THE PREVALENCE OF ANTIBIOTIC PRESCRIPTION AMONG WOMEN ATTENDING ANTENATAL CARE CLINIC IN A SUBMUNICIPAL HOSPITAL AND ITS EFFECT ON BIRTH OUTCOMES AND NEONATAL HEALTH

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DECLARATION

I **Kwame Opoku-Agyeman** declare that the work presented is my own original work and as far as I am concerned it contains no material prevoiusly presented or published by another person except where due acknowledgment has been made in the work.

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DEDICATION

This work is dedicated to my lovely daughter, Elise Abena Opoku-Agyeman whose smiles keep me going everyday

The greatest want of the world is the want of men--men who will not be bought or sold, men who in their inmost souls are true and honest, men who do not fear to call sin by its right name, men whose conscience is as true to duty as the needle to the pole, men who will stand for the right though the heavens fall. ***Ellen G White.***

ABSTRACT

Pregnant women are increasingly being exposed to antibiotics in the bid to reduce neonatal and maternal mortality which is of particular concern in sub-Saharan Africa. In spite of this, few studies have looked at the possible impact of the increased antibiotic exposure on the developing foetus and subsequent childhood health.

The main objectives were to evaluate the prevalence of antibiotic use in pregnant women attending antenatal care clinic in a sub-municipal hospital and their appropriateness in pregnancy. Secondly to ascertain its subsequent impact on foetal and neonatal health using birth weight, birth defect and mean Apgar scores as indicators of foetal health and incidence of neonatal sepsis, dermatitis, respiratory tract diseases, neonatal jaundice, ophthalmia neonatorum and number of hospital visits as markers of neonatal health.

The study was a retrospective cohort with primary source of data as health records of pregnancy and deliveries in the hospital. A total of 412 mother-infant pairs met the eligibility criteria out of the 2100 folders pre-selected.

The prevalence of antibiotic prescriptions among pregnant women included in the study was 65.8 %. Of these, 3.4 % were given for non-bacterial indications whiles 3.4 % received antibiotics potentially unsafe in pregnancy. A woman was about 14 (95 % CI, 5.88 - 32.46, P<0.001) times likely to receive antibiotics if delivered by caesarean section compared to natural birth. General Antibiotic exposure showed no statistically significant association with birthweight (P = 0.80), congenital birth defect (P = 0.97) and mean Apgar scores (P = 0.42). However, antibiotic exposure less than 24 hours to delivery was associated with lower Apgar scores (P = 0.002). Babies exposed to antibiotics intrapartum were at higher risk of dermatitis (RR = 2.6, 95 % CI, 1.3 - 4.9, P = 0.005), respiratory tract diseases (RR = 4.3, 95 % CI, 1.89 -

9.71, P<0.001), neonatal sepsis (RR = 4, 95 % CI, 2.1 - 7.36, P<0.001) ophthalmia neonatorum (RR=2.5, 95 % CI, 1.09 - 5.90, P = 0.024) and neonatal jaundice (RR= 2.5, 95 % CI, 0.93 - 6.71, P = 0.059) compared to non-exposed neonates. Additionally, it was observed that intrapartum antibiotic exposure was associated with a higher mean number of non-review hospital visits (P<0.001).

The antibiotic prescription rate of 65.8 % was in excess of the limit of not more than 30 % recommended by the World Health Organisation. Antibiotic use was not associated with any risk of birth defect or intra uterine growth retardation. Perinatal antibiotic exposure and caesarean birth however, were associated with lower mean Apgar scores. Antibiotic exposure with or without caesarean birth were associated with adverse health outcomes in early childhood. Rational use of antibiotic should be re-enforced in the hospital.

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Finally to my lovely family; my wife Gifty Opoku-Agyeman and sweet daughter Elise Nana Abena Opoku-Agyeman thanks for your support and patience

ACRONYMS AND ABBREVIATIONS

ANC	*Ante Natal Care*
APGAR	*Appearance,Pulse, Grimace, Activity and Respitation*
CDDEP	*Center for Disease Dynamics, Economics and Policy*
CS	*Caesarean Section*
CSF	*Cerebro-Spinal Fluid*
FDA	*Food and Drugs Authority*
G6PD	*Glucose 6 Phosphate Dehydrogenase*
IGA	*Immunoglubulin A*
NC	*Neonatal Conjunctivitis*
NJ	*Neonatal Juandice*
NS	*Neonatal Sepsis*
OR	*Odds Ratio*
PCR	*Polymearase Chain Reaction*
RR	*Relative Risk*
SDA	*Seventh-Day Adventist Hospital*
SDAHD	*Seventh-Day Adventist Hospital, Dominase.*
TLR	*Toll Like Receptor*
UN	*United Nations*
UTI	*Urinary Tract Infections*
VD	*Vaginal Delivery*
WHO	*World Health Organization*

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INTRODUCTION

1.1 BACKGROUND

Pregnant women are considered to be a special population group due to their specific susceptibility to some infectious diseases such as malaria, urinary tract infections, pelvic inflammatory disease etc. (Krishnan *et al.,* 2013; Kourtis *et al.,* 2014). The perceived increase in liability has fuelled indiscriminate and irrational use of medicines especially antibiotics at the slightest of suspicions without a thorough investigation into the possible causes. In subSaharan Africa, the situation is even much gruesome because there are inadequate well equipped laboratories to even isolate and identify causative organisms (Cheesbrough, 2006; Weber *et al.,* 2003). This often leads to irrational antibiotic prescription patterns in pregnancy resulting in unnecessary exposure of mothers to antibiotics.

Globally sub-Saharan Africa leads the scores in maternal mortality with about 510 deaths per 100,000 live births, and this is more than 62 % of the global statistic (United Nations, 2010). With the quest to reduce the health gap between developed and developing countries, it is expected that many more pregnant women are going to be exposed to medicines, especially antibiotics (Tejada, 2014).

Neonatal mortality in sub-saharan Africa averages at 32 per 1000 live births (UNICEF, 2013). Pneumonia, low birthweight, sepsis, congenital malformations and meningitis are the commonest cause of death within the neonatal period (MOH, 2014). In the quest to reduce neonatal mortality there is a need to look at prenatal events and exposures since it may affect neonatal wellbeing and health.

In some large cohort studies, antibiotic use has been linked with increased risk of developing obesity, asthma, epilepsy, febrile convulsions and eczema later in life (Mueller *et al*., 2014;

Metsälä *et al.,* 2015; Nørgaard *et al*., 2012; Miller *et al*., 2013; Tsakok *et al.,* 2013). These startling revelations are a course for concern because globally prevalence of allergic or atopic diseases like asthma, chronic obstructive pulmonary disease runs parallel to rising use of antibiotics.

Maternal microbiome, commensals or exposure to microorganisms have been proposed to be an immense predictor or determinant of foetal and neonatal health. Recent studies have shown that amniotic fluid especially in the last trimester may not be sterile but contains microorganisms which have been thought to stimulate the development of foetal immunity (Cacho & Neu, 2014). It is proposed that perturbations in the quantity, types or delay in exposure to these microbial commensals or symbionts through caesarean section or antibiotic exposure intrapartum may alter the natural colonization of foetal gut or skin (Blaser, 2011) which may adversely impair a balanced immune system development (Cacho & Neu, 2014).

LITERATURE REVIEW

1.2 HUMAN MICROBIAL DIVERSITY

Microbes are everywhere: in the soil, water and even in our bodies. Microbes cover every surface of our bodies, both inside and out (Eckburg *et al.,* 2005). We are not just single individuals but walking ecosystem with different environments harbouring different sets of microbes (Grice & Segre, 2011). A large number of these microorganisms which are bacterial species (Ursell *et al.,* 2012) are known to colonize and form complex communities, or micro-biota, at various sites within the human body such as oral mucosa, nostrils, skin, intestines, vagina etc. (Costello *et al.,* 2012). It is estimated that the human microbiota is composed of 10^{14} bacterial cells, which is 10 times more than the total number of human cells (Hattori & Taylor, 2009).

1.2.1. Microbial distribution across body surfaces

1.2.1.1 The skin

The skin has several invaginations, apocrine and sweat ducts each with different set of pH, moisture and skin thickness. These micro-environments are suitable for colonization by particular commensals or symbionts whiles inimical to other pathogenic bacteria (Proksch *et al*., 2008; Grice & Segre, 2011). For instance, the sebaceous glands produce sebum that lubricates and protects the skin but it also supports facultative anaerobes such as *Propionibacterium acnes*. This commensal also releases free fatty acids from lipids making the skin acidic which inhibits the growth of *Staphylococcus aureus* and *Streptococcus pyogenes* (Webster *et al*., 1981).

Staphylococcus epidermidis and other coagulase-negative staphylococci have been regarded as the primary bacterial colonizers of the skin but other microorganisms such as the genera *Corynebacterium, Propionibacterium* and *Brevibacterium* and the genus *Micrococcus* are also present. Gram-negative bacteria, with the exception of some *Acinetobacter* species are generally not isolated from the skin (Roth & James, 1988).

1.2.1.2 Oral cavity

The oral cavity contains commensal species made up mostly of bacteria, some viruses and fungus species (Zaura *et al.,* 2009). The composition, types and number of each microorganism is influenced by the person's oral hygiene (Avila *et al*., 2009). These commensal or symbionts form biofilms which may be capable of withstanding mechanical and antibiotic stress as well as preventing the invasion of mucosal surfaces by pathogenic organisms (Hall-Stoodley *et al.*, 2004). Their perturbations are implicated in periodontitis and gingivitis (Wade, 2013; Dewhirst *et al.,* 2010).

The mouth is a very small organ but it has multiple micro-environments that support different groups of microbes depending on their oxygen requirements, nutritional requirements and physical characteristics (Rosan & Lamont, 2000). Different genera of microorganisms find optimal environments in each of these microenvironments. Classifying the microorganisms based on their oxygen needs, the groups include obligate aerobes, obligate anaerobes (e.g. *Veillonella* and *Fusobacterium* spp.), facultative anaerobes (e.g. *Streptococci* and *Actinomyces* spp.), microaerophiles (e.g. *Helicobacter pylori*), and capnophiles (e.g. *Neisseria* spp.) (Wilson *et al*., 2005).

1.2.1.3 Vaginal mucosa

The amount and type of bacteria present in the vagina mucosa has significant implications for a woman's overall health (Ma *et al.,* 2012). The majority of bacteria in the mucosa is of the *Lactobacillus* spp. which by virtue of its ability to produce lactic, suppresses the growth of other infectious pathogens (Ravel *et al.,* 2010). The composition of the flora is not constant but varies with menstruation, pregnancy and age as well as the environment and ethnicity (Gajer *et al.,* 2012).

1.2.1.4 Gastro-intestinal tract

The intestinal microbiome is perhaps the most important microbiota in one individual and carries about 99 % of all microbes in the body (Schwabe & Jobin, 2013). The intestinal microbes are taxonomically complex and is believed to possess a strong impact on human physiology i.e. they are heavily involved in the maturation, proliferation of human intestinal cells and helping to maintain their homeostasis. Their perturbation has been linked with the development of various diseases, such as inflammatory bowel disease and obesity (Hattori & Taylor, 2009; Anderson *et al.,* 2012; Saulnier *et al.,* 2011).

1.2.2 Influence of the microbial diversity

1.2.2.1 Microbiome suppresses the growth of pathogenic bacteria

One of the very basic influence of the microbiome in humans is to prevent the invasion and colonization of mucosal surfaces by infectious or pathogenic bacteria (Kau *et al*., 2011). Some microbiota species produce biofilms which coat mucosal surfaces preventing the establishment of foreign microbes (Avila *et al.,* 2009). Some species especially those in the vagina and skin produce chemicals that change the pH of the environment or directly suppress the growth of foreign microbes. A classic example of this is the occurrence of pseudomembranous colitis caused by *Clostridium difficile* colonization after the use of antibiotics such as clindamycin

(Jobe *et al*., 1995). Antibiotics kill susceptible microbes thus allowing the overgrowth of the non-susceptible *clostridia* spp. which causes the disease.

1.2.2.2 Microbiome and immune system development

Some researchers have proposed that the microbiome "educates" the immune system (Kelly & Mulder, 2012). The microbes outnumber our own cells 10 to 1 and so the immune system needs to learn very quickly to distinguish between the body's own cells, the cells of the microbiome and pathogenic bacteria.

It is known that the programming of the immune cells to recognize the difference and to produce regulatory or memory T cells needs to occur quite early either intrapartum or immediately after birth (Blaser, 2011). Any situation that leads to alteration in microbial diversity, delay or lack of exposure adversely affects the maturation of the immune system resulting in autoimmune disorders or allergic diseases (Proal *et al.,* 2013; Ueda *et al.,* 2010). In a related study, mice born naturally had more intestinal microbes than those delivered through caesarean and their immune systems were expressed differently even after reestablishment of microbiome in the two groups (Hansen, 2014).

It is postulated that the specific interaction between the commensals and the host immune system results in the production of specific cytokines or chemokines which may help keep a balance between pro-inflammation and anti-inflammation (Hattori & Taylor, 2009). This is outlined in Figure 1.1.

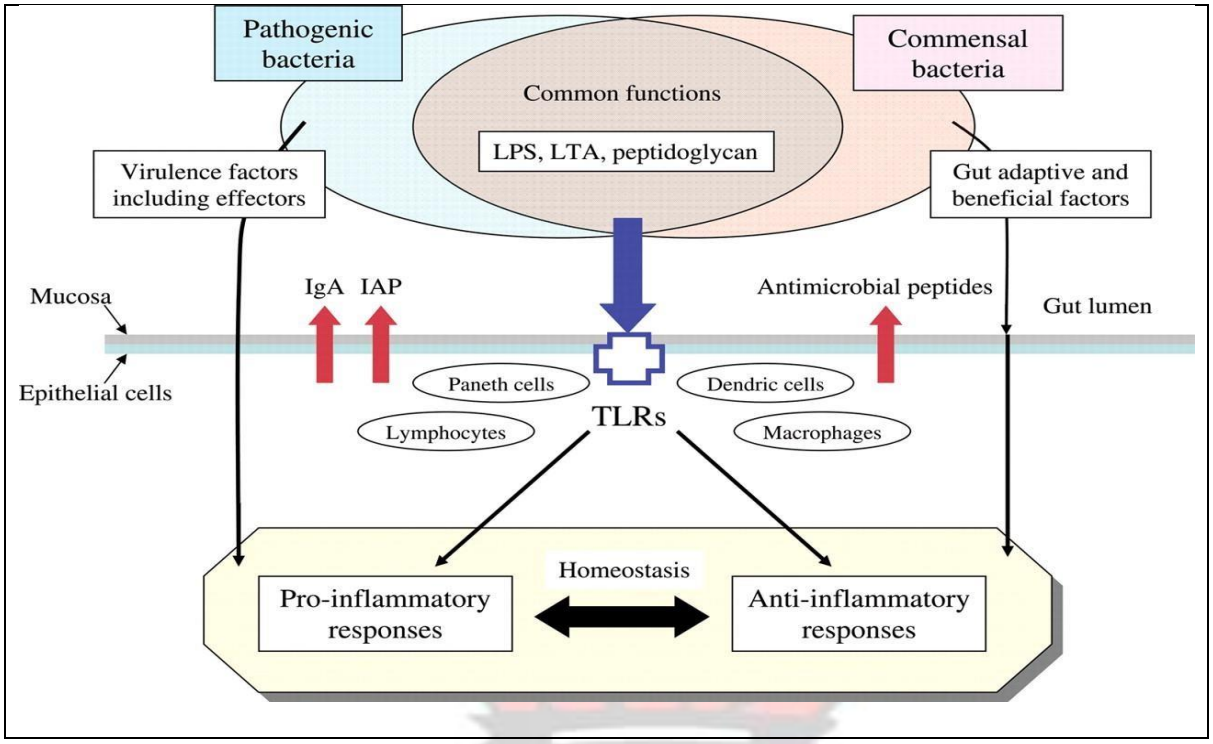

FIGURE 1. 1 **The role of the microbiome and pathogens in homeostasis of inflammation**.
(Adopted from Hattori & Taylor, 2009)

Molecular interactions between the host, commensal bacteria and pathogenic bacteria. Commensal bacteria possess specific functions tailored to the gut habitat and are helpful to host cells, including maintenance of homeostasis, but also include functions such as those of TLRs that signal immune responses to pathogens. Host cells produce various antimicrobial substances such as IgA, IAP and antimicrobial peptides at the frontline to suppress excessive immune response to commensal bacteria, while maintaining awareness to pathogens equipped with various virulence factors to evade the host defence system.

A decrease in number or diversity of commensals reduces the expression of anti-inflammatory responses tilting the homeostatic balance in favour of pro- inflammatory factors such as IgA. This is consistent with several studies that have linked the use of antibiotics and caesarean section with increased incidence of allergic and atopic diseases later in life (Blaser, 2011).

1.2.2.3 The microbiome and cancer

It is a well-known fact that inflammation is a very important component of carcinogenesis

(Grivennikov *et al.*, 2010; Dalgleish & O'Byrne, 2006). Cancers are likely to arise at sites of regular infections, irritation and inflammation (Coussens & Werb, 2002). A loss of eubiosis arising from an imbalance of the microbiota allows the colonization or excess growth of pathogenic bacteria. This situation leads to the production of pro-inflammatory mediators which may activate the inflammatory cascade (Schwabe & Jobin, 2013). For instance *Helicobacter pylori* colonization has been linked to the risk of gastric mucosa associated lymphoid tissue (MALT) lymphoma (Wotherspoon *et al*., 1993). Some studies have suggested that re-establishment of the gut microbiota could be a therapeutic option in the prevention of colon or gastric cancers (Bultman, 2014).

1.2.2.4 The microbiome and nutrition

The intestinal microbiota has the capacity to synthesize a myriad of nutrients especially vitamins needed by both microbial and host systems alike (Krajmalnik-Brown *et al.,* 2012; Kelly, 2010). These include cobalamin, pyridoxal phosphate a cofactor involved in a variety of enzymatic interconversions and amino acid metabolism, pantothenic acid, niacin, biotin, tetrahydrofolate and vitamin K. The microbiota also affects the absorption of key minerals like iron. In experimental animals, gut microbiome depleted animals have less ability to absorb iron and more likely to lose iron in faeces because microbes have evolved the ability to synthesize siderophores that trap iron making them available for reabsorption (Kau *et al.*, 2011).

1.2.2.5 The microbiome and obesity pandemic

Livestock consumes over 80 % of global antibiotics produced (Philpott, 2013; US FDA, 2010). This is fuelled by the observation that sub-therapeutic doses of antibiotics effectively increase the conversion rate of food to flesh/fat deposit (Gaskins *et al*., 2002). Likewise several cohort

studies have reported that antibiotic exposure in early life, caesarean section and intrapartum antibiotic use is associated with the risk of obesity (Bendiksen, 2013; Tejada, 2014).

The gut microbiota produce folate and cobalamin which possibly could affect host DNA expression through methylation patterns, whiles fermentation of polysaccharides could modify chromatin structure and gene transcription via histone acetylation (Kau *et al*., 2011).

1.2.3. Acquisition and establishment of microbiome

1.2.3.1 Intrapartum transfer

Maternal transfer of microbial genome is the most important mode of acquisition of an individual's microbiome (Funkhouser & Bordenstein, 2013). Previously, researchers believed that amniotic fluid and placenta were sterile and this was largely due to the fact that attempts to obtain growth cultures from aseptically taken fluids were negative. However, with invention of polymerase chain reaction (PCR) using 16S ribosomal DNA-based technology, a myriad of microbial genes have been elucidated (DiGiulio *et al*., 2008; Aagaard *et al.*, 2014). One study analysed the microbial content of meconium of neonates with intact membranes prior to delivery. It was reported that meconium was non-sterile and its microbial composition was different from that of the vaginal flora implying that it could only have originated intrapartum (Mshvildadze *et al.,* 2010). Amniotic fluid analysis using PCR have identified the presence of non-pathogenic commensals such as *Firmicutes, Tenericutes, Proteobacteria, Bacteroidetes,* and *Fusobacteria* phyla (Aagaard *et al*., 2014).

1.2.3.2 Mode of delivery

During caesarean birth, there is little interaction between mothers' vaginal microbiome and foetus (Koenig *et al.,* 2011). During natural birth however, as a baby passes through the vaginal canal it is exposed to the several microbes localized in the vaginal mucosa. This was confirmed

by Jakobsson *et al*. (2013) in a study in which it was realized that neonatal microbiome immediately after natural birth was much similar to the mothers' ecology whilst those born by caesarean had an ecology similar to the skins of those who partook in the procedure (Dominguez-Bello *et al.*, 2011).

1.2.3.3 Lactation.

Analysis of aseptically taken milk from mothers have also revealed it contains microbes especially *Lactobacillus* which is the dominant microbe in babies' breastfed. Furthermore, it was observed that microbial density and composition differed among mothers (Martín *et al.*, 2007). In one study, the faecal matter of breastfed and artificial or formula-fed babies were analysed using 16S RNA sequencing and culture methods. The results indicated that besides *Bifidobacteria* and *Bacteroids*, breast-fed infants had mostly lactic acid bacteria, such as *Streptococci* and *Lactobacilli* whereas formula-fed infants possessed a flora with more *Staphylococci* and *Clostridia* species (Harmsen *et al.*, 2000).

1.2.3.4 Dietary choices

The dietary choices of an individual preferentially encourages the growth of some types of commensals than others (Flint *et al.*, 2012). In a study by Supatjaree *et al*. (2014), analysis of faecal matter of vegetarians and omnivores revealed significant differences in diversity of the intestinal microbiome even though the subjects in the study shared similar ethnicity. Arora and Sharma (2011), also revealed that vegetarian diets or diets rich in carbohydrate fibre are associated with higher *Bacteroids to Firmicutes* ratio whilst the converse is true for diets rich in fats and animal proteins (Arora and Sharma, 2011). In a mouse study which mimicked the dietary changes that occur with travelling across continents, Dey *et al.* (2015) observed that bacteria species and density changed with each dietary regimen peculiar to each area.

The environment also plays a very significant influence in the establishment and acquisition of a unique microbiota. Individuals brought up in "cleaner societies" (urban) surroundings have a diversity much different from those who live on farms or in rural environments (Chen *et al*., 2012).

1.2.4 Antibiotic use, maternal infections and microbial ecology

Antibiotic use is known to be one of the most important mode of perturbations in the composition of the microbiome (Theriot *et al.,* 2014; Preidis & Versalovic, 2009). Most of the human microbiome is of bacteria origin and so any course of antibiotic has the capacity to adversely affect the numbers and types (Manichanh *et al.,* 2010). For instance, bacteria inherently resistant to an antibiotic will preferentially survive and replicate compared to a susceptible bacteria which can be totally deleted or reduced to very low levels (Jernberg *et al.,* 2010; Sommer & Dantas, 2011).

Antibiotic exposure before the establishment or programming of neonatal immune system could result in aberrant and unhealthy development of the immune system (Schulfer & Blaser, 2015). As discussed earlier, microbiome educates the immune system to distinguish between host cells, the microbiome and pathogens through the production of T helper or memory cells. When this is lacking host defences could attack own cells resulting in autoimmune disorders such as destruction of pancreatic beta cells in diabetes mellitus. Antibiotic use in early life could also provide the necessary milieu for the development of allergic diseases (Schulfer & Blaser, 2015). As stated earlier, the immune system thrives on a delicate equilibrium of antiinflammatory and pro-inflammatory responses. The microbiome ensures that proinflammatory factors are held in check whiles maintaining adequate response to pathogens and so antibiotic exposure before the establishment of the equilibrium could result in

hypersensitivity to a lot of agents because the immune system may already be primed towards pro-inflammation.

Pregnancy presents with increased susceptibility to infectious diseases perhaps due to the unique immunological compensation and physiological conditions that come with it (Hill *et al*., 1973). Maternal lymphocytes obtained during the second and third trimester have been shown diminished proliferative responses to soluble antigens. Urinary tract infections during pregnancy coupled with premature rapture of membranes have been known to be associated with low birth weights, sepsis and higher risk of eclampsia (Matuszkiewicz-Rowińska *et al.*, 2015; Emamghorashi *et al.*, 2012)

1.3 ANTIBIOTICS

The discovery of antibiotics or "miracle drugs" as they were popularly called, is one of the most important and invaluable breakthroughs of science in the world (Dong *et al.*, 2008). The discovery of penicillin in 1928 by Sir Alexander Fleming (Lewis, 2013) marked the golden era or foundation stone for the science of antibiotics and since then a lot more chemical compounds have been discovered or synthesized.

The perceived efficacy of antibiotics against infectious micro-organisms has led to its indiscriminate and unwarranted use in treating all manner of perceived infectious diseases irrespective of the actual causative organism. The World Health Organization (WHO) and other researchers generally agree that up to 50 % of all antibiotics prescribed are unnecessary (WHO, 2012; CDDEP, 2015)

The indiscriminate use of antibiotics comes with its own inherent consequences. Globally rates of antibiotic resistance has overtaken the rate at which newer, safer and more effective antibiotics are being discovered (CDDEP, 2015; Cizman, 2003). Moreover antibiotic resistance

has been documented to increase cost of health care and duration of hospitalisations. In 2014, the WHO officially declared that antibiotic resistance is a public health concern (WHO, 2014).

1.4 SAFETY OF MEDICINES IN PREGNANCY

Medicine use in pregnancy always comes with a level of risk to the developing foetus and mother. It is not ethical to conduct clinical trials in pregnant women and so studies of drug exposure and safety are mostly retrospective in nature and their suitability for use are inferred from previous exposures and animal models. In order to minimize some of these risks medicines are grouped into categories A, B, C, D and X based on their suitability and level of risk. Outlined below in Table 1.1 is the FDA classification of medicines in pregnancy.

TABLE 1.1 **US -FDA medicine in pregnancy classification chart.**

Category	Definition	Explanation
A	Generally acceptable	Controlled studies in women show no evidence of fetal risk
B	May be acceptable	Either animal studies show no risk but human studies not available or animal showed minor risk but human studies were not done and showed no risk
C	Use with caution if benefits outweigh risk	Animal studies have shown risk but human studies are not available or neither human or animal studies have been done
D	Use in life-threatening emergencies when no safer drug is available	Positive evidence of human foetal risk is available
X	Do not use in pregnancy	Risks involved outweigh potential benefits. Safer alternatives available.

1.4.1 Antibiotics considered "safe" in pregnancy

Based on their perceived efficacy and safety in pregnancy some antibiotics have found regular use in pregnancy for the prevention and treatment of ailments. The mechanism of action, pharmacokinetics and appropriateness for use in pregnancy of some of the frequently encountered antibiotics are outlined below.

The beta-lactam antibiotics have found a wide acceptability and use in pregnancy because of their relative safety in pregnancy. They are bactericidal agents which kill susceptible microbes by inhibiting the synthesis of peptidoglycan cell wall needed to maintain cell morphology (Rowley & Miller , 1948; Tipper & Strominger, 1965; Michel *et al*, 1980). This family of antibiotics include the penicillins, cephalosporins, carbapenems and monobacatams. These antibiotics are generally assigned to pregnancy category B by the US- FDA and although some are known to be excreted in human milk, adverse effect on the child is unlikely.

Erythromycin and azithromycin cross the placenta in small amounts and are categorized as B whiles clarithromycin is a class C drug in pregnancy (Centers for Disease Control and Prevention, 1993). Erythromycin estolate, however is contraindicated because of drug-related hepatotoxicity (McCormack *et al*., 1977). The macrolides are generally compatible with breastfeeding by the American Academy of Paediatrics (Committee on Drugs, 2001).

Clindamycin is a protein synthesis inhibitor and it has been classified in category B by the US FDA. Clindamycin solution which contains benzyl alcohol as a preservative can cross the placenta and is associated with a fatal "gasping syndrome" in neonates. Its use is not recommended in breastfeeding and so an alternate drug may be preferred since it is excreted in milk and may have detrimental effects on the gastrointestinal flora (Spízek *et al.,* 2004). Metronidazole is well distributed into body tissues and fluids, such as vaginal secretions, seminal fluid, saliva, cerebrospinal fluid and breast milk with the exception of the placenta (Lamp *et al.,* 1999). Metronidazole has been classified as category B in pregnancy but its use may be contraindicated during the first trimester because of a risk of teratogenicity (Kazy *et al.,* 2005). Metronidazole is excreted in human milk at levels similar to maternal serum levels, and infant serum levels can be similar to infant therapeutic levels.

1.4.2 Antibiotics considered "unsafe" in pregnancy

Some antibiotics considered potentially harmful to mother or foetus have proved to be harmful in either animal studies or actual retrospective studies done in women. Their use however, is considered feasible if potential benefits outweigh risk to mother or foetus except when it is in the X category which forbids its use in pregnancy.

Chloramphenicol is a protein synthesis inhibitor and it is well distributed in all body tissues and fluids including the CSF (Friedman *et al.*, 1979; Ambrose, 1984; Wisseman *et al.*, 1954). It has been assigned pregnancy category C but use in late pregnancy has been associated with adverse effects in the neonate (i.e. grey baby syndrome and bone marrow suppression) and so some experts consider it contraindicated in pregnancy (Briggs & Freeman, 2008). Chloramphenicol is excreted into human milk (Matsuda, 1984). Adverse effects noted in nursing infants, include refusal of the breast, bloating, and vomiting.

The tetracyclines are bacteriostatic agents which inhibits protein synthesis by binding to the 30S ribosome. They are well distributed in tissues, body fluids, breastmilk and foetus (Schnappinger & Hillen, 1996; Brodersen *et al.*, 2000). It is assigned to pregnancy category D by the US FDA. Studies in animals have revealed evidence of embryo-toxicity and teratogenicity, as well as toxic effects on skeletal and teeth development (Bevelander *et al.*, 1960, Bevelander, 1961). It is excreted into human milk in small amounts (Committee on Drugs, 2001).

The aminoglycosides are protein synthesis inhibitors predominantly effective against gram negative bacteria (Davis, 1987). A notable adverse effect is ototoxicity and nephrotoxicity (Prayle *et al.*, 2010). Aminoglycosides cross the placenta and there is a potential risk of foetal nephrotoxicity and ototoxicity. There are reports of foetal eighth cranial nerve toxicity with permanent bilateral deafness after exposure to aminoglycosides during pregnancy (Committee

on Drugs, 2001). They have been assigned to pregnancy category D by the US FDA. Aminoglycosides are excreted into human milk in small amounts. Due to poor oral bioavailability, systemic toxicity in the nursing infant is unlikely (Matsuda, 1984).

Sulphonamides, trimethoprim and pyremethamine are inhibitors of folic synthesis in susceptible bacteria. The sulphonamides are p-aminobenzoic acid (PABA) analogues and they inhibit dihydropteroate synthase (Henry, 1943). Trimethoprim and pyremethamine inhibit dihydrofolate reductase the last step in the synthesis of folic acid in susceptible bacteria. They are distributed widely to tissues and fluids and can also penetrate into placenta and foetus (Klimowicz, 1992). The sulphonamide/trimethoprim or pyremethamine combinations have an FDA pregnancy category of D: There is positive evidence of human foetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

The fluoroquinolones are synthetic antimicrobials with rapid bactericidal activity. The quinolones block bacterial DNA synthesis by inhibiting bacterial topoisomerase II (DNA gyrase).and topoisomerase IV (Hooper, 2000). The fluoroquinolones are well absorbed orally and distributed widely in body fluids and tissues with about 50-1000 % concentration in foetus. US FDA classifies it as pregnancy category C. It is excreted in breast milk and so a decision should be made to discontinue breastfeeding or discontinue the drug, taking into account the importance of the drug to the mother.

1.5 ANTIBIOTIC USE AND MATERNAL HEALTH

In Ghana, Maternal mortality has been high at a national average of 451 deaths per 100,000 live births (Ghana Maternal Health Survey, 2007) although maternal mortality rate of more than 700 has been recorded in studies carried out in some districts.

One of the specific steps to reduce maternal and neonatal mortality is to ensure adequate health care which includes improved access to medicines (UN, 2000). Preterm delivery, premature rapture of membranes and group B streptococci colonization are identified with significant risk to mother and baby. As a result, antibiotics are often prescribed in pregnancy for prophylactic and curative purposes without a thorough consideration of their potential effect on the developing foetus (Thinkhamrop *et al.*, 2015).

1.6 MATERNAL FACTORS AND BIRTH OUTCOMES

As a baby develops in the mother's womb, it is exposed to several factors that the mother is exposed to and some of these are the mother's nutrition, medicines, and environment (Kim *et al.*, 2012). Most of maternal factors are harmless and some may even promote neonatal health. Sometimes inadvertent exposures to some agents such as tobacco smoke, some drugs and even maternal depression and stresses (Rondó *et al*., 2003) are known to adversely impair optimum intra-uterine growth. This results in conditions such as low birthweight and congenital defects.

Several studies including those by Brotnow *et al.* (2015) and Bhaskar *et al*. (2015) have also identified maternal socio-economic factors such as marital status, age, occupational status and body mass index as good indices of intra-uterine health. Three very important parameters that are good predictors of intrauterine health and growth are Apgar scores, birthweight and development of congenital defects.

1.7 INDICATORS OF FOETAL HEALTH

1.7.1 Birthweight

Birthweight is one of the most sensitive and certainly the most important measure of the wellbeing of neonates (Lemons *et al.*, 2001; Shrimpton, 2003). Birth weight is often considered as an indicator of health status of a given society and moreover, elevated population mean birth weight has been linked to good maternity care and healthy living conditions (Kramer, 1987). Weight at birth is directly influenced by the general level of health of the mother. Birth weight is governed by two major processes: duration of gestation and intrauterine growth rate. The WHO has classified birthweights into these classes outlined in Table 1.2. Low birthweight or intra-uterine growth retardation is defined as birthweight below the 10th percentile of the recommended gender-specific birthweight for gestational age reference curves (Williams *et al.*, 1982; Waterlow *et al.*, 1977).

The WHO declared that West Africa had LBW rate of 10-20% with range of mean birth weight between 2800-3000g (WHO, 2013). Low Birth Weight is caused by either a short gestational period or retarded intrauterine growth (or a combination of both). Birth weight is a proxy measure of intrauterine malnutrition/restriction and is a primary determinant of foetal and neonatal mortality, morbidity and chronic diseases (McCormick, 1985; Mosley and Gray, 1983).

TABLE 1. 2 **Classification of babies based on birthweight**

Weight	**Classification**
Less than 1.5 kg	Very low birthweight (VLBW)
1.5 kg - 2.5 kg	Low Birth Weight (LBW)
2.5 kg - 4.0 kg	Normal Birth Weight (NBW)
More than 4.0 kg	High Birthweight (HBW)

Source: ***WHO 1977***

1.7.2 Apgar Scores

The Apgar score is used to evaluate neonatal well-being immediately after birth (Apgar, 1966; Dassah *et al.*, 2014). Though the Apgar score was not originally intended to predict long-term health outcomes, it does nonetheless inform about prognosis beyond the neonatal period (Straube *et al*., 2010 ; Nelson & Ellenberg, 1981). It has been known for a while that Apgar score is a good predictor of survival in infancy. The score is normally taken at 1 and 5 minutes postpartum but it may be repeated if there is neonatal distress. A score of 7 or more is regarded as an indication of a normal neonatal condition and a score of three or less is taken as a reason for special concern. The scoring chart is as shown in Table 1.3

TABLE 1. 3 **The Apgar score Chart (Virginia Apgar, 1953)**

	0 (Points)	1	2
Appearance	Blue or pale all over	Blue extremities, but torso pink	Pink all over
Pulse	None	< 100	≥ 100
Grimace	No response	Weak grimace when stimulated	Cries or pulls away when stimulated
Activity	None	Some flexion of arms	Arms flexed, legs resist extension
Respirations	None	Weak, irregular or gasping	Strong cry

0-3 Critically Low, 4-6 Fairly Low, 7-10 Generally Normal

1.7.3 Congenital birth defects

Birth defects may be defined as structural, sensory, chromosomal, metabolic or neurodevelopmental abnormalities present at birth. It remains an important public health issue because they are a cause of foetal and infant mortality as well as lifelong disabilities (Kim *et al.,* 2012). The causes of birth defects remain largely a mystery. In a developing country like Ghana, where poverty, disease, malnutrition and lack of access to health care predominate, birth defects impose an enormous personal and societal consequence according to the Institute of Medicine report, (2003). Currently, at least 7.9 million people are born each year with a birth defect in the world according to Global Report on Birth Defects. Based on the report's estimates, birth defects affect about 4 % of live births in high-income countries and about 8 % in low-income countries, with a global average of about 6 % (Christianson *et al.*, 2005).

In many regions birth defects are the largest single cause of infant deaths. In most situations the environment imposes an avalanche of possible stimuli, some beneficial, many neutral, and others possibly harmful. A relatively small proportion of birth defects can be attributed, at least in part, to specific environmental causes such as maternal disease (e.g. rubella), lifestyle (smoking) or use of pharmaceuticals (e.g., valproic acid) (Weinhold, 2009). Notwithstanding,

the majority of birth defects are considered the result of multiple environmental and/or genetic causes acting together.

Some previous studies have linked the use of sulphonamides and nitrofurantoins with anencephaly, hypoplastic left heart syndrome, anophthalmia or microphthalmos, hypoplastic left heart syndrome and atrial septal defects (Crider *et al.*, 2009). Lin *et al.* (2012) also proposed that babies exposed to amoxicillin intrapartum were at a greater odds of cleft lip or palate compared to unexposed children.

1.8 INDICATORS OF NEONATAL HEALTH

In 2015, the WHO estimated that about 45 % of all under-five neonatal death occurred in the neonatal period (WHO, 2015) whiles about 99 % of all neonatal deaths take place in developing countries, mostly in homes and communities (Bhutta *et al*., 2005). An interesting fact is that about 75 % of neonatal deaths happen in the first week (Lawn *et al.*, 2005). Ensuring neonatal survival is a key element in the quest to reduce all under-five mortality in the world.

1.8.1 Neonatal sepsis

Neonatal sepsis is a leading cause of neonatal mortality and hospital admissions (Peterside *et al.*, 2015; Seale *et al.*, 2009). It is estimated to cause about 30 % of all neonatal deaths worldwide (Roca *et al.*, 2015). Neonatal sepsis is classified as early onset when it occurs within the first 72 hours of life and late onset when it occurs after 72 hours (Sankar *et al.*, 2008). It is believed to be usually caused by organisms found in the maternal genital tract, labour room or operating theatre while late onset sepsis is perceived to be from nosocomial or communityacquired infection. New-borns are particularly susceptible to sepsis as a result of their immature immune system (Peterside *et al.*, 2015). Common risk factors for neonatal sepsis

in SubSaharan Africa are prematurity, low birth weight, pro- longed rupture of foetal membranes and maternal peri-partum pyrexia.

Staphylococcus aureus, Group B *Streptococcus*, *Escherichia coli*, *Klebsiella*, *Listeria monocytogenes* and *Neisseria meningitides* are commonly isolated from blood culture (Hamer *et al*., 2015).

1.8.2 Respiratory tract diseases

Neonates are be-devilled with allergic and infectious respiratory diseases alike although allergic diseases seem to be on the higher side. Diseases of respiratory tract are among the commonest of conditions and account for a large percentage of hospital consultations and antibiotic prescription in general practice (Nyquist, 1998) but interestingly only about 20 % of such infections are of bacteria origin

Several studies designed to look at antibiotic exposure either intrapartum or early childhood and risk of allergic respiratory tract disease have yielded very conflicting results. For instance Leickly (2003) in a study found no association between antibiotic use and allergic respiratory tract diseases but other studies by Droste *et al.* (2000) and Pistiner *et al.* (2008) found higher risk of respiratory diseases among infants exposed to antibiotics or who were delivered by caesarean birth.

Brauer *et al.* (2002) as well as other researchers have identified a parallel relationship between environmental pollution and the development of allergic respiratory tract diseases. In one study which looked at disease severity with peak times of traffic air- pollution, it was observed that number of hospital admissions for allergic respiratory tract disease such as asthma coincided with high environmental pollutants such as smoke and fumes (Brauer *et al.*, 2002). It is worth also noting that other authors have identified a positive correlation between maternal

microbiome and incidence of respiratory tract diseases (Funkhouser & Bordenstein, 2013; Schwabe & Jobin, 2013; Murk & Risnes, 2015).

The "hygiene hypothesis" has been proposed by some authors as a mechanism for the high prevalence of allergic respiratory tract diseases such as asthma (Risnes *et al.*, 2011). In this theory scientist have linked this phenomenon with increasing cleanliness and lack of exposure to microbial commensals or symbionts allowing the immune system to tip in favour of proinflammatory and allergic reactions mediated by type 2 T-helper cells.

1.8.3 Dermatitis

Dermatitis is an inflammation of the skin often characterised by swelling, redness and erythematous, weeping or crusting patches. It may be caused by either allergy, atopy or infectious pathogens (Wolff *et al.*, 2013). The cause of dermatitis is still unclear but it is believed to be a dysfunctional interplay between the immune system and skin development (Dominguez-Bello *et al.*, 2010). Neonatal skin is immature, less thick and much prone to traumatic breakage in skin making neonates at risk of various skin conditions (Lund *et al.*, 2001).

It is known that the microbiome of babies born naturally resemble that of the vaginal flora dominated by *Lactobacillus*, *Prevotella*, or *Sneathia* spp. whiles those of babies born through caesarean are much similar to the operating room or skin of mother also dominated by *Staphylococcus*, *Corynebacterium*, and *Propionibacterium* (Dominguez-Bello *et al.*, 2010; Capone *et al.*, 2011; Grice & Segre, 2011; Sarkany & Gaylarde, 1968).

In some studies the perturbations in microbial exposure caused by antibiotics or delay in exposure caused by caesarean section has been linked to increased risk of atopic dermatitis and other allergic diseases (Wohl *et al.*, 2015; Renz-Polster *et al.*, 2005).

1.8.4 Neonatal conjunctivitis

Ophthalmia neonatorum is an inflammation of the conjunctiva with discharge manifesting within the first 28 days of life. This condition also known as neonatal conjunctivitis can result in visually disabling complications. The World Health Organization (WHO) reports that 20 - 79 % of vision loss in children could be attributed to neonatal conjunctivitis (WHO, 1986).

It could be of bacteria, chemical or allergic origin though the majority is due to viral infection (Azari & Barney, 2013). Infective conjunctivitis may be acquired through passage through an infected vaginal canal. Screening of women just before delivery or prophylactic antibiotic drops have helped to greatly reduce its prevalence (Moore & MacDonald, 2015). Erythromycin, gentamycin and chloramphenicol eye drops or ointment are frequently used as prophylactic treatments for babies born vaginally.

Organisms commonly implicated in neonatal conjunctivitis are *Chlamydia trachomatis, Neisseria gonorrhoea, Staphylococcus aureus, Staphylococcus epidermidis* and *Escherichia coli* (Palafox *et al.*, 2011).

1.8.5 Neonatal jaundice

Jaundice occurs when bilirubin which is a by-product of red blood cell degradation builds up at rate which exceeds the rate of conjugation by the liver. Up to 60 % and 80 % of term and preterm infants respectively may experience jaundice. Most of the cases are benign and resolve with time but there may be serious complications such as the development of kernicterus in neonates. Onset within 24 hours are linked with Rhesus factor or other blood incompatibilities between mother and child however, onset after 24 hours is linked with sepsis, breastfeeding, haemorrhage or glucose six phosphate dehydrogenase (G6PD) deficiency (Maisels, 1995; Huang *et al.*, 2004).

Wei *et al.* (2015) observed in a study that jaundiced neonates were about 2-2.5 times likely to develop any form of allergic diseases compared to babies who never experienced any such condition. In a similar study, it was observed that maternal diabetes, pregnancy induced hypertension, caesarean section, epidural anaesthesia, blood type O and male sex posed a significant risk factor for neonatal jaundice (Gale *et al.,* 1990). Several cohort studies have also established an association between oxytocin use during labour and the development of hyperbilirubinemias (Chalmers *et al.,* 1975; Phuapradit *et al*., 1993).

1.9 JUSTIFICATION FOR STUDY

Pregnancy presents with significant risk of morbidity and mortality. To prevent these lots of pharmacological interventions including increased use of antibiotics have been proposed and implemented worldwide (Roca *et al.*, 2015). However, data on the impact of this increasing use of antibiotics on foetal development, immune system development and neonatal health in a developing country like Ghana is virtually non-existent.

Secondly, there is little data available on the prevalence of antibiotic exposure or prescription among pregnant women.

1.10 AIM

The main aim of the study was to determine the prevalence of antibiotic use in pregnancy among women attending Ante-natal Care (ANC) Clinic at Dominase SDA hospital and their subsequent effect on birth outcomes and early childhood health.

1.11 SPECIFIC OBJECTIVES

- To ascertain the prevalence of antibiotic exposure of pregnant women attending regular antenatal care clinic in Dominase Seventh-Day Adventist Hospital.
- To find out the kind of antibiotics prescribed and their appropriateness in pregnancy.

- To ascertain the effects of prenatal antibiotic exposure on birth outcomes on the neonate using birth weight, Apgar scores and incidence of congenital birth defects.
- To assess the impact of prenatal antibiotic exposure on the health of the child (first 3 months) using the development of dermatitis, respiratory tract infections, neonatal jaundice, neonatal sepsis and neonatal conjunctivitis and number of non-review postnatal hospital visits as specific indicators.

CHAPTER TWO

METHOD

2.1 STUDY DESIGN

The first part of the study which looked at prevalence and pattern of antibiotic prescription was basically descriptive whiles the second part of the study which looks at antibiotic utilisation and foetal or neonatal health was a retrospective cohort study. The primary target was of pregnant women who attended antenatal care (ANC) clinic and delivered live babies at Seventh-Day Adventist Hospital (SDAH), Dominase in the Bekwai Municipality of Ashanti region. Only live deliveries were considered because there had to be health records of the baby within the first three months of life.

The primary source of data was patients medical records filed in the hospital between 2011 and 2015.

The Inclusion criteria were as follows

- The patient should have attended at least three ANC at the hospital after confirmation of pregnancy either by ultrasonography or Human Chorionic Gonadotrophic (HCG) detection method.
- Should have delivered a live singleton baby at the facility.
- Attended at least two post-natal hospital visits at the facility

The exclusion criteria were as follows

- Multiple gestation
- No record of postnatal visits
- Deliveries of referral cases from other hospitals

Multiple of twin gestation were excluded because of the known risk of low birthweight associated with it and the difficulty of adjusting for it because of the rarity of the event. The following birth outcomes were chosen as indicators of intra-uterine health; birthweight, Apgar scores and presence of congenital birth defect. The occurrence of neonatal sepsis, conjunctivitis, respiratory tract diseases (RTD), neonatal jaundice, dermatitis and number of non-scheduled review or post-natal visits were recorded and analysed. These were used as specific indicators for neonatal health.

Antibiotics as used in this study is comprise only of antibacterial agents excluding anti-fungal and antiviral agents.

2.2 ETHICS STATEMENT

The permission to do this research in Seventh-Day Adventist Hospital, Dominase was permitted by the hospital management committee (attached as appendix C). Permission from individuals was not feasible since the primary source of data was medical records of patients filed in the hospital. Patients' names were excluded in the data collection to protect patient confidentiality.

Ethical clearance has been given by the Committee on Human Research, Publications and Ethics, Kwame Nkrumah University of Science and Technology, School of Medical Sciences and Komfo Anokye Teaching Hospital, Kumasi (attached as appendix B).

2.3 STUDY AREA

Seventh-Day Adventist Hospital, Dominase (SDAHD) is located in Dominase which is off the Kumasi - Bekwai highway. Dominase is located about 19 km from Kumasi .The hospital is

located in a populated sub-municipal in the Bekwai Municipal Assembly located in the Ashanti Region. The Hospital serves about thirty six thousand four hundred and nine people in

Dominase as well as receive referrals from other sister hospitals. The vision of the hospital is "*to strive to become a Christian Municipal Centre of Excellence*" and the mission is "*Hospital is committed to providing holistic health services in an efficient, effective, and client sensitive manner with motivated staff within Christian principles and government policies"*

The choice of this facility was very strategic and significant for the purposes of this study. The sub-municipal served by the hospital is predominately rural with no pharmacy and very few of the communities even have a chemical shop. This could possibly reduce the incidence of unprescribed antibiotics which can confound the study. Attendants to the Antenatal clinic are always advised to avoid out- of- hospital medicines use. Secondly because of the policy of "capitation" clients tend to stick to a particular hospital throughout the pregnancy unless referred to another for further treatment.

The hospital has forty- five bed capacity with a gyneacology and obstetric unit with a resident gyneacologist. The hospital runs an antenatal care (ANC) clinic which attends to an average of eighty pregnant women a day. The hospital also runs a full general surgery unit with a resident general surgeon.

2.4 SAMPLE SIZE

The Bekwai municipality has a fertility rate (*p)* of 110.5 per 1000 women (Ghana Statistical Service, 2010), and assuming a margin of error (*d*) of 0.05 and a *Z* value of 1.96 for a confidence level of 95 %, a minimum of 151 folders of pregnant women were required for the study using the mathematical equation by Cochran (1977).

$$n = \frac{Z^2 p(1-p)}{d^2}$$

2.5 SAMPLING METHOD

For our study, folder numbers of all live babies born in the hospital between January, 2011 and September, 2015 were retrieved from the registration book at the maternity unit. Five hundred folder numbers were randomly selected for each of the five years from the registration book, making a total of 2500 folders. The biostatics department was able to retrieve 2100 folders. Each folder of mother-baby pairs was subsequently screened using the inclusion and exclusion criteria. A total of 412 mother-baby pairs met the selection criteria.

2.6 DATA CAPTURE, ANALYSIS AND PRESENTATION

Socio-economic data of patients under study was recorded. The parameters recorded were mothers' age at birth, gravida, marital status, occupational status, religious affiliation and mode of delivery. Parameters of baby recorded at birth were gender, weight, Apgar scores and congenital defect.

Data obtained from the medical records were transferred unto a data capture form which is attached as Appendix A, the secondary data was later collated, scrutinized and analysed using IBM Statistical Package for Social Sciences (SPSS) version 21. Graphs and tables were made using Microsoft excel 2013 edition and Graph Pad Prism version 6.

Pearson Chi-square test was used to analyse categorical variables such as the count of the presence or absence of a disease condition. Relative risk and Odds ratio were used as a measure of the degree of association between a condition (outcome) and comparable groups. Birthweight, Apgar scores, and number of hospital visits were analysed as continuous variables with the mean values as the test statistic. Students T- test and One way analysis of variance

(one-way Anova) was used to analyse the difference in mean values between a set of comparable groups or values. Bonferroni was used as the post-hoc test after one- way Anova.

A p-value less than 0.05 was considered statistically significant.

2.7 LIMITATION

The design of the study could not totally account for possible out-of- hospital antibiotic use. The choice of a rural community with few chemical shops and no pharmacy was expected to reduce this potential confounder.

It was also expected that some of respondents may visit other hospitals after birth resulting in loss to follow up. To reduce this confounder, mother and baby pairs should have attended at least two post-natal visits.

The National Health Insurance Scheme runs a "capitation policy" where a patient chooses one primary health care facility for their needs. The policy also reduces patients moving from one hospital to another because if a patient visits another hospital they have to pay hospital charges.

Only the route of delivery was considered and so there was no distinction between elective and emergency cases as well as the indication for the caesarean birth.

CHAPTER THREE

RESULTS

This section of the document presents the results of data analysed from 412 mother-baby pairs that met the eligibility criteria.

3.1 SOCIO -DEMOGRAPHIC DATA AND MODE OF DELIVERY

3.1.1 Socio –demographic data

Mothers' age at birth ranged from 13 to 44 years with a mean age of 26.3 ± 6.40 years. The mode was 26 years. About 61.4 % of pregnant women were between 20 to 30 years. Teenage pregnancies accounted for 13.7 % of all pregnancies and 7.1 % of patients were above 35 years. Married women constituted 82.2 % as against 17.8 % unmarried. Unmarried teenagers constituted 62.1 % of all single pregnant women (Appendix E).

Employment data was obtained on 367 patients. Farmers constituted the mode with 126 (34.3 %), followed by petty traders, hairdressers, students, seamstresses, teachers with 78 (21.3 %), 51 (13.9 %), 43 (11.7 %), 21 (7.4 %) and 8 (2.2 %) respectively. Unemployed clients were 25 (7.3 %). The majority of the women in the study were in the informal sector. The results are summarized in Table. 3.1.

Data on religious affiliation was available for 365 of the 412 clients' analysed. At 90 % clients who visited the hospital and subsequently delivered there were Christians and the remainder were either Muslims or traditionalists (Table. 3.1).

The average gravida per pregnant woman was 3.07 ± 2.03. The maximum and minimum gravida were 14 and 1 respectively. A total of 412 babies were delivered of which 198 (52.5 %) were males, while females numbered 178 (47.5 %) corresponding to a sex ratio of 110.5.

TABLE 3. 1 **Socio-demographic data of women**

		Frequency	Valid Percent	Cumulative Percent
MARITAL STATUS	MARRIED	304	82.2	82.2
	SINGLE	66	17.8	100.0
MOTHERS AGE AT BIRTH	19 YEARS AND BELOW	56	13.7	13.7
	20-30 YEARS	251	61.4	75.1
	31 YEARS AND ABOVE	102	24.9	100.0
OCCUPATIONAL STATUS	FARMER	126	34.3	34.3
	TRADER	78	21.3	55.6
	STUDENT	43	11.7	67.3
	TEACHER	8	2.2	69.5
	SEAMSTRESS	27	7.4	76.8
	HAIRDRESSER	51	13.9	90.8
	NURSE	3	.8	91.6
	UNEMPLOYED	27	7.4	99.0
	OTHERS*	4	1.0	100.0
RELIGIOUS AFFILIATION	CHRISTIAN	333	91.2	93.0
	MUSLIM	24	6.6	99.7
	TRADITIONAL	8	2.2	100.0
GRAVIDA	1-3	212	68.8	68.8
	4 AND ABOVE	96	31.2	100.0
	Total	412	100.0	

*Others include sprayer, baker, secretary and army officer

3.1.2 Method of delivery

Caesarean section accounted for 26.7 % (110) of all deliveries whilst normal vaginal delivery was 73.3 % (302). The percentage of caesarean section in all deliveries increased gradually from 19 % in 2012 to 44 % in 2015 (FIGURE 3. 1).

Ages below 20 years, 20 to 30 years and above 31 years accounted for 12.5 %, 27.5 % and 33.3 % respectively. From the results it could be seen that likelihood of caesarean section increases with age of mother at delivery and less likely in women below 20 years (P = 0.017, 95 % CI, K = 8.17). Married women were at a higher odds of caesarean section compared with unmarried women (OR = 2.2, 95 % CI, 1.1 - 4.5, P = 0.027). Cross tabulation of caesarean section with occupational status, gravida and religious affiliation showed no statistically significant association (TABLE 3.2).

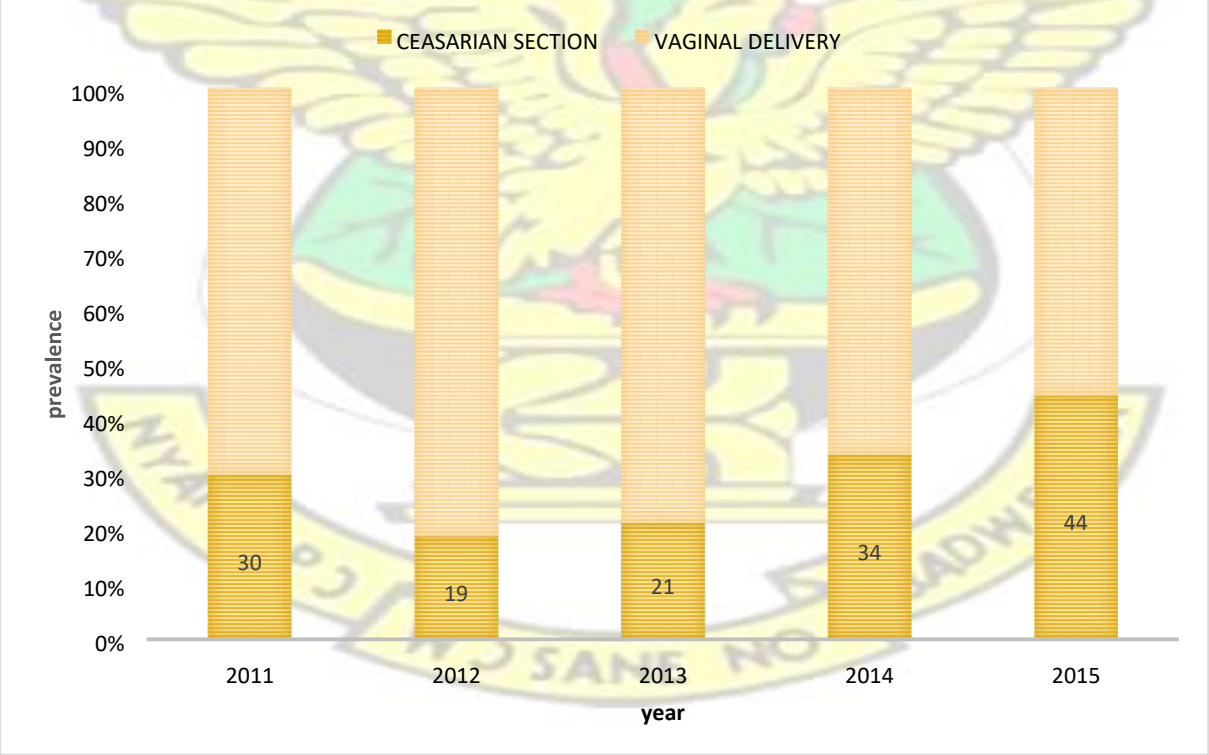

FIGURE 3. 1 Method of delivery from 2011-2015

TABLE 3. 2 **Crosstabulation of method of delivery**

		METHOD OF DELIVERY			
		CEASARIAN SECTION	**VAGINAL DELIVERY**	**Total**	**SIGN**
MARITAL STATUS	MARRIED	86(28.3%)	218(71.7%)	304	**P=0.027**, K=4.87
	SINGLE	10(15.2%)	56(84.8%)	66	DF=1, OR=2.2
AGE OF MOTHER AT BIRTH	19 YEARS AND BELOW	7(12.5%)	**49(87.5%)**[a]	56	**P=0.017**, K=8.17
	20-30 YEARS	69(27.5%)	182(72.5%)[b]	251	DF=2
	31 YEARS AND ABOVE	34(33.3%)	68(66.7%)[b]	102	
OCCUPATIONAL STATUS	EMPLOYED	79(26.6%)	218(73.4%)	126	P=0.054, K=5.84
	STUDENT	11(25.6%)	32(74.4%)	78	DF=2
	UNEMPLOYED	13(48.8%)	14(51.2%)	43	
DENOMINATION	CHRISTIAN	90(27.0%)	243(73.0%)	333	P=0.635, K=0.910
	MUSLIM	5(20.8%)	19(79.2%)	24	DF=2
	TRADITIONAL	3(37.5%)	5(62.5 %%)	8	
GRAVIDA	1-3	46(21.7%)	166(78.3%)	212	P=0.22, K=1.51
	4 AND ABOVE	27(28.1%)	69(71.9%)	96	DF=1, OR=0.71
Total		**110(26.7%)**	**302(73.3%)**	**412**	

[a] represents cells that rejects the null hypothesis at $p<0.05$ [b] represents cells that assumes the null hypothesis at $p<0.05$

3.2 PREVALENCE OF ANTIBIOTIC EXPOSURE, TRENDS OF ANTIBIOTIC PRESCRIPTION AND THEIR APPROPRIATENESS IN PREGNANCY

3.2.1 Prevalence of antibiotic exposure and disease conditions

Antibiotic exposure showed a decline from 76.0 % in 2012 to 54.8 % in 2013, however there was a steady increase of 54.8 % in 2013 to a peak of 77.8 % in 2015 (FIGURE 3.2). About two out of three (65.8 %, n=271) women attending ANC clinic in the hospital were exposed to an antibiotic at one point during pregnancy. There was a steep rise in antibiotic exposure with advance in stage of pregnancy ($p<0.001$, $k = 407.8$). Third trimester exposures accounted for 79.0 % (214) of all exposures whiles first trimester exposures were the least 16.6 % (45). Only twelve women representing 4.40 % were exposed to antibiotics in all three trimesters (FIGURE 3.3).

Antibiotic exposure among women who delivered by caesarean section was higher than those who delivered naturally (OR = 13.8, 95 % CI, 5.9 - 32.5, K = 55.47). However, only 5.5 % (6) went through gestation and CS without receiving antibiotics (TABLE 3.3). Antibiotic exposure less than 24 hours to delivery accounted for 42.4 % of all antibiotic exposures in pregnancy and about 84 % of all such pregnant women went through caesarean section.

There was no association between occupational status and the odds of individual being prescribed antibiotics (Table 3.3).

40 % of the women went through pregnancy without any pregnancy related health condition. Of the remaining 60 %, urinary tract infection (UTI) recorded the mode with 143 accounting for about 41 % of all diagnosis, followed by malaria (28 %) and respiratory tract infections (12 %) (Appendix D). Urinary tract infections was the highest cause of antibiotic prescriptions followed by premedication for caesarean sections and respiratory tract infections with 42.0 %, 14.3 %, and 12.4 % respectively (FIGURE 3.4).

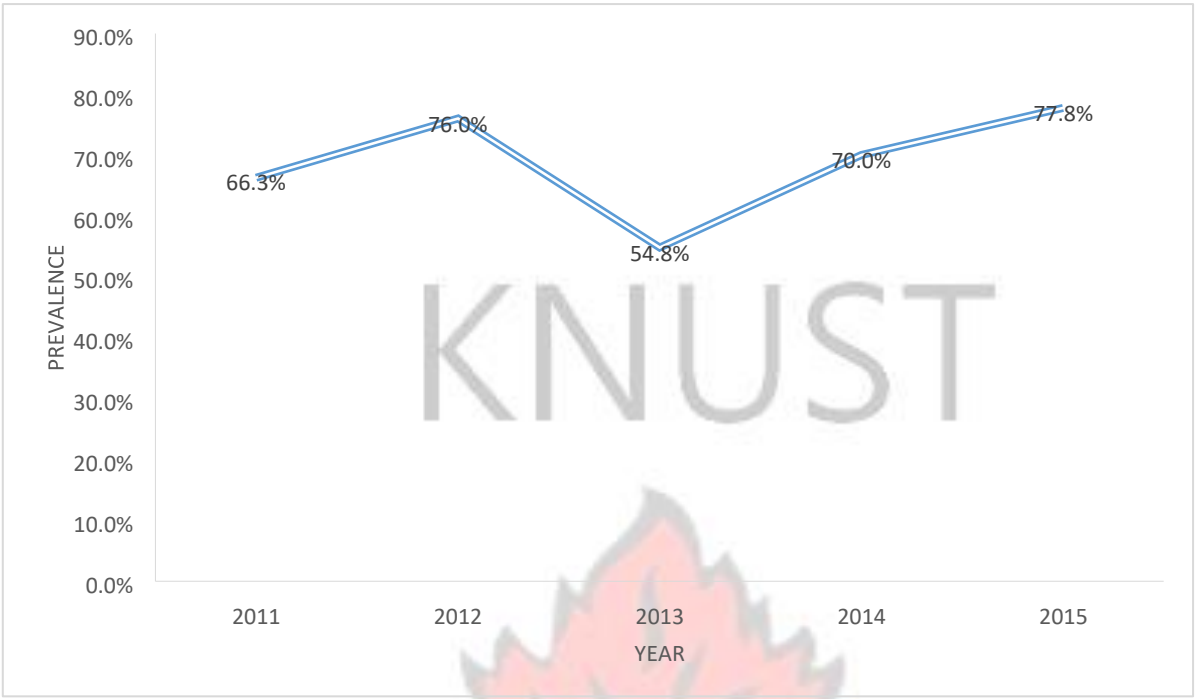

FIGURE 3. 2: **Trends in antibiotic exposure from 2011-2015.**

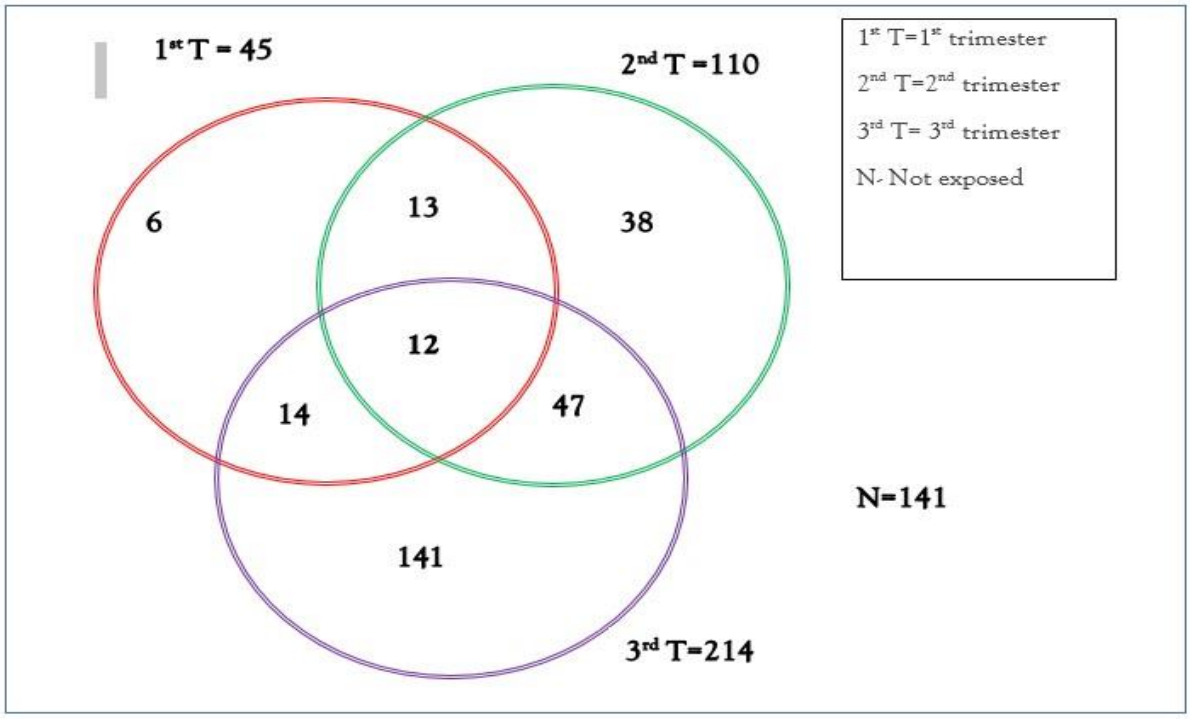

FIGURE 3. 3 : Distribution of antibiotic use and trimester of exposure

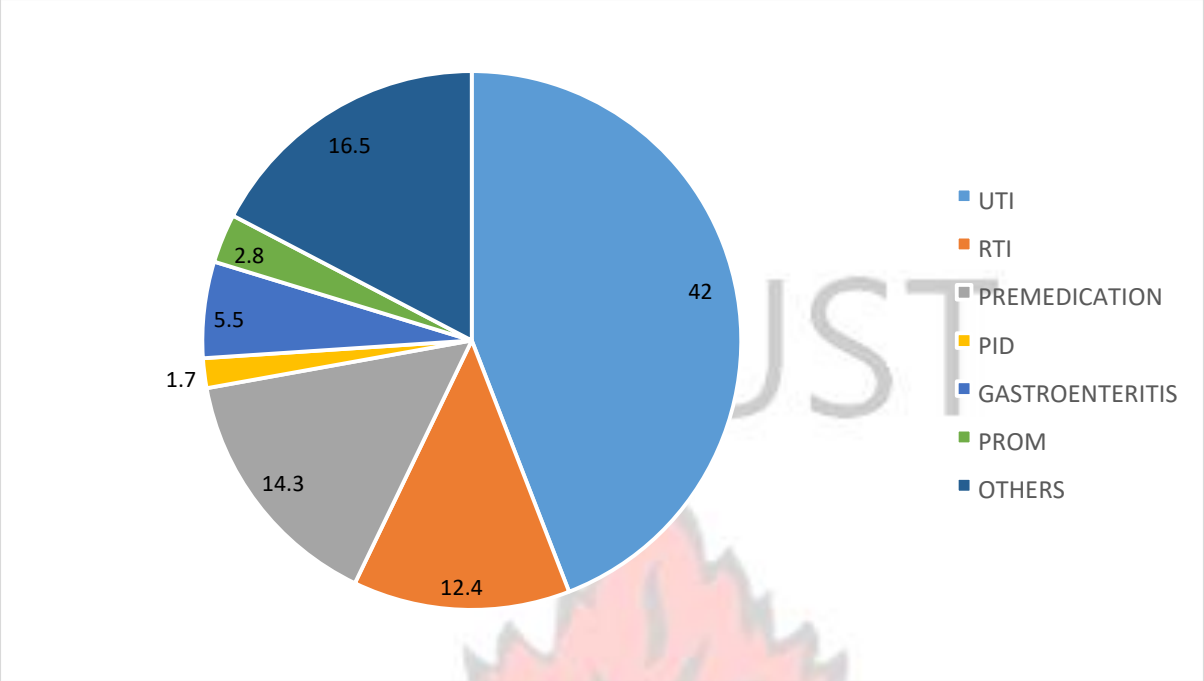

FIGURE 3. 4 Percentage of diagnosis accounting for antibiotic prescriptions

***UTI-urinary tract infection, RTI-respiratory tract infection, PID-pelvic inflammatory disease, PROM- premature rapture of membranes**

TABLE 3. 3: Antibiotic exposure and Socio-demographic factors

		ANTIBIOTIC EXPOSURE			
		YES	NO	Total	SIGN.
MARITAL STATUS	MARRIED	197(64.8%)	107(35.2%)	304	P=0.77,DF=1,
	SINGLE	44(66.7%)	22(33.3%)	66	k=0.83,OR=0.97
AGE OF MOTHER AT BIRTH	19 AND BELOW	32(57.1%)	24(43.9%)	43	P=0.357, DF=2
	20 TO 30YEARS	167(66.5%)	8(33.5%)	238	K=2.058
	31 YEARS AND ABOVE	69(67.6%)	33(32.4%)	96	
OCCUPATIONAL STATUS	EMPLOYED	182(64.6%)	105(37.4%)	126	P=0.61, K=10.06
	STUDENT	27(62.8%)	16(37.2%)	43	
	UNEMPLOYED	19(70.4%)	8(29.6%)	27	
DENOMINATION	CHRISTIAN	219(65.8%)	114(34.2%)	333	P=0.368, K=1.99
	MUSLIM	15(62.5%)	9(37.5%)	24	DF=2
	TRADITIONAL	5(62.5%)	3(37.50%)	8	
GRAVIDA	1 TO 3	117(60.9%	75(39.1%)	192	P=0.066, K=3.38
	4 AND ABOVE	67(72.0%)	26(28.0%)	93	DF=1 OR=0.83
METHOD OF DELIVERY	CEASARIAN SECTION	104(94.5%)	6(5.5%)	110	**P<0.001**, K=55.47
	VAGINAL DELIVERY	167(55.3%)	135(44.7%)	302	DF=1 OR =13.8
TOTAL		271(65.8%)	141(34.2%)	412	

3.2.2 Class of antibiotics prescribed.

Cephalosporins were the most prescribed antibiotics representing 37.6 %, followed by penicillins and nitroimidazoles with 29.8 % and 24 % respectively. Quinolones and sulphonamide/trimethoprim represented about of 2.1 % antibiotics prescribed (FIGURE 3.5).

Cephalosporin, penicillin and nitroimidazoles (predominantly metronidazole) showed a steep rise in use from first trimester to third trimester. Macrolides on the other hand saw a minimal rise. Use of quinolones and co-trimoxazole however declined to zero in third trimester (FIGURE 3.6).

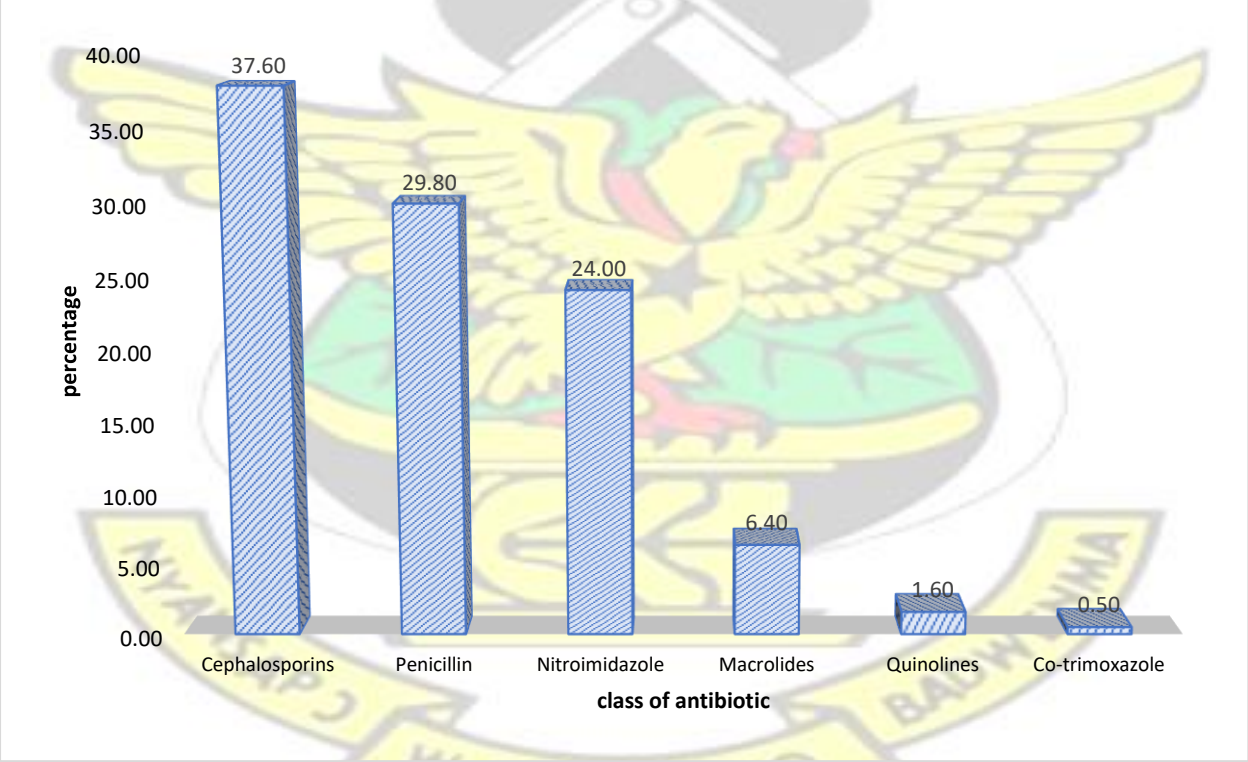

FIGURE 3. 5: Percentage proportions of class of antibiotics prescribed

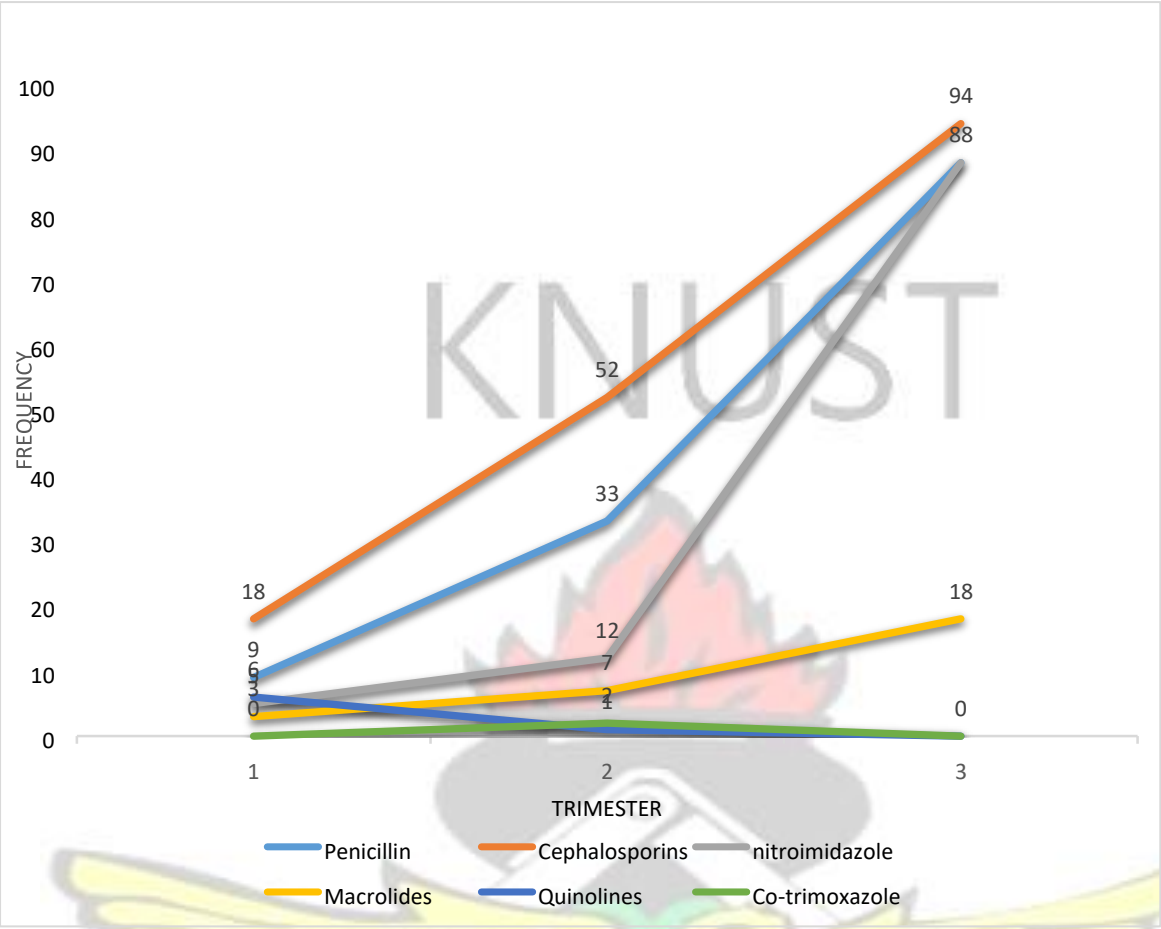

FIGURE 3. 6: Frequency and class of antibiotic use in first, second and third trimesters

3.2.3 Safety and appropriateness of antibiotics in pregnancy

The FDA classifications for the drugs prescribed in the study fell into classes B, C and D with classes A and X recording no prescriptions. Most of the drugs fell into category B with 96.6 % followed by C and D with 2.9 % and 0.5 % respectively (FIGURE 3.7).

It was observed that some antibiotics were prescribed without due justification i.e. there was drug –diagnosis mismatch and this constituted about 3.5 % of all prescriptions issued.

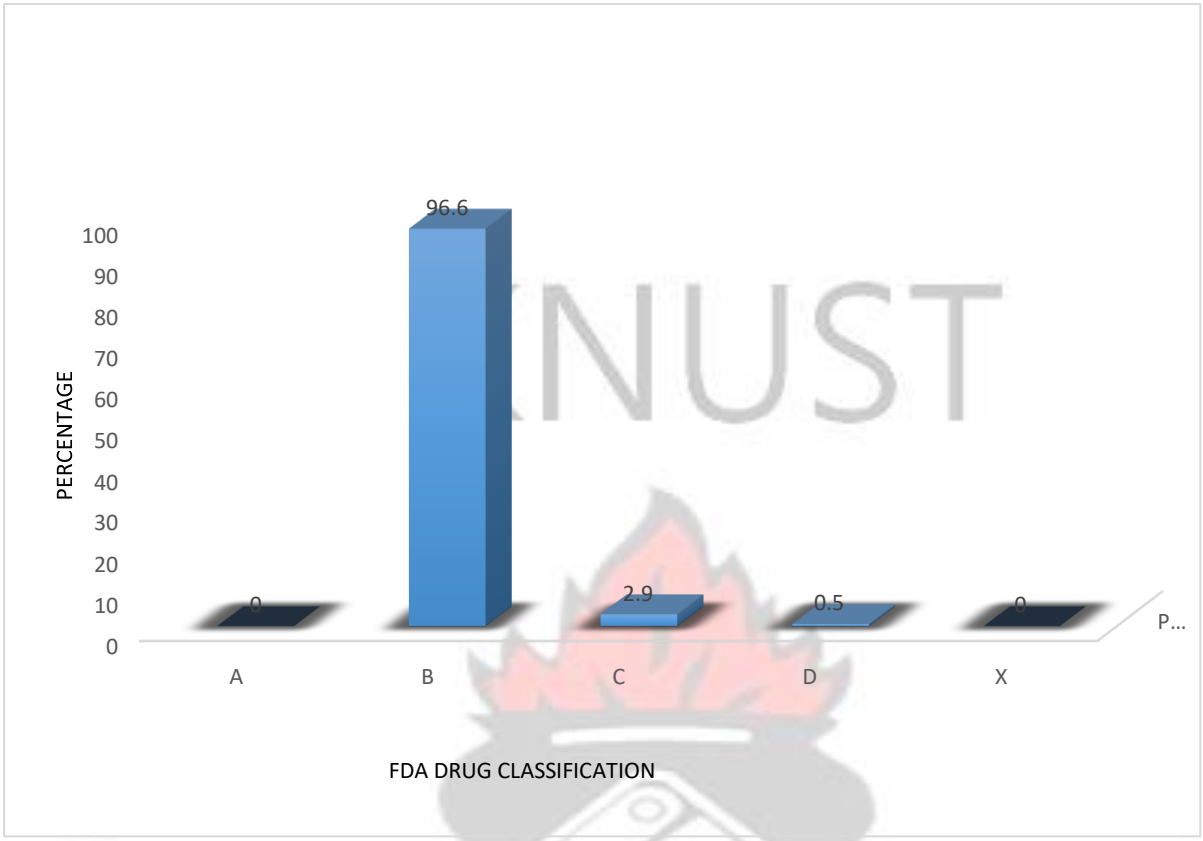

FIGURE 3. 7: FDA classification of antibiotics prescribed in the study

3.3 INTRAPARTUM ANTIBIOTIC EXPOSURE AND BIRTH OUTCOMES

3.3.1 Antibiotic exposure and birthweight

The mean birthweight of babies delivered at the facility was 2.96 ± 0.56 kg. The minimum weight recorded was 1.0 kg and maximum weight was 4.7 kg. Birthweight was classified into categories as based on the WHO classification as seen in Table 1.2. VLBW and LBW accounted for 1.8 % and 19.3 % respectively. HBW accounted for 3.4 % (14) of all babies delivered.

Mean birthweight between exposed group and unexposed group was 2.986 ± 0.58 and 2.971 ± 0.53 (P = 0.80, K = 0.06, 95 % CI). The difference in mean birthweight of babies delivered through CS and VD was not statistically significant (p=0.997, F = 0.01, 95 % CI). Generally, there was a direct relationship between mothers' socio-economic status and birthweight. Birthweight of babies born to married and unmarried women was 3.02 ± 0.56 and 2.74 ± 0.52 respectively (p<0.001, F = 12.74, 95 % CI). Likewise, teenage mothers and students gave birth to babies with lower weights at birth (Table 3.5).

TABLE 3. 4: Shows the distribution of birthweights

Category		Frequency	Valid Percent	Cumulative Percent
Valid	VLBW	7	1.8	1.8
	LBW	77	19.3	21.0
	NBW	302	75.5	96.5
	HBW	14	3.5	100.0
	Total	400	100.0	
Total		412		

TABLE 3. 5: Antibiotic exposure and Weight at birth

				95% Confidence Interval for Mean			
MARITAL STATUS	**N**	**Mean**	**Std. Deviation**	**Lower Bound**	**Upper Bound**	**F**	**P**
MARRIED	298	3.0185	.55615	2.9551	3.0819	12.74	**0.001**
SINGLE	65	2.7492	.52697	2.6187	2.8798		
AGE GROUP							
19 YEARS AND BELOW	55	**2.7509[a]**	.47808	2.6217	2.8802	7.041	**0.001**
20-30 YEARS	242	2.9535[b]	.56280	2.8822	3.0248		
31 YEARS AND ABOVE	100	3.0985[b]	.57302	2.9848	3.2122		
OCCUPATIONAL STATUS							
EMPLOYED	287	3.0005 [b]	.56716	2.9346	3.0664	4.22	**0.016**
STUDENT	43	**2.7349 [a]**	.58223	2.5557	2.9141		
UNEMPLOYED	27	3.0000 [b]	.47129	2.8136	3.1864		
RELIGION							
CHRISTIAN	324	2.9799	.57610	2.9170	3.0429	1.006	0.367
MUSLIM	23	2.8152	.48040	2.6075	3.0230		
TRADITIONAL	8	2.8750	.52304	2.4377	3.3120		
GRAVIDA							
1-3	206	2.8733	.50535	2.8039	2.9427	10.37	**0.001**
4 AND ABOVE	95	3.0832	.56684	2.9677	3.1986		
MODE OF DELIVERY							
CEASARIAN SECTION	103	2.9617	.59178	2.8460	3.0773	0.00	0.997
VAGINAL DELIVERY	297	2.9614	.55161	2.8985	3.0244		
ANTIBIOTIC EXPOSURE							
YES	261	2.9563	.57973	2.8857	3.0270	0.06	0.80
NO	139	2.9712	.52740	2.8828	3.0597		

[a] represents cells that reject the null hypothesis.
[b] represents cells that fail to reject the null hypothesis.

3.3.2 Apgar scores and antibiotic exposure

The mean Apgar score (MAS) was 8.36 ± 1.29. A maximum of 10 and minimum of 2 were recorded. There was no statistically significant difference in mean Apgar scores of babies exposed or unexposed to intrapartum antibiotics i.e. 8.242 ± 1.3 vs 8.32 ± 1.62 (P = 0.414, F = 1.59, 95 % CI). Mean Apgar score however, in those exposed to antibiotics less than 24 hours postpartum was statistically lower than in those unexposed i.e. 7.86 ± 1.72 vs 8.4 ± 1.30 respectively (P = 0.002, F = 13.65, 95 % CI).

Babies born naturally had MAS statistically higher than those born by caesarean section i.e. 8.42 ± 1.23 vs 7.86 ± 1.87(P = 0.003, F= 8.98, 95 % CI). Younger mothers, unmarried women and mothers with less gravida had significantly higher MAS compared with older (P = 0.046), married (P = 0.018) and higher gravida (P = 0.034) mothers respectively at 95 % confidence interval (Table 3.6).

TABLE 3. 6: Antibiotic exposure and mean Apgar scores.

	N	Mean	Std. Deviation	95% Confidence Interval Lower Bound	95% Confidence Interval Upper Bound	F	P
MARRIED	282	8.2553	1.36637	8.0952	8.4155	5.606	**0.018**
SINGLE	62	8.6855	.89733	8.4576	8.9134		
AGE GROUPS							
19 YEARS AND BELOW	53	**8.6132** [a]	1.06356	8.3201	8.9064	3.02	**0.046**
20-30 YEARS	232	8.4073 [b]	1.27964	8.2418	8.5729		
31 YEARS AND ABOVE	93	8.0968 [b]	1.42999	7.8023	8.3913		
OCCUPATIONAL STATUS							
EMPLOYED	272	8.3162	1.32435	8.1581	8.4743	0.241	0.786
STUDENT	41	8.4024	1.25110	8.0075	8.7973		
UNEMPLOYED	25	8.4800	.95175	8.0871	8.8729		
RELIGION							
CHRISTIAN	311	8.3296	1.33497	8.1806	8.4785	0.18	0.835
MUSLIM	21	8.4286	1.15418	7.9032	8.9540		
TRADITIONAL	1	9.0000					
GRAVIDA							
1-3	200	8.5350	1.21807	8.3652	8.7048	4.545	**0.034**
4 AND ABOVE	88	8.1989	1.26523	7.9308	8.4669		
MODE OF DELIVERY							
CEASARIAN SECTION	100	8.0300	1.67093	7.6985	8.3615	8.981	**0.003**
VAGINAL DELIVERY	281	8.4769	1.11018	8.3465	8.6072		
ANTIBIOTIC EXPOSURE							
YES	248	8.2984	1.30929	8.1346	8.4621	1.59	0.208
NO	133	8.4737	1.26179	8.2573	8.6901		

PERINATAL ANTIBIOTIC EXPOSURE							
YES	104	7.9663	1.69560	7.6366	8.2961	13.65	**0.003**
NO	277	8.5072	1.07337	8.3803	8.6342		

[a] represents cells that reject the null hypothesis at $p<0.05$, [b] represent a cell that does not reject the null hypothesis at $p<0.05$

3.3.3 Antibiotic exposure and risk of birth defects.

A total of 6 birth defects were observed in the study representing 1.5 % of all babies born. There were 2 babies with Cleft lip alone while one developed cleft lip with cleft palate. Two babies developed mega cephalous whiles only one baby had webbed feet. Intrapartum antibiotic exposure irrespective of trimester of exposure was not associated with any significant risk of birth defect (RR = 1, 95 % CI, 0.19 – 5.70, P = 0.97). There was no statistically significant association between marital status (P = 0.94), mothers age at birth (P = 0.361), occupation (P = 0.630), parity (P = 0.94) and religion (P = 0.49). Females had higher incidence of birth defects than males i.e. 2.2 % vs 1.0 % (RR = 2.2, P = 0.343, 95 % CI) (Table 3.7).

TABLE 3. 7 **Antibiotic exposure and risk of birth defects.**

		BIRTH DEFECT			
		YES	**NO**	**Total**	**significance**
MARITAL STATUS	MARRIED	5(1.6%)	299(98.4 %)	304	P=0.940, K=0.006
	SINGLE	1(1.5%)	65(98.5%)	66	DF=1, RR=1.1
AGE OF MOTHER AT BIRTH	19 YEARS AND BELOW	1(1.8%)	55(98.2%)	56	P=0.361, K=2.037
	20-30 YEARS	5(2.0%)	246(98.0%)	251	DF=2
	31 YEARS AND ABOVE	0	102	102	
OCCUPATION	EMPLOYED	3(1%)	294(99%)	297	P=0.630, K=0.924
	STUDENT	1(2.3%)	42(97.7%)	43	DF=2
	UNEMPLOYED	0	27	27	
DENOMINATION	CHRISTIAN	5(1.5%)	328(98.5%)	333	P=0.487, K=784
	MUSLIM	0	24	24	DF=2
	TRADITIONAL	0	8		
Gravida	1-3	2(0.9%)	210(99.1%)	212	P=0.935, K=0.007
	4 AND ABOVE	1(1.0%)	95(99.0%)	96	DF=1, RR=0.90

MOTHER EXPOSED TO ANTIBIOTIC	YES	4(1.5%)	268(98.5%)	272	P=0.97, K=0.001
	NO	2(1.4%)	138(98.6%)	140	DF=1, RR=1
GENDER	FEMALE	4(2.2%)	175(97.8%)	179	P=0.343, K=0.900
	MALE	2(1.0%)	196(99.0%)	198	DF=1, RR=2.2

3.4 INDICATORS OF NEONATAL HEALTH

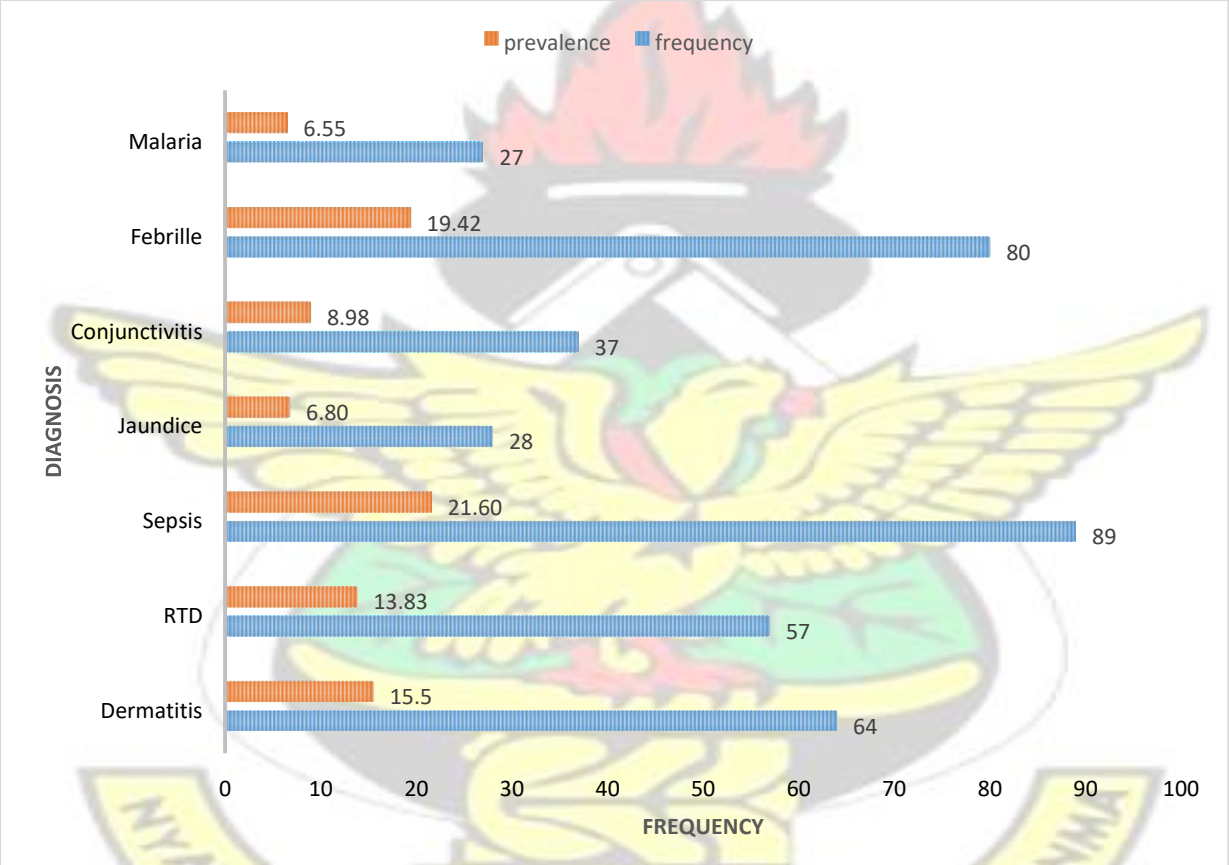

FIGURE 3. 8: Top 7 Diseases in Neonates encountered in the study

3.4.1 Dermatitis and antibiotic exposure.

A total of sixty-four (64) babies were diagnosed with dermatitis representing 15.5 % of all neonates studied (FIGURE 3.8). Dermatitis was based on prescribers diagnosis recorded in patient medical records.

Out of the 64 babies diagnosed with dermatitis, 47 (82.5 %) were born to mothers prescribed antibiotics during the course of pregnancy. The relative risk (RR) of disease if exposed was 2.6 (95 % CI, 1.3 - 4.9, P = 0.005). The relative risks of dermatitis when exposed to antibiotic in first, second, third and all trimesters were 3.4, 2.0, 2.1 and 4.5 respectively. After adjusting for the influence of method of delivery babies exposed to antibiotics intrapartum were 2.3 (95 % CI, 1.15 - 4.79, P = 0.017) times at risk of dermatitis compared to those unexposed.

Babies delivered by caesarean section were 1.4 (95 % CI, 0.80 - 2.52, P = 0.23) times at risk of dermatitis compared with naturally born babies. Babies who were exposed to antibiotics and subsequently underwent caesarean birth were not significantly at higher risk of dermatitis compared with those who were delivered naturally (RR=1.12, 95 % CI, 0.62 - 2.16, P = 0.69). Mothers sociodemographic factors; marital status (P = 0.7), occupation (P = 0.98) and gravida (P = 0.14), were not associated with any significant risk of dermatitis in neonates.

TABLE 3. 8: Antibiotic exposure and risk of dermatitis

		DERMATITIS			
		YES	NO	Total	significance
MOTHER EXPOSED TO ANTIBIOTIC	YES	52(19.2%)	219(80.8%)	271	K=8.06,**P=0.005**
	NO	12(8.5%)	129(91.5%)	141	DF=1, **RR=2.6**
METHOD OF DELIVERY	CEASARIAN SECTION	21(19.1%)	89(80.9%)	110	K=1.447, P=0.229
	VAGINAL DELIVERY	43(14.2%)	259(85.8%)	302	DF=1 RR=1.42
METHOD OF DELIVERY (adjusted)[1]	CEASARIAN SECTION	21(20.4%)	82(79.6%)	103	DF=1, P=0.689
	VAGINAL DELIVERY	30(18.4%)	133(81.6%)	163	K=0.160, RR=1.16
PERINATAL ANTIBIOTIC EXPOSURE	YES	24(20.9%)	91(79.1%)	115	K=3.461,P=0.063
	NO	40(13.5%)	257(86.5%)	297	DF=1 RR=1.70
MOTHER EXPOSED TO ANTIBIOTIC(adjusted)[2]	YES	30(18.9%)	129(81.1%)	159	K=5.70, **P=0.017**
	NO	12(9.0%)	121(91%)	133	DF=1, **RR=2.34**
MARITAL STATUS	MARRIED	52(17.1%)	252(82.9%)	304	K=0.15, p=0.70
	SINGLE	10(15.2%)	56(84.8%)	66	DF=1, RR=1.15
AGE OF MOTHER AT BIRTH	19 YEARS AND BELOW	9(16.1%)	47(83.9%)	56	P=0.451, K=1.59
	20-30 YEARS	43(17.1%)	208(82.9%)	251	DF=1
	31 YEARS AND ABOVE	12(11.8%)	90(88.2%)	102	
DENOMINATION	CHRISTIAN	51(15.3%)	282(84.7%)	333	**P=0.008**,K=9.706
	MUSLIM	1(4.2%)	23(95.8%)	24	DF=2
	TRADITIONAL	4(50%)	4(50%)	8	

[1] after excluding babies not exposed to antibiotics, [2] after excluding babies delivered by caesarean birth.

GRAVIDA	UP TO 3	28(13.2%)	184(86.8%)	212	K=2.215, P=0.137
	4 AND ABOVE	19(19.8%)	77(80.2%)	96	DF=1
OCCUPATION	EMPLOYED	47(15.8%)	250(84.2%)	297	P=0.986, K=0.027
	STUDENT	7(16.3%)	36(83.7%)	43	DF=2
	UNEMPLOYED	4(14.8%)	23(85.2%)	27	

3.4.2 Respiratory tract disease and antibiotic exposure

Respiratory tract diseases included rhinitis, chest infection, pneumonia, bronchiolitis and any other condition related to the respiratory tract. No distinction was made between infectious and allergic respiratory tract diseases.

The prevalence of respiratory tract diseases (RTD) in the exposed and unexposed group was 18.5 % (50) and 5.0 % (7) respectively. The relative risk of RTD if exposed to antibiotics intrapartum was 4.3 (95 % CI, 1.89 - 9.71, P<0.001). The adjusted Relative Risk of RTD in neonates depending on trimester of exposure was 3.3, 2.1, 3.4 and 6.6 for 1^{st}, 2^{nd}, 3^{rd} and all trimesters respectively. After adjusting for method of delivery, the relative risk of respiratory tract diseases if exposed to antibiotics was 3.2 (95 % CI, 1.25 - 8.18, P = 0.011) (TABLE 3.9).

Caesarean-born babies were more likely to suffer from respiratory tract diseases compared with naturally born i.e. 25.2 % (27) vs 9.2 % (27) (RR = 3.35, 95 % CI, 1.97 - 6.23, p<0.001). Among the neonates exposed to intrapartum antibiotics, caesarean birth was associated with about thrice the risk of respiratory tract diseases compared with the naturally born (RR = 2.65, 95 % CI, 1.45 - 5.18, P = 0.001). Cross tabulation of socio-demographic factors against risk of respiratory tract diseases showed no significance at 95 % confidence interval (TABLE 3.9).

TABLE 3

. 9: Antibiotic exposure and risk of respiratory tract diseases

		RESPIRATORY TRACT DISEASES		Total	
		YES	NO		significance
MOTHER EXPOSED TO ANTIBIOTIC	YES	50(18.5%)	221(81.5%)	271	K=13.9, **P<0.001**
	NO	7(5.0%)	134(95.0%)	141	DF=1 **RR=4.30**
METHOD OF DELIVERY	CEASARIAN SECTION	29(26.4%)	81(73.6%)	110	K=19.76, **P<0.001**
	VAGINAL DELIVERY	28(9.3%)	274(90.7%)	302	DF=1 **RR=3.502**
METHOD OF DELIVERY (adjusted)[1]	CEASARIAN SECTION	29(28.2%)	74(71.8%)	103	K=10.13, **P=0.001**
	VAGINAL DELIVERY	21(12.9%)	142(87.1%)	163	DF=1, **RR=2.74**
PERINATAL ANTIBIOTIC EXPOSURE	YES	30(26.1%)	85(73.9%)	115	K=20.88, **P<0.001**
	NO	27(26.1%)	270(90.9%)	297	DF=1 **RR=3.52**
MOTHER EXPOSED TO ANTIBIOTIC(adjusted)[2]	YES	21(13.0%)	140(87.0)	161	K=6.454,**P=0.011**
	NO	6(4.5%)	128(95.5%)	134	DF=1, **RR=3.2**
MARITAL STATUS	MARRIED	44(14.5%)	260(85.5%)	304	K=0.248,P=0.618
	SINGLE	8(12.1%)	58(87.9%)	66	DF=1, RR=1.22
AGE OF MOTHER AT BIRTH	19 YEARS AND BELOW	4(8.7%)	42(91.3%)	46	K=2.138,P=0.343
	20-30 YEARS	41(15.7%)	220(84.3%)	261	DF=2
	31 YEARS AND ABOVE	12(11.8%)	90(88.2%)	102	
DENOMINATION	CHRISTIAN	44(13.2%)	289(86.8%)	333	K=0.010, P=0.920
	MUSLIM	3(12.5%)	21(87.5%)	24	DF=2,
	TRADITIONAL	1(14.3%)	7(85.7%)	8	
GRAVIDA	1 TO 3	26(12.3%)	186(87.7%)	212	K=0.647, P=0.421
	4 AND ABOVE	15(15.6%)	81(84.4%)	96	DF=1, RR=0.77
OCCUPATION	EMPLOYED	38(12.8%)[b]	259(87.2%)	126	K=6.07, **P=0.048**
	STUDENT	5(11.6%)[b]	38(88.4%)	78	DF=2,
	UNEMPLOYED	**8(29.6%)[a]**	19(70.4%)	27	

TABLE 3 C

[1] after excluding babies not exposed to antibiotics, [2] after excluding babies delivered by caesarean birth [a] represents cells that reject the null hypothesis at $p<0.05$, [b] represents cells that does not reject the null hypothesis at $p<0.05$.

3.4.3 Neonatal sepsis and antibiotic exposure

Prevalence of neonatal sepsis among babies delivered was 22.1 %. Prevalence of neonatal sepsis among those exposed to antibiotics was 29.5 % (76) compared to 9.6 % (13) in unexposed group. Babies exposed to intrapartum antibiotics were 4 (95 % CI, 2.1 - 7.36, P<0.001) times more prone to developing sepsis after birth compared to unexposed neonates. After adjusting for the confounding of method of delivery, the adjusted relative risk of neonatal sepsis if exposed was 2.1 (95 % CI, 1.04 - 4.2, P = 0.030). The relative risks of disease depending on the trimester of exposure was 1.0, 1.1, 3.3 and 4.5 for 1st, 2nd, 3rd and all trimesters respectively.

Prevalence of neonatal sepsis in CS and VD was 43.4 % (46) and 15.0 % (43) respectively. Moreover babies delivered through CS were about 4.4 times at risk of neonatal sepsis compared to naturally born babies (95 % CI, 2.67 - 7.18, P<0.001). In the exposed cohort, caesarean birth was associated with about three times the risk of respiratory morbidities (RR = 3.50, 95 % CI, 2.01 - 6.01, P<0.001).

A Cross tabulation occupation status (P = 0.134), age (P = 0.85), gravida (P = 0.65) and risk of neonatal sepsis revealed no statistically significant difference at $p<0.05$.

.10: rosstabulation of neonatal sepsis

		NEONATAL SEPSIS		Total	
		YES	NO		significance
MOTHER EXPOSED TO ANTIBIOTIC	YES	78(28.8%)	193(71.2%)	271	K=20.6,**P<0.001**
	NO	13(9.2%)	128(90.8%)	141	DF=1, **RR=3.98**
METHOD OF DELIVERY	CEASARIAN SECTION	47(42.7%)	63(57.3%)	110	K=37.1, **P<0.001**
	VAGINAL DELIVERY	44(14.6%)	258(85.4%)	302	DF=1, **RR=4.38**
METHOD OF DELIVERY (adjusted)[1]	CEASARIAN SECTION	46(44.7%)	57(55.3%)	103	K=20.47,**P<0.001**
	VAGINAL DELIVERY	31(19.0%)	132(81.0%)	163	DF=1, **RR=3.50**
PERINATAL ANTIBIOTIC EXPOSURE	YES	55(47.8%)	60(52.2%)	115	K=61.4, **P<0.001**
	NO	36(12.1%)	261(87.9%)	297	DF=1, RR=6.64
MOTHER EXPOSED TO ANTIBIOTIC-(adjusted)[2]	YES	30(19.0%)	128(81.0%)	158	K=4.46, **P=0.035**
	NO	13(10.1%)	116(89.9%)	129	DF=1, **RR=2.091**
MARITAL STATUS	MARRIED	65(21.4%)	239(78.6%)	304	K=0.058, P=0.81
	SINGLE	15(22.7%)	51(77.3%)	66	DF=1, RR=0.925
AGE OF MOTHER AT BIRTH	19 YEARS AND BELOW	8(17.4%)	38(82.6%)	46	K=0.73, P=0.695
	20-30 YEARS	60(23.0%)	201(77.0%)	261	DF=2
	31 YEARS AND ABOVE	22(21.6%)	80(78.4%)	102	
DENOMINATION	CHRISTIAN	72(21.6%)	261(78.4%)	333	K=0.150, P=0.70
	MUSLIM	6(25.0%)	18(75%)	24	DF=2
	TRADITIONAL	2(25.0%)	6(75.0%)	8	
GRAVIDA	UP TO 3	47(22.2%)	165(77.8%)	212	K=0.003, P=0.65

TABLE 3 C

	4 AND ABOVE	21(21.9%)	75(78.1%)	96	DF=1, RR=1.017
OCCUPATION	EMPLOYED	65(21.9%)	232(78.1%)	126 78	K=0.256,P=0.88
	UNEMPLOYED	7(25.9%)	20(74.1%)		DF=2
	STUDENT	10(23.3%)	33(76.7%)	43	

[1] after excluding babies not exposed to antibiotics, [2] after excluding babies delivered by caesarean birth

3.4.4 Ophthalmia neonatorum and antibiotic exposure

The term "neonatal conjunctivitis" was chosen to represent any diagnosis of a prescriber listed as follows; neonatal conjunctivitis, septic or bacterial conjunctivitis, allergic conjunctivitis and ophthalmia neonatorum. The prevalence of conjunctivitis was found to be 8.98 % (37) among the neonates studied (FIGURE 3.8).

Prevalence of neonatal conjunctivitis in babies in the exposed and unexposed group was 11.8 % (32) and 5 % (7) respectively. Babies in the exposed group had a relative risk of 2.5 (95 % CI, 1.09 - 5.90, P = 0.024). When method of delivery was adjusted for, the RR reduced to 2.0 (95 % CI, 0.80 - 5.05, P = 0.129). Perinatal antibiotic exposure was associated with a relative risk of 1.61 (95 % CI, 0.86 - 3.38, P = 0.126) compared to those unexposed.

The prevalence of antibiotic exposure in babies born by CS and VD were 12.7 % (14) and 8.3 % (25) respectively. Caesarean section was associated with a relative risk of 1.6 (95 % CI, 0.81- 3.23, P = 0.172) compared to babies delivered vaginally.

A crosstab between mother's age (P = 0.189), religion (P = 0.628), marital status (P = 0.976), gravida (P = 0.538) and occupation (P = 0.729) and prevalence of neonatal conjunctivitis showed no statistically significant association at 95 % confidence interval (TABLE 3.11).

.11: rosstabulation of neonatal conjunctivitis

		NEONATAL CONJUNCTIVITIS		Total	Significance
		YES	NO		
MOTHER EXPOSED TO ANTIBIOTIC	YES	32(11.8%)	239(88.2%)	271	K=5.06, **P=0.024**
	NO	7(5.0%)	134(95.0%)	141	DF=1, **RR=2.56**
METHOD OF DELIVERY	CEASARIAN SECTION	14(12.7%)	96(87.3%)	110	K=1.862, P=0.172
	VAGINAL DELIVERY	25(8.3%)	277(91.7%)	302	DF=1, RR=1.6
METHOD OF DELIVERY (adjusted)[1]	CEASARIAN SECTION	14(13.6%)	89(86.4%)	103	K=0.61, P=0.434
	VAGINAL DELIVERY	17(10.4%)	146(89.6%)	163	DF=1, RR=1.35
PERINATAL ANTIBIOTIC EXPOSURE	YES	15(13.0%)	100(87.0%)	115	K=2.382, P=0.123
	NO	24(8.1%)	273(91.9%)	297	DF=1, RR=1.61
MOTHER EXPOSED TO ANTIBIOTIC-	YES	16(10.1%)	143(89.9%)	159	K=2.30, P=0.129

[1] after excluding babies not exposed to antibiotics, [2] after excluding babies delivered by caesarean birth

TABLE 3 C

MARITAL STATUS	MARRIED	28(9.2%)			K=0.001, P=0.976
	SINGLE	6(9.1%)	60(90.9%)	66	DF=1, RR=1.01
AGE OF MOTHER AT BIRTH	19 YEARS AND BELOW	6(10.7%)	50(89.3%)	56	P=0.189, K=3.392
	20-30 YEARS	28(11.2%)	223(88.8%)	251	DF=2,
	31 YEARS AND ABOVE	5(4.9%)	97(95.1%)	102	
DENOMINATION	CHRISTIAN	33(9.9%)	300(90.1%)	333	P=0.628, K=0.932
	MUSLIM	2(8.3%)	22(91.7%)	24	DF=2
	TRADITIONAL	0	8	8	
			126(94.7%)	133	
(adjusted)$_2$	NO	7(5.3%0	276(90.8)	304	DF=1, RR=2.0
GRAVIDA	1-3	20(9.4%)	192(90.6%)	212	p=0.538, k=0.379
	4 AND ABOVE	7(7.3%) DF=1,	89(92.7%)	96	RR=1.324
OCCUPATION	FARMER	25(8.4%) p=	272(91.6%)	297	0.729, k=0.633
	STUDENT	5(11.6%)	38(88.4%)	43	DF=2
	UNEMPLOYED	3(11.1%)	24(88.9%)	27	

3.4.5 Neonatal jaundice and antibiotic exposure

The prevalence of neonatal jaundice in the babies followed up was 6.8 % (28) (FIGURE 3.8). The relative risk of neonatal jaundice if exposed to antibiotic at any point in pregnancy was 2.5 (95 % CI, 0.93 - 6.71, P = 0.059). Perinatal exposure however was not associated with any significant risk of neonatal jaundice (RR = 1.7, 95 % CI, 0.79 - 3.84, P = 0.165).

Babies who went through caesarean birth were about 1.6 times at risk of jaundice compared with naturally born babies (95 % CI, 0.71 - 3.53, P = 0.264). A cross tabulation of neonatal jaundice with marital status, age of mother, religion, and gravida showed no statistical significance (TABLE 3.12).

.12: rosstabulation of neonatal jaundice

		NEONATAL JAUNDICE		Total	significance
		YES	NO		
MOTHER EXPOSED TO ANTIBIOTIC	YES	23(8.5%)	248(91.5%)	271	K=3.58, P=0.059
	NO	5(3.5%)	136(96.5%)	141	DF=1, RR=2.52

TABLE 3 C

METHOD OF DELIVERY	CEASARIAN SECTION	10(9.1%)	100(90.9%)	110	K=1.248,P=0.264
	VAGINAL DELIVERY	18(6.0%)	284(94.0%)	302	DF=1, RR=1.57
METHOD OF DELIVERY (adjusted)[1]	CEASARIAN SECTION	10(9.7%)	93(90.3%)	103	K=0.24, P=0.624
	VAGINAL DELIVERY	13(8.0%)	150(92%)	163	DF=1, RR=1.2
PERINATAL ANTIBIOTIC EXPOSURE	YES	11(9.6%)	104(90.4%)	115	K=1.931, P=0.165
	NO	17(5.7%)	280(94.3%)	297	DF=1,RR=1.74
MOTHER EXPOSED TO ANTIBIOTIC-(adjusted)[2]	YES	1(5.3%)	18(94.7%)	19	K=0.006, P=0.940
	NO	16(5.7%)	266(94.3%)	282	DF=1, RR=0.924
MARITAL STATUS	MARRIED	19(6.3%)	285(93.8%)	304	K=0.003, P=0.654
	SINGLE	4(6.1%)	62(93.9%)	66	DF=1 RR=1.03
AGE OF MOTHER AT BIRTH	19 YEARS AND BELOW	3(6.5%)	43(93.5%)	46	K=1.67, P=0.435
	20-30 YEARS	20(7.7%)	241(92.3%)	261	DF=2,
	31 YEARS AND ABOVE	4(3.9%)	98(96.1%)	102	
DENOMINATION	CHRISTIAN	18(5.4%)	315(94.6%)	333	K=5.65, P=0.056
	MUSLIM	1(4.2%)	23(95.8%)	24	DF=2
	TRADITIONAL	2(25.0%)	6(75.0%)	8	
GRAVIDA	UP TO 3	11(5.2%)	201(94.8%)	212	K=0.001, P=0.994
	4 AND ABOVE	5(5.2%)	91(94.8%)	96	DF=1
OCCUPATION	EMPLOYED	22(7.4%)	275(92.6%)	126	K=1.97,P=0.373
	STUDENT	1(2.6%)	42(97.4%)	78	DF=2
	UNEMPLOYED	1(3.7%)	26(97.7%)	43	

[1] after excluding babies not exposed to antibiotics, [2] after excluding babies delivered by caesarean birth

3.4.6 Mean number of hospital visits and antibiotic exposure

The average number of hospital visits was used as a marker of the general wellbeing or health of the neonate. Normal post-natal review visits or scheduled visits were excluded from the count of visits unless the child presented with an adverse medical condition which needed a medical attention. The test statistic used was the mean number of visits. The average number of visits was 0.57 ± 0.99. The range was 0.0 to 6.0 visits.

Intrapartum antibiotic exposure was associated with a higher mean number of visits compared with non-exposed babies' i.e. 0.73 ± 1.1 vs 0.20 ± 0.6 (95 % CI, $p<0.001$, $F = 21.2$). After adjusting for method of delivery, the association between antibiotic exposure and Mean visits was still significant (95 % CI, $p<0.001$, $F = 13.92$).

Caesarean-born babies were more likely to report to the hospital for any health related condition compared to natural birth i.e. 1.0377 ± 1.27 vs 0.4047 ± 0.80 respectively (95 % CI, $p<0.001$, $F = 34.90$). There was no statistically significant association between number of visits and other socio-economic factors of mother (Table 4.13).

TABLE 3 C

.13: rosstabulation of average number hospital visits

MOTHER EXPOSED TO ANTIBIOTIC	Mean	Std. Deviation	95% C I Lower Bound	95% C I Upper Bound	F	P
YES	0.7293	1.09633	0.597	0.8617	21.12	**<0.001**
NO	0.2662	0.63218	0.1602	0.3722		
PERINATAL EXPOSURE						
YES	1.0631	1.28826	0.8207	1.3054	42.00	**<0.001**
NO	0.3844	0.76966	0.296	0.4727		
METHOD OF DELIVERY						
CEASARIAN SECTION	1.0377	1.27185	0.7928	1.2827	34.9	**<0.001**
VAGINAL DELIVERY	0.4047	0.80275	0.3133	0.496		
METHOD OF DELIVERY (ADUSTED)[1]						
CEASARIAN SECTION	1.0101	1.2737	0.7561	1.2641	12.332	**0.001**
VAGINAL DELIVERY	0.5404	0.8803	0.4034	0.6774		
MOTHER EXPOSED TO ANTIBIOTIC (ADJUSTED)[2]						
YES	0.5250	0.87560	0.3883	0.6617	13.920	**<0.001**
NO	0.2030	0.51873	0.1140	0.2920		
MARRIED	0.5652	1.01908	0.4492	0.6812	0.043	0.840
SINGLE	0.5938	0.88585	0.3725	0.8150		
19 YEARS AND BELOW	0.5536	0.82945	0.3314	0.7757	0.083	0.920
20-30 YEARS	0.5854	0.98500	0.4617	0.7091		
31 YEARS AND ABOVE	0.5400	1.07703	0.3263	0.7537		
CHRISTIAN	0.5443	0.98003	0.4377	0.6510	1.416	0.244

[1] after excluding babies not exposed to antibiotics. [2] after excluding babies delivered by caesarean birth.

MUSLIM	0.5217	0.84582	0.1560	0.8875		
TRADITIONAL	1.1250	0.83452	0.4273	1.8227		
1 TO 3	0.5096	0.94787	0.3800	0.6392	1.23 0	0.268
4 AND ABOVE	0.6421	0.99910	0.4386	0.8456		
EMPLOYED	0.5864	1.01945	0.4696	0.7033	0.535	0.586
STUDENT	0.5250	0.84694	0.2541	0.7959		
UNEMPLOYED	0.3846	0.80384	0.0599	0.7093		

CHAPTER FIVE

DISCUSSION

In this study, antibiotic exposure among women attending Antenatal care clinic at SeventhDay Adventist Hospital, Dominase were analysed. The rational for this study was to ascertain if indeed antibiotic exposure had any effect on birth outcomes and neonatal health. Babies in the study were followed for the first three months to ascertain if maternal use of antibiotics affected the health of the new born in terms of dermatitis, sepsis, respiratory tract disease, jaundice, conjunctivitis and number of hospital visits.

A total of 412 mother-baby pairs met the inclusion criteria. The minimum and maximum maternal age at birth was similar to the 15 - 49 age bracket captured in the 2010 population census for Bekwai municipal. It was however worrying that, teenage mothers constituted 13.7 % of women in the study. Young or teenage mothers are themselves dependent on parents and guardians for support (Agyei *et al.,* 2000).

Majority of the respondents were engaged in the informal sector and this was consistent with the report of the population and housing census, 2010. The religious distribution of mothers in the study reflected the demographics presented by the same report with about 9 in 10 women being Christians and the rest being either Muslims or Traditionalist (Ghana Statistical Service,

TABLE 3 C

2010). The average gravida of 3 per mother is an indication of a very high fertility considering that the mean age of mother at birth and mode was 26 years.

More males were born in the study period and this was similar to that reported in the population and housing census report which indicated that age bracket between 0-14years have more males but it reverses as the population or age groups mature because of higher mortality among males (Ghana Statistical Service, 2010).

The caesarean section rate among the women studied was 26.7 % which was much higher than the WHO acceptable limits of 10-15 % (WHO, 1985). The rates of caesarean delivery saw a steady increase from 2011 to 2015 and this is consistent with other reports from developing and developed countries (Menacker, 2005). In that report, the World Health Organisation stated that there was no possible justification for rates higher than 15 % (Betran *et al.*, 2015). The increase in caesarean rates sets up a vicious cycle because nulliparous women who go through caesarean section have about 95 % risk of going through it again in the second or subsequent births (Solheim *et al*., 2011; Placek & Taffel, 1980). This worldwide drive for caesarean birth could also be linked to the convenience of getting to choose the date and time of birth. There is also a general perception that caesarean section is associated with lower incidence of maternal and neonatal mortality (Stanton & Holtz, 2006; Weaver *et al.*, 2007; Black *et al.*, 2015). However, this perception is not always the reality since several studies have identified significant increase in risk to mother and child after caesarean section compared to natural birth. In some reports, post caesarean women experienced higher mortality, severe sepsis, wound infection, haematoma and thromboembolic events, urgent hysterectomy, still births in subsequent pregnancies and other life threatening infections (Kacmar *et al*., 2003; Koroukian, 2004; Liu *et al*., 2007; Leth *et al*., 2009; Bodner *et al.*, 2011). It is worth stating that caesarean section also presents with a heavy financial burden on the Insurance schemes as well as on patients (Liu *et al*., 2007).

Risk of caesarean section increased with increasing age of mother at birth and this was coherent with other studies by Richards *et al*. (2016) and Martel *et al.* (1987). Socio-economic factors of mother such as gravidae, occupation, and religion were not associated with any significant risk of caesarean section and this relationship is similar to a study by Kozhimannil *et al.* (2014).

About 2 out of 3 women (65.8 %, n=271) were exposed to an antibiotic at a point during pregnancy and this was higher than an earlier report by Ahiabu *et al*. (2015) in the eastern region of Ghana in which antibiotic exposure in the general population was as high as 59.9 %. Similar trends were seen in Jordan where up to 61 % exposure rates were seen (Otoom *et al.*, 2002). WHO/International Network for the Rational Use of Drugs indicators recommend that total antibiotic exposure rates should not be higher than 30 %. The higher exposure in less developed countries could be due to lack of adequate laboratory facilities to do culture and sensitivity before initiating empirical antibiotic therapy. In the developed countries where antibiotic prescription is well regulated, lower exposures are recorded (Dashe & Gilstrap, 1997).

In 2013, antibiotic exposure saw a major reduction when the hospital set up drugs and therapeutic committee to curb the increased use of antibiotics in the hospital. The effect of this interventions was very profound as exposure rates drastically reduced confirming earlier reports that conscious interventions and rational medicine use is associated with lower antibiotic use (Davey *et al*., 1996).

Women who went through caesarean section were more likely to receive pre-surgical prophylactic antibiotics. This practice was in line with some studies that have linked antibiotic prophylaxis to lower incidence of wound infection and endometritis (Smaill & Grivell, 1996; Costantine *et al.*, 2008).

Risk of antibiotic exposure was highest in the last trimester and so was the incidence of respiratory tract infections, urinary tract infections and gastritis. Third trimesters exposure also included prophylactic antibiotic use before surgery and so it was quite expected to be highest.

The United States Food and Drugs Authority (US FDA) classifies cephalosporin, penicillin and metronidazole as pregnancy category B rendering them relatively safe to use in pregnancy and

hence their extensive use. Macrolides though Category B, were not used extensively perhaps because of its well documented history of gastrointestinal disturbances which is a major undesired effect in pregnancy. Macrolides have the ability to directly stimulate the motilin receptors or cause the release of motilin which stimulate a propulsive action in the stomach (Periti *et al.,* 1993).

The US FDA classifies quinolones, sulphonamides and trimethoprim into categories *C*, *D* and *C* respectively which may imply potential ability to cause harm to a developing foetus. Quinolones have been known to concentrate in amniotic fluid up to a thousand fold of maternal serum levels and tissues. It has been linked to intra-uterine growth retardation and defective growth in cartilage and bone (Lee *et al.,* 2015). Sulphonamides and trimethoprim are anti-folate antibiotics which cause inhibition of growth of bacteria by competitive inhibition of dihydrofolate reductase. Folic acid is an integral co-enzyme needed in the early stages of pregnancy for cell growth and replication and so these antibiotics are considered potentially harmful by the US FDA. It is probable that prescribers were not aware of pregnancy status because there was no recorded use in the last trimester. Some studies thus recommend for routine pregnancy tests for women in their reproductive stages (Köksal *et al*., 2013).

Anatomically, the uterus sits directly on the urinary bladder and so increase in weight of the uterus as pregnancy advances exerts a proportional pressure on the bladder. This causes urinary stasis and this could explain the rise in incidence of UTI with progression of pregnancy (Masinde *et al*., 2009). Similarly, as the uterus expands out and up it pushes the stomach reducing its volume and this could explain the observed increase in frequency of gastritis and heart burns with growth of the foetus (Köksal *et al*., 2013).

The mean birthweight of babies delivered at the facility was 2.96 ± 0.56 and this was similar to a report by Abubakari *et al*.(2015). There was no significant difference in birthweights

between babies whose mothers were exposed to antibiotics and those not exposed. A study by Vidal *et al.* (2013) reported a similar pattern and it could therefore be assumed that antibiotic did not affect intra-uterine growth and health.

There was a significant association between mother's socio-economic factors such as age, marital status, occupation and gravidae and birthweight. This association has been observed and reported in other studies earlier published. (Brotnow *et al*., 2015; Bhaskar *et al*., 2015; Xaverius *et al*., 2015). Older mothers were more likely to be economically stable, enjoy the support of a husband, have higher gravida and such as may have better nutrition as compared to younger or teenage mothers who on the other hand were at a higher risk of malnutrition and anaemia (Kramer, 1987; Rondó *et al.*, 2003; Bhaskar *et al*., 2015).

Babies born to mothers who received antibiotics less than 24 hours to delivery or subsequently had caesarean birth had mean Apgar scores much lower than those unexposed or had vaginal birth. Even after adjusting for method of delivery, perinatal antibiotic use, caesarean birth or both were significant risk factors for low Apgar scores at delivery. This is consistent with a study by Burt *et al*. (1988) in which similarly, babies born vaginally had much higher Apgar scores compared to caesarean born.

Older mothers and women with higher gravida had babies with mean Apgar scores lower than younger mothers or women with less gravida. Hemminki & Gissler (1996) and Straube *et al*. (2010) identified similar patterns and concluded that births by older women could be a potential medical problem in infants. The significance of higher gravida with lower Apgar scores could actually be confounded by maternal age since generally older mothers tend to have higher gravida than younger mothers. Generally, economic factors of mother showed no correlation with mean Apgar scores and this has been confirmed in other studies (Straube *et al.*, 2010).

A total of six birth defects representing 15 per 10000 live births of all babies were recorded in the study and this was similar to study in Africa revealing that prevalence birth defects was between 5.2 to 75.4 per 10000 live births (Zaganjor *et al*., 2014). Other authors (Alfarra *et al*., 2011; Figueiredo *et al*., 2015) have postulated that maternal diet low in folic acid in the first trimester agrees very well with incidence of orofacial clefts and neural tube defects (Sayed *et al*., 2008). Intrapartum antibiotic exposure as well as socio-economic factors of mother was not a significant risk factor in the development of any birth defect as seen in this study.

There is difficulty in arriving at a specific diagnosis or type of dermatitis in neonates since a myriad of conditions can result in skin eruptions or inflammation of the skin (Antaya, 2010). For the purposes of our study and difficulty in distinguishing between the different types of dermatitis, prescriber diagnosis of dermatitis was accepted irrespective of the cause or treatment given.

Babies exposed to antibiotics intrapartum irrespective of time of exposure were 2.6 times more likely to develop dermatitis compared to those unexposed. However, perinatal exposure (less than 24 hours to delivery) was not associated with a significantly increased risk of disease and this was comparable with a study by Wohl *et al*. (2015). Even after adjusting for the confounding of method of delivery on antibiotic exposure the relative risk of dermatitis in exposed infants was still significant. It could also be deduced from the study that multiple courses of antibiotics or third trimester exposures presented with highest risk of dermatitis. Caesarean born babies were slightly at higher risk of dermatitis compared with natural birth.

From the study, neonates exposed to antibiotic intrapartum irrespective of time of exposure were about 4 times likely to develop respiratory tract disease compared to unexposed neonates. Furthermore, antibiotic exposure across all trimesters were associated with the highest risk of disease. Mothers given perinatal antibiotics had babies who were more likely to suffer from respiratory tract diseases. Lapin *et al*. (2014) and Stokholm *et al*. (2014) also identified

intrapartum antibiotic as a significant risk factor for not only asthma and other allergic diseases but infectious diseases as well later in life. This could be due to alterations in the microbiome which play a role in the maturation of the immune system (Blaser, 2011).

Babies delivered through caesarean showed a higher tendency to suffer respiratory tract diseases when compared to vaginal birth. Furthermore, among babies who were exposed to antibiotics, caesarean birth was a significant risk factor for respiratory morbidities. Both antibiotic exposure and caesarean birth alter the acquisition and establishment of a healthy microbiome. Thus, caesarean birth after antibiotic exposure possibly further reduced maternal transfer and acquisition of a healthy microbial ecology.

Babies born to mothers prescribed antibiotics at any point were at a higher risk of suffering from sepsis. However, the risk of disease was highest in all trimester exposures. Even after adjusting for the influence of method of delivery, there was a strong association between antibiotic exposure and risk of sepsis.

From the study it was realized that there was a four-fold elevated risk of sepsis among babies born through caesarean section compared with vaginal delivery. Furthermore, though antibiotic exposure or caesarean section were associated with a higher risk of sepsis, the risk was highest in babies who were exposed and subsequently had caesarean birth. Jernberg *et al*. (2010) postulates that events that disturb the microbiological niche in humans may have long lasting effects because of the development of resistance strains or deletions of bacterial flora needed to suppress the growth of pathogens.

The prevalence of neonatal conjunctivitis among babies studied was much lower compared to an expected prevalence of 23 % (Palafox *et al.,* 2011). Globally, the prevalence is on the decline but it is still a major challenge in the developing countries, perhaps due to poor antenatal and

post-natal care of mother and neonate screening. Though it is mostly benign, severe forms can result in severe sepsis and visual impairment (Moore & MacDonald, 2015; Kumaresan & Mecaskey, 2003). From the results of the study, intrapartum antibiotic exposure and caesarean birth were associated with a higher risk of neonatal conjunctivitis contrary to a report by Bell *et al*. (1994) that transmission of maternal infection caused by *C. trachomatis*, one of the common causal agents of conjunctivitis was highest among babies born naturally.

One interesting observation among the subjects studied was that all babies born naturally received prophylactic antibiotic (gentamycin or chloramphenicol) eye drop whiles caesarean-born babies did not probably, due to the well-known risk factor of neonatal conjunctivitis in natural birth. Prophylactic use of antibiotic eye drops immediately after vaginal birth has been proven to be effective in reducing the incidence of ophthalmia neonatorum (Dias *et al.*, 2013). This fact seems to have confounded the results.

Neonatal jaundice among the cases studied was highest in antibiotic exposures across all trimesters especially in the third trimester even after adjusting for method of delivery. However, perinatal antibiotic use was not associated with any increased risk of neonatal jaundice. Gale *et al*. (1990) in a large cohort study of neonates in Jerusalem reported that the likelihood of neonatal jaundice was higher among babies delivered by caesarean section compared to natural birth and similarly, in this study babies born by caesarean were about 1.6 times at risk of neonatal jaundice compared with natural birth.

Babies exposed to intrapartum antibiotics any time during pregnancy were more likely to visit the hospital to receive any form of medical attention than babies not exposed and this was significant even after adjusting for the method of delivery. Caesarean birth was also linked with a higher mean count of hospital visits compared with vaginal birth. It could be deduced

from these findings that antibiotic exposure and caesarean birth are independently associated with a higher count of non-review hospital visits in the neonate.

From the study, it was shown that intrapartum antibiotic exposure, caesarean section or both were linked with lower quality of health or poorer health outcomes in early childhood (0-90 days). Babies exposed to antibiotics especially in third trimester or all trimesters irrespective of antibiotic prescribed and subsequently had caesarean birth were more likely to suffer from dermatitis, respiratory tract morbidities and clinical sepsis. As a result, they were more likely to visit the hospital often for medical attention.

Antibiotic use generally disturbs the microbial ecology either by complete deletion or reduction in levels of susceptible microbes or selective proliferation of resistant species. It is known that each microbial community controls the growth and replication of other species thus ensuring a dynamic equilibrium and symbiosis (Kau *et al.*, 2011). The development of pseudomembranous colitis caused by *Clostridium* spp. after the use of some antibiotics is a classic example of the control and dynamic equilibrium that exists in our microbiome (Kamada *et al.*, 2013).

Caesarean birth reduces the numbers and types of microbiome transferable to the progeny and several researchers have identified that even among siblings those born naturally have a microbiome much similar to those of the parent than those born artificially (Dominguez-Bello *et al.*, 2011; Jakobsson *et al.*, 2013). It has been documented in some animal model experiments that babies born naturally had a higher diversity of microbiome and a highly similar microbiome to their mother compared to babies born by caesarean. The infant microbiota diversifies and resembles that of an adult with advance in age especially with the introduction of solid foods (Yatsunenko *et al.*, 2012). As a child matures, the environmental influence on

gut microbiome increases and shapes the diversity. Until then, any activity that reduces or prevents healthy microbiota transfer to child either intrapartum or at birth could have adverse consequence on neonatal or early childhood health.

The development of the immune system and acquisition of specific as well as general immunity depends on interaction between the host cell and the microbiome of an individual. When this interaction is altered because of lesser diversity of the microbiome, the integrity of the immune system is affected and could result in occurrence of both infectious, allergic and immune disorder (Zeissig & Blumberg, 2014). The same reason could account for the phenomenon seen with babies born through caesarean section who had poorer health outcomes.

Epigenetic factors have been known to affect the expression of transcription genes needed to regulate the population of T cells. Bacterial metabolites and short fatty acid chains have been implicated in modification of histone bodies (Kamada & Núñez, 2014). This affects the wrapping of DNA and this could affect how tightly or loosely a section of the DNA is available for transcription. Changes in T cell populations could be a reason for the observed differences in health outcomes between neonates who had altered microbiota and those who were not (Zeissig & Blumberg, 2014). This confirms the phenomenon seen in other animal models in which restoration of a normal microbiome in experimented mice does not restore a balanced immune system. It is worth noting that these epigenetic changes occur during foetal and early life and may be irreversible once established.

The phenomenon observed in the study generally linked antibiotic exposure irrespective of type of antibiotic used, and caesarean delivery to lower neonatal health among babies. Antibiotics have been lifesaving since the discovery of penicillin and will continue to be essential in our quest to reduce maternal and neonatal death. In the face of growing antibiotic resistance with

its attendant increase in cost of health care, this study offers one more reason why monitoring and rational use of antibiotics especially in pregnancy should be strengthened.

CHAPTER SIX

CONCLUSION

- The results of the study in a way support the hypothesis that maternal antibiotic use may adversely affect neonatal health.

- The prevalence of antibiotic prescription among pregnant women was 65.8 %. This prevalence is quite high when compared to the WHO standard of not more than 30 % exposure rates.

- Cephalosporins were the most prescribed antibiotics in the study followed by penicillins and nitroimidazoles (predominantly metronidazole).

- Prescriptions for the treatment of urinary tract infections represented 42 % of all antibiotics prescribed followed by premedication for caesarean section with 14.3 %.

- Antibiotics considered potentially harmful to the developing foetus constituted 3.4 % of all antibiotics prescribed.

- Antibiotic prescriptions for non-bacterial diagnosis or indications constituted 3.5 % of prescriptions.

- Risk of antibiotic exposure increased with advance in the stage of pregnancy.

- Antibiotic exposures irrespective of trimester of exposure, did not adversely affect intra-uterine growth or birthweight, Apgar scores and the development of birth defects in the study. However, babies exposed to perinatal antibiotics were more likely to have lower Apgar scores.
- Teenage or unmarried mothers were likely to have babies with lower birthweights.
- Babies born to older mothers were likely to have lower Apgar scores compared to younger women.

- The relative risks of dermatitis, neonatal sepsis, conjunctivitis and respiratory tract diseases were highest in babies exposed to antibiotics intrapartum.

- Antibiotic administration less than 24 hours to delivery was strongly associated with a risk of neonatal sepsis and respiratory tract diseases but showed a weak association with neonatal jaundice, dermatitis and conjunctivitis.

- Naturally born babies were less likely to suffer from neonatal sepsis, respiratory tract diseases, dermatitis and neonatal jaundice when compared to caesarean birth.

- Babies whose mothers were prescribed antibiotics and subsequently had caesarean birth were at higher risks of respiratory tract disease and sepsis compared with those who were just exposed.

- Babies exposed to antibiotics intrapartum or had caesarean delivery were likely to visit the hospital more often within the first three months of life.

RECOMMENDATION

- Hospitals should set up drugs and therapeutic committees to re-evaluate the antibiotic prescriptions among clients.

- There should be a thorough evaluation of all caesarean sections in the hospital, with special emphasis on reducing the number of caesarean births. Caesarean birth rate is on a steep increase and steps should be taken to curb its upward surge.

- Care should be taken when prescribing medicines to women in their reproductive ages to avoid the risk of drugs contra-indicated or unsafe in pregnancy.

- There should be conscious effort to improve diagnoses and inculcate microbial sensitivity testing to ensure better antibiotic stewardship.

FURTHER STUDIES

1. Follow up of babies exposed to antibiotics or had caesarean birth up to one year
2. Rational use of antibiotics in pregnancy, looking at their suitability for the disease condition, duration of treatment and suitability in pregnancy.
3. To ascertain the impact of single or multiple courses of antibiotics on neonatal health.
4. Replication of study in another rural community and urban locality comparing to see if different socio-economic status will give similar results.
5. Intrapartum antibiotic exposure and risk of allergic diseases at five years.

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APPENDICES

Appendix A

DATA CAPTURE FORM

Folder no Age Occupation Residence
Marital status M/D/S Parity year Religion

Trimester one (0-3 MONTHS)

Date	Diagnosis	weight	antibiotics	Other drugs

Trimester two (3-6MONTHS)

Date	Diagnosis	weight	Antibiotics	Other drugs

Trimester three (6-9Months)

Date	Diagnosis	weight	Antibiotics	Other drugs

Delivery

……

……

……

Birth outcome

Type of delivery Child birth weight Apgar Scores sex M/F

Estimated Blood Loss any abnormality? If yes what

Any comments……..

Neonatal health 0-3 months

Date	Diagnosis	weight	Antibiotics	Other drugs

Appendix B **ETHICAL CLEARANCE CERTIFICATE**

KWAME NKRUMAH UNIVERSITY OF SCIENCE AND TECHNOLOGY
COLLEGE OF HEALTH SCIENCES
SCHOOL OF MEDICAL SCIENCES / KOMFO ANOKYE TEACHING HOSPITAL
COMMITTEE ON HUMAN RESEARCH, PUBLICATION AND ETHICS

Our Ref: CHRPE/AP/347/16

7th July, 2016.

Mr. Kwame Opoku-Agyeman
Post Office Box KS 13055
ADUM-KUMASI.

Dear Sir,

LETTER OF APPROVAL

Protocol Title: ***"Prevalence of Antibiotic Prescription among Women Attending Antenatal Care Clinic in a District Hospital and its Effect on Birth Outcomes and Neonatal the Health."***

Proposed Site: ***Maternity and Antenatal Care Clinic, SDA Hospital, Dominase.***

Sponsor: ***Principal Investigator.***

Your submission to the Committee on Human Research, Publications and Ethics on the above named protocol refers. The Committee reviewed the following documents:

- A notification letter of 9th March, 2016 from the SDA Essumejaman Hospital, Bekwai-Ashanti (study site) indicating approval for the conduct of the study in the Hospital.
- A Completed CHRPE Application Form.
- Research Proposal.
- Data Capture Form.

The Committee has considered the ethical merit of your submission and approved the protocol. The approval is for a fixed period of one year beginning 29th June, 2016 to 28th June, 2017, renewable thereafter. The Committee may however, suspend or withdraw ethical approval at anytime if your study is found to contravene the approved protocol.

Data gathered for the study should be used for the approved purposes only. Permission should be sought from the Committee if any amendment to the protocol or use, other than submitted, is made of your research data.

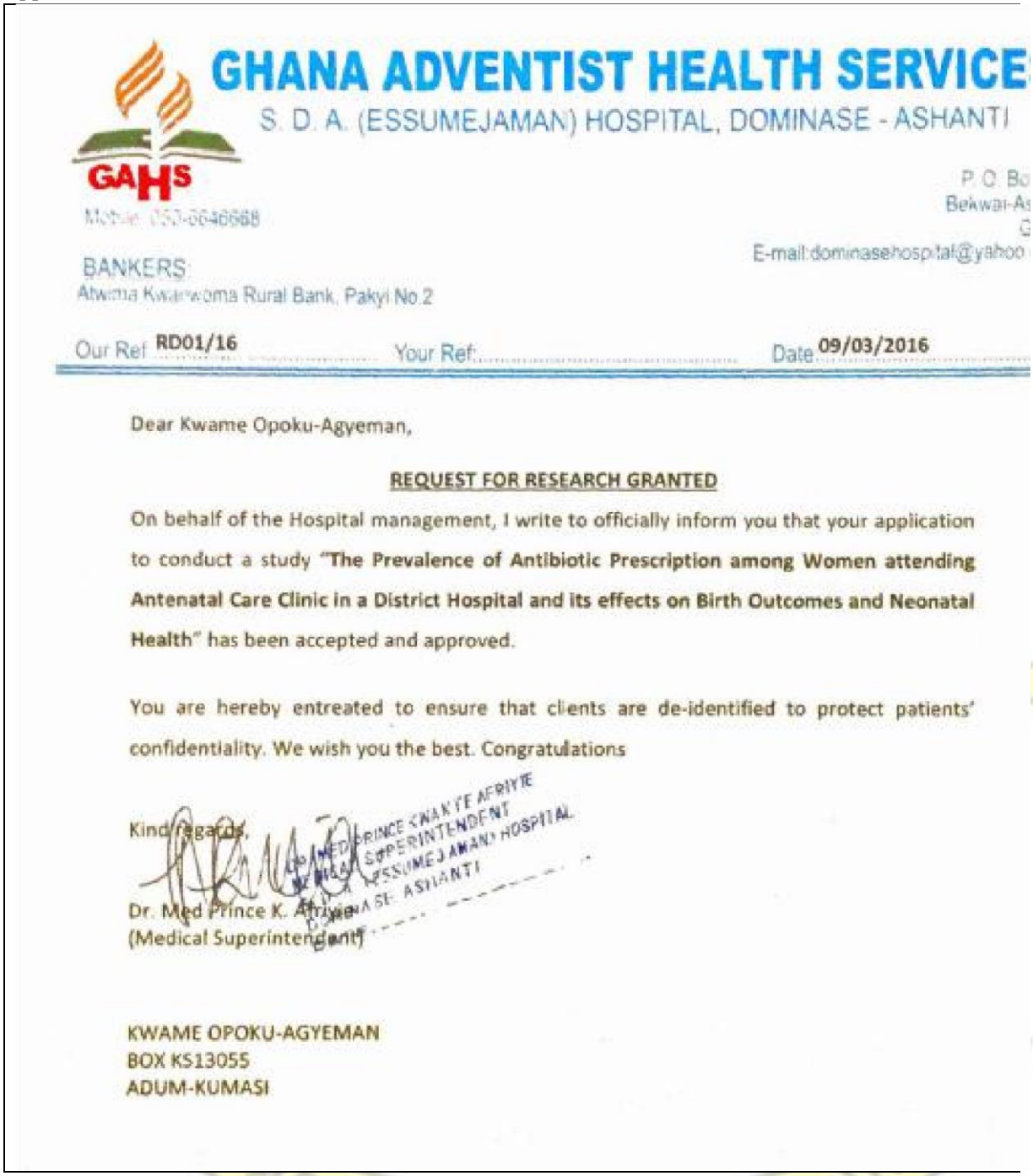
The Committee should be notified of the actual start date of the project and would expect a report on your study, annually or at the close of the project, whichever one comes first. It should also be informed of any publication arising from the study.

Yours faithfully,

Osomfuor Prof. Sir J. W. Acheampong MD, FWACP
Chairman

Room 7 Block J, School of Medical Sciences, KNUST, University Post Office, Kumasi, Ghana
Phone: +233 3220 63248 Mobile: +233 20 5453785 Email: chrpe.knust.kath@gmail.com / chrpe@knust.edu.gh

Appendix C **APPROVAL FROM HOSPITAL**



GHANA ADVENTIST HEALTH SERVICE

S. D. A. (ESSUMEJAMAN) HOSPITAL, DOMINASE - ASHANTI

P. O. Bo
Bekwai-As
G
E-mail:dominasehospital@yahoo

Mobile: 050-6646668

BANKERS:
Atwima Kwanwoma Rural Bank, Pakyi No 2

Our Ref: RD01/16 Your Ref: Date: 09/03/2016

Dear Kwame Opoku-Agyeman,

REQUEST FOR RESEARCH GRANTED

On behalf of the Hospital management, I write to officially inform you that your application to conduct a study "**The Prevalence of Antibiotic Prescription among Women attending Antenatal Care Clinic in a District Hospital and its effects on Birth Outcomes and Neonatal Health**" has been accepted and approved.

You are hereby entreated to ensure that clients are de-identified to protect patients' confidentiality. We wish you the best. Congratulations

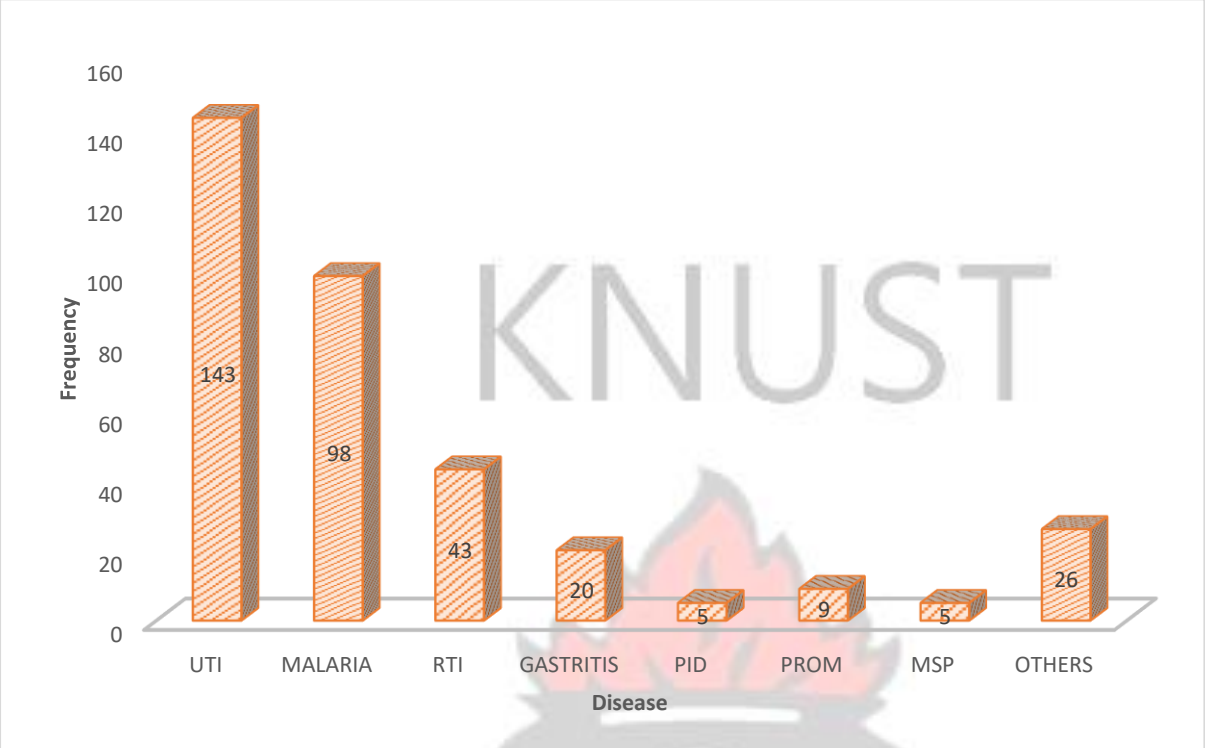
Kind regards,

DR. MED. PRINCE KWAKYE AFRIYIE
SUPERINTENDENT
ESSUMEJAMAN HOSPITAL
DOMINASE- ASHANTI

Dr. Med Prince K. Afriyie
(Medical Superintendent)

KWAME OPOKU-AGYEMAN
BOX KS13055
ADUM-KUMASI

Appendix D



PREGNANCY RELATED HEALTH CONDITIONS

Appendix E

Age of mother at birth (binned) and marital status crosstabulation

			MARITAL STATUS		
			MARRIED	SINGLE	Total
AGE OF MOTHER AT BIRTH (Binned)	19 YEARS AND BELOW	Count	13	41	54
		% within AGE OF MOTHER AT BIRTH (Binned)	24.1%	75.9%	100.0%
		% within MARITAL STATUS	4.3%	62.1%	14.7%
	20-30 YEARS	Count	202	23	225
		% within AGE OF MOTHER AT BIRTH (Binned)	89.8%	10.2%	100.0%

		% within MARITAL STATUS	66.9%	34.8%	61.1%
	31 YEARS AND ABOVE	Count	87	2	89
		% within AGE OF MOTHER AT BIRTH (Binned)	97.8%	2.2%	100.0%
		% within MARITAL STATUS	28.8%	3.0%	24.2%
Total		Count	302	66	368
		% within AGE OF MOTHER AT BIRTH (Binned)	82.1%	17.9%	100.0%
		% within MARITAL STATUS	100.0%	100.0%	100.0%