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Prevalence and Antimicrobial Susceptibility Pattern of *Neisseria gonorrhoeae* in Kumasi, Ghana

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Authors' contributions

This work was carried out with the collaboration of all authors. Authors DOA and RO designed the study, performed the statistical analysis, wrote the protocol and first draft of the manuscript. Authors CKA, AB, EAA and FAA managed the analyses of the study and edited the final manuscript for intellectual content. Authors MKT and SBA managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Background: In most African countries, including Ghana, treatment of the *Neisseria gonorrhoeae* infection is based on syndromic management owing to lack of laboratory equipment and resources in primary care facilities where most patients first visit.
Aim: The aim of this study was to determine the prevalence of *Neisseria gonorrhoeae* and evaluate its susceptibility pattern to standard antimicrobials used for empirical treatment of the infection in patients that attended Ellolab Diagnostic Centre at Kumasi from November 2014 to July 2017.
Methodology: Four hundred and twenty-seven (427) clinical specimens from suspected patients were cultured on chocolate agar. Positive cultures were tested for resistance against twelve

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antimicrobial agents using the disk diffusion method.
Results: *N. gonorrhoeae* was identified in 117 of the clinical samples. This represents an overall prevalence of 27.4%, with 39.3% and 60.7% occurring in males and females respectively. Maximum cases were observed in the 16-24 age group. Interestingly, the organism showed high levels of resistance to the nationally recommended drugs for first-line empirical treatment; Ceftriaxone 85.5%, Ciprofloxacin 46.2% and Amikacin 1.7%.
Conclusion: The local susceptibility trends of *N. gonorrhoeae* need to be monitored closely in order to establish appropriate local empirical therapy.

Keywords: Neisseria gonorrhoeae; antimicrobial agents; sexually transmitted infection; prevalence.

ABBREVIATIONS

STI : Sexually transmitted infection;
PID : Pelvic inflammatory disease;
MDR : Multidrug-resistant;
ESC : Extended-spectrum cephalosporin;
PBP : Penicillin binding protein.

1. INTRODUCTION

Gonorrhea is the second most common bacterial sexually transmitted infection (STI) and is caused by *Neisseria gonorrhoeae*, a gram negative intracellular diplococci [1]. This infection usually affects various mucosal sites including pharynx, and conjunctivae, lower genital tract such as urethra, cervix, Bartholin's glands, and Skene's glands as well as the anorectal canal [2]. It could spread further from the lower genital tract to the upper genital tract, uterine tubes, and peritoneal cavity as well as other important systemic sites [3]. Humans happen to be the only natural host [4]. *Neisseria gonorrhoeae* has gained global attention over the years because of therapy failures due to increasing multi-drug resistance [5].

In most African countries, including Ghana, treatment of the infection is based on syndromic management due to lack of laboratory equipment and resources in primary health care facilities which serve as the first point of call for people suspected of the infection [6]. Treatment failure could result in the development of serious complications [7] such as developing of pelvic inflammatory disease (PID), urethritis, cervicitis and Fitz-Hugh-Curtis syndrome in women [8,9]. Untreated pregnant women can even pass this infection on to their babies during delivery and can result in neonatal conjunctivitis which when left untreated, which may lead to blindness [10]. Infected males may present with symptoms that appear two to five days post infection and is often accompanied by painful sensation when urinating and purulent discharge from the urethra. Untreated gonorrhea in men can result in epididymitis and infertility [11,12]. Treatment failure as a result of antimicrobial resistance has become global health nemesis due to widespread multi-drug resistance [13]. Unfortunately, the emergence of multi-drug-resistant (MDR) *N. gonorrheae* strains in Africa is met with under-resourced STI control programmes, as funds and technical expertise are being directed to other public health priorities, such as HIV/AIDS, hepatitis, and tuberculosis [14].

Antimicrobial therapy forms a significant part of treatment in Ghana. In the case of gonorrhea and other STIs, most physicians tend to rely on empirical treatment due to lack of appropriate laboratory facilities for culture and sensitivity testing of the bacteria, coupled with the fact that the patient bears the cost of the laboratory services, and in quite a number of instances, culture and sensitivity tests may not be requested at all. The use of antimicrobials is very rift among the general populace. This is attributable to easy access to over-the-counter drugs, physicians prescribing antimicrobials when they are not needed and/or prescribing for outpatients, the wrong antimicrobials such as the extended spectrum agents for the treatment of viral, parasitic and other non-bacterial pathogens without ordering for laboratory tests to confirm the etiology of the disease [15]. Others incorporate antimicrobials to traditional or herbal drugs or concoction for remedy. All these have contributed to the development of resistant strains of the bacteria [16]. Although gonococcal resistance has been reported worldwide, surveillance data in most African countries are few or absent which allow the infection to go unnoticed. This study aimed at bringing to the fore relevant data and information to help monitor and evaluate the rapid pattern of change of antimicrobial susceptibility and resistance because of their implication for public health.

2. MATERIALS AND METHODS

2.1 Area of Study

The study was carried out at Ellolab Diagnostic Centre, Kumasi Ghana, a health facility which also serves as a referral centre for many physicians in the Kumasi metropolis and beyond. Clinical specimens were collected from November 2014 to July 2017.

2.2 Specimen Collection and Processing

Clinical symptoms like dysuria, urethritis and painful urination, penile and vaginal discharge of whitish colouration and characteristic odour and appearance (thick, viscous, mucoid) were routinely inquired to suspect the infection. Urethral (male), vaginal (female) discharges were collected from patients early in the morning under strict aseptic conditions. A sterile swab was used to collect the specimen and subsequently inoculated on chocolate agar. The inocula and agar were then incubated at $37^{O}C$ enriched with CO_2 for 24-36 hours. Positive bacterial growth was established and Gram-stained, and subsequently examined under a light microscope (Olympus CX 22, Japan) for the presence of Gram-negative diplococci. Relevant biochemical tests were carried out to confirm the culture and microscopic results. The disc diffusion antimicrobial sensitivity test was subsequently done for the positive cultures using antimicrobial sensitivity discs on Mueller Hinton agar (Oxoid Ltd). Antimicrobial discs tested against the positive isolates were ampicillin (10 U), cefuroxime (30 µg), ceftriaxone (30 µg), tetracycline (30 µg), erythromycin (15 µg), amikacin (10 µg), gentamicin (15 µg), ciprofloxacin (5 µg), cefotaxime (30 µg), levofloxacin (25 µg), cotrimoxazole, chloramphenicol (30 µg) (Oxoid Ltd). *Neisseria gonorrhoeae* strain ATCC 49226 was used as a control. Antimicrobial susceptibility results were interpreted as susceptible >20, intermediate 15-19, and resistant ≤ 14 using the standard table supplied by the Clinical and Laboratory Standards Institute [17]. There were no ethical matters concerned with this study, as results from routine laboratory diagnosis of clinical samples constituted the data for analysis; no particular identifiable group of patients were involved and their individual identities could not be traced.

2.3 Statistical Analysis

Data were analyzed using statistical package for social sciences (SPSS) version 21. The data were analyzed using Chi-square ($\chi 2$) and proportion tests. Chi-square test was applied to test whether significant association exists between *Neisseria* infection and variables under study. P values < 0.05 were considered statistically significant. Mantel-Haenzel common odds ratio was used to estimate the resistance among gender.

3. RESULTS

3.1 Demographic Characteristics

A total of 427 cases were evaluated for gonorrheae at Ellolab Diagnostic Centre. Minimum age, maximum age and mean age were 16, 71 and 30 respectively, with standard deviation (SD) being 9.56. Out of the 427 cases, 117 suspected patients were confirmed positive for gonococcal infection while 310 were negative. Of the 117 positive cases, the minimum age was 18 and the maximum age was 63. Mean age and SD were 31 and 10.137 respectively.

3.2 Prevalence of *N. gonorrhoeae*

The overall prevalence of *N. gonorrhoeae* infection was 27.4% (Table 1). Proportion test showed that this value was significantly higher ($p<0.05$) than the previously recorded prevalent rates for Ghana, 0.6%. Though the prevalence in females (28.3%) was found to be higher, it was not significantly different from that of males (26.1%) [$z=1.11$, $p=0.291$, $p>0.05$]. The age group 16-24 recorded the highest frequency of cases whereas the least came from age group 45 and above cohort (Table 2). Out of the 117 positive cases of *N. gonorrhoeae* infection, 46 (39.3%) were males whereas 71 (60.7%) were females (Table 2).

Table 1. Prevalence of *N. gonorrhoeae* infection among the gender

	n (total)	Prevalence	p-value
Male	46 (176)	26.1%	>0.005
Female	71(251)	28.3%	
Total	117(427)	27.4%	

3.3 Antimicrobial Susceptibility Test

The susceptibility patterns of the gonococcal isolates (n=117) were tested against 12

antimicrobial agents by the agar disc diffusion method. WHO recommends disuse of antimicrobial agent if the resistance threshold reaches 0.05. The highest resistance was observed for erythromycin and tetracycline at 99.1% and 94.0% respectively whereas the highest susceptibility of 97.6% was recorded for Amikacin (Table 3). Increased resistance to the national recommended first-line antimicrobials ciprofloxacin (46.2%) and ceftriaxone (85.5%) was observed. Strikingly, 9 out of the 12 drugs used recorded resistance greater than 50%.

3.4 Resistance Pattern of the National Protocol Drugs

Resistance pattern among the sexes on the two drugs recommended in the national protocol (ceftriaxone and ciprofloxacin), and the proposed alternative drug gentamicin is presented in Table 4. As indicated, males and females demonstrated significant difference in their resistance patterns to ciprofloxacin but exhibited no significant difference on ceftriaxone and gentamicin. The proportion of resistance of gentamicin to ciprofloxacin and ceftriaxone, and ceftriaxone to ciprofloxacin revealed significant differences (Table 5).

Table 2. Distribution of *N. gonorrhoeae* among the age group

Age group	Male n (%)	Female n (%)	Total
16-24	13(11.1%)	26(22.2)	39
25-34	16(13.7%)	21(17.9%)	37
35-44	13(11.1%)	18(15.4%)	31
45 and above	4(3.4%)	6(5.1%)	10

Table 3. Antimicrobial susceptibility of *N. gonorrhoeae* to standard antimicrobials

Antibiotic	Susceptible n (%)	Moderate n (%)	Resistant n (%)
Erythromycin	0(0)	1(0.9)	116(99.1)
Tetracycline	0(0)	7(6.0)	110(94.0)
Amikacin	114(97.4)	1(0.9)	2(1.7)
Chloramphenicol	2(1.7)	16(13.7)	99(84.6)
Cefuroxime	3(2.6)	7(6.0)	107(91.4)
Ceftriaxone	7(6.0)	10(8.5)	100(85.5)
Ciprofloxacin	30(25.6)	33(28.2)	54(46.2)
Gentamicin	24(20.5)	61(52.1)	32(27.4)
Cefotaxime	3(2.6)	8(6.8)	106(90.6)
Ampicillin	5(4.3)	4(3.4)	108(92.3)
Cotrimoxazole	1(0.9)	11(9.4)	105(89.7)
Levofloxacin	12(10.2)	29(24.8)	76(65.0)

Table 4. Mantel-Haenzel common odds ratio estimate of resistance among gender

M-H common odds ratio					
Gender	Antibiotic	Estimate	95% CI		p-value
			Lower limit	Upper limit	
Male /Female	Ceftriaxone	0.600	0.196	1.832	0.369
	Ciprofloxacin	3.124	1.425*	6.848*	0.004*
	Gentamicin	0.928	0.405	2.126	0.859

*Ho: there is no association between the prevalence of N. gonorrheae and occurrence of resistance among the gender. Hi: there is a relationship between the two variables. *=statistically significant*

Table 5. Proportion of resistance to Gentamicin and Ciprofloxacin plus Ceftriaxone, and Ceftriaxone to Ciprofloxacin

Antibiotics		Estimate for difference	p-value
Gentamicin	Ciprofloxacin	-0.188	0.002*
	Ceftriaxone	-0.581	0.000*
Ceftriaxone	Ciprofloxacin	0.393	0.000*

**=statistically significant*

4. DISCUSSION

Gonococcal infection is usually transmitted *via* sexual intercourse, and a male has a 22-50% risk of acquiring the infection after a single exposure to an infected female, whereas the risk to a female after similar exposure to an infected male is 60-70% and increases to 100% with more than two exposures [18]. Due to its asymptomatic nature in women, it is believed that the actual prevalence is likely to be twice what is usually reported [19,20]. Comparing the available methods of diagnosis, microscopic identification of intracellular Gram-negative diplococci has a relatively high sensitivity and specificity for the diagnosis of gonorrhea in men with a sensitivity > 90% in symptomatic men, a sensitivity of 50-75% in asymptomatic men, and a specificity of > 90% for both symptomatic and asymptomatic female [21,22]. Bacterial culture for *N. gonorrhoeae* has a test specificity of more than 99% [21] and a sensitivity of 85-95% for urethral and endocervical infection [23]. Unlike the nucleic acid amplification test (NAATs), it allows for antimicrobial susceptibility testing. NAAT specificity (96.1 to 99.85%) is slightly lower than bacterial culture, usually resulting in slightly higher risk of false positive results [23,24]. These factors informed the decision to use both microscopy and bacterial culture methods of diagnosis in this study.

The overall prevalence of *N. gonorrheae* in this study was significantly high compared to earlier studies conducted in Ghana which reported a prevalence of 0.6%; [25] 6.0% by culture and 18% by NAAT ($p < 0.05$) [26]. The present study thus underscores the progressive prevalence of the bacteria. The relatively high prevalence in this study possibly reflects the true state of gonorrheae in Ghana, considering the relatively longer duration of this study (November 2014- July 2017). The prevalence of *N. gonorrheae* reported in this study was however, lower than what was reported in Port Elizabeth, South Africa, where 35 out of 80 swab samples were found to be positive for *N. gonorrheae* infection [27].

Maximum number of cases in this study were observed among the age group 16-24. This may be attributed to the fact that this cohort is sexually active and easily engage in casual and unsafe sex, and lack the knowledge to detect early disease symptoms. Whereas other researchers in Ghana [28] identified male gender as a significant predictor for gonorrheae in their study, in this current study, the highest prevalence was recorded in females. There also was no significant statistical association between gender and prevalence of the bacteria nor were there significant differences between the prevalence rates among males and females. The high prevalence in females may be due to the asymptomatic manifestations in women and also a higher chance of seeking medication or other treatment by men compared to women since symptoms manifest early in males [29]. This may be supported by the fact that the resistance to ciprofloxacin (which is orally administered, easy to access over the counter and routinely prescribed by clinicians) was significant in males than females in our study. There was no association in the observed prevalence and resistance to ceftriaxone and gentamicin because both are administered intramuscularlly and thus restricted to hospital use, confirming the fact that, unregulated usage of a particular antimicrobial agent could lead to antimicrobial resistance in the agent. [29]

All the isolates were resistant to at least three of the antimicrobial agents used, representing a multi-drug resistance of 100%. The high level of resistance to ampicillin, tetracycline and erythromycin observed in this study has also been reported elsewhere [27,28,30-32]. Erythromycin and tetracycline are the recommended drugs for the treatment of chlamydial infections, [33] and most cases of gonorrheae also present with chlamydial co-infection. However, since syndromic diagnosis does not differentiate between gonorrheae and chlamydial infection, patients with gonococcal infections are exposed to this group of drugs, [27,34] because, the national standard protocol for the treatment of chlamydia requires that these drugs are administered for 7 days [35]. This eventually exerts selective pressure on strains of *N. gonorrhoeae* that leads to mutations in key genes [27,32]. The high level of resistance to penicillin and penicillin-derivatives such as ampicillin and tetracycline in the last two decades has made these antimicrobial agents obsolete as a treatment option for gonococcal infection [36]. Therefore, the high level of resistance to these drugs recorded in this study was expected.

Low level of susceptibility to fluoroquinolones was quite similar to another study in Ethiopia [31]. In addition, the resistance to Ciprofloxacin observed in the study confirms an earlier one carried out in Ghana where all the isolates demonstrated resistant to ciprofloxacin [28].

Remarkably, resistance to ciprofloxacin was significantly associated with gender (CI =95%, p-value=0.025, *OR*=2.933, CI=1.146-7.507). This is of great concern because ciprofloxacin is recommended in the national protocol as first-line treatment option. Reports from South Africa indicate that ciprofloxacin is no longer used to treat presumptive gonococcal infections in the country [37]. Additionally, *N. gonorrhoeae* resistance to ciprofloxacin greater than 50% has been reported in other parts of the world, [27,30,38] suggesting a widespread resistance.

The efficiency of extended-spectrum cephalosporins (ESCs) for the treatment of gonococcal infections has been described by many studies [28,31,32,39] yet, recent studies have reported a continuing decreased susceptibility to ceftriaxone and cefixime [40]. This study also recorded a high level of resistance to this class of drugs, confirming this alarming development. Mutant mosaic penicillin binding protein (PBP) 2 alleles have been noted to be the elemental resistance determinant to ESCs [41]. A non-mosaic PBP IX allele containing P551L substation has also been associated with increased MICs for ESCs [40]. This overwhelming resistant rate may be due to the sporadic, indiscriminate and intense prescription and use of these drugs, easy availability outside the hospitals, and many antimicrobials over the counter for self-medication.

The aminoglycosides are both bacteriostatic and bactericidal agents that exert their activity by irreversibly binding to the 30S ribosomal proteins thereby inhibiting bacterial protein synthesis [42]. Two of this class of drugs used in this study were amikacin and gentamicin. Amikacin recorded the least resistance and compares favorably with WHO threshold of 5%. The possible explanation is that the drug is expensive and not easily available outside the hospitals. This drug may be novel for treatment or used as second line treatment options for gonorrheae. The only drawback is the fact that it is very expensive and associated with high toxicity. The number of isolates susceptible to gentamicin was higher than ceftriaxone but same as ciprofloxacin. Nevertheless, resistance to gentamicin was lower over the study period compared to the ciprofloxacin and ceftriaxone. These two drugs are very important because they are the national protocol drug for gonococcal infection. Statistically, significant differences were observed in the resistance between gentamicin and ceftriaxone (z value=11.06, $p < 0.05$), and gentamicin and ciprofloxacin (z value =3.04, $p<0.05$). Gonococci isolates have been observed to have a high susceptibility to gentamicin *in vivo* in Malawi, with a clinical cure rates of approximately 95% when used in combination with doxycycline [41,43,44]. Hence, possibly, a little increase in the dosage may produce a greater susceptibility in the bacteria when used as a single dose therapy or when combined with doxycycline, and therefore might exhibit similar potency as Amikacin with few side effects and cost. To this end, gentamicin can be used in place of the national protocol drugs ciprofloxacin and ceftriaxone which are fast losing their potency against *N. gonorrhoeae*.

5. CONCLUSION

This study has revealed a relatively high prevalence for gonococcal infection in presumptive patients in Kumasi, Ghana. Furthermore, the age group 16-24 and females were the most affected cohorts and therefore could be considered as high-risk groups. The recovered isolates demonstrated high resistance to the available antimicrobial agents recommended in the national protocol for empirical treatment. Notwithstanding, more than half of the isolates were either susceptible or slightly sensitive to gentamicin. Gentamicin is therefore the appropriate agent to be used as a substitute to the nationally recommended protocol drugs, since the most potent drug amikacin is usually associated with high level of toxicity. Additionally, unless antimicrobial susceptibility test is carried out, the following drugs ampicillin, tetracycline, erythromycin, chloramphenicol, levofloxacin, cotrimoxazole, cefuroxime, ceftriaxone, cefotaxime, and ciprofloxacin should not be used for the treatment of gonococcal infection in Ghana.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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