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Contribution to the Study of Antibiotic Sensitivity of *Streptococcus pneumoniae* Strains in Spinal Cerebral Fluids in Bangui from 2017 to 2022

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ABSTRACT

A prospective and analytical study was carried out from January 2017 to December 2022, at the National Laboratory of Clinical Biology and Public Health (LNBCSP) in Bangui. 352 samples of cerebrospinal fluid (CSF) were confirmed out of 2065, coming from the four hospitals in Bangui. This study aimed to evaluate the evolution of antibiotic sensitivity to strains of *Streptococcus pneumoniae*. CSF had been collected from patients who presented with meningeal syndromes. Based on the leukocyte count (White blood cells ≥ 5 mm^3), an aliquot was transferred to trans-isolate medium and sent to the LNBCSP for confirmatory testing, culture and determination of antibiotic sensitivity. The antibiotic sensitivity of *Streptococcus pneumoniae* strains was tested according to the methods recommended by the Antibiogram Committee of the French Society of Microbiology. The data collected was entered into Excel 2010 to be analyzed with Epi Info 7.2. Ficher's exact test, chi^2 at the 5% threshold ($p < 0.05$) was used to compare proportions and analyze associations between variables. The average sensitivity rate to β-lactams was 74.43%. The sensitivity rate of Fluoroquinolones was 54.54%. That of levofloxacin was 87%. The average rate of sensitivity to β-lactams for the age group under 5 years old was 79.25%. That of fluoroquinolones was 52.59%. Levofloxacin had 90.37%. The average sensitivity rate to β-lactams for the age group over 5 years

old was 76.03%. Fluoroquinolones had 45.16%. Levofloxacin had 69.58%. The average sensitivity rate to β-lactams for males was 76.68%. Fluoroquinolones had 54.26%. That of levofloxacin was 83.40%. The sensitivity rate to β-lactams for females was 74.41%. That of fluoroquinolones was 51.16%. Levofloxacin had 67.44%. Cyclins had 28.68%. The study noted an association between age and sensitivity ($p < 0.05$; CI [1.05 - 2.57]). Strains of *Streptococcus pneumoniae* were always detected in the CSF. The average rate of sensitivity to macrolides was 36.93%; aminoglycosides 28.69%; phenicols 63.35%; sulfonamides 39.2%. These results could suggest a reduced sensitivity to β lactams.

1. INTRODUCTION

Bacterial meningitis remains a therapeutic emergency and a public health problem because of the high fatality rate and the complications it causes. Worldwide, over the past decades, the incidence of bacterial meningitis in children has declined, but the disease burden remains high in adults, with mortality up to 30% [1]. In the regions of sub-Saharan Africa, the meningitis belt comprising 26 countries, stretching from Senegal in the West to Ethiopia in the East, is plagued by meningitis epidemics [2, 3]. In adults, meningitis is a frequent cause of hospitalization in medical services in Bangui with the main germs *Streptococcus pneumoniae*, *Neisseria meningitidis and Haemophilus influenzae* [4]. In children, the most common germs are *Streptococcus pneumoniae* and *Haemophilus influenzae* (Hib) [5, 6]. *Streptococcus pneumoniae* belongs to the genus streptococcus of the family Streptococcaceae. These are facultative aero-anaerobic gram-positive cocci [7]. They appear in pathological products as lanceolate and encapsulated diplococci, often in the shape of a "candle flame" or short chains. These germs belong to the commensal flora of the upper airways of humans and rarely of animals [7]. The virulence of these germs is linked to the presence of the polysaccharide capsule which makes them resistant to phagocytosis by polynuclear cells. Pneumococci is transmitted by aerosols and can induce an infectious process upon contact with the respiratory mucosa. They are responsible for upper respiratory tract infections. They have the ability to spread hematogenously. They can constitute metastatic infectious foci: purulent meningitis, arthritis, peritonitis, etc. [8]. *Streptococcus pneumoniae* is responsible for more than 1.5 million deaths per year from pneumonia, meningitis, and sepsis [9-11]. It represents the most common germ in both children and adults [10-13]. The introduction of antibiotics in the 20th century into the protocol for treating infectious diseases successfully reduced mortality and morbidity and increased life expectancy [14]. Unfortunately, the misuse of antibiotics has contributed to the emergence of the phenomenon of resistance throughout the world. In addition to these factors, using antibiotics in livestock farming to prevent the appearance of diseases or accelerate their growth greatly favors the appearance of resistance in bacterial strains. Antibiotics have also been found in foods following their misuse in agriculture to fight bacteria; the consumption of these foods could cause bacterial strains to become resistant to these antibiotics [15, 16]. Antibiotic resistance is today a major public health threat on a global scale. The epidemiology of antibiotic resistance varies depending on region and use. The WHO has predicted that until 2050, antibiotic resistance in infectious diseases risks becoming the leading cause of death from disease and will be responsible for more than 10 million deaths per year compared to 700,000 currently [17].

The phenomenon of natural mutation of antibiotic resistance genes has allowed them to develop a means of defense [18, 19]. According to the WHO and studies carried out in central Cameroon, the rate of consumption of antibiotics in the world is increasing and estimated at 65% from 2015 to 2020 [20]. Bacterial resistance to antibiotics has become one of the main threats to public health worldwide due to mortality estimated at 70,000 deaths per year [21-24]. *Streptococcus pneumoniae* is naturally sensitive to antibiotics, particularly β-lactams. In the latter, some strains become increasingly resistant to β-lactams [25, 26]. *Streptococcus pneumoniae* strains, following methylation by the ErnB gene of 23S rRNA, have become resistant to antibiotics from the macrolide family in 25% of cases. This results in a low-level resistance phenotype [27, 28]. In France, cross-resistance has been noted in pneumococcal infections involving Erythromycin in

80% of cases, Tetracycline in 69%, and Cotrimoxazole in 24% of cases [29]. The abusive use of fluoroquinolones in pneumococcal infections leads to an increase in resistance [30]. According to CDC, the overall prevalence of fluoroquinolone resistance is less than 1%. However, levofloxacin, moxifloxacin, and gemifloxacin are active against pneumococcus [31]. This phenomenon affects children as much as adults [32].

In Central African Republic, some studies have been carried out in the area of antibiotic sensitivity on strains of *Streptococcus pneumoniae*. These results showed that the strains remain resistant to β-lactams (penicillin and oxacillin) [6]. Despite the existence of a disease control department, the resistance of bacterial strains poses a public health problem. It is in this context that this study is being carried out, the general objective of which is to evaluate the evolution of antibiotic sensitivity of *Streptococcus pneumoniae* strains in meningitis in Central African Republic.

2. METHODOLOGY

From January 2017 to December 2022, the National Laboratory of Clinical Biology and Public Health (LNBCSP), received LCS from the four hospitals of Bangui in CAR (The Pediatric Hospital-University Complex, the Maman Elisabeth University Hospital, the Community University Hospital, the Central African Sino Friendship University Hospital Center). These health establishments are Central Reference Hospitals with services of different specialties. They receive all cases referred from peripheral health facilities that do not have an adequate technical platform for quality and appropriate care. The patients presented with meningeal syndromes [13]. Samples were systematically collected and analyzed in hospital laboratories. Based on the leukocyte count (White blood cells $\geq$ 5 mm^3), an aliquot was transferred to a trans-Isolate medium and sent to the LNBCSP. A total of 352 CSF samples were retained out of 2065 received for confirmation tests and antibiogram. Sampling was based on specific criteria. Cytology was based on white blood cell count/mL greater than or equal to 5. Gram stain results showing encapsulated gram-positive diplococcci. Results of the latex particle agglutination test for soluble antigens. Confirmation was made by culture, or real-time PCR testing.

2.1. Diagnosis of Cerebrospinal Fluid

The macroscopic aspects made it possible to note the color, turbidity, deposits, or clots. Cytology, Gram staining with the Cypress diagnostics kit, and the Latex agglutination test were carried out. The culture of the bacterial species was carried out on chocolate agar media, supplemented with a polyvitex mixture and fresh or cooked blood to isolate and identify the germs in question [33]. The Pastorex Meningitidis Kit, Bio-Rad, made it possible to recognize the biotype or serotype by agglutination reactions on the slide. The real-time PCR test had been used to identify Streptoccocus Pneumoniae because of its high sensitivity and specificity. The QIAampR Viral RNA Mini Kit (250) Cat. No. 52906 (USA) was used for the extraction of DNA from CSF. The Qiagen protocol respects the 4 main steps to follow during DNA extraction and purification. An additional step to help the lysis of the bacterial wall had been added compared to the manufacturer's instructions. A volume of 200 µL of CSF was treated with a mixture of lysozyme (0.04 g/ml final) and mutanolysin (2500 units/ml final) prepared extemporaneously in TE buffer (10 mM Tris-HCl, 1 mM EDTA, pH 8.0). To obtain DNA from Gram-positive bacteria, mutanolysin and lysozyme were used to destroy the cell wall in the presence of Proteinase K and incubated at 56˚C. The aim of bacterial lysis was to destroy the bacterial wall in order to make the DNA accessible. Subsequently, 20 µl of proteinase K were added to this suspension. A volume of 200 µl of viral lysis buffer (AVL) was added and incubated at 56˚C for 30 minutes. The precipitation phase made it possible to separate the DNA from the other constituents of the bacteria such as proteins, lipids and carbohydrates. For this, 200 µL of ethanol was added to the mixture. Then, the mixture was transferred to a Qiagen column, inserted into a 2 ml collection tube. Washing was carried out using 500 µl of wash buffer 1 (AW1), then a volume of 500 µL of the second buffer (AW2) was added. A volume of 100 µl of elution buffer was added to the column, incubated at room temperature for one minute. The DNA contained in the tube was then stored at −20˚C until use. The separate rooms had been used for the preparation of "clean" reactions and the addition of "dirty"

DNA. Sufficient quantities of working dilutions of primers and probes were prepared. For the lytA gene, the mixture consists of a pair of primers (Forward primer and Reverse primer) and a probe or Probe. The primers used for the detection of the gene of the *S. pneumoniae* species were Forward primer 373 and Reverse primer 424. The different reaction mixtures were distributed in the wells of the plate due to 23 µL in the pre-PCR room before to be transported to the dirty room for the addition of 2 µL of DNA. Water had been used in place of a clinical sample to detect contaminants during the extraction process (Negative Control); reference DNA from an organism of the target gene was used for the positive control. The reaction mixtures of 23 µL volume were supplemented with 2 µL of DNA extracted from each bacterial strain in each well of the plate. For each amplification series, a well containing only the reaction mixture was used as a negative control. A second well containing positive DNA (target gene) was used as a positive control. Finally, a third well containing PCR water (sterile) for quality control of sample extraction. The reaction corresponds to the succession of a certain number of cycles each comprising three stages, namely denaturation, hybridization and elongation. The denaturation of the DNA had been carried out at 94˚C, the double-stranded DNA had become under the action of the temperature two strands of single-stranded DNA. The specificity of rtPCR is the emission of fluorescence by the probe at the denaturation step, allowing the hybridization of the primers in order to have an elongation of the target under the action of Taq polymerase. This amplification process continues with pairing of primers to the 3' end of the target DNA after denaturation. At the same time, there is elongation of the DNA and cleavage of the probe. Thus, the two double-stranded DNA strands are formed, and the cycle repeats up to 50 times. During the different amplification cycles (50), the lytA gene of the species *S. pneumoniae* was determined in real time with a number of cycles less than 35. The rtPCR data analyzes were successful when the SDS software was used generated a Threshold cycle value (threshold cycle (Ct)). This Threshold value is fixed in the exponential phase of the amplification curve [34, 35].

The *in vitro* study technique called antibiogram made it possible for each strain to determine its sensitivity to antibiotics, according to the recommendations of the French Society of Microbiology (CASFM) [33]. Thirteen antibiotic discs (Biorad, Marnes-la-coquette, France) belonging to 5 different families were tested: Ceftriaxone (CRO: 30 µg), Cefotaxime (5 µg), penicillin (P: 10 µg), Oxacillin (OX: 5 µg), ampicillin (AM: 10 µg), Chloramphenicol (C: 30 µg), Ciprofloxacin (CIP: 5 µg), levofloxacin (5 µg); Ofloxacin (5 µg); gentamycin (CN: 10 µg), Cotrimoxazole (25 µg), erythromycin (15 µg), Tetracycline (30 µg). The reference strain *Escherichia coli* ATCC 25922 was used as a positive quality control strain. It was stored in a bead cryotube at −70˚C in glycerol broth and an agar medium without inoculation of a CSF sample was also used for negative quality control [33]. A bacterial suspension prepared on the Mac Farland scale was used. The antibiogram was carried out by the agar diffusion technique using disks impregnated with antibiotics giving inhibition zones whose diameter was measured using a vernier caliper or a graduated double decimeter. From the measurement of the inhibition diameter, we can deduce the approximate value of the minimum inhibitory concentration (MIC). In the antibiogram, one or more concentrations of antibiotics are taken into account. These are the critical concentrations which make it possible to define the sensitive, intermediate and resistant categories. In the case of meningitis, strains sensitive to penicillin G with a minimum inhibitory concentration (MIC) less than or equal to 0.0064 mg/L and or having a diameter greater than or equal to 20 mm around the oxacillin disk are considered sensitive [33]. The critical concentrations of other b- lactams (cefotaxime, ceftriaxone) are between 0.5 and 2 mg/L according to the Antibiogram Committee of the French Society of Microbiology (CASFM). In the case of meningitis, sensitive intermediate category strains with an intermediate level of resistance are considered resistant but in the event of respiratory infection, at high doses, the strains are considered sensitive. The results are qualitative [33].

2.2. Data Analysis

The data collected were entered into Microsoft Excel software (Redmond, Washington, USA) then exported and analyzed using Epi-Info 7.2 software (WHO, Geneva, Switzerland and CDC, Atlanta USA), the texts were entered using World 2010 software (Redmond, Washington, USA). The quality of the data was as-

sessed by looking for duplicates, outliers, and missing data to be excluded, corrected, or completed. Fisher-Exact and Yates tests were used to compare proportions. The relative risks (RR) or odds ratio (OR) were calculated to control the confounding factor. Univariate and multivariate analyses by logistic regression were used to determine the association between variables, and a p-value < 5% was assumed to be statistically significant.

3. RESULTS

From January 2017 to December 2022, 2065 LCS were examined, 352 of which, or 17.05%, were confirmed to the LNBCSP. Client ages ranged from 0.1 to 92 years with an average of 25 years. The mode was 3 years. Clients under five years old represented 38.35% and the male gender predominated (n = 223).

The male/female ratio was 1.72. **Figure 1** presents the evolution of *Streptococcus pneumoniae* strains identified by year with the different diagnostic tests used. Among the tests, real-time PCR is a very sensitive method for detecting germs.

Table 1 presents antibiotic susceptibility data for *Streptococcus pneumoniae*. The average rate of sensitivity to β-lactams was 74.43%. That of fluoroquinolones was 54.54%. Cyclins had an average sensitivity rate of 30.11%; macrolides 36.93%; aminoglycosides 28.69%; phenicols 62.82%; sulfonamides 67.89%.

Table 2 presents the average antibiotic sensitivity rate of *Streptococcus pneumoniae* in age groups.

In the age group under five years, the sensitivity rate to β lactams was 79.25%. For fluoroquinolones it was 52.59%; cyclins had a sensitivity rate of 37.03%; the sensitivity rate to aminoglycosides was 38.51%; the sensitivity rate to macrolides, phenicols, and sulfonamides was respectively 52.59%, 80.74% and 62.22%. In the age group over five years the sensitivity rate to β lactams was 76.03%; the sensitivity rate to fluoroquinolones was 45.16%; cyclins had 25.80%, aminoglycosides, 22.58%. The sensitivity rate to phenicols and sulfonamides was 52.53% and 71.42% respectively.

Table 3 presents the average antibiotic sensitivity rate of *Streptococcus pneumoniae* strains according to sex.

The male sex had a sensitivity rate to β lactams of 76.68%. That of fluoroquinolones was 54.26%. The sensitivity rate to cyclins, aminoglycosides, macrolides, phenicols, and sulfonamides was respectively 30.94%; 26.90%; 29.59%; 62.78%, and 67.26%. In females, the sensitivity rate to β lactams was 74.4%; fluoroquinolones had 53.67%. The sensitivity rate to cyclins was 28.68%; for Aminosides 31.78%; macrolides 34.10%; phenicols and sulfonamides 63.56% and 41.86% respectively.

Table 4 presents the association between *Streptoccocus pneumoniae* antibiotic susceptibility and sociodemographic characteristics.

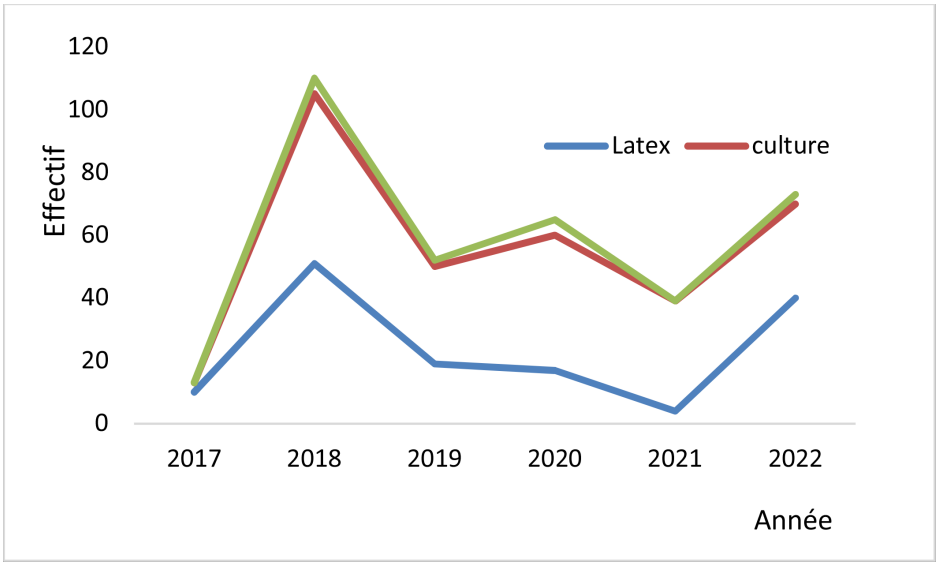

Figure 1. Evolution of *Streptococcus pneumoniae* strains identified according to tests by year.

Table 1. Data on antibiotic sensitivity of *Streptococcus pneumoniae* strains in Bangui from 2017 to 2022.

Years	2017 n = 13	2018 n = 110	2019 n = 52	2020 n = 65	2021 n = 39	2022 n = 73	Total N = 352
Antibiotics	%	%	%	%	%	%	%
Penicillin G	31	38	44	49	49	40	42.33
Ampicillin	85	84	81	88	82	84	83.81
Oxacillin	77	64	79	75	74	68	70.74
Ceftriaxone	85	84	92	91	87	89	87.78
Cefotaxime	92	89	79	89	85	90	87.5
β-Lactamines	**76.92**	**71.82**	**75**	**78.46**	**74.36**	**73.97**	**74.43**
Ofloxacin	54	56	19	23	44	32	30.07
Ciprofloxacin	85	64	67	15	10	5	43.75
Levofloxacin	92	89	88	85	82	86	86.93
Fluoroquinolones	**76.92**	**70**	**57.69**	**41.54**	**46.15**	**41.09**	**54.54**
Tetracycline	38	42	27	22	28	22	30.11
Gentamicin	38	45	31	11	28	16	28.69
Erythromycin	69	31	27	52	31	37	36.93
Chloramphenicol	77	40	67	68	64	89	62.82
Cotrimoxazole	69	65	77	46	72	82	67.89

Table 2. Evolution of the antibiotic sensitivity rate of *Streptococcus pneumoniae* strains by year, according to age group in Bangui from 2017 to 2022.

Years	2017 (N = 13)		2018 (N = 110)		2019 (N = 52)		2020 (N = 65)		2021 (N = 39)		2022 (N = 73)	
Age range per year	<5 n = 5	≥5 n = 8	<5 n = 43	≥5 n = 67	<5 n = 25	≥5 n = 27	<5 n = 23	≥5 n = 42	<5 n = 19	≥5 n = 20	<5 n = 20	≥5 n = 53
Antibiotics	%	%	%	%	%	%	%	%	%	%	%	%
Penicillin G	40	25	30	43	40	48	35	57	32	65	35	42
Ampicillin	60	100	81	85	96	67	96	83	95	70	90	81
Oxacillin	80	75	74	85	80	78	91	67	84	65	85	62
Ceftriaxone	100	75	98	75	96	89	100	86	95	80	95	87
Cefotaxime	100	88	93	87	92	67	96	86	95	75	90	91

Continued

β-lactamines	**76**	**72.6**	**75.2**	**75**	**80.8**	**69.8**	**83.6**	**75.8**	**80.2**	**71**	**79**	**72.6**
Ofloxacine	40	63	51	60	40	0	39	14	47	40	40	28
Ciprofloxine	60	100	84	51	76	59	30	7	53	20	55	6
Levofloxacin	100	88	98	84	96	81	96	79	95	70)	90	85
Fluoroquinolones	**66.67**	**83.67**	**77.67**	**65**	**70.67**	**46.67**	**55**	**33.33**	**65**	**43.33**	**61.67**	**39.67**
Tetracycline	40	38	37	45	40	15	35	14	37	20	35	17
Gentamycin	40	38	41	48	32	30	30	0	42	15	45	6
Erythromycin	60	75	70	7	48	7	39	60	32	30	55	30
Chloramphenicol	80	75	88	9	2	56	74	64	74	55	80	92
Cotrimoxazole	60	75	70	63	56	96	78	29	58	85	40	98

Table 3. **Evolution of the antibiotic sensitivity rate of *Streptococcus pneumoniae* strains by year according to sex in Bangui from 2017 to 2022.**

Years	**2017 N = 13**		**2018 N = 110**		**2019 N = 52**		**2020 N = 65**		**2021 N = 39**		**2022 N = 73**	
Sex	M n = 8	F n = 5	M n = 70	F n = 40	M n = 35	F n = 17	M n = 40	F n = 25	M n = 25	F n = 14	M n = 45	F n = 28
Antibotics	%	%	%	%	%	%	%	%	%	%	%	%
Penicillin G	25	40	28.57	55	40	52.94	47.5	52	40	64.28	40	39.28
Ampicillin	87.5	80	74.28	100	82.5	76.47	92.5	80	88	71.42	86.66	78.57
Oxaxacilline	62.5	100	72.85	47.5	85.71	100	87.5	56	76	71.42	79.48	67.85
Ceftriaxone	75	100	74.28	100	91.42	94.11	85	60	88	85.71	91.11	82.14
Cefotaxime	87.5	100	87.14	92.5	88.57	58.82	92.5	84	84	85.71	91.11	89.28
β-Lactamines	**62.5**	**50**	**67.14**	**80**	**77.14**	**64.71**	**80**	**68**	**76**	**78.57**	**75.55**	**71.43**
Ofloxacine	37.5	80	58.57	52.5	17.14	23.52	17.5	32	36	57.14	33.33	28.57
Ciprofloxacin	100	60	60	70	65.71	70.58	15	16	32	42.85	20	17.85
Levofloxacin	100	80	84.28	97.5	91.42	82.35	82.5	88	84	78.57	84.44	89.28
Fluoroquinolones	**75**	**60**	**67.14**	**72.5**	**57.14**	**58.82**	**37.5**	**48**	**52**	**57.14**	**46.66**	**46.42**
Tetracycline	37.5	40	45.71	35	25.71	29.41	20	24	32	21.42	20	25
Gentamicin	37.5	40	40	55	28.57	35.29	10	12	28	28.57	17.77	14.28
Erythromycin	62.5	80	11.42	15	28.57	23.52	42.5	68	28	28.57	40	32.14
Chloramphenicol	62.5	100	40	40	62.85	76.47	75	56	60	64.28	40	89.28
Cotrimoxaxole	62.5	80	68.57	60	74.28	82.35	40	56	68	78.57	84.44	78.57

Table 4. **Association between antibiotic sensitivity of *Streptococcus pneumoniae* strains and socio-demographic characteristics in Bangui from 2017 to 2022.**

	Chi^2	IC (95%)	*p*
Age range per year			
[0 - 5]	4.81	1.05 - 2.57	***0.01***
5+			
Sex			
Male	0.28	0.57 - 1.37	0.3
Female			

Antibiotic susceptibility to pneumococcal strains was associated with age ($p < 0.05$).

There is therefore a significant association between sensitivity to *Streptoccocus pneumoniae* antibiotics and age group ($p < 0.01$). However, there is no association with sex ($p > 0.05$).

4. DISCUSSIONS

The antibiotic resistance profile of *Streptococcus pneumoniae* strains is important for optimal treatment and monitoring of patients. This prospective study carried out at the LNBCSP focused on the evolution of the antibiotic sensitivity rate on strains of *Streptococcus pneumoniae* in Bangui, from 2017 to 2022. The average age was 22 years with a minimum of 0, 1, and a maximum of 92 years. The age range was 3 years. These results are similar to those of a study carried out by Ramdani-Bouguessa *et al.* in 2015 in Algeria where children under 5 years old were more affected (73%). Another study carried out by Amin. M, *et al.* presented the same results. In Burkina Faso between 2011 and 2013 Kambire *et al.* obtained similar results with a rate of 44.01% [17, 36, 37]. The distribution of isolated strains had varied over time, going from 3.69% in 2017 to 20.74% in 2022 with a peak in 2018 at 31.25%. This result is similar to that of Mc Carthy *et al.* in a study carried out in 2017 in Ireland, the frequency of cases varies over time [38]. Studies carried out by Lakehal *et al.* in 2017 and Hamani Zohra *et al.* in 2013 in the Wilaya of Bejaia showed similar results which were respectively 26% and 25%. Compared to the results of studies carried out by Dia *et al.* in 2013 (59.49%) in Senegal [39]. The frequency was above that found in our study. This result would be related to the geographical location of Senegal. The decrease in the frequency of cases could also be explained by the introduction of vaccination against *Streptococcus pneumoniae* in the Expanded Immunization Programs recommended by the WHO [40]. The study of sensitivity to different families of antibiotics showed an average sensitivity rate of 74.43% for β-lactams, of which 87.78% was due to ceftriaxone; The average rate of sensitivity to Fluoroquinolones was 54.54% and 86.93% concerned Levofloxacin. This result is in line with the results of a study carried out by the CDC where the prevalence of resistance to Fluoroquinolones is less than 1% but Levofloxacin is active against strains of *Streptococcus pneumoniae* [30]. The average rate of sensitivity to cyclins was 30.11%. The average rate of sensitivity to aminoglycosides was 28.69%, and that to macrolides 36.93%; phenicols 62.82% and sulfonamides 67.89%. These results corroborate with those of Barbara Spellerberg in the clinical biology textbook where the cross-resistance concerning tetracyclines was 69%; erythromycin 80% and cotrimoxazole 24% [28]. Studies carried out by the National Reference Center for Pneumococci in 2016 and another study carried out by Regine Cherazard *et al.* in 2017 showed that strains of *Streptococcus pneumoniae* following genetic modifications became resistant to macrolides [26, 27]. Compared to the results of the study conducted by Boisset Sandrine in Grenoble in France in 2015, strains of *Streptococcus pneumoniae* are naturally sensitive to antibiotics

[30]. The sensitivity rate of β lactams to strains of *Streptococcus pneumoniae* was stable with a percentage of 78.46 in 2020 and 91 for Ceftriaxone. The age group under 5 years old has an average sensitivity rate to β lactams of 79.25%. The sensitivity rate increased from 74.41% in 2018 to 82.60% in 2020. The average sensitivity rate to Fluoroquinolones was 52.59%. Levofloxacin had a sensitivity rate of 100% in 2017. This result corroborates with those of the recommendations of the Antibiogram Committee of the French Society of Microbiology of 2022 [33]. The age group over 5 years old had an average sensitivity rate to β lactams of 76.03%. The sensitivity rate to amoxicillin was 100% in 2017 and that of penicillin G was 25% in 2017 and 65% in 2021. The change in sensitivity to β lactams increased from 100% in 2017 to 66.66% in 2019. These results support those of Cassini Alessandro *et al.* in a study where the phenomenon of resistance affects children as well as adults [32]. The male sex had an average sensitivity rate to β lactams of 76.68%. The change in the sensitivity rate increased from 62.5% in 2017 to 80% in 2020. The sensitivity rate to fluoroquinolones was 54.26% during the study period. It went from 75% in 2017 to 37.5% in 2020. The sensitivity rate to tetracyclines, aminoglycosides, and macrolides was respectively 30.94%; 26.90%, and 29.59%. The sensitivity rate to phenicols and sulfonamides was 62.78% and 67.26% respectively. The average sensitivity rate to β lactams was 74.41% for females. It was slightly decreasing from 80% in 2017 to 68% in 2020. The sensitivity rate of fluoroquinolones was 53.48%. Its evolution went from 80% in 2017 to 44% in 2020. The sensitivity rate of cyclins, aminoglycosides, and macrolides was less than 40%. This high rate of resistance would be due to the accessibility of this antibiotic on the market at a good price and its misuse would explain the trends in their resistance. These data support the results of the study carried out by the Epibac network where aminoglycosides are naturally resistant to pneumococci [41]. Compared to other studies carried out by Spellerberg B *et al.* in 2007 the results were similar to those obtained in our study [29]. The sensitivity rate to phenicols and sulfonamides was 63.56% and 41.86% respectively. This study showed an association between age and the rate of antibiotic sensitivity to strains of *Streptococcus pneumoniae*. The age group over 5 years old was more sensitive with 35.51% compared to 22.73% (80/352) in the age group under 5 years old. This result was statistically significant with $p < 0.05$ and a confidence interval between 1.01 and 2.52. However, there is no association between sex and antibiotic sensitivity to pneumococci ($p > 0.05$).

5. CONCLUSION

According to the results of the antibiotic sensitivity study, the strains of *Streptococcus pneumoniae* were sensitive to ampicillin and ceftriaxone. On the contrary, they had acquired resistance to penicillin G. Resistance to antibiotics continues to develop given the self-medication and misuse of these antimicrobials in Bangui. A molecular biology study to determine resistance genes could shed light on this subject.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest regarding the publication of this paper.

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