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ORIGINAL RESEARCH

The Trend of Antibiotic Consumption After the COVID-19 Pandemic: Approach to Future Outbreaks

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Background: Earlier reports suggested high rates of antibiotic utilization among COVID-19 patients despite the lack of direct evidence of their activity against viral pathogens. Different trends in antibiotic consumption during 2020 compared to 2019 have been reported.

Purpose: The objective of this study is to assess the impact of COVID-19 pandemic on antibiotic consumption in the presence of active Antibiotic Stewardship Program.

Methods: This study represented a five years assessment of the consumption of the commonly prescribed antibiotics measured as DDDs/100-Bed Days. We analyzed the data by using nonparametric Friedman and Friedman tests to compare the antibiotic consumption before and during the three subsequent waves of COVID-19.

Results: Antibiotic consumption through the DDDs/100-BD has shown reduction in the median of antibiotics consumption of most antibiotics during the period of COVID-19 as compared to the pre-COVID-19 period, which was significant for meropenem and ciprofloxacin, except colomycin that slightly increased. Significant reduction in the consumption of imipenem and meropenem during the second and third waves as compared to the pre-COVID period. Throughout the years, significant reductions were observed between 2018 and 2019 (p=<.001), 2018 and 2020 (p=0.008), and 2018 and 2022 (p=0.002).

Conclusion: The reduction in antibiotic consumption is attributed to the strong influence if the ASP and the reluctance of people to visit hospitals during the COVID-19 pandemic. Other related COVID-19 precautions such as physical distance, good hand hygiene, facemasks, that resulted in the prevention of secondary bacterial infections have contributed to the reduction in antibiotic utilization during the pandemic.

Keywords: antimicrobial stewardship, ASP, COVID-19, defined daily doses, DDD, antibiotic consumption, Saudi Arabia

Introduction

Earlier reports suggested high rates of antibiotic utilization among COVID-19 patients despite the lack of direct evidence of their activity against viral pathogens.[1–3] A meta-analysis study showed a significant elevation of antibiotic prescribed for COVID-19 patients beyond the estimated prevalence of co-bacterial infections.[4] Bacterial co-infections among COVID-19 patients have been undoubtedly reported at low rates.[5] Therefore, the utilization of antibiotics in routine COVID-19 management has not been recommended.[6] However, patients with COVID-19 may develop secondary nosocomial infections with bacteria and fungi because of critical illness and prolonged hospitalizations. There is high concern that antimicrobials might be overused. This is because COVID-19 patients may receive both empiric and

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pathogen-directed broad-spectrum antimicrobials. Notwithstanding, it has been reported that more than half of the COVID-19 patients received antibiotics, while 72% of these did not have laboratory evidence of bacterial infection.[5] In fact, the prevalence of bacterial co-infection with COVID-19 was low.[7–11]

Different trends in antibiotic consumption during 2020 compared to 2019 have been reported.[12] At the beginning of the pandemic, there was an increase in the prescribed antimicrobial due to early reports indicating that secondary bacterial infection resulted in great mortality.[13] It has been demonstrated that covid-19 pandemic associated with an increase in antimicrobial consumption.[14–16] Subsequently, a higher antimicrobial resistance rate among COVID-19 patients has been detected during the first 18 months of the pandemic.[17]

The overall monthly antibiotics consumption is higher during first wave but not during subsequent ones.[18] In addition, there was a significant correlation between the number of hospitalized patients and the consumption of antibiotic.[18] Moreover, the number of ICU patients correlate with the consumption of antibiotic, especially broad-spectrum antibiotic.[18] Other studies detected a higher antibiotic consumption during 2020 than the pre-COVID-19 period.[10,19] A meta-analysis study showed a lower consumption in high-income countries than in lower- and middle-income ones.[20] In addition, a study provided an increase in antibiotic consumption defined by DDD per 100 bed during the first wave of COVID-19.[21]

The rate of antibiotic prescribed was higher during the COVID-19 pandemic followed by a decline below the minimum prescriptions during the lockdown period.[22,23] On the other hand, study has shown no difference in antibiotic consumption during and before covid-19.[24] In addition, the study revision the medical record showed decrease in antibiotic prescription during first lockdown.[2,25]

A previous study demonstrated that 100% of the COVID-19 patients received antibiotic regardless to the severity of illness.[26] Another study showed 78% prescribed antibiotic in COVID-19 patients associated with a severe clinical presentation at admission.[16] In other cohort study 72% of the patients received antibiotic for lower respiratory tract infection despite only 6% were identified bacterial pathogen.[11] One study demonstrated a high resistance against erythromycin by *staphylococcus aureus*.[27] Another study demonstrated amoxicillin-clavulanic as the most common utilized followed by ceftriaxone in tertiary care center.[28]

According to a study, the amount of consumption decreased with some kind of antibiotics such as amoxicillin-clavulanate decreased slightly from 37% in 2017 to 36.1% in 2019 and 34.8% in 2020.[21] Piperacillin with beta-lactamase inhibitor pattern also went down from 10.7% to 9.2% and 7.0% in 2015, 2019, and 2020, respectively.[21] However, other antibiotics increased during the covid-19 such as meropenem increased from 3.9% in 2015 to 5.1% and 7.6% in 2019, 2020, respectively.[21] Ciprofloxacin slightly increased during 2019 compared with 2015 followed by a decrease in 2020.[24]

Antibiotic Stewardship Programs (ASPs) play a crucial role in monitoring antibiotic utilization that will prevent the emergence of drug resistance during the pandemic.[29] A study to assess the impact of the ASP showed a significant reduction in empiric antibiotic consumption before and after the implementation of the guidelines in COVID-19 patients.[30] The guidelines published by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Disease Society of America (IDSA) outline the general framework of an ASP.[31] Every program needs to be customized for the needs, institutional culture, resistance, antimicrobial use patterns, and resources specific to the area.[32] However, due to lack of knowledge and expertise, the implementation of ASP in Saudi Arabia hospitals remains low.[33]

The pattern of COVID-19 epidemiology in Saudi Arabia fluctuated with increases and decreases in terms of new cases, mortality, active cases, and virulence.[34] There was a delineating phase of early infections, heightened spread, fast decline, stabilization, second-wave, and full control. The lack of information on antibiotic consumption and limited reports from Saudi Arabia revealed gaps that need to be urgently filled. The objective of this study is to assess the impact of COVID-19 pandemic on antibiotic consumption in the presence of active ASP.

Materials and Methods

This retrospective study was approved by the Armed Forces Hospitals Eastern Province, Saudi Arabia Institutional Review Board (IRB Protocol No. AFHER-IRB-2022-033). Informed consent obtained from the study participants prior to study commencement. The ASP team of KFMMC hospital consists of an experienced doctor and a pharmacist who

specialize in treating infectious diseases usually lead the ASP. Members with multidisciplinary backgrounds (eg, adult and paediatric medicine, microbiology, infection control, and surgery) should ideally be included in the ASP. Resources allotted for information technology support are especially crucial for offering precise data on the use and resistance of antibiotics, and a path for targeted systemic interventions by limiting and preauthorizing the antimicrobials to the infectious diseases physicians. An ASP's supporting administrative framework is available. The ASP reports to leaders of the medical staff as well as the pharmacy and therapeutics committee. We obtained monthly data on commonly prescribed antibiotics associated with higher potentiality of emerging resistance at the pharmacy of King Fahad Military Medical Complex during the period to December 2022. These included piperacillin/tazobactam, imipenem, meropenem, vancomycin, and ciprofloxacin, and colomycin. This is the largest tertiary hospital of 335 beds in Eastern province, Saudi Arabia. To assess the potential impact of the COVID-19 pandemic on the selected antibiotics, the five-year study period was divided into three epidemiologically distinct periods for COVID-19. These included baseline period before COVID-19 pandemic (January 18 to end of February 2020), the first wave (March 2020 to December 2020), the second wave (January 2021 to December 2021), and third wave (January 2022 to December 2022).[35,36] The amounts of DDDs/100-Bed Days were calculated according to the WHO standard.[37]

Statistical Analysis

The collected data was analyzed using SPSS v.26. The inferential statistical analyses were conducted to assess the impact of COVID-19 on the program via non-parametric tests due to violation of normality assumption and the non-normally distributed values were displayed as medians with interquartile ranges (IQR). A nonparametric Wilcoxon signed-rank test for all antibiotics was used. A nonparametric Friedman test was used with post hoc to compare antibiotic consumption before COVID-19, and the three subsequent waves of COVID-19. We also used a nonparametric Friedman test with post hoc to compare antibiotic consumption within different years from 2018 until 2022.

Results

Table 1 shows the antibiotics being assessed in this study, along with the corresponding pharmacological class for each drug and anatomical therapeutic chemical (ATC) code and the WHO Aware classification for each medication. With the exception of colomycin, which is classified as reserved, all other antimicrobials are categorized as watch antibiotics.

Table 2 indicates a decrease in the antibiotic consumption as DDDs/100 BD after COVID-19 pandemic compared to the pre-COVID-19 period in all antibiotics except for colomycin that slightly increased. The median of the antibiotic consumption was not statistically significant when comparing the periods before and after COVID-19 period for piperacillin/tazobactam, imipenem, vancomycin and colomycin. However, there was a statistically significant reduction in the median of antimicrobial consumption of meropenem and ciprofloxacin during the period of COVID-19 as compared to the pre-COVID-19 period.

Table 1 Antibiotic Consumption Classified the Antibiotics According to the WHO AWaRe Category

Antibiotic	Class	ATC Code	Category
Piperacillin/tazobactam	Beta-lactam/beta-lactamase-inhibitor_anti-pseudomonal	J01CR05	Watch
Imipenem	Carbapenems	J01DH51	Watch
Meropenem	Carbapenems	J01DH02	Watch
Vancomycin	Glycopeptides	J01XA01	Watch
Ciprofloxacin	Fluoroquinolones	J01MA02	Watch
Colomycin	Polymyxins	J01XB01	Reserve

Table 2 Antimicrobial Consumption as a Median DDDs/100-BD Before and After COVID-19 Pandemic

Antibiotic	DDDs/100 Before Covid-19 Period		DDDs/100 After Covid-19		P-value
	Median	IQR	Median	IQR	
Piperacillin/tazobactam	388	439	313	106	0.112
Imipenem	72	205	52	47	0.112
Meropenem	423	530	294	187	0.019
Vancomycin	119	117	106	49	0.310
Ciprofloxacin	44	60	26	15	0.016
Colomycin	25	85	27	26	0.218

Table 3 Median Antibiotic Consumption as a Median DDDs/100-BD Before and During the Three Waves of COVID-19 with the Interquartile Range (IQR) and the Pairwise Comparison

Antibiotic	Pre-COVID		First Waves		Second Waves		Third Waves		Friedman Test		Post Hoc Analysis	
	Median	IQR	Median	IQR	Median	IQR	Median	IQR	Chi-Square	P-value	Pairwise Comparisons*	P-value
Piperacillin/ tazobactam	388	439	365	230	304	188	307	69	3	0.293	–	–
Imipenem	72	205	67	927	45	58	46	47	15	0.001	1 vs 4 1 vs 3	0.001 0.019
Meropenem	423	530	424	693	295	173	225	163	18	<0.0001	1 vs 4 1 vs 3 2 vs 4	0.002 0.011 0.034
Vancomycin	119	117	92	87	102	27	135	39	12	0.007	1 vs 3 1 vs 2	0.015 0.19
Ciprofloxacin	44	60	29	8	23	64	26	18	13	0.004	1 vs 4 1vs 2	0.003 0.044
Colomycin	25	85	31	30	20	20	29	25	17	<0.0001	1 vs 3 1 vs 2	0.001 0.003

Notes: *(1)=non-Covid-19 (January 18 to end of February 2020), (2)= first wave (March 2020 to December 2020), (3)=second wave (January 2021 to December 2021), (4) = third wave (January 2022 to December 2022).

Table 3 shows the Friedman test of the antibiotic consumption before and the subsequent three waves of COVID-19 pandemic as DDDs/100 BD. The test indicated a non-significant reduction in the antibiotic consumption for piperacillin/ tazobactam within all period. Post hoc analysis with a Bonferroni correction indicated a significant reduction during the first wave as compared to the pre-COVID period for ciprofloxacin and colomycin but not for other antibiotics. On the other hand, a significant reduction consumption of imipenem and Meropenem during the second and third waves as compared to the pre-COVID period.

We used the Friedman test with post hoc analysis to analyze antibiotics consumption during different years (Table 4, Figure 1). There was no significant difference in the consumption of piperacillin/tazobactam between the years. However, the DDD consumption of imipenem, meropenem, vancomycin, ciprofloxacin, and colomycin, varied between the years. Significant reductions were observed between 2018 and 2019 (p=<.001), 2018 and 2020 (p=0.008), and 2018 and 2022 (p=0.002). There

Table 4 Antibiotic Consumption as a Median DDDs/100-BD During 2018–2022 for All and the Friedman Test with Post Hoc Analysis

Antibiotic	2018		2019		2020		2021		2022		Friedman Test		Post Hoc Analysis	
	Median	IQR	Median	IQR	Median	IQR	Median	IQR	Median	IQR	Chi-Square	P-value	Pairwise Comparisons	P-value
Piperacillin/tazobactam	541	1185	388	113	325	222	304	188	307	69	4	0.380		
Imipenem	247	219	32	23	62	44	44	57	45	47	24	<0.0001	2019 vs 2018 2022 vs 2018 2021 vs 2018	<0.001 0.002 0.008
Meropenem	836	401	286	162	397	410	294	173	224	163	29	<0.0001	2022 vs 2020 2022 vs 2018 2019 vs 2018 2021 vs 2018	0.012 <0.001 0.003 0.003
Vancomycin	211	98	94	35	92	59	102	26.4	135	38	16	0.002	2021 vs 2018 2019 vs 2018 2020 vs 2018	0.006 0.012 0.045
Ciprofloxacin	79	29	18	17	27	11	22	63	26	17	19	0.001	2019 vs 2018 2020 vs 2018 2021 vs 2018 2022 vs 2018	0.001 0.008 0.012 0.019
Colomycin	113	118	10	9	27	32	20	20	28	25	25	<0.0001	2019 vs 2022 2019 vs 2018 2021 vs 2018 2020 vs 2018	0.039 <0.001 0.003 0.019

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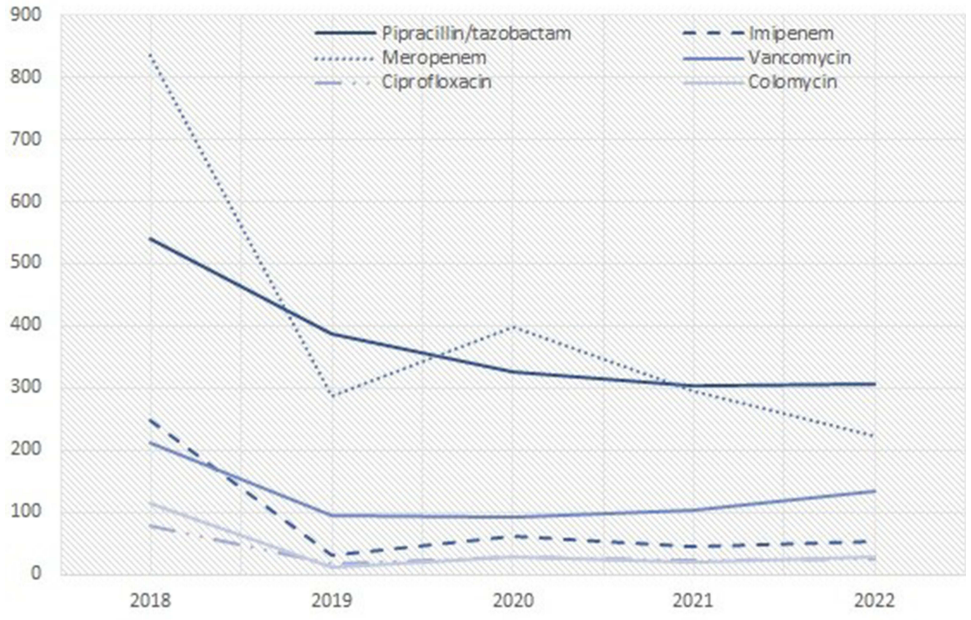

Figure 1 Antibiotic consumption as a median DDDs/100-BD during 2018–2022.

was a significant decrease in DDD consumption between 2018 and 2019 (P=0.003) and 2018 and 2021 (p=0.003), and 2018 and 2022 (p=<.001). Vancomycin and ciprofloxacin consumptions decreased over the years. Additionally, the post hoc test demonstrated a significant reduction between 2018 and the subsequent years (p=0.001,0.008,0.012, and 0.019).

Table 5 indicates the number of patients admitted due to COVID-19 and their mortality rate at KFMMC hospital during 2019–2022. The average COVID-19 mortality rate was 1.1%. The average admission due to COVID-19 infections during the pandemic was 22.0%.

Discussion

Potential overuse and unreasonable antibiotic prescribing have become a serious healthcare threat. This can affect patient safety, increase the risk of drug's side effects, and lead to the progressive antimicrobial resistance. More than 70% of upper respiratory tract infections were treated with antibiotics, although viruses are the leading cause.[38] In fact, antibiotic prescribing has become a more common practice in many countries since the COVID-19 pandemic.[39]

We evaluated the impact of COVID-19 on the ASP and antibiotic consumption through the DDDs/100-BD. Five of the studied antibiotics belong to the watch group class that have higher resistance potential and of the highest priority

Table 5 Number of Patients Admitted Due to COVID-19 and Their Mortality Rate at KFMMC Hospital During 2019–2022

Year	Total Admission	Covid-19 Cases	Admitted Covid-19 Cases (%)	Bacterial Co-Infection (%)	Mortality (%)
2019	14,176	–	–	–	–
2020	10,954	1080	266 (24.6)	30 (11.3)	12 (1.1)
2021	12,965	1916	374 (19.5)	27 (7.2)	26 (1.4)
2022	12,418	1573	364 (23.1)	29 (8.0)	14 (0.9)
Total	50,513	4569	1004 (22.0)	86 (8.6)	52 (1.1)

agents among the critically important antibiotics. Only one antibiotic belongs to the reserved group, the last resort options that should be reserved for treatment of confirmed or suspected infections due to multi-drug-resistant organisms.

A statistically significant reduction in the median of antibiotics consumption of meropenem and ciprofloxacin was encountered during the period of COVID-19 as compared to the pre-COVID-19 period. Similar findings have been reported worldwide.[2,22,23,25,40–42]

In fact, sustained reductions in antibiotics consumption since the onset of the pandemic has been reported in many occasions worldwide.[2] This reduction is attributed to the strong influence if the hospital antibiotic stewardship program and the reluctance of people to visit hospitals during the COVID-19 pandemic. Moreover, the reduction in antibiotic utilization during the pandemic can be attributed to pandemic related precautions such as physical distance, good hand hygiene, facemasks, which resulted in the prevention of secondary bacterial infections. In addition to that, the reduced number of primary care consultation secondary to lockdown has resulted in fewer prescriptions and less utilization of antibiotics for mild and self-limiting infections, also applying stewardship program. The reduction of meropenem consumption was reported during the pandemic.[43] Another study reported a reduction in ciprofloxacin during the same period.[44,45] In contrast, our study has detected a slight increase in colomycin consumption. Other studies showed an overall increase in the consumption use of antibiotics.[43–45]

Another study noticed an initial increase in the antibiotics consumption during the first months of the pandemic followed by a decline below the expected levels during the national lockdown.[22] Empiric use of broad-spectrum antimicrobial was also observed in patients with COVID-19 during hospitalization. During the first COVID-19 wave, azithromycin, amoxicillin/clavulanic acid, amoxicillin, hydroxychloroquine, and doxycycline were frequently prescribed in most health-care facilities.[20] Azithromycin was the most commonly prescribed. A rapid decrease was observed following the reports that proved no benefit of using azithromycin among COVID-19 patients.

This study indicated a non-significant difference in the antibiotic consumption for piperacillin/tazobactam throughout the entire study duration. However, a statistically significant difference in prescribing imipenem between the pre-COVID -19 and the third wave intervals.

Conclusion

The rationalized and wise use of antibiotic therapy should be encouraged. The hospital ASP should be assured to reduce inappropriate antibiotic prescribing, especially during pandemics. Future studies are needed in order to evaluate macrolide resistance trends among pneumococcal strains, especially now after the COVID-19 pandemic, since azithromycin was vastly used as an empiric treatment of COVID-19.[46] High antibiotic consumption found in COVID-19 patient's demands an implementation of appropriate antimicrobial stewardship interventions during the pandemics. The use of antibiotic stewardship techniques that have been successfully used to lessen the effects of COVID-19 should be broadly promoted and used to guide future pandemic responses.

Co-infections and secondary infections, including those brought on by antibiotic resistance microorganisms with must be evaluated among COVID-19 patients. It is necessary to use diagnostic stewardship to identify patients who are most likely to benefit from antibiotic therapy and to decide when antibiotics can be safely withheld, raised, or with-drawn. Healthcare facilities are heavily burdened by coronavirus disease in 2019, especially while treating patients who have co-occurring conditions. The incidence of resistant pathogen infections and the use of antibiotics may be impacted by antimicrobial stewardship and advancements in diagnostic procedures that increase the precision of diagnosing bacterial infections. The average prevalence of the bacterial co-infection among COVID-19 cases was 8%. The global prevalence of bacterial coinfections among COVID-19 cases was 20.97% of which 5.20% prevalence of the respiratory subtype and 4.79% prevalence of the gastrointestinal subtype 52.

Understanding antimicrobial resistance requires careful monitoring and analysis of data on antibiotic consumption. Antimicrobial stewardship initiatives have been sug-gested by the World Health Organization as a crucial tactic to reduce antibiotic resistance. These antimicrobial stewardship strategies can be informed by research on antibiotic usage. The findings may offer information on the emergence of antibiotic resistance and can be used to evaluate antimicrobial stewardship programs' methods for influencing pre-scribing. It is possible to track trends in

prospective research and compare it to other healthcare environments on a national and regional scale. The COVID-19 pandemic has had a positive impact on the spread of multi-drug-resistant pathogens. Overall, a positive impact on the spread of pathogens and multidrug-resistant infections can be seen when general precautions against the spread of infectious diseases such as social distancing, reducing travel and improving personal hygiene. In addition, the pandemic has accelerated the development of new technologies, such as mRNA vaccines, which can be used to fight other diseases. Future measures to manage new outbreaks of infectious disease should emphasize the importance of social distancing and hand washing, but discourage the overuse of disinfectants, biocides and antimicrobials.

Although the study included a five years data collected from the largest medical center in the area, it still represented specific geographical and healthcare setting, which may limit the applicability of its conclusions to other regions with different healthcare infrastructures and pandemic responses.

Abbreviations

COVID-19, Coronavirus Disease 2019; DDD, Defined Daily Doses; ASP, Antimicrobial Stewardship; ICU, Intensive Care Unit; IRB, Institutional Review Boards; WHO, World Health Organization; IQR, Interquartile Ranges; ATC, Anatomical Therapeutic Chemical.

Data Sharing Statement

The datasets utilized and analyzed in this research are accessible from the corresponding authors upon request in the future without any specific rationale.

Ethical Statement

This study, which was in compliance with the Declaration of Helsinki, received ethical approval from the Ethics Committee of the Armed Forces Hospitals Eastern Province, Saudi Arabia Institutional Review Board (IRB Protocol No. AFHER-IRB-2022-033).

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Disclosure

The authors declare that they have no conflicts of interest in this work.

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