

Comparative analysis of antimicrobial drug sensitivity in the population of Kyrgyzstan: Pre-and Post-COVID-19 pandemic

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ABSTRACT

Antimicrobial resistance (AMR) has become a global health issue, with the increased use of antibiotics during the COVID-19 pandemic to minimize acute mortality potentially leading to a long-term spike in AMR fatalities. In this study, we investigated the influence of the COVID-19 pandemic on Kyrgyz antimicrobial resistance and raised awareness of the dangers of antibiotic misuse. This observational retrospective cross-sectional study investigated clinical samples for pathogenic and conditionally pathogenic microbiota. Every tenth patient was sampled, according to the Laboratory Center for Disease Prevention and State Sanitary and Epidemiological Supervision research. The isolated microorganisms were identified and antibiotic-sensitive tested on Muller-Hinton agar with nine antibacterial groups by disc diffusion. The cohort study of 419 coronavirus-infected patients found 64.4% (n = 270) positive PCR results and 35.5% (n = 149) negative results. 10.7% (n = 45) had a light infection, 17.4% (n = 73) had a moderate infection, 35.8% (n = 150) had a severe infection, and 9.5% (n = 40) had a very serious illness. The new coronavirus cases expanded rapidly, causing pneumonia and antibiotic use in most LMICs, including countries like Kyrgyzstan. Also, Ciprofloxacin, ceftriaxone, azithromycin, and levofloxacin resistance rose 30% during COVID-19. In the COVID-19 pandemic, infection prevention, rational antibiotic usage, and AMR monitoring must be strengthened.

Keywords: Pandemic, COVID-19, Sensitivity, Resistance, Antibacterial drugs

Introduction

The new coronavirus (COVID-19) pandemic caused by the SARS-COV-2 virus has brought a global crisis in the field of medicine and economics. During the pandemic, a large number of patients are admitted to hospitals for treatment with broad-

acting antibiotics [1, 2]. Treatment of patients with COVID-19 with antimicrobial drugs is based on the presence of clinical manifestations similar to bacterial and fungal infections, as well as clinical guidelines for the treatment of coronavirus infection. In the clinical guidelines of the Kyrgyz Republic, as in other countries, the protocols indicate the criteria for prescribing antimicrobial therapy for patients with COVID-19 [3]. The widespread spread of multi-resistant strains of pathogens can significantly reduce the effectiveness of antimicrobial therapy and long-term use of antibacterial drugs leads to an increase in antibiotic resistance, i.e., in which the microbe strain is immune to the action of one or more types of antibiotics. This is the evolution of a microorganism to achieve high stability and maintain its vital activity. It is important to note that the resistance of microorganisms to antibiotics is variable and

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depends on the frequency of use of a particular drug. The resistance of microorganisms to antibiotics varies in different regions and cities, but in one territory it is constant for certain pathogens over certain periods [4].

Currently, there is a widespread misconception among the population that antibiotics such as azithromycin, amoxicillin, amoxiclav, ceftriaxone, etc. are effective in treating COVID-19. In addition, patients with suspected self-isolation and confirmed asymptomatic cases of COVID-19 use antibiotics at home. Currently, there is a rapid increase in the number of multidrug-resistant microorganisms, and the global outbreak of COVID-19 also has some important implications for the development of antimicrobial resistance [5, 6]. An increasing number of studies indicate an increase in AMR after treating patients with COVID-19 with antibiotics, but the analysis of existing AMR and the comparative range of associated pathogens is still unclear. There is a clear indication that excessive consumption of antimicrobials in humans has led to the emergence of resistant pathogens that negatively affect human health [7].

This study is aimed at finding how the pandemic affected the spread of antibiotic-resistant bacteria, including those hard to treat or impossible to treat with antibiotics. We believe that antibiotic resistance may have become more common in Kyrgyzstan during the COVID-19 pandemic. Our objective is to increase knowledge and understanding of the risks associated with excessive and inappropriate use of antibiotics, particularly in developing nations and Low and Middle-Income Countries (LMICs).

Materials and Methods

We used an observational retrospective study using a cross-sectional design randomized study with a selection of clinical material for pathogenic and conditionally pathogenic microflora from every 10 patients from the journal of research of the laboratory Center for Disease Prevention and State Sanitary and Epidemiological Supervision with the function of coordinating the activities of the Osh Region Service (CPZ, GSEN and FKDSOO) for the period 2018 and 2023 years, with materials of hospitalized patients in the Osh Inter-regional United Clinical Hospital (OMOKB) with a diagnosis of coronavirus infection. Identification and determination of the sensitivity of isolated microorganisms with 9 groups of antibacterial drugs using the disc diffusion method on Muller-Hinton Agar (MHA). The material for the study was a pharyngeal and nasal swab and sputum. To control the quality of determining the sensitivity of microorganisms to antibiotics, the control strain of *Staphylococcus* spp, *Streptococcus* spp, and *Streptococcus pneumoniae* was tested in parallel with the testing of clinical isolates, streptococcus pneumoniae.

Also, a comprehensive search was conducted across seven databases—PubMed, MEDLINE, EMBASE, Scopus, Cochrane, Web of Science, and CINAHL—using keywords to identify pertinent studies on antibiotic resistance (AR) during the COVID-19 pandemic. The following keywords were used:

COVID-19, pandemic, antibiotic resistance, public health, PRISMA, AR increase, and literature review. The search covered literature published from December 2019 to May 2022, adhering to PRISMA guidelines. A total of twenty-three studies met the inclusion criteria for this review. The synthesized data indicate a notable increase in antibiotic resistance during the COVID-19 pandemic. We conducted a comprehensive analysis of antibiotic usage among hospitalized patients, evaluating adherence to clinical guidelines versions 1 through 7. Data analysis was performed utilizing Excel 2019 and Microsoft Word.

Ethical approval

The Ethical Committee of the Osh State University of the Ministry of Health of the Kyrgyz Republic, The Local Ethics Committee approved the study (Protocol No. 24FHD/04.10.23). Informed permission was waived since the culture findings were obtained anonymously from the laboratory's computerized database, with no patient characteristics identified. All techniques were carried out in conformity with the standards and regulations established by The Local Ethics Committee.

Results and Discussion

During the examination of 419 individuals diagnosed with COVID-19 infection, it was shown that 64.4% (n = 270) tested positive for PCR, whereas 35.5% (n = 149) tested negative. Out of the total number of patients, 45 (10.7%) had a light course, 73 (17.4%) had a moderate course, 150 (35.8%) had a severe course, and 40 (9.5%) had a very severe condition. The fast dissemination of a novel coronavirus infection was concomitant with the emergence of pneumonia and the use of antibacterial medications. Although COVID-19 is caused by a virus, antibiotics were often used during the pandemic to treat COVID-19 infections, particularly when there was a suspicion of a subsequent bacterial infection [8]. Despite clinical guidelines specifying that antibiotics should only be used in specific cases of coronavirus infection, such as when bacterial pneumonia is present and there is an increase in CRP, calcitonin, and neutrophil leukocytosis, there is widespread use of antibiotics even in mild cases of coronavirus infection [9]. Since the beginning of the illness, antibiotics such as ciprofloxacin, levofloxacin, azithromycin, and ceftriaxone have been administered. Among these individuals, 77.7% tested positive for PCR analysis, whereas 23% tested negative. Nevertheless, the clinical recommendations discourage the prescription of antibiotics for patients with low severity, especially when the PCR analysis yields positive results (**Figure 1**).

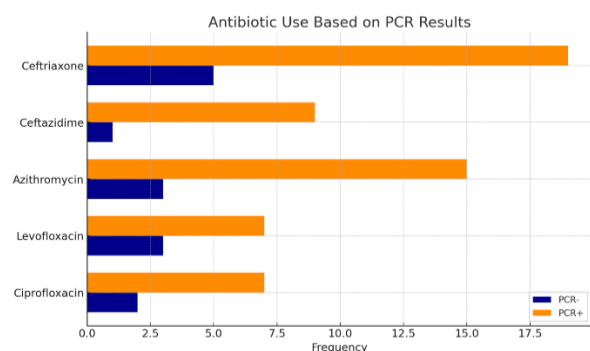


Figure 1. Use of antibiotics by PCR results

Figure 1 indicates that from the entire sample of 419 patients, we specifically analyzed 45 individuals who had a moderate form of coronavirus infection and received outpatient treatment with

antibiotics. The pharyngeal smear test findings of 45 patients with moderate severity revealed the presence of *Staphylococcus aureus* in 1 patient, *Pneumococcus pneumoniae* in 2 patients, *Streptococcus pneumoniae* in 8 patients, *Streptococcus pneumoniae* in 6 patients, and no other pathogenic bacteria were detected. To assess the efficacy of the antibacterial medications used, the susceptibility of the majority of isolated staphylococci to antibiotics was evaluated.

Table 1 demonstrates that in cases with a moderate course of coronavirus infection with a positive PCR result, it is not recommended to use antibiotics. The population of Osh City often uses antibiotics such as Ampicillin, Penicillin, Azithromycin, Amoxicillin, Ceftriaxone, Cefzim, Levofloxacin, and Ciprofloxacin. However, these antibiotics have shown resistance against *Staphylococcus*.

Table 1. The degree of sensitivity, of *Staphylococcus* to antibiotics in % (n=29)

Antibiotics	Total n = 29				Delay zone up to 15 mm				Growth zone	
	PCR+ (n = 18)		PCR - (n = 11)		R-0		I-up to 15		S	
	abs	%	abs	%	PCR +	PCR -	PCR +	PCR -	PCR	PCR-
Penicillin	18	62	11	37,9	14	7	4	4	0	0
Amoxicillin	18	62	11	37,9	9	7	6	3	1	1
Ampicillin	18	62	11	37,9	10	4	5	6	2	1
Ceftriaxone cefemed	18	62	11	37,9	6	3	8	5	4	3
Zefzim	18	62	11	37,9	3	1	8	6	7	4
Azithromycin	18	62	11	37,9	12	5	6	5	0	1
Amikacin	18	62	11	37,9	1	1	2	5	15	5
Ciprofloxacin	18	62	11	37,9	5	2	9	6	4	3
Levofloxacin	18	62	11	37,9	7	3	6	6	5	2

Note: R-steady, I-low sensitivity, S-sensitive

The current importance of examining the antibiotic susceptibility of pathogenic and opportunistic bacteria isolated from individuals before the outbreak and treated for viral infections in hospital settings in Osh during the COVID-19 pandemic is evident in **Table 1**. The bacteria causing community-acquired pneumonia, *Staphylococcal*, *streptococcal*, and *pneumococcal* infections,

were the main subjects of the study. Before the epidemic, 177 macro samples in all were selected; subsequently, 178 samples were selected for 2023 after the epidemic. These samples allowed one to investigate the pharyngeal mucus sensitivity. 466 samples in all were examined; after the conclusion of the current coronavirus epidemic, 1470 samples were examined (**Table 2**).

Table 2. Detection of *staphylococcus* spp, *streptococcus* spp, str. *pneumoniae* from residents of Osh for the period 2018 and after the 2023 coronavirus pandemic

	Years				Gender				Age							
	2018		2023		F		M		0-24		25-44		45-64		65	
	n=177	%	n= 178	n%	N	%	n	%	n	%	n	%	n	%	n	%
Sputum																
Staphylococcus	45	25.4	40	22.4	26	57.7	19	42.23	10	22.2	18	40	9	20	28	62
Streptococcus	83	46.8	115	64.6	11	13.2	72	86.7	8	9.6	25	30.1	10	12	15	18
Pneumococcus	49	27.6	123	69.1	15	30.6	24	48.9	15	30.6	12	24.4	16	32.6	14	28.5
Mucus from the pharynx																
	n=466		n=1470		49		19		34		10		13		11	
Staphylococcus	68	14.5	282	19.1	49	72	19	27.9	34	50	10	14.7	13	19.1	11	16.1
Streptococcus	395	84.7	1172	79.7	213	53.9	182	46.6	199	50.3	56	14.1	1	0.2	1	0.2
Pneumococcus	3	0.6	16	1	2	66.6	1	33.3	0	0	2	66.6	1	33.3	1	33.3

This is because community-acquired pneumonia is mostly identified in these specimens. According to the data shown in **Table 2**, the elimination of pneumococcal infection from sputum was determined to be 94.2%. Women have a position of

power and control when it comes to distinguishing between genders. The majority of individuals are between the age range of 65 years and older. The samples obtained from pharyngeal and nasal swabs show a significant amount of streptococcus discharge.

This condition is seen in persons of both sexes, with a prevalence above 57%. The age range of those affected by isolated strains of *Streptococcus* spp is restricted to individuals aged 1 to 15, and the incidence rate surpasses 71%. The *Staphylococcus* spp strains obtained from sputum and pharyngeal tests show a higher prevalence in women, perhaps because of the higher frequency at which women seek medical attention [10].

A total of 28% of patients diagnosed with *Staphylococcus saprophyticus* are between the ages of 1 and 7, while over 42% of patients are over the age of 40. An analysis was conducted to determine the resistance of *Staphylococcus* spp, *Streptococcus* spp, and *Str. pneumoniae* strains. The data used for this analysis was obtained using the disc diffusion technique, which is used to determine sensitivity [11-14].

Figure 2 shows the specific relevance of antibiotic sensitivity markers. In 2018, the strain of *Streptococcus pneumoniae* exhibited a greater degree of sensitivity to fluoroquinolones, with a sensitivity rate of 81.8% for ciprofloxacin. It also had a high sensitivity to third-generation cephalosporins such as ceftriaxone and cefotaxime, as well as resistance to second-generation cephalosporins like cefaclor [15]. This bacteria strain has a sensitivity rate of over 50% to third-generation aminoglycosides, such as amikacin and meropenem. However, it has a relatively low sensitivity to second-generation antibiotics like gentamicin within this antibiotic category. There is a tendency of resistance to tetracyclines 23.8%, macrolides 21.8%, and natural penicillins (penicillin 17.3%), as shown in **Figure 2**.

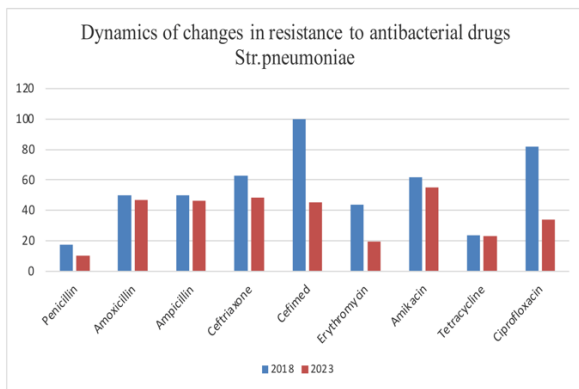


Figure 2. The graph illustrates temporal changes in resistance patterns to commonly used antibiotics

Our results and **Figure 2** suggest that *Streptococcus pneumoniae*'s antibiotic sensitivity has altered dramatically in 2023. Ciprofloxacin had an 81.8% high sensitivity rate in 2018; by 2023 this figure plummeted to 36%. Furthermore clearly shows a drop in cephalosporin sensitivity; from 62.5% in 2018 to 48.2% in 2023. Furthermore, whereas second and third-generation cephalosporins were somewhat popular in 2018, fourth-generation cephalosporins now show a greater sensitivity rate [16]. Penicillin and its derivatives have also evolved a resistance rate above fifty percent. According to the 2018 antibiotic chart, *Staphylococcus* spp. Strains exhibited resistance to all tested antibiotics. Specifically, resistance to penicillin derivatives was observed in 74.81% of cases, with penicillin

showing 83.33% resistance, ampicillin 80%, and amoxicillin 50% [11, 17-19].

Both third-generation cephalosporins, ceftriaxone and cefotaxime, showed 76.1% and 42.1% respectively; their sensitivity coefficient against staphylococcal infections as of 2018 was 59%. Of the aminoglycosides, amikacin and meropenem showed the greatest efficacy among 90% of isolates responding. Resistance rates among *Staphylococcus* ranged from 52% to macrolides, 86.66% to tetracyclines, and 70% to penicillin derivatives [20-23].

In comparison to 2018, the data from 2023 indicate a slight change in the antibiotic sensitivity of *Staphylococcus* spp. (**Figure 3**). For aminoglycosides, the sensitivity to gentamicin, a second-generation antibiotic, decreased from 45.45% in 2018 to 33.33% in 2023. However, the sensitivity to third-generation aminoglycosides remains high, albeit with a slight reduction of 5% compared to 2018. Sensitivity to first-generation (ciprofloxacin) and second-generation (levofloxacin) fluoroquinolones has remained relatively stable, though resistance to ciprofloxacin has increased by 10%. Carbapenems exhibit limited sensitivity coefficients (imipenem 70%, meropenem 86.9%), but this group of antibiotics is generally not used to determine the sensitivity of staphylococcal infections, as shown in **Figure 3**. *Streptococcus* strains, according to 2018 data, show average sensitivity coefficients for fluoroquinolones such as ciprofloxacin (80.6%) and levofloxacin (75%) [24]. Additionally, higher-than-average sensitivity is observed for third-generation aminoglycosides (amikacin 81.81%) and second-generation gentamicin (66.66%). Regarding cephalosporins, *Streptococcus* spp. Demonstrate sensitivity to fourth-generation antibiotics (cefepime 79.3%) and third-generation antibiotics (cefotaxime and ceftriaxone). *Streptococcus* spp. also shows good sensitivity to cefazolin. However, representatives of this strain exhibit low sensitivity to tetracyclines, macrolides, and penicillin derivatives [25, 26].

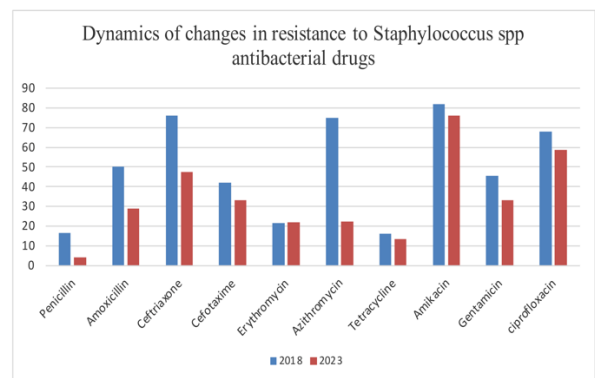


Figure 3. The figure highlights shifts in resistance trends across various antibiotics over the study period.

An analysis of 2023 data in **Figure 4** reveals a 90% reduction in the use of tetracycline and glycopeptide antibiotics for *Streptococcus* spp. Compared to 2018, maintaining consistent efficacy against all tested isolates. Macrolides exhibited a sensitivity coefficient of 9%, a significant decline from over 40%

in 2018. Sensitivity to penicillins indicates an ongoing trend of antibiotic resistance, yet ampicillin (46.4%) and amoxicillin (48.6%) demonstrate stable sensitivity against staphylococcal infections. Notably, antibiotics employed during the COVID-19 pandemic for treating mild cases, such as ceftriaxone, azithromycin, and ciprofloxacin, show a reduction in sensitivity exceeding 30%.

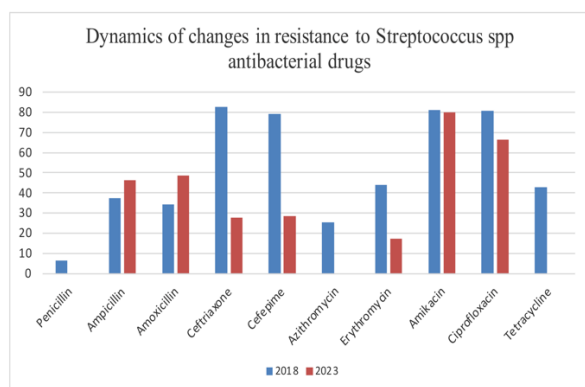


Figure 4. The graph demonstrates the evolution of resistance profiles, emphasizing variations in susceptibility to different antimicrobial agents.

Conclusion

Widespread distribution of antibiotics, improper self-administration of antibiotics, empirical prescribing practices, and prescriptions by general practitioners all aggravate antimicrobial resistance (AMR), which is still a serious and growing threat in worldwide healthcare systems. The results of this research reveal that these practices greatly contribute to increased AMR levels, especially concerning medications often overused during the epidemic like ceftriaxone, azithromycin, and ciprofloxacin—which have demonstrated a sensitivity drop surpassing 30%). The noted drop in antibiotic sensitivity emphasizes how urgently improved infection control plans, sensible antimicrobial usage directed by WHO and Ministry of Health recommendations, and adherence to Antimicrobial Stewardship Programs (ASP) are needed. The public and healthcare professionals need to be educated on how to use antibiotics appropriately for both routine medical care and public health emergencies. These initiatives are crucial to stop the continuous development and spread of antimicrobial resistance therefore ensuring the effectiveness of antimicrobial treatments for the next generations. Moreover, our thorough investigation of antibiotic use and resistance trends reveals important new directions. Along with consistent effectiveness across all studied isolates, the usage of tetracycline and glycopeptide antibiotics against *Streptococcus* spp. has dropped since 2018. On the other hand, macrolides show a worrying drop in sensitivity, which contrasts with earlier recorded better effectiveness rates in 2018. Penicillins clearly show emerging resistance tendencies; ampicillin and amoxicillin maintain constant sensitivity against staphylococcal infections. Furthermore, our analysis highlights a notable decline in the

sensitivity of antibiotics usually used during the COVID-19 epidemic: ciprofloxacin, azithromycin, and ceftriaxone, thus showing changing resistance dynamics in clinical settings. These results underline the dynamic character of AMR and support the crucial need for constant monitoring and sensible antibiotic control. Future studies should give top priority to understanding the fundamental causes of these resistance tendencies and creating focused treatments to thus minimize their effects on public health.

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Conflict of interest: None

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Ethics statement: The Ethical Committee of the Faculty of Medicine at Osh State University approved the study (Protocol no. 24-FHD/04.10.2023). Informed permission was waived since the culture findings were obtained anonymously from the laboratory's computerized database, with no patient characteristics identified.

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