Original Research Article

Empirical antibiotic prescription pattern among patients in a Nigerian tertiary hospital, Is there evidence of irrationality?

ABSTRACT

Background: Resistance to antibiotics is spreading rapidly around the world with its associated morbidity and mortality. Infections are becoming increasingly difficult to treat resulting in increasing cost of medical care. In low income countries with high infectious disease burden, antibiotic resistance is reported to be accelerated by irrational prescriptions in health facilities. In the absence of adequate resources, many clinicians engage in empirical antibiotic prescriptions some of which their appropriateness is questionable. There is need for laboratory evidence to justify empirical antibiotic use in the light of increasing resistance to commonly prescribed antibiotics.

Aims: This study aims to determine empirical antibiotic prescription pattern and to determine rationality using resistance profile of common bacterial isolates in the hospital.

Methods: Antibiotic prescriptions in the NHIS department and antibiogram records were obtained from pharmacy and laboratory records respectively. Analysis was carried out using descriptive statistics and comparison between antibiotics prescribed and their respective resistance pattern were compared to determine rationality.

Results/Discussion: The Penicillins and Quinolones were the most prescribed class of antibiotics and resistance range between 30 – 90% and 3 – 23% respectively. Resistance to other antibiotics was high thus making empirical prescriptions irrational in most of the cases. These findings have been consistently reported in several studies so widespread empirical antibiotic prescriptions are not in tandem with principles of rational drug use.

Conclusion: Antibiotic resistance is common among hospital isolates, so there is need to emphasize that prescriptions be based on laboratory evidence of microbial sensitivity.

Keywords: Antibiotics, Empirical prescription, rational drug use, Microbial resistance

INTRODUCTION

Antibiotics have been the cornerstone of modern medical care particularly in bacterial infections. Since the introduction of antibiotics over eight decades ago, infections that would have otherwise caused life threatening are now treatable. Infections from surgery, immunosuppression, traumatic injuries and prophylaxis have dramatically improved survival. In recent years however, reports of increasing microbial resistance have become consistent across a broad range of microorganisms [1-5]. Infections that were once treatable are now becoming difficult to treat resulting in increased morbidity and mortality, high cost of medical care and threatening global public health [6-10]. There is global evidence of the decline of effectiveness of antibiotics across all classes, there is however country and regional variations in antimicrobial resistance pattern [11].

Microbial resistance is reported to be a significant factor in mortality related to infectious diseases annually [12]. In less developed countries with high infectious disease burden and absence of reliable data, estimates of mortality also run into hundreds of thousands annually [13-15]. The rise in antimicrobial resistance in low income countries is related to a number of factors including easy availability of antibiotics, self-medication, extensive use in agriculture, and failure in infectious disease control system in healthcare facilities etc.[16,17] and irrational prescription practices [18-22].

Antibiotic prescription practices vary widely between countries and healthcare facilities; factors which have been reported to influence antibiotic use includes infectious disease burden, prescription habit of clinicians, microbial resistance pattern, regulatory control, standard treatment guidelines, availability and economic factors [23-31]. In resource scarce setting where routine empirical antibiotic use is widespread, prescription pattern vary widely [22]. For instance, some studies reported that Fluoroquinolones, Penicillins and Cephalosporins are the most prescribed class of antibiotics [22,32] while other studies reported high level use of Beta lactams [17,33].

The relationship between irrational antibiotic use and microbial resistance is well established and the current trend of antibiotic use is suggestive of an ongoing problem irrespective of healthcare setting. Among the most commonest microorganisms whose resistance to antibiotics is of global concern are *Escherichia coli, Streptococcus pneumoniae, Shigella species, Neisseria gonorrhea* and non typhoidal Salmonella Typhi [34-40]. Empirical antibiotic use is widely reported in literature either in the form of self-medication or irrational use in healthcare facilities, studies have reported that up to 50% of antibiotic prescriptions may be in the form of empirical prescriptions [41]. Microbial sensitivity results are rarely used in many health facilities because of poor healthcare infrastructure and paucity of qualified manpower [42,43]. In many healthcare facilities where laboratory services are available, antibiotic prescriptions are not routinely based on microbial sensitivity result which is a common cause of irrational antibiotic use [26,41,44], antibiotic prescription studies have reported high levels of irrational use and an increasing level of resistance to commonly used antibiotics [23,45].

While it may be impractical to wait for antibiotic sensitivity tests before in all clinical situations, it is important that empirical prescription of antibiotics is regulated so as preserve their effectiveness and limit risk of treatment failure due to microbial resistance. It's not clear if microbial resistance containment measures such as antibiotic stewardship programs, continuing education for prescribers, patient education and regulatory control are contributing to improved antibiotic use in developing countries due to absence of reliable data [46-48]. In Nigeria there are few published studies that used microbial sensitivity pattern as a basis for determining level of irrational antibiotic prescriptions in healthcare facilities, so this study is an attempt in that direction.

In addition using World Health Organization quality prescribing indicators, it is important that antibiotic use should reflect the dynamics of prevailing microbial sensitivity pattern. Physicians have for a long time viewed antibiotics as "magic bullets" for all infectious disease, that perception should now give way to the new reality that "bugs" no long respond to therapy as before. It is expected that treatment of bacterial infections should have been based on laboratory evidence to qualify as rational antibiotic use. This appears not to be the case at the moment even in many tertiary healthcare facilities in the country; this must change as high level of microbial resistance is a potential threat to public health.

Objectives: To determine empirical antibiotic use pattern and compare with resistance of common bacterial isolates as the basis of assessing the rationality of prescriptions.

METHODS

Setting: The study was carried out among patients insured by national health insurance scheme receiving at the University of Maiduguri teaching hospital, North east Nigeria.

Study design: This is a cross sectional retrospective study of prescriptions given to outpatients that filled their prescriptions in the NHIS pharmacy of the hospital.

Data collection: Prescription records were obtained from National health insurance scheme [NHIS] pharmacy covering the period between January 2017 and May 2018. A total of 5079 antibiotic containing prescriptions were used for this study. All eligible prescriptions selected had patient NHIS numbers clearly indicated. Prescription records that are incomplete, illegible and those not written on NHIS prescription forms were excluded. Information relating to antibiotics, duration of therapy, number of drugs per prescription, antibiotic prescription errors and demographic data were extracted

Data analysis: The data was entered into SPSS 21 and analyzed using descriptive statistics. Irrational prescriptions were determined by comparing antibiotics prescribed and resistance level from laboratory results of outpatients. Prescriptions were also reviewed for prescription errors, dosage errors, formulation errors and frequency of administration errors.

RESULTS

Demographic data showed that females were about two thirds of patients and majority of them were below 40 years old [Figure 1 and 2].

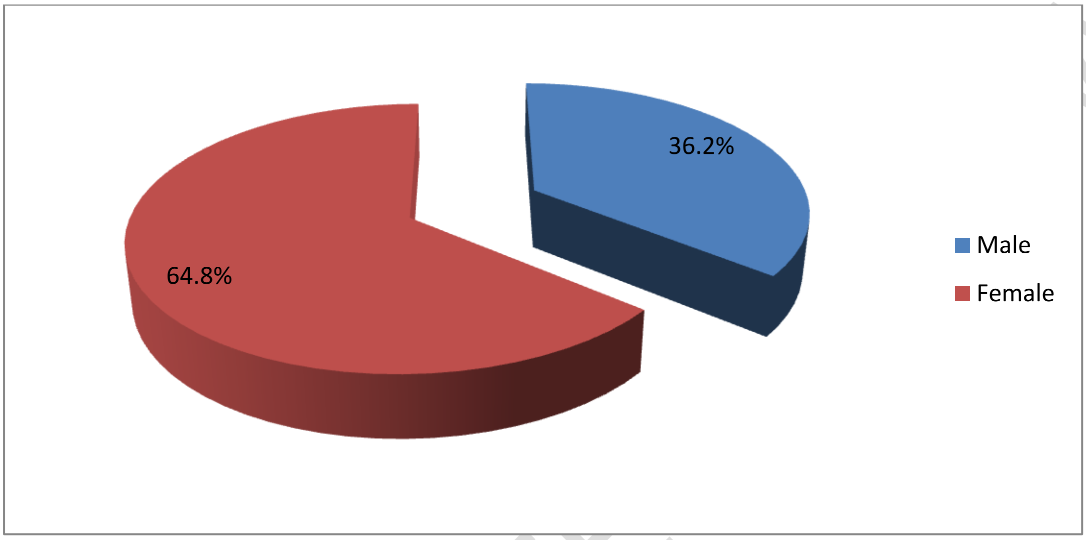

Figure 1: Gender distribution

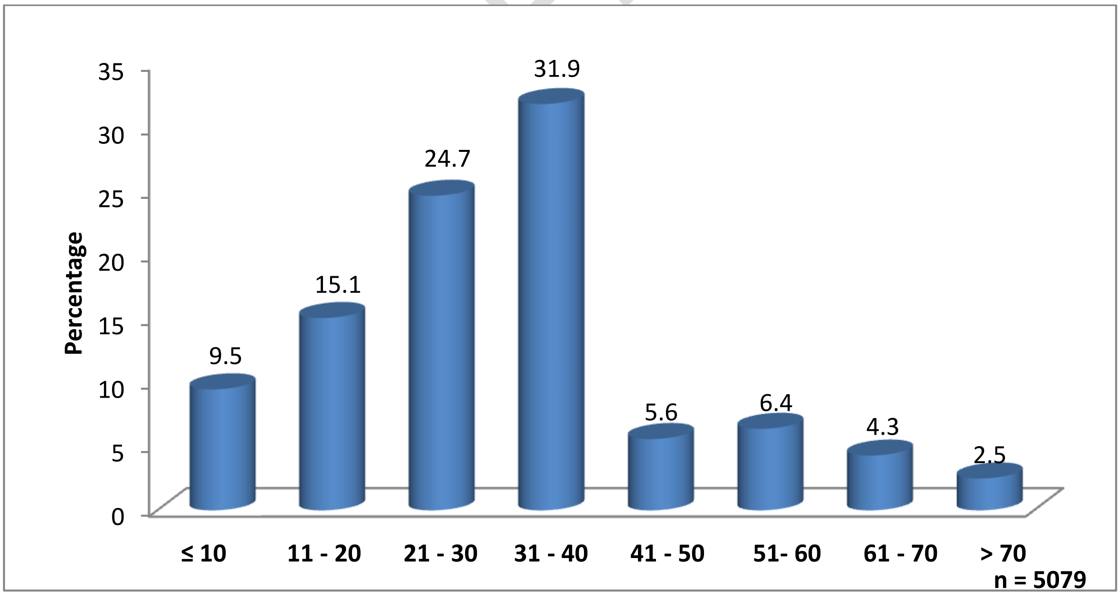

Figure 2: Age distribution

Prescription analysis showed that Penicillins [39%] accounted for the largest group of antibiotics given to patients. This was followed by Quinolones and Metronidazole with prescription rate of 25% and 17.8% respectively. Among individual antibiotics Amoxicillin + Clavulanic acid, Metronidazole and Ciprofloxacin were the most prescribed representing 28.2%, 17.8% and 13.1% respectively [Table 1].

Table 1: Antibiotics prescription pattern [n = 5079]

Name of drug	Number [%]
Amoxicillin + Clavulanic acid	1433 [28.2]
Amoxicillin	448 [8.8]
Ampicillin + Cloxacillin	108 [2.1]
Ciprofloxacin	663 [13.1]
Azithromycin	75 [1.5]
Cefuroxime	217 [4.3]
Ceftriaxone	13 [0.3]
Cephalexin	11 [0.2]
Erythromycin	294 [5.8]
Clarithromycin	56 [1.1]
Clindamycin	17 [0.3]
Levofloxacin	378 [7.4]
Metronidazole	906 [17.8]
Ofloxacin	146 [2.9]
Sparfloxacin	58 [1.1]
Doxycycline	187 [3.7]
Cotrimoxazole	38 [0.7]
Nitrofurantoin	23 [0.5]
Lincomycin	8 [0.2]

Antibiotic combination therapies were present in 12.8% of prescriptions; the most common was Penicillins + Metronidazole accounting for more than half of combination therapies. Metronidazole was found in 93.8% prescriptions in combination with different classes of antibiotics. The Quinolones were also found in 24.4% of prescriptions with other classes of antibiotics [Table 2].

Table 2: Antibiotic combination therapy [n = 652]

Antibiotic combinations	Number [%]
Quinolones + Metronidazole	138 [21.2]
Penicillins + Metronidazole	357 [54.8]
Penicillins + Macrolides	13 [1.9]
Cephalosporins + Metronidazole	7 [1.1]
Macrolides + Metronidazole	49 [7.5]
Lincomycin + Metronidazole	6 [0.9]

Cotrimoxazole + Metronidazole	6[0.9]
Quinolones + Tetracycline	21 [3.2]
Penicillins + Tétracycline	7 [1.1]
Tetracycline + Metronidazole	48 [7.4]

Prescription errors involving wrong dosage and frequency of dosing were found in 15.6% of prescriptions. A breakdown of errors showed that dosage errors accounted for 51.3% and wrong dosing frequency occurred in 48.7% of prescriptions with errors. The highest number of errors occurred with Cephalosporins and macrolides representing about 45% for each of them [Table 3].

Table 3: Prescription errors [n - 797]

Drugs	Dosage errors [%]	Dosing frequency errors [%]
Penicillins	17 [2.1]	18 [2.2]
Cephalosporins	178 [22.3]	189 [23.7]
Macrolides	187 [23.5]	173 [21.7]
Quinolones	19 [2.4]	4 [0.5]
Lincomycins	8 [1.1]	4 [0.5]
Total	**409 [51.3]**	**388 [48.7]**

A comparison of empirical antibiotic prescription pattern and bacterial resistance pattern [Table 4] reveal that most antibiotics given to patients without laboratory confirmation of sensitivity may be considered to be irrational. For instance, resistance to most commonly prescribed Amoxicillin + Clavulanic acid, Cotrimoxazole and Clindamycin may be inappropriate because resistance is as high as 20 – 90%. Resistance to Quinolones is generally below 20% while that of the Macrolides is between 6 – 40%. Empirical prescription of antibiotics against these isolates is likely to result in treatment failure as many strains are becoming resistant to commonly used antibiotics. The result also highlights the problem of resistance to third generation Cephalosporins and older generation Quinolones.

Table 4: Comparison of microbial resistance level and antibiotic prescription pattern [%]

Drug	*SA* [n= 259]	*EC* [n = 138]	*KP* [n = 109]	*CF* [n = 99]	*PS* [n = 25]	*PA* [n = 23]	*HS* [n = 38]	*Average resistance* [%]	PIA [%] Range
Amoxicillin+ Clavulanic acid	73.4	88.0	90.3	73.3	90.9	64.4	39.7	74.3	39 - 90
Cloxacillin	66.4	32.1	23.0	31.7	---	29.8	51.2	39.0	NA
Clarithromycin	25.8	6.9	22.2	19.4	---	32.5	14.6	20.2	6 - 32
Clindamycin	49.4	20.7	21.5	22.8	---	32.5	42.7	31.6	20 – 49
Cotrimoxazole	71.3	74.2	73.5	55.5	84.1	53.5	29.7	63.1	29 – 84
Erythromycin	33.7	12.3	21.7	16.9	13.6	29.8	40.6	24.1	12 – 40

Gentamycin	12.2	30.8	40.9	26.9	27.8	10.5	9.1	22.6	NA
Ceftriaxone	10.9	41.4	50.6	30.6	42.4	36.8	6.1	31.3	6 – 50
Ampiclox	13.2	---	1.9	5.7	4.5	---	22.1	9.5	1 – 22
Amoxicillin	13.7	1.6	5.4	14.1	18.2	5.3	29.7	12.6	1 – 29
Norbactin	9.6	3.1	10.9	11.4	9.1	5.3	23.6	10.4	NA
Ciprofloxacin	11.8	14.1	8.7	6.2	4.5	5.3	22.1	10.4	4 – 23
Perfloxacin	3.9	1.6	8.9	5.7	4.5	5.3	----	4.9	NA
Nalidixic acid	6.1	10.7	15.2	14.9	13.6	5.1	6.1	10.2	NA
Streptomycin	6.4	1.6	5.4	8.6	4.5	----	6.1	5.4	NA
Ofloxacin	3.8	14.5	17.2	14.6	21.2	----	----	14.3	3 – 21
Levofloxacin	6.9	14.2	12.3	9.3	----	5.3	----	9.6	5 – 14
Chloramphenico	5.9	5.9	1.9	5.7	----	----	17.6	7.4	NA
Tetracycline	15.1	40.3	41.1	34.7	77.3	47.4	17.1	39.0	15 – 77

Key: SA = Staph aureus, EC = Escherichia coli, Klebsiella pneumonia, CF = Coliform species, PS = Proteus species, PA = Pseudomonas aeruginosa, HS = Haemolytic streptococci, PIA = potentially inappropriate antibiotic , NA = not applicable

DISCUSSION

Antibiotic prescription pattern in a healthcare facility represents the overall influence of multiple factors. The result of this study showed that Penicillins, Quinolones and Macrolides were the most frequently prescribed antibiotics. Individual antibiotics prescription prevalence showed that Amoxicillin + Clavulanic acid, Metronidazole and Ciprofloxacin were the most prescribed. This result is in contrast to other studies [24,28,49,50,51,52]. Several studies have reported high rate of irrational antibiotic prescription and a significant percentage were empirically prescribed for patients [26,41,53,54].

High rate of empirical prescription of antibiotics is generally related to poor health infrastructure, inadequate human capacity, poor regulatory control and lack of antibiotic stewardship program in many developing countries like Nigeria [42,55,56] . There have been suggestions that empirical antibiotic use is not only related to inadequate or absent laboratory services, but also due to failure to utilize them even where they are available [57].

There is ample evidence in literature that variations in antibiotic prescribing practices have both clinical and non-clinical factors. Irrational empirical antibiotic prescription practice is said to be one of the major contributors to microbial resistance which is reported to be rising globally. The results of this study showed that 39 – 90% of seven common bacterial isolates were resistant to Amoxicillin + Clavulanic acid, similar high level of microbial resistance was also observed for Cotrimoxazole [29 – 84%], Tetracycline [17 – 77%], Ceftriaxone [6 – 50%] and Gentamycin [9 – 40%]. The high level of antibiotic resistance level in this study is comparable to many other studies, though differences exist in the magnitude [58-62].

This high level of multidrug resistance to commonly encountered pathogens is suggestive of the fact that empirical antibiotic prescription is no longer justified. Many patients will not achieve clinical and/or bacteriological clearance of infections. Literature evidence showed that high level of resistance have been reported *for E. coli, Staphylococcus aureus*, *Klebsiella pneumoniae, Pseudomonas aeruginosa* etc. [10,63,64,65]. Antimicrobial resistance is a global phenomenon and no region or country is spared, so there is need accelerate containment effort at the facility level. To preserve low cost broad spectrum antibiotics there should be renewed focus on laboratory confirmation of microbial susceptibility results before antibiotics are prescribed [66-69].

This is particularly urgent with increasing evidence of multidrug resistant strains of microorganisms being found in healthcare facilities [45,70]. Apart from the Quinolones, Methicillin and Chloramphenicol other antibiotics recorded more than 20% resistance to seven bacterial isolates; this should be a cause of concern to facility level providers and policy makers.

Prescription errors frequently occur and it's a common cause of irrational antibiotics use particularly as it relates to dosage, frequency of administration, formulation, timing, duration of treatment, appropriateness [71-73]. The prevalence of errors observed in this study associated with correct dosage and frequency of administration is totally preventable if basic standard of prescription writing are implemented. These errors can negatively affect clinical outcomes, prolong morbidity and may ultimately result in death; there is also increased risk of adverse drug reactions particularly among the most vulnerable [74,75].

There is urgent need to change current antibiotic prescribing practice in the light of increasing multidrug microbial resistance to the most commonly prescribed antibiotics. Results of this study suggest that apart from the Quinolones with relatively lower resistance profile, other antibiotics may be associated with higher frequency of treatment failure. In order to achieve improvement in antibiotic prescription practices multidisciplinary teams should be set up to manage antibiotic stewardship program in the hospital. This program is being implemented worldwide as an attempt to slow down resistance in many healthcare facilities. There is evidence that successful implementation of stewardship programs in hospitals has improved antibiotic prescribing practices and use elsewhere [76-78]. A number of studies that looked at the impact of antibiotic stewardship programs showed that most studies have differing assessment tools and there are challenges with quality of evidence [79-82]. Majority of outcomes studies showed positive improvement in both clinical and economic outcomes for patients [76, 83]. While it is acknowledged that empirical antibiotic use is permissible in acute clinical conditions, it should be reserved for emergencies where laboratory confirmation of microbial sensitivity may be delayed. The healthcare system in this country and patients cannot afford further explosion of microbial resistance to cheap commonly available antibiotics.

Conclusion: Resistance to commonly prescribed antibiotics is high and that makes most empirically prescribed antibiotics to be irrational. It is imperative that emphasis be placed on laboratory confirmation of microbial sensitivity as the basis antibiotic prescription.

Competing interests: None

Ethical approval: This was obtained from the health research ethics committee of University of Maiduguri teaching hospital

REFEREES

1. Centre for disease dynamics, economics and policy. State of the world's antibiotics 2015. CCDEP. Washington DC. USA
2. ECDC 2013. Antimicrobial resistance surveillance in Europe 2012. European centre for disease prevention and control [ECDC] Stockholm, Sweden. Nov 15. 2013
3. Costelloe C, Metcalfe C, Lovering A, Mant D, Hay AD. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: Systematic review and Meta-analysis. BMJ 2010. 340: c2096
4. Egbule O. Antibiotic susceptibility pattern of Escherichia coli and Shigella species isolated from diarrhoea stool of children. Bayero J Pure Appl Sci 2013. 6(1): 62 – 66
5. Abdu A, Aboderin AO, Elusiyan JB, Kolawole D, Lamikanra A. Sero-group distribution of Shigella in Ile-Ife, Southwest Nigeria. Trop Gastroenterol 2013. 34(3): 164 – 169
6. Duru E, Aghahowa O, Umoren F. Bacterial agents associated with infantile diarrhoea and their antimicrobial susceptibility pattern in PorthHarcourt, South-South Nigeria. J Med Sci Public Health 2014. 3(1): 1 – 12
7. Yah S, Eghafona N, Enabulele I, Aliyu H. Ampicillin usage and Ampicillin resistance [AMPR] plasmids mediated Escherichia coli isolated from diarrhoeagenic patients attending some teaching hospitals in Nigeria. Shiraz –E Med J 2006. 7(4): 1 – 12
8. Akinjogunla O, Eghafona N, Ekoi O. Diarrhoeagenic Escherichia coli [DEC]. Prevalence among in and ambulatory patients and susceptibility to antimicrobial chemotherapeutic agents. Afr J Bacteriol Res. 2009. 1(3): 034 – 038
9. *Abdullahi M, Olonitoda S, Inabo I. Isolation of bacteria associated with diarrhoea among children attending some hospitals in Kano metropolis, Kano State Nigeria. Bayero J Pure Appl Sci 2010. 3(1)*

10. Nsofor CA, Iroegbu CU. Antimicrobial resistance profile of Escherichia coli isolated from five major geopolitical zones of Nigeria. Afr J Bacteriol Res 2013. 5(3): 29 – 34
11. World Health Organization. Antimicrobial resistance: Global report on surveillance 2014. Geneva, Switzerland. WHO 2014
12. Centre for disease control and prevention CDC 2013. Antibiotic resistance threats in the United States. Atlanta.
13. Laxminarayan R, Duse A, Wattal C, Zaidi AKM, Wertheim HFL, Sumpradit N et al. Antibiotic resistance – the need for global solutions. The Lancet Infect Dis 2013. 13(12): 1057 – 1098
14. Kayange N, Kamugisha E, Mwizamholya DL, Jeremiah S, Mshana SE. Predictor of positive blood culture and death among neonate with suspected neonatal sepsis in a tertiary hospital, Mwamza – Tanzania. BMC Pediatr 2010. 10(1): 39
15. Roca A, Quinto L, Abacassamo F, Morais L, Valles X, Espasa M, Sigauque B et al. Invasive Haemophilus influenza disease in children less than five years of age in Manhica, a rural area of Southern Mozambique. Trop Med Int Health 2008. 13(6): 8181 – 8186
16. Marshell BM, Levy SB. Food animals and antimicrobials: impacts on human health. Clin Microbiol Rev 2011. 24(4): 718 – 733
17. Chen ED, Anong DN, Akoachere J-FKT. Prescribing pattern and associated factors of antibiotic prescription in primary healthcare facilities of Kumbo east and Kumbo West health district, North West Cameroon. PlosOne 2018, 13(3): e0193353
18. Mbam LA, Monekosso GL, Asongalem EA. Indicators and pattern of prescription of antibiotics at the Buea regional hospital of Cameroon. J Health Sci Dis 2015. 6(1): 1 - 7
19. Erah PO, Olumide GO, Okhamafe AO. Prescribing pattern in two healthcare facilities in Warri, Southern Nigeria; A comparative study. Trop J Pharm Res 2003. 2(1): 175 – 182
20. Alam MM, Parveen F, Arah F, Igbal MJ, Saha RR. Prescribing trends in the outpatient department in a territory hospital in Bangladesh. Bangladesh Med J 2011. 4: 2
21. Igbiks T, Joseph OE. Drug prescription pattern in a Nigerian tertiary hospital. Trop J Pharm Res 2012. 11(1): 146 – 152
22. Eshiet UI, Effiong GS, Akwaowoh AE. The use of antibiotics in a Nigerian tertiary healthcare facility. Am J Biomed Sci Engineering. 2015. 1(3): 25 – 31
23. Anyanwu N, Arigbe-Osula M. Pattern of antibiotic use in a tertiary hospital in Nigeria. Eur J Hosp Pharm Sci Pract 2012. 19: 195
24. Kaur A, Bhagat R, Kaur N, Shafiq N, Gautam V, Malhotra S, Suri V, Bhalla A. A study of antibiotic prescription pattern in patients referred to tertiary care centre in Northern India. Therap Adv Infect Dis 2018. 5(4): 63 – 68
25. Cui D, Liu X, Hawkey P, Li H, Wang Q, Mao Z, Sun J. Use of and microbial resistance to antibiotics in China: a path to reducing antimicrobial resistance. J Int Med Res 2017. 45(6): 1768 – 1778
26. Abdu-Aguye SN, Haruna A, Shehu A, Labaran KS. An assessment of antimicrobial prescribing at a tertiary hospital in North western Nigeria. Afr J Pharmacol Therap 2016. 5(4): 229 – 234

27. Nasir IA, Babyo A, Emeribe AU, Sani NO. Surveillance for antibiotic resistance in Nigeria: challenges and possible solution. Trends in Med Res 2015. 10(4): 106 – 113
28. Umar LW, Isah A, Musa S, Umar B. Prescribing pattern and antibiotic use for hospitalized children in a Northern Nigerian teaching hospital. Ann Afr Med 2018. 17(1): 26 – 32
29. Prah J, Kizzie-Kayford J, Walker E, Ampofo-Asiama A. Antibiotic prescription pattern in a Ghanian healthcare facility. Pan Afr Med J 2017. 28: 214
30. Akinyandenu O, Akinyandenu A. Irrational use and non-prescription sale of antibiotics in Nigeria: A need for change. J Sci Innovative Res 2014. 3(2): 251 – 257
31. *Gebeyehu E, Bantie L, Azage M. Inappropriate use of antibiotics and its associated factors among urban and rural communities of Bahir city administration, Northwest Ethiopia. PlosOne 2015. 10(9)*
32. Shankar RP, Partha P, Shenoy NK, Easow JM, Brahmadathan KN. Prescribing patterns of antibiotics and sensitivity patterns of common micro-organisms in the internal medicine ward of a teaching hospital in Western Nepal: a prospective study. Ann Clin Microbiol and antimicrob 2003. 2: 7
33. Mollahaliloglu S, Alkan A, Donortas B, Ozgulcu S, Akici A. Assessment of antibiotic prescribing at different hospitals and primary healthcare facilities. Saudi Pharm J 2012. 21: 281 – 291
34. Kariuki S, Gordon MA, Feasey N, Parry CM. Antimicrobial resistance and management of invasive Salmonella disease. Vaccine 2015. 33[Suppl 3]: C21 – C29
35. Reuland EA, al Naiemi N, Raadsen SA, Savelkoul PHM, Kluytmans J, Vandenbroucke-Grauls E. Prevalence of ESBL – producing Enterobacteriacea in raw vegetables. Europ J Clin Microbiol Infect Dis 2014. 33(10): 1843 – 1846
36. *Lu PL, Liu YC, Toh HS, Lee YL, Lui YM, Ho CM, Hsueh PR et al. Epidemiology and antimicrobial susceptibility profiles of gram negative bacteria causing UTI in the Asia – Pacific region 2009 – 2010 results from the study for monitoring antimicrobial resistance trends [SMART]. Int J Antimicrob Agents 2012. 40 [Suppl 1]: S37 – S43*
37. Leopold SJ, van Leth F, Tarekegu H, Schultz C. Antimicrobial drug resistance among clinically relevant isolates in sub Saharan Africa: A systematic review. The J Antimicrob Chemother 2014. 69(9): 2337 – 2357
38. *Storberg V. ESBL – producing Enterobacteriacea in Africa: A non systematic literature review of research published 2008 – 2012. Infect Ecology Epidemiol 4. Doi:10.3402/iee.v4.20342*
39. Le Doare K, Brelick J, Heath PT, Sharland M. Systematic review of antibiotic resistance rates among gram negative bacteria in children with sepsis in resource limited countries. J Pediatr Infect Dis Soc 2014. 4(1): 11 – 20
40. Salles MSC, Zurita J, Mejia C, Villegas MV. Persistent gram negative infections in the outpatient setting in Latin America. Epidemiol Infect 2013. 141(12): 2459 – 2472
41. Oduyebo OO, Olayinka AT, Iregbu KC, Verspoten A, Goosens H, Nwajiobi-Princewill PI, Jimoh O, Ige TO, Aigbe AI, Ola-Bello OI, Aboderin AO, Ogunsola FT. A point prevalence survey of antimicrobial prescribing in four tertiary hospitals. Ann Trop Pathol 2017. 8: 42 – 46

42. Petti CA, Polage CR, Quinn TC, Ronald AR, Sande MA. Laboratory medicine in Africa: A barrier to effective healthcare. Clin Infect Dis 2006. 42: 377 – 382
43. Diakema DJ, Pfalter MA. Rapid detection of antibiotic resistant organism carriage for infection prevention. Clin Infect Dis 2013. 56: 1614 – 1620
44. Egbuchulam N, Anyika EN, Soremekun RO. Antibiotic prescribing practices for hospitalized children with suspected bacterial infection in a paediatric hospital in Nigeria. J Hosp Admin 2018. 7(4): 36 – 43
45. Sani RA, Garba SA, Oyewole OA. Antibiotics resistance profile of gram negative bacteria isolated from surgical wounds in Minna, Bida, Kontagora and Suleja areas of Niger State. Am J Med Med Sci 2012: 2(1): 20 – 24
46. Brooks L, Shaw A, Sharp D, Hay AD. Towards a better understanding of patients perspectives of antibiotic resistance and MRSA: a qualitative study. Fam Pract 2008. 25. 341 – 348
47. Buttler CC, Rollinick S, Pill R, Maggs-Rapport F, Stott N. Understanding the culture of prescribing: Qualitative study of general practitioners and patients perceptions of antibiotics for sore throat. BMJ 1998. 317: 637 – 642
48. Kumar S, Little P, Britten N. Why do general practitioners prescribe antibiotics for sore throat? Grounded theory interview study. BMJ 2003. 321: 138
49. *Carneiro M, Ferraz T, Bueno M, Koch BE, Foresti C Lena VF et al. Antibiotic prescription in a teaching hospital: a brief assessment. Rev Assoc Med Bras 2011. 57(4): 414 – 417*
50. Al-Johani K, Reddy SG, Mushayt AS, El-Housseiny A. Pattern of prescription of antibiotics among dental practitioners in Jeddah, KSA: A cross sectional survey. Niger J Clin Pract 2017. 20: 804 – 810
51. Kourlaba G, Gkrania-Klotsas E, Kourkourni E, Mavrogeorgos G, Zaoutis TE. Antibiotic prescribing and expenditures in outpatients' adults in Greece 2010 – 2015: Evidence from real world practice. Euro Surveill 2016. 21(26): Pll = 30266
52. Akram A, Megha R, Irfanul H, Pravina A, Rahul I, Ram D, Sheetal K, Isha. Study of prescription pattern of antibiotics in the medicine department in a teaching hospital: A descriptive study. Int J Toxicol Pharmacol Res 2014. 6(2): 43 – 46
53. Abhijit K, Jain P, Upadhyaya P, Jain S. A study monitoring pattern of antibiotics in a tertiary care hospital in North India. Int J Basic Clin Pharmacol 2014. 3: 1006 – 1011
54. Fahmzad A, Eydian Z, Karimi A, Shiva F, Armin S, Ghanae RM, Fallah F, Tabatabaei SR, Shirvani F et al. Antibiotic prescribing in neonates of seventeen Iranian hospitals. Arch Pediatr Infect Dis 2017. 5(4): e61530
55. Hunter B, Harbarth S, Nathwani D; ESCMID study group for antibiotic policies [ESGAP]. Successful stories of implementation of antimicrobial stewardship: A narrative review. Clin Microbiol Infect 2014. 20: 954 – 962
56. Tiong JJ, Loo JS, Mai CW. Global antimicrobial stewardship: A closer look at the formidable implementation challenges. Front Microbiol 2016. 7: 1860
57. Kimang'a AN. A situational analysis of antimicrobial drug resistance in Africa. Are we losing the battle? Ethiop J Health Sci 2012. 22: 135 – 143

58. Shahriar M, Hossain M, Kabir S. A survey of antimicrobial sensitivity pattern of different antibiotics on clinical isolates of *Escherichia coli* collected for Dhaka City. Bangladesh. J Appl Sci Environ Manage 2010. 14(3): 19 – 20
59. Masyeni S, Sukmawati H, Siskayani AS, Dharmayanti S, Sari K. Antimicrobial susceptibility pattern of pathogens isolated from various specimens in Denpasar – Bali: A two years retrospective survey. Biomed Pharmacol J 2018. 11(1): 493 – 502
60. Saba CKS, Amenyona JK, Kpordze SW. Prevalence and pattern of antibiotic resistance of *Staphylococcus aureus* from door handles and other points of contact in public hospitals in Ghana. Antimicrob Resistance Infect Control 2017. 6: 44
61. Fadeyi A, Zumuk CP, Raheem RA, Nwabuisi C, Desalu OO. Prevalence and antibiotic susceptibility pattern of EBSL producing *Klebsiella* from clinical specimens in a Nigerian tertiary hospital. Afr J Infect Dis 2006. 10(1): 32 – 37
62. Ray J, Paul R, Haldar A, Mondol S. A study on antibiotic resistance pattern of Escherichia coli isolated from urine specimens in east India. Int J Med Sci Public Health 2015. 4(12): 1670 - 1674
63. Ojo-Bola O, Oluyege AO. Antibiotic resistance of bacteria associated with pneumonia in HIV/AIDS patients in Nigeria. Am J Infect Dis Microbiol 2014. 2(6): 138 – 144
64. Abubakar EM. Antimicrobial susceptibility pattern of pathogenic bacteria causing urinary tract infections at the specialist hospital Yola, Adamawa State, Nigeria. J Clin Med Res 2009. 1(1): 001 – 008
65. Pattanayak C, Patanaik SK, Datta PP, Panda P. A study of antibiotic sensitivity pattern of bacterial isolates in the intensive care unit of a tertiary care hospital in Eastern India. Int J Basic Clin Pharmacol 2013. 2(2): 153 – 159
66. Timothy OO, Olusesan FJ, Adesola BO, Temitayo AA, David FO, Ige OO. Antibiotic resistance pattern of bacterial isolates from cases of urinary tract infections among hospitalized and outpatients at a tertiary health facility in South Western Nigeria. Ann Trop Med Public Health 2014. 7: 130 – 135
67. Radfar M, Fallahi M, Kazemian M, Borhani S. A comparative evaluation of microbial pattern and microbial sensitivity in a level III NICU between two decades. Arch Pediatr Infect Dis 2017. 5(2): e39299
68. Ahmed NH, Hussain T. Antimicrobial susceptibility pattern of leading pathogens isolated from laboratory confirmed blood stream infections in a multispecialty sanatorium. J Global Infect Dis 2014. 6(4): 141 – 146
69. Bernabe KJ, Langendorf C, Ford N, Ronat JB, Murphy RA. Antimicrobial resistance in West Africa: a systematic review and Meta-analysis. Int J Antimicrob Agents 2017. 50: 629 – 639
70. Chakraborty S, Moshina K, Sarker PK, Alam MDZ, Sayem SMA. Prevalence, antibiotics susceptibility profiles and ESBL production in *Klebsiella pneumoniae* and *Klebsiella oxytoca* among hospitalized patients. Periodicum Biologocum 2016. 118(1): 53 – 58
71. Aronson JK. Medication errors; Definitions and classification. Br J Clin Pharmacol 2009. 67: 599 – 604

72. Patel I, Balkrishnan R. Medication error management around the globe: An overview. Indian J Pharm Sci 2010. 72: 539 – 545
73. *Sutradhar KB, Saha A, Huda NH et al. Irrational use of antibiotics and antibiotic resistance in Southern rural Bangladesh: perspectives from both the physicians and patients. Annual Res Rev Biol 2014. 4(9): 1421 – 1430*
74. Stuckey ER. Prevention of medication errors in the pediatric in patient setting. Pediatr 2003. 112: 431 – 436
75. Miller MR, Robinson KA, Lubomski LH, Rinke ML, Pronovost PJ. Medication errors in pediatric care : A systematic review of epidemiology and an evaluation of evidence supporting reduction strategy recommendations. Qual Saf Health Care 2007. 16: 116 – 126
76. Davey P, Brown E, Charani E et al. Interventions to improve antibiotic prescribing practices for hospital in-patients. Cochrane Database Syst Rev 2013. 4: CD003543
77. Schuts EC, Hulscher MEJL, Mouton JW et al. A systematic review and meta-analysis of current evidence on hospital antimicrobial stewardship objectives. Lancet Infect Dis 2016. Pii: S1473 – 3099 (16) 0065 – 7
78. Jan-Willem H, Ron Hendrix D, Poleman R, Maarten J, Niesters HG, Potsma MJ, Sinha B, Friedrich AW. Measuring the impact of antimicrobial stewardship programmes. Expert Rev of Antimicrob Infect Ther 2016. 14(6): 569 – 575
79. Howard P, Pulcini C, Levy Hara G et al. An international cross sectional survey of antimicrobial stewardship programmes in hospitals. J Antimicrob Chemother 2015. 70: 1245 – 1255
80. Lesprit P, Landelle C, Brun-Buisson C. Clinical impact of unsolicited post prescription antibiotic review in surgical and medical wards: a randomized controlled trial. Clin Microbiol Infect 2013. 19: 91 – 97
81. Fleet E, Gopal Rao G, Patel B et al. Impact of implementation of a novel antimicrobial stewardship tool on antibiotic use in nursing home: a prospective cluster randomized controlled pilot study. J Antimicrob Chemother 2014. 69: 2265 – 2273
82. Taconelli E, Cataldo M, Paul M et al. STROBE-AMS: recommendations to optimize reporting of epidemiological studies on antimicrobial resistance and inform improvement in antimicrobial stewardship. BMJ Open 2016. 6: e010134
83. McGowan J. Antimicrobial stewardship programs – the state of the art in 2011: focus on outcome and methods. Infect Control Hosp Epidemiol 2012. 33: 331 – 337.