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Identification and Antibiotic Resistance Profile of Uropathogenic Bacteria from Sexually Active Women with Bacterial Vaginosis

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Abstract

Background: Urinary tract infections (UTIs) in women with bacterial vaginosis (BV) continue to pose tremendous health concerns and require appropriate use of antibiotics for effective case management. This study determined the prevalence, etiology and antibiotic resistance profile of uropathogenic bacteria isolated from sexually active women with BV in Lagos Nigeria. **Method:** A total of 258 sexually active women presenting with gynaecological complaints at the maternal and child unit of twenty Primary Health Care Centres in Lagos Nigeria from May 2017 to March 2018 were consecutively enrolled with consent. Bacterial vaginosis was diagnosed based on Amsel criteria. Midstream urine samples were collected aseptically, analyzed for bacterial pathogens and antibiotic susceptibility using standard microbiological methods. **Results:** BV was diagnosed in 184 (71.3%) with 69.2% also having UTI. Ninety four (36.4%) had UTI predominantly caused by Gram negative bacteria (96.8%). The organisms isolated were *Escherichia coli* 79 (84.0%), *Klebsiella pneumoniae* 5 (5.3%), *Pseudomonas aeruginosa* 4 (4.3%), *Proteus mirabilis* 3 (3.2%) and *Staphylococcus saprophyticus* 3 (3.2%). The pathogens elicited high resistance (66.7% - 100%) to tetracycline, amoxicillin-clavulanic acid, nitrofurantoin and cephalosporins, and moderate resistance (50%) to ofloxacin by *P. aeruginosa* strains. The isolates were susceptible (100%) to piperacillin-tazobactam and meropenem. Multi-drug resistance (MDR) was

observed among 97.8% of the bacteria isolated. **Conclusion:** Findings from this study indicate high occurrence of UTI caused by MDR pathogens among sexually active women with BV with emerging evidence of poor clinical utility of nitrofurantoin and other commonly used first-line antibiotics against UTI. Further studies on non-bacterial aetiology of BV, molecular characterization of *S. saprophyticus* and Gram Negative Bacteria UTI are recommended.

Keywords

Urinary Pathogens, Antibiotics Susceptibility, Bacterial Vaginosis, Women

1. Introduction

Bacterial vaginosis (BV) is the most common vaginal infection found in women of reproductive age and is estimated to occur in 5% to 70% of women [1] [2]. It is the commonest cause of unpleasant vaginal odour and discharge in women of reproductive age [3] [4]. It increases the risk of acquiring Human Immunodeficiency Virus and other sexually transmitted infections such as gonorrhoea, trichomoniasis, miscarriage, preterm labour, preterm delivery and postpartum complications such as endometritis and wound infections in pregnant women [5] [6]. BV is caused by a reduction in hydrogen peroxide–producing strains of lactobacilli in the vaginal flora. This leads to an elevated vaginal pH and increased levels of proteolytic enzymes (e.g., sialidase), organic acids, and volatile amines. This change in pH allows an overgrowth of multiple types of anaerobic, mycoplasmic, and Gram-negative bacteria. Women with a dominant population of vaginal lactobacilli are at a lower risk of UTI compared to women with more diverse microbiota, consisting of Gram negative anaerobes, Actinobacteria, and other Firmicutes. Also, women with BV have 2.2- to 13.7-fold increased risk of UTI [7] [8] [9].

Urinary tract infections (UTIs) are among the most commonly encountered bacterial infections in primary care and also represent the most common antibiotic-resistant infections in primary care [10] [11] leading to repeat consultations and problems for clinicians in selecting the right treatments. Globally, there are about 150 million individuals who are diagnosed with UTI [12]. UTIs have been associated with cystitis, pyelonephritis with sepsis, pre-term birth [13] [14] [15]. Women are more susceptible to UTI than men [16] [17] due to short urethra, absence of prostatic secretion, pregnancy and ease of contamination of the urinary tract with faecal flora [18]. *Escherichia coli* is the most prevalent uropathogen in patient with UTI, both in the community and hospitals [19] [20] [21]. However, other bacterial uropathogens implicated in UTI in women include *K. pneumoniae*, *P. aeruginosa*, *Proteus* spp. [22] [23] [24]. Of great concern is the recurrence of UTI among sexually active women despite treatment [25] [26]. This recurrence has been linked to co-infection caused by BV [27] [28] [29] [30] [31].

Antibiotics are considered the most effective method of treatment for bacterial infections but their indiscriminate, prolonged, empirical or incorrect usage has contributed greatly to the development of resistant strains [32] [33]. Resistance rate of uropathogens to commonly prescribed antibiotics has increased globally [34]. The multiple aetiologic agents, rising resistance to antibiotics, limiting treatment option can result in treatment failures and increased cost of health care [35]. There is limited data on the co-occurrence of UTI and BV among sexually active women in Nigeria. This study was carried out to determine the prevalence, antibiotic resistance of urinary tract pathogens among sexually active women with bacterial vaginosis. The information obtained in this study will be used for effective management of UTI among this group of women.

2. Materials and Methods

2.1. Study Design

This is a cross sectional study carried out from May 2017 to March 2018 among 258 sexually active women, aged 18 to 49 years that presented with gynaecological complaints at twenty flagship Primary Health Care centres in each of the 20 local government areas of Lagos State. This study involved BV screening, collection of urine samples, urinary culture, identification of uropathogens and antibiotic susceptibility testing.

2.2. Ethical Approval and Informed Consent

The study was approved by Nigerian Institute of Medical Research Institutional Review Board (IRB/15/306) and permission was obtained from Lagos State Primary Health Care Board. Random sampling was used in selection of participants and the patients were enrolled by convenience. Women of child bearing age from 18 to 49 years who engaged in regular heterosexual sex and had not taken antibiotics in the last one month were included in the study. Written informed consent was given by all participants. A pretested structured questionnaire was used to obtain socio-demographic data and reproductive history of sexually transmitted infections. Symptoms were extracted from case record forms of the participants.

2.3. Sample Collection, Culture and Identification

One High Vaginal Swab (HVS) was collected with sterile swab stick using sterile disposable speculum. Participants were given well-labelled sterile universal containers to collect 5 - 10 ml of mid-stream urine. The specimens were transported to Clinical Diagnostic Laboratory Nigerian Institute of Medical Research for processing. Wet preparations from HVS samples were prepared in physiological saline and examined by light microscopy (×10, ×40 objectives). Amsel criteria were used for the diagnosis of BV. At least three of the four criteria were considered positive—presence of clue cells in wet mount (epithelial cells that appear to be coated in bacteria), vaginal pH > 4.5, release of a fishy odour on addition of

10% potassium hydroxide (positive "whiff" test) and a thin homogenous discharge. The urine specimens were cultured on MacConkey, Cysteine Lactose Electrolyte Deficient and Blood agar using standard sterile bacteriological loop (0.01 ml). The plates were incubated at 37˚C for 24 hours. Colonies were counted and UTI was diagnosed based on significant colony count of $\geq 10^5$ CFU/ml for the organisms.

Gram staining technique was used to differentiate the isolates into Gram-positive and Gram-negative by observing whether they were blue-black or red-stained, respectively [36]. Gram-positive isolates were cultured on mannitol salt agar (MSA); colonies that did not ferment mannitol (pink colonies), did not exhibit coagulase, deoxyribonuclease (DNase) activity and were resistant to novobiocin were considered to be *S. saprophyticus*. The Gram-negative isolates were characterized using standard biochemical tests which include oxidase, kligler iron agar (KIA), citrate utilization, indole and urease [37].

2.4. Antibiotic Susceptibility Test

Antibiotic susceptibility testing was conducted on Muller Hinton agar using a standard disc diffusion method according to CLSI guidelines [38]. The antibiotic discs used for tests were Amoxicillin-clavulanic acid (30 µg), Nitrofurantoin (300 µg), Gentamicin (10 µg), Ofloxacin (5 µg), Ceftazidime (30 µg), Tetracycline (30 µg), Cefuroxime (30 µg), Cefixime (5 µg), Erythromycin (5 µg), and Cloxacillin (5 µg), Vancomycin (30 µg), Piperacillin-Tazobactam (110 µg), Meropenem (10 µg). *E. coli* ATCC 25922 and *Staph aureus* ATCC 25923 were used as control.

2.5. Statistical Analysis

Data from questionnaire and laboratory investigation was analyzed using SPSS version 23. Descriptive statistics was used to summarize the data. Chi-square was used to assess differences in the proportions of BV positive and negative patients.

3. Results

The sociodemographic characteristics and reproductive history of the sexually active women who participated in the study are summarized in **Table 1**. More than seventy percent (76.2%) of the women in 40 - 49 years age group had BV followed by 73.8% and 72.4% from 20 - 29 and 30 - 39 years age group respectively. Majority (67.4%) of the women were aged 30 - 49 years, civil servants (42.6%), lived in the urban area (82.6%), had low income (58.1%), completed tertiary education (56.6%) and had more than one life time sexual partner (66.7%). Further analysis showed that 108 (41.9%) of the women had first sexual activity at age 21 - 25 years. There was significant association of BV with sexual debut less than 10 years ($p = 0.02$). Only 63 (24.4%) of the participants were pregnant at enrolment into the study and 38 (60.3%) of them had BV compared to 25 (39.7%) without BV ($p = 0.013$). Majority (67.4%) had vaginal delivery of

Table 1. Sociodemographic characteristics and reproductive history of sexually active women with and without bacterial vaginosis.

Variables	Number of Participants	Bacterial vaginosis		Chi square test P value
		Pos n (%)	Neg n (%)	
Age group				
<19	21 (8.1)	11 (52.4)	10 (47.6)	
20 - 29	42 (16.3)	31 (73.8)	11 (26.2)	
30 - 39	174 (67.4)	126 (72.4)	48 (27.6)	
40 - 49	21 (8.1)	16 (76.2)	5 (23.8)	0.245
Marital status				
Single	30 (11.6)	23 (76.7)	7 (23.3)	
Married	228 (88.4)	161 (70.6)	67 (29.4)	0.491
Level of education				
None	4 (1.6)	4 (100)	0 (0.0)	
Primary	2 (0.8)	2 (100)	0 (0.0)	
Secondary	106 (41.1)	78 (73.6)	28 (26.4)	0.18
Tertiary	146 (56.6)	100 (68.5)	46 (31.5)	
Religion				
Christianity	201 (77.9)	146 (72.9)	55 (27.4)	
Islam	56 (21.7)	37 (66.1)	19 (33.9)	0.337
Occupation				
Trader	64 (24.8)	51 (79.7)	13 (20.3)	
Civil servant	110 (42.6)	80 (72.7)	30 (27.3)	0.117
Self employed	43 (16.7)	29 (67.4)	14 (32.5)	
Unemployed	41 (15.9)	24 (58.5)	17 (41.5)	
Residence				
Rural	45 (17.4)	34 (75.6)	11 (24.4)	
Urban	213 (82.6)	150 (70.4)	63 (29.6)	0.489
Monthly Income				
No income	21 (8.1)	14 (66.7)	7 (33.3)	0.792
Low (<$60)	150 (58.1)	106 (70.7)	44 (29.3)	
Middle ($60 - $600)	87 (33.7)	64 (73.6)	23 (26.4)	
Reproductive history				
Pregnant				
Never pregnant	63 (24.4)	41 (65.1)	22 (34.9)	0.208
Pregnant before	195 (75.6)	143 (73.3)	52 (26.7)	

Continued

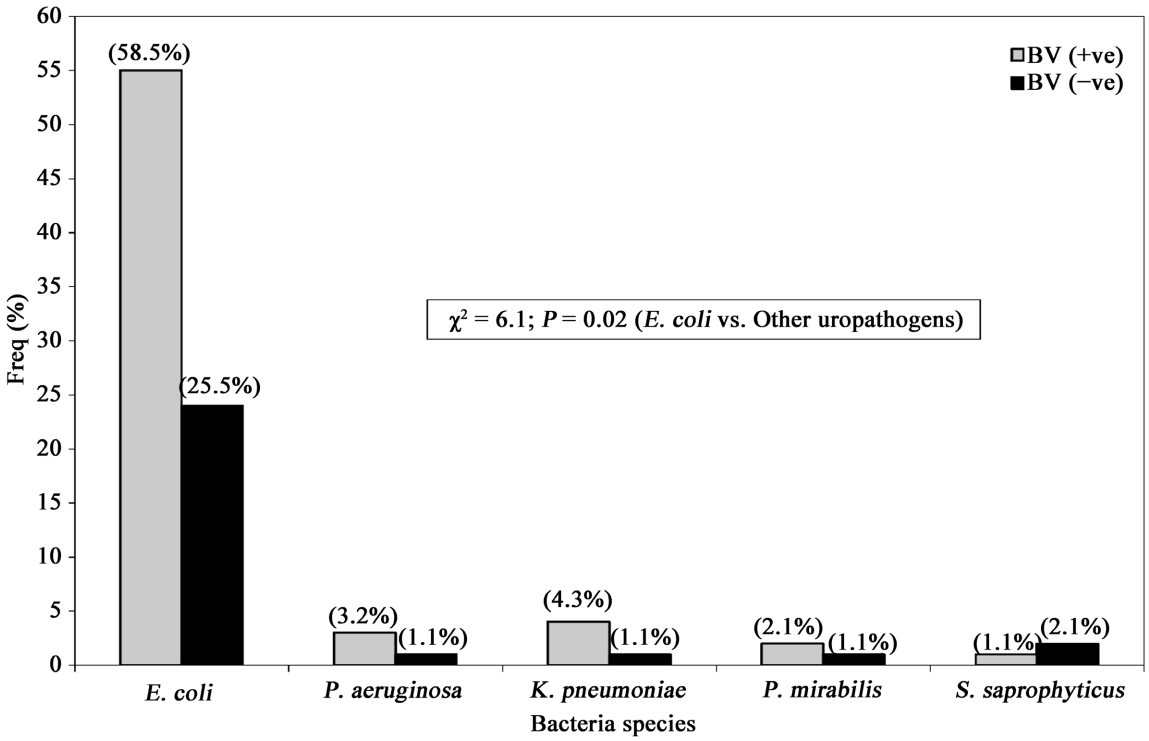
Pregnant now				
Yes	63 (24.4)	38 (60.3)	25 (39.7)	0.013
No	108 (41.9)	87 (80.6)	21 (19.4)	
Not sure	87 (33.7)	59 (67.8)	28 (32.2)	
Life birth				
None	21 (8.1)	15 (71.4)	6 (28.6)	
≥1 life birth	174 (67.4)	128 (73.6)	46 (26.4)	0.834
Method of child delivery				
Caesarian section	84 (32.6)	56 (66.7)	28 (33.3)	
Vaginal delivery	174 (67.4)	128 (73.6)	46 (26.4)	0.251
Temination of pregnancy				
Abortion	43 (16.7)	30 (69.8)	13 (30.2)	0.056
Miscarriage	22 (8.5)	20 (90.9)	2 (9.1)	
Number of life time sexual partners				
1	86 (33.3)	58 (67.4)	28 (32.6)	
2 - 5	172 (66.7)	126 (73.3)	46 (26.7)	0.33
Age at sexual debut (years)				
<10	1 (0.4)	1 (100)	0 (0.0)	0.02
11 - 15	21 (8.1)	19 (90.4)	2 (9.5)	
16 - 20	85 (32.9)	55 (64.7)	30 (35.3)	
21 - 25	108 (41.9)	72 (66.7)	36 (33.3)	
26 - 30	43 (16.7)	37 (86.0)	6 (14.0)	

children and 73.6% of them had BV. More than sixteen percent (16.7%) of the women terminated their pregnancy through abortion and 69.8% of them had BV. Only 21 (8.1%) of the participants reported history of family planning using injectables and 14 (66.7%) of them had BV. Pattern of the symptoms elicited by the women included vaginal discharge only (49.2%), lower abdominal pain (8.9%), vaginal itching (8.1%), vaginal itching and discharge (6.6%), foul odour from vagina (5.8%), itching and lower abdominal pain (3.9%).

Out of the 258 cultures performed, only 94 (36.4%) had significant bacteriuria. Ninety-one (96.8%) were Gram negative bacteria while 3 (3.2%) were Gram positive bacteria. On the whole, the prevalence of UTI and BV was found to be 94 (36.4%) and 184 (71.3%) respectively. Almost seventy percent (69.2%) of the women with BV had UTI. The uropathogenic bacteria isolated were *E coli* (30.6%), *K. pneumoniae* (1.8%), *P. aeruginosa* (1.6%), *Proteus mirabilis* (1.2%) and *S. saprophyticus* (1.2%). Further analysis showed that majority (58.5%) of

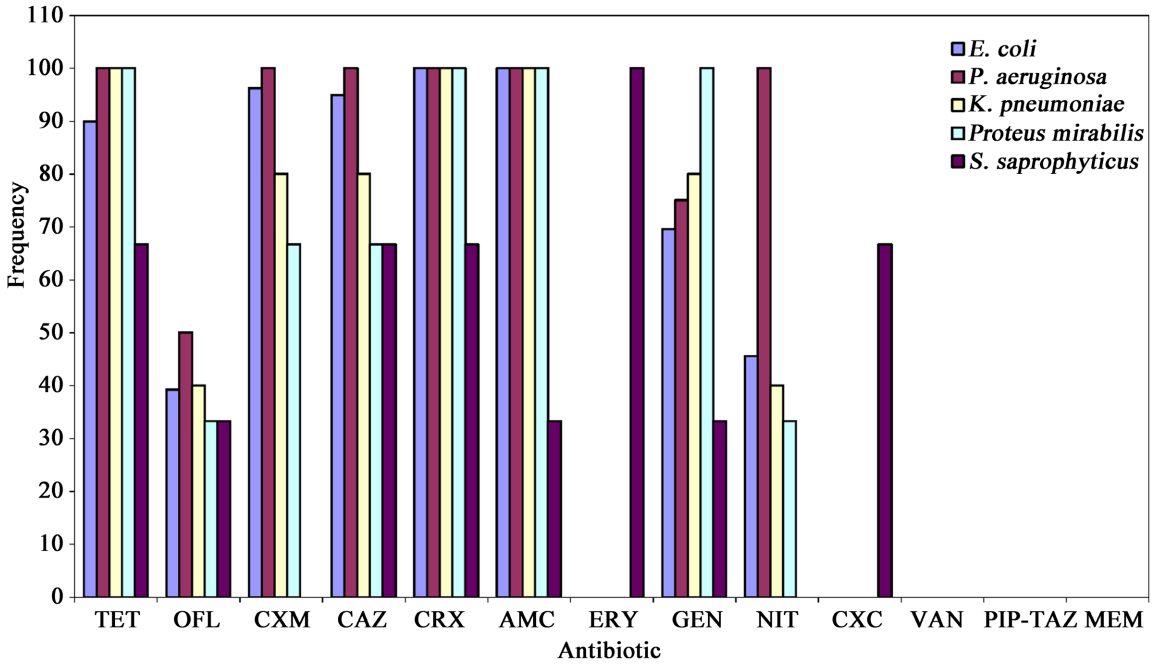
the women with BV and UTI had *E. coli* as the urinary pathogen while 25.5% had only *E. coli* (Figure 1). There was significant association between BV and *E. coli* (p = 0.02). Also, 3.2% of the participants had *P. aeruginosa* and BV, 4.3% had *K. pneumoniae* and BV, 2.1% had *P. mirabilis* and BV while 1.1% of each of the women with *P. aeruginosa*, *K. pneumoniae*, *P. mirabilis* don't have BV. Only 1.1% had *S. saprophyticus* and BV while 2.1% had only *S. saprophyticus*.

Figure 2 shows the antibiotic resistance profile of the isolated uropathogenic bacteria. All isolates were 100% sensitive to piperacillin-tazobactam and meropenem. *S. saprophyticus* was 100% sensitive to vancomycin. Overall, the highest level of resistance was observed in amoxicillin-clavulanic acid (100%) and cefuroxime (100%) for Gram negative and erythromycin (100%) for Gram positive bacteria. *P. aeruginosa* was 100% resistant to tetracycline, nitrofurantoin, cefixime and ceftazidime. *P. mirabilis* was 100% resistant to tetracycline and gentamicin while *K. pneumoniae* was 100% resistant to tetracycline only. *E. coli* isolates showed 98% resistance to cefixime followed by ceftazidime (94.9%), tetracycline (89.9%), gentamicin (69.6%), nitrofurantoin (45.6%) and ofloxacin (39.3%) whereas *P. aeruginosa* showed 50% resistance to ofloxacin and 75% (gentamicin). Eighty percent of *K. pneumoniae* isolates were resistant to cefixime, ceftazidime, gentamicin followed by 40% resistance to ofloxacin and gentamicin. *P. mirabilis* showed 33.3% resistant to ofloxacin, nitrofurantoin and 66.7% to cefixime, ceftazidime. *S. saprophyticus*, the only Gram positive bacteria



BV (+ve) = Bacterial vaginosis positive; BV (−ve) = Bacterial vaginosis negative. P < 0.05 was significant.

Figure 1. Distribution by species of the bacteriologic etiology of urinary tract infection among the sexually active women with and without bacterial vaginosis.



TET = Tetracycline; OFL = Ofloxacin, CXM = Cefixim, CRX = Cefuroxim, AMC= Augmentin, ERY = Erythromycin, GEN = Gentamicin, NIT= Nitrofuratioin, CXC = Cloxacillin, VAN =Vancomycin, PIP-TAZ = Piperacillin = Tazobactam. MEM = Meropenem

Figure 2. Antibiotic resistance profile of the isolated uropathogenic bacterial strains.

isolated demonstrated 66.7% resistant to tetracycline, ceftazidime, cefuroxime, cloxacillin and 33.3% to ofloxacin, gentamicin, amoxicillin-clavulanic acid. Multi-drug resistance (MDR) was observed among 97.8% of the bacteria isolated.

4. Discussion

The occurrence of UTI in women with BV has been well reported. However, more data are needed with regard to incriminating pathogens and their antibiotic resistance profile among sexually active women in Nigeria. In this study, the prevalence of UTI among women with BV is 69.2%. This prevalence is lower than the report (75%) by Amatya *et al.* [31]. However, it is higher than the result by Gupta *et al.* (21.2%) [39], Sumati and Saritha (42.27%) [7], Lamichhane *et al.* (23.4%) [40], Hillerbrand *et al.* (13.6%) [9]. The disparity may be due to differences in study populations and number of sexual partners. Majority (73.3%) of the women with multiple sex partners had BV, this may have increased the risk of UTI. BV provide polarization of pathogens due to reduction of vaginal lactobacilli and increase in pH. Therefore, UTI screening should be integrated with BV screening especially in women with multiple sex partners.

The present study also confirmed high burden of BV among sexually active women in Nigeria as reported previously by Victor *et al.* [41], Awoniyi *et al.* [42]. BV was highest (76.2%) in the age group 40 - 49 years. However, Gupta *et al.* [39] and Lamichhane *et al.* [40] reported BV prevalence of 78.7% and 80.6% respectively in age group 21 - 30 years. The greater infection prevalence in the 21

- 30 years age group could be related to the fact that this is among the most reproductively active age and has the highest sexual exposure.

As a potential factor that could complicate the management of BV in sexually active Nigerian women, common risk factors identified were multiple sex partners and age at first sexual activity which has also been reported by Verstraelen *et al.* [43], Vodstrcil *et al.* [44] and Fethers *et al.* [45]. The study found out that all the women with primary or no education had BV. This finding agrees with what Ajayi *et al.* [46] reported that BV was more commonly found among those with little or no education. However, Bitew *et al.* [47] reported that BV was higher in women with primary and secondary education compared to illiterates. In accordance with our study, there is no significant association between BV and the number of abortions [47]. The present study revealed significant association of BV with pregnancy ($p = 0.013$). BV is common problem in pregnant women and studies by Afolabi *et al.* [48], Das *et al.* [49], Kiran *et al.* [50], Isik *et al.* [51] showed BV to be a risk factor for adverse obstetric and gynaecological outcomes.

This study identified five different types of pathogen namely *E. coli*, *K. pneumoniae*, *P. aeruginosa*, *P. mirabilis* and *S. saprophyticus*. This is unlike previous studies by Bhavana *et al.* [52] and Gupta *et al.* [39] who found only *E. coli*, *Klebsiella* spp., *Citrobacter* spp., *Providencia* spp., *P. aeruginosa*, *Acinetobacter baumannii*, *S. aureus*, *Enterococci*, coagulase negative staphylococci (CONS) and *E. coli*, *Klebsiella* spp., *Enterobacter* spp., *Staphylococcus* spp. respectively. This shows that new pathogens are emerging as causes of UTI in BV and may vary from one region to another.

The antibiotic resistance pattern showed that the pathogens were resistant to most of the commonly used first-line antibiotics. This study shows that piperacillin-tazobactam, meropenem are effective antibiotics for UTI management in BV caused by Gram negative bacteria. Studies by Bhavana *et al.* [52] showed that *E. coli* was not sensitive to piperacillin-tazobactam. This may be due to differences in the use of the antibiotics. Vancomycin was found to be the effective antibiotics for managing UTI caused by *S. saprophyticus* in BV. Bhavana *et al.* [52] reported that CONS showed 100% sensitivity to vancomycin and cefixime.

Multi-drug resistance was observed among 97.8% of the bacteria isolated. Studies by Belete [53], Wabe *et al.* [54] and Onyango *et al.* [55] reported 80.4%, 57.1% and 96% respectively. In another study, Gessese *et al.* reported MDR in all isolates [56]. The high prevalence of MDR seen in this study can be as a result of indiscriminate use of antibiotics. Also, bacteria can acquire resistance genes from plasmids and other transferred genetic material. Moreover, some bacteria like *E. coli* form biofilms on the mucosal lining of the bladder to resist antibiotic treatment and host immune response [57]. There is need for precautionary use of antibiotics while managing UTI in BV. UTI screening and antibiotic susceptibility test should be integrated among sexually active women. This will help to prevent maternal health outcomes.

In conclusion, there is a high level of resistance among UTI isolates in sexually active women with BV. Antibiotics stewardship and resistance surveillance

should be conducted regularly. Counseling and education of patients on adherence to prescribed treatment, proper hygenic practices, and treatment of symptomatic sex partners, are critical for improving patient outcomes and preventing recurrence. Future research work should embark on molecular characterization of urinary pathogens from this group of women. Women with BV have UTI more than women without BV; therefore, BV screening should be conducted for women carrying out UTI test.

5. Limitations of the Study

1) The study was done in Primary Health Care centres only. The secondary, tertiary and private facilities were not taken into consideration. Therefore, the findings cannot be extrapolated to the general population.

2) The study was carried out in one state which is a representative of a geopolitical zone. The other five zones were not included so the results cannot be generalized for the whole country.

Conflicts of Interest

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

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Appendix

Questionnaire

Identification and antibiotic resistance profile of uropathogenic bacteria from sexually active women in Lagos, Nigeria

ID. No: ……..

Name of Health Personnel (interviewer):

Health facility:

Interview starts:……. Interview ends:……. Date:……..

Please, circle the appropriate answer.

Section A: Background of Respondents

1. Age (last birthday): ……

2. Marital status: (a) Single (b) Married (c) Divorced (d) Separated (e) Widowed

3. How many children do you have?

(a) None (b) 1 (c) 2 (d) 3 (e) 4 (f) >4

4. Level of education: (a) None (b) Primary (c) Secondary (d) Tertiary

5. Religion: (a) Christianity (b) Islamic (c) Traditional (d) Others (specify)……

6. Occupation: (a) Trader (b) Unemployed (c) Civil servant (d) Self- employed

(e) Retired (f) Housewife (g) Student (h) Others (specify)……

7. Which location do you live? (a) Rural area (b) Urban area (c) Semi-urban area

8. What is your estimated income monthly?

(a) <N10,000 (b) N10,000 - N50,000 (c) N51,000 - N100,000

(d) N101,000 - N150,000 (e) N151,000 - N200,000 (f) N201,000 and above

Section B: Reproductive History

9. Have you been pregnant before? (a) Yes (b) No

10. If your answer to Question 9 is yes, how many children have you given birth to alive?

(a) 1 (b) >1

11. What method did you use in delivering you children?

(a) Vaginal (b) Operation (c) Vaginal & Operation

12. Has your pregnancy been terminated before (miscarriage or abortion)?

(a) Yes (b) No

13. If your answer to Question 12 is yes, was the miscarriage or abortion

(a) induced (b) spontaneous

14. Have you had still birth in your life time?

(a) Yes (b) No

15. If your answer to Question 14 is yes, how many times?

(a) 1 (b) >1

16. Do you have history of family planning?

(a) Yes (b) No (c) Not applicable

17. If your answer to Question 16 is yes, what type of family planning are you using?

(a) Natural (b) Barrier methods (c) Injectables (d) IUD

(e) oral contraceptives (f) spermicides (g) Not applicable

18. Are you pregnant now? (a) Yes (b) No (c) not sure

Section C: Risk Behaviour

19. What is the number of your lifetime sexual partners?

(a) 1 (b) 2 - 5 (c) 6 - 10 (d) >10 (e) Don't remember

20. What was your age at first sexual activity

(a) less than 10 years (b) 11 - 15 years (c) 16 - 20 years

(d) 21 - 25 years (e) 26 - 30 years (f) >30 years

Section D: Symptoms (From Case Record Form)

21. (a) vaginal itching (b) lower abdominal pain (c) rash (d) pelvic pain (e) genital blisters or ulcers

(f) discharge (g) small boils around the vagina (h) foul odour from vagina

(i) painful urination (j) others (specify) ……

……

……

……