ORIGINAL RESEARCH

Antimicrobial Resistance Of Streptococcus Pneumoniae Among Preschool-age Children

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Abstract

Introduction. This research aimed to investigate the prevalence of S. pneumonia isolates among preschool-age children and analyze the susceptibility and resistance patterns of these isolates to investigated antimicrobial drugs before and after the onset of the Coronavirus disease 2019 (COVID-19).

Methods. The data for this study were gathered retrospectively over a two-year period (1 January 2018 – 31 December 2018 and 1 January 2022 – 31 December 2022) at the Public Health Institution "Health Center Brcko", Bosnia and Herzegovina. In the observed period, a total of 2287 swabs were performed.

Results. Among the total 214 clinical samples with isolated S. pneumoniae, 68% belonged to male patients. 47% of those samples were collected within the age group of 0-2 years. Multiresistance was identified in 92 isolates. Before the Covid-19 pandemic, S. pneumoniae isolates exhibited the highest sensitivity to cefuroxime and ceftriaxone, (99.1%), while after the Covid-19 pandemic, the highest sensitivity was demonstrated to norfloxacin (99.0%).

Conclusion. It is essential to use antibiotics rationally to prevent the further increase of resistance, especially multidrug resistance, in S. pneumoniae.

Keywords: antimicrobial resistance, Streptococcus pneumoniae, children

INTRODUCTION

Streptococcus pneumonia is one of the most prevalent opportunistic pathogens globally (1). This Gram-positive pathogen is a commensal of the human nasopharynx and plays a significant role as a causative agent in pneumonia, otitis media, sepsis, and meningitis worldwide. The incidence of the disease is highest at the extremities of life, affecting very young children and the elderly. According to the World Health Organization, Streptococcus pneumonia is responsible for the deaths of over 500,000 children annually on a global scale (2).

Pneumococci are transmitted between individuals through close contact and aerosols. Colonization is deemed a prerequisite for disease, although numerous colonized individuals may remain asymptomatic (3).

It is associated with high morbidity, mortality (causes 11% of deaths in children aged under 5 years) and global economic burden (4, 5). Despite advancements in treatment that led to a decrease in the case-fatality ratio of pneumococcal meningitis, it still stood at 25–27% in Europe and the Americas in 2015. In Africa, during the same year, the rate was notably higher, reaching as high as 61% (6).

The majority of pneumococci possess capsules, featuring surfaces made up of intricate polysaccharides, that play a crucial role in determining the pathogenicity of pneumococci and serve as the foundation for their classification into serotypes. As of today, more than 100 serotypes of S. pneumoniae have been identified (7). S. pneumoniae has developed increased resistance to multiple classes of antibiotics, which adds complexity to the treatment of pneumococcal infections (8, 9). According to the previous study in our country by Karcic et al., pneumococcus exhibited the highest resistance to erythromycin, clindamycin, and trimethoprim-sulfamethoxazole (10).

This research aimed to investigate the prevalence of S. pneumoniae isolates across various hospital and outpatient samples among preschool-age children and to analyze the susceptibility and resistance patterns of S. pneumoniae isolates to investigated antimicrobial drugs before and after the onset of the Covid-19 pandemic.

MATERIALS AND METHODS

Patients and Study Design

The data for this study were gathered retrospectively over a two-year period (1 January 2018 – 31 December 2018 and 1 January 2022 – 31 December 2022) at the Public Health Institution "Health Center Brcko", Bosnia and Herzegovina.

Methods

Clinical specimens included a nasal swab, throat swab, and ear swab. In the observed period, a total of 2287 swabs were performed. All samples were collected and transported to the Department of Microbiology following standard protocols for obtaining clinical material for microbiological examination. Hospital samples were taken from the Department of Pediatrics at the Public Health Institution "Health Center Brcko", and out-of-hospital samples were taken on an outpatient basis.

In the processing of the collected samples, three Petri dishes were employed: one for the Optochin test, and the other two for assessing resistance or sensitivity to specific antibiotics.

The optochin test serves to identify S. pneumoniae, an alpha-hemolytic streptococcus that typically exhibits sensitivity to optochin, while other types of alpha-hemolytic streptococci tend to be resistant. After incubation, the zone of growth inhibition is examined. If the diameter of the zone is ≥14 mm, the tested isolate is deemed sensitive to optochin. Conversely, if the zone of inhibition is less than 14 mm, it is likely not S. pneumoniae. In the case of resistance (where the diameter of the zone equals the disk's diameter), a deoxycholate lysis test is necessary, as a few pneumococci may exhibit resistance to optochin. Positive and negative controls are also essential in this process.

The antibiogram is conducted through the disc diffusion method, wherein antibiotic-soaked discs are placed on agar media that has been inoculated with the tested pathogen. Subsequently, there is an incubation period of 18 hours ± 2 hours, after which the diameter of the zone of inhibition around each disc is measured.

The antibiogram follows EUCAST recommendations. Based on the readings of the diameter of the growth inhibition zone, the tested strain is categorized as either S (Susceptible) or R (Resistant). The following

antibiotics were used to assess sensitivity/resistance in S. pneumoniae: amoxiclav, cefuroxime, cefixime, ceftriaxone, cefpodoxime, erythromycin, clindamycin, tetracycline, norfloxacin, chloramphenicol, and trimethoprim/sulfamethoxazole.

Multidrug Resistance (MDR) refers to bacteria's resistance to three or more antibiotics, encompassing at least one antibiotic from three or more distinct antibiotic groups.

The Ethics Committee of the Public Health Institution "Health Center Brčko" provided consent and approval for the retrospective use of data from the Department of Microbiology. The study was conducted in accordance with the Convention on Human Rights and the Helsinki Declaration on the Rights of Patients in Biomedical Research.

Statistical Methods

The results underwent analysis through standard statistical methods, employing the SPSS computer program for statistical analysis (SPSS-Statistical Package for Social Sciences) version 21.0. The findings were presented as both absolute numbers and percentage values. The analysis of categorical variables involved the use of the Chi-square test or Fisher exact test. Statistical significance was set at a p-value of <0.05.

RESULTS

This research was retrospective, spanning a two-year period: 2018 (prior to the Covid-19 pandemic) and 2022 (post the Covid-19 pandemic). During this time frame, a total of 214 antibiogram results from clinical samples, with S. pneumoniae isolation, were analyzed and processed – comprising 109 results from 2018 and 105 from 2022.

Among the total 214 clinical samples, 145 (68%) belonged to male patients.

Among the 214 S. pneumoniae samples analyzed, 100 (47%) pertain to patients within the age group of 0-2 years, while 114 (53%) were from patients within the age group of 3-6 years. The largest number of S. pneumoniae isolates was obtained from nasal swabs (185), followed by throat swabs (28) and ear swabs (1).

Out of the total 214 S. pneumoniae isolates, multiresistance was identified in 92 isolates. Among these, 17 isolates demonstrated resistance to three antibiotics from distinct drug groups. Specifically, 7 isolates exhibited simultaneous resistance to erythromycin, clindamycin, and tetracycline, 3 isolates were resistant to erythromycin, clindamycin, and trimethoprim-sulfamethoxazole, 2 isolates to erythromycin, clindamycin, and cefixime, and the remaining 5 isolates displayed resistance to different antibiotics concurrently.

In 24 samples, simultaneous resistance to 4 antibiotics was observed, with the highest number (10) displaying resistance to erythromycin, clindamycin, tetracycline, and cefixime. Additionally, 7 isolates exhibited resistance to erythromycin, clindamycin, tetracycline, and trimethoprim-sulfamethoxazole, 5 isolates to erythromycin, clindamycin, trimethoprim/sulfamethoxazole and cefixime.

Moreover, resistance to 5 antibiotics was identified in 41 isolates. Among these, 37 isolates demonstrated resistance to erythromycin, clindamycin, tetracycline, trimethoprim/sulfamethoxazole, and cefixime.

Furthermore, 8 isolates exhibited resistance to 6 antibiotics. Among these, 4 isolates were resistant to erythromycin, clindamycin, tetracycline, trimethoprim/sulfamethoxazole, cefixime, and norfloxacin, while the other 4 isolates showed resistance to erythromycin, clindamycin, tetracycline, trimethoprim/sulfamethoxazole, cefixime, and chloramphenicol.

Regarding resistance to 7 antibiotics, this was observed in two samples, both displaying resistance to erythromycin, clindamycin, tetracycline, trimethoprim/sulfamethoxazole, cefixime, chloramphenicol, and norfloxacin.

Before the Covid-19 pandemic, S. pneumoniae isolates exhibited the highest sensitivity to cefuroxime and ceftriaxone, recording 108 (99.1%), while the lowest sensitivity was observed for trimethoprim/sulfamethoxazole, with 45 isolates (43.1%) (Figure 1).

After the Covid-19 pandemic, Streptococcus pneumoniae isolates demonstrated the highest sensitivity to norfloxacin, recording 104 (99.0%), while the lowest sensitivity was observed for erythromycin, with 63 isolates (61.9%) (Figure 2).

A significant difference was identified in the frequency of sensitivity of S. pneumoniae isolates to cefuroxime, cefixime, clindamycin, tetracycline, norfloxacin and trimethoprim/sulfamethoxazole before and after the Covid-19 pandemic. (Table 1).

DISCUSSION

Streptococcus pneumoniae is a significant pathogen that can lead to the development of pneumococcal disease. This disease primarily affects individuals with weakened immune systems, young children (typically up to two years of age), and the elderly. Immunocompromised children with underlying health conditions are particularly vulnerable to developing severe forms of the disease, along with various complications, resulting in a higher mortality rate. The occurrence and frequency of S. pneumoniae infections in children raise particular concern, especially in developing countries where vaccination programs may not be well-established, despite the availability of vaccines against S. pneumoniae for an extended period.

Developing countries are currently grappling with a notable surge in antimicrobial drug resistance, primarily stemming from unauthorized sales and unregulated use of antibiotics. The resistance of Streptococcus pneumoniae isolates to antimicrobial drugs shows substantial variation from one country to another. Nevertheless, numerous studies highlight a prevalent and concerning frequency of resistance among pneumococcal isolates. This emphasizes the urgent need for improved regulation and awareness to curb unauthorized antibiotic use and address the growing challenge of antimicrobial resistance (11).

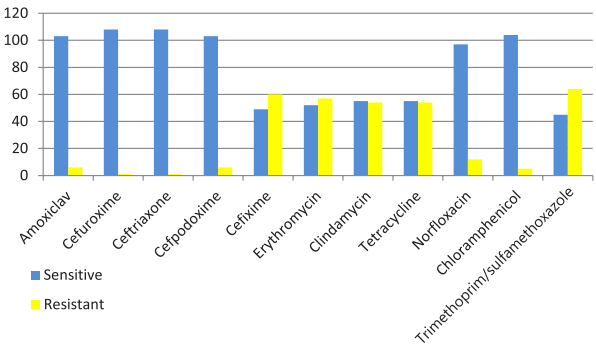

Figure 1. Sensitivity and resistance of Streptococcus pneumoniae to antibiotics before the COVID-19 pandemic

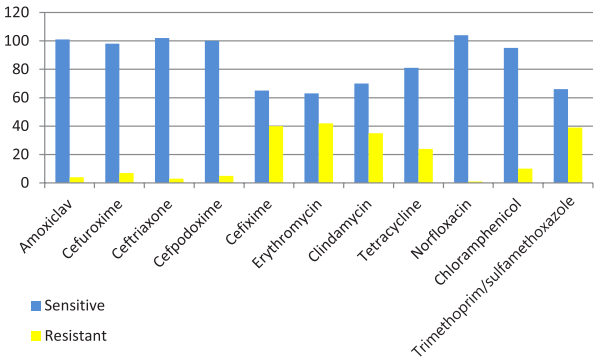

Figure 2. Sensitivity and resistance of Streptococcus pneumoniae to antibiotics after the COVID-19 pandemic

Table 1. Sensitivity and resistance to specific antibiotics before and after the pandemic

	before COVID-19		after COVID-19		p value
	sensitivity	resistance	sensitivity	resistance	
cefuroxime	99.10%	0.90%	93.30%	6.70%	0.029
cefixime	45%	55%	61.90%	38.10%	0.013
clindamycin	50.50%	49.50%	66.70%	33.30%	0.016
tetracycline	50.50%	49.50%	77.10%	22.90%	0.001
norfloxacin	89%	11%	99.05%	0.95%	0.002
trimethoprim/sulfamethoxazole	41.30%	58.70%	62.90%	37.10%	0.002

COVID-19 Coronavirus disease 2019; p - level of significance

In our study, the highest frequency of resistance among beta-lactam antibiotics was observed with cefixime, a third-generation cephalosporin commonly used for oral treatment. In 2018, resistance to cefixime was noted in 55% of cases, while after the pandemic, in 2022, resistance was recorded in 38.1% cases.

For cefuroxime, a second-generation cephalosporin, resistance was documented in 0.9% cases in 2018, and it increased to 6.7% in 2022, indicating a significant rise in resistance after the pandemic. Ceftriaxone, a third-generation cephalosporin for parenteral use, showed resistance in 0.9% of isolates before and 2.9% after the pandemic, suggesting a slight increase in resistance to ceftriaxone. Resistance to cefpodoxime, a third-generation cephalosporin for oral use, was recorded in 5.5% of patients before and 4.8% after the pandemic. Resistance to amoxiclav was 5.5% before the pandemic and 3.8% after the pandemic in our study.

Studies conducted over the years in various regions have reported high levels of resistance to penicillin in Streptococcus pneumoniae. For example, in China, the reported resistance was 88.3%, while in Russia, Nigeria, Canada, and Ethiopia, resistance levels ranged from 28% to 26.1% and 17.5%, respectively. In Central Africa and Tunisia, the incidence of penicillin resistance was slightly lower at 6% and 1.2%, respectively. The notable resistance to penicillin, as indicated by these studies, suggests that the empirical use of penicillin for treating suspected pneumococcal infections is no longer recommended (11-17).

In the presented study, where a combination of amoxicillin and clavulanic acid was used, a significantly lower frequency of resistance was observed compared to studies focusing on penicillin resistance.

The frequency of resistance to cephalosporins was found to be significantly lower in the mentioned studies compared to penicillin resistance. This suggests that cephalosporins may retain effectiveness against pneumococcal infections in regions where penicillin resistance is high (12-17).

In our study, resistance to erythromycin among Streptococcus pneumoniae isolates was recorded at 52.3% in 2018 and 40% in 2022. Comparatively, higher levels of resistance were reported in other regions, such as Canada (100%), China (95.2%), and Ethiopia (59.6%), while lower levels were observed in Russia (26%) and Pakistan (29.7%) (11, 13, 15, 18).

Resistance to clindamycin was observed in 49.5% of patients in 2018 and 33.3% in 2022 in our study. Comparatively, a higher rate of resistance was reported in a similar study conducted in China (95.8%), while in Canada, resistance was recorded in 40.6% of patients.

Regarding tetracyclines, our study showed a high rate of resistance, with tetracycline resistance found in 49.5% of patients in 2018 and 22.9% in 2022. Other similar studies also reported a significantly higher degree of resistance to tetracyclines, such as in China (93.6%) and Nigeria (73.5%), while resistance to tetracyclines in Ethiopia was recorded in 38.6% of isolates (11,12, 14, 15).

In our study, resistance to norfloxacin was reported in 11% of subjects in 2018 and it decreased to 1% in 2022. Comparatively, a low rate of resistance to levofloxacin was also observed in other countries, such as Germany (0.2%) and India (6%). However, Italy recorded a much higher rate of resistance to levofloxacin at 29%. These variations underscore the importance of regional and local surveillance to monitor antibiotic resistance patterns and guide appropriate treatment strategies (19-21).

As for chloramphenicol, the study reported resistance in 4.6% of subjects in 2018, increasing to 9.5% in 2022. Notably, a significantly higher rate of resistance to chloramphenicol was recorded in Nigeria (60%). In contrast, Central Africa (18.9%) and Ethiopia (17.5%) reported lower rates of resistance than Nigeria but higher than what was observed in our study (11, 14).

In our study, resistance to trimethoprim/sulfamethoxazole was observed in 58.7% of respondents in 2018, which decreased to 37.1% in 2022. Comparatively, higher rates of resistance to trimethoprim-sulfamethoxazole were found in other regions, such as Nigeria (96.2%), Pakistan (86.6%), Central Africa (69%), China (66.7%), and Russia (57%) (12-14, 16, 18).

Multidrug resistance (MDR), defined as infections caused by bacteria resistant to multiple antibiotics, poses a significant challenge as it limits the options for effective antimicrobial therapy. In our study, out of a total of 214 isolates, 92 showed resistance to three or more antibiotics, highlighting the prevalence of multidrug-resistant strains of Streptococcus pneumoniae. These strains commonly exhibited resistance to erythromycin, clindamycin, tetracycline, cefixime, and trimethoprim/sulfamethoxazole. Additionally, the results revealed a consistent pattern of co-resistance, particularly with erythromycin, clindamycin, and tetracycline.

Addressing the issue of multidrug resistance requires comprehensive strategies, including prudent antibiotic use, improved surveillance, and the development of new therapeutic approaches to combat infections caused by resistant strains.

The empiric treatment of pneumococcal infection often involves a combination of two or more antibiotics, and it may require a longer duration of therapy, especially for invasive forms of pneumococcal disease. Such situations can contribute to the development of resistance to multiple antibiotics in patients.

Interestingly, in our study, a decrease in resistance to a greater number of antibiotics was observed in 2022 compared to 2018. As stated by Meng et al., the resistance rates of S. pneumoniae to erythromycin, clindamycin, and tetracycline were maintained at a high level (> 85%) over the 4-year period (2018-2021); no penicillin-, moxifloxacin- or vancomycin-resistant strains were detected (22).

CONCLUSION

Despite extensive efforts to alleviate the impact of pneumococcal disease, it persists as a significant public health concern. The emergence of resistance to commonly used antimicrobials, observed on a global scale, adds complexity to the treatment of pneumococcal infections.

According to the results of the study, there is a need for the rational use of antibiotics to prevent the further escalation of resistance, particularly multidrug resistance, in Streptococcus pneumoniae.

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Declaration of Patient Consent: Written, informed consent was obtained from all volunteers in the study.

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