	7	34	41
XDR	13	16	29
XDR-CRE	0	1	1
Total	160	126	286

When the pandemic was in its preliminary stages, challenges were created by the interplay of unsuitable and excessive use of antibiotics and insufficient access to suitable treatment. The infections caused by pathogens that occur simultaneously with COVID-19 after being admitted to the hospital or being diagnosed with COVID-19 are known as co-infections. On the other hand, secondary infections are those that occur following the start of COVID-19 and are typically linked to healthcare. These infections are aggravated by invasive processes and the intake of immunosuppressant drugs [17; 18]. Empirical therapy at the hospital admission is based on possible co-infections,

whereas antibiotic use following the hospital admission is driven by secondary infections, which can be prevented by undertaking appropriate infection prevention and control measures. The findings of meta-analyses showed that a bacterial or fungal infection was diagnosed in 7 to 8% of the COVID-19 patients admitted [5; 19; 20]. These infections were more prevalent in patients admitted to the intensive care unit (ICU) (8-14%) compared to patients in other departments (4-6%). According to the results, co-infections were recorded in merely 3.5% of the patients (95% CI 0.4 to 6.7%) and secondary infections were found to occur in 14.3% of the patients (95% CI 9.6 to 18.9%). Mycoplasma species, Pseudomonas aeruginosa and Haemophilus influenzae were the bacterial co-pathogens found most often, which is contradictory to the results of our study [21; 22]. These studies, however, had heterogeneous criteria for co-infections and sampling for co-pathogens. Hence, it is important to have prospective, well-formulated studies using suitable definitions. Though low levels of bacterial infection were reported, there was high use of antibiotics in COVID-19 patients: antibiotics had been administered to 71.9% (95% CI 56.1 to 87.7%) of COVID-19 patients [21].

It is important to note that fluoroquinolones and third-generation cephalosporins constituted 74% of the antibiotics prescribed. An increase in the use of amoxicillin-clavulanic acid in the initial weeks of the pandemic was seen, which was essentially done to counter co-infections. Subsequently, an increase in the use of broader spectrum drugs was noted, mainly to counter secondary infections [23; 24]. There was a considerable increase in antibiotic days of treatment for every 1000 bed days of care at a hospital independent of a COVID-19 epicentre in the USA from March 2020 to June 2020. The increases were mainly noted for macrolides and non-antipseudomonal penicillin, which the hospital prescribed as the primary treatment for community-acquired pneumonia [9]. On the contrary, co-infections may be underestimated because of the empirical and extensive use of antibiotics in COVID-19 patients. At present, there is inadequate data from low- and middle-income countries (LMICs) that presents differences in the use of antibiotics and presence of co-infections. Lucien et al. recently discussed the need to perform studies on the global evolution of AMR during the pandemic, concentrating on the issues encountered by LMICs [23].

There are various hypothetical justifications for the difference in the percentage of patients suffering from bacterial co-infections or secondary infections and those using antibacterial agents. For example, it may be due to the reaction to the medical uncertainties in the best management of COVID-19 patients in the initial weeks of the pandemic. The opportunities to carry out informed therapy instead of administration of antibiotics on an empirical basis was reduced because of the risk of medical staff getting infected with COVID-19, the limited health resources and issues with supply chain that decreased the collection of samples for microbiological assessments. The decrease in antibiotic stewardship activities is possibly because of healthcare resources and experts being redirected to the response to COVID-19 [25].

Most of the COVID-19 patients (80%) are managed on an outpatient basis because they suffer from uncomplicated illness. Though very few studies have been carried out dealing with COVID-19 cases in the community, there is well-documented evidence of inappropriate use of antibiotic in self-limiting, viral upper respiratory tract infections in non-hospitalized environments [26; 27]. Therefore, inappropriate usage of antibiotics is equally prevalent, if not more, in community settings, particularly where antibiotics can be acquired online and from informal drug suppliers, without the need of a prescription.

According to the findings of research, there is a lower use of antibiotics in COVID-19 outpatients and in hospitals independent of COVID-19 epicentres [28; 29]. The correlation between modifications in antibiotic use in the community and possible side effects in the future should be monitored. If lockdowns and social distancing measures are removed, there may be an increase in the occurrence

of infections and the number of people requiring healthcare services, and this may lead to higher antibiotic prescriptions. This would be further exacerbated with an increase in prevalence of seasonal influenza and other respiratory viruses. Using surveillance systems and simple, timely and affordable differential diagnostics, along with support for research projects, would help in determining where there is overuse of antibiotics and how antibiotic use effects the epidemiology of drug-resistant infections. This is specifically required in LMICs, where there is limited data on the use and resistance of antibiotics.

There is inadequate knowledge about the effect of the COVID-19 pandemic on AMR [30]. There would possibly be positive effects of concentrating on the significance of hand hygiene and appropriate use of personal protective equipment (PPE). However, because of the high number of patients and lack of availability of PPE, the transmission of multi drug-resistant bacteria is possibly increased. The data available should offer better information regarding antibiotic prescription in the COVID-19 pandemic. It was suggested by WHO in a recent bulletin that AMS functions should be incorporated as an element of the COVID-19 pandemic response across the overall health system by carrying out five measures, which include the adoption of a research agenda to prevent the occurrence of AMR diseases and infections [31; 32].

The vulnerability of the healthcare system has become evident in the COVID-19 pandemic. This is more evident in LMICs and in resource-limited settings lacking in infrastructure and staff and that are not adequately prepared to handle pandemics or other contingencies [33; 34; 35]. Infection rates, antibiotics usage and subsequent increase or decrease in antibiotic resistance may be distinct in most of these settings. For COVID-19 as well as AMR, laboratory infrastructure, diagnostic ability and surveillance are unreliable, and often not available in various LMICs settings [36].

Furthermore, there are evidently suboptimal, and in most cases, unsustainable infection prevention and control policies, personnel and practice. In those settings where it is not easy to get antibiotics without prescription and where there is widespread availability of substandard and fake medicines, expectations for regulated use of antibiotics are not easy to implement. Along with this, there are limited socio-behavioural interventions like physical distancing and hand hygiene, and majority of the population is living in deprived conditions, particularly in high population density regions, like informal settlements, where access to sanitation services and clean water is substandard. Furthermore, LMICs also face the challenge of simultaneously managing the threat of multiple infectious diseases. A more serious disease and higher death rates in patients co-infected with TB and COVID-19 is shown in the preliminary reports [37]. As long as the existing trends are not reversed, there will possibly be a similar impact of increasing levels of MDR TB on LMICs in the future, with estimates indicating that drug-resistant TB will account for 2.6 million of the overall 10 million annual deaths caused by AMR by the year 2050 [38; 39]. An exit strategy from COVID-19 for most LMICs may not be of a short-term nature pharmacologically, and a greater number of community-based approaches are presently being examined [40].

4. Conclusions

The economic and societal effect of an unregulated infectious disease has become evident in the COVID-19 pandemic, which is similar to what has been forecasted for AMR in various reports. The COVID-19 pandemic has several consequences, one of which is the vital potential effect on AMR by altering the use of antibiotics and health-seeking behaviour, and also through infection prevention and control measures. It is vital to identify these effects on AMR for supporting good practices and giving priority to research. In terms of predictable AMR, exhibiting a proactive approach will

prevent us from being reactive in the future, which we have to be in terms of the COVID-19 pandemic. However, if AMR is not addressed, it may have similar outcomes that span over a greater time frame. Whether or not new or developing antibiotic resistance in areas having low rates earlier will arise in COVID-19 patients is not known; hence, retrospective and prospective clinical and microbiology studies need to evaluate this.

References

1 CLANCY, C. J.; NGUYEN, M. H. Coronavirus Disease 2019, Superinfections, and Antimicrobial Development: What Can We Expect? Clin Infect Dis, v. 71, n. 10, p. 2736-2743, 12 17 2020. ISSN 1537-6591. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/32361747 >.

2 NETWORK, E. A. R. S. Surveillance of antimicrobial resistance in Europe 2018. 2018.

3 LYNCH, C.; MAHIDA, N.; GRAY, J. Antimicrobial stewardship: a COVID casualty? Journal of Hospital Infection, v. 106, n. 3, p. 401-403, 2020. ISSN 0195-6701.

4 YANG, X. et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. The Lancet Respiratory Medicine, v. 8, n. 5, p. 475-481, 2020. ISSN 2213-2600.

[5] RAWSON, T. M. et al. Bacterial and Fungal Coinfection in Individuals With Coronavirus: A Rapid Review To Support COVID-19 Antimicrobial Prescribing. Clin Infect Dis, v. 71, n. 9, p. 2459-2468, 12 03 2020. ISSN 1537-6591. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/32358954 >.

[6] ABELENDA-ALONSO, G. et al. Antibiotic prescription during the COVID-19 pandemic: a biphasic pattern. Infection Control & Hospital Epidemiology, v. 41, n. 11, p. 1371-1372, 2020. ISSN 0899-823X.

[7] BEOVIĆ, B. et al. Antibiotic use in patients with COVID-19: a 'snapshot'Infectious Diseases International Research Initiative (ID-IRI) survey. Journal of antimicrobial chemotherapy, v. 75, n. 11, p. 3386-3390, 2020. ISSN 0305-7453.

[8] VELASCO-ARNAIZ, E. et al. Pediatric antimicrobial stewardship in the COVID-19 outbreak. Infection Control & Hospital Epidemiology, v. 42, n. 5, p. 642-644, 2021. ISSN 0899-823X.

[9] BUEHRLE, D. J. et al. Antibiotic consumption and stewardship at a hospital outside of an early coronavirus disease 2019 epicenter. Antimicrobial agents and chemotherapy, v. 64, n. 11, p. e01011-20, 2020. ISSN 0066-4804.

[10] NESTLER, M. J. et al. Impact of COVID-19 on pneumonia-focused antibiotic use at an academic medical center. Infection Control & Hospital Epidemiology, v. 42, n. 7, p. 915-916, 2021. ISSN 0899-823X.

[11] ORGANIZATION, W. H. Record number of countries contribute data revealing disturbing rates of antimicrobial resistance; 2020 2020.

[12] NIEUWLAAT, R. et al. Coronavirus Disease 2019 and antimicrobial resistance: parallel and interacting health emergencies. Clinical Infectious Diseases, v. 72, n. 9, p. 1657-1659, 2021. ISSN 1058-4838.

[13] ZHOU, M.; ZHANG, X.; QU, J. Coronavirus disease 2019 (COVID-19): a clinical update. Frontiers of medicine, v. 14, n. 2, p. 126-135, 2020. ISSN 2095-0225.

[14] LAI, C.-C. et al. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges. International journal of antimicrobial agents, v. 55, n. 3, p. 105924, 2020. ISSN 0924-8579.

[15] BERENGUER, J. et al. Characteristics and predictors of death among 4035 consecutively hospitalized patients with COVID-19 in Spain. Clinical Microbiology and Infection, v. 26, n. 11, p. 1525-1536, 2020. ISSN 1198-743X.

[16] SAFDAR, N.; MAKI, D. G. The commonality of risk factors for nosocomial colonization and infection with antimicrobial-resistant Staphylococcus aureus, enterococcus, gram-negative bacilli, Clostridium difficile, and Candida. Annals of internal medicine, v. 136, n. 11, p. 834-844, 2002. ISSN 0003-4819.

[17] BENGOECHEA, J. A.; BAMFORD, C. G. SARS-CoV-2, bacterial co-infections, and AMR: the deadly trio in COVID-19? EMBO molecular medicine, v. 12, n. 7, p. e12560, 2020. ISSN 1757-4676.

[18] LANSBURY, L. et al. Co-infections in people with COVID-19: a systematic review and meta-analysis. Journal of Infection, v. 81, n. 2, p. 266-275, 2020. ISSN 0163-4453.

[19] LANGFORD, B. J. et al. Bacterial co-infection and secondary infection in patients with COVID-19: a living rapid review and meta-analysis. Clinical Microbiology and Infection, 2020. ISSN 1198-743X.

[20] GARCIA-VIDAL, C. et al. Incidence of co-infections and superinfections in hospitalized patients with COVID-19: a retrospective cohort study. Clinical Microbiology and Infection, v. 27, n. 1, p. 83-88, 2021. ISSN 1198-743X.

[21] VAUGHN, V. M. et al. Empiric antibacterial therapy and community-onset bacterial coinfection in patients hospitalized with coronavirus disease 2019 (COVID-19): a multi-hospital cohort study. Clinical Infectious Diseases, v. 72, n. 10, p. e533-e541, 2021. ISSN 1058-4838.

[22] CHANG, C.-Y.; CHAN, K.-G. Underestimation of co-infections in COVID-19 due to non-discriminatory use of antibiotics. Journal of Infection, v. 81, n. 3, p. e29-e30, 2020. ISSN 0163-4453.

[23] LUCIEN, M. A. B. et al. Antibiotics and antimicrobial resistance in the COVID-19 era: Perspective from resource-limited settings. International Journal of Infectious Diseases, v. 104, p. 250-254, 2021. ISSN 1201-9712.

[24] HUGHES, S. et al. Bacterial and fungal coinfection among hospitalized patients with COVID-19: a retrospective cohort study in a UK secondary-care setting. Clinical Microbiology and Infection, v. 26, n. 10, p. 1395-1399, 2020. ISSN 1198-743X.

[25] HUTTNER, B. et al. COVID-19: don't neglect antimicrobial stewardship principles! Clinical Microbiology and Infection, v. 26, n. 7, p. 808, 2020.

[26] DEKKER, A. R.; VERHEIJ, T. J.; VAN DER VELDEN, A. W. Inappropriate antibiotic prescription for respiratory tract indications: most prominent in adult patients. Family practice, v. 32, n. 4, p. 401-407, 2015. ISSN 1460-2229.

[27] GULLIFORD, M. C. et al. Continued high rates of antibiotic prescribing to adults with respiratory tract infection: survey of 568 UK general practices. BMJ open, v. 4, n. 10, p. e006245, 2014. ISSN 2044-6055.

[28] STEVENS, R. W. et al. Antimicrobial prescribing practices at a tertiary-care center in patients diagnosed with COVID-19 across the continuum of care. Infection Control & Hospital Epidemiology, v. 42, n. 1, p. 89-92, 2021. ISSN 0899-823X.

[29] VADUGANATHAN, M. et al. Prescription fill patterns for commonly used drugs during the COVID-19 pandemic in the United States. Jama, v. 323, n. 24, p. 2524-2526, 2020. ISSN 0098-7484.

[30] RAWSON, T. M. et al. Antimicrobial use, drug-resistant infections and COVID-19. Nature Reviews Microbiology, v. 18, n. 8, p. 409-410, 2020. ISSN 1740-1534.

[31] CONDES, E.; ARRIBAS, J. R. Impact of COVID-19 on Madrid hospital system. Enfermedades Infecciosas Y Microbiologia Clinica, v. 39, n. 5, p. 256, 2021.

[32] TARTARI, E. et al. Perceived challenges of COVID-19 infection prevention and control preparedness: A multinational survey. Journal of Global Antimicrobial Resistance, v. 22, p. 779, 2020.

[33] GETAHUN, H. et al. Tackling antimicrobial resistance in the COVID-19 pandemic. Bulletin of the World Health Organization, v. 98, n. 7, p. 442, 2020.

[34] Antimicrobial Resistance Benchmark. The Access to Medicine Foundation. https://accesstomedicinefoundation.org/media/uploads/downloads/5e270aa36821a_Antimicrobial_Resistance_Benchmark_2020.pdf. 2020

[35] LAI, C.-C. et al. Global epidemiology of coronavirus disease 2019 (COVID-19): disease incidence, daily cumulative index, mortality, and their association with country healthcare resources and economic status. International journal of antimicrobial agents, v. 55, n. 4, p. 105946, 2020. ISSN 0924-8579.

[36] BONG, C.-L. et al. The COVID-19 pandemic: effects on low-and middle-income countries. Anesthesia and analgesia, 2020.

[37] DUBBINK, J. H. et al. COVID-19 treatment in sub-Saharan Africa: if the best is not available, the available becomes the best. Travel Medicine and Infectious Disease, v. 37, p. 101878, 2020.

[38] O'NEILL, J. Tackling drug-resistant infections globally: final report and recommendations. 2016.

[39] ERASE, D. R. T. T. T. The Urgent Threat of TB Drug Resistance.

[40] WALKER, P. G. et al. The impact of COVID-19 and strategies for mitigation and suppression in low-and middle-income countries. Science, v. 369, n. 6502, p. 413-422, 2020. ISSN 0036-8075.