IMPACT OF ANTIBIOTIC STEWARDSHIP INTERVENTIONS ON COMPLIANCE WITH SURGICAL ANTIBIOTIC PROPHYLAXIS IN OBSTETRICS AND GYNAECOLOGY SURGERIES IN NIGERIA

ABUBAKAR USMAN

UNIVERSITI SAINS MALAYSIA

2018

IMPACT OF ANTIBIOTIC STEWARDSHIP INTERVENTIONS ON COMPLIANCE WITH SURGICAL ANTIBIOTIC PROPHYLAXIS IN OBSTETRICS AND GYNAECOLOGY SURGERIES IN NIGERIA

by

ABUBAKAR USMAN

Thesis submitted in total fulfilment of the requirement of the Degree of Doctor of Philosophy

August 2018

ACKNOWLEDGEMENT

All praises are due to Almighty Allah, the King of kings and Lord of the World, for the gift of life, unlimited bounties, and the opportunity to complete my Doctor of Philosophy journey. May Allah send peace and salutations to the Holy Prophet, Muhammad (SAW), his family and household, his companions and all those who trend his path until the Day of Judgement Amin!

It is indeed true that Doctor of Philosophy is mighty and filled with numerous unavoidable challenges. However, working under the supervision of **Prof Dr Syed Azhar Syed Sulaiman** made me hurdle the challenges I encountered during my studies. I wish to thank you for the fatherly and scholarly support, academic and moral advice, encouragement, and mentoring. I cannot pay you back but I wish you success and Allah's mercy in all your endeavours. I will also like to appreciate Universiti Sains Malaysia for the opportunity given to me to serve as a Graduate Assistant during the period of my study.

I wish to acknowledge the immense contribution of my field supervisors; **Prof Jamilu Tukur** and **Prof A.G. Adesiyun**, during this research. The Heads of Departments of Obstetrics and Gynaecology, Consultants, Registrars, House officers, and Nurses in the participating hospitals also deserve acknowledgement for their support during the study. To my colleagues at Ibrahim Badamasi Babangida Specialist Hospital, Minna, and Universiti Sains Malaysia, Penang, I am very grateful to you for your support, cooperation and encouragement. I pray you all excel in your various endeavours.

My acknowledgement would be incomplete without mentioning the names of **Umar Liman**, **Zakariya Uba Zango**, and **Umar Rayyanu** for their kind hospitality during my data collection in Nigeria. Sir Isaac Newton once said “If I have seen further than others, it is by standing upon the shoulder of giants.” I have come a long way standing on two unshakable pillars; **Abubakar** and **Maimuna Muhammad Mokwa** (my parents). I reserve my deepest gratitude for you because your unalloyed parental love, care, support, encouragement, advice, and prayers were pivotal to my success today. I pray Almighty Allah spare your lives to reap the fruit of your labour. To my siblings and fiancée, thank you so much for the support, care, encouragement and patience during my studies. Glory be to Allah!

Abubakar Usman

Penang, Malaysia

August 2018

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

KESAN PENGAWASAN ANTIBIOTIK ATAS PROFILAKSIS ANTIBIOTIK UNTUK PEMBEDAHAN DALAM BIDANG PEMBEDAHAN OBSTETRIK DAN GINEKOLOGI DI NIGERIA

ABSTRAK

Jangkitan tapak pembedahan (SSI) ialah jangkitan kedua yang paling biasa dalam bidang perubatan di Nigeria. Insidens SSI lebih tinggi dalam pembedahan obstetrik dan ginekologi (O&G). Profilaksis antibiotik digunakan untuk mengelakkan SSI. Terdapat bukti bahawa wujud prevalens tinggi profilaksis antibiotik yang salah di Nigeria. Walau bagaimanapun, takat masalah ini dalam O&G belum dikaji. Kajian ini menilai prevalens kesalahan dalam profilaksis antibiotik untuk pembedahan O&G dan mengimplementasi langkah-langkah persuasif untuk mengubah tabiat preskripsi. Selain itu, kajian ini mengukur kesan pengawasan antibiotik kepada penggunaan antibiotik serta implikasi klinikal dan kewangan. Kajian pra dan selepas intervensi ini telah dijalankan di Jabatan O&G di 3 hospital semasa tempoh pra-intervensi dan di 2 hospital semasa tempoh selepas intervensi dengan tempoh 12 minggu untuk setiap fasa. Intervensi yang diimplemantasi ialah: pendidikan doktor perubatan, audit dan maklum balas, dan perkembangan serta implementasi protokol profilaksis antibiotik. Subjek kajian sebanyak 218 pesakit diperlukan untuk setiap fasa. Data dianalisis dengan SPSS versi 23. Sebanyak 248 pesakit direkrut semasa tempoh pra-intervensi termasuk 226 pesakit dari 2 hospital di mana kajian selepas intervensi dijalankan. Tempoh selepas intervensi melibatkan 238 pesakit. Kajian ini menunjukkan bahawa tidak terdapat perbezaan signifikan dalam usia, tempoh tinggal di hospital dan anggaran kehilangan darah antara 2 kumpulan tersebut. Terdapat perbezaan signifikan dalam klasifikasi luka dan jenis pembedahan. Keputusan menunjukkan bahawa terdapat penggunaan antibiotik spektrum yang berleluasa (gabungan perencat beta-laktam / beta-laktamase) sebanyak 73.4% dan cephalosporin generasi ketiga (30.2%), dan antibiotik dengan spektra aktiviti yang berlebihan (71.4%) di tiga hospital semasa tempoh pra-intervensi. Masa pemberian profilaxis antibiotik adalah optimal dalam 16.5% daripada kes manakala tempoh profilaksis dipanjangkan dalam semua kes (min purata = 8.7 ± 1.0 hari). Pematuhan kepada masa pemberian dan tempoh profilaksis antibiotik meningkat sebanyak 29% (dari 14.2% kepada 43.3%) dan 21.8% (dari 0% kepada 21.8%) masing-masing selepas intervensi (P <0.001). Terdapat penurunan secara signifikan dalam penggunaan cephalosporin generasi ketiga (8.6%; P = 0.032), preskripsi berlebihan (19.1%; P <0.001), dan kos profilaksis antibiotik ($ 4.20 / prosedur; P <0.001). Selain itu, densiti penggunaan antibiotik untuk profilaksis menurun sebanyak 3.8 Dosis harian yang ditetapkan (DDD) untuk setiap prosedur (daripada 16.7 DDD / prosedur kepada 12.8 DDD / prosedur) selepas intervensi. Pengurangan penggunaan antibiotik tidak menjejaskan keputusan klinikal; insiden SSI semasa pesakit tinggal di hospital menurun daripada 4% dalam kumpulan pra-intervensi kepada 3.4% dalam kumpulan selepas intervensi (P = 0.722). Langkah-langkah pengawasan antibiotik mengubah tabiat preskripsi secara signifikan dan mengurangkan beban klinikal dan kewangan. Walau bagaimanapun, intervensi tidak berjaya kerana perbezaan besar antara bukti klinikal dan amalan profilaksis antibiotik untuk pembedahan di Nigeria. Kajian masa depan harus mengimplementasi intervensi terbatas dengan pendekatan persuasif yang digunakan dalam kajian ini.

IMPACT OF ANTIBIOTIC STEWARDSHIP INTERVENTIONS ON COMPLIANCE WITH SURGICAL ANTIBIOTIC PROPHYLAXIS IN OBSTETRICS AND GYNAECOLOGY SURGERIES IN NIGERIA

ABSTRACT

Surgical site infection (SSI) is the second most common healthcare associated infection in Nigeria. The incidence of SSI is higher in obstetrics and gynaecology surgeries. Antibiotic prophylaxis is used to prevent SSIs. Evidence demonstrates high prevalence of antibiotic prophylaxis errors in Nigeria. However, the magnitude of the problem in obstetrics and gynaecology surgeries has not been studied. This study evaluated the prevalence of antibiotic prophylaxis errors in obstetrics and gynaecology surgeries and implemented persuasive interventions to change the prescriber's behaviour. In addition, this study measured the impact of stewardship interventions on antibiotic utilization, clinical, and economic outcomes. This pre- and post-intervention study was conducted in the Department of Obstetrics and Gynaecology in 3 hospitals during the pre-intervention period and 2 hospitals in the post-intervention period. The duration of each phase was 12 weeks. The interventions implemented include: education of clinicians, audit and feedback, and development and implementation of antibiotic prophylaxis protocol. A sample size of 218 patients in each phase was required. Data was analysed using SPSS version 23. A total of 248 patients were recruited during the pre-intervention period, out of which 226 patients were from the 2 hospitals that participated in the post-intervention period. In the post-intervention period, 238 patients were involved. There was no significant difference in the age, length of hospitals stay, and estimated blood loss between the 2 groups. Difference in wound classification, and type of surgery was significant. The results show that there was pervasive use of broader spectrum antibiotics (beta-lactam/beta-lactamase inhibitor combinations (73.4%) and third generation cephalosporin (30.2%), and antibiotics with redundant spectra of activity (71.4%) in the three hospitals during the pre-intervention period. Time of administration of antibiotic prophylaxis was optimal in 16.5% of the cases while duration of prophylaxis was prolonged in all the cases (mean duration = 8.7 ± 1.0 days). Compliance with time of administration and duration of antibiotic prophylaxis were increased by 29% (from 14.2% to 43.3%) and 21.8% (from 0% to 21.8%) after the intervention respectively ($P < 0.001$). There were significant decrease in the use of third generation cephalosporin (8.6%; $P = 0.032$), redundancy (19.1%; $P < 0.001$), and costs of antibiotic prophylaxis ($ 4.20/procedure; $P < 0.001$). In addition, density of antibiotics use for prophylaxis declined by 3.8 Defined Daily Dose (DDD) per procedure (from 16.7 DDD/procedure to 12.8 DDD/procedure) after the intervention. The decrease in antibiotic utilization did not compromise clinical outcomes; incidence of SSI during hospitalization dropped from 4% in the pre-intervention group to 3.4% in the post-intervention group ($P = 0.722$). Antibiotic stewardship interventions significantly improved prescribing outcomes, and reduced clinical and economic outcomes. However, the interventions were unsuccessful because there is still a huge gap between available evidence and practice of surgical antibiotic prophylaxis in Nigeria. Future studies should target implementing restrictive interventions in combination with the persuasive approach utilized in this study.

CHAPTER ONE

INTRODUCTION

1.1 Introduction

The prevalence of healthcare associated infections is "strikingly high" in developing countries. About 16% of hospitalized patients in developing countries are diagnosed with healthcare associated infections, compared to 7.1% and 4.5% in Europe and the United States respectively [1]. Surgical Site Infection (SSI) is the most common healthcare associated infection in developing countries; cumulative incidence is 5.6% [1]. The cumulative incidence of SSIs in sub-Sahara Africa (14.8%) is higher than developing countries [2]. Studies have shown that the incidence of SSIs in Nigeria is between 9.1% and 30.1% [3-5]. This is higher than the cumulative incidence reported for European countries (2.7 per 100 procedures) and the United States (2.4 per 100 procedure) [1]. In Nigeria, SSI rate varies across surgical disciplines, with higher rate in obstetrics and gynaecology ward (47.5%) than surgical ward (39.5%) [6].

Surgical Site Infections are associated with significant morbidity, mortality and healthcare costs. Risk of mortality and admission to intensive care unit is two times higher in patients with SSIs compared with those without SSI. In addition, the odds of hospital readmission are 6 times higher in patients with SSI compared to those without SSI. Furthermore, SSIs are associated with increased length of hospitals stay; duration of hospitalization is prolonged by an average of 12 days (extra 6.5 days during first and 5.5 days during readmission) [7]. Moreover, the extra healthcare cost of treating surgical patients who develop SSIs was estimated as $ 5,000 [7]. Another study revealed that SSIs increased cost of healthcare ($ 10,500) and length of hospitalization (4.3 days) in patients who had vascular and general surgeries [8]. Broex et al. submitted that SSIs double the direct cost of medical care and length of hospitalization [9].

Although, SSI constitutes significant clinical and economic burden both to the patient and the society, these infections and the associated implications are preventable [1]. Strategies for preventing SSIs include: administration of surgical antibiotic prophylaxis, infection control (skin disinfection, equipment sterilization), and control of blood sugar level [10-12]. However, non surgical antibiotic prophylaxis interventions are outside the scope of this thesis. Surgical antibiotic prophylaxis is defined as the administration of antibiotic prior to incision with the ultimate goal of preventing surgical wound infections. Surgical antibiotic prophylaxis is like a two-edge sword; appropriate use provides beneficial therapeutic effect while inappropriate use produce detrimental public health effects (wound infection, adverse effect, and antibiotic resistance) [13]. The efficacy of antibiotic prophylaxis is influenced by several factors; choice of antibiotic, time of administration, dose, re-dosing (in prolong surgery) and duration of antibiotic prophylaxis [14]. Inappropriate use of antibiotic prophylaxis is associated with some consequences. For example; selection of broad spectrum antibiotic increases the cost of antibiotic prophylaxis and hastens emergency of resistance to life-saving antibiotics. Suboptimal time and dose (particularly in obese patients) of antibiotic prophylaxis makes the patient vulnerable to post-surgical wound infections. Prolonged duration of antibiotic prophylaxis is not superior to single dose and it is associated with antibiotic resistant infections [15].

1.2 Surgical antibiotic prophylaxis practice in Nigeria

In Nigeria, antibiotics are the most common prescriptions in both inpatient and outpatient settings. Studies have shown that 28.1% – 83.5% of prescriptions contain at least one antibiotic [16-20]. Inappropriate use or prescription of antibiotic is not uncommon in Nigeria. Patients purchase antibiotics without prescriptions despite the prescription-only dispensing regulation. In fact, about 58% of antibiotics dispensed in outpatient pharmacy have no prescription. This unethical practice is associated with sub-therapeutic dosing of antibiotics [18]. Over-the-counter purchase of antibiotic provides the stimulus for self-medication [21]. There are few studies that evaluated the prevalence of surgical antibiotic prophylaxis errors in Nigeria. These studies demonstrated that errors associated with choice, dose, time of administration and duration of surgical antibiotic prophylaxis are common in Nigeria [22, 23].

1.2.1 Selection of antibiotic(s) for surgical prophylaxis

The World Health Organization recommends that antibiotics used for surgical prophylaxis should not be used extensively in medical practice. In other words, antibiotic selected for surgical prophylaxis should not be the first-line agent for treatment of infections. In view of this, first generation cephalosporin (cefazolin), second generation cephalosporin (cefoxitin, cefotetan, cefuroxime) and penicillin (ampicillin) were recommended [11]. In Nigeria, a wide range of broader spectrum antibiotics are prescribed for surgical prophylaxis. Common antibiotics used for surgical prophylaxis includes: third generation cephalosporins, fluoroquinolones, beta-lactam plus beta-lactamase inhibitor, aminoglycosides and metronidazole [23, 24]. In addition, multiple antibiotics with different mechanisms of action are also prescribed for surgical antibiotic prophylaxis [23].

Another problem with selection of antibiotics for surgical prophylaxis is redundancy. Redundant antibiotic combination is defined as the administration of two antibiotics with overlapping spectra of activity on the same day for two consecutive days during the same admission, and which lacks evidence to demonstrate synergy for the treatment of a single indication [25]. The major type of redundancy encountered is dual anaerobic antibiotic combination. This is defined as the use of metronidazole or clindamycin with another anaerobic antibiotic (beta-lactam/beta-lactamase inhibitors, carbapenems, cephamycins, moxifloxacin or tigecycline) on the same day for 2 consecutive days during the same hospitalization [26]. This is with the exception of patients receiving treatment for *Clostridium difficile* colitis and biliary tract infections (cholecystitis and cholangitis) [26, 27]. This type of medication error is overlooked by most clinicians.

A Nigerian Randomized Trial compared the effectiveness of pre-incision antibiotic prophylaxis to post-cord clamp administration in reducing SSIs among women who had caesarean section. All the patients received a combination of amoxicillin-clavulanic acid and metronidazole (redundant anaerobic combinations) either before incision or after cord-clamping [28]. The use of redundant antibiotics in patients undergoing trial depicts the dearth of knowledge regarding the spectrum of antibiotic activity among Obstetricians in Nigeria.

At the root of inappropriate antibiotic selection is lack of knowledge pertaining to principles of antibiotic selection for surgical prophylaxis. An observational study conducted in Nigeria found inadequate knowledge of antibiotic prophylaxis among surgeons. Seventy percent of surgeons prescribed ceftriaxone for surgical antibiotic prophylaxis. However, more than 50% do not know common pathogens isolated from surgical wounds in their respective hospitals. This is an indicator of inappropriate antibiotic selection for surgical prophylaxis [24]. Another survey found that Nigerian anaesthetists had insufficient knowledge of antibiotic selection with over 70% indicating the need for more education pertaining to the principles of antibiotic selection [29]. In addition, there is a misconception among physicians that expensive and broad spectrum antibiotics are more effective than inexpensive narrow spectrum agents [30]. This contributes to the inappropriate selection of antibiotic for surgical prophylaxis.

1.2.2 Timing of surgical antibiotic prophylaxis

Evidence based guidelines recommend that intravenous surgical antibiotic prophylaxis should be administered within 60 minutes before incision [31, 32]. However, timing of antibiotic prophylaxis was inappropriate in a substantial proportion of surgical cases in Nigeria. An observational study found that only 55.8% of surgical procedures received antibiotic prophylaxis before incision [22]. The authors argued that lack of surgical antibiotic prophylaxis protocol hinders compliance with timing of antibiotic prophylaxis [22]. Another study showed that only 35.3% of paediatric surgeries received preoperative prophylactic antibiotics. Although, over 70% of the patients had clean-contaminated and contaminated surgeries, only one – third of the study population received antibiotic prophylaxis. The remaining 64.7% received therapeutic antibiotics. This denotes both inappropriate time and duration of antibiotic prophylaxis in many cases [23].

Suboptimal timing of surgical antibiotic prophylaxis is a medication error that makes patient vulnerable to post-operation wound infections. A systematic review and meta-analysis of studies that evaluated the impact of different timing of antibiotic prophylaxis on SSIs illustrated that administering antibiotic prophylaxis more than 120 minutes before incision was associated with 5-times higher risk of SSIs. In addition, administration of prophylaxis after incision doubles the risk of SSIs compared to pre-incision administration [33].

Low compliance with the timing of antibiotic prophylaxis may be attributed to lack of knowledge among healthcare professionals in Nigeria. To buttress this point, a cross sectional study concluded that health professionals in Nigeria had poor knowledge regarding optimal timing of surgical antibiotic prophylaxis [34]. Another cross-sectional study demonstrated that anaesthetists' knowledge regarding timing of surgical antibiotic prophylaxis was insufficient. In fact, more than 80% indicated they need more training on appropriate timing antibiotic prophylaxis [29]. In addition, lack of surgical antibiotic prophylaxis protocol has been mentioned as a reason for non-compliance with timing of antibiotic prophylaxis [22].

1.2.3 Duration of surgical antibiotic prophylaxis

Evidence-based guideline recommends administration of single dose antibiotic prophylaxis in patients who undergo surgery. Additional doses may be required in certain circumstances (when blood loss exceeds 1000ml or prolonged duration of surgery). However, duration of surgical antibiotic prophylaxis should be less than 24 hours after completion of surgery [32]. Several studies have demonstrated the non-inferiority of single dose antibiotic prophylaxis compared to multiple doses [35, 36].

There is limited evidence to demonstrate compliance with the duration of antibiotic prophylaxis in Nigeria. A cross-sectional study conducted among orthopaedic surgeons in Nigeria found that only 42% administered single dose surgical antibiotic prophylaxis [24]. Moreover, a retrospective study involving 1,300 paediatric abdominal surgery (over 70% were either clean-contaminated or contaminated wound) found that 65% of the patients received therapeutic antibiotics. The duration of antibiotic therapy was not stated. The fact that patients received antibiotic therapy where prophylaxis is indicated denotes possible extension of duration of antibiotic use beyond 24 hours after completion of surgery [23]. A 4-year cohort study found that prolonged duration of antibiotic prophylaxis (> 48 hours) among patients who had coronary artery bypass graft surgery was not associated with significant decrease in SSIs. However, the odds of antibiotic resistant infection was 1.6 times higher among patients receiving antibiotic prophylaxis for a more than 48 hours after completion of surgery (P = 0.027) [15].

1.2.4 Surgical antibiotic prophylaxis prescribing etiquette in the hospitals

Obstetricians and Gynaecologists in the participating hospitals (Ahmadu Bello University Teaching Hospital, Aminu Kano Teaching Hospital) were grouped into 4 - 5 teams. Each team comprises of a Senior Consultant Obstetrician and Gynaecologist, Consultant Obstetricians and Gynaecologists, Senior Registrars, Registrars, and House Officers. Each team was headed by a Senior Consultant (usually a Professor) who decides the choice, dose, time of administration and duration of antibiotic prophylaxis for the team. Prescriptions were written by any member of the team and must align with the decisions of the team leader.

1.3 Implications of non-compliance with surgical antibiotic prophylaxis in Nigeria

Non-compliance with surgical antibiotic prophylaxis measures is associated with some clinical, economic, and microbial implications. The implications of non-compliance with surgical antibiotic prophylaxis recommendations in Nigeria are discussed below;

1.3.1 Surgical Site Infections in Nigeria

Surgical site infections (SSIs) are the second most common nosocomial infections in Nigeria. SSIs account for 30.7% of all healthcare acquired infections [6]. Studies have reported high incidence of SSIs in Nigeria. The incidence of SSIs in Nigeria was between 9.1% and 30.1% [3-5]. This is higher than cumulative incidence reported for developing countries (5.6 per 100 procedures), European countries (2.9 per 100 procedures) and the United States (2.7 per 100 procedures) [1]. Higher incidence of SSIs in Nigeria in comparison to developing and developed countries could be explained by non-compliance with the timing of surgical antibiotic prophylaxis. Evidence from a recent systematic review and meta-analysis highlighted the importance of timing on the risk of SSIs. The reviewers concluded that antibiotic prophylaxis should be administered within 60 minutes before incision [33]. Antibiotic prophylaxis administered outside this time window carries an additional risk of post-operation infections. When administered more than 120 minutes before incision or after incision risk of SSI is increased by 5- and 2-times respectively [33].

1.3.2 Definition of Surgical Site Infections (SSIs)

The Centre for Disease Control and Prevention (CDC), and the National Healthcare Safety Network guidelines defined Surgical Site Infection (SSI) as any infection that occur either at the site of incision or in any other part of the body within 30 days in procedures with no implant or within 1 year in implant-related procedures [37]. SSIs are categorized into 2 major classes; incisional and organ/space SSI [37].

1.3.2(a) Incisional Surgical Site Infection

This type of SSI occurs within 30 post-surgical days and is localized to the site of incision [37]. Incisional SSIs are further classified into 2; superficial incisional and deep incisional SSIs.

i) Superficial incisional Surgical Site Infection

Superficial incisional SSI is defined as any post-surgical infection that manifests within 30 days, limited to the skin or subcutaneous tissue of the incision, and meets at least one of the following criteria [37];

- Purulent discharge from the superficial incision
- Isolation of microorganism(s) from tissue or fluid collected aseptically from the superficial incision
- Patient exhibits at least one sign or symptom of infection; localized pain, swelling or heat, and deliberate opening of the wound by a surgeon except where culture result indicated the contrary
- Superficial incisional SSI diagnosis the surgeon or attending physician [37].

ii) Deep incisional Surgical Site Infection

Deep incisional SSI is defined as an infection localized to the muscle and fascial layers of the incision occurring within 30 days after non-implant related surgery and after 1 year in implant-related surgical procedures. In addition, the infection should satisfy at least one of the following criteria [37];

- Purulent discharge from the deep incision
- Deep incision break down or deliberate opening of the wound by a surgeon when the patient has at least one of the following sign or symptom of infection: fever (> 38°C), localized tenderness or pain, except where culture indicates otherwise
- An abscess involving the deep incision discovered through direct wound inspection, during reoperation, or by histopathologic or radiologic examination
- Diagnosis of deep incisional SSI by the surgeon or attending physician [37].

1.3.2(b) Organ/space Surgical Site Infection

Organ/space SSI is an infection that occurs within 30 post-surgical days in surgery without implant or 1 year post-surgery in implant-related procedures and involves any part of the body other than the superficial and deep incision. The infection should satisfy at least one of the following criteria [37];

- Purulent discharge
- Culture positive result from a tissue or fluid collected aseptically from the organ/space

- Abscess or other evidence of infection involving the organ/space found during direct wound inspection, during reoperation, or by histopathologic or radiologic examination
- Diagnosis of organ/space SSI made by the attending physician or surgeon [37].

1.3.3 Antibiotic Resistant Surgical Site Infections in Nigeria

Antibiotic resistance is a product of inappropriate use of antibiotic for empirical, therapeutic or prophylactic purposes. Several studies conducted in Nigeria found that SSI represents a greater proportion of antibiotic resistant infections. These infections include both gram negative and gram positive infections. Among gram positive bacteria, Methicillin Resistant *Staphylococcus aureus* (MRSA) is a common culprit. Studies reported that the proportion of SSIs in all MRSA isolates in Nigeria ranged between 18.6% and 75% [38-42]. Similarly, substantial proportions of Extended Spectrum Beta-Lactamase (ESBL) producing *enterobacteriaceae* isolates are from surgical wound specimens. Wound specimen represents 21.4% – 77.8% and 67% of all ESBL producing *E. coli* and *Klebsiella pneumoniae* isolates respectively [43, 44].

Possible explanation for the high rate of antibiotic resistant SSIs is the overuse of antibiotic prophylaxis; bearing in mind the role of poor infection control. There is no evidence to demonstrate the correlation between antibiotic prophylaxis error and incidence of antibiotic resistant SSIs in Nigeria. However, studies conducted in other parts of the world showed significant association between antibiotic overuse and the isolation of antibiotic resistant pathogens in infected surgical wounds. A prospective cohort study found that prolonged duration of antibiotic prophylaxis among patients who had coronary artery bypass graft (CABG) surgery was a significant risk factor for cephalosporin resistant *enterobacteriaceae* and vancomycin resistant *enterococci* infections [15]. In addition, a 5-year case-control study conducted among oncology surgical patients in Mexico concluded that prolonged duration of antibiotic prophylaxis (more than 24 hours after completion of surgery) increased the risk of third generation cephalosporin resistant *E. coli* SSIs by 6-folds [45].

1.3.4 Increased cost of surgical antibiotic prophylaxis

Non-compliance with duration of antibiotic prophylaxis increases healthcare cost. The additional cost of prolonged antibiotic prophylaxis in Nigeria is unknown. However, studies conducted in other parts of the world shows that a substantial healthcare cost is incurred as a result of prolonged duration of antibiotic prophylaxis [46].

1.4 Strategies to address non-compliance with surgical antibiotic prophylaxis

Factors associated with non-compliance to surgical antibiotic prophylaxis measures and their possible implications in Nigeria were discussed above. These challenges could be addressed through implementation of antibiotic stewardship interventions. Antibiotic stewardship is a program involving interventions designed and implemented to reduce inappropriate use (indication, selection, route, dose, timing and duration) of antibiotics for empirical, prophylactic and therapeutic purposes [47-50]. The main goal of antibiotic stewardship is to improve patient's clinical outcomes, and minimize adverse effects and antibiotic resistance [47-50]. Secondary goal of these interventions is to reduce health care cost [47, 49, 51]. Compliance with antibiotic prophylaxis measures could be improved through the development and implementation of a local antibiotic prophylaxis protocol [52]. In addition, training of surgeons regarding the principles of antibiotic prophylaxis has been proven to improve compliance [53]. Furthermore, audit of compliance with antibiotic prophylaxis measures and feedbacks are effective antibiotic stewardship interventions [54]. Although, restrictive interventions such as automatic stop order and personalized antibiotic prophylaxis set are effective in optimizing use of antibiotics among surgical patients [55], such strategies require huge manpower and capital which are deficient in Nigeria. Therefore, the strategies to be implemented (develop and implement protocol, education, audit and feedback) are chosen because they are neither capital nor labour intensive.

1.5 Nigerian Healthcare system

Nigeria is a country located in West Africa. It has 36 states and a Federal Capital Territory, and an estimated population of over 170 million people. The healthcare system in the country comprises of both orthodox and traditional medicine. Healthcare institutions in the country are either government (public) or private-owned hospitals. Nigeria operates a 3-tier system of government which includes: Federal, State, and Local Governments. Public healthcare facilities in Nigeria are categorized into 3; primary, secondary and tertiary health institutions. Primary healthcare facilities are distributed in each local government and are funded by Local, State and Federal government. This is the first point of care for patients. Secondary health facilities are the general hospitals, which are funded by state governments and receive referral from primary health institutions. Tertiary hospitals are referral centres and provide more sophisticated health services. This category includes: Teaching Hospitals, Federal Medical Centres and National Ear, Eye and Orthopaedic Hospitals. These centres serve as teaching, training and research hospitals in Nigeria. At least one tertiary hospital is present in all the 36 states of the federation and the federal Capital Territory, Abuja. Tertiary health institutions in Nigeria are funded solely by the federal government.

Teaching hospitals being training and referral centres are expected to provide the best healthcare services in the country. They provide a wide range of services including: medical, surgical, paediatric, obstetrics and gynaecology, critical care, oncology, diagnostic, microbiological, nursing, anaesthetic and pharmaceutical services. Surgical services provided by Nigerian teaching hospitals include: general surgery, orthopaedic, paediatric, urologic, ophthalmic, Ear, Nose and Throat (ENT), neurosurgery, obstetrics and gynaecology, oncologic, dental, and cardiac surgeries among others. Obstetrics and gynaecology surgeries are the most common surgical intervention in Nigeria. They represent about 35% of all elective and emergency surgical interventions. In addition, incidence of SSIs was 21.6% and 16.7% in obstetrics and gynaecology surgeries respectively [56]. Another study revealed that obstetrics and gynaecology had significantly higher incidence of SSIs (47.5%) compared to surgical units (39.5%) [6].

The high cost of healthcare services is a serious concern for patients, healthcare providers and policy makers in Nigeria. This is particularly more worrisome among surgical patients. A study demonstrated that the overall cost of surgical healthcare services in Nigeria was about $ 450 per admission [57]. Patient or patient's relatives pay for the medical and surgical services provided by the hospitals. Sources of healthcare financing among surgical patients includes: patient's personal savings, family members, sales of property, organizations and loans. However, major sources of medical care finance are patient's personal savings and family members [58]. In view of the numerous challenges associated with healthcare finance and the ultimate goal of achieving universal healthcare coverage, the National Health Insurance Scheme (NHIS) was introduced by the Nigerian Federal Government in 1999.

The National Health Insurance Scheme (NHIS) was launched with the goal of providing health care services to all Nigerian at an affordable cost. The implementation of the program started in 2005, enrolling federal civil servants and 4 dependants each. The program provides coverage for medical services and medications. Each enrolee is required by law to pay 10% of the costs of healthcare services and consumables. The scheme provides health insurance coverage to about 5 million Nigerians (only 3 percent of the country's population) [59]. The remaining 165 million pay for medical services from their purse.

1.6 Rational of the study

The importance of compliance with surgical antibiotic prophylaxis measures cannot be overemphasized, based on the issues highlighted above. Compliance with antibiotic prophylaxis effectively lower the risk of SSIs and prevent emergence of antibiotic resistant pathogens. The few studies that evaluated compliance with surgical antibiotic prophylaxis in Nigeria were conducted in orthopaedic surgical settings. There is lack of data to demonstrate compliance with surgical antibiotic prophylaxis measures in obstetrics and gynaecology surgeries in Nigeria. Obstetrics and gynaecology surgeries are the most frequency surgical interventions in Nigeria. In addition, these surgeries have higher SSIs. Evaluating compliance with surgical antibiotic prophylaxis measures is an importance prerequisite to identify areas that require intervention.

There is also lack of evidence to show the impact of antibiotic stewardship interventions on compliance with surgical antibiotic prophylaxis measures in Nigeria. Stewardship interventions effectively improve compliance with antibiotic prophylaxis measures, and improve clinical outcomes. In addition, the interventions also reduce the cost of antibiotic prophylaxis and incidence of antibiotic resistant infections. These positive impacts make antibiotic stewardship interventions rewarding.

1.7 Significance of the study

This study would provide a glimpse of rate of surgical antibiotic prophylaxis errors in obstetrics and gynaecology surgeries in Nigeria. In addition, the result of the study will give an insight into antibiotic consumption and cost of surgical antibiotic prophylaxis among women who had various obstetrics and gynaecology surgeries. Furthermore, the results of this research will provide data on the impact of antimicrobial stewardship interventions on prescribing, clinical, and economic outcomes in obstetrics and gynaecology unit in Nigeria. It is our wish that results from this study would provide evidence to inform hospital administrators about the urgent need to implement hospital-wide antimicrobial stewardship program.

1.8 Study objectives

1.8.1 Main objective

The main objective of this study is to determine the effectiveness of antibiotic stewardship interventions in improving compliance with surgical antibiotic prophylaxis measures for obstetrics and gynaecology surgeries.

1.8.2 Specific objectives

The specific objectives of this study are:

1. To evaluate compliance with antibiotic prophylaxis measures (antibiotic selection, including redundancy; timing; and duration) and determine the Defined Daily Doses (DDD) of surgical antibiotic prophylaxis among women who had obstetrics and gynaecology surgeries.
2. To evaluate the knowledge and perception of obstetricians and gynaecologists regarding surgical antibiotic prophylaxis.
3. To evaluate the impact of antibiotic stewardship interventions on compliance with antibiotic prophylaxis measures (antibiotic choice, timing, and duration) and incidence of surgical site infection.
4. To determine the impact of antibiotic stewardship interventions on antibiotic utilization (DDD/100 procedures) and cost of antibiotic prophylaxis.

CHAPTER TWO

LITERATURE REVIEW

2.1 Incidence of surgical site infections

Surgical site infections (SSIs) are the most common Healthcare Associated Infections (HAI) affecting surgical patients. In Europe, SSI is the third most common HAI and it represents 15.8% and 28% of all HAIs in Germany and Norway respectively [60, 61]. In Nigeria, SSIs are the second most common HAI infection and constitutes 30.7% of all infections acquired in healthcare settings. It is second to urinary tract infection which represents about 44% of all HAIs [6]. Incidence of SSIs varies between developed and developing countries. In US, the incidence of SSIs ranges between 2% – 5% [1, 62] while the cumulative incidence in European countries was 2.9% [1]. In Germany, a national surveillance study reported that the incidence of SSIs was 1.3% [63]. In developing countries, SSIs is the most common HAI; cumulative incidence was 5.6 infection per 100 surgical procedures [1].

In Nigeria, there is no national surveillance data to demonstrate the incidence of SSIs at a country level. However, evidence from few studies indicated SSI occur in 9.1% – 30.1% of patients who undergo surgery [3-5]. In addition, the incidence of SSIs varies across surgical disciplines. The incidence of SSIs is higher in obstetrics and gynaecology unit (47.5%) than surgical unit [6]. In another study, cumulative SSI rate in post-natal and gynaecology unit (19.7%) was ranked second after male surgical ward (25.9%) [56].

2.2 Morbidity, mortality and healthcare costs associated with surgical site infections

Surgical Site Infections are associated with significant morbidity, mortality and healthcare cost. Mortality and admission to intensive care unit is two-times higher in patients with SSIs, compared to those without SSI. In addition, the odds of hospital readmission are 6 times higher in patients with SSI than those without SSI. Furthermore, SSI is associated with increase length of hospitals stay; duration of hospitalization is prolonged by an average of 12 days [7]. Moreover, the estimated direct extra healthcare costs incurred in the treatment of SSIs was $ 5,000 - $ 10,500 [7, 8]. SSIs doubles the direct healthcare cost and length of hospitalization in patients who undergo surgery compared to those without SSIs [9].

2.3 Risk factors for surgical site infections

There are several risk factors for SSI in Obstetrics and Gynaecology patients. These includes: age (< 19 years), preterm gestation, prolonged duration of labour, duration of ruptured membrane greater than 12 hours, vertical incision, chorioamnionitis and diabetes mellitus. In addition, pre operative hematocrit, blood transfusion and abdominal hysterectomy were also significant predictors of infection [64].

A similar study in India revealed that the prevalence of SSI in the department of Obstetrics and Gynaecology was 7.84%. Risk factors for surgical site infections in this study included age, vaginal examination, American Society of Anaesthesiologists score greater than 3, suboptimal timing of antibiotic prophylaxis, duration of surgery, post-surgical length of stay and presence of medical illness. Prevalence of SSI was higher in Gynaecologic procedures (10.3%) compared to Obstetric procedures (1.2%) [65].

In Tanzania, the prevalence of SSI among women undergoing caesarean section was 10.9%. Six independent predictors of SSI were identified; these include hypertensive disease of pregnancy, severe anaemia, multiple vaginal examinations, prolonged surgery, surgical wound class III and operations performed by Junior doctors [66]. In Nigeria, one study demonstrated that prolonged labour, long operation time, heavy intra-operative blood loss and blood transfusion are significantly associated with an increased risk of SSIs among women undergoing caesarean section [3].

One meta-analysis concluded that obesity increases the risk of SSIs among orthopaedic patients by 2-folds [67]. In addition, another meta-analysis demonstrates that a 5-unit increase in BMI result in a 21% increase in the risk of SSIs among patients undergoing spinal surgery [68]. A study illustrated that diabetes mellitus, obesity, smoking, urinary tract infections, hypertension, blood transfusion and cerebrospinal fluid leak are significantly associated with increased risk of SSIs in spinal surgery. This meta-analysis found insufficient evidence to demonstrate increased risk of SSIs by male gender, use of alcohol and steroid use [69]. A recent meta-analysis concluded that there is an association between diabetes mellitus and SSIs. The rate of SSIs is 1.53 times higher in diabetic patients compared to their non-diabetic counterparts [70].

2.4 Surgical wound classification

Surgical wound class is an important predictor of SSIs. Surgical wounds are classified into 4 groups based on the level of microbial contamination. These include: clean, clean-contaminated, contaminated, and dirt surgical wound. Table 2.1 summarize the criteria for classification of surgical wound.

Table 2.1: Surgical wound classification

Classification	Definition
Clean	An uninfected operative wound in which no inflammation is encountered and the respiratory, alimentary, genital, or uninfected urinary tracts are not entered. In addition, clean wounds are primarily closed and, if necessary, drained with closed drainage. Operative incisional wounds that follow non-penetrating (blunt) trauma should be included in this category if they meet the criteria.
Clean-contaminated	Operative wounds in which the respiratory, alimentary, genital, or urinary tracts are entered under controlled conditions and without unusual contamination. Specifically, operations involving the biliary tract, appendix, vagina, and oropharynx are included in this category provided no evidence of infection or major break in technique is encountered.
Contaminated	Includes open, fresh, accidental wounds. In addition, operations with major breaks in sterile technique (e.g., open cardiac massage) or gross spillage from the gastrointestinal tract, and incisions in which acute, non-purulent inflammation is encountered are included in this category.
Dirty	Includes old traumatic wounds with retained or devitalized tissue and those that involve existing clinical infection or perforated viscera. This definition suggests that the organisms causing postoperative infection were present in the operative field before the operation.

Adapted from [11]

Available data illustrates that surgical wound classification is an independent risk factor for SSIs. Incidence of SSI is significantly higher in contaminated and dirty surgical wounds compared to clean and clean-contaminated wounds [8, 71]. A systematic review of studies conducted in developing countries concluded that the cumulative incidence of SSIs in clean, clean-contaminated, contaminated and dirty wound class were 7.6%, 13.7%, 14.3%, and 39.2% respectively [1].