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Urinary tract infections in Maiduguri-city, Nigeria: a 2005-2009 clinical survey of Fluoroquinolones Activities against *Staphylococcus Aureus* acting as second most isolated Etiological Pathogens.

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ABSTRACT

The increasing resistances to several antibiotic classes have forced pressures on fluoroquinolones (FQs) use. Even among FQs, resistances are growing due to rapid spreading of adaptive measures. We investigated *Staphylococcus aureus* urinary tract infections (UTIs) to understand its infectivity patterns, sensitivity trends to FQs, multi-fluoroquinolone resistant patterns, and fluoroquinolones' interactivity relations from January 2005 to December 2009. 211 (13.3%) *Staphylococcus aureus* were isolated from 1590 urine cultured samples having its peak infectivity in 2006 with 28.4% and least proportion (10.9%) in 2005. *Staph aureus* UTIs were higher in women (41.7%) than men (20.4%) in those between 10 and 30 years, but beyond this age range, this trend was reversed (16.6% for men and 3.3% for women). The overall activities of the FQs during the 5 years periods range from 41% in norfloxacin to 85% in ofloxacin and resistance rates of the pathogen have out-grown sensitivity for norfloxacin and nalidixic acid. Age dependent increase in resistance was correlated for ciprofloxacin ($P=0.003$) and norfloxacin ($P<0.01$) up to 50 and 60 years respectively and overall resistance change (23.9% in 2005 to 47.1 in 2009) of FQs was found to be significant ($P<0.01$). The activities of ciprofloxacin against norfloxacin-resistant and pefloxacin-resistant *Staph aureus* were consistently higher than ofloxacin ($P<0.005$ and $P<0.05$ respectively). Co-fluoroquinolone-resistant *Staph aureus* increased from 8.7% in 2005 to 24.1% in 2009. Most ciprofloxacin and ofloxacin resistant *Staph aureus* UTI may have no suitable alternative among the quinolones currently in use in the region, necessitating the need for the introduction of newer quinolones.

Keywords: *Staphylococcus aureus*, *Staph aureus* UTI, Urinary Tract Infection, uropathogenic *Staphylococcus aureus*, norfloxacin-resistant *Staphylococcus aureus*, Ciprofloxacin, Fluoroquionolones

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INTRODUCTION

Infections caused by *Staph aureus* are of great concern in any clinical setting not only because of its intrinsic virulence, or its ability to cause a diverse form of life-threatening infections, or its ability to adapt to different environmental conditions[1,2] but also because resistances offered by this pathogen is in the increase and difficult to handle resulting to several mortalities. *Staph aureus* bacterium is known to cause diseases affecting the bloodstream, skin, respiratory, gastro-intestinal, renal, ocular, ear, nose, throat, and genitor-urinary systems with high mortality rate. For example, the mortality of *S. aureus* bacteremia is between 20–40% despite the availability of effective antimicrobials[3] and is now considered as one of the leading cause of nosocomial infections.

The trend in *Staphylococcus aureus* resistance pattern from inception was very minimal when chemotherapeutic agents (penicillins) were first directed against the pathogen in the 1940s but rapidly became resistance with over 80% resistant *Staph aureus* cases in both hospital and community isolates established in the 1960s[4]. As more of its molecular structures became known, several agents have been targeted to destroy the pathogens using several pathways. However, the pathogen has always thrive over the years due to its production of β-lactamase enzymes against the β–lactam antibiotics or methicillin resistance strain through the expression of mecA gene responsible for synthesis of penicillin-binding protein 2a (PBP2a).[5,6] *Staph aureus* has also shown rapid development of resistance against the fluoroquinolones as a result of spontaneous chromosomal in the target of the antibiotic, topoisomerase IV or DNA gyrase, or by the induction mutations of a multidrug efflux pump[4] while resistance to vancomycin has long been reported[7]. *Staph aureus* has developed resistances to other different classes of antibiotics developed to date[1] and resistances to newer generations of antibiotics are also common[8].

The incrimination of *Staph aureus* in urinary tract infections has been known for many decades ago. Although its uropathogenic nature may vary from one region of the world to another, but a more challenging problems posed by *Staphylococcus aureus* in several quarters is the problem of resistances to multiplicity of antibacterial agents used in infectious disease therapy resulting into diverse quality health concerns that varies from one region to another. UTI in general attracts over 8.3% physician visits per year and *Staph aureus* associated UTI can occur in bladder, urethra or kidney[9]. Symptoms of *Staph aureus* UTI varies depending on the site of the urinary tract and the extent of infection. For instance, lower UTIs can affect the urethra, bladder and prostate (in men) and presenting with the symptoms that include dysuria, urinary urgency and

urgency, supra-pubic pain and heaviness[10]. But when the ureter and the kidneys are involved as in pyelonephritis, systemic signs and symptoms like leukocytosis, fever, chills, lower abdominal pain, flank pain, nausea and vomiting are involved[9] but gender and frequent catheter use are the most identified risk factors while enlarged prostate gland and kidney stone are also other risk factors

The management of UTI with an appropriate antibiotic therapy follows an approach that require to obtained information on local resistance rates and an on-going surveillance to be conducted to monitor changes in susceptibility of uropathogens as well as to guide in clinical decision making. This present study therefore surveyed the present activities status of the fluoroquinolones to *S. aureus* isolates from urine in patients with clinical evidence of UTI. *Staphylococcus aureus* was the chosen pathogen because it is one of the most common pathogens that frequently offer resistance to a wide range of antibiotic. UTI was studied disease since it is one of the most common diseases occurring in both hospital and community setting where several antibiotics may have been used without success prior to seeking for tertiary hospital cares. Also the quinololones class of antibiotics was surveyed because previous findings have established a high resistance rates in the region to several other class of antibiotics when evaluated from several infectious sites[11,12] leaving the quinolone as one of the few treatment options available in the region.

The study was aimed at investigating trends in urinary tract infection caused by *Staphylococcus aureus*, the changing patterns of the activities of the fluoroquinolones against *Staph aureus* UTI, multi-fluoroquinolone-resistances to *Staph aureus* UTI and its patterns; and to investigate the inter-activity relations of the fluoroquinolones from 2005 to 2009.

MATERIALS AND METHODS

Sampling

1590 cases of urinary tract infections comprising 785 males and 805 females aged below 1 year to 95 years were assessed between January 2005 and December 2009 in individuals suspected to have UTI following the presented clinical signs/symptoms and confirmed with microbiological assay of their urine specimens.

Isolation and Identification of Staph aureus

Midstream urine samples were obtained from patients with suspected urinary tract infection into clean urine specimen bottles previously sterilized. Urine samples were examined to establish staphylococcal involvement through inoculation on McConkey agar (Lab M, UK) media plates

and were incubated for 24 hours at 37^{o}C. These isolates were examined for colonial morphology and lactose fermenters were excluded while gram staining were carried out on the non-lactose fermenters and thereafter using normal saline solution, microscopic examination was carried out with microscope using x10 and x40 objectives. This aimed at selecting gram positive cocci with grape bunch morphology.

Staph aureus strains were identified on isolates using catalase tests by adding a drop of 3% H_2O_2 and making an innoculum of 18 hours old culture of the organism on the drop using a sterile loop wire. *Staphylococcus* was considered positive with the production of effervescence. *Staphylococcus* was further identified by streaking the suspected pathogen on mannitol salt agar and incubated at 37^{o}C for 24 hours aerobically. *Staph aureus* was identified as colony with a change of color from red to yellow.

Staph aureus Sensitivity Assay

Antimicrobial sensitivities were performed with the disc concentrations of nalidixic acid (30µg) and fluoroquinolones agents like norfloxacin (30µg), pefloxacin (10µg), ciprofloxacin (10µg) and ofloxacin (10µg) using the Kirby Bauer Disc Diffusion Method in accordance with the National Clinical Laboratory Standards Institute (CLSI). These discs were fixed firmly on agar plate with the aid of sterile forceps and at 2 cm apart. About 30 minutes were allowed for the diffusion of the antimicrobial agents to take place before the plates were incubated at 37^{o}C for 24 hours. Zones of inhibitions around the discs were determined by measuring the diameter of inhibition zone and were compared with standard antibiotic resistance chart.

Statistical analysis

Chi square analysis was performed to determine the level of significant difference (if any) between the activities of two or more fluoroquinolone agents and between individual agents at different years. The P-value was set at $P<0.05$, 0.01 and 0.005 significant values wherever applicable. Trends in increase or decrease with years were performed with correlation statistics using Statistical Package for Social sciences (version 16).

RESULTS AND DISCUSSION

UTI associated with _S. aureus_

The distribution of *Staph aureus* isolated in urine specimens from 2005 to 2009 (Table 1) indicated a total isolates of 211 (13.3%) out of the 1590 isolated pathogens during the periods making *the* pathogen to rank second to *E. coli* as most abundant pathogens causing UTI in the region. UTI caused by *Staph aureus* peaked in 2006 with 28.4% while the least cases were

recorded in 2005 with 10.9%. The recorded isolates in this study were particularly high between 2006 and 2008 when compared with results obtained in other regions. However, the 10.9% and 11.8% *Staph aureus* associated UTI respectively recorded in 2005 and 2009 were found consistent with the 5-15% range reported worldwide[13] but values obtained other than these two years were observed higher than world range. Many researchers similarly reported that *Staph aureus* UTI are increasing in some quarters and have been reported as the most isolated pathogen in some area[14]. For example, as high as 27.3% and 33.6% prevalence cases were reported in Edo and Bayelsa States, Nigeria[15,16] and 18% isolates were obtained in Ethiopia[17].

Table 1: Distribution pattern of isolated uropathogenic *S. aureus* from 2005 to 2009

		Number Isolated per Year					
Pathogens	Gender	**2005**	**2006**	**2007**	**2008**	**2009**	**Total (%)**
S. aureus	Male	12	29	24	23	17	105(49.8%)
	Female	11	31	22	34	8	106 (50.2%)
	Total	23	60	46	57	25	211 (100%)
	Percentage	**10.9%**	**28.4%**	**21.8%**	**27.0%**	**11.8%**	**(100%)**

UTI incidences caused by *Staph aureus* are almost in equal proportion in both male and female genders, being 49.8% and 50.2% respectively in contrast to the significant higher proportions recorded in female over male by some authors in certain quarter[14].

The age and gender distribution of patients with *Staph aureus* UTI

The age and gender distribution of patients with *Staph aureus* UTI is as shown in Figure 1. The distribution pattern for the male gender is skewed toward low frequency of higher age group with a mean and standard deviation of 31.18 ± 22.47 years while that of the female showed similar pattern with the mean and standard deviation of 25.0 ± 10.19 years. However, the mean age and standard deviation for the general population (male and female combined) is 28.13 ± 18.36 years. As observed, male children below ten years indicated significant higher cases of *Staph aureus* UTI compared with their female counterpart, but the preponderance for the disease is higher in female subjects who are between ten and forty years (41.7%) compare to male subjects (20.4%) and thereafter, a reversal in trends were observed (16.6% for men and 3.3% for women). Similarly UTI was higher among men who are above 40 years when compared with women who are of similar age strata. However, these observed differences were not found to be significant. Nevertheless, our results may have suggested that several interplays of factors including those relating to closer anatomical structure of women urethra to the anus, diaphragm use, sexual behavior, new sex partner, pregnancy and post-menopausal women can serve as gender related risk factors that impact the course of the disease in women compare to men[18].

Many studies have linked catheter use and its associated *Staph aureus* UTI among the geriatric age group as specific related risk factors capable of causing UTI [18,19], although this link could not be established in this study, it is probable that it may contribute partly or wholly to higher *Staph aureus* UTI in male than female above 50 years.

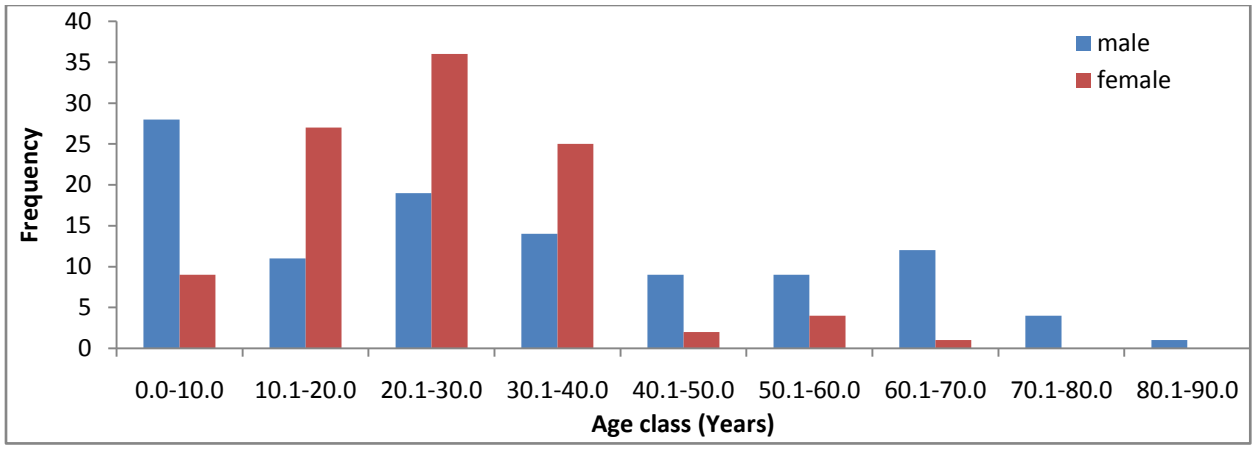

Figure 1: Age distribution of patients with *Staph aureus* UTI between 2005 and 2009

Quinolones activities against Uropathogenic *Staph aureus*

The activities of quinolones against urinary tract isolated pathogenic *Staph aureus* between 2005 and 2009 are as shown in Table 2. Both ciprofloxacin and ofloxacin recorded peak activity profile in 2005 but the 40.2% and 43.8% respectively lost in the activities of ofloxacin and pefloxacin between 2007 and 2009 were found significant ($P<0.005$ and $P<0.025$ respectively). The least activities were recorded with all the agents in 2009 except ciprofloxacin whose activities decreased by 10.8% between 2005 and 2007. The rapid losses of activities recorded with ofloxacin between 2005 to 2006 and 2008 to 2009 recorded no significant difference.Other quinolones similarly indicated lowest activities in 2009 but the overall activity of ofloxacin (85.6%) over ciprofloxacin (76.5%) indicated no significant difference. Some authors have similarly reported higher activities of ofloxacin over other quinolones like norfloxacin, pefloxacin and ciprofloxacin in Ibadan, western Nigeria[20].

The rapid fall in the activities in 2009 that affected all the fluoroquinolones except ciprofloxacin is worrisome although the area witnessed an upsurge in *Staph aureus* bacteria isolated in 2009 from several other infectious sites coinciding with periods of limited accessibility to medical care. Even though resistances to the fluoroquinoles are capable of evolving during the course of treatmentand many strains of *staph aureus* are known to exhibit resistance to the fluoroquinolones[21] but the relationship with this observed pattern is unknown and require further investigation on subsequent trends. This notwithstanding, there is continuous worry over the

future use of fluoroquinolone to treat UTI associated with *Staph aureus* or other infections caused by the pathogen in the region.

Table 2: Quinolones activities pattern against uropathogenic *S. aureus* between 2005 and 2009

Antibiotics	% activities of antibiotics against *S. aureus* (n = tested pathogens)					
	2005	2006	2007	2008	2009	Total (%)
Ciprofloxacin	91.3% n=23	70.4% n=54	79.5% n=44	73.2% n=56	78.3% n=23	76.5% n=200
Ofloxacin	100% n=10	75.7% n=37	95.2% n=21	94.4% n=18	50.0% n=4	85.6% n=90
Pefloxacin	93.3% n=15	87.5% n=24	93.8% n=16	66.7% n=36	50.0% n=4	80.0% n=95
Norfloxacin	31.6% n=19	54.0% n=50	37.8% n=37	43.4% n=53	25.0% n=20	41.9% n=179
Nalidixic acid	33.3% n=3	0.0% n=6	33.3% n=3	0.0% n=2	0.0% n=3	11.1% n=18

As for ciprofloxacin, its activity against *Staph aureus* decreases by 21% between 2005 and 2006 while changes occurring subsequently appeared insignificant (Table 2) but pefloxacin also appeared to have shown relatively insignificant decrease before 2007 followed by a steady increase that was significantly correlated with increase in year up to 2009 ($P<0.01$)(Fig 2). Norfloxacin activities were observed to significantly drop from 54% in 2006 to 25% in 2009 ($P<0.05$). These losses in activities are high when compared to the 9.8% decrease in some fluoroquinolones against *Staph aureus* associated UTI[22]. The result indicated a rapid loss in activities of all the fluoroquinolones except ciprofloxacin in 2009.

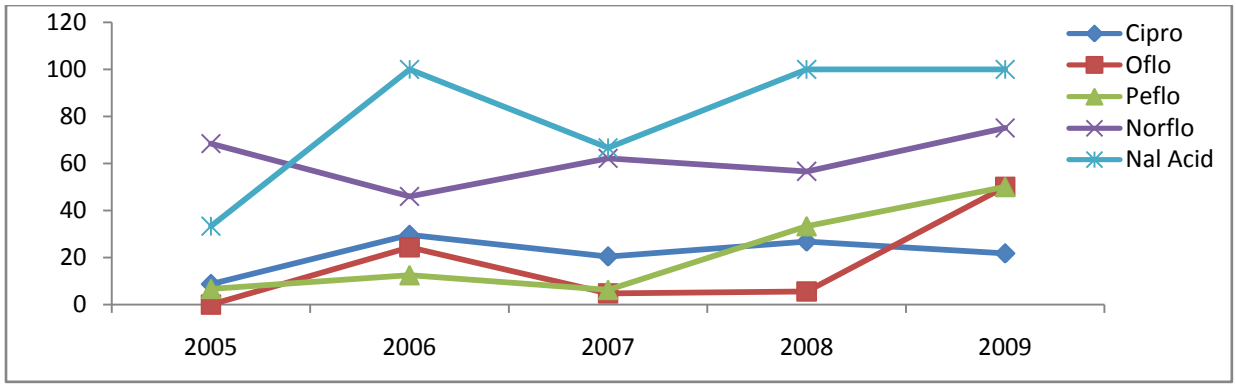

Figure 2: Trends in resistance pattern of quinolones to *Staph aureus* from 2005-2009

Key:Cipro=ciprofloxacin, Oflo=ofloxacin, peflo=pefloxacin, Norflo=norfloxacin, Nal Acid=Nalidixic acid

Figure 2 further showed that high resistance rates were recorded with most agents in 2006 but while trends in resistance growth pattern for norfloxacin was significantly correlated ($P<0.05$) between 2006 and 2009, that of pefloxacin and ofloxacin ($P<0.05$) were between 2007 and 2009.

When the total susceptibility and resistance of this pathogen was computed for each agent from 2005 to 2009 (Fig 3), the result showed that resistance rates have out-grown sensitivity rates for norfloxacin and nalidixic acid only but resistances of ciprofloxacin and pefloxacin are nearly similar. However, while the resistances of pefloxacin and ciprofloxacin are almost 20%; that of ofloxacin is fast approaching this point. It is worthy of note that some treatment guidelines recommend the use of alternative agent in the treatment of condition in regions where percentage resistance of certain agents has risen to 20% or beyond.

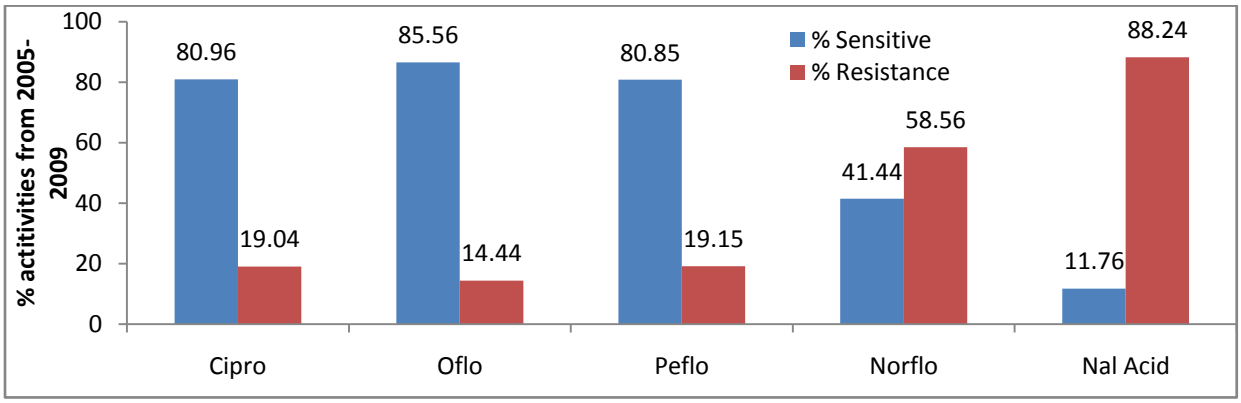

Figure 3: Percentage total susceptibility and Resistance of *Staph aureus* to each agent from 2005 to 2009

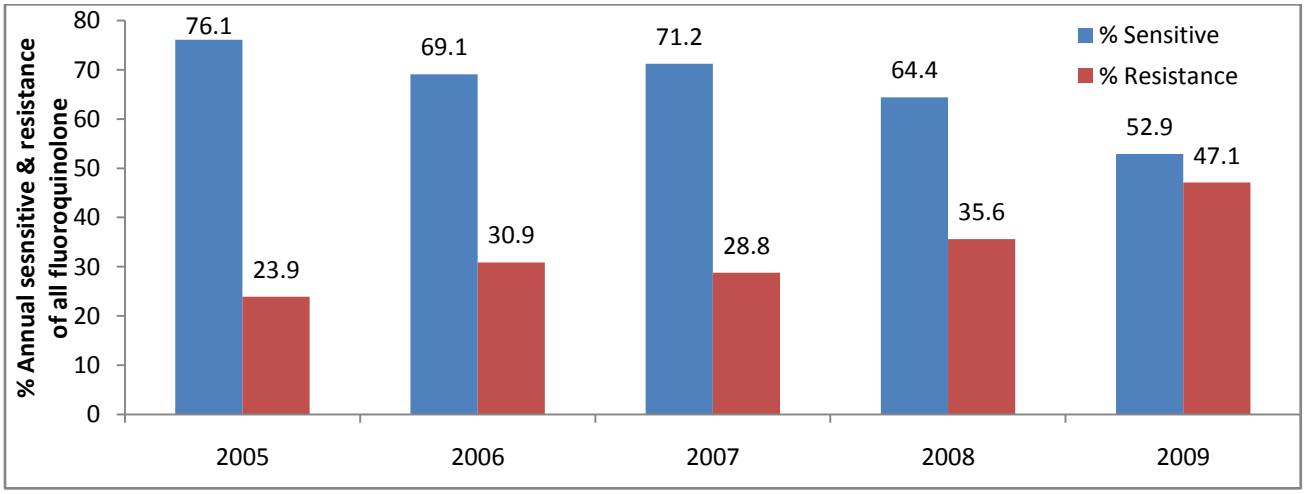

Figure 4: Annual sensitivity and resistance changes for all quinolones (exempting Nalidixic acid)

Similarly when the cumulative activities of all the quinolones (exempting nalidixic acid) were assessed each year for cumulative trends in their sensitivity and resistance (Fig 4), the overall resistance change of 23.9% in 2005 to 47.1% in 2009 (representing 23.2%) was found to be statistically significant ($P<0.01$) and also showed significant correlation ($P = 0.037$) during these periods. As observed, the worst affected year is 2009 where resistance rates approaches equal

proportion with sensitivity rates. These staggering increases (23.2%) within 5 years duration are of concern particularly when compared with reduction in fluoroquinolone resistances reported in other regions. For example, a reduction in resistance rates from 34.4% in 2007 to 24.6% in 2011 was reported in Canadian hospitals[23]. Similarly, Lafaurie and associates[24] reported a reduction in resistance growth of fluoroquinolones to methicillin resistance *Staph aureus* of 27% to 21% between 2000 and 2010. But in France, a significant reduction from 34.7% to 22.6% of MRSA to the fluoroquinolones was reported[25]. These results are sending signals of future limitations in the chemotherapeutic application of these agents in the zone.

Trends in Age related resistance pattern of the quinolones between 2005 and 2009

The result of trends in age related resistance pattern of the quinolones is as shown in Fig 5. The results showed that age related proportional resistance of *Staph aureus* increase (P=0.003) with ciprofloxacin up to 60 years and with norfloxacin between 10 to 50 years (P<0.01). In contrast however, ofloxacin showed age related proportional decrease in *Staph aureus* resistance between 10 to 50 years (P<0.01). Although the patterns observed with other agents are neither consistent nor correlated, but the peak ages of *Staph aureus* resistance for ciprofloxacin and nalidixic acid are 50 and 60 years respectively.

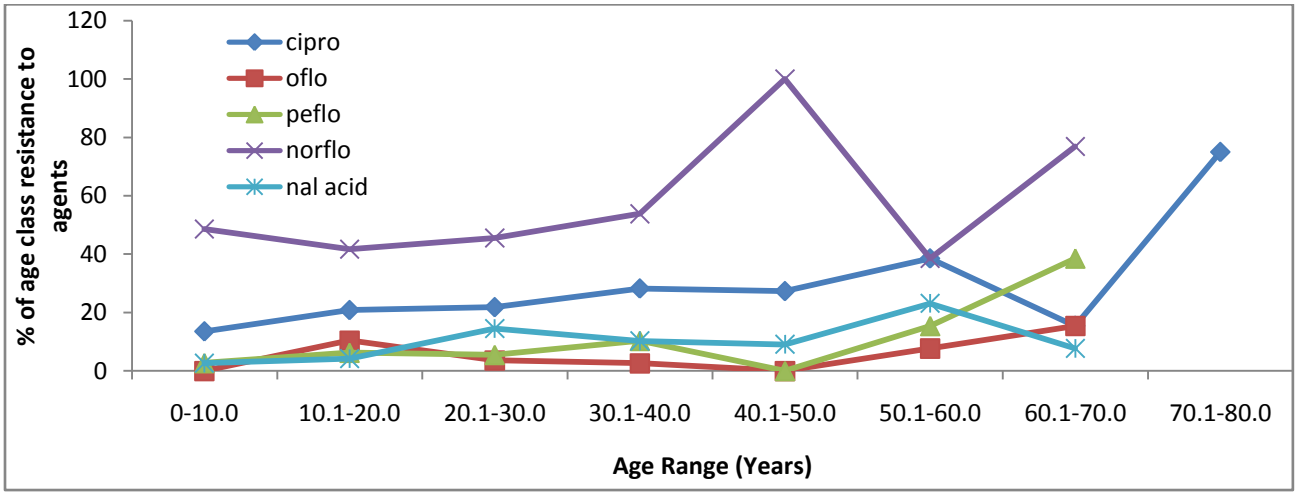

Figure 5: Percentage resistance pattern of the quinolones with respect to age

Inter-activities relation of the quinolones against *Staph aureus*

The high proportion of bacterial resistances to most other agents have resulted into increasing recommendations of the quinolone[26] but even among the quinolones, resistance between them is growing fast because the pathogenic bacteria are capable of rapidly spreading resistance factors against chemotherapeutic agents of similar or dissimilar class. For example, the activities of pefloxacin and ofloxacin against nalidixic acid-resistant *Staph aureus* urine isolates are nearly

uniform (Table 3) with no recorded significant difference (P>0.05) existing between them, but the higher activities of ciprofloxacin against norfloxacin-resistant and pefloxacin resistant *Staph aureus* (being 61% and 50% respectively) over ofloxacin (being 34.6% and 16.7% respectively) (Table 3) indicated statistical significant difference (P<0.005 and P<0.05 respectively) between them. Ciprofloxacin has similarly been previously reported to have superior activities against norfloxacin-resistant *Staph aureus* isolated from other infectious site in the region during a similar period although its values here are much lower when compared with the 74.5% and 75% respectively recorded with ciprofloxacin against the norfloxacin-resistant and pefloxacin resistant *Staph aureus* in that study[27]. The study of the inter-activities of the fluoroquinolone is relevant as it gives an overview of resistance pattern and guide clinicians with information on empiric use of these agents when treatment failures are observed or anticipated. The trio of pefloxacin, ciprofloxacin and ofloxacin may be suitable alternatives to nalidixic acid-resistant-UTI-*Staph aureus* while norfloxacin resistant-UTI-*Staph aureus* may be treated with ciprofloxacin alone in the region. Out of the 43 isolated UTI resistant *Staph aureus* to ciprofloxacin, only 13 (30.2%) and 12 (27.9%) may be successfully treated with pefloxacin and ofloxacin respectively (Table 3). In a similar vein, only 4 (each) of the 12 ofloxacin-resistant-UTI-*Staph aureus* may be treated with pefloxacin and ofloxacin respectively (Table 3). The clinical implication of these findings is that some of the ciprofloxacin and ofloxacin resistant *Staph aureus* associated UTI may have no suitable alternative among the quinolones currently in use in the region, suggesting that newer quinolones may be required.

Table 3: Comparison of Inter-activities of Quinolones to resistant uropathogenic *Staph aureus*

No. of Staph aureus resistance to	No. (%) of Resistance *Staph. aureus* that are sensitive to other quinolones									
	Nal. acid		Norfloxacin		Pefloxacin		Ciprofloxacin		Ofloxacin	
Nalidixic acid (n=16)	XXX		1	(6.3%)	10	(62.5%)	11	(68.8%)	10	(62.5%)
Norfloxacin (n=104)	0	(0.0%)	XXX		31	(29.8%)	64	(61.5%)	36	(34.6%)
Pefloxacin (n=18)	0	(0.0%)	4	(22.2%)	XXX		9	(50.0%)	3	(16.7%)
Ciprofloxacin (n=43)	0	(0.0%)	6	(14.0%)	13	(30.2%)	XXX		12	(27.9%)
Ofloxacin (n=12)	0	(0.0%)	0	(0.0%)	4	(33.3%)	4	(33.3%)	XXX	

Pattern of Co-fluoroquinolone Resistant *Staph aureus*

Co-fluoroquinolone-resistant *Staph aureus* isolates from urine specimens of both male and female patients increased from 8.7% in 2005 to 24.1% in 2009 (average = 25.1%) (Table 4).

Although this increase is not significant (P>0.05), but the rising patterns of co-resistance may constitute a complex mix and may possibly be connected with the poor enforcement of key regulations guiding the utilization of antibiotic in the country, health-care practice failures, increasing dependent on the quinolones or their overuse, patient's own characteristics factors and antibiotic resistance constitute a complex mix that is associated with the observed trend in this study. Although some factors like prevalence of fake and counterfeit drugs that contributed to resistance development in the past has been drastically reduced by the sustained effort of the country's drug regulatory agency, it is hopeful that when other aspects are given similar attention, problem of resistance will be minimized.

Table 4: Pattern of Multi-fluoroquinolone resistance to *Staph aureus***

Year	2005	2006	2007	2008	2009	Total
Multi-FQ resistance	2	21	8	16	6	53
Number tested	23	60	46	57	25	211
% multi-FQ resistance	8.7%	35.0%	17.4%	28.1%	24.0%	25.1%

**This is defined as resistance of pathogen to two or more of the 4 used fluoroquinolone (excluding nalidixic acid)

CONCLUSION

From this 5 years surveyed periods of antibacterial activities against *Staph aureus* associated UTI, resistant rates were observed to have out-grown sensitivity rates with norfloxacin and nalidixic acid while the cumulative resistance rate has almost reached 20% each for ciprofloxacin and pefloxacin compared to 14% recorded with ofloxacin. All agents recorded high activities loss in 2009

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