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ETIOLOGIC AGENTS OF LOWER RESPIRATORY TRACT INFECTIONS AMONG PATIENTS ATTENDING TUBERCULOSIS CLINIC IN BENIN CITY, NIGERIA

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ABSTRACT

The emergence of HIV has reawakened the tuberculosis (TB) scourge and infected patients are prone to opportunistic infections, this study was carried out to determine the HIV status and etiologic agents of Lower respiratory tract infections (LRTI) among tuberculosis suspected patients in Benin City, Nigeria. The study was cross sectional. A total of 276 patients attending tuberculosis clinic were recruited. Questionnaires were filled for each patient. Blood and sputum specimens were collected in plain and sterile containers respectively and transported immediately to the laboratory. Blood samples were screened for the presence of HIV antibodies. The sputum specimens were then cultured following standard microbiological procedure, and thereafter processed using the GeneXpert MTB/RIF assay. Emergent bacterial colonies were identified and susceptibility testing was carried out following standard microbiological techniques. A total of 118 (42.8%) non-mycobacterial bacterial agents were recovered from the patients. Patients were more likely to be culture positive for LRTI in comparison with TB infection (p < 0.0001). There was no association between TB and HIV status (OR = 0.6161, 95%CI = 0.226, 1.648, p = 0.4474). HIV positive patients were more likely to be culture positive for bacterial agents and *Klebsiella pneumoniae* was more likely to be recovered (p = 0.0338). The fluoroquinolones, gentamicin and ceftriaxone-sulbactam were the most active antibacterial agents against bacterial isolates. The prevalence of LRTI in this study was 52.2%. The study draws attention on the need for physicians to request for bacteriological culture (non-mycobacterial) alongside the TB diagnostic algorithm in suspected TB cases.

Keywords: Tuberculosis, HIV, opportunistic infections, patients, bacteria.

AGENTS ETIOLOGIQUES DES INFECTIONS DU TRACTUS RESPIRATOIRE INFÉRIEUR CHEZ LES PATIENTS SOUFFRANT DE LA CLINIQUE DE TUBERCULOSE DANS LA VILLE DU BENIN, NIGERIA

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ABSTRAIT

L'émergence du VIH a réveillé le fléau de la tuberculose (TB) et les patients infectés sont sujets à des infections opportunistes, cette étude a été réalisée pour déterminer le statut VIH et les agents étiologiques des infections respiratoires basses chez les patients suspects de tuberculose à Benin City, Nigeria. L'étude était transversale. Un total de 276 patients fréquentant la clinique de la tuberculose ont été recrutés. Des questionnaires ont été remplis pour chaque patient. Les échantillons de sang et d'expectoration ont été recueillis dans des récipients simples et stériles respectivement et transportés immédiatement au laboratoire. Des échantillons de sang ont été examinés pour la présence d'anticorps anti-VIH. Les échantillons d'expectoration ont ensuite été cultivés suivant la procédure microbiologique standard, puis traités en utilisant le test GeneXpert MTB / RIF. Des colonies bactériennes émergentes ont été identifiées et des tests de sensibilité ont été effectués suivant des techniques microbiologiques standard. Un total de 118 (42,8%) agents bactériens non mycobactériens ont été récupérés chez les patients. Les patients étaient plus susceptibles d'être positifs à la culture pour le LRTI par rapport à l'infection tuberculeuse (p <0,0001). Il n'y avait pas d'association entre la tuberculose et le statut VIH (OR = 0,6161, IC 95% = 0,226, 1,648, p

Les patients séropositifs étaient plus susceptibles d'être positifs à la culture pour des agents bactériens et Klebsiella pneumoniae était plus susceptible d'être récupérée (p = 0,0338). Les fluoroquinolones, la gentamicine et le ceftriaxone-sulbactam étaient les agents antibactériens les plus actifs contre les isolats bactériens. La prévalence de LRTI dans cette étude était de 52,2%. L'étude attire l'attention sur la nécessité pour les médecins de demander une culture bactériologique (non mycobactérienne) parallèlement à l'algorithme de diagnostic de la TB dans les cas suspects de TB.

Mots-clés: Tuberculose, VIH, infections opportunistes, patients, bactéries.

INTRODUCTION

Acute lower respiratory tract infections (LRTIs) are a persistent and pervasive public health problem which causes a greater burden of disease worldwide than malaria, cancer, human immunodeficiency virus infection, or heart attacks (1). LRTIs affect all age groups and vary in severity from non-pneumonic LRTI in a young healthy adult to pneumonia or life threatening exacerbation in a patient with severe disabling chronic obstructive pulmonary disease (COPD) (2).

A variety of micro-organisms can cause LRTIs namely bacteria, viruses, parasites and fungi[3]. Several studies have outlined bacterial etiologic agents causing LRTIs to include the Gram positive cocci (*Staphylococcus* spp and *Streptococcus pneumoniae*), Enterobacteriaceae and oxidase positive rods (2, 3). The etiologic agent of tuberculosis (TB); *Mycobacterium tuberculosis* has also been implicated as playing a key role in the global burden of LRTI (4).

TB is the ninth leading cause of death worldwide and the leading cause from a single infectious agent, ranking above HIV/AIDS (5). In 2016, there were an estimated 1.3 million TB deaths among HIV-negative people and an additional 374,000 deaths among HIV-positive people[5]. Nigeria remains uniquely placed among the high burden countries where HIV, TB and drug-resistant TB are prevalent (5, 6).

The direct observed treatment short course (DOTS) program by WHO was instituted in the 1990's in developing countries to provide antibiotics for patients and have an effective TB control program (4). This has guaranteed patients' attending tuberculosis clinics early diagnosis of the disease, access to anti-TB treatment and an uninterrupted supply of anti-TB drugs (7).
However, the differential diagnosis of TB from bacterial pneumonia is not straightforward as it could present with similar signs and symptoms as LRTIs of other etiologies (8, 9). While preference is given to detection of TB owing to Nigeria's high burden of the disease (5), patients presenting with such signs and symptoms may have other etiologic agent(s). Moreover, HIV has been shown as a risk factor for opportunistic LRTI (6). It is against this background that this study was conducted to determine the HIV status and etiologic agents of LRTI among patients attending tuberculosis clinic in Benin City, Nigeria.

MATERIALS AND METHODS

Study Area:

The study was conducted at the University of Benin Teaching Hospital (UBTH) in Benin City, Nigeria. UBTH is a tertiary hospital with 700 beds and 20 wards, serving the specialist healthcare needs of Edo State and 6 to 10 other neighboring States.

Study Population

A total of 276 patients (non-repetitive) attending tuberculosis (DOTS) clinic were enrolled for the study. Structured questionnaires were given to patients. . The study was conducted between 3rd July 2017 and 28th February, 2018.

Ethical Consideration

Ethical approval was sought and obtained from the Ethical Committee of UBTH with protocol number: ADM/E 22/A/VOL. VII/1489.

HIV screening

Venous blood was obtained from all participants. Five milliliters of blood sample was collected into properly labeled plain containers, samples were sent to the laboratory and HIV serological tests were carried out on the centrifuged blood samples. For the detection of HIV-1 and HIV-2 antibodies in the blood, Determine® HIV-1/2 Test cards (Inverness Medical, Japan), Unigold™ Kit (Trinity Biotec, Ireland) and HIV - 1/2 Stat- Pak® Assay (Chembio Diagnostic Systems, USA) according to the national algorithm (10). These methods are immunochromatographic and detect the presence of antibodies to HIV-1 and HIV-2 in human blood and are read in-vitro having more than 99.9% sensitivity and 99.75% specificity.

Sputum collection and processing:

Sputum specimens were collected from these patients in sterile wide-mouth containers and sent to the Medical Microbiology Laboratory, University of Benin Teaching Hospital for microbiological analysis. Specimens were processed within two hours after collection. Specimens were cultured on blood, chocolate and MacConkey agar plates respectively. Films were made from the sputum specimens and

stained by Gram's method. Cultures with significant growth were identified following standard microbiological techniques (11).

TB Screening:

Sputum samples were thereafter processed for detection of TB using GeneXpert MTB/RIF automated system. Testing was performed according to the manufacturer's instructions. Sample reagent was added to untreated sputum at a ratio of 2:1. This was manually agitated and kept for 10 min at room temperature, then shaken again and kept for 5 min; 2 ml of the inactivated material was thereafter transferred to the test cartridge, inserted into the test platform and run (12). The system automatically interpreted all results from measured fluorescent signal into the following categories: invalid, if PCR inhibitors were detected with amplification failure, negative or positive. Positive results were scaled into 4 categories (very low, low, medium, high) depending on bacterial load and defined susceptible or resistant to rifampicin depending on detection of mutations in *rpoB* gene.

Disc susceptibility test

Disc susceptibility tests were thereafter performed on all bacterial isolates using the British Standard for Antimicrobial Chemotherapy (BSAC) method (13). The following antibacterial discs were used; Ciprofloxacin (5 µg), Ofloxacin (5 µg), Levofloxacin (5 µg), Sulfamethoxazole-trimethoprim (25 µg), Clindamycin (2 µg), Cefotaxime (30 µg), Cefuroxime (30 µg), Cefixime (5 µg), Ceftriaxone-sulbactam (30/15 µg) and Gentamicin (10 µg) (all from Axiom, India).

Statistical analysis

The data obtained were analyzed with statistical tools namely chi square as appropriate using the statistical software INSTAT® (GraphPad Software Inc, La Jolla, CA, USA).

RESULTS

Of this 276 patients that participated in this study, 26 (9.4%) patients were positive for TB only, 105 (38.0%) were culture positive while 13 (4.7%) patients were both culture and TB positive. The prevalence of LRTI (TB + non-TB) in this study was 52.2%. Patients were more likely to be culture positive (non-TB) for LRTI in comparison with tuberculosis infection ($p < 0.0001$) (Table 1).

TABLE 1: PREVALENCE OF TUBERCULOSIS AND OTHER BACTERIAL AGENTS AMONG 276 PATIENTS WITH SIGNS AND SYMPTOMS OF LRTI IN BENIN CITY, NIGERIA

Patients	Number positive
TB only	**26 (9.4)**
Culture only	**105 (38.0)**
TB + Culture	**13 (4.7)**

TB = tuberculosis, n = 276, p < 0.0001

A total of 51 (18.5%) patients were HIV positive, 46 of these patients were TB negative while 5 (12.8%) were infected with TB. There was no association between TB infection and HIV status among patients attending DOTS clinic (OR = 0.6161, 95%CI = 0.226, 1.648, p = 0.4474). (Table 2).

TABLE 2: PREVALENCE OF HIV AND TUBERCULOSIS AMONG PATIENTS ATTENDING TUBERCULOSIS CLINIC IN BENIN CITY, NIGERIA

Patients	Number Tested	HIV Positive (%)	OR	95%CI	p
TB positive	39	5 (12.8)	0.616	0.226, 1.648	0.4474
TB negative	237	46 (19.4)			

TB = uberculosis, n = 276.

A total of 118 (42.8%) non-mycobacterial bacterial agents were recovered from patients in this study. In relation to bacterial etiologic agents of LRTI among patients attending DOTS clinic and their HIV status, a total of 30 HIV positive patients (58.8%) were culture positive for bacterial agents while 88 patients (39.1%) that were HIV negative were culture positive. HIV positive patients were more likely to be culture positive for bacterial agents causing LRTI (p = 0.0158). *Klebsiella pneumoniae* showed high prevalence among HIV positive and HIV negative patients with 23.5% and 11.1% respectively but was more likely to be

recovered from HIV positive patients attending DOTS clinic (p = 0.0338) (Table 3).

TABLE 3: ETIOLOGIC AGENTS OF LRTI IN RELATION TO HIV SERO-STATUS

Organism	No of isolates	No HIV positive (n = 51)	No HIV negative (n = 225)	p
CoNS	5	0	5 (2.2)	0.6221
S. aureus	18	6 (11.8)	12 (5.3)	0.1721
S. pneumoniae	2	1 (2.0)	1 (0.4)	0.8155
E. coli	3	0	3 (1.3)	0.9352
Klebsiella pneumoniae	37	12 (23.5)	25 (11.1)	0.0338
***Enterobacter* spp**	21	4 (7.8)	17 (7.6)	0.9442
***Citrobacter* spp**	2	1 (2.0)	1 (0.4)	0.8155
***Acinetobacter* spp**	5	0	5 (2.2)	0.6221
***Providencia* spp**	5	0	5 (2.2)	0.6221
***Alkaligenes* spp**	2	1 (2.0)	2 (0.9)	0.5051
H. influenzae	12	4 (7.8)	8 (3.6)	0.3294
P. aeruginosa	5	1 (2.0)	4 (1.8)	0.9295
Total	118	30 (58.8)	88 (39.1)	0.0158

CoNS- Coagulase negative staphylococci, number in brackets = value in percentage

In relation to gender and infection rate, there was no statistically significant relationship (p = 0.6848). The age group 51-60 yrs showed the highest infection rate for LRTI with 67.5%. When compared with other age groups however, there was no statistical significance (p = 0.0717). Also, educational status, occupation and marital status of patients did not significantly affect the prevalence rate of LRTI due to bacterial agents (p >0.05). (Table 4)

TABLE 4: EFFECT OF SOCIO-DEMOGRAPHIC FACTORS ON BACTERIAL LRTI

Factor	Division	No of Patients (n = 276)	No Culture Positive	p
Gender	Male	122 (44.2)	50 (41.0)	0.6848
	Female	154 (55.8)	68 (44.2)	
Age	0-10	17 (6.2)	7 (41.2)	0.0717
	11-20	17 (6.2)	10 (58.8)	
	21-30	57 (20.7)	20 (35.1)	
	31-40	49 (17.8)	19 (38.8)	
	41-50	44 (15.9)	18 (40.9)	

	51-60	40 (14.5)	27 (67.5)	
	61-70	26 (9.4)	12 (46.2)	
	≥ 71	26 (9.4)	11 (38.9)	
Educational status	No Formal	24 (8.7)	10 (41.6)	0.9986
	Primary	53 (19.2)	22 (41.5)	
	Secondary	96 (34.8)	41 (42.7)	
	Tertiary	103 (37.3)	44 (42.7)	
Marital Status	Single	83 (30.1)	36 (43.4)	0.7864
	Married	161 (58.3)	66 (41.0)	
	Divorced	9 (3.3)	5 (55.6)	
	Widow(er)	23 (8.3)	11 (47.8)	
Occupation	Business/Trading	70 (25.4)	32 (45.7)	0.1952
	Artisan	30 (10.9)	19 (63.3)	
	Civil/Public Servant	30 (10.9)	10 (33.3)	
	Teacher/Lecturer	16 (5.8)	6 (37.5)	
	Unemployed	20 (7.2)	8 (40.0)	
	Student	47 (17.0)	22 (34.9)	
	Others	63 (22.8)	22 (34.9)	

Number in brackets = value in percentage

The distribution of bacterial agents implicated in patients that were TB positive is shown on Figure 1. Out of 39 TB positive patients, 13 (33.3%) yielded bacterial growth. *Klebsiella pneumoniae* showed the highest prevalence of bacterial agents co-infecting TB-positive patients.

The fluoroquinolones (ciprofloxacin, ofloxacin and levofloxacin), gentamicin and ceftriaxone-sulbactam showed high activity against bacterial agents isolated. Sulfamethoxazole-trimethoprim showed moderate activity while cefuroxime, cefotaxime, cefixime and clindamycin showed poor activity to bacterial agents isolated (Table 5).

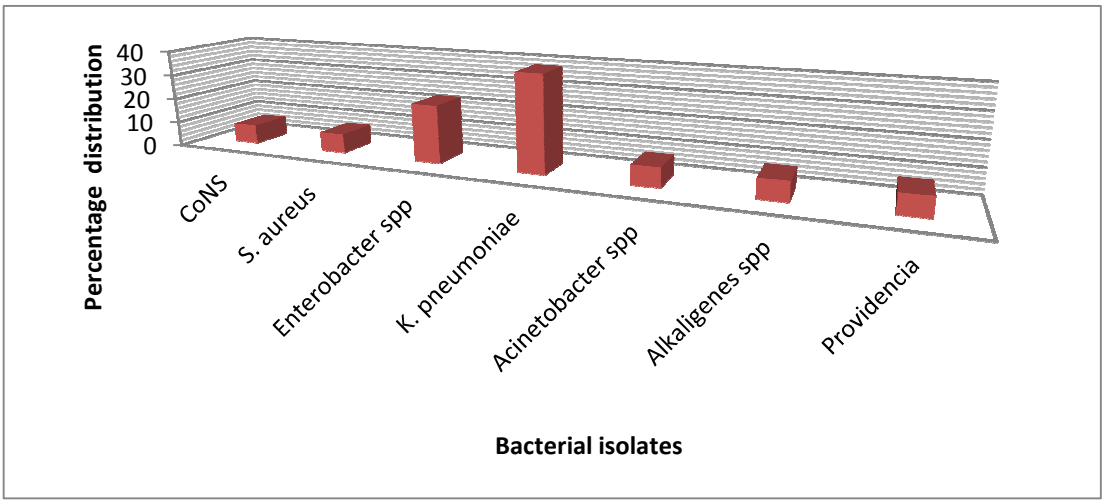

FIGURE 1: PERCENTAGE DISTRIBUTION OF BACTERIAL ISOLATES AMONG PATIENTS HAVING TUBERCULOSIS

TABLE 5: ANTIMICROBIAL SUSCEPTIBILITY PATTERN OF BACTERIAL AGENTS CAUSING LRTI IN BENIN, NIGERIA

Organism	No of isolates	CIP	OFX	LVX	SXT	CD	CTX	CXM	CFX	CRS	GEN
CoNS	5	3 (60.0)	3 (60.0)	3 (60.0)	3 (60.0)	1 (20.0)	1 (10.0)	1 (10.0)	0	3 (60.0)	4 (80.0)
S. aureus	18	14 (77.8)	13 (72.2)	12 (66.7)	10 (55.6)	5 (27.8)	5 (27.8)	1 (5.6)	3 (16.7)	16 (88.9)	18 (100)
Streptococcus pneumoniae	2	1 (50.0)	1 (50.0)	1 (50.0)	1 (50.0)	1 (50.0)	1 (50.0)	1 (50.0)	1 (50.0)	2 (100)	1 (50.0)
***Citrobacter* spp.**	2	2 (100)	2 (100)	2 (100)	0	ND	1 (50.0)	0	1 (50.0)	2 (100)	1 (50.0)
***Enterobacter* spp.**	21	18 (85.7)	17 (81.0)	17 (81.0)	13 (61.9)	ND	13 (61.9)	3 (14.3)	8 (38.1)	18 (85.7)	17 (81.0)
Escherichia coli	3	2 (66.7)	2 (66.7)	2 (66.7)	1 (33.3)	ND	1 (33.3)	1 (33.3)	0	2 (66.7)	2 (66.7)
Klebsiella pneumoniae	37	34 (91.9)	33 (89.2)	33 (89.2)	16 (43.2)	ND	18 (48.6)	6 (16.2)	12 (32.4)	27 (73.0)	26 (70.3)
***Acinetobacter* spp**	5	3 (60.0)	3 (60.0)	3 (60.0)	1 (20.0)	ND	1 (20.0)	1 (20.0)	1 (20.0)	4 (80.0)	3 (60.0)
***Providencia* spp.**	5	4 (80.0)	4 (80.0)	4 (80.0)	4 (80.0)	ND	2 (40.0)	1 (20.0)	2 (40.0)	4 (80.0)	4 (80.0)
***Alkaligenes* spp.**	3	3 (100)	3 (100)	3 (100)	1 (33.3)	ND	2 (66.7)	0	2 (66.7)	2 (66.7)	2 (66.7)
Haemophilus influenzae	12	3 (25.0)	4 (33.3)	3 (25.0)	1 (8.3)	ND	2 (16.7)	0	1 (8.3)	10 (83.3)	3 (25.0)
Pseudomonas aeruginosa	5	5 (100)	5 (100)	5 (100)	3 (60.0)	ND	0	0	0	2 (40.0)	4 (80.0)

Abbreviations: CIP-Ciprofloxacin, OFX-Ofloxacin, LVX-Levofloxacin, SXT-Sulfamethoxazole-trimethoprim, CD-Clindamycin, CTX-Cefotaxime, CXM-Cefuroxime, CFX-Cefixime, CRS-Ceftriaxone-sulbactam, GEN-Gentamicin. Number in brackets = value in percentages, ND= not done, CoNS = Coagulase negative *staphylococci.*

DISCUSSION

In this study, patients under the clinical suspicion of having TB and enrolled in the DOTS clinic were more likely to be infected with non-mycobacterial bacterial agents ($p < 0.0001$). Although no previous Nigerian study has considered etiologic agents in TB suspected patients, our finding is in tandem with a previous Cameroonian study in which majority of patients attending tuberculosis clinic were culture positive (8). TB could cause debilitating illness and present with similar signs and symptoms as LRTI of other etiologies (8, 9). The current algorithm in tuberculosis clinics in Nigeria excludes culture for non-mycobacterial bacterial agents; our study however suggests a need to review this.

HIV is a known risk factor for acquiring tuberculosis infection (14). Patients who are HIV positive and infected with TB have been previously shown to be 17 times more likely to develop active TB than people not infected with HIV (15). Among patients attending TB clinic in our study however, HIV was not a risk factor for TB although 12.8% of TB positive patients were co-infected with HIV. Our findings could be due to the fact that most patients were attending tuberculosis clinic for the first time and were being screened for TB unlike previous studies in which the pool of patients were from people living with HIV/AIDS (PLWHA) (15), or known TB patients (14). In these studies, a significant association was observed between HIV and TB. The prognosis for HIV/TB co-infection is however usually not favorable as globally, the recovery rate is about 73% with mortality rates being high (4). This study therefore justifies the screening of patients attending TB clinic for HIV as early detection would be helpful in tackling both infections.

The major causes of morbidity and mortality in HIV infected persons are opportunistic infections which vary from region to region (16). Among the

opportunistic infections associated with HIV, diseases like pneumonia of bacterial origin occur at a rate many times higher in HIV infected patients than in the general population (16). In this study, HIV positive patients were more likely to be co-infected with non-mycobacterial bacterial agents ($p = 0.0158$). This finding tallies with a similar study (8). Among patients showing signs of LRTI in Nepal, HIV positive patients were shown to be significantly more likely to be infected with bacterial pathogens (46.6%) than the HIV negative group (27%) (16).

Klebsiella pneumoniae was more likely to be co-infecting patients with HIV than any other bacteria in this study. This finding is in congruence with previous studies in Nigeria and Nepal (3, 16). It however differs from a similar study in Cameroon where *Streptococcus pneumoniae* showed high prevalence among HIV positive patients (8). Pathogenicity of *K. pneumoniae* is largely due to the production of a polysaccharide-rich cell surface that provides protection from the inflammatory response (17). In HIV infections where there is a defective immune response, these strains may colonize the lungs and worsen treatment outcomes if proper antibacterial therapy is not immediately instituted.

K. pneumoniae also showed high prevalence among bacteria co-infecting TB patients. *K. pneumoniae* has been known to mimic pulmonary reactivation tuberculosis because it presents with hemoptysis and cavitating lesions (9). It is equally difficult to treat because of the organism's thick capsule (17). In our setting, patients who are TB positive begin the treatment course in the TB clinic; little attention is accorded the possibility of a co-infecting bacterium. This may lead to inadequate care and poor treatment outcomes.

The role of gender in LRTI varies. Previous studies in Nigeria, Cameroon and Nepal observed no significant difference between male and females (3, 8, 16). Our finding was in tandem with these studies as there was no significant relationship between gender and LRTI. Our finding was however in contrast with an Indian study where males were more likely to have LRTI (2). In another Nigerian study, 54.7% of females in comparison with 45.3% of males had LRTI; this finding was however not subjected to statistical analysis (18).

Patients within the age group 51-60 yrs had a comparatively higher prevalence rate of LRTI with 67.5% in this study, although this finding was not statistically significant. This finding agrees with several other studies in which age did not significantly affect LRTI (8, 18). In the same vein, educational status, marital status and occupation type did not play a contributory role in LRTI prevalence although artisans had a comparatively higher prevalence rate of LRTI (63.3%). This may be due to occupational exposure among persons in this group namely carpenters, cement workers, stone cutters and so on. These occupations have been previously shown to predispose patients to LRTI (6).

The fluoroquinolones and gentamicin showed high efficacy against bacterial isolates in this study. This finding agrees with two Nigerian studies (3, 18). Ceftriaxone-sulbactam also showed remarkable efficacy. This drug is relatively new in our setting. Sulfamethoxazole-trimethoprim showed moderate activity against bacterial isolates. This finding strikingly differs from Egbe *et al*'s study which showed 0% efficacy (3). Owing to the local antibiotic rotation policy, the drug had been withdrawn for about 6 years and was recently re-introduced. This may explain the moderate potency of this drug. Also, cefuroxime, cefixime and cefotaxime showed poor activity especially to Gram negative bacterial isolates. The presence of extended spectrum β-lactamase- and AmpC β-lactamase- producing bacteria has been recently demonstrated among clinical specimens including sputum (33.9% and 9.7% respectively) in Benin, Nigeria (19). This may have played roles in the high level of resistance observed to these cephalosporins. Also, antibiotic abuse is rife in our setting and over-the-counter purchase is rampant (3, 19). Practices like this may create selective pressure and ensure the survival of resistant bacterial strains in the hospital and community settings.

Conclusion: The prevalence of LRTI in this study was 52.2%. Patients attending tuberculosis clinic with signs and symptoms of LRTI were more likely to be infected with bacteria (non-mycobacterial). Some of these patients had co-infection of TB and HIV, HIV and opportunistic bacteria, and TB and other opportunistic bacteria. *K. pneumoniae* was more likely to be the bacterial agent in these instances. The study draws attention on the need for physicians to request for bacteriological culture (non-mycobacterial) alongside TB algorithm for diagnosis in suspected TB cases.

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