THE USE AND SAFETY OF ANTIBIOTIC THERAPY IN PREGNANT WOMEN

By

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Preface

This dissertation is presented in an article format. The findings of the study are presented in chapter three and chapter four as manuscripts, as required by the regulations of the University of KwaZulu-Natal. The manuscript in chapter three has been submitted for publication to Health SA Gesondheid. The systematic review manuscript in chapter four has been submitted for publication to BMC Systematic Reviews. The references used in the manuscripts were cited according to the instructions/ guidelines for authors as required by the journals.

This dissertation consists of five chapters as follows:

Chapter 1: Provides an introduction and explains the rationale and significance of the study. The aims, objectives, and methodology of the study are also highlighted.

Chapter 2: Comprises of existing literature and highlights the prevalence of infection as well as the use, safety, and risk perception of antibiotics in pregnancy.

Chapter 3: Manuscript I entitled, ''Antibiotic use among pregnant women: KwaZulu-Natal'' was written according to the author guidelines and submitted for publication to Health SA Gesondheid.

Chapter 4: Manuscript II entitled, ''Awareness and risk perception of antibiotic use among pregnant women: A mixed-methods systematic review'' was written according to the author guidelines and submitted for publication to BMC Systematic Reviews.

Chapter 5: Provides a summary of the findings, future recommendations, limitations, and strengths of the study with a general conclusion.

Declaration 1: Dissertation submission

This is to certify that the contents of this dissertation are the original work of:

Student: Sasha Naidoo (219050835)

Signed: 

Date: 08/08/2020

As the student's supervisor and co-supervisors, we have approved this dissertation for submission.

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Date: _____

Declaration 2: Plagiarism

I, Sasha Naidoo, declare that:

1. The research reported in this dissertation, except where referenced, is my original work.
2. This dissertation has not been submitted for any degree or examination at any other university.
3. This dissertation does not contain other persons' data, pictures, graphs, or other information unless specifically acknowledged as being sourced from other persons.
4. This dissertation does not contain other persons' writing, unless specifically acknowledged as being sourced from other researchers. Where other written sources have been quoted, then:

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This is to certify that the contents of this thesis are the original work of Miss Sasha Naidoo and as the candidate's supervisor/ co-supervisors, I have approved this thesis for submission.

Signed:

Dr Frasia Oosthuizen: _____ Date: _____

Dr Varsha Bangalee: _____ Date: _____

Dr Kofi Mensah: _____ Date: _____

Declaration 3: Ethical approval

Ethical approval for this study was obtained from the Biomedical Research and Ethics Committee (BREC) at the University of KwaZulu-Natal (UKZN). Reference number: BE330/19 - Annexure 1. Permission to conduct this study was approved by the KwaZulu-Natal Department of Health (KZN-DoH). Reference number: KZ_201906_005 - Annexure 2. Permission from Inkosi Albert Luthuli Central Hospital (IALCH) was also obtained from management and the Head of Department – Annexure 3.

Declaration 4: Manuscript publication

My contribution to the project was as follows:

Sasha Naidoo: Author – contributed to the project by performing all literature reviews, data and statistical analyses, interpretation of the results, manuscript preparation as well as writing and compiling of the dissertation.

The contributions of others to the project were as follows:

Dr Frasia Oosthuizen: Supervisor – supervision of the concept of the study, the review, and editing of the manuscripts and dissertation.

Dr Varsha Bangalee: Co-Supervisor – review and editing of manuscript I and dissertation.

Dr Kofi Mensah: Co-Supervisor – review and editing of manuscript II and dissertation.

Dedication

I dedicate this thesis and give special thanks to my parents and grandparents for their continuous love, support, and encouragement throughout my academic career. Their guidance and motivation will continue to inspire me.

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List of acronyms and abbreviations

AIDS	Acquired Immunodeficiency Syndrome
AMR	Antimicrobial Resistance
DoH	Department of Health
FDA	Food and Drug Administration
HIV	Human Immunodeficiency Virus
IM	Intramuscular
IV	Intravenous
JBI	Johanna Briggs Institute
KZN	KwaZulu-Natal
MMSR	Mixed Methods Systematic Review
NHI	National Health Insurance
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PIL	Patient Information Leaflet
SDGs	Sustainable Development Goals
STIs	Sexually Transmitted Infections
TB	Tuberculosis
UTI	Urinary Tract Infection
WHO	World Health Organization

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Abstract

Background

Antibiotic therapy in pregnant women has significantly increased in the effort to reduce maternal and neonatal deaths. However, antibiotic exposure may negatively affect the developing foetus. Information on the use, safety, and impact of antibiotics on birth outcomes and maternal-foetal health in low and middle-income countries are limited. This study aims to evaluate the use of antibiotics among pregnant women by quantifying antibiotic use and commenting on their safety profile. Furthermore, the risk perception of antibiotics among pregnant women, across all geographic regions, were determined.

Method

Patient demographics and treatment information were obtained from MediTech®; an electronic patient information database, from January 2019 to July 2019. Descriptive and analytical measures were used to describe both patient demographics and antibiotic treatment variables. A systematic review was conducted to determine the risk perception of antibiotics among pregnant women. A systematic search for studies from January 2000 to December 2019 were performed using four databases, which included: PubMed, Scopus, CINAHL, and Psycinfo. The systematic review involved the categorisation of data into relevant themes and sub-themes; data transformation and outcomes were discussed using narrative and thematic synthesis.

Results

A total of 416 antibiotic prescriptions, issued to 184 patients, were reviewed. Penicillins (39.7%), macrolides (13.0%), and combination penicillin-and-beta-lactam inhibitors (12.3%) were reported as the most commonly prescribed antibiotics in pregnancy. Most antibiotics were prescribed for diseases of the circulatory system (36.1%). A significant correlation was found between the duration of therapy and the age of the patient (>20, p=0.0009, 20-29, p=0.017, 30-42, p=0.03). The systematic review identified a total of 1539 articles, of which 14 studies met the inclusion criteria. The selected studies

included four regions: Europe, America, Asia, and Africa. Limited studies were found in low and middle-income countries, especially among rural communities.

Conclusion

Penicillins remain as the most common antibiotic used in pregnant women. However, the use of other antibiotic classes apart from the commonly used beta-lactams are also increasing, showing evidence of antibiotic resistance. In addition, the influence of perception significantly affects antibiotic use among pregnant women.

Chapter 1: Introduction

Chapter one provides the overall context for the study. The background of the study, the problem statement, and rationale of the study are mentioned. The aim, objectives, and a brief methodology are also included.

1.1 Background

Pharmacoepidemiology is defined as, “the study of the uses and effects of drugs in well-defined populations’’ (Yang and West-Strum, 2010). Pharmacoepidemiology studies, quantify and study drug use patterns, the appropriateness of use, drug safety, medication adherence, and identify predictors for medication use. It involves the use of pharmacokinetic and pharmacodynamic studies to predict the effect of a drug on the patient (Yang and West-Strum, 2010). These studies also allow for the identification of the contributory factors that determine the occurrence and distribution of diseases in specific populations (Torre and Martins, 2012).

Pharmacovigilance and drug safety are key elements of pharmacoepidemiology (Yang and West-Strum, 2010). Pharmacovigilance is defined by the World Health Organization (WHO) as, “the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects, or any other drug-related problem” (World Health Organization, 2002). Pharmacovigilance is a critical component for determining the benefit to risk ratio of medicines. The goal of pharmacovigilance is to promote the rational and safe use of medicines, minimise the risks, and maximise the benefit of medicine use (Jalali, 2018).

Pharmacotherapy in pregnant women is currently not optimised (Stock and Norman, 2019). The involvement of pregnant participants in drug studies has been negligible for a considerable period. This exclusion is due to the risk of potential fetotoxicity. Fetotoxicity refers to “the functional changes that can occur to the foetus as a result of medication use’’ (Henderson and Mackillop, 2011). Thus, the available safety information and clinical evidence for medicine use in pregnant women are limited.

Many studies on drug use in pregnancy are therefore retrospective. These study types can only determine associations between exposure and the possibility of potential side effects (Crider et al., 2009).

Drugs cannot be classified as teratogens without careful consideration of the dose, route, duration, and gestational period of the treatment (Polifka and Friedman, 2002). Treatments commonly used in pregnancy are thus often out-dated and untested, not optimised in dose, and are often prescribed without adequate safety information (Polifka and Friedman, 2002; Adam et al., 2011).

Antibiotics are the most frequently prescribed drugs in pregnancy as the treatment of infection is critical to the health of both the mother and foetus (Mensah et al., 2017). However, only a few classes of antibiotics have an established safety-record with studies been conducted to evaluate the direct link between the drug and major congenital malformations (Lamont, Blogg, and Lamont, 2014). There have been a few studies that have investigated the short-and-long-term effects of common antibiotics on the foetus and have published new safety data, highlighting the benefits and concerns of antibiotic therapy (Broe et al., 2014; Lamont, Blogg, and Lamont, 2014).

The perception of risk is a multidimensional concept that could potentially adversely affect pharmacotherapy. Risk perception is defined as ‘’beliefs about the potential harm or the possibility of a loss’’ (Molina et al., 2013). The subjective judgment that people make about the characteristics and severity of risk could affect adherence, compromising the health and safety of the mother and foetus (Molina et al., 2013). All pregnancies have a 2-3% risk of congenital anomalies but unrealistic perception may have detrimental effects on maternal-foetal health (Hollier, 2000). The study of risk perception is pertinent to understanding how women perceive the use of medicines to ensure safety and efficacy (Alemu and Wolle, 2019).

Antibiotic use is significantly increasing in pregnant women (Broe et al., 2014). The quantification of antibiotics among a population of pregnant women allows for the identification of prescribing patterns and the review of current safety data. Additionally, the study of antibiotic risk perception

significantly contributes to the improvement of maternal health. This study highlights the need for the continuous assessment of antibiotic safety profiles and the role of perception of medicine safety in pharmacotherapy.

1.2 Problem statement

Currently, there is no standardised approach to the rational, safe, and effective use of antibiotics in pregnant women. Ethical concerns limit the availability of clinical evidence that is available in this population. Prescribers use a risk-benefit approach to treat pregnant patients based on the trimester of pregnancy, the severity of the illness, and potential foetal risk. The emerging crisis of antibiotic resistance significantly affects the use of antibiotics in pregnant women with the overuse and misuse of these drugs being key drivers of Antimicrobial Resistance (AMR). The epidemic of AMR is changing the way antibiotics are used, increasing mortality and morbidity, and greatly increasing the cost of health care. The management and use of antibiotics have clinical, economic, and environmental implications.

1.3 Rationale and significance of the study

The rationale for this study was to evaluate the use of antibiotics in pregnant women. This study provides an overview of the currently prescribed antibiotics used among pregnant women in a public health care facility and comments on the appropriateness of the drug, dosage, route, and safety to ensure rational, safe, and effective drug use.

1.4 Aims and objectives

The aim is to evaluate the use of antibiotics among pregnant women. This was achieved through the following objectives:

- To quantify antibiotic use in pregnant patients in a public healthcare facility.
- To comment on the rationale for antibiotic use among pregnant patients.
- To evaluate the safety profile of antibiotics used during pregnancy.

- To determine the risk perception of antibiotic use among pregnant women in low, middle, and high-income countries.

1.5 Methodology

1.5.1 Study design

A retrospective quantitative study was done to describe antibiotic use among pregnant women in a public sector hospital. Furthermore, the perception of antibiotic use among pregnant women was determined through a systematic review.

1.5.2 Data Source

Patient demographics and treatment information was obtained from MediTech®, an electronic patient information database, utilised by the study site. The study site was a tertiary-quaternary public sector hospital, located in one of the metropolitan areas of South Africa. This large-scale hospital functions electronically and is the first hospital to have developed a public/ private affiliation in the provision of patient care and services. Data were collected for a period of seven-months.

1.5.3 Data collection

A data collection template was developed and the necessary information was extracted from MediTech®. The information was recorded on a workbook in Microsoft Excel®. Data extracted included patient demographics and information on antibiotic use; name, dose, route of administration, frequency of administration, and duration of treatment.

1.5.4 Data analysis

Descriptive and analytical measures were used to describe both patient demographics and antibiotic treatment variables. Data analysed were presented in the form of frequency tables and graphs. Quantitative data such as patient demographic data were analysed in terms of descriptive statistics.

The HIV status of the patients was also considered. The class of the antibiotic used in pregnant patients were highlighted to examine whether antibiotic use was rational and safe.

1.5.5 Data Management

Data collected were stored on a password-protected computer. Data will be removed upon completed dissemination of results.

1.5.6. Systematic Review

The Joanna Briggs Institute (JBI) guidelines for mixed-methods systematic reviews (MMSRs) and the Preferred Reporting Items for Systematic Reviews (PRISMA) guidelines were followed (Johanna Brigg Institute, 2019). A systematic search for studies from January 2000 to December 2019 was performed using four databases, which included: PubMed, Scopus, CINAHL, and Psycinfo. A data extraction template was used to record; the author's name, year of publication, country, setting, study design, socio-demographic description, sample size, and the main findings. The systematic review involved the categorisation of data into relevant themes and sub-themes; data transformation and outcomes were discussed using narrative and thematic synthesis.

1.6 Confidentiality

All information was kept confidential. Patient names were coded. Individual patients' written informed consent for the data extraction was not needed, as only anonymised, retrospective data were utilised.

1.7 Ethical approval

Ethical approval was obtained from the Biomedical Research and Ethics Committee (BREC) located at the University of KwaZulu-Natal (UKZN); (ethical approval number: BE330/19 - Annexure 1), KZN Department of Health (KZN-DoH), and Inkosi Albert Luthuli Central Hospital (IALCH). Ethical clearance was not required to perform the systematic review.

Chapter summary

This chapter has provided an outline of the study. The significance of the research, aim, objectives, and methodology of the study are discussed. The following chapter provides a theoretical basis for the study.

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Chapter 2: Literature review

1.1 Introduction

Chapter two provides an overview of maternal health and the implementation of universal health coverage in South Africa. An in-depth review of antibiotic therapy in pregnant women is provided with emphasis on the prevalent infections experienced in pregnancy and the modulated immune response. The effect of pregnancy on pharmacokinetic and pharmacodynamic properties of drugs are also mentioned. The risks of prescription antibiotics and the ongoing crisis of AMR is further discussed in this chapter. The chapter concludes with the Health Beliefs Model (HBM) and the link to risk perception is explained with reference to the use of antibiotics.

1.2 Maternal health in low and middle-income countries

Maternal health in low and middle-income countries remains relatively poor (Say et al., 2006). Countries, predominantly in sub-Saharan Africa and South Asia, are responsible for more than half of the maternal deaths that occur globally (World Health Organization, 2019b). This global crisis is due to the socio-economic plight within these fragile settings that contribute to the decline in maternal health (Brand South Africa, 2016; World Health Organization, 2019a) .

South Africa, similar to other middle-income countries is fraught with a high burden of disease, financial constraints, high unemployment rates, low educational levels, and poverty (Gous, 2019; Koko, 2019). The population living in poverty has drastically increased by 3.1 million in a period of four years with 27.7% of people being unemployed (Gous, 2019; Koko, 2019). Hence more than three quarter of South Africans are largely reliant on the public health care sector. This results in an over-burdened health care system. Thus, these determinants negatively affect the level of maternal health care received by pregnant women (Statistics South Africa, 2017; Mathew and Mash, 2019; Tucker, Chalkidou, and Pillay, 2019).

Women in high-income countries receive on average four antenatal visits by skilled health care professionals, whilst also receiving postpartum care. In contrast, in low and middle-income countries such as South Africa, that goal is not met, with only 40% of pregnant women receiving the recommended visits (World Health Organization, 2019a). Women in low and middle-income countries have on average many more pregnancies than women in high-income countries, thus contributing to the high maternal mortality and morbidity rates (Say et al., 2006). Increased pregnancies are mainly due to the low levels of education, lack of information, and poor access to family planning (Say et al., 2006).

In addition, maternal mortality is higher in rural areas, among poorer and less educated communities (World Health Organization, 2019b). In emerging countries, conditions related to pregnancy and childbirth constitute the second leading cause of death among women of reproductive age, subsequent to the human immunodeficiency virus (HIV) and the acquired immunodeficiency syndrome (AIDS). Statistics illustrate a concern as 810 women died every day from preventable causes related to pregnancy in the year 2017 (World Health Organization, 2019b). This can be attributed to poor accessibility to treatment together with a shortage of skilled health care professionals to offer treatments, the misdiagnosis of maternal conditions, and the misuse of medicines (Statistics South Africa, 2017; World Health Organization, 2019).

The socio-economic determinants that affect maternal health need to be addressed with the aid of global strategies in an effort to reduce maternal deaths. This can be achieved by identifying barriers that limit access to quality health care, ensuring that there is universal health coverage, and preventing inappropriate use of medicines especially those that are a result of economic challenges (O'Donnell, 2007).

1.3 Implementation of the National Health Insurance (NHI) to curb health inequalities

The implementation of the NHI aims to achieve the countries sustainable development goals (SDG's) by providing universal health coverage. Public–private collaborations can play an important role in alleviating resource shortages that affect the public sector population (Department of Health, 2008).

South Africa as well as other low and middle-income countries, face several health inequalities. Epidemiologically, South Africans are affected by a quadruple burden of disease particularly among the country's lower socio-economic population (Goyena and Fallis, 2019). HIV, AIDS, tuberculosis (TB), maternal and neonatal mortality, and non-communicable diseases remain prevalent among these countries with 99% of these deaths occurring in Africa (Goyena and Fallis, 2019).

According to WHO, sub-Saharan Africa accounts for a significant percentage (66%) of global maternal deaths (World Health Organization, 2019b). Therefore, it is imperative for governments to ensure that women have access to quality care before, during, and after childbirth in the aid to improve the maternal mortality ratio (O'Donnell, 2007; Abdulai and Adams, 2016).

Currently, 1.2 million women in South Africa fall pregnant every year (Department of Health, 2013). The public health sector provides services to more than one million of these women as opposed to the private sector that treats only 140 thousand pregnant women annually with the aid of the majority of the countries health professionals and health care resources (Department of Health, 2013).

Public sector facilities are faced with countless challenges and are often criticised on their core quality standards. The lack of staff, long waiting times, cleanliness, stock availability, inadequate medical equipment, infection control, and the safety of both staff and patients are some of the problems that continue to persist, which compromise patient care (Matthew and Mash, 2019). These concerns remain as the public health care system serves the majority of the population (80%) while being under-resourced and overburdened. The increasing burden of disease and the continuous inward migration

of people from rural to urban areas continue to strain the health care system (O'Donnell, 2007; Mathew and Mash, 2019).

Private sector hospitals and medical schemes have always been unaffordable for the vast majority of South Africans, worsening over time as a result of increasing annual contribution rates (Department of Health, 2013). The current two-tiered health care systems subsequently expose most South Africans to sub-optimal conditions of health care, contributing to the inequalities in our current system. In addition, it is unsustainable, costly, and hospital-centric (Department of Health, 2013).

The goal to provide a coherent and unified health system is being pursued through the phased introduction of the NHI by aligning the two parallel health systems. The NHI, is a health financing system that pools funds in the effort to provide accessible quality health services for all South Africans based on their health care needs, irrespective of socio-economic status (Tucker, Chalkidou, and Pillay, 2019).

In Africa, countries such as Ghana, Nigeria, Rwanda, Kenya, and Mali have commenced with universal health coverage as a key strategy to shift from high hospital expenditure towards primary care with the introduction of public-private partnerships to expand health coverage (Twum et al., 2018; Mathew and Mash, 2019).

The populations with the greatest health care needs, including vulnerable groups such as pregnant women, the elderly, immunocompromised patients, and particularly those experiencing difficulties in obtaining care will be prioritised (O'Donnell, 2007).

This system will allow pregnant women to access maternal health services throughout their pregnancy and post-delivery with safe, effective, quality, and cost- effective medicines. Universal access to basic health care is a highly desirable goal which must be striven for. The NHI aims to narrow the health gap, expand health coverage, and achieve equitable health outcomes among all South Africans (Benatar, 2013).

1.4 An overview of antibiotic therapy in pregnancy

In low and middle-income countries, the incidence of diseases that are of bacterial origin constitute as a major cause of morbidity and mortality (Haak and Radyowijati, 2003). Antibiotics hold a fundamental role in the treatment of infection to combat mortality and morbidity rates (Haak and Radyowijati, 2003).

Antibiotic use in pregnant women has increased globally. A Danish study conducted between the years of 1999-2000 found that 29% of pregnancies were prescribed an antibiotic (Norgaard et al., 2012). Subsequently, a study in Norway, found that 42.5% of women were exposed to antibiotics (Engeland et al., 2008). Similarly, a study by Broe et al. reported that the prevalence of systemic antibiotic therapy in pregnancy was found to be 41.5% (Broe et al., 2014). This validates the increasing rate of antibiotic use over the last two decades.

Women receive numerous prescriptions to prevent maternal-neonatal complications and antibiotics account for nearly 80% of all prescription medication, commonly used to treat infections that frequently occur in pregnancy (Haak and Radyowijati, 2003; de Tejada, 2014; Bookstaver et al., 2015). However, the majority of the available antibiotics may be teratogenic and could have toxic effects on the developing foetus; similarly, an untreated infection may also be associated with significant foetal risk (Nahum, Uhl, and Kennedy, 2006).

Pregnant women can acquire any infection that may be encountered in a non-pregnant population, although the severity of the infection may substantially differ leading to unfavourable outcomes (Kourtis, Read, and Jamieson, 2014). As the pregnancy advances, changes in the hormonal and metabolic levels play a significant role in the adaptation of physiological functions with complex alterations in the immune system, recognising pregnancy as a risk factor (Kourtis, Read, and Jamieson, 2014).

Pregnant women, therefore, constitute a vulnerable population and particular consideration is required when prescribing (Nahum, Uhl, and Kennedy, 2006). The use of antibiotics presents as a challenge, as the infection needs to be treated, but the foetus needs to be protected from the possible side effects of the medication (Stokholm et al., 2014). Antibiotic use during pregnancy, is therefore, considered to be a risk-benefit decision (Bookstaver et al., 2015).

Antibiotic therapy in pregnancy is complex and multi-layered (Henderson and Mackillop, 2011). Currently there is inadequate information on the safety of medicine use in pregnancy and even the current risk classification systems may analyse and construe the risk of the drugs differently (Amann et al., 2006).

Reported side effects of antibiotics are not the only concern with regards to their usage. The misuse of these agents plays a vital role in the development of antibiotic resistance, particularly in those antibiotics used to treat prevalent diseases. Antibiotic resistance is currently escalating and antibiotics that were once viable medicines have lost their efficacy (Haak and Radyowijati, 2003; de Tejada, 2014). In addition to safety and the concerning issue of AMR, the perception of antibiotic use among women also needs to be studied.

It is imperative to analyse the determinants, the use, potential risks, and perceptions involving systemic antibiotic prescribing during pregnancy, which may lead to the development of more effective policies and programs in the future (Amann et al., 2006).

1.4.1 The classification and prevalence of infections in pregnancy

WHO classifies infection according to three categories; pregnancy-specific infections, infections exacerbated by pregnancy, and incidental infections, as shown in Table 1 (Turner, 2019).

Table 1 Classification of maternal infections aligned with WHO (Turner, 2019)

Classification of maternal deaths
1. Pregnancy-specific infections
Chorioamnionitis
Endometritis
Lactational mastitis
Site of perineal trauma
Surgical site, e.g. caesarean
2. Infections exacerbated by pregnancy
Urinary tract infections
Influenza
Listeriosis
Hepatitis E
Herpes simplex virus
Malaria
3. Incidental infections
Lower respiratory tract infection
Tuberculosis
Sexually transmitted diseases

Every pregnant woman and new-born are at risk of an infection. A recently published study by the WHO, Global Maternal Sepsis Study (GLOSS) conducted among 52 countries, reported that the chorion and amnion, the urinary tract, and the skin or soft tissue are the three most prevalent sources of infection among pregnant women, especially in areas where HIV/AIDS are widespread (Torgovnik, 2020).

Infections are the primary cause of about 35 thousand maternal deaths every year (World Health Organization, 2017). Infection, if left untreated, leads to sepsis. Sepsis is one of the leading causes of maternal mortality worldwide despite the major advances made in their treatment, killing more than one million new-born's every year. The WHO recently defined maternal sepsis as, "a life-threatening condition causing organ dysfunction resulting from infection during pregnancy, childbirth, post-abortion, or postpartum period'' (World Health Organization, 2017).

The WHO estimates that the global prevalence of maternal sepsis in developed countries was 4.4% among live births, while in low and middle-income countries there is currently a lack of statistical data. However, it is estimated that sepsis accounts for one in ten maternal deaths globally (Turner, 2019; Torgovnik, 2020).

Some of the non-obstetric risk factors for sepsis are anaemia, obesity, impaired immunity, diabetes, hepatitis, HIV/AIDS, age, ethnicity, and low socio-economic backgrounds. The obstetric risk factors in pregnancy include; a history of *group B Streptococcal* infection, vaginal discharge, a history of pelvic infection, prolonged spontaneous rupture of membranes, amniocentesis, cervical cerclage, caesarean section, vaginal trauma, wound haematoma, and the incidence multiple pregnancies (Bamfo, 2013).

Sexually transmitted infections (STIs), primarily of bacterial origin, are a common epidemic and pose as a health burden to pregnant women specifically in underprivileged countries such as Southern Africa and Asia (Wynn et al., 2020). STIs are aggravated by pregnancy and are associated with adverse neonatal outcomes that may result in pre-term birth, low-birth, or stillbirth. A systematic review by the Sexually Transmitted Infection Clinical Trial Group (STAR) found that the prevalence of curable STIs was particularly high among pregnant women in low-income countries (Wynn et al., 2020). Additionally, a study facilitated by WHO, found that prematurity and its associated complications were the largest contributor to mortality in children (Harrison and Goldenberg, 2016). The rate of preterm birth increased to one in ten babies in the United States and is higher among neonates of Black ethnicity. Almost three million stillbirths are caused by STIs and if untreated, it could lead to eye and lower respiratory tract infections resulting in potential corneal damage or blindness (Wynn et al., 2020). It was also estimated that every year almost two million pregnant women are diagnosed with Treponema infections, whereas 520 thousand present with complications, such as intrauterine foetal death, low birth weight, and congenital syphilis in neonates (Plagens-Rotman et al., 2019). Chlamydia Trachomatis is also one of the most prevalent sexually transmitted bacterial infections worldwide with estimates that 92 million new cases occur annually (Silva et al., 2011).

Urinary tract infections (UTIs) in pregnancy are also significantly associated with maternal morbidity and adverse pregnancy outcomes, including preterm birth and low birthweight. It was reported that pregnant women are at an increased risk of developing UTIs primarily due to a shift in the position of the urinary tract and hormonal changes during pregnancy enable bacteria to move up the urethra to

the kidney, which may lead to the development of bacteriuria (Demilie et al., 2012). A population-based study, conducted among the rural inhabitants of Bangladesh, reported that the prevalence of UTIs among pregnant women were found to be 8.9% while 4.5% of these women were asymptomatic (Lee et al., 2020). The common risk factors in this population included malnutrition, primiparity, and low paternal education (Katona and Katona-Apte, 2008; Schnarr and Smaill, 2008). The major uro-pathogens were *E.coli*, *Klebsiella*, and the various *Staphylococcal* species (Lee et al., 2020). An Ethiopian hospital based prospective study yielded similar results where *E.coli* was the most common bacteria isolated followed by *Staphylococcal* microorganisms (Demilie et al., 2012). The major contributing factor for isolating higher rates of *E.coli* is due to urinary stasis in pregnancy which facilitates the colonisation of *E.coli* (Imade et al., 2010). In addition, poor genital hygienic practices by pregnant women during their pregnancy could also contribute to the development of infection (Schnarr and Smaill, 2008). The likelihood of vaginal *E.coli* in pregnancy can also occur if the individual has a pet that resides in the home. A retrospective study indicated that pets are hosts for both pathogenic and non-pathogenic bacteria and women who have pets showed a higher incidence (7%) of *E.coli* colonisation compared to women living without any pets. The increased rate of UTIs associated with live-in animals require greater use for oral antibiotics (Einarson, Shuhaiber, and Koren, 2001; Fluit and Schmitz, 2001; Stokholm et al., 2014; Lee et al., 2020)

Respiratory tract infections are representative of incidental infections and can lead to acute respiratory distress syndrome in pregnancy (Kourtis, Read, and Jamieson, 2014). The estimated prevalence of antepartum pneumonia is similar to that of non-pregnant women. *Streptococcus pneumoniae* accounts for 15-20% of all pneumonia cases (Sheffield, 2009). *Mycoplasma pneumoniae* or *Legionella* are commonly reported causative species (Sheffield, 2009). Pneumonia in pregnancy is associated with a higher rate of morbidity and mortality than in non-pregnant women. Furthermore, respiratory infections, like TB, also contributes to maternal mortality (Mnyani and McIntyre, 2011). The greatest burden of TB infection is in resource poor countries, however, developed countries have seen an upsurge in the occurrence of TB over the past few years as a result of immigration. A

retrospective study in London, showed an increase in the number of pregnant women with TB, while a South African study indicated that 70% of deaths in women were from TB and pneumonia as a result of HIV infection (Black, Brooke, and Chersich, 2009). Pregnancy, is not associated with an increased risk of TB, but a general increase in the incidence of TB will lead to an increase in TB infection rates in pregnant women (Mnyani and McIntyre, 2011).

Other common infections specific to pregnancy, include breast, perineal, and surgical site infection. These sources of infection are visible and more apparent, as it is characterised by localised pain, erythema, or discharge (Turner, 2019). These types of infections rarely lead to maternal bacteraemia, or sepsis unless they are left untreated. Infections specific to pregnancy are strongly associated with a breach in the physical integrity of the skin (Turner, 2019). When such breaches occur, antibiotic prophylaxis is the key to avoiding the onset of maternal sepsis (Turner, 2019).

Improved hygiene and living conditions, the use of antibiotics, and the progression within acute hospital care has led to major reductions in critical illnesses or death associated with sepsis (Ford and Scholefield, 2014). Despite this, there had been a sudden increase in deaths due to genital tract sepsis, particularly from community acquired *group A Streptococcal disease*, causing several maternal deaths in low-income countries (Centre for Maternal and Child Enquiries, 2011). Sepsis is emerging as the most common cause of direct maternal death in the United Kingdom (Centre for Maternal and Child Enquiries, 2011). A health disparity exists, with up to three times higher maternal death rates in low and middle-income countries compared to high-income countries (Bamfo, 2013).

Previously, there has been a lack of health care guidelines for the management of sepsis in pregnant women but with the newly structured care and management plans, the correct diagnosis, and the timely treatment of infection in pregnant women will prevent these avoidable maternal deaths (World Health Organization, 2017).

1.4.2 The modulated immune response in pregnancy

The immunology of pregnancy has been proven to be considerably complex. Many reviews support the idea that the immune system is suppressed which consequently increases the susceptibility of bacterial and viral infections influencing the vulnerability of the pregnant population (Mor and Cardenas, 2010; Mor, Aldo, and Alvero, 2017).

The fundamental feature of the immune system is to protect the host from external pathogenic invasion through a reinforced network of recognition, communication, trafficking, and repair. This process will depend on the immune system's ability to recognise the pathogen and co-ordinate cell migration to protect the mother and developing foetus (Mor, Aldo, and Alvero, 2017).

To facilitate implantation, inflammation in the womb occurs which initially alters the state of the immune system to tolerate the semi-allogeneic foetus. In a non-pregnant state, the body's immune system would recognise this as a foreign invasion and attack the cells to prevent inflammation, but in pregnancy this inflammatory cascade is essential (Mor and Cardenas, 2010; Hewings-Martin, 2017).

Once implantation occurs, the uterine endometrium is rapidly infiltrated by foetal trophoblast cells which develops into the decidua, an immunologically active tissue, anchoring the placenta (Hanna et al., 2006; Wells, 2007; Mjosberg, Berg, and Jenmalm, 2010). However, this invasion needs to be properly regulated to protect the physical integrity of the uterine wall of the mother (Hanna et al., 2006).

Thus, the decidua is constantly changing throughout the pregnancy (Nagamatsu and Schust, 2010). Natural killer cells and macrophages are local decidual cells, that are important regulators that facilitate tolerance of foetal trophoblasts and adjust to the limitations of their invasion ((Wells, 2007; Nagamatsu and Schust, 2010). When placental circulation is established, the peripheral blood also comes into close contact with foetal cells, specifically, villous trophoblasts. This may affect the peripheral maternal immune response (Hanna et al., 2006). T-cells are also found in the decidua and

may play a role in immunoregulation. In addition, dendritic cells that are present may be involved in immune-tolerance induction and may impair the clearance of pathogens increasing the disease severity (Kourtis, Read, and Jamieson, 2014).

The presence of immune cells in pregnancy is therefore not associated with a response to 'foreign attack' but facilitates and protects the pregnancy. The immune system throughout the pregnancy is in an altered state that is active, functional, and is carefully controlled resulting in a modulated immune response that may increase the risk of infection (Mor and Cardenas, 2010).

1.4.3 The general approach for antibiotic use in pregnancy

Pregnant patients require special attention regarding the use of antibiotics. Health care professionals must assure that the prescription will be effective, but also safe, as numerous drugs have the ability to cross the placenta. There is the challenge of reaching the therapeutic concentration while avoiding the risk of adverse drug reactions that may harm the foetus (Leekha, Terrell, and Edson, 2011; Kourtis, Read, and Jamieson, 2014).

The selection of an antibiotic with a safety record is recommended (Norwitz and Greenberg, 2009). It is proven that some antibiotics are considered safer to use while others are completely avoided. Penicillins, cephalosporins, and macrolides have been used in pregnancy for many years with no reported detrimental side effects and are the common classes of antibiotics that are used in pregnant women today. Antibiotics such as tetracyclines and fluoroquinolones are contraindicated due to their potential for inducing permanent congenital and developmental anomalies (Jalali, 2018).

Penicillins are the most widely prescribed antibiotic in pregnancy and are considered as the first line of treatment when presented with infection. Macrolides and cephalosporins are reserved for patients whom are allergic or intolerant to penicillin therapy (Bookstaver et al., 2015). The use of aminoglycosides, sulphonamides, nitrofurantoin, and trimethoprim will be dependent on the severity

of the infection and the trimester of pregnancy where the benefits surpass the risk (Leekha, Terrell, and Edson, 2011).

The initiation of therapy in the first trimester is generally avoided, as this is the stage where the foetus is at the highest risk for developing foetal abnormalities, due to it being the period where foetal structural development occurs (Leekha, Terrell, and Edson, 2011). Literature recommends that a narrow spectrum antibiotic is more favourable as opposed to a broad-spectrum antibiotic being used in pregnancy. It is also crucial that the lowest possible effective dose is used for the shortest duration, followed by the prompt replacement of an oral agent in the process of recuperation (Norwitz and Greenberg, 2009).

Therefore, it is essential that antibiotic treatment is only prescribed and initiated when there is confirmation of infection followed by obtaining an accurate diagnosis and using an antibiotic that is befitting to the needs of the host (Norwitz and Greenberg, 2009).

1.4.4 Antibiotic safety and the effects associated with prescription antibiotics

Antibiotic safety is a fundamental concern in pregnancy (Nahum, Uhl, and Kennedy, 2006). Pregnant women represent a population where individuality is the epitome of therapy, ensuring that every patient is carefully assessed for the possibility of experiencing side effects before being prescribed any medication (Nahum, Uhl, and Kennedy, 2006). Antibiotics are widely prescribed in obstetrics and some of these drugs have the potential to be embryonically harmful (Amann et al., 2006).

The effects of an antibiotic may present immediately or could manifest over an extended period -of-time (Broe et al., 2014; Bookstaver et al., 2015). Maternal anaphylaxis is a common example and is characterised as an immediate effect. It may have fatal effects on the foetus, due to compromised oxygen levels, exposing the developing new-born to the probable risk of hypoxic-ischaemic encephalopathy and permanent central nervous system damage. These effects could result in miscarriage, congenital abnormalities, or even neonatal death (de Tejada, 2014).

Some of the long-term effects could manifest as a result of the gut microbiota, in both the mother and infant being altered. This may potentially interfere with the maturation of the immune system influencing childhood advancements and sourcing the risk of low birth weight. Other long-term effects may include; childhood asthma, obesity, allergy, atopic dermatitis, autism, diabetes, cerebral palsy, and epilepsy (Barros et al., 2010; Ledger and Blaser, 2013; de Tejada, 2014; Rejno et al., 2014; Mueller et al., 2015; Anitha et al., 2018; Panduru et al., 2020). Antibiotic administration during pregnancy also contributes to alterations in the composition of the commensal vaginal microbiota which effectively protects against the proliferation of pathogenic bacteria (Stokholm et al., 2014).

The physiological changes that occur in the body are known to alter the pharmacokinetic and pharmacodynamic properties of the medication, contributing to the risk of medicine use in pregnancy. The normal embryonic development, may be affected which could render the antibiotic as a dysmorphogenic agent (Amann et al., 2006; Nahum, Uhl, and Kennedy, 2006; Rossiter, 2020). An analysis concerning the risk of eleven broad spectrum antibiotics; benzathine penicillin, phenoxymethylpenicillin, amoxicillin, chloramphenicol, ciprofloxacin, doxycycline, levofloxacin, rifampicin, clindamycin, gentamicin, and vancomycin, was conducted. All eleven antibiotics were able to cross the placenta entering the foetal compartment. The concentration for four of these antibiotics (ciprofloxacin, clindamycin, levofloxacin, and vancomycin) were of the same enormity or higher in the amniotic fluid as compared to in the maternal blood (Nahum, Uhl, and Kennedy, 2006; Menezes, Malek, and Keelan, 2011). The pharmacokinetic properties of the medicine and the potential toxicity that may result emphasises the level of caution that is required (Anderson, 2005).

Prior to the obstetric use of antibiotic agents, pregnancy was recognised as a risk factor for severe complications but with the use of antibiotics they are now treatable. However, there are still important therapeutic implications that must be considered for both the developing foetus and mother when using these drugs (Kourtis, Read, and Jamieson, 2014). There is currently inadequate

data available for medicines that can be used in pregnant women making it a challenge to consider any antibiotic as ''safe'' (Bookstaver et al., 2015; Jalali, 2018).

1.4.5 The effect of the physiological changes in pregnancy on the pharmacokinetic and pharmacodynamic properties of the drug

Pregnancy is a physiological state which encompasses hormonal and anatomical changes (Augustine, Ladyman, and Grattan, 2008). This places significant biological demands on a woman. To cope with these immense demands, the hormones of pregnancy are released to allow the body to adapt to the various maternal physiological functions (Costantine, 2014). These adaptations that occur within the major organ systems in the body, subsequently affect the pharmacokinetic and pharmacodynamic properties of the drug (Costantine, 2014; Stock and Norman, 2019).

The upsurge in the secretion of progesterone and oestrogen, is vital for the body in an effort to support the requirements and maturation of the foetus. This rise leads to delayed gastric emptying and prolonged transit time, intensifying gastric pressure within the bowel (Liu et al., 2002). The absorption of the active constituent may be profoundly affected by the gastrointestinal system. Delayed gastric emptying is a major factor correlated to the oral bioavailability of the drug. The time taken to reach the peak concentration (Tmax) of the drug is increased, thereby, lowering the maximum concentrations (Cmax), thus hindering the oral bioavailability of the drug. The incidence of nausea and vomiting in pregnancy may also lower drug plasma levels. Additionally, as a consequence of these elevated sex hormones, drug metabolism is altered. The drug metabolising enzymes including those involved in phase I (reduction, oxidation, or hydrolysis) or phase II metabolism (glucuronidation, acetylation, methylation, and sulphation) undergo changes (Zhou and Ma, 2018). The alkalisation of the gastric pH may also increase ionisation of weak acids, reducing the absorption of drugs (Liu et al., 2002).

The heart also plays a major role in the pharmacodynamic alterations. The myocardial contractility, cardiac compliance, and the ventricular wall mass increases. These changes increase both the heart

rate and stroke volume resulting in a higher maternal cardiac output (Pacheco, Costantine, and Hankins, 2013). The uterine blood flow also increases as a result, although the exact origin of the increased blood volume is not fully understood. The mechanism may be through nitric oxide mediated vasodilatation, increased arginine vasopressin production, and mineralocorticoid activity accompanied by water and sodium retention, leading to hypervolemia (Carbillon, Uzan, and Uzan, 2000). The pregnancy induced hypervolemia is thought to provide a survival advantage, however, the increase in blood, water, and plasma volume including capillary hydrostatic pressure, increases the volume of distribution of various drugs within the body. This fluctuation in volume require higher dosages of the antibiotic particularly if the drug is composed of a hydrophilic integrant (Carbillon, Uzan, and Uzan, 2000).

In addition, the kidney is one of the main sources responsible for elimination affecting drug disposition and influencing the drugs bioavailability. In pregnancy, the glomerular filtration rate in the kidney is accelerated affecting the elimination of renally excreted substrates resulting in a shorter half-life. Ampicillin, cefuroxime, cefazolin, and piperacillin are the common antibiotics that are renally excreted (Anderson, 2005).

Lastly, the transplacental diffusional capacity of the foeto-maternal membrane increases as it begins to mature and thin throughout the different gestational stages. This results in drug concentrations being 10-15% lower in the latter stages of pregnancy requiring the need for higher dosages (Costantine, 2014; Zhou and Ma, 2018). The descending albumin levels lead to reduced protein binding displaying higher concentrations of the unbound drug, thus increasing the bioactivity of drugs that may be protein bound (Costantine, 2014).

The physiological metamorphoses that pregnancy induces has significant pharmacodynamic and pharmacokinetic effects on the use of antibiotics. These modifications occur throughout the major anatomical structures to support the growth of the foetus make it challenging to treat infections in pregnant women where the strength, dose, dosing interval, and duration of the drug has to be

carefully tailored to needs of the individual (Bookstaver et al., 2015). Research indicates that firm data on pharmacokinetics as well as efficacy and the optimal use of medicines are still extremely limited, but recommendations can be made using existing information (Stock and Norman, 2019).

1.4.6 The Pregnancy and Lactation Labelling Rule (PLLR)

The Food and Drug Administration (FDA) plays an important role in advocating the safety of medicines in pregnant women. Prescribing during pregnancy and lactation involve complex maternal and foetal risk–benefit considerations. The primary objective of the FDA is to provide detailed prescribing information in a manner that is clear and useful to clinicians when prescribing (Feibus, 2008).

The FDA previously classified drugs according to categories (A, B, C, D, and X), as shown in Table 2. However, this classification system did not allow for the adoption of new information and did not accurately communicate the degree of foetal risk. It was determined that the FDA categories were not helpful in assisting health care providers to effectively balance the risk and benefit of the drug, resulting in poor clinical decisions (Food and Drug Administration, 2017; Food and Drug Administration, 2019).

Table 2 The FDA assigned pregnancy categories (Food and Drug Administration, 2017)

Category A	Adequate and well-controlled studies in pregnant women have not shown an increased risk of foetal abnormalities.
Category B	Animal studies have revealed no evidence of harm to the foetus. However, there are no adequate and well-controlled studies in pregnant women that have shown adverse effects or alternatively, adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the foetus.
Category C	No animal studies have been conducted or animal studies have shown an adverse effect. However, there are no adequate and well-controlled studies in pregnant women.
Category D	Adequate and well controlled studies in animals or pregnant women have demonstrated positive evidence of foetal abnormalities. However, the benefits of therapy may outweigh the potential risk.
Category X	Adequate and well-controlled studies in animals or pregnant women have demonstrated positive evidence of foetal abnormalities. The use of this product is contraindicated in women who are or may become pregnant.

The Pregnancy and Lactation Labelling Rule (PLLR) has recently been implemented and will replace the FDA categories (Food and Drug Administration, 2019). This regulation will be implemented for new drugs that are being registered and will subsequently be phased in for older drugs over a period of time. The new pregnancy rule consists of three categories: pregnancy exposure registry, risk summary, and clinical considerations (Pernia and Demaagd, 2016). The PLLR will provide a narrative summary of the risks of a drug during pregnancy. In addition, it will provide supporting data that is required in labelling to provide more reliable information for clinicians. Information will be based on; human and animal studies, post marketing surveillance, pharmacokinetic properties, and time and duration of exposure (Food and Drug Administration, 2019).

The PLLR allows for clinicians to make decisions based on a wider array of information. The implementation of this new regulation will be a step forward in optimising drug usage in pregnant women (Food and Drug Administration, 2019).

1.4.7 The implications of antibiotic resistance in pregnant women

The discovery of antibiotics is known as one of the greatest advances that fortify modern medicine by progressively increasing life expectancy. However, the complacent use of these novel drugs over the last few decades has introduced a global health crisis. The clinical misuse of antibiotics is a major determinant, catalysing the emergence of drug resistance consequently affecting all population groups (Haak and Radyowijati, 2003; Leekha, Terrell, and Edson, 2011; Blair et al., 2015).

In 2014, the World Health Assembly expressed serious apprehension regarding antibiotic resistance due to the peril of inappropriate antibiotic use (de Tejada, 2014). The extensive use of antibiotics in the community and in hospitals contribute to this epidemic. Majority of studies proved that 25-68% of antibiotic prescriptions in a hospital setting were deemed sub-optimal (Charani, Cooke, and Holmes, 2010).

Bacterial organisms have become intrinsically resistant to antibiotics via the exchange of genetic material and chromosomal mutations resulting in the emergence of multi-drug resistant bacteria commonly known as superbugs (Davies and Davies, 2010). The various classes of *Streptococcus*, *Staphylococci*, *Enterobacteriaceae*, and *Pseudomonas* are considered as the main causative agents in respiratory, urinary, and cutaneous infections. These bacteria are now resistant to practically all of the long-established classes of antibiotics (Davies and Davies, 2010). It is projected that two million people are infected with antibiotic resistant bacteria annually, with 23 thousand deaths occurring in the United States and 25 thousand deaths occurring in Europe, both, as a result of multi-drug resistant bacterial infections (Blair et al., 2015).

The contributing factors of antibiotic resistance are multi-plex and involve different rationale ensuing its use (Haak and Radyowijati, 2003). Firstly, the misdiagnosis and injudicious prescribing etiquette of antibiotics by health care professionals, especially for viral acquired infections, greatly influence the inactivation of the molecular mechanism of the drug, simultaneously affecting the rate of resistance. A study conducted in the United States indicated that antibiotic use is unnecessary in almost half of the patients that receive treatment (Charani, Cooke, and Holmes, 2010; Leekha, Terrell, and Edson, 2011; Barlam et al., 2016). Prolonged prophylaxis and the practice of empiric antibiotic therapy when there is no evidence of positive cultures or the continuation of therapy when the patient shows no response were confirmed as the most common errors resulting in resistance (de Tejada, 2014). In addition, the lack of basic knowledge, focusing only on the benefits of antibiotics with little concern for long-term consequences together with the use of poorly designed guidelines contribute to these imprudent decisions (Mulder et al., 2018).

During the last decade, resistance to penicillins, macrolides, and cephalosporins have increased significantly (Barlam et al., 2016). Pregnant women have used these antibiotics for years with no reported detrimental effects, but they are gradually becoming less effective requiring the use of broader spectrum antibiotics where safety has not been established (Walsh and Wright, 2005). A study

conducted in Bangladesh expressed the growing concern of antibiotic resistance among participants as gram-negative uro-pathogens were highly resistant to ampicillin, azithromycin, and second and third generation cephalosporins. Studies conducted in South-East Asia, reported that 16-68% of *E.coli* isolates and 34–81% of *Klebsiella* isolates were resistant to third generation cephalosporins (Lee et al., 2019).

Antibiotics are revolutionary drugs. The study of microbiology, antibiotic consumption, and the emergence of resistance are the fundamental principles of antibiotic stewardship that need to be understood in order to implement strategies using a multi-faceted approach, especially in developing countries (Charani, Cooke, and Holmes, 2010).

1.5 The influence of health behaviour and the perception of risk on drug therapy

The understanding of beliefs, awareness, knowledge, and perception of medicines are vital to attain optimal drug therapy. These are significant factors that influences the success of medicine use in any population. Thus, the understanding of perception offers an opportunity to contribute to the provision of optimised health care (Ssemaluulu and Adome, 2006; Alomi et al., 2018).

The Health Beliefs Model (HBM) provides a conceptual framework to assist in the understanding of health behaviour and perception (Glanz and Bishop, 2010). This model has been successfully adapted to fit diverse, multi-cultural, and contemporary contexts (Griffin, 2011; Scarinci, Bandura, and Hidalgo, 2012). It provides five paradigms that predict health behaviour; risk susceptibility, risk severity, benefits, barriers to action, and cues to action (Champion and Skinner, 2008). The model may assist health care providers in achieving the desired drug therapy response.

The perceived risk of medicine use is a key aspect that affects health behaviour and may contribute to unrealistic beliefs (Mulder et al., 2018). The knowledge of medicine use is important in preventing drug-related problems such as; non-adherence or termination of therapy, especially when the benefits of drug therapy supersedes the risk (Zaki and Albarraq, 2014). In addition, the insufficient provision of

medicine information could be an alternative explanation for the unwillingness to use necessary medicines that are regarded as safe in pregnancy (Widnes, Schjott, and Granas, 2012).

Studies have revealed that the perception women have regarding any medication is generally over-estimated in comparison to the actual risk profile of the medicine (Widnes et al., 2013; Mitchell and McClean, 2014). Women source information from health care professionals, Patient Information Leaflets (PILs), family, friends, and the internet (Mulder et al., 2018). Some of these sources may contribute to the unrealistic perception of risk (Nordeng, Ystrom, and Einarson, 2010; Mulder et al., 2018).

The perception of the patient may also vary depending on various socio-economic predictors such as; level of health literacy, age, level of education, parity, geographical region, and most importantly their beliefs and opinions that affect their ability to make well informed health decisions (Widnes and Schjott, 2017).

There are numerous aspects that are pertinent to address when approaching the issue of realistic risk perceptions. To assess and provide realistic risk estimates, both pregnant women and physicians need access to factual sources of information enabling confidence in appropriate drug use and prescribing (Nordeng, Ystrom, and Einarson, 2010). Furthermore, the provision of advice and information by physicians and pharmacists can positively or negatively affect a patient's perception. Positively-framed advice, therefore, may allow for the evaluation of the medicines beneficial uses rather than focusing on the possibility of harm (Mulder et al., 2018).

The understanding of risk perception, particularly among pregnant women may assist in providing interventions in their health behaviour, ensure adherence, and promote awareness of medicines among this population (Alomi et al., 2018).

Chapter Summary

This chapter highlighted the prevalence of infection, the implications of antibiotic use, and its safety in pregnant women. The chapter also focused on health behaviour and its impact on the use of antibiotics.

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Chapter 3: Manuscript I

Introduction

Chapter three describes the use of antibiotics among pregnant women in a public sector hospital. The study quantifies antibiotic usage and comments on the trend, rationale, and safety profile of those antibiotics.

The chapter is presented in manuscript format in accordance with the College of Health Sciences guidelines for dissertation submission at the University of KwaZulu-Natal (UKZN).

The manuscript has been submitted for publication to the journal: Health SA Gesondheid (see Annexure 4). This chapter has been written, formatted, cited, and referenced according to the journal's submission guidelines. The journal instructions to the author can be viewed in Annexure 5.

Antibiotic use among pregnant women in a public hospital: KwaZulu-Natal

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Abstract

Background

Most pregnant women are exposed to medication during pregnancy. Antibiotics are among the more frequently prescribed medicines in pregnant women and the use of antibiotics are increasing. However, with limited studies available in this population, the safe use of antibiotics in pregnancy remain a concern.

Aim

This study aims to quantify the use of antibiotics among pregnant women and comment on the rationale and safety profile of those prescribed.

Setting

A tertiary and quaternary public hospital located in Durban, KwaZulu-Natal.

Methods

Demographic and treatment information of women were collected retrospectively from January 2019 to July 2019. A total of 184 pregnant patients, having received antibiotic therapy, were included in the study. Data were obtained from an electronic database and were recorded using Excel®. Descriptive and analytical measures were used to analyse both patient demographics and treatment variables.

Results

A total of 416 antibiotic prescriptions, issued to 184 patients, were reviewed. Penicillins (39.7%), macrolides (13.0%), and combination penicillin-and-beta-lactam inhibitors (12.3%) were reported as the most prescribed antibiotics. Rifamycin (2.9%), hydrazides (2.2%), and aminoglycosides (1.9%) were less frequently prescribed. Most antibiotics were prescribed for diseases of the circulatory system

(36.1%). A significant correlation was found between the duration of therapy and the age of the patient (>20, p=0.0009, 20-29, p=0.017, 30-42, p=0.03).

Conclusion

Several classes of antibiotics are used in pregnancy despite the lack of available safety data and clinical evidence. Informing women of the potential side effects and keeping abreast with new information plays an important role in the safe, rational, and effective use of medicines that contribute to improving maternal health.

Introduction

Antibiotic use in pregnancy is increasing and antibiotics account for a significant percentage of all medication that is prescribed in pregnancy (Broe et al., 2014; Kuperman and Koren, 2016). According to a European study, one out of every four pregnant women is prescribed an antibiotic (Santos, 2010; Stokholm et al., 2013; Bookstaver et al., 2015).

The use of antibiotics in pregnancy is attributed to the fact that pregnancy predisposes the body to infection. Hormone fluctuations and changes in immunity are the primary causes for increasing the body's susceptibility to infection (Cherney, 2016). Genitourinary infections are the most frequently occurring illness contributing to the upsurge in antibiotic use (Lee et al., 2019, 2020). According to a recent study, 72% of antibiotic treatment is a result of vaginal candidiasis, urinary, and respiratory tract infections (Amann et al., 2006).

Antibiotic safety is an essential factor when considering its use in pregnancy. Antibiotics may be teratogenic and may have both short- or long-term effects on the foetus (Vidal et al., 2013). Several modifying influences may affect the severity of teratogenicity. These include; the gestational period of the pregnancy, the dose and duration of therapy, genetic predisposition, environmental factors, and the degree of drug transfer across the placenta (Amann et al., 2006; Nahum, Uhl, and Kennedy, 2006; Ledger and Blaser, 2013; Rossiter, 2020).

There remains a degree of inadequate evidence regarding the safety of antibiotics used in pregnancy due to ethical limitations (Bookstaver et al., 2015). Clinical trials among the pregnant population are restricted, hence the teratogenicity of various medicines are unknown (Crider et al., 2009). A review regarding antibiotic use stated that approximately only ten percent of medicines used in pregnancy are supported by safety data (Adam, Polifka, and Friedman, 2011).

The primary aim of this study was to evaluate the use of antibiotics among pregnant women attending a public health care facility. The main objective of the study was to quantify the types of antibiotics

used in pregnant women. The secondary objectives were to comment on the trends, rationale, and safety profile of the prescribed antibiotics. While the Pregnancy and Lactation Labelling Rule (PLLR) has come into effect for all new drugs registered in the United States and is being phased in for older drugs, medication use in this study was classed according to the "A to X" categories of the Food and Drug Administration (FDA) (Feibus, 2008; Food and Drug Administration, 2017; Food and Drug Administration, 2019).

Research methods and design

Study design and setting

This retrospective study was conducted over seven months (January 2019 to July 2019) at a tertiary and quaternary public hospital, centrally located in Durban, KwaZulu-Natal (Department of Health, 2017).

Study population and sampling strategy

The selected population consisted of both in-patients and out-patients. Participants included in the study met the following eligibility criteria:

- 18 years of age or above.
- Female and pregnant.
- Treated with an antibiotic as an inpatient or outpatient.

Details around antibiotic use, diagnosis, patient demographic information, and HIV status were recorded.

A total of 184 patients met the inclusion criteria. This sample size was large enough to allow for a detailed analysis of antibiotic usage as each patient received an average of two to three prescriptions, yielding a total of 416 prescriptions.

Data collection

Data was obtained from a software programme called MediTech®. MediTech® electronically stores patient files and treatment information. A pre-designed data collection tool was used to record available demographic and treatment information from patient files (Appendix 1). The template was developed according to guidelines by the World Health Organisation (WHO) that included key antimicrobial use indicators designed specifically for the collection of data in hospitals (USAID, 2012). Data on the following elements were recorded:

- Demographics (age, ethnicity, risk of pregnancy, and HIV status).
- Antibiotic name.
- Dose.
- Route of administration.
- Frequency of administration.
- Duration of treatment.

All information collected were kept confidential. Patient names were coded and records were kept in a password protected device. Individual patients' written informed consent for the collection of data were not needed, as only anonymised, retrospective data were extracted.

Data analysis

Descriptive and analytical measures were used to describe both patient demographics and treatment variables. Measures of central tendency such as the frequency, mean, and median were calculated. Antibiotic usage patterns among the participants were then identified. The quantitative data values are represented in frequency distribution tables by grouping them into categories as well as in a frequency distribution bar chart. The linear relationship between the patient demographics and treatment variables were established using correlation analysis. The relationship between duration,

age, HIV co-infection, and the number of prescriptions were investigated using the Chi-square test. The level of significance was set at $\alpha=0.05$.

The results were classified using the FDA safety categories as follows: Category B are drugs where animal studies may or may not have revealed evidence of harm to the foetus; however, there are no adequate and well-controlled studies in pregnant women. Category C are drugs where animal studies may or may not have been conducted to show adverse effects, but there are no adequate and well-controlled studies in pregnant women. Category D are drugs where adequate, well-controlled studies in animals or pregnant women have demonstrated positive evidence of foetal abnormalities. However, the benefits of therapy may outweigh the potential risk (Food and Drug Administration, 2019).

Eliminating Bias

The probability for biased selection was eliminated as a probability sampling method was adopted which included every participant who visited the hospital from January to July 2019. Secondly, data were collected using a pre-designed tool and the extraction of data were not performed by medical staff who prescribed or dispensed the antibiotics.

Ethical approval

Ethical approval was sought from the relevant bodies; the Biomedical Research and Ethics Committee (BREC) located at the University of KwaZulu-Natal (UKZN) (Annexure 1), KZN Department of Health (KZN-DoH) (Annexure 2), and the Head of Department and Chief Executive Officer (CEO) at the study site (Annexure 3).

Results

Demographic and general characteristics

Patient demographic data for 184 pregnant women are shown in Table 1. Less than 10% of the study population were between the age of 18-20. The majority of women were evenly distributed between the other two remaining age groups (20-29, 30-42). Almost 92% of the study population were Black African women, with a small percentage being Asian women (4.9%), White women (1.6%), and women of Mixed-race (1.1%). Many of the women (82.1%) were reportedly single, 12% being married while the marital status of the remaining women (6.0%) were not reported. A significant percentage (63.1%) of women were in their third trimester of pregnancy, with less than 35% of pregnancies being categorised as high risk. A large percentage of women (45.7%) who were included in the study were co-infected with HIV. Most women visited this tertiary facility between two to five times during their pregnancy.

Correlations investigated

Demographic variables correlated with the duration of antibiotic treatment, included:

- Age group (>20, p=0.0009, 20-29, p=0.017, 30-42, p=0.03).
- Gestational week (p=0.4).
- HIV co-infection (p=0.9).
- High-risk pregnancy (p=0.9).

Table 1 Characteristic and demographic data of participants, n=184

Demographics	Frequency N	%
Age		
18>20	14	7.6
20-29	86	46.7
30-42	84	45.7
Race		
Black	169	91.8
Asian	9	4.9
White	3	1.6
Mixed-race	2	1.1
Other	1	0.5
Marital status		
Married	22	12
Single	151	82.1
Not reported	11	6.0
Gestational weeks		
0-13	0	0
14-26	3	1.6
27-40	116	63.0
Not reported	65	35.3
High-risk pregnancy		
Yes	63	34.2
No	121	65.8
HIV Co-infection		
Yes	84	45.7
No	100	54.3
Inpatient days		
<3	46	25.0
4-14	88	47.8
18-88	50	27.2
Outpatient visits		
<=1	57	31.0
2-5	84	45.7
5-15	43	23.4

Quantifying antibiotic usage in pregnancy

A description of the different antibiotic classes and their prescribed frequencies are shown in Table 2. A total of 416 prescriptions were dispensed to 184 patients, with each woman receiving more than one course of antibiotic therapy during their pregnancy. Most women received an average of one to two prescriptions, with 8.7% of patients receiving more than four prescriptions during their pregnancy. A large percentage (88.9%) of prescriptions were FDA category B antibiotics with the remaining 11.1% being category C and D. Penicillins were the most frequent class (39.7%) of antibiotics prescribed to pregnant women followed by macrolides (13.0%) and combination penicillin- and- beta-lactam inhibitors (12.3%). The use of nitrofurantoin (8.1%) and carbapenems (6.3%) were also among the commonly used antibiotics, although they were slightly less prescribed in comparison to macrolides and beta-lactams. Other antibiotics such as rifamycin, hydrazides, aminoglycosides, fluoroquinolones, and trimethoprim-sulphonamide combinations were sparingly prescribed.

Table 2 Frequencies of the prescribed antibiotic classes and the respective FDA categories, n=184

FDA categories	Antibiotic class	Frequency	%
B	Combination of penicillin and beta-lactam inhibitors	51	12.3
	Carbapenems (except imipenem-category C)	26	6.3
	Glycopeptides	3	0.7
	Imidazoles	20	4.8
	Lincosamides	3	0.7
	Macrolides	54	13.0
	Nitrofurantoin	34	8.1
	Penicillins	165	39.7
	Third generation cephalosporins	13	3.1
	Topical antibiotics	1	0.2
	Total	**370**	**88.9**
C	Amphenicols	3	0.7
	Fluoroquinolones	5	1.2
	Hydrazides	9	2.2
	Polymyxins	2	0.5
	Rifamycins	12	2.9
	Trimethoprim - sulphonamide combinations	7	1.7
	Total	**38**	**9.2**
D	Aminoglycosides (except gentamycin-category C)	8	1.9
	Total	**8**	**1.9**
	Total	**416**	**100**

Category B antibiotics commonly prescribed

The five most frequently prescribed category B antibiotic classes and their respective dosing characteristics, including the route of administration and indication, are described in Table 3. Phenoxymethylpenicillin (pen V) was the most prescribed penicillin antibiotic (74.5%). Among the combination penicillins, amoxicillin-clavulanic acid was commonly used (21.8%). Azithromycin was the only prescribed macrolide and meropenem was one of the frequently prescribed carbapenems.

The strength, dosing frequency, and average duration varied among the different classes with most women receiving an oral or intravenous (IV) dose of administration, while few received treatment intramuscularly (IM). Most antibiotics were given for seven days or less. Phenoxymethylpenicillin was an exception as the average duration for this antibiotic was nine days. The remaining penicillin classes, nitrofurantoin, and carbapenems were commonly used for four to seven days. Macrolides were frequently prescribed for less than or equal to three days.

Table 3 Characteristics of frequently prescribed FDA category B antibiotic classes

Antibiotic class	Description	Strength (mg)	Dosing frequency	Average duration (Days)	Route of administration	Common indication by disease category	No of prescriptions
Penicillins	Amoxicillin	500, 1000	8 Hourly	4	Oral IM[1]	Diseases of the circulatory system	24
	Flucloxacillin	250-500	6 Hourly	6	Oral		8
	Pen V[2]	125, 250	12 Hourly	9	Oral		123
	Ampicillin	1000	8 Hourly	4	IV[3]		1
	Benzathine benzyl-penicillin	2400	Once-daily	1	IM		9
Total							**165**
Macrolides	Azithromycin	250, 500, 1000	Once-daily	3	IV Oral	Diseases of the circulatory system	54
Total							**54**
Combination of penicillins and beta-lactam inhibitors	Amoxicillin/ clavulanic acid	375 1000 1200	8 Hourly 12 Hourly 8 Hourly	4	Oral IV	Diseases of the circulatory system	36
	Piperacillin/ tazobactam	2250 4500	8 Hourly	3	IV		15
Total							**51**
Nitrofurantoin	Nitrofurantoin	50 100	6 Hourly	5	Oral	Diseases of the genitourinary system	34
Total							**34**
Beta-lactam carbapenems	Imipenem/ cilastatin	500, 1000	6-8 Hourly	4	IV	Diseases of the genitourinary system	5
	Meropenem	500, 1000	6-8 Hourly	3			21
Total							**26**

[1] Intramuscular
[2] Pen V - Phenoxymethylpenicillin
[3] Intravenous

Category C and D antibiotics commonly prescribed

Table 4 indicates the prescribed category C and D antibiotics with their subsequent characteristics. Rifamycins (2.9%), hydrazides (2.2%), and aminoglycosides (1.9%) were the three most prescribed category C and D drug classes. Amikacin was used more often in comparison to gentamicin. Quinolones were prescribed to five patients. Chloramphenicol, as a topical antibiotic, was prescribed to three patients. Colistin was used in two patients.

More than 67% of the antimycobacterial agents (rifamycins and hydrazides) were dispensed for periods longer than eight days. Half the women who were treated with aminoglycosides received the drug for three days or less, while the other half received it for four to seven days. Fluoroquinolones were mostly prescribed for a short period of fewer than five days. Trimethoprim-sulphonamide combinations were dispensed to seven patients, with most patients receiving treatment for approximately 20 days.

Table 4 Characteristics of frequently prescribed FDA category C and D antibiotic classes

Antibiotic class	Description	Strength and dosing frequency (mg)	Dosing frequency	Average duration (Days)	Route of administration	Common indication by disease category	No. of prescriptions
Rifamycins	Rifampicin	450-600	Daily	7	Oral	Diseases of the respiratory system	12
Total							12
Hydrazides	Isoniazid	100-300	Daily	23	Oral	Diseases of the respiratory system	9
Total							9
Aminoglycosides	Amikacin	250, 500, 900, 1000	Once-daily	3	IV	Diseases of the genitourinary system	7
	Gentamicin	240		3			1
Total							8
Trimethoprim - sulphonamide combinations	Co-trimoxazole	160/800 320/1600	12 Hourly 6 Hourly	22	Oral	Diseases of the genitourinary system	7
Total							7
Fluoroquinolones	Ciprofloxacin	500	12 Hourly	5	Oral IV	Diseases of the circulatory system	5
Total							5
Amphenicols	Chloramphenicol		12 Hourly	28	Topical	Diseases of the skin and tissue	3
Total							3
Polymyxins	Colistimethate (Colistin)	80 160	12 Hourly 8 Hourly	8	IV	Other specified diseases complicating pregnancy and childbirth that were not mentioned	2
Total							2

Disease Categories

Figure 1 shows the percentage of prescriptions that were dispensed for the main categories of infections. Majority of prescriptions were for infections of the blood and circulatory system (36.1%), followed by other specified infections (29.9%), and genitourinary infections (13.2%). Endocrine and metabolic infections (6.7%) and infections of the nervous system (5.5%) contributed to a smaller number of prescriptions.

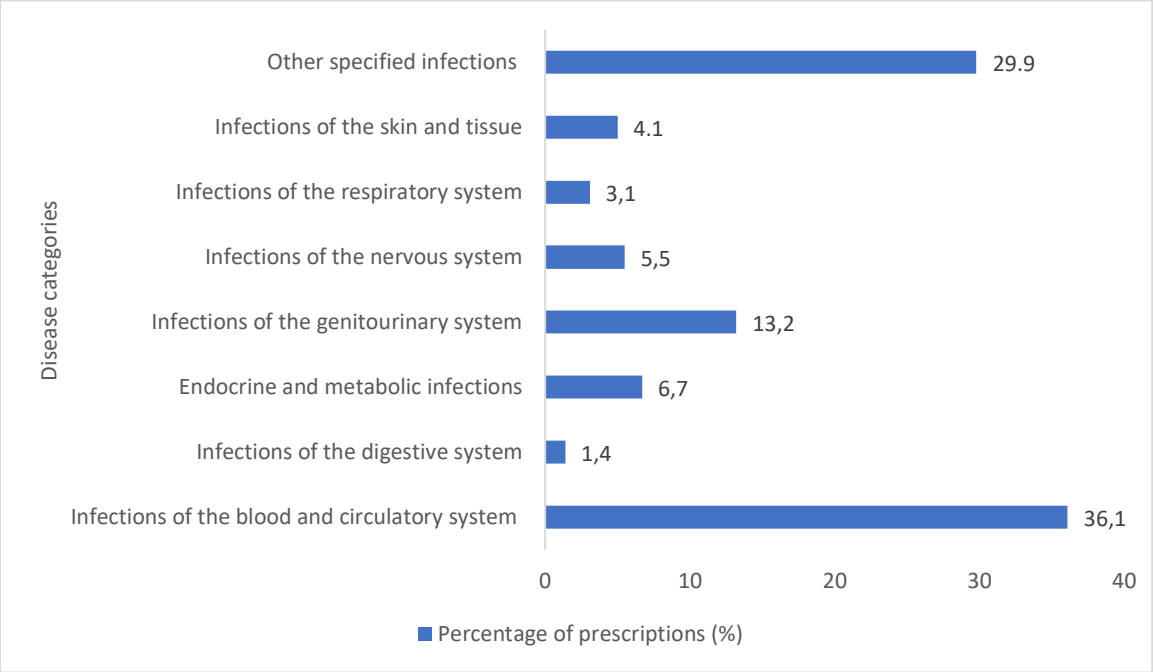

Figure 1 The percentage of prescriptions allocated to each disease category

Discussion

This study aimed to evaluate the trends in antibiotic use among pregnant women and to comment on their rationale and safety profile.

A significant correlation was established between the age of a patient and the duration of the antibiotic course. As the age increased, the duration of therapy increased (>20, p=0.0009, 20-29, p=0.017, 30-42, p=0.03). No previous studies have investigated this relationship. It is possible that with age, the difference in hormone levels and changes in the patients' immune response may contribute

to a longer recovery, hence the longer duration of treatment. However, this may differ among individuals and various studies (Erickson and Banks, 2019). This explanation, therefore, cannot be generalised.

The prevalence of the human immunodeficiency virus (HIV) in South Africa remains high and considering the large percentage of HIV-positive women in this study, it was expected that the duration of antibiotic therapy and the number of prescriptions dispensed to these women would be higher compared to HIV-negative pregnant women (Cohn and Clark, 2014; Ntlantsana, 2019). There was, however, no significant correlation between HIV status and antibiotic use or treatment duration ($p=0.9$). This might be an indication of the positive impact of antiretroviral (ARV) therapy decreasing the possible risk of infection in HIV-positive individuals; similarly, these results were found in KwaZulu-Natal and Nigeria, although this explanation cannot be extrapolated to the general population and is limited to this study (Mepham et al., 2011; Ntlantsana, 2019; Calder, Hara, and Tabatabai, 2020).

The gestational period is an important factor that influences antibiotic therapy. Multiple studies advise against the use of drugs in the first trimester as the foetus is still developing (Knothe and Dette, 1986; Shaaban et al., 2020). In our study, no patients were treated with an antibiotic in their first trimester of pregnancy. The majority of patients received treatment in their third trimester, with only a few women receiving treatment in their second trimester. A recent Cochrane review evaluated the use of antibiotics in the second and third trimester. The review established that there was no increased risk of congenital abnormality between the two trimesters. However, the authors concluded that there was insufficient evidence to fully evaluate possible foetal harm (Thinkhamrop et al., 2015).

As to be expected, almost two-thirds of the study population received a beta-lactamase sensitive agent with phenoxymethylpenicillin, used most commonly. These antibiotics remain widely prescribed in pregnancy (Heikkilä and Erkkola, 1994; Bookstaver et al., 2015). Current literature indicates the high use of beta-lactams, especially penicillins in pregnant women, due to its longstanding safety record. Literature indicates that beta-lactams represent approximately 65% of all antibiotic treatment used

during pregnancy, with penicillins accounting for 30% (Heikkilä and Erkkola, 1994; Bookstaver et al., 2015). Similar results were obtained from our study, indicating that 61% of all antibiotics prescribed to pregnant women belonged to a beta-lactam class. We, however, found a slightly higher percentage (39.7%) of women being treated with penicillin in comparison to this northern European study. The results from our study are therefore consistent with the current trends of antibiotic therapy in pregnancy (Anitha et al., 2018).

Our study found that the duration for penicillins ranged from one to nine days and was typically within the normal prescribing guidelines. However, the hydrophilic nature of these compounds makes them more water-soluble; hence, the potential for lower serum concentrations, due to a more rapid renal clearance. Observational studies have also documented these changes resulting in lower concentrations especially in the third trimester (Frederiksen, 2001; Anderson, 2005). These changes may lead to pharmacokinetic alterations that require dose adjustments or careful monitoring and assessment (Costantine, 2014). Dose adjustments in this study were not evident.

As resistance to commonly used drugs increases, the use of other antibiotic classes will need to be sought where the safety profile has not yet been established presenting as a challenge (Walsh and Wright, 2005; Lamont, Blogg, and Lamont, 2014). Empiric antibiotic prescribing due to financial and practical implications also contribute to the crisis of antibiotic resistance. In this study, the impact of bacterial resistance was already apparent in that some women could not be administered first-line agents (penicillin monotherapy) but were placed on combination penicillins, cephalosporins, and carbapenems. Observantly, combination penicillins-and-beta-lactam inhibitors, were used in 12% of patients. Additionally, two patients were administered colistin, a drug that is not registered in South Africa and reserved for highly resistant patients (Mendelson et al., 2018).

Azithromycin, a sub-class macrolide, and nitrofurantoin were also among the commonly prescribed antibiotics. Macrolide prescribing during pregnancy is not uncommon as similar results have been reported elsewhere for both macrolides and nitrofurantoin (Ramsey et al., 2003; Sarkar et al., 2006;

Dinur et al., 2013; Fan et al., 2020). The use of macrolides in pregnancy is however a growing concern (Fan et al., 2020). Significantly, a recent study by Fan et al. followed children from birth to 14 years of age (Fan et al., 2020). It was concluded that macrolide prescribing in any trimester was associated with an increased risk of genital malformation whereas a previous cohort of 1033 women exposed to macrolides (erythromycin, azithromycin, clarithromycin, or roxithromycin), reported that there were no association with this drug and the development of major abnormalities in the foetus (Dinur et al., 2013; Fan et al., 2020).

Nitrofurantoin, an antibiotic specific for the urinary system, was used in this study. Some studies reported no severe malformation during pregnancy while others found conflicting evidence. A meta-analysis consisting of eight studies did not demonstrate any link between nitrofurantoin exposure in women and major congenital malformation. However, other studies indicated that nitrofurantoin might increase the risk of haemolytic anaemia in pregnant patients with severe glucose-6-phosphate dehydrogenase deficiency (Crider et al., 2009; van de Mheen et al., 2014). The National Birth Defects Prevention Study (NBDPS) found a significant association between nitrofurantoin use during pregnancy and cleft lip and palate (Crider et al., 2009). These adverse effects have not been commonly reported and nitrofurantoin remains an option for treatment of urinary tract infections in pregnant women, although due to its potential to cause harm its use should be reconsidered (van de Mheen et al., 2014).

Two carbapenems, meropenem and imipenem-cilastatin, were used in this study. Carbapenems are broad-spectrum beta-lactams and are typically reserved for infections that are resistant to penicillin and cephalosporin antibiotic therapy (Heikkilä and Erkkola, 1994; Blanca-Lopez et al., 2019). The use of these antibiotics during pregnancy were minimal, indicating that they were possibly the only viable option available despite the paucity of safety data (Heikkila, Renkonen, and Erkkola, 1992; Mendelson et al., 2018).

Safety and efficacy information of antibiotics are usually very limited in pregnancy due to ethical implications around clinical testing in pregnant females. Some category B antibiotics such as phenoxymethylpenicillin, ceftriaxone, nitrofurantoin, metronidazole, and clindamycin are used, and are effective in pregnancy as also found in this study (Bookstaver et al., 2015). However, they cannot be classified as completely safe (Bookstaver et al., 2015). It has been reported that the use of clindamycin should be restricted, while the use of metronidazole in pregnancy is contra-indicated by the manufacturer (Rossiter, 2020).

Approximately 11% of all antibiotics used were category C or D agents. Anti-mycobacterial agents, specifically the class of hydrazides and rifamycin, represented about 5% of the category C drugs. This is expected as just less than half of this study population are HIV-positive (Loto and Awowole, 2012). The burden of Tuberculosis (TB) has increased and trans-versed with the high incidence of HIV, as 75% of TB patients are HIV-infected. TB may be prevalent during pregnancy as a result of immunological changes, stress, and poor nutrition, particularly if there is an immunodeficiency or a co-existing disease. Studies have indicated that despite women being on combination ARV therapy, signs of TB may still appear. The WHO recommendation for treatment of TB in pregnant women is the same as for non-pregnant women and is based on standard therapy for six months, prolonged to a minimum of nine months (Adhikari, 2009).

Restricted use among the other category C and D antibiotic classes were observed and anticipated as a result of restricted safety data and the possible teratogenic effects it may have on the foetus. A very small percentage of women in this study received these antibiotics. As aminoglycosides, fluoroquinolones, chloramphenicol, and trimethoprim-sulphonamide combinations are generally contraindicated in pregnancy unless the benefit of the drug exceeds the risk (Einarson, Shuhaiber, and Koren, 2001; Michalak et al., 2017; Yefet et al., 2018).

Patients who were prescribed aminoglycosides and fluoroquinolones received them for the shortest possible duration. Research states that aminoglycosides should be avoided due to its potential to

cause ototoxicity, nephrotoxicity, and neuromuscular blockade. Only a few cases of neonatal ototoxicity have been recorded following short-term administration and the drug may be used in pregnant women with careful monitoring (Chow and Jewesson, 1985). It is advised that possible risks should be explained, especially in the first trimester. The use of fluoroquinolones in pregnancy remains controversial. In this study, only five patients of a total of 184 received a fluoroquinolone. A systematic review by Yefet et al. assessed the safety of quinolones in pregnancy and reported no major congenital malformations (Yefet et al., 2018). The data suggest that, although fluoroquinolones were shown to cause possible harmful effects in some animal models, it is usually under higher concentrations. Although, in 2016, the FDA updated its warnings, for both oral and injectable fluoroquinolones (Acar et al., 2019). The authors illustrated that when the drug is used systemically, it may be associated with disabling and potentially permanent side effects, which can involve the disruption of tendons, joints, muscles, and nerves. Besides the effects mentioned, it could even induce type 2 diabetes. This was a result of an increase in the number of reports about fluoroquinolone toxicity and long-term complications. The FDA has since introduced significant restrictions to its use (Michalak et al., 2017; Yefet et al., 2018; Acar et al., 2019).

Theoretically, sulphonamides are contra-indicated in the third trimester due to the potential risk of neonatal haemolysis, methemoglobinemia, and the fear of kernicterus, although practical evidence of this risk is sparse (Sivojelezova et al., 2003). In this study, seven prescriptions for trimethoprim-sulphonamide combinations were dispensed to women who were in the third trimester of pregnancy for an average duration of 22 days. The use and long duration of this antibiotic might be due to the antibiotics beneficial uses exceeding its risk.

Chloramphenicol is one of the few antibiotics that is completely avoided in pregnancy due to the risk of neonatal toxicity, particularly grey baby syndrome (Amstey, 2000; Chung and Kwok, 2004). It was observed that three patients received this drug for a duration of 28 days, although it was in the form

of an eye ointment. There is a very small probability that large amounts of the drug would be absorbed systemically which could harm the infant (Chung and Kwok, 2004).

According to several studies, the majority of antibiotics are used to treat genitourinary infections in pregnancy (Ghouri, Hollywood, and Ryan, 2019). Observantly, a large percentage of women in this study were treated predominantly for systemic infections, while infections of the genitourinary tract were the third most treated. This could be as a result of women attending a tertiary hospital for the treatment of more severe infections.

Implications and recommendations

There is currently a paucity of data regarding antibiotic use in pregnancy and further research should be done in this field. It is recommended that health care professionals keep abreast with new safety data that is continuously being published and incorporate that information into prescribing practices to ensure the safe use of antibiotics in this vulnerable population. It is also essential that more studies follow up on the side effects that drugs have on pregnant women.

Limitations

There are a few limitations to the study. The study was conducted in one site, in one town, and only included individuals that visited the hospital between January and July 2019 with a moderate study population. The results, therefore, cannot be extrapolated to either the national public/ private sector population or the general South African population. There were also very limited patient demographic data that could be extracted from patients' records. There was inadequate time to follow up on those patients to identify whether their infants were affected by the antibiotic therapy that was received. Despite these limitations, this study contributes to research in this population group and builds on the evidence that currently exists.

Conclusion

This study shows that despite the lack of clinical evidence, many classes of antibiotics are used in pregnancy apart from those with a safety record. The long-term reliance on antibiotics that are considered safer to use has led to emerging resistance resulting in the use of broad-spectrum or alternative agents where safety has not yet been established. Patients should be educated and encouraged to be a part of the decision-making process. The role of healthcare professionals in risk assessment and evaluation of available evidence for optimal antibiotic selection, dosing, duration of therapy, and monitoring is pertinent to improving maternal health.

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Competing interests

The authors have declared that no competing interest exists.

Authors' contributions

SN was the principal researcher. SN, VB, and FO were responsible for the study conceptualisation and design. SN analysed and interpreted the data along with VB and FO. SN wrote the article and all authors reviewed it.

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Data availability statement

The data that support the findings of this study are available from the corresponding author (SN) upon reasonable request.

Disclaimer

The content is solely the responsibility of the authors and does not necessarily represent the official views of DRILL and the National Institutes of Health.

Chapter summary

Chapter three highlighted the importance of drug safety and pharmacovigilance of antibiotics in pregnancy. The chapter also addressed the use of antibiotics among a pregnant population and provided a review of the current safety profile of those drugs. Furthermore, antimicrobial resistance and its implications were addressed.

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Chapter 4: Manuscript II

Introduction

The experiences, attitudes, and beliefs of pregnant women towards the use of antibiotics are discussed in chapter four. A systematic approach was used to evaluate the risk-benefit perception of women regarding medicines during pregnancy.

Chapter four is in manuscript format in accordance with the College of Health Sciences guidelines for dissertation submission at the University of KwaZulu-Natal (UKZN).

This chapter is presented as a systematic review and was submitted for publication to the journal: BMC Systematic Reviews (Annexure 6). The protocol for the systematic review is also included in this chapter and was registered on Open Science Framework (OSF): Registration DOI: https://doi.org/10.17605/OSF.IO/SFZG3. The systematic review was written, formatted, cited, and referenced according to the journal's submission guidelines. The author guidelines can be viewed in Annexure 7.

4.1 Systematic review protocol

Title

Awareness and risk perception of antibiotic use among pregnant women: A mixed-methods systematic review protocol

Authors

Sasha Naidoo; Henry Michael; Frasia Oosthuizen; Kofi Mensah

Background and rationale

The use of antibiotics in pregnancy is steadily increasing (Broe et al., 2014). However, antibiotics only account for a small percentage of the total congenital abnormalities experienced in pregnant women and the incorrect use or avoidance of these drugs may have life-threatening consequences (Zaki and Albarraq, 2014).

In 2019, WHO predicted that more than 141 million children will be born, with approximately 200 thousand maternal deaths occurring. Deaths among pregnant women are common in low-income countries (World Health Organization, 2019). In addition, an estimated 8 million infants are born with severe congenital disability (Haak and Radyowijati, 2003; World Health Organization, 2019). Low and middle-income countries in comparison to high-income countries, are more likely to be at risk from potential teratogens due to several socio-economic determinants. These may include low educational attainment, poverty, increased prevalence of infection, poor maternal nutrition, strained economies with poor regulation, and access to medication (Reardon et al., 2002; World Health Organization, 2008).

Literacy is an important socio-economic determinant that forms the foundation of health literacy (Sorensen et al., 2012). Health literacy among any population plays a significant role in understanding the risk of teratogenicity, obtaining health information, and making informed decisions (Kindig, Panzer, and Nielsen-Bohlman, 2004). For many individuals living in both, low income and middle-

income countries, the lack of health literacy skills are a significant obstacle to effective health communication and contributes to higher maternal morbidity and mortality rates (Ngoh, 2009).

Women in low-income countries that have sub-optimal literacy and health literacy, trust that if a healthcare professional prescribes a medicine, it is safe. They lack the need for health information, show poor ability to understand, are unaware of the adverse effects or risk it may accompany and are more likely to take a medicine that should be avoided, directly affecting maternal-foetal health (Ozawa and Walker, 2011; Dellicour et al., 2013; Lupattelli et al., 2014).

In high-income countries, there is sufficient information to suggest that women are aware of the risk of medicines in pregnancy although they may perceive an unrealistic elevated risk which may influence the termination of a healthy pregnancy (Nordeng, Ystrom, and Einarson, 2010; Lupattelli et al., 2014). A misperception of elevated risk may also lead to inappropriate decisions regarding pregnancy outcomes (Damase-Michel et al., 2008).

While there is substantial research that assess the awareness, knowledge, and perception of people regarding medicine use, to our knowledge there are no systematic reviews that focus on the teratogenic risk perception among pregnant women especially in resource poor settings, with high fertility rates and low literacy rates with minimal educational attainment (Csajka et al., 2014). The lack of disclosure by health care professionals regarding negative pregnancy outcomes may also impact the severity of the problem (Dellicour et al., 2013).

It is imperative to understand the socio-cultural context and the perceived risk of potential teratogens among pregnant women to advocate correct antibiotic use. It is imperative that health care providers use evidence-based information to ensure effective communication, promote adherence, and provide safe and effective medicine use that contribute to improving maternal, neonatal, and child health (World Health Organization, 2008; Nordeng, Ystrom, and Einarson, 2010).

Review question

What are the factors that determine the risk perception regarding antibiotic use among pregnant women and how does the perceived risk influence the use of antibiotics in this population?

Aim

The study aims to assess the use, knowledge, and beliefs of antibiotics among pregnant women and to compare disparities among low, middle, and high-income countries.

Objectives

- To assess the level of awareness regarding the risks and benefits of antibiotic use in pregnant women.
- To evaluate the factors influencing the risk perception of antibiotic use in pregnant women.
- To assess the relationship between risk perception and antibiotic use in pregnant women.

Methodology

The Joanna Briggs Institute (JBI) guidelines for mixed methods systematic reviews (MMSRs) will be followed from design to reporting (Johanna Brigg Institute, 2019). The review protocol will be registered on OSF (Open Science Framework, 2020).

Eligibility criteria

Inclusion Criteria

The PICo framework will be used to determine the eligibility of this study.

- P- Population/ participants: Pregnant women, ≥ 18 years old.
- I- Phenomena of interest: Risk perception on antibiotic use.
- Co- Context: Low-income countries, middle-income countries, and high-income countries.

Exclusion studies:

- Studies that do not include pregnant women.
- Non-English studies.
- Studies not having the outcome of interest.

Types of studies

- This review will consider primary quantitative, qualitative, and mixed methods studies. Quantitative studies will include descriptive and analytical cross-sectional studies. Qualitative studies will include studies that are semi-structured, focus group discussions (FGD), individual, or one-on-one interviews. Mixed methods studies will only be considered if data from the quantitative or qualitative components can be extracted.
- Only studies published in the English language will be included.
- Studies published from 2000 to the present will be included to ensure relevance to current practice.

Main outcomes

- Risk perception scores of antibiotics in pregnant women.
- Beliefs about antibiotic use in pregnancy.

Secondary outcomes

- Studies that have only perception of teratogenic risk as the outcome will be included.
- Studies showing adherence to antibiotics as an outcome of risk perception will be included.
- Studies showing factors influencing risk perception of antibiotic use in pregnancy.

Information sources

A comprehensive search will be conducted using the following databases: PubMed (MEDLINE), Scopus, CINAHL, and Psycinfo. Google scholar will be accessed for grey literature. The references of selected studies will also be examined for other primary studies that may have been missed.

Search strategy

The search strategy will aim to locate both published and unpublished studies. An initial limited search of MEDLINE was undertaken to identify articles on the topic. The search strategy for MEDLINE via PubMed has been attached (Appendix 2). Keywords and free texts were developed for four themes: Antibiotics (also including 'medicines') to capture studies where antibiotics are discussed as sub-themes, pregnancy, risk perception, and awareness. The search strategy, including all identified keywords and index terms, will be adapted for each included information source.

Data selection and extraction

Selection

This systematic review will be assessed and completed by three reviewers (SN, HM, and KM). Screening of the title/ abstract and full article screening will be done independently by two reviewers for eligibility (SN and HM). The rate of the agreement will be calculated. Disagreements will be resolved by the third reviewer (KM). All identified citations will be exported into Mendeley and duplicates will be removed.

Data extraction

A standardised data extraction tool will be used to record the relevant information from the included studies. The tool will consist of: study title, authors, aim, year, country, sample size, sample description (age, gestational age, parity), data type (qualitative, quantitative, or mixed-methods), methodology for data collection (telephone, web-based, face-to-face, FGD), response rate, antibiotics, and references. Also, educational attainment/ level of knowledge, the perceived risk or benefit of medicine

use during pregnancy, and factors influencing perception. The key findings, study strengths, and limitations will also be extracted. Furthermore, qualitative data will comprise of themes or subthemes with corresponding illustrations.

Data transformation

The quantitative data will be converted into 'qualitised data'. This involves transformation into thematic descriptions of the quantitative results from observational studies including the quantitative component of mixed methods studies in a way that will answer the review questions.

Data synthesis and integration

A convergent integrated approach will be applied according to the JBI methodology (Johanna Brigg Institute, 2019). This will involve assembling the 'qualitised' data with the qualitative data. The collected data will be categorised and pooled together based on similarity in meaning to produce a set of integrated results.

Risk of Bias

To assess the quality of the study, the Mixed Method Appraisal Tool (MMAT), version 2018 will be used (Hong et al., 2018).

Analysis of subgroups or subsets

Group-based patterns within and between studies affecting the risk perception of antibiotics in pregnant women will be noted. These may relate to geography, age, gestational age, and culture.

Ethical consideration

Ethical approval will not be required as no individual data will be used. The results will be disseminated by publication in a peer-reviewed journal.

Study timeline

October 2019 – January 2020

Study personnel

Reviewer 1: Sasha Naidoo

Reviewer 2: Henry Michael

Reviewer 3: Dr Frasia Oosthuizen

Review 4: Dr Kofi Mensah

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4.2 Systematic review

Awareness and risk perception of antibiotic use among pregnant women: A mixed methods systematic review.

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Abstract

Background

The perception of risk significantly affects the decision to take an antibiotic during pregnancy. Understanding womens' beliefs and their demographic and socio-cultural context allow for effective antibiotic treatment among this vulnerable population. This study aimed to explore the perceived risk of antibiotic therapy and to assess the factors that influence its use in the pregnant population.

Method

PubMed, Scopus, CINAHL, and Psycinfo were systematically searched by two reviewers for studies published between January 2000 to December 2019. The quality of the selected articles was critically appraised using a standardised tool. We stratified analysis according to themes based on the framework of the Health Beliefs Model (HBM). The PRISMA guidelines and JBI guidelines for mixed-method systematic reviews were followed.

Results

A total of 1539 articles were identified, of which 14 studies met the inclusion criteria. The selected studies included four regions: Europe, America, Asia, and Africa. Limited studies were found in low and middle-income countries, especially among rural communities. The majority of women attained tertiary qualifications and expressed a misconceived belief of risk.

Conclusion

An unrealistic misconception of risk among pregnant women were observed in European and Asian studies, while a lack of safety and awareness of antibiotic use was discovered in an African population. A significant link between risk perception, educational attainment, and health literacy was found among the studies.

Keywords

Risk, benefit, awareness, pregnancy, perception, beliefs, antibiotics

Introduction

The use of medicines in pregnancy is a cause for concern and uncertainty among women (1). Infection during pregnancy is common and may be inevitable, requiring the need for treatment. It is reported that between 62-80% of medication prescribed in pregnancy, is an antibiotic; hence one out of every four pregnant women is treated with one (2–4).

Several concerns have been raised regarding the safety of antibiotics used in pregnancy (5–7). Antibiotics can be teratogenic or cause short- or long-term effects on the foetus. Some antibiotics are considered safer to use, while others are to be completely avoided. This raises the challenge of reaching the therapeutic concentration while avoiding the risk of adverse drug reactions that may harm the foetus; health care professionals therefore make decisions based on guidelines that allow them to weigh the benefits and risks against the severity of the illness (8–10).

Womens' beliefs and attitudes about medicine use are likely to significantly influence antibiotic therapy in pregnancy. The attitude and behaviour of pregnant women play an essential role, especially in circumstances when the untreated disease may be more harmful than the prescribed medicine. Pregnancy is a known determinant for poor medication adherence and several studies report that women have an unrealistic perception of risk regarding antibiotic use (11,12). The discernment of the patient may also vary depending on their level of health literacy, age, level of education, parity, geographical region, and most importantly their beliefs and opinions affecting their ability to make well-informed health decisions (11,13).

A study conducted in the Netherlands concluded that most patients were "concerned" or "very concerned" about miscarriage and congenital disabilities. However, recent studies observed that women tend to overestimate the degree of teratogenic risk, a similarity found in several other high-income countries (11,14). Womens' perception of risk towards medicine in pregnancy thus is an important factor that affects the use of medication (12).

There is substantial research that assesses the awareness, knowledge, and perception of people regarding medicine use but to our knowledge, there are no systematic reviews that focus on the risk-benefit perception of antibiotics among pregnant women, especially in resource-poor settings, with high fertility rates, low literacy rates, and minimal educational attainment (15). Understanding the socio-cultural context and the perceived risk of potential teratogens among pregnant women is crucial for advocating correct antibiotic use.

The primary aim of the study is to assess knowledge and beliefs of antibiotic use in pregnant women, and to compare disparities among low, middle, and high-income countries by identifying the factors that determine the risk perception and evaluating its influence on the use of these drugs.

Methods

Protocol and registration

The Joanna Briggs Institute (JBI) guidelines for mixed methods systematic reviews (MMSRs) and the Preferred Reporting Items for Systematic Reviews (PRISMA) guidelines were followed from design to reporting (16). The review protocol was registered on Open Science Framework (OSF) (17). Registration DOI: https://doi.org/10.17605/OSF.IO/SFZG3

Eligibility criteria

Inclusion Criteria

The PICo framework was used to determine the eligibility of this study.

- P- Population/ participants: Pregnant women, ≥ 18 years.
- I- Phenomena of interest: Risk perception of antibiotic use.
- Co- Context: All countries; no restriction on geography.

Studies were included if they were published in the English language, included pregnant women that were aged 18 years or older, and discussed the phenomena of interest. Only primary quantitative, qualitative, and mixed methods studies were included. Quantitative studies included descriptive and

analytical cross-sectional studies. Qualitative studies included studies that were semi-structured, involved focus group discussions (FGD), individual, or one-on-one interviews.

Search strategy and sources

A systematic search for studies from January 2000 to December 2019 were performed using four databases, which included PubMed, Scopus, CINAHL, and Psycinfo. The search strategy was piloted and approved by two reviewers SN and HM and composed of variations of the following search terms: risk, benefit, perception, awareness, pregnancy, and antibiotics. This search was conducted to acquire patient perspectives across all countries. An additional search for grey literature was conducted on Google Scholar and the references of these articles were searched.

Study selection, quality appraisal, and data extraction

Titles and abstracts were screened by two independent reviewers (SN and HM) and articles were selected for full screening based on the inclusion criteria. Full article screening was also independently done by both reviewers (SN and HM). Inter-rater reliability in the title/ abstract and full text screening were calculated using Cohen's kappa coefficient (κ). The included studies were assessed for quality using a standardised critical appraisal tool for mixed-method studies (MMAT) (Appendix 5) (18). A methodological selection of questions were used to assess each article. The quantitative and qualitative components were assessed separately using their respective tools. Every question had a response of ‘‘yes’’, ‘’no’’, or ‘’can’t tell’’. No articles were excluded based on low quality. An overall quality score could not be calculated using this tool.

Data from the included studies were extracted by the primary reviewer (SN) using a data extraction template on Microsoft® Excel and later checked by the secondary reviewer (HM). Author’s name, year of publication, country, setting, study design, socio-demographic description, sample size, and the main findings were recorded. Additionally, educational attainment / level of knowledge, the perceived

risk or benefit of medicine use during pregnancy, factors influencing perception and limitations of the study were also recorded (Appendix 6).

Data analysis, data transformation, and data integration

The extracted data were arranged into various themes and subthemes that were similar among the selected studies. The data obtained from quantitative studies were transformed into 'qualitised data' by narrative and thematic synthesis. A convergent integrated approach was then applied according to the JBI methodology (16). This involved assembling the 'qualitised' data with the qualitative data to categorise and pool data based on similarity in meaning to produce a set of integrated results.

The selected themes were based on the theoretical framework of the HBM. Key elements of this model focus on individual beliefs about health conditions, which predict individual health-related behaviours (19). The model defines the key factors that influence health behaviour and is divided into five main domains: perceived susceptibility, perceived severity, perceived benefits, perceived barriers to action, and exposure to factors that prompt action as shown in Figure 1 (19). A concept map was generated to show the theme linkage, shown in Figure 3. The primary themes are related to - trust, illness perceptions, perceived risk or benefit, and information sources.

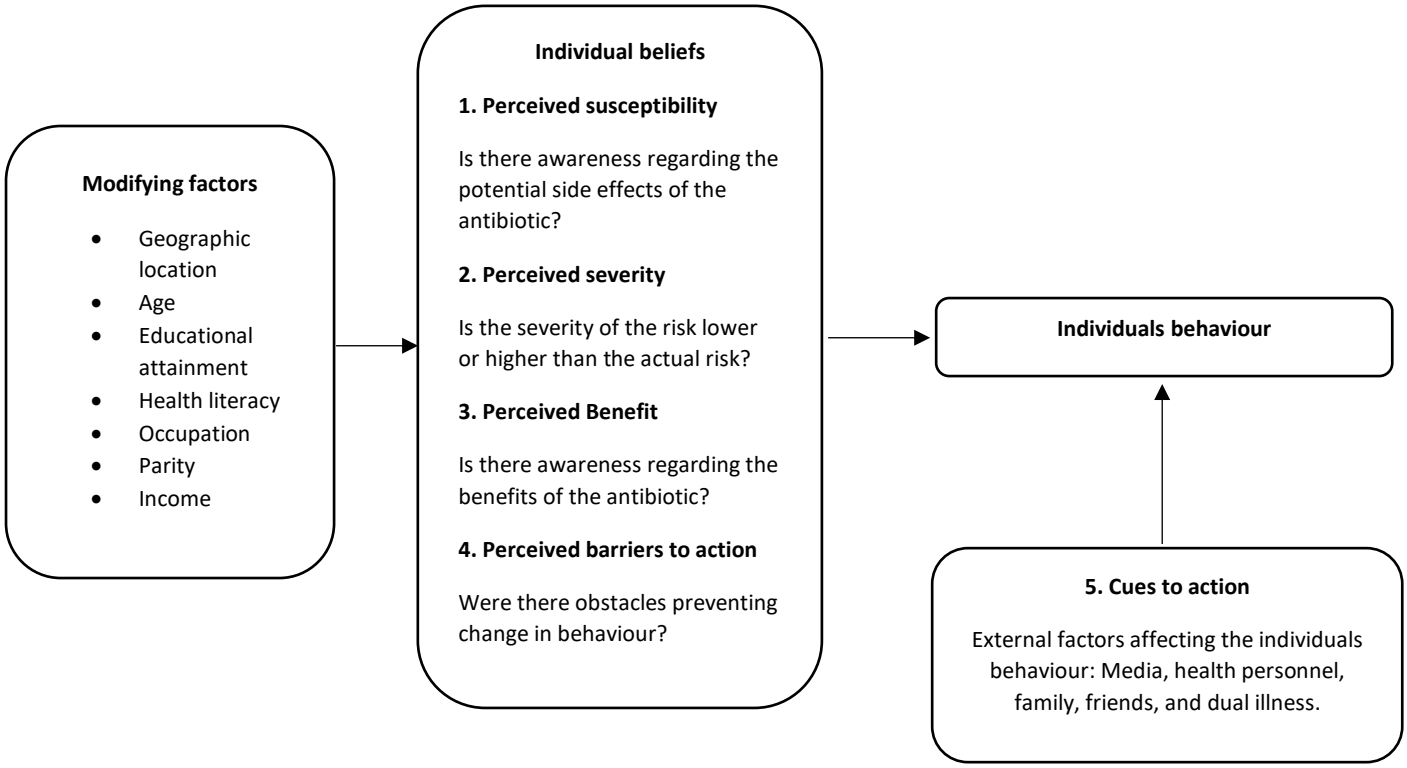

Figure 1 A summary explaining the Health Beliefs Model (HBM) (19)

Results

The database search identified 1539 records. A total of 359 duplicate records were removed. One thousand one hundred and eighty (1180) articles were independently screened by authors SN and HM. One thousand one hundred and sixty-nine (1169) irrelevant articles were excluded. Eleven studies were retrieved from the four databases. An additional search from Google Scholar and the references of articles that were selected for full-text review yielded three results. Only 14 studies met the inclusion criteria for this review. The rate of agreement was calculated at each step to obtain an overall of 98.8% using Cohen's kappa coefficient (κ=0.82). Any disagreements were resolved by the third reviewer (KM). A flow chart summarising the selection process is shown in Figure 2 (20,21).

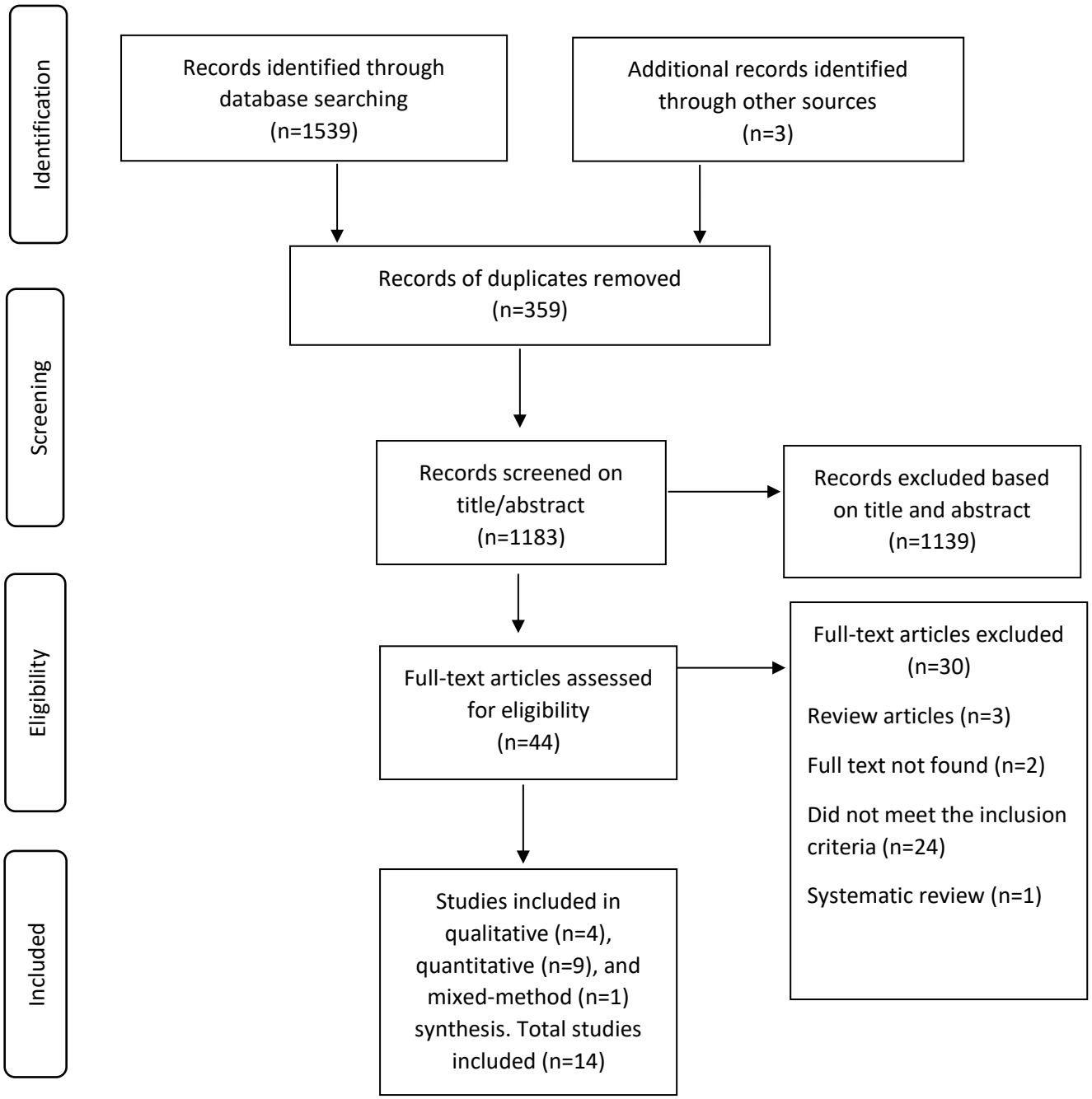

Figure 2 The systematic selection process reported according to PRISMA guidelines (20)

Study characteristics

The review included 14 studies that were published from the year 2000-2019. Nine (n=9) studies were published between the years 2012 and 2019. Most studies were carried out in Europe (n=9), with only a few studies conducted in America (n=1), Asia (n=3) and Africa (n=1). One study was a multinational study that included 18 countries in Europe. The studies were either qualitative, quantitative, or mixed-methods cross-sectional studies. The sample size varied among the different articles. The mean sample size for participants in this study was 707, with a range of 20-4999 participants. The objectives of the studies differed significantly, although they included various multi-dimensional aspects of the risk or benefit of antibiotics. Only four studies focused primarily on antibiotic use in pregnancy, whereas others (n=10) included antibiotics as a sub-category.

Socio-demographic variables

Almost all the studies included participants that attained either high or middle education, with most women aged between 20-40 years. A significant portion of women who participated in the studies were in their third trimester and reported that they were previously pregnant with one or more children. Many of the studies were done in urban areas with only one study that recruited participants from predominantly rural settlements in Saudi Arabia. Additionally, only a single study was diverse in its recruitment as participants from urban, semi-rural, and rural areas from one private and one public hospital were selected. Women were selected from either obstetric care facilities or tertiary hospitals in eight studies (9,11,22–27), while the other studies included women that were active on different social media platforms and websites (12,28–32). The majority (n=9) of studies did not disclose whether their participants were employed, however, four studies did include participants that were and two of those studies included women that worked in the health care sector (11,23,29,32). Most of the studies included in this review consisted of similar population groups; only a single study consisted of a multicultural patient population with high levels of socio-economic deprivation and mixed educational backgrounds.

Table 1 Characteristics of included studies (n=14)

Author and year	Country	Study design	Sample size	Aim	Main findings
Mulder et al. (2018) (11)	Netherlands	Quantitative	136	To evaluate the perception of risks and benefits of medication use during pregnancy and associations with socio-demographic characteristics.	Most drugs were perceived relatively low in risk and high in benefit. Antibiotics had one of the highest benefit scores. The major concern of pregnant women was having a child with birth defects (35%), having a miscarriage (35%), and the future development of allergic diseases (23%). High-risk scores were reported more by women in the first trimester of pregnancy.
Ghouri et al. (2019) (28)	UK (England, Scotland, Wales, Northern Ireland)	Qualitative	205 threads from 675 online users	To explore womens' experiences of UTIs in pregnancy, to develop an understanding of their concerns, and to encourage behaviours that facilitate the appropriate use of antibiotics.	The main concern of the mother was the effect of the UTI on the foetus. A few women expressed reluctance and questioned the use of antibiotics during pregnancy. A small proportion of women were uncertain of how the antibiotic might affect the foetus or their child's immunity in the long term but for the remaining majority, antibiotics were perceived as the safest and most effective treatment.
Alsaleh et al. (2019) (22)	Saudi Arabia	Quantitative	253	To assess the knowledge of pregnant women regarding the use and awareness of antibiotics.	The educational level, economic level, and the stage of pregnancy significantly affected knowledge and awareness of antibiotic use, p=0.006, p=0.002, p=0,003. Women with a bachelor's degree and a higher economic status had a higher awareness than other participants.
Kenyon et al. (2006) (23)	UK (A single region)	Qualitative	20	To explore women's experiences of being recruited to ORACLE, a randomised controlled	Most women had the perception that there was a possible benefit to their babies and no harm.

				trial of antibiotics in pre-term labour.	Women were confident and trusting in their health professionals and reported that they were told there was no harm to the study.
Bulabula et al. (2019) (24)	South Africa	Quantitative	301	To establish the knowledge, attitudes, and practices (KAP) regarding antibiotic use and self-medication among pregnant women.	Pregnant women with a lower K-score were most likely to self-medicate. More than half of the women disagreed with the statement that antibiotics should not be bought over the counter, with 17% purchasing antibiotics over the counter without a doctor's prescription. While 36% treated the flu with an antibiotic.
Sanz et al. (2001) (25)	Spain	Quantitative	81	To assess the perception of teratogenic risk of common medicines by professionals and laypeople.	The risk perception among pregnant women were over estimated. The true risk for amoxicillin and erythromycin were estimated to be <5%, while the perceived teratogenic risk was 40,4% and 38,7%.
Mashayekhi et al. (2009) (26)	Iran	Quantitative	400	To obtain information regarding the awareness of Iranian pregnant women about the effects of drugs in pregnancy.	It was found that 1-13%, perceived that antibiotics were safe in pregnancy, while the majority over-estimated the risk of antibiotics.
Zaki et al. (2014) (9)	Saudi Arabia	Quantitative	760	To assess medication use, knowledge, and beliefs about medications among pregnant women in Saudi Arabia.	A large percentage (59%) of participants mentioned that all the antibiotics listed (penicillin, ampicillin, amoxicillin, cloxacillin, cephalosporins, erythromycin, gentamicin, amikacin, streptomycin, sulphonamides, and tetracyclines) should be avoided. It was reported that 44.7% agreed that it was better for the foetus, if medicines are used than to have an untreated illness during pregnancy, while 31% disagreed and 23,7% were uncertain.

Nordeng et al. (2010) (29)	Norway	Quantitative	866	To assess pregnant womens' beliefs about medications. Secondly, to investigate whether beliefs during pregnancy were associated with socio-demographic characteristics and personal medication use during pregnancy.	Significant associations were observed between education, occupation, and attitude. Less-educated women believed medicines were harmful and herbal remedies were safe. Women with higher education were more reluctant to use medicines during pregnancy. Women with health-related jobs were more knowledgeable about the risk of untreated illnesses.
van Gelder et al. (2019) (30)	Netherlands	Qualitative	1224	To evaluate the availability and accuracy of social media content on the perceived safety of medication use during pregnancy.	A large proportion of the posts had contained inaccurate information regarding antibiotic use. It was reported that the over-estimation of safe medicines could affect adherence which could impair maternal or foetal health.
Widnes et al. (2013) (27)	Norway	Quantitative	171	The aim of the present study was to examine differences in risk perception between pregnant women and their corresponding general practitioners (GPs). Secondly to investigate confidence in medicine use during pregnancy, through texts from Patient Information Leaflets (PILs).	Risk perception of the pregnant women were higher than the risk perception of their GP's with lowered confidence in use. PILs could influence patient adherence to prescribed medicines or recommended medicines in need of treatment.
Nyholm et al. (2019) (12)	Denmark	Qualitative	10	To explore in-depth, the perceptions of medication use among pregnant women during their pregnancy.	Majority of women overestimated the risk. Women believed that it was less safe to take medicines during pregnancy. It was reported that conversations with physicians had a calming effect.

					Some women received conflicting information from the internet.
Bonari et al. (2005) (31)	Canada	Quantitative	100	To determine the risk perception of antidepressants in comparison to antibiotics and gastric medications by pregnant women with depression. Secondly, to identify the determinants that influence women in their decision making regarding the continuation/ discontinuation of medication during pregnancy.	There was a high initial risk perception. Despite receiving reassuring information, 15% of women chose to discontinue their medication as compared to 1% of antibiotic users. Counselling had a major impact on medication continuation. The level of education, age, and other socio-demographic factors did not correlate with the decision outcome in this study.
Lupattelli et al. (2014) (32)	America and Europe (18 countries)	Quantitative	4999	To explore the role of maternal health literacy in relation to perception of medication risk, beliefs about medication, and non-adherence to prescribed pharmacotherapy during pregnancy.	A high-risk perception score was determined for penicillin antibiotics. Majority of women had medium health literacy and high educational attainment.

Table 2 Sociodemographic characteristics of included studies (n=14)

Study	Socio-demographic characteristics				
	Geography	**Educational attainment**	**Age/ age group (years)**	**Mean trimester**	**Parity**
Mulder et al. (2018)	Europe (Netherlands)	Middle-high educational level	31 -	Third	Reportedly 71.3% of women had children.
Ghouri et al. (2019)	Europe (UK)	High (degree qualification)	30-40	-	-
Alsaleh et al. (2019)	Asia (Saudi-Arabia)	Middle – high	20-40	Third	Reportedly 64.6% of women had children.
Kenyon et al. (2006)	Europe (UK)	Middle	-	Second and third	The majority of women had children.
Bulabula et al. (2019)	Africa (South Africa)	Middle	29	Second and third	The majority of women had children.
Sanz et al. (2001)	Europe (Spain)	-	-	-	-
Mashayekhi et al. (2009)	Asia (Iran)	High	20-29	-	Half of the women had children.
Zaki et al. (2014)	Asia (Saudi Arabia)	High	20–40	-	The majority of women had children.
Nordeng et al. (2010)	Europe (Norway)	High	-	-	-
van Gelder et al. (2019)	Europe (Netherlands)	-	-	-	-
Widnes et al. (2013)	Europe (Norway)	High	30	First and second	The majority of women had children.
Nyholm et al. (2019)	Europe (Denmark)	High	30	Third	Most women were pregnant for the first time.
Bonari et al. (2005)	North America (Canada)	-	-	-	-
Lupattelli et al. (2014)	Europe (18 countries)	Middle and high	25	Second	Most women were pregnant for the first time.

Associations between perception and demographic variables

Several population-based studies assessed the relationship between perception and the different demographic variables; educational attainment, economic level, trimester, and parity.

Education and health literacy

Multiple studies reported the educational level of the participants; however, only four of these studies investigated the direct influence of education or health literacy on risk perception (9,22,24,29). Most women in this study had medium health literacy and a high level of educational attainment.

The level of education attained and its effect on knowledge and awareness regarding antibiotic use was significant in a Saudi Arabian study (p=0.006) (22). Women with tertiary education demonstrated higher awareness in comparison to the other participants, accompanied by an elevated perception of risk (9,24,29).

Pregnant women with lower educational levels were more likely to be doubtful about drugs in comparison to those with higher education (32). Lupattelli et al. reported that low literate women were often younger, single, or divorced with no previous children compared to their adequately literate counterparts and were more likely to have a higher risk perception (32). In contrast, Bulabula et al. reported that almost 60% of women thought that it was acceptable to buy antibiotics over the counter, expressing a lower perception of risk (24).

Other studies indicate that women with low or medium health literacy were more likely to be non-adherent to prescribed systemic antibiotics. Women with higher education were more reluctant to use medication during pregnancy (9,29). This contrasting interpretation indicates that there was no unanimity regarding the association between risk perception and education among the different articles.

Economic level

A significant association between the economic level of the women and the impact on knowledge and awareness were shown in two studies (22,24). The first study, is a cross-sectional study conducted in Saudi Arabia, which discussed that women who obtained a bachelor's degree generally had a higher economic status, which was strongly associated with antibiotic awareness and subsequently knowledge (p=0.002) (22). Secondly, Bulabula et al. explained that the economic level contributed to the reason for antibiotic use and whether it was used with or without a prescription (22).

Trimester of pregnancy and parity

Two studies reported the perceived risk scores of medicine use during the first two trimesters of pregnancy and it was shown that there were a significantly higher risk in the first and second trimester in comparison to the third trimester (p=0.003 and p=0.07) (11,22). Lower benefit scores of medicines were perceived if women were single and nulliparous (p=0.006) (11). In a South African cohort of pregnant women, the mean knowledge-score of antibiotic use and awareness was satisfactory and it was reported that pregnant women with a lower knowledge score were most likely to self-medicate with an antibiotic (24).

Antibiotic prevalence and use

The prevalence of antibiotic use was mentioned in six articles ranging from 2.6-33% (9,11,22,24,29,31). A variety of penicillins, nitrofurantoin, ciprofloxacin, erythromycin, metronidazole, and cephalosporins were some of the commonly reported antibiotics. Penicillins were mentioned in four studies (9,25,28,32). The risk perception for this class of antibiotics well exceeded its true risk in all four studies.

Factors that influenced risk perception

The perception of risk was influenced by several contributing factors. These factors included the patient-physician relationship, perceived susceptibility to potential adverse reactions, the perceived severity of risk, and awareness regarding the benefits of antibiotic therapy.

Patient-physician relationship and trust

Patient-physician relationship was an overarching theme that was observed in two cross-sectional studies conducted among White European women (23,28). The level of education varied among the two studies (23,28). A qualitative analysis study by Ghouri et al. consisted of women that were predominantly tertiary graduates. In contrast, a qualitative study by Kenyon et al. included women that only completed secondary education, yet an element of trust was observed in both studies (28). Education was interlinked to the concept of trust. Women with a tertiary qualification trusted but were still aware of the possibility of harm, whereas women who obtained only secondary schooling also demonstrated a level of trust but lacked awareness and essential knowledge.

Evidence:

Ghouri et al. (2019) (28)

''Doc wouldn't prescribe it, if it is dangerous."

''The doc said, it wouldn't do me any harm and it is better than not taking them, just in case I had needed them."

"I don't think you should feel guilty as the doc would have given you antibiotics that wouldn't affect your baby.''

''Antibiotics are one of the few things that they are really sure about giving to pregnant women, precisely because we get infections.''

''My doctor said it was safe to use the cystitis relief sachets along with drinking plenty of water and cranberry juice and apparently it should go within 48 hours.''

Kenyon et al. (2006) (23)

''At 32 weeks with [baby's name] and I was just kind of laying on the bed and the doctors came in and asked me if I wanted to take part in the trial. We just agreed straight away because we both felt that it was too early for him to be born and if there was a chance to stop it, we wanted to take it.''

''It's only antibiotics which a doctor would give you if you've got a cold or a cough. I just felt as if it couldn't do us any harm and it wasn't causing either me or my baby any harm in any way.''

Perceived susceptibility, implications of a dual risk, and prenatal attachment

The concern of a dual risk was present in five studies from Europe and Asia, where women were highly educated (9,12,23,28,29). Women perceived the risk of taking antibiotics to be significantly high but were faced with a conflicting decision when experiencing an illness. The risk of an untreated illness was weighed against the possible effect of the antibiotic during pregnancy. Most women had doubts about using these medicines, but some identified with the benefits of the antibiotic in the event of an illness (12). The fear of the foetus being harmed by the illness was more of a concern than the side effects of the antibiotic primarily due to prenatal attachment (28).

Evidence:

Ghouri et al. (2019) (28)

''Hi, I'm 6 + 4 and had a scan today. I got to see a little heartbeat, but the only problem was traces of blood in my urine. They gave me antibiotics for what they suspect is a UTI. I am just worried now after seeing the heartbeat that taking the antibiotic will do something to the baby.''

"Untreated UTIs can lead to permanent kidney damage and premature labour. I'm not trying to scare you and I'm sure you'll be fine, but could you get in touch with your MW [midwife] and get their opinion."

''Doc wouldn't prescribe if it is dangerous. It's more dangerous to leave a UTI, as at its worst it can cause kidney issues and miscarriage.''

Nyholm et al. (2019) (12)

''Most women had doubts about using medicines, but some said that medicines should not be avoided at all cost. A few said that if a medicine needed to treat a disease was avoided, it could cause harm to the child. Some said it would be better for the mother to get well instead of being ill.''

''I have been on penicillin during pregnancy because it's not beneficial if I'm ill. It is better to get over it. For example, if I have a urinary tract infection, it's not good for the foetus, it makes my uterus hard and the only way to treat it, is with medicine.''

Medicine Information sources

Multiple studies integrated the different sources of information that were referred to by the women. Gynaecologists, general physicians, pharmacists, and mid-wives were the most commonly consulted health personnel, although, one study mentioned a lack of direction or advice from physicians (31). Others obtained information from PILs, family, friends, and the internet. It was reported that some information on social platforms may be inaccurate and predominantly highlights the risks of antibiotics compared to the benefits (9,11,26,27,29–31). Counselling was proven to be beneficial in two studies, enhancing adherence and demonstrating a decline in comparison to the initial risk perception (31,33).

Perceived severity of risk

The perceived risk among the majority of the studies (n=10) were reportedly higher than the actual risk (9,12,22,25,26,28–32). Women were most concerned about congenital anomalies, miscarriage, premature birth, and the long-term effects that the antibiotic may have on the developing foetus (11,12,23,28).

Evidence:

Ghouri et al. (2019) (28)

''Personally, I would be wary of it [antibiotics] because there is a link between taking antibiotics in the late stages of pregnancy and the baby having eczema or allergies. I took antibiotics in late pregnancy and my daughter has multiple food allergies and eczema.''

"Cranberry juice is good as well. If it is mild this may flush the infection out and is gentler than antibiotics, which will be likely to cause thrush.''

''I'm petrified that taking amoxicillin will harm the baby!''

Nyholm et al. (2019) (12)

''The majority of women felt that medicines could have unknown long-term adverse effects on their baby for example: heart failure, reduced fertility, social difficulties in school, growth disorders, asthma, and allergies.''

"If there is some kind of revelation that is not discovered yet, it is possible that in 20 years from now there might be a higher risk for something we do not know yet."

Nordeng et al. (2010) (29)

"Reportedly 87% agreed that they were more cautious about using medicines when they were pregnant. While 61,5% agreed that if they were ill and not pregnant, they would have taken medicines, but it was better to abstain. However, 87,4% agreed that they have a higher threshold for medicines when pregnant.''

''Reportedly 43,4% agreed that all medicines can be harmful for the foetus.''

Perceived benefits of antibiotic treatment

Despite the significant number of women who have acquired a high-risk perception towards the use of antibiotics, some women still recognised the benefits of these drugs. Five studies included participants that were aware of the risk of antibiotics but also mentioned the benefits (9,11,23,28,29).

Evidence:

Ghouri et al. (2019) (28)

''I'm surprised that they haven't given you any antibiotics straight away as it can cause early labour or a small baby if left untreated. Mine's been in my kidneys, the pain has been horrendous. Don't suffer if you need to ring and ask for antibiotics.''

Kenyon et al. (2006) (23)

''I was all for it. They found out that antibiotics do help. It's therefore helping thousands of women, isn't it? "

Nordeng et al. (2010) (29)

''Reportedly, 42,1% agreed that treatment with medicines during pregnancy saves the lives of unborn children.''

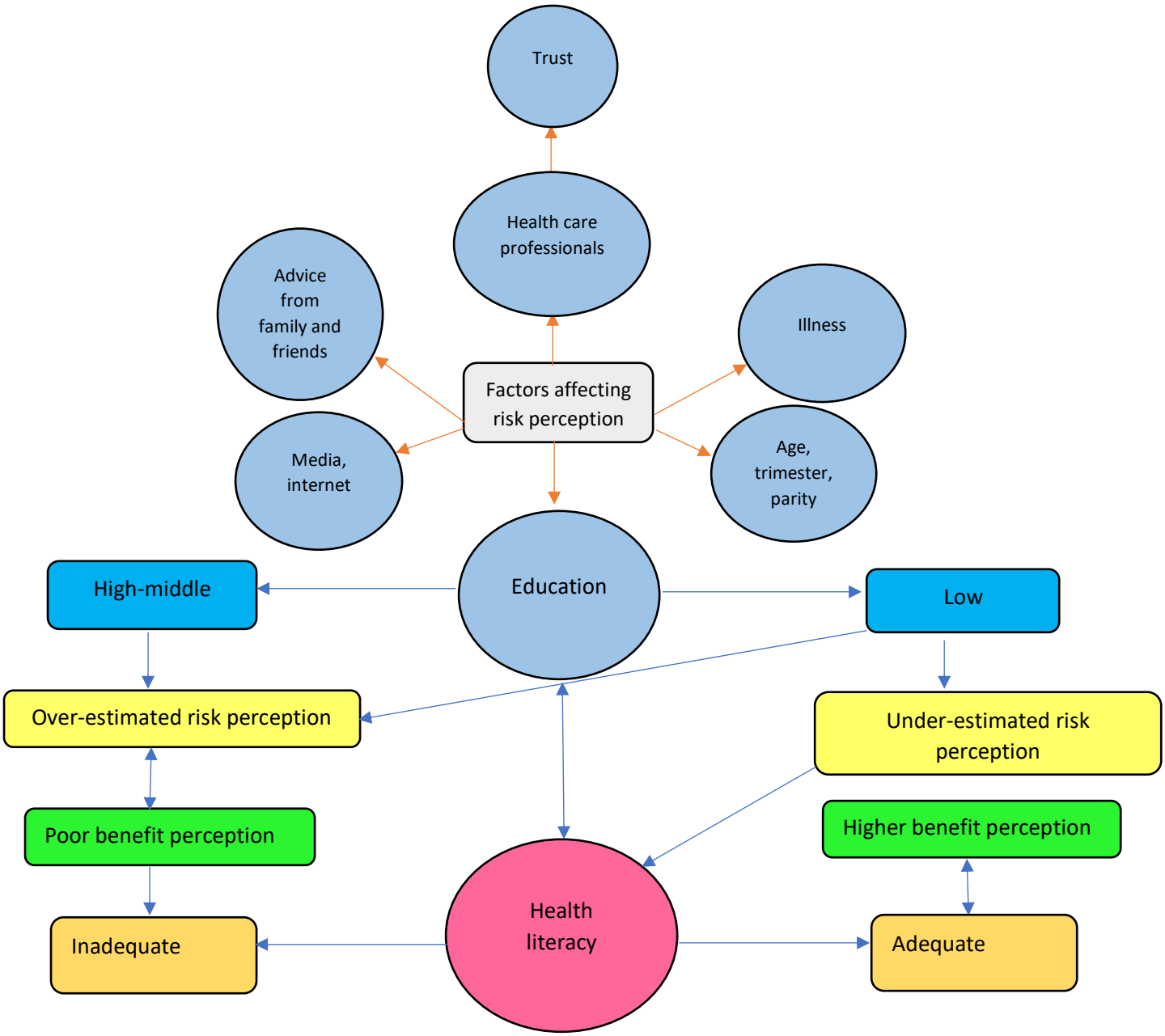

Figure 3 A concept map summarising risk perception in this review

Discussion

This systematic review aimed to assess the knowledge, beliefs, and practice of antibiotics among the pregnant population. To our knowledge, this is the first mixed-methods systematic review to investigate the risk perception of antibiotic use in pregnant women. Most individuals believed that antibiotics were detrimental during pregnancy and should be avoided, while others recognised the advantages.

Risk perception is a multi-dimensional precursor to understanding health behaviour in preventing risk (34). This multi-faceted concept revealed that the perception related to medicines significantly depended on an individual's geographical region, education, and health literacy. In addition, the HBM was utilised to provide a cohesive overview of the perceived susceptibility, severity, and benefits of antibiotic use (35).

Firstly, the perceived risk of antibiotic use among pregnant patients in this study was closely linked to a women's level of education. There was sufficient information to suggest that women with a higher degree of educational attainment in high-income countries were more often fearful and were more likely to over-estimate the risk in comparison to the actual risk profile of the medicine. This agrees with the concept explained in a recent article by Bonari et al. which discusses that the apparent fallacious perception of risk regarding medication, is strongly influenced by the phenomenon of probability, which proves to conceive a notion of unrealistically high-risk perceptions (11,13,33).

Most women believed that antibiotics were teratogenic and may have future adverse effects on the foetus. Miscarriage, premature birth, and congenital abnormalities were some of the prime concerns mentioned. However, an American journal affirms that only 1% of all birth defects are as a result of maternal drug use. Only a few medicines have been proven as teratogenic (FDA classified category D and category X drugs), with studies reporting that the risk of malformation for most drugs, do not exceed the baseline figures of 2- 4% (25,27,36). Notably, in several studies, penicillin, an FDA classified category B antibiotic, was grouped as having the same risk in comparison to confirmed teratogens,

known to be strictly avoided in pregnancy. This indicates that many women with high educational attainment still collectively group all these drugs as being harmful, a commonality also found in another study (11). Adequate or high educational attainment, therefore, does not necessarily translate to a high health literacy level (9,29). A misperception of elevated risk may lead to inappropriate decisions regarding pregnancy outcomes that may lead to poor adherence, discontinuation of treatment, and even the termination of a healthy and wanted pregnancy (37).

In some studies, it was observed that although women may perceive an unrealistic elevated risk, they are still aware of the benefits of medicines in pregnancy, especially women in health-related occupations. They showed a more positive attitude towards medicines as they acquired a higher degree of health literacy, allowing for a more educated and informed perception in comparison to other women (9,11,29).

Women with lower educational attainment also demonstrated a high-risk perception and agreed that medicines did more harm than good, were addictive, and poisonous. They were more skeptical about drugs in comparison to those with higher education (9). Although, a Kenyan study reported that women show reluctance to take a medicine that may be beneficial, not because they are aware of the risk of the medicines, but because the drug predisposes them to nausea and vomiting, which may contribute to this negative belief (38).

Secondly, the behaviour and perception of antibiotic use were largely influenced by the risk of an untreated maternal ailment. The distress of a dual risk gave a false sense of perception among studies as the perceived risk of antibiotics appeared to be low. However, this was not the case as the perceived risk still remained high, but the concern of having an illness that had the possibility to worsen was greater (9,12,23,28,29).

Thirdly, trust in health personnel was a pertinent factor that affected health behaviour. A single study reported that women felt that antibiotics were one of the few things that clinicians were sure about prescribing to pregnant women. This revealed that some women were confident in their health care

professionals. Women from both high and low educational backgrounds displayed a significant level of trust. Women from higher educational backgrounds may not necessarily be more health literate, but they are aware of the possibility of experiencing side effects. In contrast, females with inadequate education, living in rural communities that comprise of predominantly low literate individuals, also display significant levels of trust but they have limited or no knowledge of drug safety and the possible adverse drug reactions. They firmly believe that if a healthcare professional prescribes a medicine, it is safe. They lack the need for health information, show poor ability to understand, and are more likely to take a medicine that should be avoided, directly affecting maternal-foetal health (7,38,39). A study that was conducted in the Vientiane Capital, Lao explains a similar phenomenon (40).

A serious concern among women in low and middle-income countries was low risk perception and self-medication. Bulabula et al. reported that almost 20% of women purchased antibiotics over the counter or without a medical prescription to treat the common cold or flu during pregnancy (24). Women in these communes lack essential knowledge and skills to make educated decisions. They would instead prefer to consume a traditional herbal remedy, considering its use safer than taking medicine prescribed by a health care professional. This could suggest a lack of trust in the health care domain especially in developing areas, although this concept needs to be investigated further (41,42).

An Ethiopian study revealed that more than half of the women who were pregnant used over the counter medicines and the majority of those were antibiotics (43). This behaviour may be a commonality in other low-middle income countries; however, further research is required. Women are, therefore, at a higher risk of experiencing possible adverse effects despite the low percentage of congenital anomalies (40,41). A recent study conducted in Ghana reported that about 94% of infants born with birth defects were reported to come from low and middle-income countries. In the event that an abnormality does occur, it was perceived by society that this socially marginalised group had engaged in some taboo or incest, resulting in the abnormality (38,44). However, there is limited information relating to risk perception and pregnancy in developing countries.

The concern of self-medication in these poorer communities may also contribute to the crisis of antibiotic resistance. Antibiotic resistance is steadily increasing in low and middle-income societies and is a global challenge associated with high morbidity and mortality rates (45).

Lower risk perception was also noticed in women who were previously pregnant and had one or more children in comparison to nulliparous women. Women in the third trimester of pregnancy demonstrated a lower risk perception and were more willing to consider the benefits of antibiotics (9,11,22,24,26,27,32).

Lastly, the persuasive nature of the internet and media played a significant role in a women's decision considering its rapid response to obtaining information. Women used this platform as a reference for medical information, contributing to the issue of receiving conflicting information that is most often not evidence-based (9,11,24,26,28–30). Studies revealed that women also acquired information from PILs although this source may provide restricted and indefinite evidence, in a language that may be too complex for patients to understand (12,46). This negatively shapes the perspective of both the health care professional and the patient. This is evident in a study by Widnes et al. which reported unrealistically high-risk perception among physicians. At the same time, pregnant women reported with an even higher misperception compared to their physicians. The lack of factual sources of information may be a reason for this (36).

Health care professionals have an essential role to play when advocating the use of medication in pregnancy. This is critical, especially when pregnant women are diagnosed with an infection and require antibiotic therapy to lower the risk of miscarriage, abortion, or preterm birth in contrast to dealing with the complications of the antibiotic (13).

In this review, counselling was proven to have a beneficial effect on lowering risk perception. Mulder et al. revealed that women were convinced more easily to identify with the health benefits of certain medicines, such as antibiotics, as compared to other classes of medicines (33). The provision of positively framed advice and information by physicians and pharmacists can affect a patient's

perception allowing for the evaluation of the medicines advantageous uses rather than focusing on the possibility of harm. Individually tailored information provided by drug information centres and full disclosure by health care professionals regarding adverse pregnancy outcomes contributes to this goal (11,38).

Literacy and health literacy among any population plays a significant role in understanding the risk of teratogenicity, obtaining health information, and making informed choices (47). Literacy forms the foundation of health literacy, which has been closely linked to perception and beliefs. According to WHO, Africa has a 65% literacy rate as compared to the 94% literacy rate in America, with two-thirds of this percentage being women (48,49). For many individuals living in both, low-income and high-income countries, the lack of health literacy skills are a significant obstacle to effective health communication (50).

Educating women in rural and poor societies about the danger of self-medication, possible uses, and side effects of antibiotics in a language that is understood by them may improve health literacy among these vulnerable populations. It is also necessary to address the general fear and hesitation of antibiotics in low, middle, and high-income populations allowing them to obtain a more realistic perception.

There is currently limited research regarding the effect of socio-demographic characteristics on the knowledge and the practice of antibiotic use in the pregnant population. Understanding potential misconceptions and identifying existing gaps will contribute to the development of necessary interventions to encourage practical and prudent use of antibiotics.

Limitations

A few limitations were identified throughout this study. This review was done using a relatively limited number of databases for the identification of potentially eligible studies. A substantial number of studies were conducted in high-income European countries, with only a few studies investigating risk

perception in middle-income countries while no studies were obtained from low-income societies. The included studies lacked diverse, multi-ethnic, and multi-racial population groups with varying levels of socio-economic standing and educational backgrounds as the majority of the participants were European women having obtained tertiary education. Risk perception of antibiotic therapy was not a focus instead was common sub-category in most of the studies. This study was only confined to the English language and excluded unpublished articles; hence results cannot be generalised.

Conclusion

The majority of women in high-income countries with high educational attainment, having some degree of health literacy were persuaded by the prospect of risk, resulting in an over-estimated risk perception. Women with lower educational levels in rural low-income societies with minimal or no health literacy were more likely to be submissive and unfamiliar with the concern of risk. These two extremities of risk perception negatively affect the use of antibiotics and may result in sub-optimal therapy. It is imperative that health care providers use evidence-based information to ensure effective communication, promote adherence, and provide safe and effective medicine use that contribute to improving maternal, neonatal, and child health (51,52).

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Author contributions

The articles were screened and selected by SN and HM. The data were extracted and organised by SN. The final manuscript was prepared by SN, then edited, and approved by HM, FO, and KM. All authors read and approved the final manuscript.

Availability of data and materials

All data supporting the conclusions of this article were retrieved from four electronic databases as mentioned in the article.

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Ethics approval and consent to participate

Not applicable

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Consent for publication

Not applicable

Chapter summary

An in-depth investigation into perception and antibiotic use was explored fulfilling the final objective of this dissertation. The factors that influence womens' beliefs and its impact on health decisions were highlighted. The following chapter will summarise and conclude the dissertation.

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Chapter 5: Conclusion

The final chapter highlights the overall findings of the study, describes the limitations and significance of the study, in addition to providing recommendations for future research.

5.1 Summary of findings

The aim of this study was to evaluate the use of antibiotics among pregnant women. To achieve this, the following objectives were met:

- Quantifying antibiotic use in pregnant patients.
- Commenting on the rationale for antibiotic use among pregnant patients.
- Evaluating the safety profile of antibiotics used during pregnancy.
- Determining the risk perception of antibiotics among pregnant women in both low, Middle, and high-income countries using a systematic approach.

Conclusions were drawn and summarised based on each objective.

- Penicillins were quantified as the most used antibiotic in pregnancy and accounted for 39.7% of prescriptions followed by macrolides (13%) and combination penicillin-and-beta-lactam inhibitors (12.3 %). Phenoxymethylpenicillin was the most prescribed penicillin. Azithromycin was the only macrolide used among this population and amoxicillin/ clavulanic acid combination was the most prescribed penicillin-and-beta-lactam inhibitor. Polymyxins were the least prescribed antibiotic class among the pregnant women.
- Almost 40% of antibiotics were prescribed for infections of the blood and circulatory system with 13% of prescriptions been dispensed for genitourinary tract infections. The remainder were for bacterial complications that implicated the endocrine and metabolic system (6.33%), nervous system (5.53%), skin and tissue (4.09%) and the respiratory tract (3.13%).

- Penicillins are considered to be the safest antibiotic used in pregnancy with no reported teratogenic effects. Macrolides and nitrofurantoin show a growing concern regarding safety in the pregnant population with carbapenems having limited safety data. Other classes such as metronidazole and clindamycin are used and are effective in pregnancy, however they cannot be classified as completely safe.
- An unrealistic perception of risk among pregnant women were observed in European and Asian studies, while a lack of safety and awareness of antibiotic use was discovered in an African population. A significant link between risk perception, educational attainment, and health literacy were found among the studies.

5.2 Significance of the study

This study signifies the importance of drug safety and pharmacovigilance in pregnancy. Regardless of the limited availability of safety evidence, antibiotics are still commonly used to treat pregnant women. The appropriate and correct use of antibiotics are crucial to ensure that the mother and foetus are not harmed, there is improvement in maternal health, and use of these drugs are judicious. The study also signifies the importance of understanding how women perceive the use of antibiotic therapy and the influence of risk perception on medicine behaviour, adherence, and non-adherence.

5.3 Strengths

The studies contribute to and strengthens existing literature while addressing the gaps in the current knowledge of antibiotic safety and risk perception in pregnancy. The findings of this study can assist health care prescribers to be more aware when prescribing and ensure the effective use of antibiotics through positive communication.

5.4 Limitations

The quantitative study was restricted to a single tertiary hospital in the public sector; hence the trends and use of antibiotics in pregnant women from private-sector institutions were not taken into

consideration. Additionally, time constraints prevented the collection of data over a longer period. The systematic review was limited in its selection of databases and was restricted to only published studies which were of the English language; hence unpublished studies and studies of other languages were excluded.

5.5 Recommendations

- This study was restricted to one tertiary hospital in the public sector. Further studies should focus on hospitals in the private sector as well as hospitals in other provinces to get a broader perspective on antibiotic use and prescribing in pregnant women.
- Antibiotic resistance is an emerging issue that significantly affects the use of antibiotics in pregnant women and hence further research should be conducted in this field.
- Health care professionals need to keep abreast with new evidence that becomes available on the safety of antibiotics.
- Future studies should focus on the attitude and perception of antibiotics in pregnant women in low and middle-income countries as limited research exists in these settings.

Chapter summary

The final chapter highlighted the important aspects of the study and identified the gaps in the current literature with future recommendations.

Annexures

Annexure 1: Letter of ethical approval obtained from BREC

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

18 September 2019

Ms S Naidoo (219050835)
School of Health Sciences
College of Health Sciences
sashanaidoo@ymail.com

Dear Ms Naidoo

Protocol: To quantify and evaluating the safety profile of antibiotics used amongst the pregnant population by analysis of patient records obtained from a public sector facility Degree: MPharm
BREC Ref No: BE330/19

EXPEDITED APPLICATION: APPROVAL LETTER

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application received on 17 April 2019.

The study was provisionally approved pending appropriate responses to queries raised. Your response received on 12 September 2019 to BREC letter dated 11 July 2019 has been noted by a sub-committee of the Biomedical Research Ethics Committee. The conditions have been met and the study is given **full ethics approval** and may begin as from 18 September 2019. **Please ensure that outstanding site permissions are obtained and forwarded to BREC for approval before commencing research at a site.**

This approval is valid for one year from **18 September 2019.** To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2015), South African National Good Clinical Practice Guidelines (2006) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be **noted** by a full Committee at its next meeting taking place on **08 October 2019.**

Yours sincerely

Prof V Rambiritch
Chair: Biomedical Research Ethics Committee

cc: Postgrad Admin: nenep1@ukzn.ac.za
Supervisor: oosthuizenf@ukzn.ac.za

Biomedical Research Ethics Committee
Professor V Rambiritch (Chair)
Westville Campus, Govan Mbeki Building
Postal Address: Private Bag X54001, Durban 4000
Telephone: +27 (0) 31 260 2486 **Facsimile:** +27 (0) 31 260 4609 **Email:** brec@ukzn.ac.za
Website: http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx

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Annexure 2: Letter of approval from the KZN Department of Health

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

Physical Address: 330 Langalibalele Street, Pietermaritzburg
Postal Address: Private Bag X9051
Tel: 033 395 2805/ 3189/ 3123 Fax: 033 394 3782
Email:
www.kznhealth.gov.za

DIRECTORATE:
Health Research & Knowledge Management

Ref: KZ_201906_005

Dear Ms S Naidoo
(UKZN)

Subject: Approval of a Research Proposal:

1. The research proposal titled '**To quantify and evaluate the safety profile of antibiotics used amongst the pregnant population by analysis of patient records obtained from a public sector hospital**' was reviewed by the KwaZulu-Natal Department of Health (KZN-DoH).

   The proposal is hereby **approved** for research to be undertaken at Inkosi Albert Luthuli Central Hospital.

2. You are requested to take note of the following:

   a. *Kindly liaise with the facility manager BEFORE your research begins in order to ensure that conditions in the facility are conducive to the conduct of your research. These include, but are not limited to, an assurance that the numbers of patients attending the facility are sufficient to support your sample size requirements, and that the space and physical infrastructure of the facility can accommodate the research team and any additional equipment required for the research.*
   b. *Please ensure that you provide your letter of ethics re-certification to this unit, when the current approval expires.*
   c. *Provide an interim progress report and final report (electronic and hard copies) when your research is complete.*

3. Your final report must be posted to **HEALTH RESEARCH AND KNOWLEDGE MANAGEMENT, 10-102, PRIVATE BAG X9051, PIETERMARITZBURG, 3200** and e-mail an electronic copy to hrkm@kznhealth.gov.za

For any additional information please contact Ms G Khumalo on 033-395 3189.

Yours Sincerely

Dr E Lutge
Chairperson, Health Research Committee
Date: 27/06/19

Annexure 3: Letter of approval obtained from Inkosi Albert Luthuli Central Hospital

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

DIRECTORATE:

Physical Address: 800 Bellair Road, Mayville, 4058
Postal Address: Private Bag X09, Mayville, 4058
Tel: 0312401058 Fax: 0312401050 Email: [illegible]
www.kznhealth.gov.za

Office of The Medical Manager
IALCH

Reference: BE330/19
Enquiries: Medical Management

10 September 2019

Ms S Naidoo (219050835)
School of Health Sciences
College of Health Sciences

Dear Ms Naidoo

RE: PERMISSION TO CONDUCT RESEARCH AT IALCH

I have pleasure in informing you that permission has been granted to you by the Medical Manager to conduct research on: **To quantify and evaluating the safety profile of antibiotics used amongst the pregnant population by analysis of patient records obtained from a public sector facility Degree.**

Kindly take note of the following information before you continue:

1. Please ensure that you adhere to all the policies, procedures, protocols and guidelines of the Department of Health with regards to this research.
2. This research will only commence once this office has received confirmation from the Provincial Health Research Committee in the KZN Department of Health.
3. Kindly ensure that this office is informed before you commence your research.
4. The hospital will not provide any resources for this research.
5. You will be expected to provide feedback once your research is complete to the Medical Manager.

Yours faithfully

.....

Dr L P Mtshali
Medical Manager

Dr N Tathiwal
Acting

Fighting Disease, Fighting Poverty, Giving Hope

Annexure 4: Manuscript cover letter and confirmation of submission to Health SA Gesondheid

Manuscript #ID no

AOSIS

MANUSCRIPT COVER LETTER

DOCUMENT VERSION 14 MAY 2019

This scholarly journal MANUSCRIPT COVER LETTER (title page) must be completed and submitted to AOSIS by the corresponding author as a supplementary document, at the manuscript submission point on to the journal website.

MY MANUSCRIPT			
Manuscript title: Antibiotic use among pregnant women in a public hospital: KwaZulu-Natal			
No of words (cross-check your word count with author guidelines): 4359	No of tables: 4	No of figures: 1	No of pages: 25

MY CHECKLIST

By completing this form I/we agree to the following:

1. I/we certify that the manuscript is within the scope of the journal.
2. I/we acknowledge that the research is novel and describes research that advances the field and adds to an active research field.
3. I/we have carefully prepared and formatted the manuscript with all the required sections present.
4. I/we certify that the language is clear and concise and relays a scientific message that clearly explains the importance of the study.
5. (if applicable) I/we certify that the study has been approved by the relevant bodies, research ethics committee(s) or institutional review board(s), e.g. institutional review board, research ethics committee, data and safety monitoring board, and regulatory authorities including those overseeing animal experiments.

CORRESPONDING AUTHOR

(FOR ALL STAGES OF THE SUBMISSIONS, REVIEW AND PUBLICATION PROCESS)

Provide the credentials of the corresponding author of the manuscript. Include their title, full name and affiliation/job title, email address, work telephone number and an alternative telephone number, as well as a postal address (to which you would be happy to have all formal correspondence sent).

Title: Miss	
Full name(s): Sasha	Surname: Naidoo
Any special consideration when communicating with you (e.g. time of day to receive phone calls)	None

AUTHOR LIST

Provide the credentials of all the authors of the manuscript, in the SAME ORDER as they need to appear in the potentially published work. All affiliations should be structured as follows: Department/Faculty, University/ Institution, City, Country. The ORCID is a pre-requisite - if you or your co-authors do not have an account, please register by following this link https://orcid.org/register.

Author 1	Author 11

aosis@hsag.co.za
To: Sasha Naidoo

Wed, Jul 15 at 3:01 PM

****
Ref. No.: 1516
Manuscript title: Antibiotic use among pregnant women in a public hospital: KwaZulu-Natal
Journal: Health SA Gesondheid
****

Dear Sasha Naidoo

Your submission has been received by the journal and will now be processed in accordance with published timelines.

Processing time guidelines are available under the journal's 'About' section, however, please note that each submission is assessed on its individual merit and in certain circumstances processing times may differ.

You can check the status of your submission in three ways:
- Journal Website: login to your account at https://hsag.co.za/index.php/hsag/author/submission/1516.
- Publisher Enquiry Service: telephone numbers are +27(0)219752602 and/or 0861000381.
- Publisher FAQ and Email Service: visit the Publisher FAQ and Email service at https://publishingsupport.aosis.co.za/index.php

You will receive additional emails from the journal as your submission passes through the phases of the editorial process.

Kind regards,
AOSIS Publishing
Health SA Gesondheid

Annexure 5: Submission guidelines for Health SA Gesondheid

Overview

The author guidelines include information about the types of articles received for publication and preparing a manuscript for submission. Other relevant information about the journal's policies and the reviewing process can be found under the about section. The **compulsory cover letter** forms part of a submission and must be submitted together with all the required forms. All forms need to be completed in English.

Original Research Article

An original article provides an overview of innovative research in a particular field within or related to the focus and scope of the journal, presented according to a clear and well-structured format. See full structure of original research articles below.

Word limit	**5000 words (excluding the structured abstract and references)**
Structured abstract	250 words to include a Background, Aim, Setting, Methods, Results, Conclusion and Contribution
References	40 or less
Tables/Figures	no more than 7 Tables/Figure
Ethical statement	should be included in the manuscript

A **systematic review** follows the same basic structure as an original research article:

- Structured abstract: Background, aim, setting, methods, results, conclusion, contribution.
- Aim and objectives: Focus on a clinical question that will be addressed in the review.
- Methods section: Describe in detail the search strategy, criteria used to select or reject articles, attempts made to obtain all important and relevant studies and deal with publication bias (including grey and unpublished literature), how the quality of included studies was appraised, the methodology used to extract and/or analyse data.
- Results: Describe the homogeneity of the different findings; clearly present the overall results and any meta-analysis.

Review Article

Review topics should be related to clinical aspects interdisciplinary health sciences and should reflect trends and progress or a synthesis of data in the following format. See full structure of review articles below. Systematic reviews are considered under original research.

Word limit	**4000 words (excluding the abstract and references)**
References	40 or less
Abstract	up to 150 words, unstructured
Tables/Figures	data in the text should not be repeated extensively in tables or figures

Editorial

Editorials are by invitation only and are intended to provide expert comment on relevant topics within the focus and scope of the journal:

Word limit	**1200 words**
Tables/Figures	a maximum of 1 figure or table
References	10 or less
Conclusion	ensure that there is a clear message in the conclusion

Cover Letter

The format of the compulsory cover letter forms part of your submission. Kindly download and complete, in English, the provided cover letter.

Anyone that has made a significant contribution to the research and the paper must be listed as an author in your cover letter. Contributions that fall short of meeting the criteria as stipulated in our policy should rather be mentioned in the 'Acknowledgements' section of the manuscript. Read our authorship guidelines and author contribution statement policies.

Original Research Article full structure

Title: The article's full title should contain a maximum of 95 characters (including spaces).

Abstract: The abstract, written in English, should be no longer than 250 words and must be written in the past tense. The abstract should give a succinct account of the objectives, methods, results and significance of the matter. The structured abstract for an Original Research article should consist of six paragraphs labelled Background, Aim, Setting, Methods, Results and Conclusion.

- Background: Summarise the social value (importance, relevance) and scientific value (knowledge gap) that your study addresses.
- Aim: State the overall aim of the study.
- Setting: State the setting for the study.
- Methods: Clearly express the basic design of the study, and name or briefly describe the methods used without going into excessive detail.
- Results: State the main findings.
- Conclusion: State your conclusion and any key implications or recommendations.
- Contribution: Concise statement of the primary contribution of your manuscript.
  Do not cite references and do not use abbreviations excessively in the abstract.

Introduction: The introduction must contain your argument for the social and scientific value of the study, as well as the aim and objectives:

- Social value: The first part of the introduction should make a clear and logical argument for the importance or relevance of the study. Your argument should be supported by use of evidence from the literature.
- Scientific value: The second part of the introduction should make a clear and logical argument for the originality of the study. This should include a summary of what is already known about the research question or specific topic and should clarify the knowledge gap that this study will address. Your argument should be supported by use of evidence from the literature.
- Conceptual framework: In some research articles it will also be important to describe the underlying theoretical basis for the research and how these theories are linked together in a conceptual

framework. The theoretical evidence used to construct the conceptual framework should be referenced from the literature.

- Aim and objectives: The introduction should conclude with a clear summary of the aim and objectives of this study.
  Research methods and design: This must address the following:

- Study design: An outline of the type of study design.

- Setting: A description of the setting for the study; for example, the type of community from which the participants came or the nature of the health system and services in which the study is conducted.

- Study population and sampling strategy: Describe the study population and any inclusion or exclusion criteria. Describe the intended sample size and your sample size calculation or justification. Describe the sampling strategy used. Describe in practical terms how this was implemented.

- Intervention (if appropriate): If there were intervention and comparison groups, describe the intervention in detail and what happened to the comparison groups.

- Data collection: Define the data collection tools that were used and their validity. Describe in practical terms how data were collected and any key issues involved, e.g. language barriers.

- Data analysis: Describe how data were captured, checked and cleaned. Describe the analysis process, for example, the statistical tests used or steps followed in qualitative data analysis.

- Ethical considerations: Approval must have been obtained for all studies from the author's institution or other relevant ethics committee and the institution's name and permit numbers should be stated here.

- Results: Present the results of your study in a logical sequence that addresses the aim and objectives of your study. Use tables and figures as required to present your findings. Use quotations as required to establish your interpretation of qualitative data. All units should conform to the SI convention and be abbreviated accordingly. Metric units and their international symbols are used throughout, as is the decimal point (not the decimal comma).

  Measures of Trustworthiness: This refers to the findings of the study being based on the discovery of human experience as it was experienced and observed by the participants. The following are the criteria of trustworthiness, credibility, transferability, dependability and confirmability to be discussed.

  Reliability: Reliability is the extent to which an experiment, test, or any measuring procedure yields the same result with repeated trials. Without the agreement of independent observers able to replicate research procedures or the ability to use research tools and procedures that yield consistent measurements, researchers would be unable to satisfactorily draw conclusions, formulate theories or make claims about the ability to generalise their research.

  Validity: Validity refers to the degree to which a study accurately reflects or assesses the specific concept that the researcher is attempting to measure. While reliability is concerned with the accuracy of the actual measuring instrument or procedure, validity is concerned with the study's success at measuring what the researchers set out to measure. Researchers should be concerned with both external and internal validity. External validity refers to the extent to which the results of a study are generalisable or transferable. Internal validity refers to:

- The rigor with which the study was conducted (e.g. the study's design, the care taken to conduct measurements and decisions concerning what was and was not measured).

- The extent to which the designers of a study have taken into account alternative explanations for any causal relationships they explore.

Discussion: The discussion section should address the following four elements:

- Key findings: Summarise the key findings without reiterating details of the results.
- Discussion of key findings: Explain how the key findings relate to previous research or to existing knowledge, practice or policy.
- Strengths and limitations: Describe the strengths and limitations of your methods and what the reader should take into account when interpreting your results.
- Implications or recommendations: State the implications of your study or recommendations for future research (questions that remain unanswered), policy or practice. Make sure that the recommendations flow directly from your findings.

Conclusion: Provide a brief conclusion that summarises the results and their meaning or significance in relation to each objective of the study.

Acknowledgements: Those who contributed to the work but do not meet our authorship criteria should be listed in the Acknowledgments with a description of the contribution. Authors are responsible for ensuring that anyone named in the Acknowledgments agrees to be named. Refer to the acknowledgement structure guide on our *Formatting Requirements* page.

Also provide the following, each under their own heading:

- Competing interests: This section should list specific competing interests associated with any of the authors. If authors declare that no competing interests exist, the article will include a statement to this effect: *The authors declare that they have no financial or personal relationship(s) that may have inappropriately influenced them in writing this article.* Read our **policy on competing interests**.
- Author contributions: All authors must meet the criteria for authorship as outlined in the **authorship** policy and **author contribution** statement policies.
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- Disclaimer: A statement that the views expressed in the submitted article are his or her own and not an official position of the institution or funder.

References: Authors should provide direct references to original research sources whenever possible. References should not be used by authors, editors, or peer reviewers to promote self-interests. Refer to the journal referencing style downloadable on our *Formatting Requirements* page.

Review Article full structure

Title: The article's full title should contain a maximum of 95 characters (including spaces).

Abstract: The abstract should be no longer than 250 words and must be written in the past tense. The abstract should give a concise account of the objectives, methods, results and significance of the matter. The abstract can be structured and should consist of five paragraphs labelled Background, Aim, Method, Results and Conclusion.

- Background: Why is the topic important to us? State the context of the review
- Aim: What is the purpose of your review? Describe the aim or purpose of your review.

- Method: How did you go about performing the review? Describe the methods used for searching, selecting and appraising your evidence.
- Results: What are the findings? What are the main findings of your literature review?
- Conclusion: What are the implications of your answer? Briefly summarise any potential implications.
- Contribution: Concise statement of the primary contribution of your manuscript.
  Introduction: Present an argument for the social and scientific value of your review that is itself supported by the literature. Present the aim and objectives of your literature review.

  Methods: Although this is not a systematic review (see instructions on original research for this type of article) it is still necessary to outline how you searched for, selected and appraised the literature that you used. Discuss any methodological limitations.

  Review findings: Present your review of the literature and make use of appropriate sub-headings. Your review should be a critical synthesis of the literature.

  Implications and recommendations: Discuss the findings of your review in terms of the implications for policy makers and clinicians or recommendations for future research.

  Conclusion: This should clearly state the main conclusions of the review in terms of addressing the original aim and objectives.

  Acknowledgements: Those who contributed to the work but do not meet our authorship criteria should be listed in the Acknowledgments with a description of the contribution. Authors are responsible for ensuring that anyone named in the Acknowledgments agrees to be named. Refer to the acknowledgement structure guide on our *Formatting Requirements* page.

  Also provide the following, each under their own heading:

- Competing interests: This section should list specific competing interests associated with any of the authors. If authors declare that no competing interests exist, the article will include a statement to this effect: *The authors declare that they have no financial or personal relationship(s) that may have inappropriately influenced them in writing this article.* Read our policy on competing interests.
- Author contributions: All authors must meet the criteria for authorship as outlined in the authorship policy and author contribution statement policies.
- Funding: Provide information on funding if relevant
- Data availability: All research articles are encouraged to have a data availability statement.
- Disclaimer: a statement that the views expressed in the submitted article are his or her own and not an official position of the institution or funder.

  References: Authors should provide direct references to original research sources whenever possible. References should not be used by authors, editors, or peer reviewers to promote self-interests. Refer to the journal referencing style downloadable on our *Formatting Requirements* page.
  Style and format

  File format

- Manuscript files can be in the following formats: DOC, DOCX, or RTF. Microsoft Word documents should not be locked or protected.

- LaTeX documents (.tex) should be converted into Microsoft Word (.doc) before submission online.
- Rich Text Format (RTF): Users of other word processing packages should save or convert their files to RTF before uploading. Many free tools are available that will make this process easier.

Length
Manuscripts should adhere to the author guidelines of the journal. There are restrictions on word count, number of figures, or amount of supporting information.

Font
Use a standard font size and any standard font family.

Special characters
Do not use the font named 'Symbol'. To add symbols to the manuscript, use the Insert → Symbol function in your word processor or paste in the appropriate Unicode character. Refer to our AOSIS house style guide on mathematical and Unicode font guidelines.

Headings
Ensure that formatting for headings is consistent in the manuscript. Limit manuscript sections and sub-sections to four heading levels. To avoid confusion during the review and production process, ensure that the different heading levels used in your work are visually distinct from one another. The simplest way to achieve this is to use different font sizes and/or a combination of bold/italics for different heading levels.

Keywords
Identify eight keywords that represent the content of your manuscript and are specific to your field or sub-field, ensure to separate each keyword with a semi-colon. Test your keywords: when you enter your keywords into the various journal and academic databases like Google Scholar, do the results include papers similar to your topic? If not, revise the terms until they do.

Layout and spacing
Manuscript text should have a 1.5 line spacing.

Page and line numbers
Include page numbers and line numbers in the manuscript file. Use continuous line numbers (do not restart the numbering on each page).

Footnotes
Footnotes are not ideal. If your manuscript contains footnotes, move the information into the main text or the reference list, depending on the content.

Language
Manuscripts must be written in British English, according to the Oxford English Dictionary (avoid Americanisms [e.g. use 's' and not 'z' spellings] and set your version of Microsoft Word default language to UK English). Refer to the AOSIS house style guide for more information.

Abbreviations
Define abbreviations upon first appearance in the text. Do not use non-standard abbreviations unless they appear at least three times in the text. Keep abbreviations to a minimum.

Illustrations
Illustrations fall into two categories:

- Figures: Photographs, drawings, diagrams, graphs, flowcharts, maps, etc.
- Tables and/or Boxes: Text and/or numbers arranged in orderly columns and rows.
  Every time a Figure, Table and/or Box is presented in your manuscript, it should be referred to three times:
- In a legend, which includes a number, a title, and its source. The legend is placed below a Figure and above a Table and/or Box. The source section should consist of the in-text citation, creator or owner and its year of creation, and any other attribution required as stipulated by the permission received (person and place) to reproduce.
- In the body of your written manuscript. You should include an in-text citation and a sentence or two about the image explaining what it illustrates and why it is there.
- As a reference entry within your reference list.

AOSIS house style
The manuscript must adhere to the AOSIS house style guide.

Referencing style guide
The manuscript must adhere to the Harvard referencing style.

Permission to use copyright material

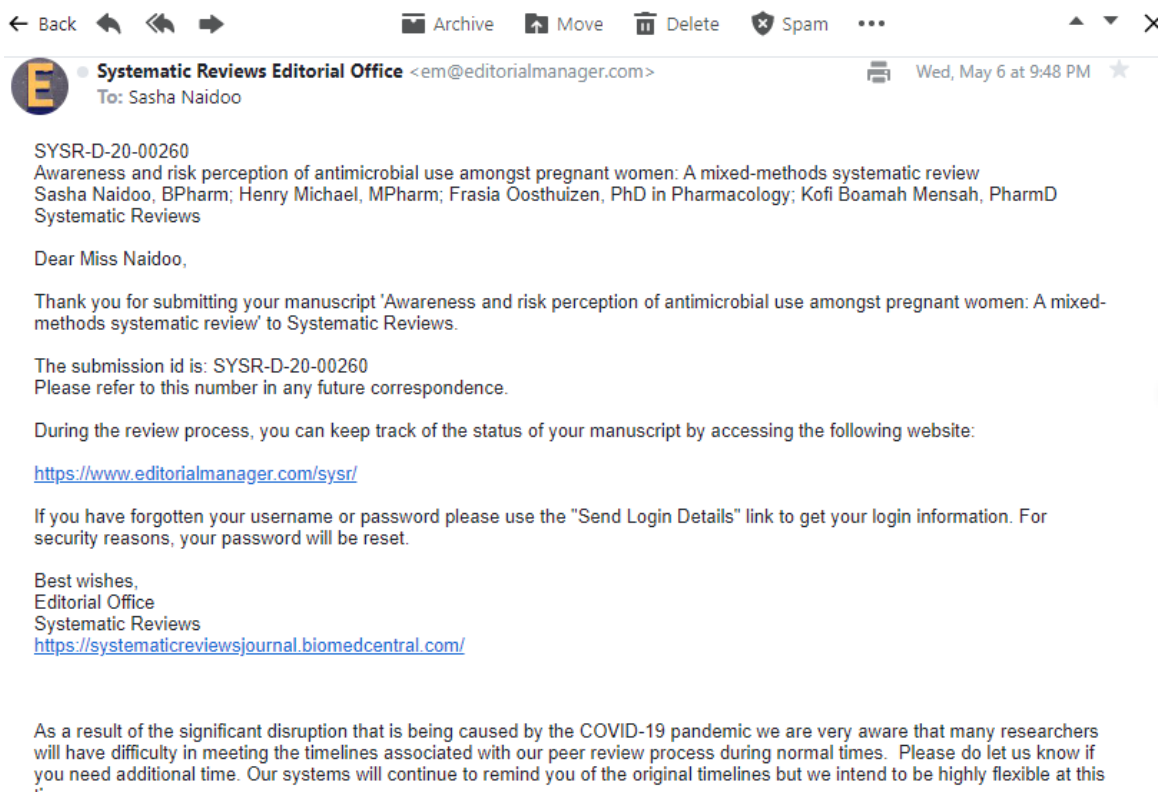
Annexure 6: Cover page and confirmation of submission to BMC Systematic Reviews

Systematic Reviews

Awareness and risk perception of antimicrobial use amongst pregnant women: A mixed-methods systematic review

--Manuscript Draft--

Manuscript Number:	
Full Title:	Awareness and risk perception of antimicrobial use amongst pregnant women: A mixed-methods systematic review
Article Type:	Research
Funding Information:	
Abstract:	Background The perception of risk significantly affects the decision to take an antibiotic during pregnancy. Understanding women's beliefs and their demographic and socio-cultural context allow for effective antimicrobial treatment among this vulnerable population. This study aimed to explore the perceived risk of antimicrobial therapy and to assess the factors that influence its use in the pregnant population. Method PubMed, Scopus, CINAHL, and Psycinfo were systematically searched by two reviewers for studies published between January 2000 to December 2019. The quality of the selected articles was critically appraised using a standardised tool. We stratified



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Systematic Reviews Editorial Office <em@editorialmanager.com> Wed, May 6 at 9:48 PM

To: Sasha Naidoo

SYSR-D-20-00260
Awareness and risk perception of antimicrobial use amongst pregnant women: A mixed-methods systematic review
Sasha Naidoo, BPharm; Henry Michael, MPharm; Frasia Oosthuizen, PhD in Pharmacology; Kofi Boamah Mensah, PharmD
Systematic Reviews

Dear Miss Naidoo,

Thank you for submitting your manuscript 'Awareness and risk perception of antimicrobial use amongst pregnant women: A mixed-methods systematic review' to Systematic Reviews.

The submission id is: SYSR-D-20-00260
Please refer to this number in any future correspondence.

During the review process, you can keep track of the status of your manuscript by accessing the following website:

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Best wishes,
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As a result of the significant disruption that is being caused by the COVID-19 pandemic we are very aware that many researchers will have difficulty in meeting the timelines associated with our peer review process during normal times. Please do let us know if you need additional time. Our systems will continue to remind you of the original timelines but we intend to be highly flexible at this

Annexure 7: Submission guidelines for BMC Systematic reviews

Preparing your manuscript

The information below details the section headings that you should include in your manuscript and what information should be within each section.

Please note that your manuscript must include a 'Declarations' section including all of the subheadings (please see below for more information).

Title page

The title page should:

- present a title that includes, if appropriate, the study design e.g.:
    - "A versus B in the treatment of C: a randomized controlled trial", "X is a risk factor for Y: a case control study", "What is the impact of factor X on subject Y: A systematic review"
    - or for non-clinical or non-research studies a description of what the article reports
- list the full names, institutional addresses and email addresses for all authors
    - if a collaboration group should be listed as an author, please list the Group name as an author. If you would like the names of the individual members of the Group to be searchable through their individual PubMed records, please include this information in the “Acknowledgements” section in accordance with the instructions below
- indicate the corresponding author

Abstract

The Abstract should not exceed 350 words. Please minimize the use of abbreviations and do not cite references in the abstract. Reports of systematic reviews should follow the PRISMA extension for abstracts. The abstract must include the following separate sections:

- **Background:** the context and purpose of the study
- **Methods:** how the study was performed and statistical tests used
- **Results:** the main findings
- **Conclusions:** brief summary and potential implications
- **Systematic review registration:** if your systematic review is registered in a publicly accessible registry, include the name of the registry and registration number.

Keywords

Three to ten keywords representing the main content of the article.

Background

The Background section should explain the background to the study, its aims, a summary of the existing literature and why this study was necessary or its contribution to the field.

Methods

The methods section should include:

- the aim, design and setting of the study
- the characteristics of participants or description of materials
- a clear description of all processes, interventions and comparisons. Generic drug names should generally be used. When proprietary brands are used in research, include the brand names in parentheses
- the type of statistical analysis used, including a power calculation if appropriate

Results

This should include the findings of the study including, if appropriate, results of statistical analysis which must be included either in the text or as tables and figures.

Discussion

This section should discuss the implications of the findings in context of existing research and highlight limitations of the study.

Conclusions

This should state clearly the main conclusions and provide an explanation of the importance and relevance of the study reported.

List of abbreviations

If abbreviations are used in the text they should be defined in the text at first use, and a list of abbreviations should be provided.

Declarations

All manuscripts must contain the following sections under the heading 'Declarations':

- Ethics approval and consent to participate
- Consent for publication
- Availability of data and materials
- Competing interests
- Funding
- Authors' contributions
- Acknowledgements
- Authors' information (optional)

Please see below for details on the information to be included in these sections.

If any of the sections are not relevant to your manuscript, please include the heading and write 'Not applicable' for that section.

Ethics approval and consent to participate

Manuscripts reporting studies involving human participants, human data or human tissue must:

- include a statement on ethics approval and consent (even where the need for approval was waived)
- include the name of the ethics committee that approved the study and the committee's reference number if appropriate

Studies involving animals must include a statement on ethics approval and for experimental studies involving client-owned animals, authors must also include a statement on informed consent from the client or owner.

See our editorial policies for more information.

If your manuscript does not report on or involve the use of any animal or human data or tissue, please state "Not applicable" in this section.

Consent for publication

If your manuscript contains any individual person's data in any form (including any individual details, images or videos), consent for publication must be obtained from that person, or in the case of children, their parent or legal guardian. All presentations of case reports must have consent for publication.

You can use your institutional consent form or our consent form if you prefer. You should not send the form to us on submission, but we may request to see a copy at any stage (including after publication).

See our editorial policies for more information on consent for publication.

If your manuscript does not contain data from any individual person, please state "Not applicable" in this section.

Availability of data and materials

All manuscripts must include an 'Availability of data and materials' statement. Data availability statements should include information on where data supporting the results reported in the article can be found including, where applicable, hyperlinks to publicly archived datasets analysed or generated during the study. By data we mean the minimal dataset that would be necessary to interpret, replicate and build upon the findings reported in the article. We recognise it is not always possible to share research data publicly, for instance when individual privacy could be compromised, and in such instances data availability should still be stated in the manuscript along with any conditions for access.

Data availability statements can take one of the following forms (or a combination of more than one if required for multiple datasets):

- The datasets generated and/or analysed during the current study are available in the [NAME] repository, [PERSISTENT WEB LINK TO DATASETS]
- The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

- All data generated or analysed during this study are included in this published article [and its supplementary information files].
- The datasets generated and/or analysed during the current study are not publicly available due [REASON WHY DATA ARE NOT PUBLIC] but are available from the corresponding author on reasonable request.
- Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.
- The data that support the findings of this study are available from [third party name] but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of [third party name].
- Not applicable. If your manuscript does not contain any data, please state 'Not applicable' in this section.

More examples of template data availability statements, which include examples of openly available and restricted access datasets, are available here.

BioMed Central also requires that authors cite any publicly available data on which the conclusions of the paper rely in the manuscript. Data citations should include a persistent identifier (such as a DOI) and should ideally be included in the reference list. Citations of datasets, when they appear in the reference list, should include the minimum information recommended by DataCite and follow journal style. Dataset identifiers including DOIs should be expressed as full URLs. For example:

Hao Z, AghaKouchak A, Nakhjiri N, Farahmand A. Global integrated drought monitoring and prediction system (GIDMaPS) data sets. figshare. 2014. http://dx.doi.org/10.6084/m9.figshare.853801

With the corresponding text in the Availability of data and materials statement:

The datasets generated during and/or analysed during the current study are available in the [NAME] repository, [PERSISTENT WEB LINK TO DATASETS].

If you wish to co-submit a data note describing your data to be published in *BMC Research Notes*, you can do so by visiting our submission portal. Data notes support open data and help authors to comply with funder policies on data sharing. Co-published data notes will be linked to the research article the data support (example).

For more information please email our Research Data Team.

Competing *interests*

All financial and non-financial competing interests must be declared in this section.

See our editorial policies for a full explanation of competing interests. If you are unsure whether you or any of your co-authors have a competing interest please contact the editorial office.

Please use the authors initials to refer to each authors' competing interests in this section.

If you do not have any competing interests, please state "The authors declare that they have no competing interests" in this section.

Funding

All sources of funding for the research reported should be declared. The role of the funding body in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript should be declared.

Authors' contributions

The individual contributions of authors to the manuscript should be specified in this section. Guidance and criteria for authorship can be found in our editorial policies.

Please use initials to refer to each author's contribution in this section, for example: "FC analysed and interpreted the patient data regarding the haematological disease and the transplant. RH performed the histological examination of the kidney and was a major contributor in writing the manuscript. All authors read and approved the final manuscript."

Acknowledgements

Please acknowledge anyone who contributed towards the article who does not meet the criteria for authorship including anyone who provided professional writing services or materials.

Authors should obtain permission to acknowledge from all those mentioned in the Acknowledgements section.

See our editorial policies for a full explanation of acknowledgements and authorship criteria.

If you do not have anyone to acknowledge, please write "Not applicable" in this section.

Group authorship (for manuscripts involving a collaboration group): if you would like the names of the individual members of a collaboration Group to be searchable through their individual PubMed records, please ensure that the title of the collaboration Group is included on the title page and in the submission system and also include collaborating author names as the last paragraph of the "Acknowledgements" section. Please add authors in the format First Name, Middle initial(s) (optional), Last Name. You can add institution or country information for each author if you wish, but this should be consistent across all authors.

Please note that individual names may not be present in the PubMed record at the time a published article is initially included in PubMed as it takes PubMed additional time to code this information.

Authors' information

This section is optional.

You may choose to use this section to include any relevant information about the author(s) that may aid the reader's interpretation of the article and understand the standpoint of the author(s). This may include details about the authors' qualifications, current positions they hold at institutions or societies,

or any other relevant background information. Please refer to authors using their initials. Note this section should not be used to describe any competing interests.

Footnotes

Footnotes can be used to give additional information, which may include the citation of a reference included in the reference list. They should not consist solely of a reference citation, and they should never include the bibliographic details of a reference. They should also not contain any figures or tables.

Footnotes to the text are numbered consecutively; those to tables should be indicated by superscript lower-case letters (or asterisks for significance values and other statistical data). Footnotes to the title or the authors of the article are not given reference symbols.

Always use footnotes instead of endnotes.

References

Examples of the Vancouver reference style are shown below.

See our editorial policies for author guidance on good citation practice

Web links and URLs: All web links and URLs, including links to the authors' own websites, should be given a reference number and included in the reference list rather than within the text of the manuscript. They should be provided in full, including both the title of the site and the URL, as well as the date the site was accessed, in the following format: The Mouse Tumor Biology Database. http://tumor.informatics.jax.org/mtbwi/index.do. Accessed 20 May 2013. If an author or group of authors can clearly be associated with a web link, such as for weblogs, then they should be included in the reference.

Example reference style:

Article within a journal

Smith JJ. The world of science. Am J Sci. 1999;36:234-5.

Article within a journal (no page numbers)

Rohrmann S, Overvad K, Bueno-de-Mesquita HB, Jakobsen MU, Egeberg R, Tjønneland A, et al. Meat consumption and mortality - results from the European Prospective Investigation into Cancer and Nutrition. BMC Medicine. 2013;11:63.

Article within a journal by DOI

Slifka MK, Whitton JL. Clinical implications of dysregulated cytokine production. Dig J Mol Med. 2000; doi:10.1007/s801090000086.

Article within a journal supplement

Frumin AM, Nussbaum J, Esposito M. Functional asplenia: demonstration of splenic activity by bone marrow scan. Blood 1979;59 Suppl 1:26-32.

Book chapter, or an article within a book

Wyllie AH, Kerr JFR, Currie AR. Cell death: the significance of apoptosis. In: Bourne GH, Danielli JF, Jeon KW, editors. International review of cytology. London: Academic; 1980. p. 251-306.

OnlineFirst chapter in a series (without a volume designation but with a DOI)

Saito Y, Hyuga H. Rate equation approaches to amplification of enantiomeric excess and chiral symmetry breaking. Top Curr Chem. 2007. doi:10.1007/128_2006_108.

Complete book, authored

Blenkinsopp A, Paxton P. Symptoms in the pharmacy: a guide to the management of common illness. 3rd ed. Oxford: Blackwell Science; 1998.

Online document

Doe J. Title of subordinate document. In: The dictionary of substances and their effects. Royal Society of Chemistry. 1999. http://www.rsc.org/dose/title of subordinate document. Accessed 15 Jan 1999.

Online database

Healthwise Knowledgebase. US Pharmacopeia, Rockville. 1998. http://www.healthwise.org. Accessed 21 Sept 1998.

Supplementary material/private homepage

Doe J. Title of supplementary material. 2000. http://www.privatehomepage.com. Accessed 22 Feb 2000.

University site

Doe, J: Title of preprint. http://www.uni-heidelberg.de/mydata.html (1999). Accessed 25 Dec 1999.

FTP site

Doe, J: Trivial HTTP, RFC2169. ftp://ftp.isi.edu/in-notes/rfc2169.txt (1999). Accessed 12 Nov 1999.

Organization site

ISSN International Centre: The ISSN register. http://www.issn.org (2006). Accessed 20 Feb 2007.

Dataset with persistent identifier

Zheng L-Y, Guo X-S, He B, Sun L-J, Peng Y, Dong S-S, et al. Genome data from sweet and grain sorghum (Sorghum bicolor). GigaScience Database. 2011. http://dx.doi.org/10.5524/100012.

Figures, tables and additional files

See General formatting guidelines for information on how to format figures, tables and additional files.

Appendices

Appendix 1: Data collection template

Data collection template

Site: Inkosi Albert Luthuli Hospital

Date:

Time:

Time period: January – July 2019

Inclusion Criteria:

- Female
- Pregnant
- 18 years of age and over
- Treated with an antibiotic

Collected by:

Patient no:	Patients demographics (Age, race, employment status, occupation, educational level, marital status, no. of children)	Inpatient/outpatient	If inpatient: How many days were spent in hospital	Trimester/ Gestational period	Diagnosis/ reason for administering the chosen antibiotic	Was sensitivity testing done: Y/N	Prescriber	Generic name of antibiotic/s prescribed Eg: Amoxicillin	Brand name of antibiotic /s Prescribed Eg: Moxypen	Class of antibiotic/s prescribed	Dosage/strength, frequency and quantity of the antibiotic/s	Dosage form	Duration of treatment	Reported side effects	Any other complications E.g. HIV positive , Diabetic, Hypertensive, high risk patient, previous miscarriage/pneumonia	Cost of treatment	Other

Appendix 2: Search Strategy for Medline via Pubmed

Theme 1: Risk perception

Risk *OR benefit* AND perception* OR perceived

Theme 2: Pregnancy

Pregnancy OR pregnant OR ante-natal OR antenatal

Theme 3: antibiotics

Antibiotic* OR anti-bacterial OR antibacterial OR drug* OR medicine* OR medication

Theme 4: awareness

Awareness

Appendix 3: PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4-5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4-5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4-7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	33-34
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4-5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5-6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4-7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2)	6

		for each meta-analysis.	

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8-9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	10,11,25-28
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	11, 25-28
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	12-18
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	19-24
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	24
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	24
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	25

Appendix 4: Search strategy for the systematic review

Date	Database searched	Search Strategy	Number of results
Original search			
21/10/19	Medline via Pubmed	**((((((((((Risk *[Text Word] OR benefit*[Text Word])) AND (perception*[Text Word] OR awareness[Text Word] OR perceived[Text Word]))) AND (pregnancy[Text Word] OR pregnant[Text Word] OR ante-natal[Text Word] OR antenatal[Text Word]))) AND (antibiotic*[Text Word] OR anti-bacterial[Text Word] OR antibacterial[Text Word] OR drug*[Text Word] OR medicine*[Text Word] OR medication[Text Word]))))) AND ("2000/01/01"[PDat] : "2019/12/31"[PDat]) AND English[lang])** Sort by: **Best Match** Filters: **Publication date from 2000/01/01 to 2019/12/31; English**	1003
22/10/19	scopus	Risk W/3 perception AND (pregnancy OR	263

		pregnant) AND antibiotic* Limited to 2000-2019 english	
22/10/19	Psychinfo	(risk perception or perceived risk) AND (pregnancy or pregnant) AND (antibiotics or antibacterial or antimicrobials or drugs or medicines) Limited 2000-2019 English only	195
23/10/19	CINAHL	(risk perception or perceived risk) AND (pregnancy or pregnant) AND (antibiotics or antibacterial or antimicrobials or drugs or medicines) Limited 2000-2019 English only	78
Total before duplicates			1539
Number of duplicates			358
Total after de-duplication			**1181**
Articles selected after title and abstract screening			**42** **(1139 did not meet the inclusion criteria)**

Articles selected after full screening			**11**
24/10/18	Grey literature- Google scholar	Risk perception of antibiotics in pregnancy	**3**
			14

Appendix 5: Critical appraisal tool (MMAT) for the systematic review is attached as a supplementary file.

Appendix 6: Data extraction template for the systematic review is attached as a supplementary file.