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Could the Increased Consumption of Azithromycin during the COVID-19 Pandemic Have Affected the Sensitivity of Bacteria of Aquatic Environment to This Antibiotic?

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Abstract

The increased consumption of azithromycin during the COVID-19 pandemic may have led to its presence in the waterways. This study aims to evaluate the effect of this situation on aquatic bacteria. *Methodology*: Over a four-month period following the official recognition of the COVID-19 outbreak in Yaoundé, water samples were collected from four rivers selected on the basis of their vicinity to care centers for COVID-19. Bacteria within azithromycin's spectrum of activity were isolated, and the antibiotic's efficacy was tested against the most frequently isolated species. The influence of COVID-19 incidence and other external factors was also assessed. *Results*: The most frequently isolated bacteria were *Bacillus* spp., *Enterococcus* spp., *Listeria* spp. and *Staphylococcus epidermidis*. These strains exhibited varying levels of sensitivity to azithromycin, ranging from 0% to 100%. The observed resistance rates were 12.5%, 14.29%, 16.67%, and 0%, respectively. Neither COVID-19 incidence, proximity to hospitals, nor rainfall significantly influenced bacterial resistance rates to azithromycin ($P > 0.05$). These resistance levels may be attributed to the relatively short exposure of bacteria to azithromycin at the sampled locations, as well as the impact of agricultural and livestock-related chemicals, such as biocides and antibiotics, present in the watershed. *Conclusion*: These results highlight the need to integrate into anti-COVID-19 activities, the monitoring of bacteria's sensitivity in aquatic environments.

Keywords

COVID-19, Azithromycin, Aquatic Bacteria, Antibiotic Resistance, Yaoundé, Rivers

1. Introduction

In Cameroon, the first case of COVID-19 was reported on March 6, 2020 [1]. Two years later, the number of people affected by SARS-Cov-2 jumped to 119,780 cases [2]. The number of COVID-19 cases in the city of Yaoundé peaked twice: in November 2020 (103 cases) and in March 2021 (118 cases) [3]. The severity of the disease can range from mild to severe and even critical forms [3]. It has been reported that Severe Acute Respiratory Coronavirus 2 (SARS-CoV2), the viral pathogen of COVID-19 affects multiple organs and that one of the major causes of death attributable to COVID-19 is cardiovascular events [4]. Among the measures deployed to respond to that pandemic, the use of azithromycin, well-known for its antibacterial, anti-inflammatory, immunomodulatory, and antiviral properties [5], has been included in patient care protocols [6]-[8]. In developing countries, deficiencies in wastewater management expose metropolitan watercourses to various pollutants, including drugs and medicinal substances [9]. It is commonly accepted that the presence of certain molecules in an environment can exert pressure on bacteria, which is likely to select resistant strains [10] [11]. Thus, Enterobacteriaceae producing spectrum beta-lactamases were isolated from wastewater with large concentrations of antibiotics [12]-[14]. Considering the increased use of antimicrobial agents, including azithromycin, during the COVID-19 pandemic [15] and the possible discharge of unmetabolized antibiotic fractions in hospital and domestic effluents [12] [16], it is logical to suspect emergence in the surrounding aquatic environment of bacterial strains resistant to the drugs used during this. The present study aims to evaluate the bacteria in the aquatic environment of the area of Yaoundé in Cameroon and the effect of increased consumption of azithromycin during the first months of COVID-19. Concretely, after identification of the bacteria taxa, the sensitivity with regards to azithromycin was evaluated, and then the influence of the incidence of COVID-19 cases and of certain environmental factors on this sensitivity was determined.

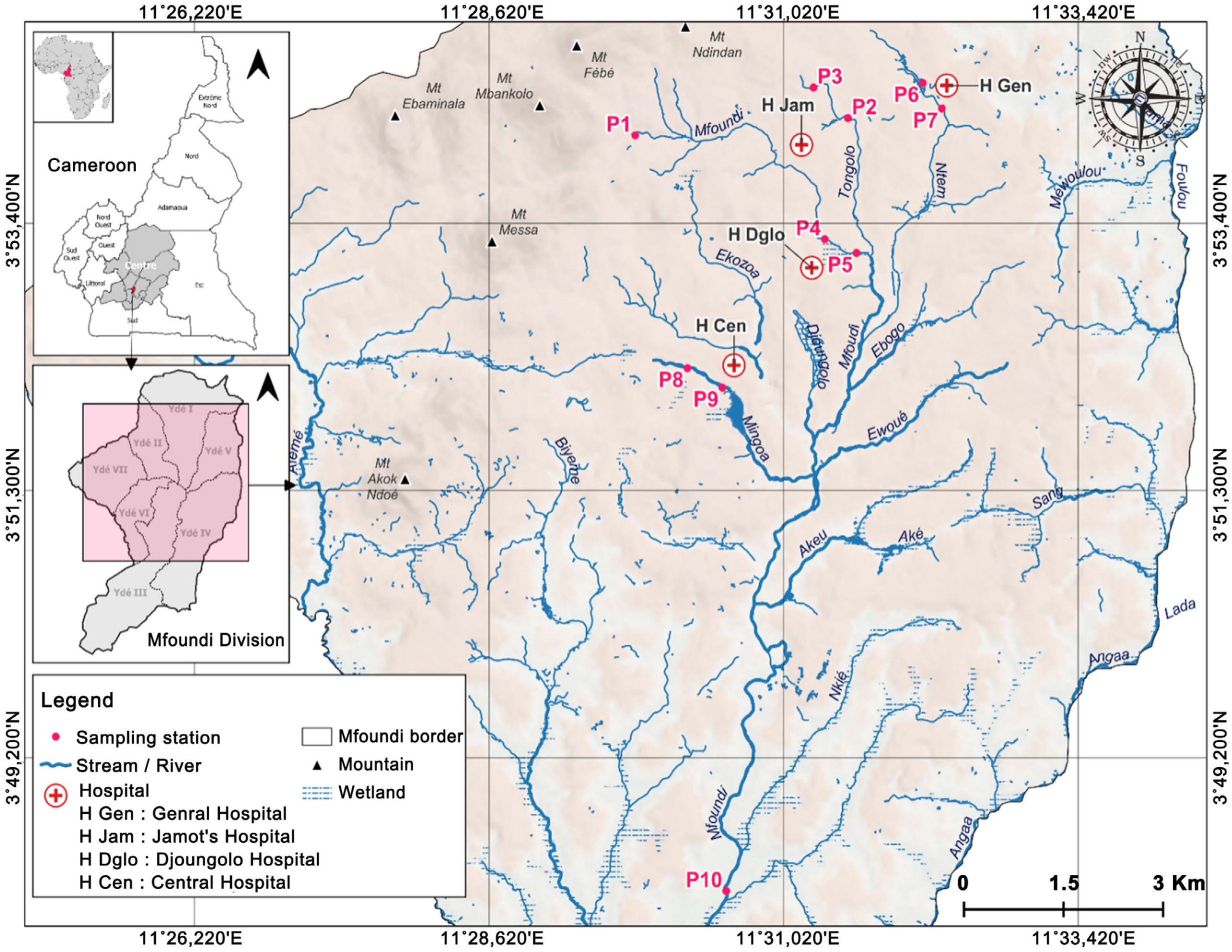
2. Material and Methods

2.1. Study Area

Yaoundé, the political capital of Cameroon, is located between the longitudes 11˚20' and 11˚40' and between the north latitudes 3˚45' and 4˚00', 200 km from the Atlantic coast. Its area is about 400 km^2, and its equatorial climate is characterized by two dry seasons and two rainy seasons. The former extends respectively from December to February and from July to August, while the latter is observed from September to November and from March to June [17]. The hydrographic network of this city is made up of the Mfoundi, the main river, and its tributaries; these drain runoff and surface water. River Mfoundi flows into the Mefou, which, in turn, flows into the Nyong River, the second-longest river in Cameroon. Permanent streams, rivers, and ponds complete this picture [18].

2.2. Water Sampling Points

Four watercourses, the Mfoundi River and three of its tributaries, namely the Tongolo, the Ntem and the Mingoa (**Figure 1**) were selected with regard to the following criteria: the size of their beds, proximity to hospitals involved in the care of COVID-19 patients, accessibility and use of water. For each watercourse, two sampling points were set up: one upstream of the concerned hospital and the other downstream of the said health facility (**Table 1**). Besides those eight sampling points (Pi), two more points (P1 and P10) were installed on the Mfoundi River, making the overall count ten sampling points. The health facilities along the watercourses selected for this study were Yaoundé Central Hospital (HCY), Yaoundé General Hospital (HGY), Jamot Hospital (HJ), and Djoungolo Hospital (HD).



SOURCES: OpenStreetMap (0SM) 2023. SCR: EPSG4326-WGS 84. Logiciel : QGIS 3.28.0. Edition: Stéphane A. NOAH. Fait le: 29-05-2023.

Figure 1. Map of the hydrographic network of the Yaoundé city indicating the watercourses and the sampling sites selected.

2.3. Collection of Water Samples

Water samples were collected once a month during the first eight months following the official acknowledgement of a COVID-19 case in Cameroon. Practically, a sterile, hermetically sealed bottle glass of 500 ml, was immersed in a water depth of 25 to 30 cm in the river. For sample collection, it was opened in the opposite direction to the water flow, filled and capped before removal. The collected samples were kept at 4˚C ± 1˚C [19] and subjected to bacteriological analysis within 24 ± 1 h.

Table 1. Description of sampling points.

Waters course	Sampling points	Geographical coordinates	Location	Pollution's sources	Using
Mfoundi	$\mathbf{P}_{1}$	N 03˚54'05.5" E 011˚29'48.7" 3m GPS	Club Bastos: Highest point on the river	Household waste	None
Tongolo	$\mathbf{P}_{2}$	N 03˚54'13.6" E 011˚31'32.7" 3m GPS	In front of the Bafia, Bafoussam travel agency); Point upstream from Jamot's Hospital	Trash bins, Latrines, Household waste	Vehicle wash
	$\mathbf{P}_{3}$	N 03˚53'21.7" E 011˚31'16.8" 3m GPS	Nkol-eton Market: Point downstream from Jamot's Hospital	Latrines, Household waste water	None
Mfoundi	$\mathbf{P}_{4}$	N 03˚53'16.5" E 011˚31'21.4" 3m GPS	Bata-Nlonkak: Behind the Bunker Hotel, upstream from the Djoungolo Hospital	Household waste water, garbage bins	Washing clothes
	$\mathbf{P}_{5}$	N 03˚53'10.0" E 011˚31'36.9" 3m GPS	New ETOA MEKI road, behind the stadium? and the laundry; point downstream from Djoungolo hospital	Household waste water, garbage bins	Cloth washing, Plant watering.
Ntem	$\mathbf{P}_{6}$	N 03˚54'30.2" E 011˚32'09.3" 3m GPS	Ngousso rail: Upstream of the Yaoundé General Hospital.	Laundromat, pigsty, household waste	Car wash
	$\mathbf{P}_{7}$	N 03˚54'18.11" E 011˚32'18.6" 3m GPS	Ngousso rail, behind the 1st laundry; Point downstream of the Yaoundé General Hospital.	Household Discharges, latrines	Car wash
Mingoa	$\mathbf{P}_{8}$	N 03˚52'15.7" E 011˚30'14.2" 3m GPS	Public works road (YEYAP camp); Point upstream from Central Hospital	Household wastewater from SIC Messa coumpound, after the Abiergue/Mingoa confluence	Cloth washing, bath
	$\mathbf{P}_{9}$	N 03˚52'06.5" E 011˚30'31.3" 3m GPS	Before the municipal lake; Point downstream of Central Hospital	Discharges from the sic Messa camp, from the laundry wastewater treatment	Washing clothes, bath.
Mfoundi	$\mathbf{P}_{10}$	N 03˚48'09.1" E 011˚30'33.2" 3m GPS	Second Mvan interchange: Lowest point on the watercourse	Building and construction works, brewery effluents, in general all city drains.	Plant watering.

2.4. Azithromycin Spectrum Bacteria Isolation

After macroscopic examination, 50 ml of each water sample was subjected to centrifugation at 2000 rpm for 15 min ± 1 min. The pellet was resuspended in 3 ml of sterile distilled water by vortexing for 1 to 2 min. The suspension thus obtained was inoculated using the quadrant technique [20] [21] on the Chapman Agar and Bile Aesculin Agar (BEA) culture media, which are selective for bacteria usually susceptible to azithromycin [21]. The Petri dishes were incubated at 37˚C ± 1˚C for 24 to 48 ± 1 h [20]. The identification of bacteria was carried out on the basis of morphological, structural, physiological, and metabolic characters [21].

2.5. Determination of Bacterial Susceptibility to Azithromycin

The choice of the bacteria to be tested was carried out on the basis of their more or less regular isolation frequency per point and per month. Bacteria taxa were isolated for at least 4 months during the 8th sampling period lasted, and at least 50% of the sampling points were retained.

The sensitivity test was carried out according to the discs diffusion method on agar medium as recommended by the Antibiogram committee of the French Microbiology Society/CA-SFM/(2019) [22]. The bacteria were classified as resistant R (resistance rate RR > 90%), inconsistently sensitive IS (10% ≤ RR ≤ 90%), or sensitive S (RR < 10%). For each bacterial taxa tested, the resistance rate was determined using the following formula:

$$\text{Resistance rate}\left(\text{RR}\right) = \frac{\text{Number of resistant strains} \times 100}{\text{Number of strains tested}}. \quad [23]$$

2.6. Determination of the Influence of Some Factors

The Spearman Correlation (r_s) was computed to determine the influence of the sensitivity of bacteria to azithromycin on the incidence of COVID-19 cases, the distance of each sampling point to the nearest health facility, and the rainfall. It is important to indicate that rainfall data was provided by Yaoundé Nsimalen Meteorological Station. R software version 4.2.3 was used to perform Spearman's correlation test.

3. Results

3.1. Bacteria Retained

Four bacterial taxa met the defined criteria, namely *Bacillus* spp., *Enterococcus* spp., *Listeria* spp. and *Staphylococcus epidermidis*. The first one was present for 7 months in all the rivers; the second one was isolated for 6 months in Mfoundi and Ntem; and the third one was identified for 4 months in Tongolo and Ntem.

For 4 months, the fourth one was found in the Mfoundi river.

3.2. Sensitivity of Bacteria to Azithromycin

All these bacteria presented an altered sensitivity to azithromycin. *Enterococcus* spp., and *Staphylococcus* spp. ranged from susceptible (S) to inconsistently susceptible (IS), *Bacillus* spp. was IS and *Listeria* spp. scaled from inconsistently susceptible (IS) to resistant (R). The susceptibility/inconsistently susceptibly and resistance profiles were found as follows: 25%/62.5%/12.5% for *Bacillus* spp., 14.29%/71.43%/14.2% for *Enterococcus* spp., 42.86%/57.14%/0% for *Staphylococcus epidermidis* and 33.33%/50%/16.67% for *Listeria* spp.; Therefore, during the outbreak of COVID-19, *Listeria* spp. was more resistant to azithromycin than

Enterococcus spp., *Bacillus* spp., and *Staphylococcus epidermidis*.

3.3. Influence of COVID-19 Incidence and of Some Environmental Factors on the Sensitivity of the Bacteria

No significant correlation ($P > 0.05$) was observed between the number of patient cases declared per month and the resistance rates of the different bacterial taxa, although *Bacillus* spp. and *Staphylococcus epidermidis* resistance rates were negatively correlated ($r_s = -0.49$; $r_s = -0.41$) while *Enterococcus* spp., *Listeria* spp. resistance rates were positively correlated $r_s = 0.7$; $r_s = 0.31$) to this factor (**Figures 2-5**) respectively.

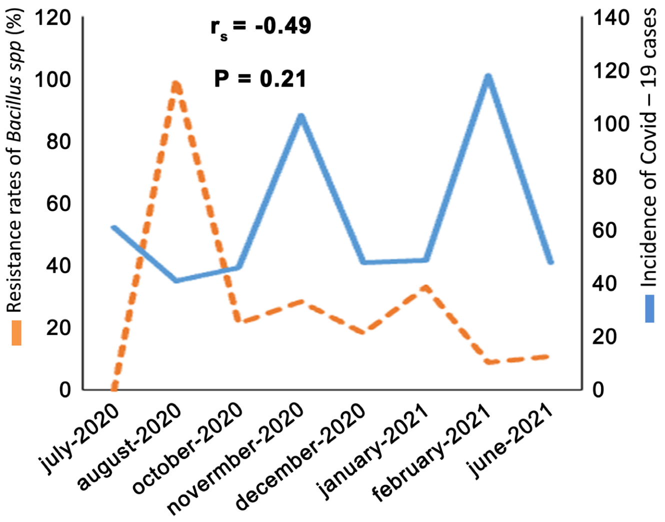


Figure 2. Evolution of monthly azithromycin resistance rates for *Bacillus* spp. and the incidence of COVID-19 cases.

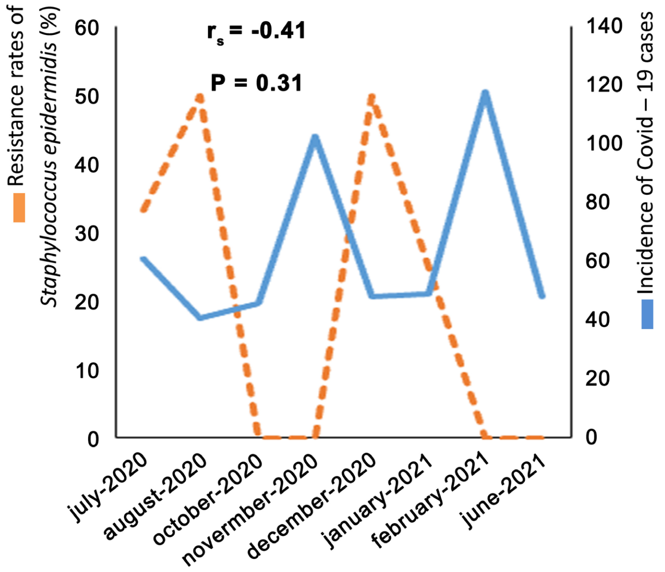


Figure 3. Evolution of monthly azithromycin resistance rates for *Staphylococcus epidermidis* and the incidence of COVID-19 cases.

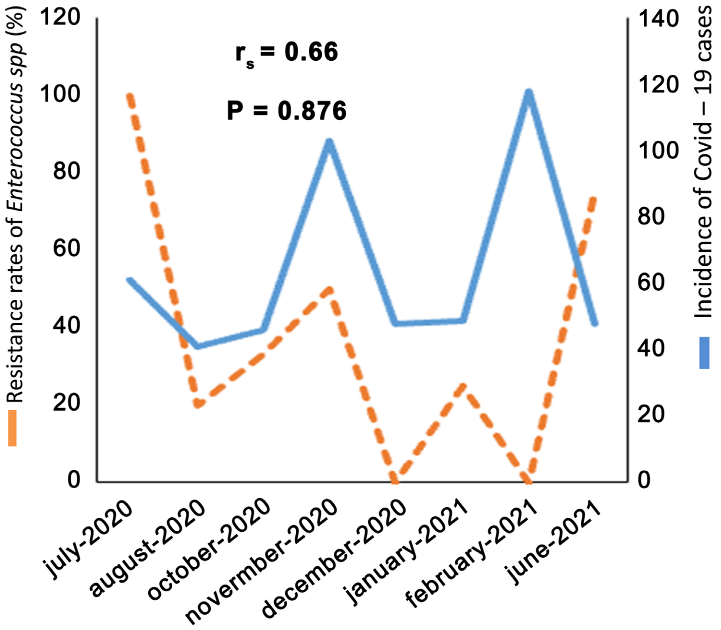


Figure 4. Evolution of monthly azithromycin resistance rates for *Enterococcus* spp. and the incidence of COVID-19 cases.

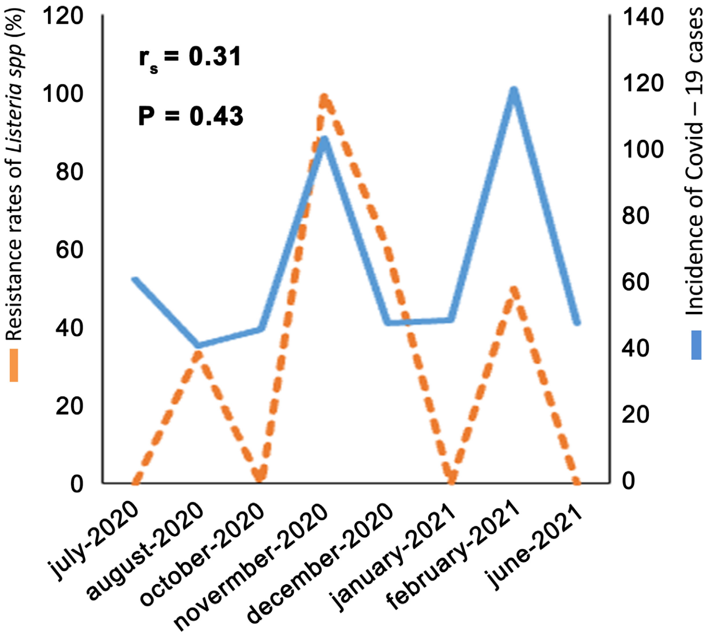


Figure 5. Evolution of monthly azithromycin resistance rates for *Listeria* spp. and the incidence of COVID-19 cases.

The distance between the sampling points and the health facilities did not influence the resistance rate of bacterial taxa to azithromycin, since no significant correlation ($P > 0.05$) was found. Although *Bacillus* spp., *Listeria* spp. and *Enterococcus* spp., resistance rates were negatively correlated ($r_s = -0.61$; $r_s = -0.40$; $r_s = -0.79$) while *Staphylococcus epidermidis* resistance rate was positively correlated ($r_s = 0.21$) to this factor (Table 2).

Table 2. Spearman's correlation values between the shortest distance from a water sampling point to a hospital, and the rate of bacteria resistance to azithromycin.

Distance: Point-Hospital (in m) Relative resistance rate of bacteria in the sampling points	Mfoundi		Tongolo		Ntem		Mingoa	
	Djoungolo hospital		Jamot hospital		Yaoundé general hospital		Yaoundé central hospital	
	P4	P5	P2	P3	P6	P7	P8	P9
	549.5	710.1	804.8	854.1	365.3	342.6	704.4	367.1
Bacillus spp.	50% IS	33.3% IS	16.6% IS	11.6% IS	22.2% IS	22.2% IS	16.6% IS	30.76% IS
	r_s = −0.610; P = 0.061							
Enterococcus spp.	60% IS	0% S	/	/	60% IS	50% IS	/	/
	r_s = −0.794; P = 0.059							
Listeria spp.	/	/	20% IS	66.6% IS	33.3% IS	100% R	/	/
	r_s = – 0.400; P = 0.600							
Staphylococcus epidermidis	0% S	75% IS	/	/	/	/	/	/
	r_s = 0.211; P = 0.789							

S: sensitive, IS: inconstantly susceptible, R: resistant, /: not identified.

The Spearman correlation coefficient (r_s) failed to highlight a clear link (P > 0.05) between rainfall and monthly bacterial resistance rates, although *Bacillus* spp., *Listeria* spp. and *Staphylococcus epidermidis* resistance rates were negatively correlated ($r_s = -0.41$; $r_s = -0.5$; $r_s = -0.27$) while *Enterococcus* spp. resistance rate was positively correlated ($r_s = 0.57$) to this factor (Figures 6-9).

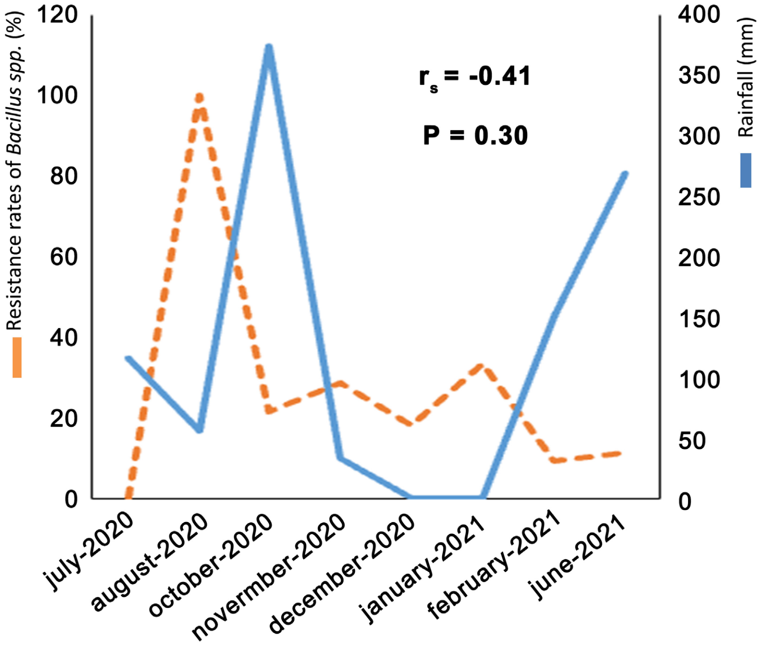


Figure 6. Monthly evolution of azithromycin resistance of *Bacillus* spp. and rainfall.

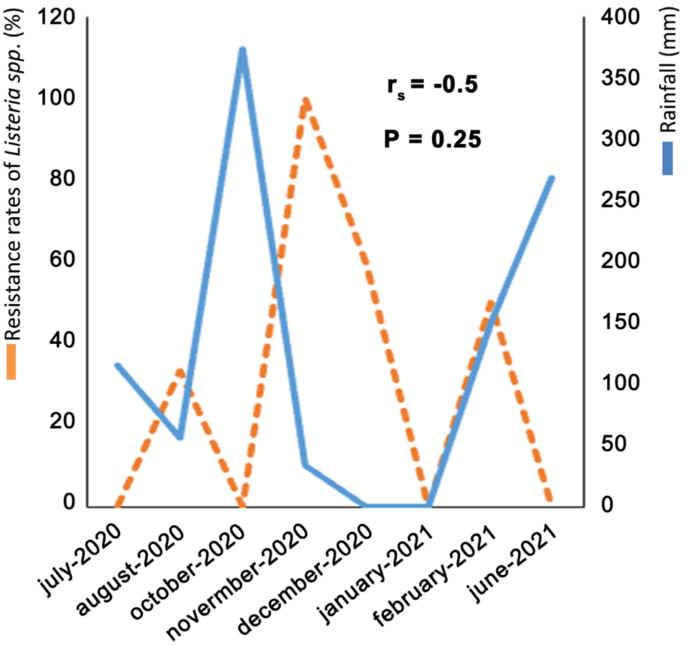


Figure 7. Monthly evolution of azithromycin resistance of *Listeria* spp. and rainfall.

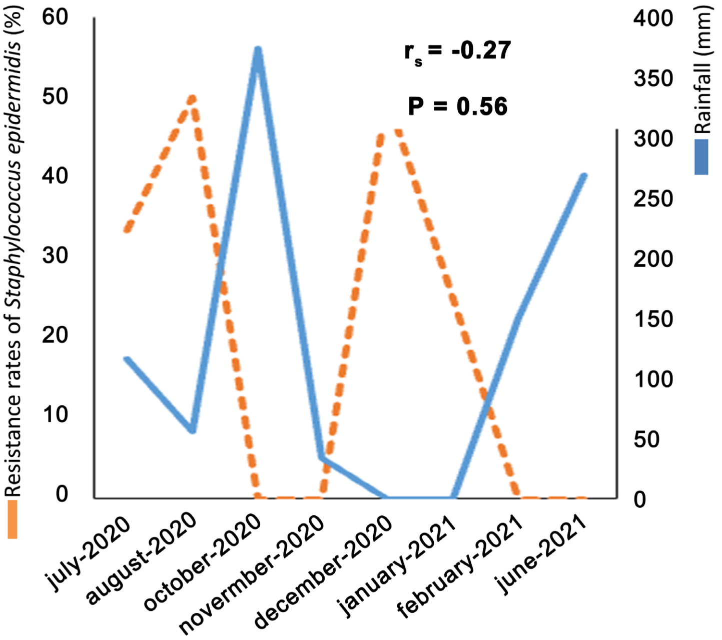


Figure 8. Monthly evolution of azithromycin resistance of *Staphylococcus epidermidis* and rainfall.

4. Discussion

During the COVID-19 outbreak, the consumption of azithromycin increased both in households and in health facilities [7].

All bacterial taxa tested showed altered sensitivity to this medical drug, since some strains revealed resistance (**Figures 2-4**, **Figures 6-8**). Several authors including Milakovic *et al.* (2020) [24], Affssap (2005) [25] and Isnard (2017) [26]

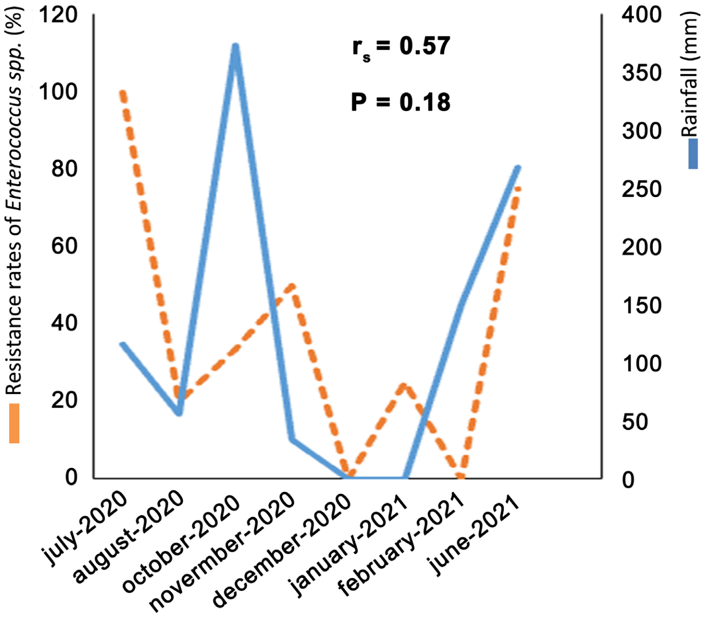


Figure 9. Monthly evolution of azithromycin resistance of *Enterococcus* spp. and rainfall.

evidenced the fact that *Enterococcus*, *Staphylococcus*, and *Listeria* species could become resistant. However, the acquired resistance rates indicated by Affssap (2005) (50% for *Listeria* spp., 50% to 70% for *Enterococcus* spp., and 70 to 80% for *Staphylococcus* spp.) [25] are significantly higher than those obtained in the present study (16.67% of *Listeria* spp. strains, 14.2% of *Enterococcus* spp. strains, 0% of *Staphylococcus epidermidis*). Nevertheless, our results show that the massive use of azithromycin did impact the studied bacteria in the Yaoundé watercourses, although slightly. This could be explained by the relatively short time exposure of bacteria at a given sampling point. Indeed, Stephen & Palumbi (2001) [27] estimated that the acquisition of resistance by bacteria in horizontal gene exchange conditions generally requires about ten years after the introduction of the antibiotic. Danner *et al.* (2019) [28] also stated that the concentration of antibiotics in freshwater, although lower than in effective clinical situations, could have direct and indirect consequences on the bacterial components of aquatic communities. In our context, the concentrations of azithromycin, which were not determined, could still be too low to modify bacterial sensitivity in the Mfoundi River network. This was confirmed by Nazareno *et al.* (2022) [29], who highlighted in their work on water bodies of Yaoundé the presence of this antibiotic's traces (1.14 to 1.21 µg/L). Furthermore, fairly high levels of resistance were observed in *Listeria* spp. (16.67%) *Enterococcus* spp. (14.29%) and *Bacillus* spp. (12.5%) compared to that observed for *Staphylococcus epidermidis* (0%) could be further explained by the influence on the watershed of the use of chemical products for agriculture and breeding of livestock, such as biocides, antibiotics, with which these bacteria could be in contact [28]. In fact, it is known that *Listeria* spp. is essentially of food origin; several authors like Liyabona Mpondo *et al.* (2021) [30] have demonstrated that their resistance to antibiotics in the environment is linked to excessive use. Although not determined in this work, certain water quality parameters, such as pH, could influence the bacteria's responses to azithromycin. Perletti *et al.* (2011) [31] indicate that its activity is reduced when the pH is acidic.

The incidence of COVID-19 cases did not impact the resistance rate of bacterial taxa to azithromycin (**Figures 2-5**) since no significant correlation ($P > 0.05$) was observed between the number of monthly declared cases and resistance rates. This could be due to the one hand, to its dosage and, on the other hand, to the use of other drugs in the treatment against COVID-19 [32]. Indeed, the national standard for non-severe COVID-19 includes oral hydroxychloroquine 200 mg twice daily for seven days and azithromycin 500 mg the first day and 250 mg from days 2 through 5 [4]. Moreover, numerous Cameroonians have recourse to traditional pharmacopeia, which, although criticized, has been massively used within the population [5]. This could have limited the use of azithromycin within the population during the health crisis.

The distance between the sampling points and the health facilities did not impact the resistance rate of any bacterial taxa to azithromycin (**Table 3**). This is probably due to the small quantities of non-metabolized azithromycin which reach domestic and hospital effluents, and cannot rapidly modify the sensitivity of the bacteria in the waters, according to the statement by Stephen & Palumbi (2001) [27].

Table 3. Spearman's correlation test between monthly rainfall and bacterial resistance (percent) to azithromycin.

Months	Average monthly rainfall (mm)	Bacteria taxa							
		Bacillus spp.		*Enterococcus* spp.		*Staphylococcus epidermidis*		*Listeria* spp.	
		Monthly relative resistance rate	Spearman's correlation value	Monthly relative resistance rate	Spearman's correlation value	Monthly relative resistance rate	Spearman's correlation value	Monthly relative resistance rate	Spearman's correlation value
jul-20	**115.7**	0	$r_s = -0.41$ P = 0.30	100	$r_s = 0.57$ P = 0.18	33.3	$r_s = -0.5$ P = 0.25	/	$r_s = -0.27$ P = 0.56
aug-20	**56**	100		20		50		33.3	
oct-20	**374**	21.42		33.3		0		/	
nov-20	**33.5**	28.57		50		0		100	
dec-20	**0**	18.18		0		50		60	
jan-21	**0**	33.33		25		25		0	
mar-21	**149.8**	9.09		/		0		50	
june-21	**268.7**	11.11		75		/		0	

/: not identified.

The influence of rainfall on bacterial resistance rates to azithromycin was not evidenced.

5. Conclusion

Sixteen months after the declaration, in the city of Yaoundé, of the first case of

COVID-19, *Bacillus* spp., *Enterococcus* spp., *Listeria* spp., and *Staphylococcus epidermidis*, which fall within azithromycin's spectrum of activity were the most frequently isolated bacteria in the watercourses of the city of Yaoundé. Their sensitivity to azithromycin was altered, since their resistance rates varied from 0% to 100 %. Dissemination in the environment of their resistant strains could be feared. These results underline the need to integrate into anti-COVID-19 activities, such as the monitoring of bacteria's sensitivity in aquatic environments.

Conflicts of Interest

The authors declare that there is no conflict of interest related to the publication of this article.

Author Contributions

NEC is the designer of the study. TMC participated in the collection and analysis of the samples as well as in the drafting of the manuscript. ANGE and ES received the collection of the samples and the analysis of the results. LBL and JA participated in the analysis of the results.

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