Antibiotic consumption in hospitals during COVID-19 pandemic: a comparative study

Published in:
Journal of Infection in Developing Countries

Publication Status:
Published online: 29/11/2022

DOI:
10.3855/jidc.17148

JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Coronavirus Pandemic

Antibiotic consumption in hospitals during COVID-19 pandemic: a comparative study

Raghda RS Hussein[1,2], Al Shaimaa Ibrahim Rabie[3], Maryam Bin Shaman[4], Ahmed Hassan Shaaban[5], Alzhraa M Fahmy[6], Mahmoud R Sofy[7], Elizabeth A Lattyak[8], Ahmed Abuelhana[9], Ibrahim A Naguib[10], Ahmed M Ashour[11], Mamoon A Aldeyab[12]

[1] *Clinical Pharmacy Department, Faculty of Pharmacy, Beni-Suef University, Beni-Suef, Egypt*
[2] *Department of Clinical Pharmacy, Faculty of Pharmacy, October 6 University, 6 October City, Giza, Egypt*
[3] *Clinical Pharmacy Department, Faiyum Oncology Center, Faiyum, Egypt*
[4] *Pharmacy Department, Prince Mohammad Medical City, Ministry of Health, Aljouf, Saudi Arabia*
[5] *Clinical Oncology Department, Faculty of Medicine, Beni-Suef University, Beni-Suef, Egypt*
[6] *Tropical Medicine and Infectious Diseases Department, Faculty of Medicine, Beni-Suef University, Beni-Suef, Egypt*
[7] *Botany and Microbiology Department, Faculty of Science, AL-Azhar University, Cairo, Egypt*
[8] *Scientific Computing Associates Corp, River Forest, IL, United States*
[9] *School of Pharmacy and Pharmaceutical Sciences, Faculty of Life and Health Sciences, University of Ulster, Coleraine, United Kingdom*
[10] *Department of Pharmaceutical Chemistry, College of Pharmacy, Taif University, Taif, Saudi Arabia*
[11] *Department of Pharmacology and Toxicology, College of Pharmacy, Umm Al Qura University, Makkah, Saudi Arabia*
[12] *Department of Pharmacy, School of Applied Sciences, University of Huddersfield, Huddersfield, United Kingdom*

Abstract

Introduction: Coronavirus disease 2019 (COVID-19) results in similar clinical characteristics as bacterial respiratory tract infections and can potentially lead to antibiotic overuse. This study aimed to determine the changes in hospital antimicrobial usage before and during the COVID-19 pandemic.

Methodology: We compared antimicrobial consumption data for 2019 and 2020. Inpatient antibiotic consumption was determined and expressed as a defined daily dose (DDD) per 100 occupied bed days, following the World Health Organization (WHO) methods. The WHO Access, Watch, and Reserve (AWaRe) classification was used.

Results: The total antimicrobial consumption in 2020 increased by 16.3% compared to consumption in 2019. In 2020, there was a reduction in fourth-generation cephalosporins (-30%), third-generation cephalosporins (-29%), and combinations of penicillins (-23%). In contrast, antibiotics that were consumed more during 2020 compared with 2019 included linezolid (374%), vancomycin (66.6%), and carbapenem (7%). Linezolid is the only antibiotic from the Reserve group on the hospital's formulary. Antibiotic usage from the Access group was reduced by 17%, while antibiotic usage from the Watch group and the Reserve group was increased by 3% and 374%, respectively.

Conclusions: The findings show a significant shift in antibiotic usage from the Access group to the Watch and Reserve groups. The Watch and Reserve groups are known to be associated with increased resistance to antibiotics. Therefore, antimicrobial stewardship should be increased and maintained during the pandemic to ensure appropriate antibiotic use.

Key words: COVID-19; antimicrobial; stewardship; resistance; antibiotic consumption.

J Infect Dev Ctries 2022; 16(11):1679-1686. doi:10.3855/jidc.17148

(Received 23 July 2022 – Accepted 25 October 2022)

Introduction

The growth and dissemination of multidrug-resistant microorganisms and low investment in antibiotic discovery hinder the successes of various contemporary medicines and cause significant public health hazards worldwide [1-3]. Antimicrobial abuse and misuse have increased the danger of onset and spread of antimicrobial resistance (AMR) in many parts of the world. A continuous increase in AMR will increase drug-resistant illness fatalities from 700,000 to 10 million per year, with anticipated expenses of up to $100 trillion globally by 2050 [4,5].

Antimicrobial use is considered to be one of the primary causes of AMR [6-8]. Monitoring and optimizing antibiotic use are critical for preventing the development of AMR [9]. The impact of AMR on the delivery of regular and urgent care services in hospitals has been widely noted. The pandemic has impacted the implementation of health awareness programs, preventive health care, and the diagnosis and ongoing management of chronic diseases [10].

Coronavirus disease 2019 (COVID-19) has resulted in a significant increase in the use of certain antibiotic agents such as carbapenems, macrolides, and lincosamides. Furthermore, studies have documented an increase in the use of Watch antibiotics during the COVID-19 pandemic in local and national hospitals [11,12]. The usual causes of this increase include increased hospital stays among patients with COVID-19 and an increase in admissions to the intensive care unit (ICU). This has led to a shortage of beds for the care of these vital patients. The potential overuse of antimicrobials happens due to the issue of bacterial co-infection [13]. This pattern is drawn from influenza, which is associated with a high co-infection prevalence (58%) [14]. In line with the latter, many of the antibiotics administered to patients with COVID-19 were potentially inappropriately indicated and unnecessary [15]. This has the potential for undesirable consequences, including an increased risk of antibiotic resistance [16].

Some researchers have already raised concerns about the pandemic's potential impact on advancing AMR hazard [17]. Based on these concerns, the World Health Organization (WHO) and several experts advise against initiating antibiotic treatment for COVID-19 cases classified as suspected or confirmed mild and against prescribing antibiotics for moderate COVID-19 (unless laboratory results confirm clinical suspicion of bacterial infection) or in critically sick patients [18]. Many low and middle-income nations, including Egypt, struggle to implement comprehensive antimicrobial stewardship programs (AMS), which have deteriorated further because of the ongoing pandemic. There have been no prior studies in Egypt to assess the utilization of antibiotics among patients hospitalized with COVID-19.

This work aimed to assess changes and patterns of antimicrobial usage before and during the COVID-19 pandemic in Beni-suef University Hospital. This was achieved by comparing annual inpatient antimicrobial consumption during one year (2019) before the COVID-19 pandemic and a year during the COVID-19 pandemic (2020).

Methodology

Setting and study design

The study was carried out in Egypt at the Beni-suef University Hospital (BUH). BUH is a teaching hospital and tertiary care center with Intensive Care Units (ICUs) and outpatient facilities that include specializations in surgical, medical, burns, oncology, gynecology, hematology, oncology, plastic surgery, orthopedics, general surgery, neurosurgery, rheumatology, ophthalmology, cardiology, maternity, and pediatrics. The hospital has 452 beds [140 (30.9%) surgical, 97 (21.4 %) ICU, and 215 (47.7%) medical].

Data collection

Data on antimicrobial use at the BUH during the years 2019 and 2020 were extracted from the pharmacy information system. This data included the consumption of intravenous and oral antibiotics prescribed to the inpatients. An Excel spreadsheet was devised and included fields for antimicrobial agents, strength, dose, quantities, and the number of occupied bed days (OBD). The collected data were then validated by manually checking for errors. The WHO/Anatomical Therapeutic Chemical (ATC) classification index was used to calculate the defined daily dose (DDD) for each antibiotic. Finally, consumption of antimicrobials was expressed as DDD per 100 OBD. All age groups, male and female, with or without comorbidities in an inpatient setting, were enrolled in the study. All datasets were anonymous with no patient identifiers and no identifiable patient information.

Statistical Analysis

Antibiotic use was analyzed using descriptive methods. A graphical representation of the data to create four quadrants was constructed using the ggplot2 package and the R statistical program [19,20]. The relative rate of change in antibiotic use (2019-2020), calculated as (DDD/100 OBD 2020 / DDD/100 OBD 2019), was represented by the y-axis. Antibiotic use (DDDs) in 2020 was represented by the x-axis. There were two antimicrobials, cefadroxil, and azithromycin, that were not used by the hospital in 2019. This renders a divide-by-zero error in the computation of the relative rate of change. Rather than omit these two antimicrobials in the graph, the rate of change was recorded to be a value greater than the largest rate of change for the remaining antimicrobials; linezolid, in this instance. A triangle symbol is used as a reference for cefadroxil and azithromycin to identify them as artificial values that have been scaled for the purpose of the chart. This chart provides a relative comparison of antibiotic use, levels, and trends. For example, antibiotics identified in the lower right quadrant represent widely used antibiotics at a lower rate when compared to the previous year. On the other hand, antibiotics identified in the upper right quadrant represent widely used antibiotics at a higher rate than in the previous year. Therefore, antibiotics identified in the upper right quadrant are potential antibiotics that may benefit from further evaluation. In order to determine antibiotics that contribute to 90% of used DDDs, we used the Drug Utilization 90% (DU90%) concept [19]. The percentage of antibiotic use (DDD%) was calculated by dividing the DDD of a certain antibiotic agent by the total use (DDD) of all antibiotics (J01); this was then expressed as a percentage by multiplying by 100. The WHO AWaRe classification (Access, Watch, and Reserve) was used to categorize the antibiotics assessed [20].

Ethics approval and consent to participate

Ethical approval was obtained from the research and ethical committee in Beni-Suef university hospital Ref. (#FWA 00015574) and is available upon request.

Results

The overall antibiotic usage in 2019 was 80.4 DDD per 100 OBD, out of which 70.83 DDD/100 OBD represented parenteral use (88.1%) and 9.57 DDD/100 OBD represented oral use (11.9%). The total antibiotic consumption in 2020 was 93.5 DDD/100 OBD, out of which 68.25 DDD/100 OBD represented parenteral use (73%) and 25.25 DDD/100 OBD represented oral use (27%). Antibiotic use in 2020 increased by 16.3 % relative to 2019. The results showed different antibiotic use patterns between 2019 and 2020 (Tables 1, 2 and 3). The most used antibiotics in 2019 were third-generation cephalosporins (42.9%), combinations of penicillins, including beta-lactamase inhibitors (16.51%), fluoroquinolones (15.25%), and carbapenems (9.16%). The most used antibiotics in 2020 were third-generation cephalosporins (30.47%), macrolides (15.12%), fluoroquinolones (14.74%), and combinations of penicillins, including beta-lactamase inhibitors (12.68%) (Table 1). The total use of antibiotics increased in 2020; however, the use of some antibiotics decreased in 2020 (compared to 2019). These include fourth-generation cephalosporins (-30%), third-generation cephalosporins (-29%), and combinations of penicillins, including beta-lactamase inhibitors (-23%) (Table 1). A marked increase in the relative rate of change was observed for the use of linezolid (374%; 0.43 DDD/100 OBD in 2019; 2.4 DDD/100 OBD in 2020) and vancomycin (66.6%; 1.3 DDD/100 OBD in 2019; 2.52 DDD/100 OBD in 2020). The use of cefotaxime decreased in 2020 (8.78 DDD/ 100 OBD) compared to 2019 (14.15 DDD/100 OBD; relative rate of change = -47%). The use of amoxicillin/clavulanic acid decreased by 44% in 2020 (4.45 DDD/100 OBD) compared to 2019 (6.89 DDD/100 OBD).

The hospital Access group's antibiotic use percentage for 2019 and 2020 was 25.1% and 20.9%, respectively. There was a 17% reduction in Access group use in 2020 relative to 2019 [(0.83 – 1)*100 = 17%; Table 2]. On the other hand, Watch group use increased in 2020 by 3% [(1.03 – 1)*100 = 3%]. The use of the Reserve group, due to the use of linezolid, increased in 2020 by 374% [(4.74 – 1)*100 = 374%; Table 2]. The most frequently used antibiotics that

Table 1. Antibiotic consumption, DDD per 100 occupied bed days, for 2019 and 2020.

Antimicrobial class	Hospital antimicrobial use 2019		Hospital antimicrobial use 2020		Relative rate of change*
	DDD/ 100 OBD	Class%	DDD/ 100 OBD	Class%	
Beta-lactamase sensitive penicillin	0.06	0.08%	0.02	2.46%	0.32
Combinations of penicillin, including beta-lactamase inhibitors	13.28	16.51%	11.86	12.68%	0.77
First generation cephalosporins	0.00	0.00%	0.12	0.12%	NA
Third generation cephalosporins	34.50	42.90%	28.49	30.47%	0.71
Fourth generation cephalosporins	3.41	4.24%	2.78	2.98%	0.70
Carbapenems	7.36	9.16%	9.16	9.79%	1.07
Combinations of sulfonamides and trimethoprim, including derivatives	0.11	0.14%	0.14	0.15%	1.13
Macrolides	0.00	0.00%	14.14	15.12%	NA
Lincosamides	5.93	7.37%	5.36	5.73%	0.78
Other aminoglycosides	0.83	1.04%	2.08	2.22%	2.14
Fluoroquinolones	12.26	15.25%	13.78	14.74%	0.97
Glycopeptide antibacterial	2.25	2.80%	3.22	3.45%	1.23
Other antibacterial	0.43	0.53%	2.36	2.52%	4.74

*Relative rate of change = class% 2020/class% 2019; OBD: occupied bed days; NA: not applicable; DDD: define daily dose.

Table 2. Antibiotic consumption utilizing the WHO AWaRe category (Access/Watch/Reserve) for 2019 and 2020.

Year	Access	Watch	Reserve
	DDD/100 occupied bed days (%)		
Hospital antimicrobial use (2019)	20.2 (25.1%)	59.8 (74.3%)	0.4 (0.5%)
Hospital antimicrobial use (2020)	19.6 (20.9%)	71.6 (76.5%)	2.4 (2.5%)
Relative rate of change*	0.83	1.03	4.74

*Relative rate of change = DDD per 100 OBD% 2020/DDD per 100 OBD% 2019; WHO: World Health Organization; DDD: define daily dose, OBD: occupied bed days.

contributed to 90% of total hospital antibiotic use are listed in Table 3.

The distribution of hospital antibiotic consumption, grouped at the class level, considering the rate of change (2019-2020) and the proportion of use (2020), is shown in Figure 1.

Discussion

The COVID-19 pandemic is occurring simultaneously with the global health catastrophe of AMR. AMR pathogens lead to increased mortality [21-23], leading to a significant financial burden. Individuals infected with COVID-19 may need to be admitted to the ICU, depending on the severity of the symptoms. Those with substantial co-morbidities may require ventilator assistance [22,24].

The current study highlights the impact of the COVID-19 pandemic on antibiotic use by hospitalized patients. As far as we know, this is the first study comparing the consumption of antibiotics before and during the COVID-19 pandemic in Egypt. We identified a decrease in the use of some antimicrobial drugs during the COVID-19 outbreak (e.g., combinations of penicillins with beta-lactamase inhibitors, third and fourth-generation cephalosporins, lincosamide, and fluoroquinolones). Ryu *et al.* reported that reduced hospitalizations due to airway respiratory tract infections (ARTIs) during the COVID-19 pandemic led to the decrease in the consumption of penicillins and beta-lactamase inhibitors [25].

Consumption of the third and fourth generations of cephalosporin and lincosamide decreased in 2020 compared to 2019. This drop-in usage may be attributed to the increased use of other antibiotics such as azithromycin. However, other studies have reported a positive incremental change in third and fourth generation cephalosporin and lincosamide consumption [26-30]. This may be related to differences in race, variations in the most common infections, and the development of resistance in treated patients.

Figure 1. Distribution of hospital antibiotic consumption grouped at the class level, considering the rate of change (2019-2020), and the proportion of use (2020).

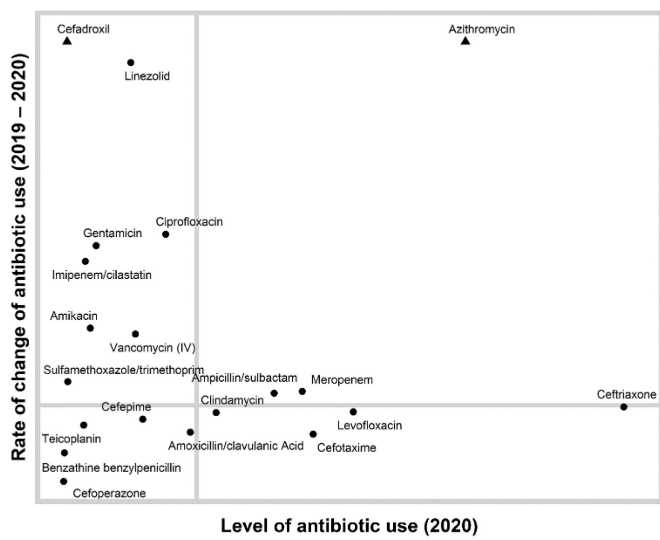

Table 3. Antibiotic use for inpatient contributed to 90% of total hospital antibiotic consumption in 2019 and 2020.

Hospital antimicrobial use (2019)				Hospital antimicrobial use (2020)			
Antimicrobials	WHO AWaRe category	DDD/100 OBD	DDD/100 OBD%	Antimicrobials	WHO AWaRe category	DDD/100 OBD	DDD/100 OBD%
Ceftriaxone	Watch	20.1	25.0%	Ceftriaxone	Watch	19.7	21.1%
Cefotaxime	Watch	14.1	17.6%	Azithromycin	Watch	14.1	15.1%
Levofloxacin	Watch	11.2	13.9%	Levofloxacin	Watch	10.2	10.9%
Meropenem	Watch	7.1	8.8%	Cefotaxime	Watch	8.8	9.4%
Amoxicillin/clavulanic Acid	Access	6.9	8.6%	Meropenem	Watch	8.4	9.0%
Ampicillin/sulbactam	Access	6.4	7.9%	Ampicillin/sulbactam	Access	7.4	7.9%
Clindamycin	Access	5.9	7.4%	Clindamycin	Access	5.4	5.7%
Cefepime	Watch	3.4	4.2%	Amoxicillin/clavulanic Acid	Access	4.5	4.8%
				Ciprofloxacin	Watch	3.6	3.8%
				Cefepime	Watch	2.8	3.0%

WHO: World Health Organization; DDD: define daily dose; OBD: occupied bed days; AWaRe WHO access, watch, reserve, classification of antibiotics for evaluation and monitoring of use.

In the present study, a decrease in fluoroquinolone usage is also reported. This is in line with many studies showing a reduction in fluoroquinolones throughout the period of the COVID-19 outbreak [25,31]. This decrease may be rationalized by the narrow indication (e.g. genitourinary infections or hospital-acquired infections) for prescribing fluoroquinolone for children and adults [25]. On the other hand, a modest increase in fluoroquinolone usage has been observed in other studies. This difference in results may arise if fluoroquinolones are used for empirical therapy rather than for a single specific antimicrobial therapy against pathogenic germs [29,30].

In this study, there was an increase in the usage of specific antibiotics during the COVID-19 pandemic period. For example, the use of meropenem (carbapenem), vancomycin (glycopeptide antibacterials), sulfamethoxazole/trimethoprim, and linezolid increased. These findings are consistent with other studies. In addition, the results demonstrated an increase in the use of azithromycin in 2020, consistent with other studies reporting increased use of azithromycin during the COVID-19 pandemic, especially in combination with hydroxychloroquine [26,32,33-35]. This could be due to physicians' prior experience with azithromycin for respiratory infections, or it could be related to widespread off-label usage of azithromycin for the treatment of COVID-19 in other countries. This widespread usage was reported in a recent study in Singapore that found similar trends in rising azithromycin intake [36]. In vitro antiviral effects of azithromycin include decreased viral multiplication, prevention of entry into host cells, and a possible immunomodulating impact [33,37]. Azithromycin has been demonstrated to help those with chronic obstructive pulmonary disease [38]. However, other studies do not support the use of azithromycin to treat patients diagnosed with mild to moderate COVID-19 because it did not lead to a reduction in the risk of subsequent hospital readmissions or deaths [39]. Studies have shown that azithromycin alone, or in combination with hydroxychloroquine is ineffective in treating COVID-19 patients admitted to hospitals [26,40-43].

The current study revealed that the utilization of total antimicrobials before the pandemic period was 80.4 DDD per 100 occupied bed days, in which the percentage of oral use was 11.9%. The total utilization of antimicrobials during the pandemic was 93.5 DDD per 100 occupied bed days, in which the percentage of oral use was 27%. Many factors may have contributed to the increased usage of antimicrobials during the COVID-19 pandemic, including initial misunderstanding of how to treat the infection, hospital overcrowding, the limited number of doctors with the necessary skills to deal with the situation, a decrease in the antimicrobial stewardship team's activity, and the lack of initial therapeutic protocols. This emphasizes the critical importance of antimicrobial stewardship in optimizing antibiotic use in hospitals, especially in emergency situations like the COVID-19 pandemic [22,27].

Strategies to optimize the rational use of antimicrobials involve encouraging local guideline implementation and timely de-escalation or discontinuation of therapy when clinical signs of unconfirmed bacterial co-infection are determined, correct antibiotic choice based on microbiological test results, and encouraging switching from intravenous to oral route as soon as appropriate. Furthermore, in order to enhance antibiotic use throughout the subsequent stages of the COVID-19 pandemic, the length of antibiotic treatment should adhere to local guidelines while closely monitoring potential multi-drug interactions or toxicity [22,27]. Total antimicrobial consumption grew by 16.3% during the COVID-19 outbreak in 2020 compared to the period before the outbreak in 2019. Changes in utilization of antimicrobials identified in relation to AWaRe classification was observed. The primary goal of the use of AWaRe is to reduce the use of antibiotics in the Watch and Reserve groups while increasing the usage of antibiotics in the Access group. By 2023, 60% of all antibiotics consumed must be from the antibiotics in the Access group [44,45]. The outcomes of this study revealed that the use of antibiotics in the Access group was (25%) in the period before COVID-19.

However, there was a significant decrease (-17%) in the percentage of people using antibiotics in the Access group (20.9%) during the pandemic. During the outbreak, usage of antibiotics in the Watch group increased by 3%, accounting for 76.5% of all cases. This category of antimicrobials is more likely to be associated with the development of AMR, demanding continuous monitoring and urgent stewardship measures; hence, the increase in antibiotic usage in the Watch group is a concern. Azithromycin and carbapenems are included in the Watch group. Our findings are consistent with a recently published study investigating the consequences of the COVID-19 period on antibiotic usage in an inpatient setting. The authors found that antibacterial consumption increased during COVID-19 [46]. Antibiotic stewardship activities in hospitals in Egypt could benefit from this knowledge. Measurement of antibiotic consumption is a critical component of antimicrobial stewardship programs because it allows us to improve good clinical practice regarding antibiotic use. A more in-depth investigation on the spread of antimicrobial resistance is needed to confirm the influence of modifications on the usage of certain broad-spectrum antimicrobials, as well as the increased use of antimicrobials in the Watch group. Our study has some limitations. The study was conducted at the hospital level, making it difficult to adjust for other factors that may have impacted the findings, for example, patient case mix and type of infections. Further research at the patient level is needed. In addition, this study was carried out in a single hospital. A multi-site study is needed to further understand the impact of the COVID-19 pandemic on antibiotic use.

Conclusions

In conclusion, the findings of this study determined the changes in antimicrobial use at the Beni Suef University Hospital in Egypt before and during COVID-19. We found a significant shift in antibiotic use from the Access group to the Watch (known to be related to increased antimicrobial resistance) and Reserve groups. More efforts are needed to monitor and improve antimicrobial stewardship actions to maintain patient safety and appropriate antibiotic usage. Furthermore, antimicrobial stewardship must be enhanced and maintained during the pandemic to ensure the rational use of antibiotics.

Acknowledgements

The authors would like to thank the Deanship of Scientific Research at Umm Al-Qura University for supporting this work with grant code 22UQU4310007DSR01.

Additionally, the authors would like to extend their sincere appreciation to Taif University Researchers Supporting Project number (TURSP-2020/56), Taif University, Taif, Saudi Arabia.

References

1. Aslam B, Wang W, Arshad MI, Khurshid M, Muzammil S, Rasool MH, Nisar MA, Alvi RF, Aslam MA, Qamar MU (2018) Antibiotic resistance: a rundown of a global crisis. Infect Drug Resist 11: 1645-1658.
2. Aldeyab M, López-Lozano J-M, Gould IM (2020) Global antibiotics use and resistance. In Babar Z-U-D, editor. Global Pharmaceutical Policy. Palgrave Macmillan. 331-344.
3. El-Sheshtawy HS, Mahdy HM, Sofy AR, Sofy MR (2022) Production of biosurfactant by *Bacillus megaterium* and its correlation with lipid peroxidation of *Lactuca sativa*. Egyptian Journal of Petroleum 31: 1-6.
4. Piddock LJV (2016) Reflecting on the final report of the O'Neill review on antimicrobial resistance. Lancet Infect Dis 16: 767-768.
5. Razzaque M (2020) Implementation of antimicrobial stewardship to reduce antimicrobial drug resistance. Expert Rev Anti Infect Ther 19: 559-562.
6. Jirjees FJ, Al-Obaidi HJ, Sartaj M, Conlon-Bingham G, Farren D, Scott MG, Gould IM, López-Lozano JM, Aldeyab MA (2020) Antibiotic use and resistance in hospitals: time-series analysis strategy for determining and prioritising interventions. Hospital Pharmacy Europe 7: 13-19.
7. Hayajneh WA, Al-Azzam S, Yusef D, Lattyak WJ, Lattyak EA, Gould I, López-Lozano J-M, Conway BR, Conlon-Bingham G, Aldeyab MA (2021) Identification of thresholds in relationships between specific antibiotic use and carbapenem-resistant *Acinetobacter baumannii* (CRAb) incidence rates in hospitalized patients in Jordan. J Antimicrob Chemother 76: 524-530.
8. Conlon-Bingham GM, Aldeyab M, Scott M, Kearney MP, Farren D, Gilmore F, McElnay J (2019) Effects of antibiotic cycling policy on incidence of healthcare-associated MRSA and *Clostridioides difficile* infection in secondary healthcare settings. Emerging Infect Dis 25: 52-62.
9. Organization WH (2015) Report of the 6th meeting of the WHO advisory group on integrated surveillance of antimicrobial resistance with AGISAR 5-year strategic framework to support implementation of the global action plan on antimicrobial resistance (2015-2019), 10-12 June 2015, Seoul, Republic of Korea.
10. Halcomb E, McInnes S, Williams A, Ashley C, James S, Fernandez R, Stephen C, Calma K (2020) The experiences of primary healthcare nurses during the COVID-19 pandemic in Australia. J Nurs Scholarsh 52: 553-563.
11. Al-Azzam S, Mhaidat NM, Banat HA, Alfaour M, Ahmad DS, Muller A, Al-Nuseirat A, Lattyak EA, Conway BR, Aldeyab MA (2021) An assessment of the impact of coronavirus disease (COVID-19) pandemic on national antimicrobial consumption in Jordan. Antibiotics 10: 690.
12. Ul Mustafa Z, Salman M, Aldeyab M, Kow CS, Hasan SS (2021) Antimicrobial consumption among hospitalized patients with COVID-19 in Pakistan. SN Compr Clin Med 3: 1691-1695.
13. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y (2020) Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. JAMA 323: 1061.
14. Lansbury L, Lim B, Baskaran V, Lim WS (2020) Co-infections in people with COVID-19: a systematic review and meta-analysis. J Infect 81: 266-275.

15. Mahmoudi H (2020) Bacterial co-infections and antibiotic resistance in patients with COVID-19. GMS Hyg Infect Control 15: Doc35.
16. Bhimraj A, Morgan RL, Shumaker AH, Lavergne V, Baden L, Cheng VC-C, Edwards KM, Gandhi R, Muller WJ, O'Horo JC (2020) Infectious Diseases Society of America guidelines on the treatment and management of patients with coronavirus disease 2019 (COVID-19). Clin Infect Dis: ciaa478.
17. Hsu J (2020) How COVID-19 is accelerating the threat of antimicrobial resistance. BMJ: m1983.
18. Baclic DCV, Murthy S, Emeriaud G, Money D, Yeung T, Poliquin G, Brooks J, Decou M, Ofner M, Waechter J (2020) Clinical management of patients with COVID-19 – 2nd Interim guidance. Available: https://canadiancriticalcare.org/resources/Documents/AMMI-CCCS-PHAC-clinical-guidance-Aug21-EN-FINAL.pdf. Accessed: 8 November 2022.
19. Hadley W (2016) Ggplot2: elegant graphics for data analysis; Springer. 213 p.
20. Team RC (2021) A language and environment for statistical computing (R Version 4.0. 3, R Foundation for Statistical Computing, Vienna, Austria, 2020).
21. Brogan DM, Mossialos E (2016) A critical analysis of the review on antimicrobial resistance report and the infectious disease financing facility. Global health 12: 1-7.
22. Khor WP, Olaoye O, D'Arcy N, Krockow EM, Elshenawy RA, Rutter V, Ashiru-Oredope D (2020) The need for ongoing antimicrobial stewardship during the COVID-19 pandemic and actionable recommendations. Antibiotics 9: 904.
23. Sofy MR, Mancy AG, Alnaggar AEAM, Refaey EE, Mohamed HI, Elnosary ME, Sofy AR (2022) A polishing the harmful effects of broad bean mottle virus infecting broad bean plants by enhancing the immunity using different potassium concentrations. Notulae Botanicae Horti Agrobotanici Cluj-Napoca 50: 12654.
24. Alanio A, Dellière S, Fodil S, Bretagne S, Mégarbane B (2020) Prevalence of putative invasive pulmonary aspergillosis in critically ill patients with COVID-19. Lancet Respir Med 8: e48-e49.
25. Ryu S, Hwang Y, Ali ST, Kim D-S, Klein EY, Lau EHY, Cowling BJ (2021) Decreased use of broad-spectrum antibiotics during the coronavirus disease 2019 epidemic in South Korea. J Infect Dis 224: 949-955.
26. Badawy IH, Hmed AA, Sofy MR, Al-Mokadem AZ (2022) Alleviation of cadmium and nickel toxicity and phyto-stimulation of tomato plant by endophytic *Micrococcus luteus* and *Enterobacter cloacae*. Plants 11: 2018.
27. Grau S, Echeverria-Esnal D, Gómez-Zorrilla S, Navarrete-Rouco ME, Masclans JR, Espona M, Gracia-Arnillas MP, Duran X, Comas M, Horcajada JP (2021) Evolution of antimicrobial consumption during the first wave of COVID-19 pandemic. Antibiotics 10: 132.
28. HamİDİ AA, Yilmaz Ş (2021) Antibiotic consumption in the hospital during COVID-19 pandemic, distribution of bacterial agents and antimicrobial resistance: a single-center study. Journal of Surgery and Medicine 5: 124-127.
29. Fouda HM, Sofy MR (2022) Effect of biological synthesis of nanoparticles from *Penicillium chrysogenum* as well as traditional salt and chemical nanoparticles of zinc on canola plant oil productivity and metabolic activity. Egyptian Journal of Chemistry 65: 1-2.
30. Gonzalez-Zorn B (2021) Antibiotic use in the COVID-19 crisis in Spain. Clin Microbiol Infect 27: 646-647.
31. Buehrle DJ, Decker BK, Wagener MM, Adalja A, Singh N, McEllistrem MC, Nguyen MH, Clancy CJ (2020) Antibiotic consumption and stewardship at a hospital outside of an early coronavirus disease 2019 epicenter. Antimicrob Agents Chemother 64: e01011-20.
32. Agha MS, Abbas MA, Sofy MR, Haroun SA, Mowafy AM (2021) Dual inoculation of *Bradyrhizobium* and *Enterobacter* alleviates the adverse effect of salinity on *Glycine max* seedling. Notulae Botanicae Horti Agrobotanici Cluj-Napoca 49: 12461.
33. Arshad S, Kilgore P, Chaudhry ZS, Jacobsen G, Wang DD, Huitsing K, Brar I, Alangaden GJ, Ramesh MS, McKinnon JE (2020) Treatment with hydroxychloroquine, azithromycin, and combination in patients hospitalized with COVID-19. International Journal of Iinfectious Diseases 97: 396-403.
34. King LM, Lovegrove MC, Shehab N, Tsay S, Budnitz DS, Geller AI, Lind JN, Roberts RM, Hicks LA, Kabbani S (2021) Trends in US outpatient antibiotic prescriptions during the coronavirus disease 2019 pandemic. Clin Infect Dis 73: e652-e660.
35. de Lusignan S, Joy M, Sherlock J, Tripathy M, van Hecke O, Gbinigie O, Williams J, Butler C, Hobbs FR (2021) Principle trial demonstrates scope for in-pandemic improvement in primary care antibiotic stewardship. medRxiv 5: 21250902.
36. Liew Y, Lee WHL, Tan L, Kwa ALH, Thien SY, Cherng BPZ, Chung SJ (2020) Antimicrobial stewardship programme: a vital resource for hospitals during the global outbreak of coronavirus disease 2019 (COVID-19). Int J Antimicrob Agents 56: 106145.
37. Tran DH, Sugamata R, Hirose T, Suzuki S, Noguchi Y, Sugawara A, Ito F, Yamamoto T, Kawachi S, Akagawa KS (2019) Azithromycin, a 15-membered macrolide antibiotic, inhibits influenza A(H1N1)pdm09 virus infection by interfering with virus internalization process. J Antibiot 72: 759-768.
38. Gibson PG, Yang IA, Upham JW, Reynolds PN, Hodge S, James AL, Jenkins C, Peters MJ, Marks GB, Baraket M (2017) Effect of azithromycin on asthma exacerbations and quality of life in adults with persistent uncontrolled asthma (AMAZES): a randomised, double-blind, placebo-controlled trial. Lancet 390: 659-668.
39. Hinks TSC, Cureton L, Knight R, Wang A, Cane JL, Barber VS, Black J, Dutton SJ, Melhorn J, Jabeen M (2021) Azithromycin versus standard care in patients with mild-to-moderate COVID-19 (ATOMIC2): an open-label, randomised trial. Lancet Respir Med 9: 1130-1140.
40. Butler CC, Dorward J, Yu L-M, Gbinigie O, Hayward G, Saville BR, Van Hecke O, Berry N, Detry M, Saunders C (2021) Azithromycin for community treatment of suspected COVID-19 in people at increased risk of an adverse clinical course in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial. Lancet 397: 1063-1074.
41. Abaleke E, Abbas M, Abbasi S, Abbott A, Abdelaziz A, Abdelbadiee S, Abdelfattah M, Abdul B, Abdul Rasheed A, Abdul-Kadir R (2021) Azithromycin in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet 397: 605-612.
42. Cavalcanti AB, Zampieri FG, Rosa RG, Azevedo LCP, Veiga VC, Avezum A, Damiani LP, Marcadenti A, Kawano-Dourado L, Lisboa T (2020) Hydroxychloroquine with or without azithromycin in mild-to-moderate COVID-19. N Engl J Med 383: 2041-2052.

43. Furtado RHM, Berwanger O, Fonseca HA, Corrêa TD, Ferraz LR, Lapa MG, Zampieri FG, Veiga VC, Azevedo LCP, Rosa RG (2020) Azithromycin in addition to standard of care versus standard of care alone in the treatment of patients admitted to the hospital with severe COVID-19 in Brazil (COALITION II): a randomised clinical trial. Lancet 396: 959-967.
44. Klein EY, Milkowska-Shibata M, Tseng KK, Sharland M, Gandra S, Pulcini C, Laxminarayan R (2021) Assessment of WHO antibiotic consumption and access targets in 76 countries, 2000–15: an analysis of pharmaceutical sales data. Lancet Infect Dis 21: 107-115.
45. El-Sheshtawy HS, Sofy MR, Ghareeb DA, Yacout GA, Eldemellawy MA, Ibrahim BM (2021) Eco-friendly polyurethane acrylate (PUA)/natural filler-based composite as an antifouling product for marine coating. Appl Microbiol and Biotechnol 105: 7023-7034.
46. Castro-Lopes A, Correia S, Leal C, Resende I, Soares P, Azevedo A, Paiva J-A (2021) Increase of antimicrobial consumption in a tertiary care hospital during the first phase of the COVID-19 pandemic. Antibiotics 10: 778.

Corresponding authors

Mamoon A. Aldeyab
Department of Pharmacy, School of Applied Sciences,
University of Huddersfield, Huddersfield, UK
Tel: +441484472825
Email: m.aldeyab@hud.ac.uk

Mahmoud R Sofy
Botany and Microbiology Department, Faculty of Science,
AL-Azhar University, Cairo, Egypt
Tel: +201002632232
Email: mahmoud_sofy@azhar.edu.eg

Conflict of interests: No conflict of interests is declared.