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ORIGINAL RESEARCH

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Bacterial co-infections, secondary infections and antimicrobial use among hospitalized COVID-19 patients in the sixth wave in Pakistan: findings and implications

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ABSTRACT

Introduction: Previous studies in Pakistan have shown considerable over prescribing of antibiotics in patients hospitalized with COVID-19 despite very low prevalence of bacterial infections. Irrational use of antibiotics will worsen antimicrobial resistance (AMR).
Methods: Retrospective analysis of medical records of patients in the COVID-19 wards of three tertiary care hospitals to assess antibiotic use during the sixth COVID-19 wave.
Results: A total of 284 patients were included, most were male (66.9%), aged 30–50 years (50.7%) with diabetes mellitus the most common comorbidity. The most common symptoms at presentation were cough (47.9%) and arthralgia-myalgia (41.5%). Around 3% were asymptomatic, 34.9% had mild, 30.3% moderate, and 23.6% had severe disease, with 8.1% critical. Chest X-ray abnormalities were seen in 43.3% of patients and 37% had elevated white cell counts, with 35.2% having elevated C-reactive protein levels. Around 91% COVID-19 patients were prescribed antibiotics during their hospital stay, with only a few with proven bacterial co-infections or secondary bacterial infections. Most antibiotics were from the 'Watch' category (90.8%) followed by the 'Reserve' category (4.8%), similar to previous COVID-19 waves.
Conclusion: There continued to be excessive antibiotics use among hospitalized COVID-19 patients in Pakistan. Urgent measures are needed to address inappropriate prescribing including greater prescribing of Access antibiotics where pertinent.

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KEYWORDS
Antibiotics; AWaRe classification; antibiotic stewardship programs; COVID-19; hospitalized patients; tertiary care; Pakistan

1. Introduction

In Pakistan, the first positive case of COVID-19 was reported on 26 February 2020 [1], which resulted in a range of activities by the government to try and prevent disease transmission in the absence of effective proven treatments and vaccines at the start of the pandemic [2,3]. These interventions in Pakistan included lockdown enforcement, social distancing, promoting hand hygiene, instigating travel restrictions, the closure of educational and religious institutes and markets as well as the establishment of COVID-19 wards in hospitals [4–8]. Alongside this, tertiary care/teaching hospitals were designated in every metropolitan city of the country to treat referral patients with COVID-19 from across the country [9].

The first COVID-19 wave peaked in Pakistan in June 2020 with more than 30,000 positive cases, which was reduced by lockdown and other measures, similar to other countries [6,10–12]. The second wave peaked in October 2020, infecting and killing more patients than during the first wave [13]. The total number of positive cases reached 332,993, along with 6,806 deaths up to 31 October 2020 [14]. The third wave was reported in April 2021, with the worst affected provinces being Punjab and Khyber Pakhtunkhwa [15,16]. More than 200 deaths were reported due to COVID-19 in Pakistan in a single day in April 2021, with the cumulative number of deaths reaching 17,530 [17]. The fourth wave of COVID-19 was documented in Pakistan in July 2021, with the highest number of positive cases reported in August 2021 [18]. The overall positivity rate was 6.78% [18]. The Omicron-driven fifth COVID-19 wave peaked in January 2022 in Pakistan, with 7586 positive cases reported in 24 hours and a greater positivity rate at over 11.5% [19,20]. In June 2022, health

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Article highlights

- In the first five waves of COVID-19 in Pakistan, there was appreciable prescribing of antibiotics in patients admitted with COVID-19, averaging 89.69% of patients among tertiary hospitals despite only 1.14% of patients having proven bacterial co-infections and 3.14% secondary infections. Alongside this, there was appreciable prescribing of 'Watch' antibiotics, averaging 93.35% of total antibiotics prescribed
- There were similar concerns in the sixth wave, with approximately 91% of patients admitted to tertiary hospitals prescribed antibiotics during their hospital stay, with again only a limited number with proven bacterial co-infections or secondary bacterial infections
- Most antibiotics prescribed were from the 'Watch' category (90.8%) followed by the 'Reserve' category (4.8%) with limited prescribing of 'Access' antibiotics
- This is a major concern, with the WHO advocating that at least 60% of antibiotics prescribed in given settings should be from the 'Access' list
- Consequently, there is an urgent need to instigate pertinent antimicrobial stewardship programs (ASPs) in hospitals in Pakistan to reduce high rates of inappropriate prescribing of antibiotics especially from the 'Watch' and 'Reserve' list. This includes patients admitted with COVID-19 in successive waves
- ASPs have been successfully introduced in other LMICs and can serve as exemplars to all key stakeholder groups in Pakistan going forward

authorities in Pakistan warned the public about the sixth COVID-19 wave when more than 330 positive cases were reported in 24 hours [21]. Countrywide, from the start of the COVID-19 pandemic up to 28 April 2023, more than 1,580,631 positive cases and 30,656 deaths due to COVID-19 have been reported in Pakistan [22]. Fortunately, the majority of patients recovered (1,548,286–98%), with most having mild-to-moderate disease symptoms. Severe and critical patients were typically treated in hospital [23].

Previous studies from Pakistan, alongside studies from others countries, including other low- and middle-income countries (LMICs), demonstrated that hospitalized COVID-19 patients were prescribed many medicines with or without evidence. These included anticoagulants, corticosteroids, hydroxychloroquine, and antivirals, including remdesivir [23–31]. Due to the viral origin of COVID-19, following national guidelines, antibiotics were not recommended prophylactically and should typically only be prescribed to patients admitted to hospital following confirmation of bacterial-co infection or secondary infection [32,33]. Despite this advice, numerous studies and reviews have revealed that antibiotics were heavily prescribed among hospitalized COVID-19 patients across countries despite very low percentages of signs of bacterial co-infection or secondary infection [34–40]. Studies, including those from Pakistan, have also reported levels of only 1.2–14.3% of hospitalized COVID-19 patients (including neonates and children) having bacterial co-infections or secondary infections [9,34,36,38,41–44]. However, more recent studies have suggested higher rates of secondary bacterial infections at 18.2% [45]. A concern was that an appreciable number of infections were resistant to antimicrobials (60.8%), with a high number of isolates also resistant (37.5%) [45]. Consequently, it is important for healthcare professionals (HCPs) to quickly review the extent of co-infections and superinfections in patients admitted with COVID-19 rather than routinely administer antibiotics [46,47]. This is because irrational and excessive antibiotic use among patients with COVID-19 can increase the threat of antimicrobial resistance (AMR) [48–50]. Studies from the Centers for Disease Control and Prevention (CDC) suggest that AMR rates have increased up to 15% in hospitalized settings due to the overuse of antibiotics in the first year of the COVID-19 pandemic [51,52]. Poor infection prevention and control measures along with a lack of appropriate antimicrobial stewardship programs (ASPs), coupled with the disruption of surveillance activities in hospitals during the current pandemic, have impacted on AMR rates, especially among LMICs [53–55]. Increasing the prevalence of AMR is a concern with AMR now one of the leading global health threats with an estimated 1.27 million deaths globally in 2019 due to bacterial AMR, and an estimated 4.95 million deaths associated with bacterial AMR [56]. Currently, the highest number of deaths and burden of AMR are in South Asian and African countries [56]. In Pakistan, both multi-drug resistance (MDR) and extensively drug resistance (XDR) cases have been reported, which threaten the nation's health [57–59]. Consequently, an urgent need to address this. Pakistan has started to address this through implementing its National Action Plan to reduce AMR. However to date, there have been many challenges and difficulties with its implementation [60–62].

To help enhance appropriate prescribing of antibiotics in hospital and reduce AMR, the WHO has developed and published the AWaRe (access, watch, reserve) classification of antibiotics [63]. Under this system, antibiotics in the 'Watch' group should ideally only be used in critical conditions, as they have a greater chance of resistance development, while those in the 'Reserve' group should only be prescribed in patients with multi-drug resistant bacteria [63,64]. The WHO's target is that at least 60% of the antibiotics prescribed should be from the 'Access' group given they are the least likely to increase antibiotic resistance [64,65].

In the first five waves of the COVID-19 pandemic in Pakistan, there was appreciable prescribing of antibiotics among patients admitted to tertiary hospitals with COVID-19. On average, antibiotics were prescribed to 89.69% of patients admitted to tertiary hospitals with COVID-19. This was despite only 1.14% of patients having proven bacterial co-infections and 3.14% secondary bacterial infections [9]. Alongside this, there was appreciable prescribing of 'Watch' antibiotics, which averaged 93.35% of total antibiotic prescribing among participating hospitals [9]. Such prescribing is a concern since, as mentioned, appreciable prescribing of 'Watch' antibiotics increases AMR. However, improving antibiotic prescribing in hospitals can be addressed with appropriate ASPs [66–68].

Consequently, we wanted to build on the findings from the first five waves to provide additional guidance to the authorities in Pakistan as they seek to reduce AMR despite the many challenges with implementing its NAP [61]. In view of this, the objectives of the current study were to evaluate the prescribing practices of antibiotics among patients hospitalized in tertiary hospitals with COVID-19 during the sixth COVID-19 wave, together with the prevalence of bacterial co-infection and secondary bacterial infections. The findings will be compared with the first five waves of COVID-19 to provide additional guidance to all key stakeholder groups in Pakistan going forward.

2. Materials and methods

2.1. Study settings, design, and population

We performed a retrospective medical record review among patients admitted onto the COVID-19 wards of three tertiary care health facilities in the Province of Punjab during the sixth COVID-19 wave. As mentioned, in June 2022, the health authorities in Pakistan warned the public about the sixth COVID-19 wave when more than 330 positive cases were reported in 24 hours [21]. This followed the first five waves, where on average 89.69% of patients in tertiary hospitals were prescribed antibiotics despite only 1.14% of patients having proven bacterial co-infections and 3.14% secondary infections [9].

The three tertiary care hospitals in this study were selected based on our previous findings [9]. The included health facilities serving as referral hospitals for all patients from primary and secondary hospitals in Punjab. Designated COVID-19 wards were established in these health facilities since the emergence of the COVID-19 pandemic in the country. Each of these hospitals had 750–1250 beds, and the COVID-19 wards in these hospitals had 40–50 beds. Punjab was also selected for our current study as it is the most populous province in Pakistan, and we have suitable background data from previous studies for comparative purposes [9,69–71].

2.2. Study variables

The data collection form was designed to collect the variables of interest based on previous studies conducted by the co-authors [9,23,28,41,43].

The following information was recorded on the data collection form:

- Demographics and disease characteristics: patient's age, sex, and length of hospital stay (in days). The age distribution of patients was grouped into categories, i.e. 10–30 years, 31–50, and >50 years based on previous studies by the coauthors [9,41]
- The presence or absence of any comorbidities, including diabetes mellitus, hypertension, cardiac disease (e.g. coronary heart disease, stroke, and peripheral artery disease), respiratory disease (chronic obstructive pulmonary disease [COPD], asthma, occupational lung diseases and pulmonary hypertension) as well as the severity of COVID-19. The severity of COVID-19 was categorized as asymptomatic, mild, moderate, severe, or critical as per the guidelines issued by the Ministry of National Health Services, Regulation and Coordination, Government of Pakistan [33]:
  a. Asymptomatic: SARS-CoV-2 infection (positive PCR) reported, but without any symptoms.
  b. Mild: Symptoms due to COVID-19 but without any hemodynamic disturbances or any chest X-ray abnormalities. The oxygen saturation in these cases was ≥94%.
  c. Moderate: Patients having a chest X-ray with infiltrates involving <50% of the total lung fields, oxygen saturation below 94% but above 90% and without severe manifestations.
  d. Severe: Those with fever and cough along with a respiratory rate <30 breaths per minute, chest X-ray with infiltrates involving more than 50% of the total lung fields, severe respiratory distress, and oxygen saturation ≤90% on room air.
  e. Critical: Presence of acute respiratory distress syndrome (ARDS) or worsening of respiratory symptoms, bilateral opacities or lung collapse in chest X-rays or CT scan and respiratory or cardiac failure.
- Presenting symptoms e.g. fever, cough, sore throat, shortness of breath, headache, or joint/muscle ache.
- Laboratory and other findings. This included chest X-rays, white blood cell counts (WBCs) and C-reactive protein (CRP) levels. The chest X-ray findings were reviewed by medical doctors and the treating physician was consulted in case of any confusion or concerns. Normal ranges of WBCs and CRP were taken from the reference mentioned on the testing kits available at these hospitals, with findings designated as elevated if above the referenced levels.
- Whether hospitalized COVID-19 patients were on oxygen therapy or not. Oxygen therapy used in these hospitals was administered via a compressed gas system through a central oxygen supply or portable cylinder via high flow nasal cannulas.
- Ward subspecialty, including medical wards or intensive care units (ICU) on admission.
- Whether hospitalized COVID-19 patients were on mechanical ventilation (positive pressure ventilation) or not.
- Details about antibiotics prescribed, which included:
  a. Number of prescribed antibiotics as well as their dose, duration of therapy, and route of administration.
  b. Antibiotics were classified according to the ATC classification and WHO AWaRe classification [63,64,72].
  c. Presence of pneumonia and bloodstream infections, which were defined as per the guidelines issued by the Ministry of National Health Services, Regulation and Coordination, Government of Pakistan [33].
  d. Presence of bacterial co-infection in patients admitted with COVID-19, i.e. bacterial infections that were identified ≤2 days after hospital admission due to COVID-19.
  e. Presence of bacterial secondary infection, i.e. bacterial infections diagnosed >2 days after admission with COVID-19.
- Other medications administered during hospital stay besides antimicrobials, including antipyretics, antitussives, antihistamines, anticoagulants, and corticosteroids.
- Immediate outcomes included whether a patient was discharged alive and well from hospital or died in hospital.

2.3. Data collection procedures

Data collection commenced after ethics approval was granted and permission obtained from the authorities and participating hospitals. Data were collected retrospectively over a period of 2 months (Feb–March 2023) by a team of investigators, after being trained on the data collection procedures by the principal investigator (ZUM). Medical record rooms for COVID-19 wards were accessed and the records of all patients admitted to these hospitals during the sixth wave of COVID-19 were thoroughly examined by the investigators. The necessary data were manually recorded onto the data collection forms. Clinical staff at the hospitals were only approached where clarity was needed in terms of accessing patient records or information recorded in the patient files such as X-ray findings and disease severity.

2.4. Inclusion and exclusion criteria

All patients who were admitted into the COVID-19 wards of the selected tertiary hospitals during the sixth wave of the COVID-19 pandemic were included in the study. Patients who were not admitted, those isolated at home, or admitted at a time other than previously mentioned, or whose medical records were incomplete upon examination were excluded from the study.

2.5. Statistical analysis

All statistical analysis were performed using SPSS version 22 for Microsoft Windows. Continuous and categorical data were expressed as means ± standard deviations and frequencies with percentages, respectively. Antibiotic usage was compared among demographic and clinical variables using an independent sample t-test and ANOVA, where appropriate. The Welch's ANOVA was used instead of classic ANOVA when the data violated the assumption of homogeneity of variances. In addition, multiple comparisons were made using Tukey HSD and/or the Games-Howell test to investigate any significance among polychotomous variables, where applicable. Multiple linear regression analysis was carried out to assess factors associated with higher antibiotic use (Dependent variable: total number prescribed antibiotics; Method: Enter). A p value of less than 0.05 was consistent with the null hypothesis being true for all statistical analyses.

2.6. Ethical considerations

As the data was retrospectively collected from patients' medical records and notes, with no data collected from patients directly, the approval committee exempted written informed consent from potential participants. This is in line with similar studies undertaken by the coauthors. No personal patient information (name, address, national identity card, or telephone number) was collected, and each patient was given a study identification number and the data was kept confidential.

3. Results

A total of 284 COVID-19 positive patients from the three hospitals were included in the analysis (Hospital 1 (H1): 74 patients; Hospital 2 (H2): 119 patients; Hospital 3 (H3): 91 patients). Demographic and clinical characteristics of the study population are given in Table 1. The majority of patients were male (66.9%) and between the ages of 30–50 years (50.7%). Overall, 41% of admitted patients were found to have at least one comorbidity. The most common comorbidity was diabetes mellitus followed by hypertension and cardiovascular disease. There was no significant difference in patients' age, gender, residence, comorbid conditions, and frequency of patients admitted to the medical wards or ICUs between the three participating hospitals (Table 1).

Regarding COVID-19 severity, 3.2% of admitted patients were asymptomatic, 34.9% had mild disease, 30.3% had moderate disease, 23.6% had severe disease and 8.1% were critical, with a significant difference in the proportion of patients with varying degrees of COVID-19 severity between the study sites (Table 1). Overall, oxygen supplementation therapy was given to 31.7% of patients whereas the invasive mechanical ventilation was required in 9.2% of the study population.

The most common symptom at presentation was a cough (47.9%) followed by arthralgia-myalgia (41.5%) and fever (36.6%). Chest X-ray abnormalities were seen in 43.3% of the patients. A significantly higher number of patients at Hospital 3 had X-ray abnormalities. More than a third (37%) had elevated white cell counts, whereas 35.2% had elevated CRP levels. Most of the COVID-19 patients (47.2%) had hospital stays of 7–14-days, with 38.4% of admitted patients having a length of stay of more than 2 weeks. We observed that a significantly higher number of patients from Hospital 3 had hospital stays >14 days versus the other study sites (Table 1).

The most commonly prescribed pharmacological class was antibiotics (91.9%) followed by corticosteroids (73.9%), antipyretics (62.7%), and antitussives (50%). A total of 457 antibiotics were prescribed to 261 patients with an average of 1.61 ± 0.86 antibiotics per patient during their hospital stay, with antibiotics usually prescribed soon after hospital admission. Nearly half of the patients (47.5%) were prescribed two antibiotics with 41% prescribed one antibiotic as shown in Table 2.

Most of the antibiotics (47.7%) were prescribed for 6–10 days, followed by >11 days (37.6%) with just 14% prescribed antibiotics for ≤5 days. More than three quarters (75.7%) of the total antibiotics prescribed were for intravenous administration.

The details of the prescribed antibiotic class and individual agents according to the ATC classification are shown in Table 3. The most frequently prescribed antibiotic class was third generation cephalosporins (31.2%) followed by macrolides (20.1%) and piperacillin plus an enzyme inhibitor (tazobactam) (13.6%). As far as the individual agents are concerned, the three most commonly prescribed antibiotics were ceftriaxone (24.9%), azithromycin (13.6%), and piperacillin plus tazobactam (13.6%). Overall, most of the prescribed antibiotics in the three hospitals (415, 90.8%) were from the 'Watch' category followed by the 'Reserve' category (22, 4.8%). Only 20 patients received 'Access' antibiotics (4.4%) as shown in Figure 1.

Comparison of the usage of antibiotics between demographic and clinical variables are shown in Table 4. Overall, a significant difference in antibiotic usage was observed between the age groups ($p = 0.011$). In the post hoc analysis

Table 1. Demographic and clinical characteristics of the study population ($N = 284$).

Variables	Total ($N = 284$)	H1 ($N = 74$)	H2 ($N = 119$)	H3 ($N = 91$)	P-value
	N (%)				
Age					
10–30 years	26 (9.2)	6 (8.1)	13 (10.9)	7 (7.7)	0.213
30–50 years	144 (50.7)	34 (45.9)	68 (57.1)	42 (46.2)	
>50 years	114 (40.1)	34 (45.9)	38 (31.9)	42 (46.2)	
Sex					
Male	190 (66.9)	50 (67.6)	80 (67.2)	60 (65.9)	0.971
Female	94 (33.1)	24 (32.4)	39 (32.8)	31 (34.1)	
Residence					
Rural	81 (28.5)	25 (33.8)	30 (25.2)	26 (28.6)	0.439
Urban	203 (71.5)	49 (66.2)	89 (74.8)	65 (71.4)	
Comorbidity*					
Yes	115 (40.5)	32 (43.2)	48 (40.3)	35 (38.5)	0.823
No	169 (59.5)	42 (56.8)	71 (59.7)	56 (61.5)	
Hospital Ward					
Medical	199 (70.1)	48 (64.9)	91 (76.5)	60 (65.9)	0.134
ICU	85 (29.9)	26 (35.1)	28 (23.5)	31 (34.1)	
Severity of COVID-19					
Asymptomatic	9 (3.2)	5 (6.8)	3 (2.5)	1 (1.1)	0.030
Mild	99 (34.9)	25 (33.8)	50 (42.0)	24 (26.4)	
Moderate	86 (30.3)	16 (21.6)	38 (31.9)	32 (35.2)	
Severe	67 (23.6)	20 (27.0)	19 (16.0)	28 (30.8)	
Critical	23 (8.1)	8 (10.8)	9 (7.6)	6 (6.6)	
Oxygen therapy					
Yes	90 (31.7)	28 (37.8)	28 (23.5)	34 (37.4)	0.043
No	194 (68.3)	46 (62.2)	91 (76.5)	57 (62.6)	
Invasive mechanical ventilation					
Yes	26 (9.2)	9 (12.2)	8 (6.7)	9 (9.9)	0.425
No	194 (68.3)	65 (87.8)	111 (93.3)	82 (90.1)	
Laboratory findings					
X-Ray abnormalities	123 (43.3)	34 (45.9)	38 (31.9)	51 (56.0)	0.002
Elevated WBCs	105 (37.0)	29 (39.2)	37 (31.1)	39 (42.9)	0.195
Elevated CRP	100 (35.2)	22 (29.7)	37 (31.1)	41 (45.1)	0.057
Length of hospital stay					
<7 days	41 (14.4)	8 (10.8)	13 (10.9)	20 (22.0)	0.001
7–14 days	134 (47.2)	37 (50.0)	70 (58.8)	27 (29.7)	
≥15 days	109 (38.4)	29 (39.2)	36 (30.3)	44 (48.4)	

NB: *Diabetes = 62 patients, Hypertension = 53 patients, cardiovascular disease = 23 patients, respiratory disease = 12 patients; CRP=C reactive protein; H=hospital; ICU=intensive care unit; WBC=white blood cell.

Table 2. Detail of prescribed antibiotics amid the sixth wave of COVID-19 in Pakistan.

Variables	Total	H1	H2	H3
	N (%)			
Number of patients prescribed antibiotics ($N = 284$)	261 (91.9)	67	109	85
Total number of prescribed antibiotics	457	126	193	138
Average number of prescribed antibiotics per patient ± SD ($N = 284$)	1.61 ± 0.86	1.70 ± 0.98	1.62 ± 0.88	1.52 ± 0.72
Number of antibiotics per patient ($N = 261$)				
One antibiotic	107 (41.0)	23	44	40
Two antibiotics	124 (47.5)	33	49	42
Three or more antibiotics	30 (11.5)	11	16	3
Duration of antibiotic therapy ($N = 457$)				
1–5 days	67 (14.7)	16	27	24
6–10 days	218 (47.7)	72	92	54
>11 days	172 (37.6)	38	74	60
Route of administration ($N = 457$)				
Oral	111 (24.3)	37	49	25
Intravenous	346 (75.7)	89	144	113

NB: H=hospital, SD=standard deviation.

(Table 5), antibiotic use was significantly higher among older hospitalized patients compared with other age groups ($p < 0.05$). There was no significant difference in antibiotic use between 31–50 year old COVID-19 patients and those under-30 year's old ($p = 0.445$).

Antibiotic use increased significantly with an increased severity of COVID-19 ($p < 0.001$; Table 4). In pairwise comparisons using Tukey's HSD test, there was no significant difference in antibiotic usage between asymptomatic and mild COVID-19 patients. Patients with moderate disease were prescribed more antibiotics than mild or asymptotic patients. Similarly, severe and critical COVID-19 cases were prescribed more antibiotics than those with mild or moderate disease and asymptomatic patients ($p < 0.05$; Table 5). The prescribing of antibiotics was significantly higher ($p < 0.05$) among ICU patients, those who required oxygen

Table 3. Prescribed antibiotics according to their ATC classification accross the three hospitals.

ATC class	Name of antibiotics (ATC code)	N (%) H1	H2	H3	Total
Third-generation cephalosporins	Ceftriaxone (J01DD04)	31 (24.6)	53 (27.5)	30 (21.7)	114 (24.9)
	Cephoperazone + beta-lactamase inhibitor (J01DD12)	9 (7.1)	12 (6.2)	8 (5.8)	29 (6.3)
Macrolides	Azithromycin (J01FA10)	26 (20.7)	42 (21.8)	24 (17.4)	92 (20.1)
Piperacillin and an enzyme inhibitor	Piperacillin + enzyme inhibitor (tazobactam) (J01CR05)	23 (18.2)	23 (11.9)	16 (11.6)	62 (13.6)
Carbapenems	Meropenem (J01DH02)	14 (11.1)	27 (14.0)	18 (13.0)	59 (12.9)
Fluoroquinolones	Ciprofloxacin (J01MA02)	4 (3.1)	7 (3.6)	10 (7.3)	21 (4.6)
	Levofloxacin (J01MA12)	1 (0.8)	4 (2.0)	5 (3.6)	10 (2.2)
	Moxifloxacin (J01MA14)	1 (0.8)	4 (2.0)	0	5 (1.1)
Other antibacterials	Linezolid (J01XX08)	6 (4.8)	5 (2.6)	11 (8.0)	22 (4.8)
Glycopeptides	Vancomycin (J01XA01)	6 (4.8)	5 (2.6)	8 (5.8)	19 (4.2)
Amoxicillin and beta-lactamase inhibitor	Amoxicillin+ Beta-lactamase inhibitors (J01CR02)	2 (1.6)	5 (2.6)	3 (2.2)	10 (2.2)
Penicillins with extended spectrum	Amoxicillin (J01CA04)	2 (1.6)	3 (1.6)	5 (3.6)	10 (2.2)
Fourth-generation cephalosporins	Cefepime (J01DE01)	1 (0.8)	3 (1.6)	0	4 (0.9)

NB: ATC=Anatomical Therapeutic Chemical Classification; H=hospital.

Table 4. Comparison of antibiotic usage among selected variables.

Variables	No. of antibiotics (Mean ± SD)	P-value
Hospital (H)		
H1	1.70 ± 0.98	0.374
H2	1.62 ± 0.88	
H3	1.52 ± 0.72	
Age		
10–30 years	1.31 ± 0.74	0.011
30–50 years	1.53 ± 0.84	
>50 years	1.78 ± 0.89	
Sex		
Male	1.66 ± 0.87	0.133
Female	1.50 ± 0.84	
Residence		
Rural	1.56 ± 0.82	0.508
Urban	1.63 ± 0.88	
Comorbidity*		
Yes	1.77 ± 0.83	0.008
No	1.50 ± 0.87	
Ward		
Medical	1.49 ± 0.80	<0.001
ICU	1.88 ± 0.93	
Severity of COVID-19		
Asymptomatic	0.56 ± 0.88	<0.001
Mild	1.26 ± 0.78	
Moderate	1.60 ± 0.60	
Severe	2.00 ± 0.85	
Critical	2.39 ± 0.94	
Oxygen therapy		
Yes	2.10 ± 0.89	<0.001
No	1.38 ± 0.75	
Invasive mechanical ventilation		
Yes	2.35 ± 0.98	<0.001
No	1.53 ± 0.81	
X-Ray abnormalities		
Yes	1.93 ± 0.85	<0.001
No	1.36 ± 0.79	
Elevated White blood cell count		
Yes	1.96 ± 0.89	<0.001
No	1.40 ± 0.78	
Elevated C-reactive protein		
Yes	1.99 ± 0.82	<0.001
No	1.40 ± 0.81	
Length of stay		
<7 days	1.10 ± 0.83	<0.001
7–14 days	1.45 ± 0.71	
≥15 days	2.00 ± 0.88	

NB: * See Table 1 for details of co-morbidities.

Table 5. Pairwise comparisons of antibiotic use among age groups, COVID-19 severity, and length of hospital stay.

			95% CI		
Comparison	Mean difference	SE	Lower bound	Upper bound	P-value*
Age (years)					
10–30 vs 31–50	−0.22	0.18	−0.65	0.21	0.445
10–30 vs > 50	−0.47	0.19	−0.91	−0.04	0.029
31–50 vs > 50	−0.25	0.11	0.00	0.50	0.048
COVID-19 severity					
Asymptomatic vs mild	−0.71	0.27	−1.44	0.02	0.064
Asymptomatic vs moderate	−1.05	0.27	−1.79	−0.31	0.001
Asymptomatic vs severe	−1.44	0.27	−2.19	−0.70	<0.001
Asymptomatic vs critical	−1.84	0.30	−2.66	−1.01	<0.001
Mild vs moderate	−0.34	0.11	−0.65	−0.03	0.022
Mild vs severe	−0.74	0.12	−1.07	−0.40	<0.001
Mild vs critical	−1.13	0.17	−1.62	−0.64	<0.001
Moderate vs severe	−0.40	0.13	−0.74	−0.05	0.015
Moderate vs critical	−0.79	0.18	−1.28	−0.29	<0.001
Severe vs critical	−0.39	0.19	−0.90	0.12	0.216
Length of hospital stay (days)					
<7 vs 7–14	−0.35	0.14	−0.69	−0.01	0.038
<7 vs > 15	−0.90	0.15	−1.25	−0.56	<0.001
7–14 vs > 15	−0.55	0.10	−0.79	−0.31	<0.001

NB: [a]Tukey HSD test.

Table 6. Factors associated with increased use of antibiotics among COVID-19 patients.

Coefficients[a]

	Unstandardized Coefficients		Standardized Coefficients			95% CI for B	
Model	B	SE	β	t	P	Lower bound	Upper bound
(Constant)	0.576	0.916		0.629	0.530	−1.228	2.379
Age	0.050	0.081	0.037	0.618	0.537	−0.110	0.210
Comorbidity	−0.006	0.105	−0.003	−0.054	0.957	−0.213	0.202
Ward type	−0.101	0.132	−0.054	−0.766	0.444	−0.361	0.159
COVID Severity	0.372	0.116	0.441	3.201	0.002	0.143	0.601
Oxygen therapy	0.000	0.227	0.000	−0.001	0.999	−0.448	0.447
IMV	−0.119	0.200	−0.040	−0.594	0.553	−0.513	0.275
Abnormal X-ray	0.082	0.153	0.047	0.535	0.593	−0.220	0.384
Elevated WBC	0.050	0.156	0.028	0.324	0.747	−0.257	0.358
Elevated CRP	−0.107	0.141	−0.059	−0.757	0.450	−0.384	0.171
Length of stay	0.059	0.114	0.047	0.514	0.608	−0.166	0.284

NB: [a]Dependent Variable: Total number of prescribed antibiotics; B=the unstandardized beta; SE=standard error for the unstandardized beta; β=the standardized beta coefficient; t=the t test statistic; P=probability value; CI=confidence interval; CRP=C reactive protein; IMV=invasive mechanical ventilation; SE=standard error; WBC=white blood cell.

therapy or mechanical ventilation, had chest X-ray abnormalities, elevated WBCs and RBCs, and increased length of hospital stay (Table 4).

Multiple linear regression was performed to confirm factors significantly associated with antibiotic use in COVID-19 patients. As shown in Table 6, COVID-19 severity [$\beta = 0.441$ (95% CI 0.143–0.601), $p = 0.002$] was found to be the only significant predictor of higher antibiotic usage keeping all the other independent variables constant.

Only 16 samples were sent to a microbiology laboratory for confirmation of bacterial co-infection and secondary bacterial infections. Out of these, only 11 samples identified a bacterial agent. The common bacterial organisms identified were *Pseudomonas aeruginosa*, *Streptococcus pneumoniae, Klebsiella* species, and *Staphylococcus aureus* (Table 7).

Regarding the treatment outcomes, six patients died in hospital (2.1%), whereas the rest recovered from the disease and were discharged from the hospital.

4. Discussion

We believe this is the first study conducted in Pakistan to document antibiotic utilization patterns among patients admitted to hospital with COVID-19 in tertiary hospitals that were established to treat these patients in the first six waves of COVID-19, describing the sixth wave in full. As a result, we are able to clearly identify any changes in the prescribing of antibiotics in admitted patients in the sixth wave compared to the first five waves of COVID-19 [9].

Firstly, our study revealed that almost all (>91%) patients hospitalized for COVID-19 admitted during the sixth wave were prescribed at least one antibiotic. This was despite a very low percentage of patients being identified with either a bacterial co-infection or secondary infection (Table 7). Whilst this is similar to the first five waves with 89.7% and 84.9% of hospitalized patients, respectively, prescribed antibiotics [9,41], which agreed with the initial systematic reviews [34–36], the situation is now changing [45]. Despite this,

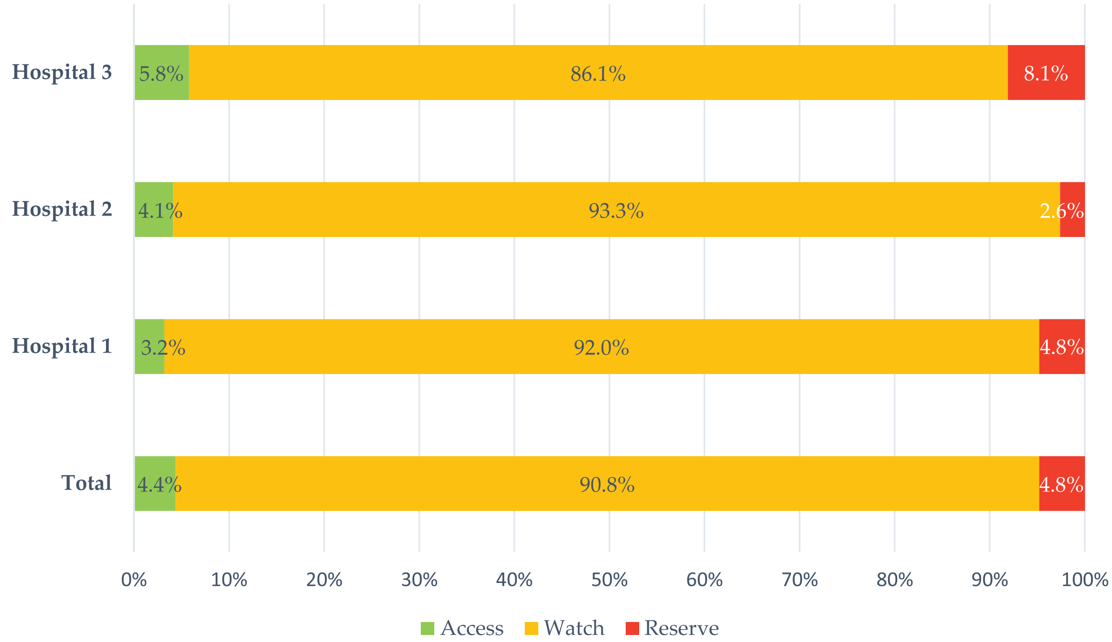

Figure 1. Prescribed antibiotics according to WHO AWaRe classification among the participating hospitals.
NB: 'Access', 'Watch' and 'Reserve' antibiotics based on the AWaRe list [63,64].

excessive prescribing of antibiotics continues to be a concern if only a limited number of patients have proven bacterial co-infection or secondary bacterial infections. Both global and national Guidelines continue to advise that antibiotics should not be prescribed to COVID-19 patients unless the patient is diagnosed with a bacterial co-infection or secondary bacterial infection [32,33]. This unnecessary and excessive antibiotic use particularly linked to COVID-19 will worsen current high rates of AMR in Pakistan unless addressed [50,54,62,73,74]. We are aware that in Scotland, 45.0% of hospitalized patients with COVID-19 were prescribed antibiotics, with 73.9% of patients prescribed antibiotics for suspected respiratory tract infections [75]. In Russia, similarly, only one-third of total hospitalized COVID-19 patients were prescribed systemic antibiotics [76]. In Japan, only 13.2% of patients seen in acute hospitals with COVID-19 were prescribed antibiotics, higher among in-patients at 16.15% [77]. In addition, more recent systematic reviews have suggested a decline in the prescribing of antibiotics for patients hospitalized with COVID-19 down from 82.3% of patients to 39.7%, perhaps reflecting greater knowledge in its treatment [78]. However, the bacterial co-infection rate was still low at 10.5% of patients [78], which was similar to the recent systematic review and meta-analysis of Langford et al. (2023) at 5.3% [45]. These combined studies provide guidance to key stakeholder groups in Pakistan regarding potential future targets for the prescribing of antibiotics in patients with COVID-19 admitted to hospital.

Nearly half the study population admitted with COVID-19 in our study received two antibiotics during their hospital stay. Whilst high with an average of 1.16 antibiotics per admitted patient, this was lower than the first five waves averaging 1.66 antibiotics per admitted patient [9], as well as a point prevalence study undertaken among tertiary hospitals, which averaged at 1.7 antibiotics per patient [41]. These findings are comparable to a study undertaken in Sierra Leone, where most of the patients hospitalized with COVID-19 were prescribed two antibiotics [79]. Our study also revealed that most of the antibiotics were prescribed for >6 days (mainly between 6 and 10 days), which was similar to the first five waves [9]. Extended prescribing is a concern as this can also increase AMR.

Secondly, we found the most frequently prescribed antibiotics in our study were ceftriaxone, azithromycin, and piperacillin plus tazobactam. Other antibiotics prescribed were meropenem and the fluoroquinolones such as ciprofloxacin and levofloxacin. Whilst these findings are in line with previous studies conducted in Punjab, where the most frequently prescribed antibiotics among hospitalized COVID-19 were ceftriaxone, azithromycin, piperacillin plus an enzyme inhibitor and meropenem [9,39,41], this is a concern. The concern is that such high prescribing rates of 'Watch' antibiotics (90.8%) and 'Reserve' antibiotics at 4.8%, with very low prescribing of 'Access' antibiotics at just 4.4%, will increase AMR rates in these hospitals. Whilst we have seen high rates of prescribing of 'Watch' antibiotics in other studies [79,80], such high use of 'Watch' antibiotics will appreciably increase AMR unless addressed [66,67]. Consequently, the WHO recommended that at least 60% of antibiotics prescribed in healthcare facilities should be from the 'Access' list [67,81,82].

In view of our findings, there is an urgent need to address concerns with the continued high rates of prescribing of antibiotics, particularly 'Watch' antibiotics, without justification among patients hospitalized with COVID-19 in Pakistan. This includes the instigation of pertinent ASPs, which have been limited to date in this and other hospitals in Pakistan exacerbated by poor knowledge of physicians regarding ASPs [83,84] There have been concerns that ASPs are more difficult to introduce in hospitals in LMICs due to available personnel and finances [85].

Table 7. Findings of culture testing.

	Number of samples ($n = 11$)		
Pathogens	Identified as co-infection	Identified as secondary infection	Total
Pseudomonas aeruginosa	-	3	3
Streptococcus pneumoniae	1	2	3
Klebsiella species	-	3	3
Staphylococcus aureus	2	-	2

However, this is changing and we have seen ASPs successfully introduced among a number of LMICs in recent years including those in Africa, the Middle East, and Asia [86–92]. Table S1 in Supplementary Material contains a number of examples of ASPs successfully introduced in hospitals in LMICs to enhance the appropriate use of antibiotics including among patients with COVID-19. These can provide exemplars to key groups, including physicians, in Pakistan as they struggle to improve antibiotic prescribing in hospitals, including patients with COVID-19, building on current guidelines. Future strategies should also include prescribing indicators based on the new AWaRe book, which gives comprehensive guidance for the management of key infections in hospitals [81,82].

In addition, it is essential that greater sensitivity testing is undertaken among hospitals in Pakistan to further guide appropriate antibiotic use thereby reducing inappropriate antibiotic prescribing and AMR. This is beginning to happen [93] and builds on current findings that the severity of COVID-19 played a key role in the prescribing of antibiotics in hospitalized patients. This is essential if Pakistan is to meet its goals outlined in the NAP.

We are aware that there are a number of limitations with this study. Firstly, we included only three tertiary care hospitals within the Punjab Province of Pakistan for the reasons stated. Secondly, we were unable to document how infection prevention and control (IPC) was implemented and how such practices changed in these health facilities over time to prevent the spread of infections, particularly among hospitalized patients. Furthermore, to understand the change of behavior during the different COVID-19 waves. Moreover, key factors associated with the development of bacterial co-infections and secondary infections were not recorded during the study. Despite these limitations, we believe our findings are robust, providing direction to all key stakeholder groups going forward.

5. Conclusion

In conclusion, we again found considerable prescribing of antibiotics among hospitalized COVID-19 patients in the sixth wave in Pakistan, similar to previous waves. This is despite a low prevalence of bacterial co-infections or secondary bacterial infections. Of equal concern is that most of the antibiotics prescribed were broad-spectrum and over 90% from the AWaRe 'Watch' list exacerbating high levels of AMR in Pakistan. This urgently requires increased instigation of IPC measures as well as ASPs across hospitals in Pakistan to rationalize future antibiotic therapy and decrease the misuse of antibiotics. As a result, help to decrease the burden of AMR in the country. We will be following this up in future studies.

6. Expert opinion

There are concerns with the high rates of prescribing of antibiotics in patients with COVID-19 admitted to tertiary hospitals in Pakistan with only a few patients with proven bacterial co-infections or secondary bacterial infections. This is a concern as high rates of inappropriate antibiotic prescribing in hospitals will increase AMR, which is already a key challenge in Pakistan. Of equal concern is that the high rates of inappropriate prescribing of antibiotics, especially Watch antibiotics, in patients with COVID-19 admitted to hospitals in Pakistan have persisted in the sixth wave. Overall, the rates and their nature seen in the sixth wave are very similar to the first five waves. This means there is now an urgent need to instigate appropriate ASPs in hospitals throughout Pakistan to improve future antibiotic prescribing. We are aware that there have been concerns with knowledge and experience of ASPs among key stakeholders in hospitals in Pakistan in the past, as well as issues of co-payments for culture and sensitivity testing. There have also been challenges with affordability of instigating ASPs in hospitals in Pakistan. However, we are aware that a number of ASPs have now been successfully introduced across LMICs in recent years to improve antibiotic prescribing, which can serve as exemplars to all key stakeholders within hospitals in Pakistan going forward.

Consequently, potential ways forward to improve the appropriateness of antibiotic prescribing in hospitals across Pakistan include developing and refining possible prescribing and quality indicators based on the AWaRe book. Potential prescribing and quality indicators can subsequently be reviewed and agreed upon by all key stakeholder groups before roll-out. However, before any instigation, proposed indicators need to be tested in appropriate protocols before roll-out across Pakistan. Along with this, there needs to be the instigation of appropriate IT systems in hospitals to be able to fully capture pertinent antibiotic prescribing data. As a result, be able to routinely monitor antibiotic prescribing against agreed indicators and guidance, and regularly feedback the findings to all key stakeholder groups in prearranged meetings. The continual use of paper-based systems to monitor current prescribing habits is both expensive and time-consuming, and often relies on students and others to collect the data. In addition, it may take a number of months to collate all the data, review current prescribing practices and feedback the findings to key stakeholder groups, with the momentum for any initiative compromised. This needs to be addressed going forward over the next 5 to 10 years as part of an overall strategy to improve medicine use in hospitals throughout Pakistan, thereby helping to reduce current high rates of AMR in Pakistan.

The instigation of electronic systems in hospitals will also prompt clinicians to include a diagnosis and rationale for any antibiotic prescribed. Alongside this, prompt a potential review date especially if initial antibiotic prescribing was empiric. Electronic systems can also provide details of current resistance patterns in case any advice in the guidelines needs to be changed with a change in resistance patterns.

Alongside instigating appropriate ASPs in hospitals in Pakistan to reduce inappropriate prescribing of antibiotic going forward, a review of current curricula for healthcare professionals (HCPs) is necessary. The objective is to make sure student HCPs are fully conversant with all key aspects of antibiotics, AMR and ASPs on qualification given current concerns. Alongside this, seek to introduce continuous professional development activities if no such activity currently exists among HCPs. This is also critical given identified knowledge gaps among qualified HCPs in Pakistan.

Overall, it is envisaged that instigating a multi-pronged approach in Pakistan, involving all key stakeholder groups, will improve future antibiotic prescribing in Pakistan leading to greater use of Access antibiotics. We will continue to monitor the situation.

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Declaration of interest

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Ethics statement

Ethical approval for the study was obtained from the Office of Research, Innovation and Commercialization (ORIC), Lahore College for Women University, Jail Road, Lahore. Reference number, ORIC/LCWU/54 with approvals also sought from the administration of participating hospitals.

Data availability statement

Additional data is available from the corresponding authors on reasonable request.

Author contribution statement

Concept and Methodology: ZUM, AB, MS, JCM, BG, CEM. Investigation/ Data Collection: ZUM, AB, HI, MS, YHK, THM. Data analysis and verification: All authors; Visualization: ZUM, AB, MS, JCM; writing original draft: ZUM, BG, CEM; writing – Review and Editing: All authors. Project supervision and administration: ZUM, BG.

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