COMPARISON OF THREE LEVELS OF ASCERTAINMENT OF ANTENATAL MEDICATION USE AT GUGULETHU MIDWIFE OBSTETRIC UNIT.

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Contents

I. DECLARATION

I, Jani van der Hoven, hereby declare that the work on which this dissertation/thesis is based on my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

In the case of multi-authored published or unpublished papers I will be the lead author and my contribution as agreed to by the relevant co-authors will be outlined in each publication. In addition, I have detailed contributions in the preface to this thesis and in the introduction to each chapter.

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II. ABSTRACT

Background

The use of medicines and/or remedies among pregnant women is common. Pregnant women are generally excluded from clinical trials due to ethical reasons. There are therefore minimal data available about the safety of most drugs during pregnancy by the time they come to the market, and post-marketing evaluation of medicine use during pregnancy is required.

In South-Africa, with mass treatment campaigns for Tuberculosis (TB) and Human Immunodeficiency Virus (HIV), the introduction of new therapeutic agents and frequent self-medication, it is important for reliable methods to determine medicine exposures, including the frequency and timing of use, to support such evaluations.

Databases about medication exposures are promising resources for pharmaco-epidemiological investigations, however the optimal method of ascertainment of medicine use during pregnancy is uncertain. Different data sources could also be better for different types of medication. To improve the quality of data, a combination of data sources may be ideal but time-consuming and expensive. By looking at and comparing three data sources: 1) self-report, 2) clinician records and 3) electronic dispensing systems, we aimed to identify the optimal method of ascertainment of antenatal medicine use for multiple medication types.

Methods

The aim of this investigation was to provide a more comprehensive reflection of the drug exposures during pregnancy and to make recommendations to strengthen routine clinical data capturing to improve maternity case reporting. The data of 988 pregnant women seeking antenatal care at Gugulethu Midwife Obstetric Unit (GMOU) in Cape Town between 2016 and

2018 were used. The three data sources consisted of self-reports gathered by an interviewer-administered questionnaire at up to three antenatal visits to the GMOU; clinical records as recorded in the Pregnancy Exposure Registry (PER); and linked electronic dispensing data obtained from the Provincial Health Data Centre (PHDC) of the Western Cape Department of Health.

Medication exposure data were coded using the Anatomical Therapeutic Chemical (ATC) Classification system, an internationally acknowledged system to classify medicine maintained by the WHO. ATC codes were assigned to active ingredients, depending on the therapeutic indication.

The three data sources were then assessed in terms of missing or overlapping information and evaluated on the level of agreement between sources using Spearman's rank coefficient and Cohen's Kappa.

Results

According to the Spearman rank test, the PER and PHDC datasets as a whole showed the highest correlation both at 1st and 5th ATC level. The overlaps between the datasets were poor and the Kappa agreement between the sources was low for most therapeutic classes, except for HIV treatments. An "almost perfect" Kappa agreement existed between anti-diabetic medication (ATC A10) reported in the self-report and PHDC datasets. Traditional, herbal, complementary and home remedies were only reported in the self-report dataset.

Conclusion

We found an overall poor agreement between data sources, with one alone not able to effectively capture all data. The datasets should thus be used in conjunction to ensure accurate and reliable record of exposure. Self-report was the best data source for traditional, home, herbal and complementary medicine exposures while the PER provided a better and more complete reflection of influenza vaccines and vitamins.

The best method of ascertaining antenatal medicine exposure therefore depends on the type of medicine being investigated, and choice of data source depends on the objectives of the investigation. This study suggests that PER, PHDC and self-report should ideally be used together since each is critical to ensure accurate, reliable and effective exposure data, although this will have resource and cost implications.

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LIST OF ABBREVIATIONS

ADME	Absorption, distribution, metabolism, elimination
ART	Antiretroviral Therapy
ATC	Anatomical Therapeutic Chemical
BANC	Basic Antenatal Clinics
EHR	Electronic Health Records
EMA	European Medicines Agency
GI	Gastrointestinal
GMOU	Gugulethu Midwife Obstetric Unit
HIV	Human Immunodeficiency Virus
HREC	Human Research Ethics Committee
IM	Intramuscular
INH	Isoniazid
IV	Intravenous
MCR	Maternity Case Record
NSAID	Non-Steroidal Anti-Inflammatory
OTC	Over-the-counter
PER	Pregnancy Exposure Registry
PHDC	Public Health Data Centre
PMTCT	Prevention of mother-to-child transmission
SOP	Standard Operating Procedures
TB	Tuberculosis
UCT	University of Cape Town
USA	United States of America

Vd	Volume of distribution
WHO	World Health Organisation
WLHIV	Women living with HIV

GLOSSARY

ATC system:	The ATC classification system is an internationally acknowledged system to classify medicine maintained by the WHO (WHO, 1996).
Clinical trials:	Any study in human subjects that are intended to discover or confirm the clinical, pharmacological, pharmacokinetic and/or pharmacodynamical effects of an investigational drug with the goal to establish the safety and efficacy of the drug.
Complementary remedies:	Refers to a broad set of remedies that are not part of the conventional medicinal approach. Complementary remedies can be utilized as mono-therapy or alongside other medication.
Exposure:	Any medicine or remedies that a participant, particularly pregnant women, may have used during the course of their pregnancy.
Herbal remedies:	Treatments that are prepared from medicinal plants.
Home remedies:	Treatments that does not require a prescription, where the effectiveness is supported by factors such as family, or cultural stories and/or rituals.
Master list:	A consolidated list of all the medication each participant used at least once in any of the three datasets. Data of all three data sources were combined into a master list.
Observational study:	A study where the researchers do not have control over the therapy of the research participants, but where the researcher observes and evaluates the results of the ongoing medical therapy.
Pharmaco-epidemiological:	The study of the utilization and the effects of medication in large number of people.
Pharmacokinetics:	The study of the absorption, distribution, metabolism and excretion of medication.
Pharmacovigilance:	The detection, assessment, understanding and prevention of adverse effects and medication-related problems.

Post-marketing surveillance:	The monitoring of medication after the approval for use.
Prospective data:	In prospective studies, the participants are followed over time and data is gathered in accordance with the study design.
Retrospective study:	A retrospective study utilizes existing data. Researchers study the medical histories of the participants.
Safety:	When there is substantive proof of the absence of harm of a medicinal product.
Self-medication:	Medication that does not require a doctor's prescription and is available over-the-counter.
Traditional remedies:	Preparations that are prepared from active ingredients with a natural origin (Alostad et al., 2018).
Validity:	Refers to the accuracy of data were collected.

1. Introduction

There are many reasons why women take medication during pregnancy. There is widespread use of medicine among women who are of childbearing age (EMA, 2005). More than 50% of pregnancies are unplanned and in the first few weeks of pregnancy, many women are exposed to agents before they know they are pregnant (Kennedy *et al.*, 2004). In addition, taking medication during pregnancy could be important for the maintenance of maternal and fetal wellbeing (Benevent *et al.*, 2017). Pregnant women take medicine to treat acute and chronic illnesses, pregnancy symptoms, infections and obstetric complications. The prevention of mother-to-child transmission of HIV (PMTCT) is emphasized in antenatal care and the World Health Organization (WHO) recommends that pregnant women who are living with HIV (WLHIV) remain on antiretroviral therapy (ART) for the PMTCT (Omonaiye *et al.*, 2018).

The use of medicine and remedies in pregnancy are reported in literature, although most data are from the developed world, with Africa under-represented. A systematic review of peer-reviewed literature published from 1989 to 2010 about the use of prescription medication on out-patients in developed countries found that between 27.0 – 93.0% of women filled a minimum of one prescription during their pregnancy, excluding vitamin supplements (Daw *et al.*, 2011).

In Africa, self-medication practices among pregnant women in a Nigerian cohort was investigated and found that 63.8% of pregnant women reported to self-medicate with herbal, over the counter (OTC) and prescription medication (Yusuff & Omarusehe, 2011). In Zimbabwe, a cross-sectional survey on the prevalence of traditional medicine use during pregnancy, conducted by an interviewer-administered questionnaire, found that the use of traditional medication during pregnancy and labour was 69.9% (Mawoza *et al.*, 2019). The

maternal use of traditional medicine was also reported in a WHO Exposure Registry study in Ghana, Kenya and Uganda: data demonstrated widespread use of traditional medicine, OTC medicine, as well as occasional alcohol use during pregnancy, and the authors emphasised the importance of discovering ways of determining accurate antenatal drug exposure data (Allen *et al.,* 2014).

There has been growth in the antenatal utilisation of homeopathic and herbal remedies because it is commonly believed that there will be no teratogenic impact on the fetus because it is "natural"; however, much of the safety evidence of homeopathic and herbal remedies is anecdotal and not all the remedies have been scientifically tested. A systematic review of the safety of the antenatal use of herbal and homeopathic remedies suggested that larger investigations must be conducted, particularly in South Africa, to establish the safety and the efficacy of remedies that are commonly used by pregnant women (Boltman-Binkowski, 2016). There is a lack of data about the safety of non-prescribed medication and remedies (including traditional medication and herbal medication), which are broadly utilised; however, infrequently investigated in pregnant women (Allen *et al.,* 2014).

As portrayed in the current literature, it is clear that the use of pharmaceuticals and other treatments are common among pregnant women even when the advantages and/or the potential risks are unknown or inadequately characterised (Stock & Norman, 2019).

Numerous studies during antenatal care show use of medications with potential dangers in pregnancy (Daw *et al.,* 2011). However, evidence for fetal adverse effects of antenatal medication exposure in humans are rare. This is because pregnant women are often excluded from clinical trials for ethical reasons, unless the medication is specifically intended for

antenatal use. In most cases, contraception must be used if a study includes women who are of childbearing age (EMA, 2005).

While pre-clinical information can be used to evaluate the potential toxicity of a drug; due to the limited information about teratogenicity and potential harmful effects on the fetus, post-marketing surveillance of antenatal medication use is essential to detect therapy-induced fetal effects (Benevent *et al.*, 2017).

There are thus minimal data on the safety, long-term effects and the pharmacokinetics (PK) of most drugs during pregnancy, with more than 98% having inadequate safety and/or PK data required to optimise dosing in pregnant women (Stock & Norman, 2019). Active ingredients that are lipid soluble, have a low molecular weight and are un-ionised can cross the placental barrier to a greater extent. Agents that don't cross the placental barrier may also have fetal impacts by adjusting the maternal physiology (Benevent *et al.*, 2017). The physiological changes during pregnancy may affect the absorption, distribution, metabolism and elimination (ADME) of drugs with possible implications for efficacy and toxicity. Although medicines or dosages may need to be adjusted during pregnancy, pregnant women do often need to continue treating pre-existing chronic conditions (Benevent *et al.*, 2017).

While only a small number of agents have been shown to have a definite teratogenic effect, the limited data on the teratogenicity of a medication does not imply safety (Rossiter *et al.*, 2014). As a result, pregnant women may be exposed to an unsafe medicine that can potentially have teratogenic complications (Mitchel *et al.*, 2011) or denied access to a safe medicine for fear of adverse effects that are unfounded. In the absence of human data, information about animal reproductive toxicology studies is typically all that is presented for the labelling of a

medication. Translating the animal risks into accurate evaluation of teratogenic effects in humans is challenging and sometimes impossible. Non-clinical studies can be useful to assess the risk in humans, and the information accessible to researchers to assess the reproductive risk after a new treatment is approved is from non-clinical investigations (EMA, 2005). However, it is not sufficient.

Therefore, scientifically acceptable information about antenatal medication exposure is an essential public health need. Without data about antenatal drug exposure, it is challenging for health care providers to advise women about the potential risks of taking a certain medication during their pregnancy. There is a need for sufficient investment and legislation to support the consideration of pregnant participants in appropriately regulated clinical trials to support drug development for obstetric and non-obstetric conditions (Stock & Norman, 2019) and help prevent another thalidomide tragedy, where worldwide about 10 000 infants were born with deformed limbs due to the mother being exposed to this medication (Council for International Organizations of Medical Sciences, 2016).

In low-income countries, such as Africa, there is a shortage of post-marketing surveillance of medication. This can delay or inhibit the determining of the safety of essential medication for illnesses that are prevalent in areas where pregnant women are especially vulnerable (Mehta *et al.*, 2012). It is also less likely that pharmaceutical companies will invest in research in resource limited settings (Ardal & Rottingen, 2015). It is therefore essential that in low-income countries cost-effective methods are established to ascertain the antenatal medicine exposure in populations that have a high burden of illness (Sangeda *et al.*, 2014). It is a particular need to determine the safety during pregnancy of treatments in areas with an increased prevalence of disease, for example, HIV/AIDS, TB and malaria (Allen *et al.*, 2014).

With the introduction of new treatments and vaccines, it is essential that reliable methods are used for ascertaining exposures during pregnancy. This is of utmost importance so that pregnant women are not denied access to medication but will prevent them being exposed to medication that is not safe during pregnancy. It is important to create standards for the recording of antenatal drug exposure (Daw *et al.*, 2011). The systematic collection can be used to signal potential complications for further investigation (Kennedy *et al.*, 2004). Prospective post-approval pregnancy exposure data are often utilized to monitor safety, despite the fact that existing exposure databases could likewise be utilized. Additionally, the data can be used to recognise risks and to quantify the long-term effect of a medication (EMA, 2005) and be used to monitor the suspected complications raised by studies in animals, clinical trials or post-marketing case reports. (Kennedy *et al.*, 2004).

In South-Africa with the mass treatment campaigns for TB and HIV, and the introduction of new therapeutic agents with an uncertain safety profile in pregnancy, it is important that we also establish reliable methods for ascertaining exposures in pregnancy. Due to the ethical challenges of pregnant participants in clinical trials, the only feasible option is to assess the safety of medication through different pregnancy exposure databases and other observational studies. In this dissertation I compared three methods, 1) self-report, 2) clinician records and 3) electronic dispensing data, to identify the optimal method to collect data for multiple medication types. By comparing the three data-sources we can determine whether one data-source can replace another - which is a time-and-resources-saving approach, or, if a combination of all three sources must be utilised to gather exposure data.

1.1 Self report

Self-report is a non-invasive way to reach many participants to gather information about antenatal drug exposure. Information can be gathered about compliance to therapy, clinical and obstetric history, i.e., researchers can tailor questionnaires to demand specific data for the analysis. However, participants may interpret questions differently and answers may not always be accurate due to a number of reasons (Gliklich *et al.,* 2014). This is because the answers of participants rely on the interpretation and comprehension of the questions (Gliklich et al., 2014). Participants may also have difficulty recalling medications accurately which may be improved though memory aids, such as the medication insert, the container or photos of the packaging (Strom, 2005:710). Moreover, as was seen the WHO Pregnancy Exposure Registry Study, women may have reservations about revealing some of their medicine use to antenatal staff because of the expected negative responses (Allen et al., 2014). There may in particular be an under-reporting of data for conditions such as sexually transmitted diseases, HIV or mental illnesses due to the fear of stigmatisation, loss of confidentiality and embarrassment.

The maternal interview approach raises concern about the accuracy of recall and introduces an element of recall bias (Strom, 2005:506). The way information is obtained is important in order to reduce this; a carefully designed questionnaire can significantly decrease the likelihood of under-reporting by prompting participants to consider medicines they may not have done without sufficient detail. Patients may have difficulty recalling medications accurately; yet these data can be necessary for pharmaco-epidemiology studies that ascertain data using questionnaires. Approaches have been developed to obtain information more accurately; for example, women can be asked to bring their medication or a list of their medication to the maternal interview.

1.2 Clinician records

Clinician records also rely on self-report to a certain extent. These are the notes and prescriptions a clinician records in a patient's hospital or clinic file. Clinician records may provide more complete and accurate data concerning the diagnosis of the patient and the indication of the medication used by the participant, although there is a risk of exposure misclassification if the women do not take the therapy as prescribed (Gliklich *et al.,* 2014). It is common, however, for records to be missing, inaccurate or unclear in clinical case notes, especially if the resources are limited as in South Africa. The infrastructure for the maintaining and storing of records may also be poor. (Mehta *et al.,* 2018). In lower-income regions, there is often unregulated access to medication (Mehta *et al.,* 2018). This can potentially have an influence on the accuracy of the recording of exposure data (Allen *et al.,* 2014).

1.3 Electronic dispensing data

Electronic health records (EHR) are the most frequently-used data source for research into pharmacoepidemiological studies (Okoli *et al.,* 2021). These data are generally more accessible, and it is a less time-consuming way to gather information about antenatal medication exposure (Franklin & Thorn, 2019). Electronic dispensing systems provide a comprehensive description of patient data such as patient demographics and medication history. Investigations using these databases can progress our knowledge of prescribing characteristics to improve patient care (Okoli *et al.,* 2021). However, electronic dispensing systems can only record information when patients receive their medication from such systems and will not capture any medicine or remedies that the participant received elsewhere. Some records of specialist/higher level care will not reflect in primary health care (PHC) databases, for example, private prescriptions, atypical antipsychotics, cancer treatments and acute hospital prescriptions, such as intravenous (IV) antibiotics (Okoli *et al.,* 2021). In addition, when using

the data of electronic dispensing systems, just like in clinician records, there is a potential risk of exposure misclassification due to the pregnant women not complying or completely stopping with therapy not accounted for by the electronic system (Gliklich *et al.*, 2014).

The best methods for collecting these data thus remain uncertain and it may be that different methods are better for different types of medication.

2. Literature review

2.1 Background

The use of medicine among pregnant women and the effect on maternal and fetal wellbeing is a rising public health concern. Medicine and remedy use may cause vulnerability and worry among pregnant women. Because pregnant women are generally excluded from clinical trials, it is hard to assess the real danger of certain agents. Although few data are available about the safety of many medications during pregnancy, some medications (e.g., isotretinoin, thalidomide) are recognised to cause serious birth defects (Fisher *et al*., 2008).

In a study on pregnant women from the United States of America (USA), the most medications that were used by the participants during their pregnancy had inadequate safety information accessible to describe the fetal risks, consequently restricting the opportunity for educated and informed clinical choices about therapy (Thorpe *et al.*, 2013). This represents a critical knowledge gap.

2.2 Objectives

The objective of this review is to evaluate studies that describe or compare antenatal medication exposure by using one or more of the three relevant methods (self-report, clinical records and electronic dispensing data).

Specific objectives are to:

- Describe the prevalence of medicine use during pregnancy in different countries, including African countries.
- Describe the data collection methods for the medications used and which data sources capture the most information.

- Identify areas that require further investigation.

2.3 Search methods

A search for relevant literature was performed through PubMed and Google Scholar. Additional sources included the references of the identified studies. The publications are observational studies and systemic reviews about any of the three relevant methods of ascertaining medication exposure during pregnancy and different patient groups, not specific to pregnancy. Studies were limited to those published in English.

The search on PubMed was conducted using the following search terms:

Medication use during pregnancy,

Pregnancy exposure databases,

Antenatal medication use/medication use during pregnancy,

Report of antenatal medication exposure,

Agreement between self-reported medication/clinician records and/or electronic dispensing data in pregnancy,

Electronic dispensing data during pregnancy,

Clinician records about medication exposure during pregnancy and

PER (Pregnancy Exposure Registry).

2.4 Pharmacovigilance

In 2013, the National department of health piloted a pregnancy exposure registry/ birth defect surveillance programme to assess the impact of ART's on birth outcomes. Pregnancies were evaluated, with the priority being the first trimester exposure. The experiment showed the worth of the PER as a way to evaluate the relationship between exposures throughout

pregnancy and adverse birth outcomes, like stillbirth, premature delivery, low birth weight, death and other abnormalities at birth, while providing evidence of the safety of first line ARV during pregnancy (Ref).

2.5 Summary of the literature on antenatal medicine exposure and exposure data collection methods

2.5.1 Prevalence of medicine use during pregnancy in countries other than South Africa

Pregnant women are increasingly exposed to medications and vaccines. The antenatal use of medicines is often reported in literature, although most data are from the developed world and there is an under-reporting of data from Africa (Yusuff & Omarusehe, 2011). Current literature demonstrates that most pregnant women have utilised at least one medication and/or remedy during their pregnancy. A systematic review of out-patients prescription drug use in developed countries demonstrated that 27.0-93.0% of pregnant women filled at least one prescription (Daw *et al.,* 2011). A study about medication exposure in Europe (Western, Northern and Eastern), North- and South America and Australia found that 81.2% of the women used at least one prescription medication and/or OTC medication during pregnancy (Lupattelli *et al.,* 2014). In the USA, over 90% of women reported that they used one or more medications (prescription and/or OTC) (Mehta *et al.,* 2019). In one multi-ethnic study (Arab/Turkish, Western and women of other countries), 83.8% of pregnant women reported using one or more medications (prescription and/or supplements) (Baraka *et al.,* 2013). In a Chinese cohort, 75.9% of the women reported that they are using one or more medication during the first trimester. The medications and supplements that were most commonly used by these women were folic acid (65.2%), vitamin supplements (14.6%), calcium supplements (12.0%), mineral supplements

(11.1%), Chinese traditional medicine (10.1%) and anti-infective medication (6.5%) (Zhu *et. al.,* 2010). In a Hispanic cohort, the medications and supplements that were most commonly used were herbal medication (19.0%), vitamins (47.0%), prenatal vitamins (77.0%), folic acid (21.0%), OTC medicine (23.0%) and prescription medication (29.0%). Twenty percent of the women in this study believed that herbal medication and vitamin supplements were "natural" and therefore safer to use during pregnancy than prescribed medicine (Bercaw *et al.,* 2010).

2.5.2 Prevalence of medicine use during pregnancy in Africa

Antenatal medicine use is less well described in Africa. In a Nigerian cohort, 63.8% of pregnant women reported to self-medicate with herbal, OTC and prescription medication (Yusuff & Omarusehe, 2011). In a Zimbabwean cohort, 69.9% of the women used traditional medication during pregnancy and labor (Mawoza *et al.,* 2019). In a study from Ghana, Kenya and Uganda, the data portrayed a widespread use of traditional and OTC medicine during pregnancy (Allen *et al.,* 2014).

In Cameroon, 73.2% of the participants took one or more medications during the first trimester of pregnancy; 80.0% was received from the hospital and 12.8% was self-medication. Forty-four percent took anti-infective medication such as antimalarials (33.6%) and antibiotics (20.8%). The other medications that were most used were analgesics (48.8%) and anti-anaemias (38.6%). Sulfadoxine/pyrimethamine, a medication that is contraindicated during the first trimester of pregnancy, was the anti-malarial most commonly (13%) (Leke *et al.,* 2018).

These investigations demonstrate that there is an expanding utilisation of medication among pregnant women across Africa, which can be an indication that there is an increase in access (Leke *et al.,* 2018)

2.5.3 Data collection methods and which data sources capture the most information

One of the general purposes of pregnancy exposure databases is to provide human data on the use of biopharmaceutical products and remedies during pregnancy. Several methods are used to gather clinically relevant data about pregnant women and women who are of childbearing age. There are many different opinions about which method is optimal and there is an absence of guidance on how to select the ideal methods. Electronic databases, dispensing records of the pharmacy, medication registries and self-reports are often utilised as data sources. The reliability and accuracy of the data on the drug exposure timing during pregnancy are two of the main methodological issues. Each system can introduce bias and there is a need for more studies to be conducted about this overlooked topic.

Medication exposure data are essential in pharmaco-epidemiology (Noize *et al.,* 2009). Epidemiological studies often rely on self-reported data as sources to investigate medication exposure (Monster *et al.,* 2002). These may be used alone or in combination with other data sources. Self-report can be subject to misunderstanding, misinterpretation and recall and social desirability bias as described above. Questions about medication use can be interpreted due to different beliefs about possible risks, benefits and cultural context. The information can have inherent methodological complications which can be due to the subjective nature of the data. Information gathered through self-report can also be under-reported (Strom, 2005:735) due to the fear of absence of confidentiality, stigmatisation (Allen *et al.,* 2013) and negative repercussions (Allen *et al.,* 2014).

The validity of the health data that are received through participants' reports about medication exposure is a significant, but under-studied area, especially in settings with limited resources.

The validity of self-report can vary for the different classes of medication (Skurtveit *et al.,* 2008). Studies have found that when antenatal medication is assessed by interviews, the questions must not be limited to open-ended questions, and it is important to also incorporate indication-oriented and/or medication-oriented questions. The more-specific questions provide an opportunity to detect the use of medication, such as of OTC and alternative medication. Recall can be increased if the study participants are provided with a list containing medication names and photographs (Strom & Schinner *et al.,* 2004).

Pharmacy records have been found to give better data if there are long review periods and for patients who use multiple and/or repeat medication. It was suggested that researchers utilise the complementary elements of each method when it is appropriate (de Jong-van den Berg *et al.,* 1993). Monster *et al*., (2002) and Strom & Schinner (2004) deduced that an acceptable agreement exists between medication use that are estimated by electronic pharmacy records and patient self-report (questionnaires and interviews).

2.5.4 Agreement between electronic pharmacy records and self-report in different populations

There are several studies comparing electronic database information and self-reports about medication exposure in different patient groups, not specific to pregnancy (Caskie *et al.,* 2006; Boudreau *et al.,* 2005 and Skurtveit *et al.,* 2008). In general, the recall was negatively affected by time since the medication exposure. There was better recall for illnesses that most people are familiar with, for example: hypertension, asthma and diabetes. The agreement was high for chronic/long-term medication and acute medication was less easily recalled (Monster *et al.,* 2002; Strom & Schinner *et al.,* 2004; Boudreau, *et al*., 2005; Caskie *et al.,* 2006 and Skurtveit *et al.,* 2008).

Agreement was greater for younger and healthier participants, and the age and wellbeing status of the participants, as well as the type of medication, should be considered when the validity of medicine data reported by participants is determined (Caskie *et al.,* 2006). It was indicated that in these populations the electronic pharmacy data can be a significant source of medication data in investigations (Boudreau, et. al. 2005) (Skurtveit *et al.,* 2008) (Caskie *et al.,* 2006) (Strom & Schinner *et al.,* 2004) (Monster *et al.,* 2002).

Several studies compared electronic database data and self-report about medication exposure for specific medication types. In a cohort of patients with hypertension, 71.0% of all medications that the participants were currently on were recalled during the self-report questionnaire and 94.0% of all the medications that were mentioned in the questionnaire were able to be traced in the pharmacy records; the recall sensitivity was 88.0% (Klungel *et al.,* 2000). For patients taking hormone therapy, the datasets demonstrated high levels of agreement and it was preferred to use questionnaires for current medication use and to use pharmacy records for past use (Norell *et al.,* 1998). For patients on psychoactive medication the agreement between the self-report data and the pharmacy data were moderate. Information gathered by questionnaire might underestimate the use of medication due to non-interest and non-participation (Haapea *et al.,* 2010).

2.5.5 Agreement between self-report and electronic medication exposure data in pregnancy

A limited number of studies have been conducted comparing self-report and electronic database data about antenatal medication use and there is an absence of methodological investigations in resource limited settings. Observation of medication safety during pregnancy regularly draw on administrative prescription registries. In a Swedish cohort it was again seen

that the agreement between the clinical antenatal records and information from the electronic pharmacy database was high for medications utilised for chronic illnesses and lower for acute conditions (Pisa *et al.,* 2015; and Sarangarm *et al.,* 2012). For acute medications, clinical record and register-based information may give incomplete exposure data due to not reporting and/or non-compliance (Stephansson *et al.,* 2011). The outcomes for some medicine groups may give false negatives because of non-compliance, for example, low compliance for short term medicine such as NSAID's (nonsteroid anti-inflammatory drugs) and antihistamines as well as non-compliance due to fear of fetotoxic side-effects (Olesen *et al.*, 2001).

No equivalent comparative studies in pregnant women were found from Africa.

2.5.6 Areas for further research

In Africa, women who are of childbearing age are commonly exposed to infectious conditions such as malaria, HIV and TB, other acute and chronic medical conditions and obstetric complications. Women are also exposed to new medication where the information on the safety during pregnancy is unknown or limited (Mehta *et al.,* 2019). It is important to determine reliable ways of determining drug exposure during pregnancy for pharmacoepidemiology studies (Boltman-Binkowski, 2016).

The best method for collecting antenatal medication exposure data is not certain and it may be that different methods are better for different types of medication. It is essential for cost-effective methods to be established to investigate antenatal medication use in low- and middle-income countries. There is a need for additional methodological research in this area to determine the most appropriate method to conduct investigations about the timing and

frequency of antenatal medication exposure. This is a significant, but under-studied area, especially in settings where the resources are limited, such as South Africa.

3. Aims and objectives

John Tukey (1962), a statistician, described data analysis as "procedures for analysing data, techniques for interpreting the results of such procedures, ways of planning the gathering of data to make its analysis easier, more precise or more accurate, and all the machinery and results of (mathematical) statistics which apply to analysing data."

The optimal method of ascertainment of medicine use during pregnancy is not yet certain. Different data sources can be superior for different medication types. To improve the quality of data, a combination of several data sources is an ideal, but time-consuming and expensive approach, which can lead to a delay in the determining of the safety profile of a medicine during pregnancy.

By looking at and comparing three data sources: 1) self-report, 2) clinician records and 3) electronic dispensing systems, we aimed to determine the optimal method of antenatal medicine use for multiple medication types.

3.1 Motivation/ Significance of research

There is a clear lack of local publications about ascertaining antenatal medication exposures. Pharmacovigilance in pregnancy is often poorly researched, especially in low- and middle-income countries. The changing risk profile of exposures over the course of gestation further complicates assessment. One of the first steps in determining accurate medicine exposures in pregnancy is a valid data collection approach. To this end, comparison of the three data sources enables one to see which data source provides the most information on different medication

types, when the use of each data source is appropriate for a specific medication type, and how much each source contributes to overall antenatal exposure. We can identify a source as appropriate if it provides sufficient data on a certain medication type being investigated. If two or more data sources provide the same information they are interchangeable and both sources are appropriate.

This allows us to identify missing and/or overlapping information between data sources, which will ultimately enable us to make suggestions for strengthening methods for data capture and improved reporting. In terms of teratogen exposures, this investigation may help future researchers to consider which data collection methods to include when investigating a specific type of medication.

These data sources were assessed in terms of overlap and missing data to investigate if different sources provide the same data and if one data source can be replaced by another. Correlation between the data sources can help future investigators when it comes to antenatal medication exposure research, because it can indicate if one data source can be replaced by another, which can mean more research can be done using a less time-consuming and expensive method as an alternative to combination all three sources. A correlation between data sources can potentially improve pharmacovigilance by enabling researchers to gather more data on the effects of antenatal medicine exposure and can be a big advance for this under-researched area. If the same data can be gathered by self-report / clinician records and electronic dispensing data, the electronic dispensing data will be much less time-consuming and economical way to gather a big volume of data.

3.2 Aim

This study aimed to compare three methods of data collection of antenatal medicine use - self report, clinician record and electronic dispensing systems. The data sources were compared by looking at different medication types reported in each data set for each participant.

2.3 Objectives

The objectives of this study are to:

1. To describe antenatal medicine exposure in a cohort of pregnant women as documented in each of the three data sources over the entire antenatal period.
2. To determine the degree of agreement between the three methods.
3. To identify if the use of a certain data source provides a more comprehensive reflection of the drug exposures compared to the other data sources.
4. To identify the strengths and weaknesses of each data source with respect to medicine exposures.

4. Methodology

4.1 Study design

This was a retrospective descriptive study comparing three data sources of antenatal medication exposure in the same cohort of patients previously collected as part of the B positive (B+) project (Appendix 2). The data sources comprised of self-report, clinical records and electronic dispensing data.

The B+ project was a prospective observational cohort study that enrolled women for an examination of pregnancy exposures of ART and assessing PMTCT. The main aim of the B+ project was to monitor the efficiency, impacts and risks of the WHO Option B+ prevention of PMTCT of HIV approach at a population level in the Western Cape Province. This project is therefore a secondary analysis of previously collected B+ data.

4.2 Population and setting

The B+ study was conducted at Gugulethu Midwife Obstetric Unit (GMOU), a primary care obstetric facility. Gugulethu is a suburb in Cape Town, Western Cape that has high levels of poverty and unemployment. GMOU is a midwife-run public health care facility within the Klipfontein Mitchell's Plain sub-structure in the Cape Town Metro region. The health services at GMOU are free and pregnant women receive health services for antenatal care and uncomplicated deliveries; if needed women can be referred to public hospitals. In 2015 the antenatal HIV prevalence at GMOU was about 30% (Phillips *et al.*, 2020).

Pregnant women attending their first antenatal visit at GMOU between 2016 and 2018, were enrolled in the B+ study and attended up to three antenatal visits, depending on the gestational

age at the first visit, and permission was given to access their medical records. The B+ project was a prospective observational cohort study that enrolled 995 women for an examination of pregnancy exposures of ART and assessing PMTCT. The main aim of the B+ project was to monitor the efficiency, impacts and risks of the WHO Option B+ prevention of PMTCT of HIV approach at a population level in the Western Cape Province.

The HIV status of the eligible women was confirmed by routine testing. Women were excluded from the B+ study if they were referred from Basic Antenatal Clinics (BANC) and if they presented to the GMOU for the first time during their labor (i.e., received no antenatal care). All participants received an obstetric ultrasound scan before or at 22 weeks gestation to determine gestational age. Women were assigned a unique study number at enrolment and this was used as an identifier to link the data of the three datasets. No personal identifiers were used.

Of the 995 women who were enrolled in the B+ study, 2 women were ineligible and 5 of the women were not pregnant and were excluded. We excluded 2 women who had elective terminations of pregnancy (TOP) before 20 weeks, 2 women who had ectopic pregnancies and 17 women where antenatal follow-up was incomplete. The data of the 967 remaining women were used in this study. No new participants were recruited.

4.3. Ethical considerations

4.3.1 Risks and benefits

This was a retrospective analysis of data that have already been collected and was a "minimal/everyday risk" level and was of minimal risk to the participants.

The main concern was the loss of confidentiality. If information is accidentally released, participants could potentially face risks of discrimination or stigmatisation and future employment problems. If the groups were then identified as having a bigger risk of having a certain disease, certain population/ethnic groups could face discrimination or stigmatisation as a result. Risks like this was minimised by keeping the information strictly confidential. Access to the information was restricted to only the members of the investigational team. No personal identifiers were included with the data and datasets were password protected.

During the original B+ cohort study, respect for the dignity of participants was prioritised. The research participants were not subjected to any harm and there was no obligation to take part in the study if they did not want to. Women signed informed consent for participation, including for access to their medical and electronic records. During the data collection, all the women were assigned a unique study number, which appeared on all of the study documents. No identifiable data were recorded on the questionnaires. The identifiers were kept separately.

This study required the use of patient clinical folder number to access the PER and the PHDC data of the cohort study participants. A list of these numbers was sent to the PHDC and the data were requested. The PER and PHDC databases were returned to the researcher using the anonymised study number and the researcher did not have access to identifiable information. The PHDC data were protected and all the analysts signed strict confidentiality contracts and consent to standard operating procedures (SOPs), which limited the unintentional risks of inappropriate identification of the participants. All the information was released while adhering to strict SOPs. All the released information is encrypted and protected by passwords.

There was no direct benefit to the participants. Only researchers may benefit from this study in terms of considering optimal ways to capture data about antenatal medication exposure. Benefit is derived from the knowledge gained.

4.3.2 Vulnerable populations

Pregnant women comprise a vulnerable population. The use of the vulnerable population was justified. This was a study of medicine use during pregnancy and it is essential that pregnant participants are included; data from non-pregnant populations would not have been adequate. The physiological changes during pregnancy can affect the absorption, distribution, metabolism and elimination of drugs with possible implications for efficacy and toxicity (Benevent *et al.,* 2017), so it would not have been possible to use anyone other than pregnant women for the purpose of this study.

The inability to appropriately gather collect pregnancy medication exposure evidence in the clinical research setting prompts uncertainty in these settings. Without information about medication during pregnancy, pregnant women and health care providers are compelled to make decisions based on substandard information. Pregnant women deserve access to safe medicines and without the correct information, there is a danger of neglecting to adequately treat pregnant women and risk harm to the fetus. Not conducting sufficient research in pregnant women potentially endangers fetal wellbeing for a far bigger proportion of pregnancies than conducting research in a monitored study would.

4.3.3 Subject information and informed consent

Full consent for the parent study was obtained from all the research participants before the start of the parent study. All women provided signed consent for participation in the cohort study

and access of their additional medical records and data for study purposes. The consent forms complied with regulatory and ethical standards. All information and consent sheets were available in English and isiXhosa. The participants had sufficient time to decide if they wanted to participate in the study. This consent form explained that all information would be kept strictly confidential and that they could contact the Human Research Ethics Committee (HREC) if they had a question or a complaint.

The participants had the option to withdraw from the study at any time and it was explained to them that withdrawing from the study would not have an impact on their health care provided by GMOU.

4.3.4 Privacy and confidentiality

The data that were used for this investigation were kept anonymous and secure. The database access was managed as indicated by IT governance standards. The privacy of the participants was protected and ensured. No names are used. Data are de-identified to keep the participants identity anonymous. Access to the information will be restricted to the members of the investigational team.

4.3.5 Ethical approvals

The study protocol and B+ protocol were approved by the University of Cape Town Human Research Ethics Committee and Western Cape Government Health research Committee (Appendices 1 - 5).

4.4 Data sources

Three data sources of antenatal medication exposure for this cohort of women were compared. The three data sources comprised of 1) self-report that was gathered by an interviewer-administered questionnaire at up to three antenatal study visits to the GMOU; 2) clinical records as recorded in the Pregnancy Exposure Registry (PER); and 3) linked electronic dispensing data (population-based linked medical record data).

4.4.1 Self-report

The self-report data were gathered as part of the B+ project by an interviewer-administered questionnaire at each antenatal visit to GMOU. The same questionnaires were administered at up to three antenatal visits to the GMOU and aimed to obtain a comprehensive report of medicine use during the preceding period. Women were asked to recall medicine use since last visit, including prescription medication, OTC medicines and remedies, traditional, herbal and home treatments. In addition, participants were asked about chronic medical conditions and treatments (for example: HIV, hypertension, cardiac, endocrine and mental health conditions) and intercurrent infections and treatments (for example: TB, sexually transmitted infections [STI] and urinary tract infections). They were asked to report on symptoms per system – respiratory, cardiac, gastro-intestinal, etc. and if present, whether they had taken any medicine or remedy to treat these. Generic and tradenames were recorded. Medicine Identification Aids with photographs of common packaging and formulations were available to the interviewers. Data from the interviews were collected on standardised forms and entered into a specific REDCap database. The data under the study number were made available for the analysis.

4.4.2 Clinician records (PER)

The Maternity Case Record (MCR) is a patient-held document that records all clinical consultations and investigations relating to pregnancy and delivery. It is completed by the attending midwives and doctors and is retained at the site of delivery after birth. The Western Cape Pregnancy Exposure Registry (PER) digitised data elements from the MCR, including medicine use of pregnant women that was recorded by the clinicians on duty. Additional medication (e.g. ART and flu injections) that were in the clinician case notes were included. Syndromic treatment for STI was collected from the STI register at GMOU. The PER was used as the data source for clinician records. Data were provided per study number.

4.4.3 Electronic dispensing systems (PHDC)

The electronic dispensing data was obtained from the Provincial Health Data Centre (PHDC) of the Western Cape. The PHDC is a health information exchange that links information from electronic, pharmacy, laboratory, community and disease specific (for example HIV and TB) sources in the Western Cape (Boulle *et al.*, 2019).

All of the patients who receive health care in government facilities in the Western Cape province are given a unique patient identifier number, which remains the same throughout all visits and across all facilities. The patient identifier assists by linking records between different patient registration systems and can be used to link the patient records across different facilities. The PHDC-provided data that used for this study were de-identified for the analysis and made available using the B+ study number only.

Patient demographics were obtained at interview and included maternal age at enrolment (years), prior pregnancies, level of education, and employment status. Existing medical conditions (for example, HIV, chronic hypertension) were documented.

4.5 Data management

Each of the 3 datasets listed the medicines used by each woman (denoted by study number) and the date of dispensing. The data were processed and organised using Microsoft Excel. The datasets were cleaned removing duplicates, errors and in certain instances were incomplete because of the method of collection and/or human error. The three datasets were converted to the same format and layout.

All medications were assessed to determine and list the active ingredient of each medication and coded using the ATC system (see below).

4.5.1 Anatomical Therapeutic Chemical classification

We constructed a list of all reported medications and then categorized them using the Anatomical Therapeutic Chemical (ATC) classification system assigning an alphabetical-numeric code per agent. The ATC classification system is an internationally acknowledged system to classify medicine maintained by the WHO (WHO, 1996). ATC codes are assigned to active ingredients depending on the therapeutic indication of the ingredient. When using the ATC classification system, the active ingredients are categorized into five different levels and according to the organ or the system in which the active ingredient/ingredients act upon, the pharmacological, therapeutic and chemical properties thereof. This classification system has fourteen main anatomical groups in the 1st ATC level (Table 1).

Each 1st level ATC group is divided 2nd, 3rd, 4th and 5th levels. Level 2 ATC is the therapeutic or pharmacological groups, 3rd and 4th level ATC is the pharmacological, chemical or therapeutic subgroups and level 5 ATC is the chemical substance (WHO, 1996).

All the medications were classified as far as possible using this system. Where possible, a full ATC code (5th level) was assigned to each of the medications that the women used during their pregnancy. We defined ART and TB treatment using the ATC coding in the South African Medicines Formulary (Rossiter *et al.*, 2014). If the women did not report using any medication on the specific dataset throughout the course of their pregnancy, it was classified as "None".

Table 1: The 1st level ATC codes (the main anatomical groups) as described by the WHO:

1st level ATC classification system
A: Alimentary tract and metabolism
B: Blood and blood forming organs
C: Cardiovascular system
D: Dermatologicals
G: Genito urinary system and sex hormones
H: Systemic hormonal preparations, excluding sex hormones
J: Anti-infectives for systemic use
L: Antineoplastic and immunomodulating agents
M: Musculo-skeletal system
N: Nervous system
P: Antiparasitic system
R: Respiratory system
S: Sensory organs
V: Various

(WHO, 1996)

4.5.2 Herbal, complementary, traditional and home remedies classification

Herbal, complementary and traditional remedies have been defined as preparations that are prepared from active ingredients with a natural origin (Alostad *et al.*, 2018), and can be classified by using the Herbal Anatomical Therapeutic Chemical Classification System (HATC), an alphabetical-numeric code per agent, similar to the ATC classification system (Farah, 2006). It was challenging to distinguish between some herbal, complementary and traditional remedies: limited data were available and not all remedies could be classified according to the HATC system. Not all of the indications of the remedies were available, so a HATC code could not be assigned to our data.

There is no clear definition available for home remedies. We defined home remedies as Home remedies could not be assigned an HATC code and were only classified as home remedies.

Therefore, herbal, complementary, traditional and home remedies were not formally classified. They were categorized as 1) Herbal and complementary remedies, 2) Traditional remedies and 3) Home remedies for the purposes of analysis.

4.6 Statistical analysis

The data were analysed using Microsoft Excel and STATA statistical package, version 16 (Stata Corporation, College Station, Texas, USA).

4.6.1 Antenatal medication exposure by using ATC coding

The higher level of the ATC coding of the self-report, PER and PHDC dataset was compared to get a more focused overview of the reported mediations. Level 1 ATC provides little detail so we investigated the data in a more granular way: the 2nd to 5th level ATC codes were used to define key medications that were used by the participants. In addition, antiretroviral therapy (ART), TB treatment, iron and folate supplements, isoniazid (INH) for TB prevention in women living with HIV, and STI treatment were categorized.

4.6.2 Master list

Data of all three data sources were combined into a master list. This enabled us to see how much each data set contributed to the full picture. The master list is a consolidated list of all the medication each participant used at least once in any of the three datasets. Each participant was looked at individually and each medication was reported only once in the master list, irrespective if it was reported in one, two or all three datasets.

The data in each dataset were summarized using descriptive statistics. We presented the medians and interquartile range (IQR) of the demographic data. Categorical variables were described using proportions and compared using frequency tables. Significance was tested using a two-sample t-test or Wilcoxon rank-sum test depending on the distribution for numerical data; and the $\chi 2$ test or Fishers Exact test for categorical data. The antenatal medication exposures using 1st level ATC were captured and ranked according to number of occurrences per data-source. This allowed us to measure the strength and direction of a monotonic association between the reported medication.

The correlation and degree of concordance between datasets were examined using rank tests and inter-rater reliability tests: Spearman rank tests and agreement for Kappa and adjusted Kappa tests, respectively.

4.6.3 Set theory

The three different data sources were analysed using set theory. Modern set theory was pioneered by Georg Cantor and Richard Dedekind (Cantor, 1874). Set theory starts with a basic binary assignment between an object (medication – n) and a set (data source – A, B or C). Set theory enables us to identify when the use of each dataset is appropriate and allows us to compare sets by determining if a data source (set) sufficiently reported medications by comparing the data sources to each other. Using mathematical logic, we could distinguish between each dataset and what it reported to conclude if there was any overlapping data and missing data.

The sets were defined as follows:

$$PER = A$$

$$PHDC = B$$

$$Self - report = C$$

$$Master\ List = n(A \cup B \cup C)$$

These sets were represented visually using venny (Oliveros, 2015) for selected agents.

We used sets to visualise total prescriptions as well as individual agents per data source.

4.6.4 Correlations using rank correlation

The data that were captured in each data set were ranked from most reported to least reported (i.e. number of women who reported each agent once or more). The data were ranked at the 1st

level and 5th ATC level. This enabled us to analyse the correlation between the different data sources.

Spearman rank:

The Spearman rank correlation on 1st and 5th ATC level were analysed to determine the similarity and contributions of number of women exposed to each medication between the data sources.

Spearman's Rank Correlation can be used to summarise the direction and the strength of a relationship between two datasets. We also tested for significance between the relationships. Spearman rank (ρ) is a non-parametric measure of rank correlation used to evaluate the relationship between two variables by a monotonic function. The closer the Spearman rank coefficient is to 1, the closer the variables are to having a perfect relationship. A high correlation would support agreement between data sources whereas a low correlation would add to the argument that a data source being underreported or missing data. In a perfect world if each data source adequately reported and flagged medications the correlation coefficient should equal 1.

Spearman rank correlation is defined as the Pearson correlation of variables that are ranked is calculated as:

$$\rho_{xy} = \frac{cov(x, y)}{\sigma_x \sigma_y}$$

where $\rho =$ Pearson correlation coefficient

$cov(x, y) =$ covariance between rank variables

$\sigma =$ standard deviation

Spearman's Rank is a statistical test that is sensitive to discrepancies in data and errors.

4.6.5 Inter-rater reliability using Cohen's κ

We determined agreement between datasets of each agent reported i.e. not the number of prescriptions but the presence/absence of an agent classified by ATC. Since Spearman's correlation does not account for observed agreement owing to chance, agreement between the datasets was evaluated by using Cohen's Kappa coefficient.

The Cohen's Kappa coefficient (κ) statistic measures the interrater reliability between data such as medication categories (McHugh, 2012). The consensus is that κ is regarded as a more robust measure than simple agreement measures since it accounts for chance agreement where correlations do not.

κ is defined as:

$$\kappa = \frac{p_o - p_e}{1 - p_e}$$

where p_o is the observed agreement between raters, and p_e is the probability of agreement by chance. For complete agreement $\kappa = 1$.

Kappa values were interpreted using the Landis and Koch categories: almost perfect (>0.80), substantial (0.61 – 0.80), moderate (0.41 – 0.60), fair (0.21 – 0.40), slight (0.00 – 0.20) and poor (<0.00) (Landis & Koch, 1977).

5. Results

5.1 Cohort description

Of the 995 women initially enrolled in the B+ study, 988 of the women were eligible. For the purposes of this study, elective terminations of pregnancy before 20 weeks gestation, the ectopic pregnancies and where the follow-up was incomplete were excluded. The data of the 967 remaining women were used (Figure 1).

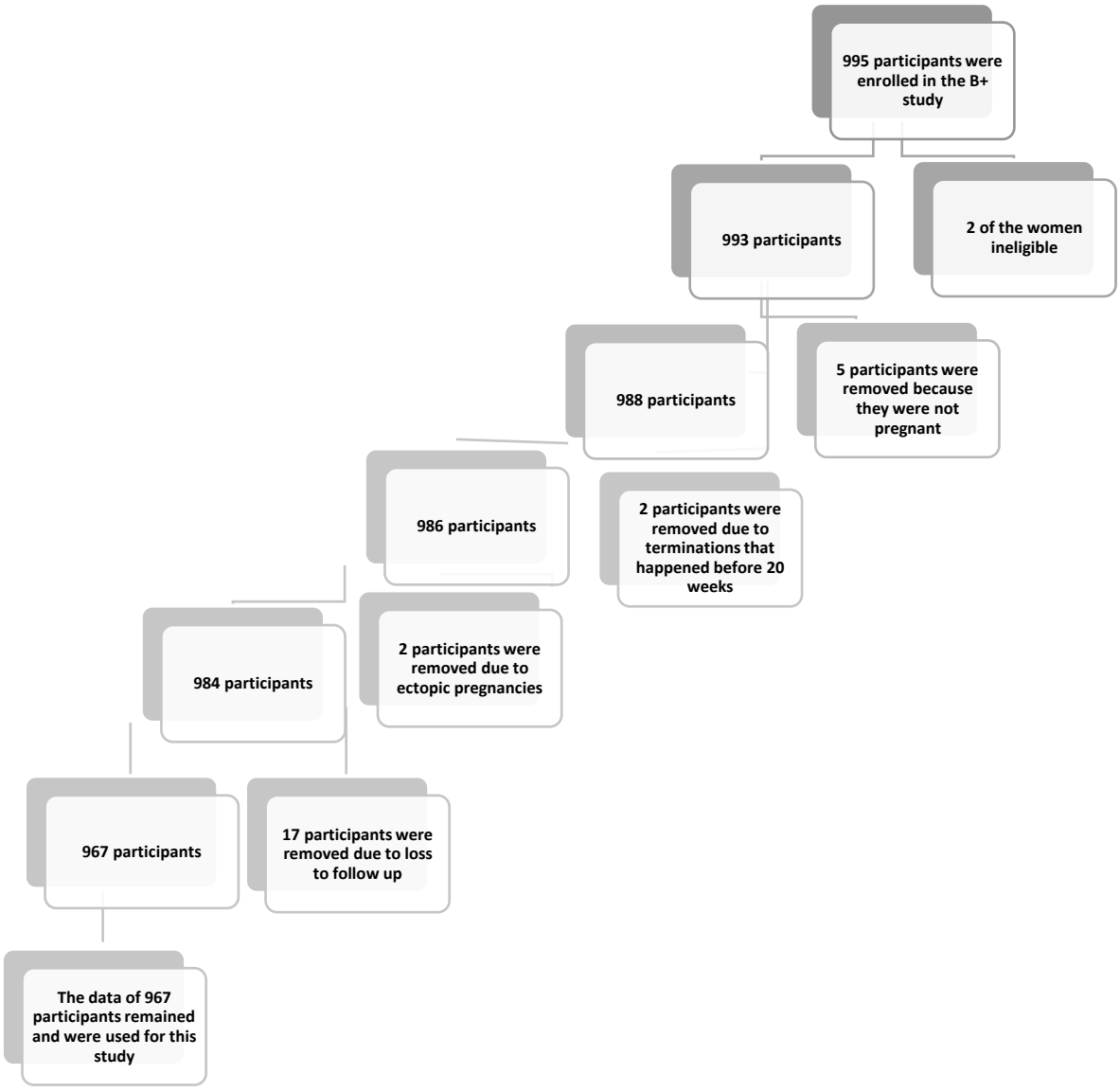


Figure 1: Defining the cohort

5.2 Anatomical Therapeutic Chemical classification

All of the exposures (excluding herbal, complementary, traditional and home remedies) were categorized using the ATC classification system. It total, there were 18892 exposures that we were able to assign 236 individual ATC codes to. Out of the 236 agents we assigned an ATC code to, we were able to classify 100.00% of those exposures to level 1 ATC, 99.58% to level 2, and 83.47% to level 5 (Table 2).

Table 2: Individual agents classified to each ATC level (excluding herbal, complementary, traditional and home remedies)

ATC classification	*N*	*%*
1st level	236	100.00%
2nd level	235	99.58%
3rd level	221	93.64%
4th level	216	91.53%
5th level	197	83.47%
Total individual agents an ATC code could be applied to	236	

5.3 Patient demographics and chronic conditions

Demographic and medical history were obtained at interview through self-report. The descriptive statistics of the participants (patient demographics) are given in Table 3.

The median age of the women at delivery was 29 years (IQR 24-35) and most fell into the 25 – 29 age range category.

Table 3: Patient demographics of the participants at enrolment (i.e. first antenatal visit)

Cohort Demographics (n=967)

Age (years) median (IQR)	29 (24 - 35)	
Age at delivery (Years)	N	%
<25	232	24.0%
25-29	283	29.3%
30-34	252	26.1%
35-39	157	16.2%
40+	43	4.5%
Prior pregnancies		
None	244	25.2%
1 to 2	589	60.9%
3+	134	13.9%
Education		
Primary School only	37	3.8%
Secondary School (incomplete)	907	93.8%
Completed School	22	2.3%
Not Reported	1	0.1%
Working status		
Employed	341	35.3%
Not employed	626	64.7%

As presented in Table 4, at the first visit 48.19% (n =466) of the women reported that they were living with HIV of whom 70% ($n = 327/466$) were on ART at the first antenatal visit; the remainder started ART during pregnancy. Apart from HIV and TB, 6.51% ($n = 63$) of the women were living with a chronic condition and 68% ($n = 43/63$) of those women were on treatment at the first antenatal visit.

In this cohort, 99.71% ($n = 965$) reported using at least one medicine and/or remedy during pregnancy in one or more of the datasets. For 2 women there were no record of exposure in any dataset (Supplementary Table 4).

When investigating the overall medicine exposures and excluding all remedies (herbal, complementary, traditional and home remedies), iron, folate and vitamin supplements, Paracetamol (N02BE01) was the exposure recorded once or more by most of the women ($n = 499$ women) in the cohort (Supplementary Table 1). Emtricitabine (J05AF09) was the most frequently reported exposure ($n = 1834$ total exposures) (Supplementary Table 2) during pregnancy and was reported by 38% of the women ($n = 374$ women) (Supplementary Table 1).

The self-report was the only dataset that captured herbal, complementary, traditional and home remedies. As presented in Supplementary Table 1 and 3, herbal, complementary, traditional and home remedies were reported by 13% (n = 123), 15% (n = 146) and 10% (n = 100) of women, respectively. Herbal and complementary remedies accounted for 1.24% (n = 236) of the total reported antenatal medicine exposures, traditional medicine for 1.2% (n = 227) and home remedies for 0.82% (n =155) (Supplementary Table 2 and 4).

Table 4: Medical history and treatments obtained at the first interview through self-report

Chronic medical conditions (n=967)	*Yes*	*%*	*On treatment (Yes)*	*%*
HIV	466	48.19%	327	70%
Tuberculosis	9	0.93%	6	67%
Diabetes Mellitus Type1 or Type 2	8	0.83%	7	88%
Hypertension	27	2.79%	21	78%
Heart disease	1	0.10%	1	100%
Asthma	16	1.65%	11	69%
Epilepsy	2	0.21%	2	100%
Thyroid disease	6	0.62%	3	50%
Mental conditions	7	0.72%	4	57%
Other medical conditions	6	0.62%	0	0%
Chronic excluding HIV & TB	63	6.51%	43	68%

5.4 Comparison of data sources using Set Theory

Combining all three data sources, there were 7472 (Supplementary Table 1) individual medication prescriptions that contributed to the 18 892 reported exposures in the Master List (Supplementary Table 2 & 4). Figure 2 shows that self-report set recorded the most exposure entries where 50% ($n = 4733$) of the total number of reported exposures were captured.

Figure 2 is a visual representation of Supplementary Table 1. As presented in Figure 2, the PHDC was the dataset that failed to capture the most exposures that the other two datasets captured. PHDC failed to capture 45% ($n = 2241$) of the total exposures that were captured in the other datasets, whereas PER and self-report failed to capture 40% ($n = 1982$) and 15% ($n = 734$) , respectively.

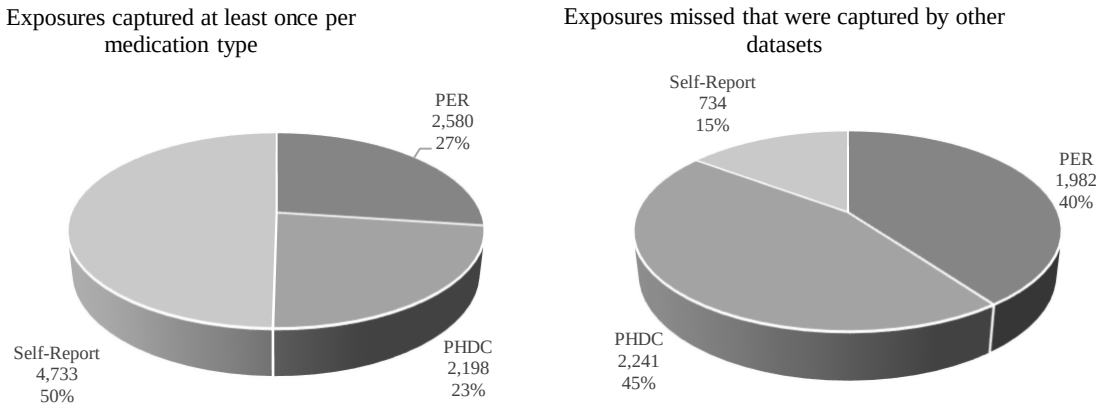


Figure 2: Data source prescription capture capability comparison with the Master List

Figure 3 shows that 372, 265 and 197 women reported ART use in the PHDC, PER and self-report, respectively. The union between PHDC and PER accounted for most of the overlapping women, with a total of 232 women.

In Figure 4 we looked at all the medicine exposures except iron, folate and vitamin supplements (pyridoxine was not excluded as it is only prescribed with isoniazid i.e. it was not a pregnancy-related supplement). Of the women who reported no medicine use, only one was common to all datasets (Figure 5).

Figure 3: Women on ART

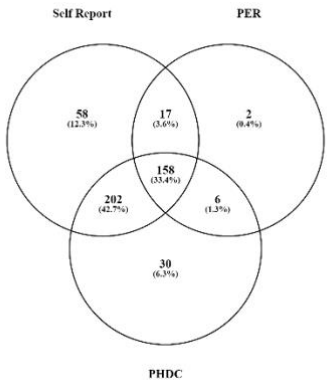


Figure 4: All medicine exposures (excluding supplements).

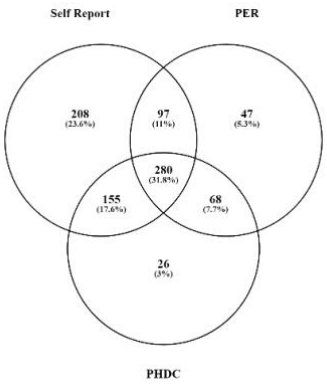
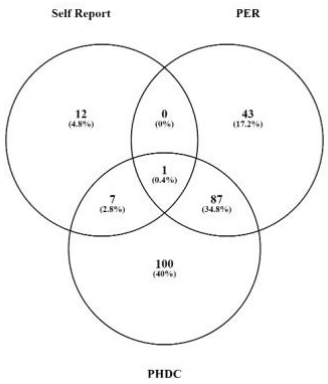


Figure 5: None



Figures 3, 4 & 5: Venn diagrams of the number of women exposed in different datasets

5.5 Tests of association

5.5.1 Spearman Rank correlation

We used a Spearman rank correlation to test the relationship between the three data sources. The Spearman rank correlation on 1st ATC level were analysed to determine the similarity and contributions between data sources. We also tested for significance between the relationships. (Table 5). On the **1st level** there were a strong relationship between the data sources. On the 1st level, the highest correlation was between PHDC and PER with a correlation coefficient of 0.93. The correlation coefficients between self-report and PHDC and self-report and PER were 0.52 and 0.57, respectively. All correlation coefficients are statistically significant at 5% level.

On the 1st ATC level by using the correlation coefficient scale, there was a good relationship between the data sources.

Table 5: Spearman rank sum co-efficient at ATC level 1

Key
rho
Number of obs
Sig. level

	PER	*PHDC*	*Self-Report*	*Master~t*
PER	1.0000			
	17			
PHDC	0.9270	1		
	17	17		
	0.0000			
Self-Report	0.5707	0.5212	1	
	17	17	17	
	0.0167	0.0319		
Master List	0.5506	0.5455	0.9540	1
	17	17	17	17
	0.022	0.0235	0.0000	

Table 6 shows the correlation coefficients on **5th level** between the data sources. The strength of the associations is much reduced. Again, the PHDC and PER had the highest correlation between data sources of 0.4.

Table 6: Spearman rank sum co-efficient at ATC level 5

Key

rho

Number of obs

Sig. level

	PER	*PHDC*	*Self-Report*	*Master~t*
PER	1.0000			
	240			
PHDC	0.4069	1.0000		
	240	240		
	0.0000			
Self-Report	0.2317	-0.1078	1.0000	
	240	240	240	
	0.0167	-		
Master List	0.5506	0.5455	0.9540	1.0000
	240	240	240	240
	0.0220	0.0235	0.0000	

5.5.2 Inter-rater reliability using Cohens κ

Table 7 presents the Cohen's Kappa inter-rater agreement results at the 2nd ATC level. Similarly to spearman rank, the numbers for some agents became too small when higher ATC levels were used.

One of the strongest agreements were for total ART exposure: substantial between PHDC and self-report (κ = 0.79) and moderate between self-report and PER (κ = 0.403) as well as PER and PHDC (κ = 0.409).

The only *"almost perfect"* agreement between any of the data sets were between PHDC and self-report were for A10: Medicine used in diabetes (κ = 0.831) and N05: Psycholeptics (κ = 0.800). There was a *"substantial"* agreement between self-report and PER for C09: Agents acting on the renin-angiotensin system (κ = 0.665) and H02: Corticosteroids (κ = 0.666); between PER and PHDC for first line ART (κ = 0.601) and second line ART (κ = 0.676); and between PHDC and self-report for C09: agents acting on the renin-angiotensin system (κ = 0.665).

A *"moderate"* agreement was found between self- report and PER for C03: Diuretics (κ = 0.461) and C10: Lipid-modifying agents (κ = 0.499); between PER and PHDC for C09: agents acting on the renin-angiotensin system (κ = 0.442) as well as R03: Drugs for obstructive airway diseases (κ = 0.541); and between PHDC and self-report for first line ART (κ = 0.461) and C02: Antihypertensives (κ = 0.412).

Table 7: Inter-dataset agreement for ATC level 2 medications (Cohen's Kappa)

Cohen's Kappa interrater agreement

Number of subjects	=	967
Ratings per subject	=	2
Number of rating categories	=	2

	PHDC versus Self-report					*Self-report versus PER*					*PER versus PHDC*				
Interrater agreement (κ)	Coef.	Strength	P>|t|	[95% Conf. Interval]		Coef.	Strength	P>|t|	[95% Conf. Interval]		Coef.	Strength	P>|t|	[95% Conf. Interval]	
A02 Drugs for acid related disorders	0.000	Poor	1.000	0.000	0.000	0.000	Poor	1.000	0.000	0.000	0.147	Slight	0.000	0.075	0.220
A03 Drugs for GI disorders	-0.004	Poor	0.011	-0.006	-0.001	0.000	Poor	1.000	0.000	0.000	0.000	Poor	1.000	0.000	0.000
A06 Drugs for constipation	0.056	Slight	0.300	-0.050	0.162	0.031	Slight	0.513	-0.062	0.124	-0.017	Poor	0.000	-0.024	-0.011
A07 Antidiarrheals	0.293	Fair	0.029	0.029	0.557	0.263	Fair	0.080	-0.031	0.557	0.178	Slight	0.257	-0.130	0.486
A10 Drugs used in diabetes	0.831	Perfect	0.000	0.668	0.994	0.305	Fair	0.066	-0.020	0.631	0.264	Fair	0.078	-0.029	0.557
A11 Vitamins	0.002	Slight	0.947	-0.060	0.064	-0.004	Poor	0.152	-0.010	0.002	0.019	Slight	0.152	-0.007	0.046
A11HA02 Pyridoxine	0.038	Slight	0.053	-0.001	0.077	-0.003	Poor	0.056	-0.006	0.000	0.020	Slight	0.152	-0.008	0.048
A12 Mineral supplements	-0.009	Poor	0.001	-0.015	-0.004	-0.004	Poor	0.118	-0.008	0.001	-0.003	Poor	0.065	-0.006	0.000
First line ART	0.461	Moderate	0.000	0.406	0.516	0.232	Fair	0.000	0.164	0.299	0.601	Substantial	0.000	0.549	0.653
Second line ART	0.216	Fair	0.023	0.029	0.402	0.120	Slight	0.160	-0.048	0.288	0.676	Substantial	0.000	0.510	0.843
B01 Antithrombotic agents	0.000	Poor	1.000	0.000	0.000	0.000	Poor	1.000	0.000	0.000	-0.001	Poor	0.158	-0.003	0.000
B03 Antianemic preparations	-0.019	Poor	0.216	-0.050	0.011	0.018	Slight	0.580	-0.045	0.081	0.027	Slight	0.010	0.007	0.048
C02 Antihypertensives	0.412	Moderate	0.001	0.164	0.660	-0.002	Poor	0.233	-0.005	0.001	0.098	Slight	0.281	-0.081	0.277
C03 Diuretics	0.378	Fair	0.000	0.174	0.582	0.461	Moderate	0.000	0.240	0.682	0.293	Fair	0.029	0.030	0.557
C08 Calcium channel blockers	-0.002	Poor	0.191	-0.004	0.001	-0.004	Poor	0.012	-0.007	-0.001	-0.002	Poor	0.233	-0.005	0.001
C09 Agents acting on the renin-angiotensin system	0.665	Substantial	0.000	0.355	0.975	0.665	Substantial	0.000	0.308	1.000	0.442	Moderate	0.033	0.036	0.848
C10 Lipid modifying agents	0.331	Fair	0.184	-0.158	0.820	0.499	Moderate	0.104	-0.102	1.000	-0.002	Poor	0.191	-0.004	0.001
D02 Emollients and protectives	0.169	Slight	0.007	0.047	0.291	-0.006	Poor	0.065	-0.012	0.000	0.092	Slight	0.138	-0.030	0.214
D04 Antipruritic agents	-0.007	Poor	0.000	-0.011	-0.003	0.000	Poor	1.000	0.000	0.000	0.000	Poor	1.000	0.000	0.000
D07 Corticosteroids	0.086	Slight	0.330	-0.088	0.261	0.000	Poor	1.000	0.000	0.000	0.000	Poor	1.000	0.000	0.000
D08 Antiseptics and disinfectants	-0.004	Poor	0.011	-0.006	-0.001	0.000	Poor	1.000	0.000	0.000	0.000	Poor	1.000	0.000	0.000
G01 Gynecological antiinfectives and antiseptics	0.112	Slight	0.034	0.008	0.216	-0.005	Poor	0.037	-0.010	0.000	0.026	Slight	0.475	-0.046	0.098
G03 Sex hormones and modulators of the genital system	-0.011	Poor	0.000	-0.016	-0.006	0.000	Poor	1.000	0.000	0.000	0.000	Poor	1.000	0.000	0.000

G04 Urologicals	0.092	Slight	0.320	-0.090	0.274	0.000	Poor	1.000	0.000	0.000	-0.006	Poor	0.001	-0.010	-0.003
H02 Corticosteroids for systemic use	-0.003	Poor	0.056	-0.006	0.000	0.666	Substantial	0.034	0.049	1.000	-0.002	Poor	0.233	-0.005	0.001
J01 Antibacterials for systemic use	0.236	Fair	0.000	0.158	0.315	0.095	Slight	0.011	0.022	0.167	0.012	Slight	0.667	-0.043	0.067
J04 Antimycobacterials	0.069	Slight	0.007	0.019	0.118	-0.006	Poor	0.068	-0.012	0.000	0.032	Slight	0.077	-0.004	0.067
J07 Vaccines	0.000	Poor	1.000	0.000	0.000	-0.006	Poor	0.705	-0.035	0.024	0.000	Poor	1.000	0.000	0.000
M01 Anti-inflammatory	0.065	Slight	0.181	-0.030	0.160	0.037	Slight	0.305	-0.033	0.106	-0.002	Poor	0.306	-0.006	0.002
N02 Analgesics	0.068	Slight	0.006	0.019	0.116	0.006	Slight	0.466	-0.010	0.021	0.004	Slight	0.848	-0.033	0.040
N03 Antiepileptics	0.399	Fair	0.150	-0.145	0.943	0.399	Fair	0.150	-0.145	0.943	0.000	Poor	1.000	0.000	0.000
N05 Psycholeptics	0.800	Perfect	0.000	0.414	1.000	0.000	Poor	1.000	0.000	0.000	0.000	Poor	1.000	0.000	0.000
N06 Psychoanaleptics	0.127	Slight	0.292	-0.109	0.363	-0.003	Poor	0.065	-0.006	0.000	-0.003	Poor	0.087	-0.007	0.001
NOVIT	0.131	Slight	0.000	0.075	0.188	0.002	Slight	0.940	-0.052	0.056	0.327	Fair	0.000	0.267	0.386
P01 Antiprotozoals	0.125	Slight	0.011	0.028	0.221	0.217	Fair	0.000	0.104	0.329	0.042	Slight	0.336	-0.044	0.128
P03 Ectoparasiticides	0.104	Slight	0.310	-0.097	0.304	-0.003	Poor	0.065	-0.006	0.000	-0.004	Poor	0.101	-0.008	0.001
R01 Nasal preperations	0.018	Slight	0.482	-0.033	0.070	0.000	Poor	1.000	0.000	0.000	0.000	Poor	1.000	0.000	0.000
R03 Drugs for obstructive airway diseases	0.206	Fair	0.014	0.042	0.369	0.117	Slight	0.009	0.030	0.205	0.541	Moderate	0.000	0.289	0.793
R06 Antihistamines	0.057	Slight	0.158	-0.022	0.135	0.027	Slight	0.182	-0.013	0.067	0.031	Slight	0.367	-0.036	0.097
S01 Ophthalmologicals	0.057	Slight	0.387	-0.072	0.186	-0.005	Poor	0.024	-0.009	-0.001	0.169	Slight	0.110	-0.038	0.377
Total ART	0.766	Substantial	0.000	0.725	0.807	0.403	Moderate	0.000	0.352	0.453	0.409	Moderate	0.000	0.355	0.463
Vitamins	0.004	Slight	0.803	-0.025	0.033	0.016	Slight	0.627	-0.048	0.079	0.029	Slight	0.008	0.008	0.051

6. Discussion

In a population where most women took medication and/or remedies during pregnancy, we compared 3 different antenatal medicine datasets using Spearman's rank and Cohen's Kappa tests.

In all three datasets, it is apparent that medication exposure throughout pregnancy is prevalent for multiple medication types. It is clear that the most exposures were reported in the self-report dataset. This can be due to the way the questions were asked. The self-report does not only account for the medication received at specific facilities, but it accounts for all the exposures during pregnancy, regardless of where the women received the medication (i.e., pharmacy, clinic, hospital, friends, family etc.). It is interesting to note that the PHDC captured the most systemic anti-infectives whereas the self-report captured the least.

According to the Spearman rank test, the PER and PHDC datasets as a whole showed the highest correlation both at 1st and 5th ATC level. However, the Kappa agreement between the datasets, which accounts for agreements occurring by chance, varied greatly according to the therapeutic class. The only "almost perfect" Kappa agreement were between anti-diabetic medication (ATC A10) reported in the self-report and PHDC datasets but the numbers were small. The overlaps between the datasets were poor and the Kappa agreement between the sources were low for most therapeutic classes, except for HIV treatments. The Kappa agreement for ART in the PHDC and self-report were substantial whereas the agreement between self-report and PER, and PER and PHDC were fair.

It is clear that self-report is the best source when investigation herbal, complementary, traditional and home remedies among this cohort of pregnant women. Self-report was also the

only source that captured any herbal, complementary, traditional and home remedies. This is reflected in an analysis conducted in Italy where self-report was the only data source that captured non-prescription medications and herbal preparations which was not captured in the electronic database (Pisa *et al.,* 2015).

Even though the group of medicines with consistently moderate or substantial agreement between all the data sources were ART, self-report recorded the most ART exposures, and if the information the women provided were reliable, this would be the best source when capturing ART exposures.

An interesting finding from the study was the poor performance of the PER data source (i.e. clinician records) for capture of overall antenatal medicine exposures. This was also the case in an analysis conducted in 2011 in Sweden that found clinical records and register-based information gave incomplete exposure data which may be due to not reporting and/or non-compliance (Stephansson *et al.,* 2011). Ideally, the PER (clinician records) can provide information about the safety of medication during pregnancy in resource-limited settings, but is subject to reliable and valid information being *sought and recorded* by the clinicians and the records retained. (Allen *et al.,* 2014).

At GMOU and other primary care facilities in South Africa, medicines are routinely distributed to the clinic in bulk to minimise pharmacy contact and reduce waiting times. The medicines are commonly dispensed from the clinic ward stock without a clinic register that records the date and duration of therapy in antenatal clinics (Mehta *et al.,* 2018). The PER gave a more complete reflection when capturing medicine commonly dispensed from ward stock, such as, influenza vaccines and vitamins. This could be because the clinicians administered the vaccines themselves and recorded in the MCR. A similar finding was reported in a validation study

comparing data from MCR's with PHDC in the Western Cape where there were no patient-linked electronic register of ward-stock items recorded in the MCR (Mehta et al., 2018).

The PHDC recorded more chronic exposures compared to the PER. This was also seen in a pilot study in Cape Town, where electronic medical records provided a better reflection of chronic antenatal exposures compared to the PER, particularly when women received care at facilities other than the antenatal unit where they initially received care, or when the exposure happened before the first antenatal visit (Mehta *et al.,* 2018).

In general, there were a higher agreement between self-report and PHDC for medicine taken chronically than occasionally. This was also the case in the Italian study, where the agreement between self-report and health database information were higher for chronic medicine (Pisa *et al.,* 2015) and is intuitive.

The only group of medicines with consistently moderate or substantial agreement between all the data sources was ART. We have found that self-report was the source that captured the most ART exposures and provided a more complete reflection of ART's compared to other data sources. Recent investigations regarding ART safety have brought attention to the significance of early recognition of ADR's (adverse drug reactions) in pregnant participants to avoid possible fatal outcomes (Moran *et al.,* 2012) (Sonderup et al., 2016). Almost 50% of the participants were living with HIV on the time of this investigation. HIV is a condition that is particularly stigmatised (Allen *et al.,* 2013). In an investigation in Italy participants were reluctant to report medicine that had a potential for stigmatisation (Pisa *et al.,* 2015). Women tend to withhold information due to a fear of a negative response (Allen *et al.,* 2013). However, we did not experience this in the cohort of women.

The recall accuracy of self-reported data has been shown to be influenced by therapeutic class, duration of use (occasional versus chronic), the way questions are asked (Pisa *et al.,* 2015) and the design of data collection materials (Strom, 2005:729). Other investigations demonstrate that participants may not know the name of exposed medicine (Chandler *et al.,* 2001).

There are many reasons why women successfully recalled and reported chronic exposures and ART exposures. Literature reveals that chronic exposures are better recalled than occasional exposures (Strom, 2005:728). Exposures with a substantial impact on a participant's life are better reported than exposures with little or no impact on a participant's life (Strom, 2005:735) which might explain why women did not withhold information about ART exposures. ART is regarded as important in sustaining life and women tend to report what they feel are significant, relevant and memorable (Allen *et al.,* 2013; and Stephansson, 2011). PMTCT is emphasized in South-African antenatal care and might influence the recall accuracy and the recording of ART in the clinical notes. Women regard ART as relevant to report because they feel a responsibility towards the health of the baby (Allen *et al*., 2013). ART dispensing requires prescription and there are specific HIV-treatment databases in the Western Cape which are reflected in the PHDC.

It is interesting to note that reporting of ART can be geographically dependent. In a study comparing methods for eliciting medication data, participants from South Africa and Tanzania were interviewed about their health and treatment, and their behaviour of reporting was investigated. In Tanzania exposures considered not relevant are not reported. Women could not name the ART drugs they were exposed to and mentioned them euphemistically, while South Africans could confidently name the ART they were exposed to. This could be due to

progress in the de-stigmatisation of HIV/AIDS due to the activism towards ART (Allen *et al.*, 2013), support clubs and empowerment (Achmat & Simcock, 2007).

Despite apparent advantages of self-report, including low cost and it being a relatively simple way to collect data, self-report has acknowledged limitations regarding the comprehension and understanding of questions posed, as well as the willingness and ability of the participant to give comprehensive responses. Recall bias is a limitation, especially in the case of a late first antenatal visit (Strom, 2005:756). Self-report answers rely on interpretation and comprehension. Questions about medication use can also be interpreted differently due to language barriers, beliefs about possible risks, benefits and cultural context. The information that is gathered through self-report can be modified due to the fear of the participant that there might be an absence of confidentiality, stigmatisation and negative repercussions (Allen *et al.*, 2013). Medication for certain conditions may not be reported because the participant may be embarrassed to discuss it with the interviewer. As a result, medicine exposures that are considered sensitive may be under-reported when using self-report (Strom, 2005:735). These limitations may be reduced by careful context-specific questionnaire design and piloting the questionnaire to check performance.

The PER digitized data elements from the maternity case record (MCR), including medicine use of pregnant women that was recorded by the clinicians on duty. The MCR is a patient-held document that records all consultations relating to pregnancy and delivery (Mehta et al., 2018). A limitation of the PER is that it relies on accurate participant report. The MCR is pre-printed with no allocated section to prompt clinicians to enquire about medicine exposures (Mehta et al., 2018). In the PER there is a lot of opportunity for inaccurate data when the clinicians do

not ask questions, women aren't telling clinicians about exposures, clinicians are not writing down the exposures properly and poor record keeping.

The way questions are asked by clinicians may also influence responses (Strom, 2005:727), for example, indication and drug-specific questions increase prevalence estimates compared to open-ended questions (Allen et al., 2014). Other studies in Africa have found women express reservations in reporting some medicines at antenatal clinic visits due to anticipated negative responses (Allen et al., 2014). Research also suggests that patient demographics (such as socio-economic factors and age), recall ability, social desirability bias and discernments about the significance or importance of data can lead to non-reporting (Allen et al., 2014).

Unlike the PER, where typically only the date and medicine names are recorded, the PHDC can give data about the dosage, duration and intervals between refills. In the case of PMTCT and HIV transmission, where birth outcomes are relevant, inquiries around the significance of degree of exposure have been raised (Chen *et al.*, 2012) (Zash *et al.*, 2017). The PHDC dataset can provide data on early antenatal exposures, but does not give information about non-compliance, borrowing or sharing of medicine and thus exposures may be overestimated (Mehta *et al.*, 2018). PHDC data are prospectively collected electronically and there is no recall bias.

6.1 Strengths

In this study we looked at a population of almost a thousand participants of whom most were exposed to medicine during pregnancy. Our study includes pregnant women living with HIV and to our knowledge, this is the only study that included women living with HIV apart from a pilot study in the Western Cape before the implementation of the PER (Mehta *et al.*, 2018). In African settings where there is a high disease burden, data regarding ART exposures is

necessary to assess the extent of exposure and the safety during pregnancy, in order that pregnant women are neither exposed to an unsafe medicine or denied access to a safe medicine.

This is the only comparative study in Africa that compares 3 data sources. Our electronic data set included both hospital and outpatient dispensing data. Other African studies utilized record review or self-report to determine antenatal medicine use, and only reported exposure, not a comparison of methods. The only other comparative African study, the pilot study in Cape Town, did not apply statistical tests for comparison and was limited to PHDC and folder reviews.

6.2 Limitations

Although secondary data may have some benefits, for example, it is easily accessible, it allows the researcher to generate new insights from a previous analysis, it is a time saving and a less expensive approach to do a study. However, limitations still exist when using retrospective data that have previously been collected. Limitations include reliability/ validity of data, sample size, the way data were collected, and data can be biased in favor of the previous researcher. Another apparent limitation of secondary data is the way questions were asked in the self-report dataset. ATC coding was not used in the self-report questionnaire, which would have ensured that medication with multiple ATC codes for different indications and combination preparations would have been classified correctly.

Apart from self-report that was collected with standardized tools by trained staff, the PHDC and the PER are routine operational databases, and we had no control over the accuracy and quality of this data and cannot account for missing data. In addition, statistical tests have inherent bias. The Kappa coefficient is affected by prevalence of a treatment, and where the prevalence is low, Kappa is not strong and does not perform well. However, the approach

accounts for agreement by chance and has been used in similar analyses (Pisa 2015 & Haapea 2010).

We compared medicine use throughout the whole pregnancy and did not take gestational age into consideration. Gestational age is important in terms of drug exposure, particularly in the first trimester of pregnancy when there is an increased risk of teratogenicity.

We were only able to assign a level 5 ATC code to 83.47% of the active ingredients reported by the women. Although ATC coding is internationally accepted and assigned by the WHO, it does not reflect all indications of a medication and can limit the results. Herbal ATC codes could not be assigned to herbal, complementary, traditional and home remedies.

6.3 Conclusions

This study demonstrated that one data source alone was not able to effectively capture all data. There was a large disparity in agreement between the data sources for medication use and agreement between the datasets varied greatly according to the therapeutic class. The best method of ascertaining antenatal medicine exposure depended on the type of medicine being investigated, as reported in the literature. Ultimately no single data source could be substituted for another since each provides an essential contribution, except for self-report that was the only source that captured herbal, complementary, traditional and home remedies and therefore cannot be substituted for PHDC and PER. Although it is acknowledged that this may have resource and cost implications, our study concludes that PER, PHDC and self-report should be used in conjunction since each are critical to ensure accurate, reliable and effective exposure data.

6.4 Recommendations

1. In agreement with reports from the higher-income regions, our findings confirm that different data sources are better for different medication types. There was very little agreement between the data sources and ideally it would be advantageous to use all 3 data sources to get the complete exposure profile, as the sources are complementary to each other.

2. Self-reported data appears to give the most complete exposure data when investigating herbal, complementary, traditional and home remedies and cannot be substituted with the PER or PHDC datasets.

3. A lot of African studies only rely on record review. Given what we have demonstrated with this study, a record review will not give accurate exposure data, except for ward stock items and may miss medicines dispensed at hospital or different obstetric sites.

4. A reliable centralised data collection system will be of value where all state and private sector medical records are linked and would contribute to the evolving of this field.

5. It is essential to improve current clinical record keeping and reporting. It will be useful for medical practitioners to attend ongoing training on the importance of accurate record keeping. Medical practitioners must be trained on how to effectively obtain information about medication exposures and how to record these exposures in the clinical notes. Accurate medical records are important for patient care and management.

6. A system should be put in place where nurses report back to the pharmacy what medicine was dispensed from ward stock so the pharmacist can update the data on the patients' profile. This can improve future investigations because there is currently no electronic footprint.

7. Given the frequent antenatal medication exposure, we need to find ways for healthcare practitioners to address the informational needs of pregnant women. It is important to empower and educate the women of South Africa about antenatal medication exposures and the importance of discussing it with their health care providers. It is important for pregnant women to be educated on the importance of reporting antenatal medication exposure, which will ultimately lead to more accurate recording of medication exposures.

8. It will be advantageous to use the internationally accepted ATC coding when preparing the self-report questionnaire. This would ensure that medication with multiple ATC codes for different indications and combination preparations would be classified correctly.

9. The current study can be improved by investigation exposures in more depth, by taking gestational age into account. Gestational age is important in terms of drug exposure and should be considered when investigating antenatal medication exposures. Another important factor is the dose of the medication, as well as the duration of therapy. It is possible for embryos to tolerate certain doses without significant change, but if the concentration exceeds the threshold, the possibility of irreversible changes will be increased. It will also be beneficial to investigate specific exposures/ drug classes.

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Appendices:

Appendix 1: Human Research Ethics Committee approval

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room G50- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-enquiries@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

04 May 2020

HREC REF: 197/2020

Dr E Kalk
CIDER
5th Floor, Falmouth Building
FHS
Email: Emma.kalk@uct.ac.za
Student: yhvjan002@myuct.ac.za

Dear Dr Kalk

PROJECT TITLE: COMPARISON OF THREE LEVELS OF ASCERTAINMENT OF ANTENATAL MEDICINE USE AT GUGULETHU MIDWIFE OBSTETRIC UNIT (M.Phil. Candidate-Ms Jani van der Hoven) sub-study linked to HREC/Ref:749/2015 & 541/2015

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

This approval is subject to strict adherence to the HREC recommendations regarding research involving human participants during COVID -19, dated 17 March 2020.

Approval is granted for one year until the 30 May 2021.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

The HREC acknowledge that the student: Jani van der Hoven will also be involved in this study.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938) **This serves as notification of annual approval, including any documentation described below.**			
☐ Approved	Annual progress report	Approved until/next renewal date	30.05.2022
☐ Not approved	See attached comments		
Signature Chairperson of the HREC/ Designee		Date Signed	6/5/21

Note: Please note that incomplete submissions will not be reviewed.
Please email this form and supporting documents (if applicable) in a combined pdf-file to hrec-enquiries@uct.ac.za.
Please clarify your plan for research-related activities during COVID-19 lockdown

Comments to PI from the HREC

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	4 May 2021		
HREC REF Number	197/2020	Current Ethics Approval was granted until	30 May 2021
Protocol title	Comparison of three levels of ascertainment of antenatal medicine use at Gugulethu Midwife Obstetric Unit		
Protocol number (if applicable)	V 1.0		
Are there any sub-studies linked to this study?		* Yes x No this is a sub-study of the projects below	
If yes, could you please provide the HREC Ref's for all sub-studies? **Note:** A separate FHS016 must be submitted for each sub-study.		749/2015 and 541/2015	

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

Principal Investigator	Emma Kalk
Department / Office Internal Mail Address	CIDER, 5th floor Falmouth Building UCT FHS Anzio Rd

1.1 Does this protocol receive US Federal funding?	☐ Yes	x * No
1.2 If the study receives US Federal Funding, does the annual report require full committee approval? **Note:** Any annual approvals for **Full Committee** review MUST be submitted on the monthly HREC submission dates. (Please send electronic copy for full committee review to hrec-enquiries@uct.ac.za)	☐ Yes	☐ No
If yes in 1.2 please complete section 1.3 below for invoicing purposes		
1.3 Annual Approval for **full committee** review	- R 3450 (inclusive of vat)	
For invoicing purposes, please provide:		
Sponsor's name		
Contact person		
Address		
Telephone number		
Email Address		

2. List of documentation for approval

Extension of approval for the protocol that was approved by HREC (197/2020).

3. Protocol status (tick ✓)

☐	Open to enrolment
☐	Closed to enrolment (tick ✓)
☐	Research-related activities are ongoing
☐	Research-related activities are complete, long-term follow-up only
✓	Research-related activities are complete, data analysis only

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

☐	Main study is complete but sub-study research-related activities are ongoing
☐	Study is closed → Please submit a Study Closure Form (FHS010)

4. Enrolment

Number of participants enrolled to date	N/A
Number of participants enrolled, since last HREC Progress report (continuing review)	
Additional number of participants still required	

5. Refusals

Total number of refusals (participants invited to join the study, but refused to take part)	

6. Cumulative summary of participants

Total number of participants who provided consent	N/A
Number of participants determined to be ineligible (i.e. after screening)	
Number of participants currently active on the study	
Number of participants completed study (without events leading to withdrawal)	
Number of participants withdrawn at participants' request (i.e. changed their mind)	
Number of participants withdrawn by PI due to toxicity or adverse events	
Number of participants withdrawn by PI for other reasons (e.g. pregnancy, poor compliance)	
Number of participants lost to follow-up. Please comment below on reasons for loss of follow-up.	
Number of participants no longer taking part for reasons not listed above. Please provide reasons below:	

7. Progress of study

Please provide a brief summary of the research to date including the overall progress and the progress since the last annual report as well as any relevant comments/issues you would like to report to the HREC:

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

This is a retrospective analysis of existing data. Risk is low and the parent studies have been approved by HREC. The protocol was approved by HREC. The literature review and methods are complete. The data were cleaned and the analysis are nearly complete. The student is finalising her dissertation. There has been no change to the risk.

8. Protocol violations and exceptions (tick ✓ all that apply)

✓	No prior violations or exceptions have occurred since the original approval
☐	Prior violations or exceptions have been reported since the last review and have already been acknowledged or approved
☐	Unreported minor violations that have occurred since the last review, as well as significant deviations not yet reported, are attached for review

9. Amendments (tick ✓ all that apply)

✓	No prior amendments have been made since the original approval
☐	Prior amendments have been reported since the last review and have already been approved
☐	New protocol changes/ amendments are requested as part of this continuing review (See note below)

Note: If new protocol changes are being requested in this review, please complete an amendment form (FHS006).
Specific changes in the amended protocol and consent/assent forms must be **bolded**, *italicised* or tracked and all changes must include a rationale.

10. Adverse events

10.1 Please provide below or attach a narrative summary of serious adverse events and/ or unanticipated problems since the last progress report. Please indicate changes made to the protocol and informed consent document(s) as a result (if not already reported to the HREC). Please comment on whether causality to any study procedure or intervention could be established.
N/A

10.2 Have participants received appropriate treatment/ follow-up/ referral when indicated (e.g. in the case of abnormal or incidental clinical findings, distress or anxiety)?		
☐ Yes	☐ No	✓ Not applicable
If yes, please describe:		

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

11. Summary of Monitoring and Audit Activities (tick ✓)

11.1 Was this study monitored or audited by an external agency (e.g. SAHPRA, FDA)?		
☐ Yes	☐ No	✓ Not applicable

11.2 Did a Data and Safety Monitoring Board publish a report?		
☐ Yes	☐ No	✓ Not applicable

11.3 If yes, please identify the agency and attach a summary of the findings.					
Agency Name		Report attached	☐ Yes	☐ No	✓ Not applicable
		DSMB report attached	☐ Yes	☐ No	✓ Not applicable

11.4 Has there been any agency, institutional or other inquiry into non-compliance in this study, or any finding of non-compliance concerning a member of the research team?	
☐ Yes	✓ No
If yes, please explain:	

12. Level of risk (tick ✓)

12.1 In light of your experience of this research, please indicate whether the level of risk to participants has:	
☐	Increased
☐	Decreased
✓	Shown no change
If there has been a change, please explain:	

12.2 Please provide a narrative summary of recent relevant literature that may have a bearing on the level of risk.
N/A

13. Statement of conflict of interest

Has there been any change in the conflict of interest status of this protocol since the original approval? (tick ✓)	
☐ Yes	✓ No

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

If yes, please explain and if necessary, attach a revised conflict of interest statement (Section #7 in the New Protocol Application Form FHS013):

14. Signature

My signature certifies that the above is complete and correct.			
Signature of PI	Erna Kerk	Date	05 May 2021

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

Appendix 2: B Positive Project Human Research Ethics Committee approval

UNIVERSITY OF CAPE TOWN
Faculty of Nealth Sciences
Human Reeearcls Ethics Committee

Room E52-24 Old Main Building
Groote Schuur Haspital
Observatory 7925
Talephona [021] 406 6338 • Facsimile [021] 406 6411
Email: shuret\a. thomas@uct.ac.za
Website: www health uct ac.za/fhs/research/humanethics/forms

14 August 2015

HREC REF: 541/1015

A/Prof A Boulle
CIDER
Public Health & Family Medicine
5*^ floor, Falmouth Building

Dear A/Prof Boulle

PROJECT TITLE: B POSITIVE: A POPULATION BABED EVALUATION OF EXPANDED (ANTI-RETROVIRAL THERAPY) ART ACCESS IN PREGNANCY (SHORT TITLE:'B POSITIVE')

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee.

It is a pleasure to inform you that the HREC has formally approved the above-mentioned study.

Approval is granted for one year until the 30a Auguet 2016.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Yours sincerely

PROFESSOR f•I BLOCKPIAN
CHAIRPERSON. FHS HUNAN RESEARCH ETHIC OSI IITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRBOOOO1938
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI),and Declaration of Helsinki guidelines.

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
Email: nosi.tsama@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

13 November 2015

HREC REF: 749/2015

A/Prof A Boulle
CIDER
Public Health & Family Medicine
Falmouth Building

Dear A/Prof Boulle

PROJECT TITLE: A POPULATION BASED EVALUATION OF EXPANDED (ANTI-RETROVIRAL THERAPY) ART ACCESS IN PREGNANCY ('B POSITIVE') Sub-study linked to 541/2015

Thank you for your letter to the Faculty of Health Sciences Human Research Ethics Committee dated 06 November 2015.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30thNovember 2016.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Yours sincerely

TBurgess

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI),and Declaration of Helsinki guidelines.

Appendix 3: Western Cape government approvals

Western Cape Government
Health

STRATEGY & HEALTH SUPPORT
Health.Research%westerncape.gov.za
!el: +27 21 483 6857: fax: *2Z 21 483 9895
5" Floor, Norton Rose House,, 8 RieDeek Street, Cape Town, 8001

REFERENCE: WC_2016RP6 286
ENQUIRIES: Ms Charlene Roderick

University of Cope Town

Anzio Rood

Observatory

Cope lown

7925

For attention: Dr Andile Nofemela. Prof London Myer, Dr Emma Kalk, Prof Andrew Boulle, Dr Mary Ann Davies, Dr Ushma Mehta, Dr Gregory Petro

Re: B positive: A population based evaluation of expanded ART (onfiretrovirol therapy) access in pregnancy.

Thank you for submitting your proposal to undertake the above-mentioned study. We ore pleased to inform *Y* thot the department has granted you approval tor your research.

Please contact following people to assist you with any further enquiries in accessing the following sites:

Gugulefhu CHC	Lungo Mokombo	021 637 1280

Kindly ensure that the following are adhered to:

1. Arrangements can be made with managers, providing that normal activities at requested facilities ore not interrupted.
2. Researchers, in accessing provincial health facilities, are expressing consent to provide the department with an electronic copy of the final feedback (annexure 9) within six months of

completion of research. This can be submitted to the provincial Research Co-ordinator (Health.ResearchCwesterncape.gov.za).

3. In the event where the research project goes beyond the estimated comp/etion date which was submitted. researchers are expected to complete and submit a progress report (Annexure 8) to the provincial Research Co-ordinator (Health.Research%westerncape.gov.za).

4. The reference number above should be quoted in all future correspondence.

Yours sincerely

DR A HAWKRI

DIRECTOR: HEALTH IMPACT ASSESSMENT

DATE:

CC: POLCKERS DIRECTOR:KLIPFONTEIN/MITCHELLS PLAIN

Western Cape Government
Health

GROOTE SCHUUR HOSPITAL

Enquiries: DrBernadette Eick
E-mail : *Bernadette.Eick@westerncape.gov.za*

Professor Andrew Boulle
Centre for Infectious Disease Epidemiology & Research
School of Public Health & Family Medicine

E-mail: Andrew.Boulle@uct.ac.za / Emma.Kalk@uct.ac.za

Dear Professor Boulle

RESEARCH PROJECT EXTENSION: A Population Based Evaluation of Expanded (Anti-Retroviral Therapy) ART Access in Pregnancy ('B- Positive')

Your recent communication to the hospital refers.

The extension of your research is approved in accordance with UCT Ethics clearance, until **30 August 2018**.

As previously mentioned:

a) Your research may not interfere with normal patient care.
b) Hospital staff may not be asked to assist with the research.
c) No hospital consumables and stationary may be used.
d) No patient folders may be removed from the premises or be inaccessible.
e) Please provide the research assistant/field worker with a copy of this letter as verification of approval.
f) Confidentiality must be maintained at all times.
g) Once the research is complete, please submit a copy of the publication or report.

I would like to wish you every success with the project.

Yours sincerely

DR BERNADETTE EICK
CHIEF OPERATIONAL OFFICER
Date: 1 November 2017
BE/vms

C.C. Mr L. Naidoo, Professor E. Weimann, Professor Denny, Professor Anthony

G46 Management Suite, Old Main Building,
Observatory 7925

Tel: +27 21 404 6288 fax: +27 21 404 6125

Private Bag X,
Observatory, 7935

www.capegateway.go.v.za

Supplementary tables

Supplementary Table 1. Women who filled one or more prescription during pregnancy per dataset (ATC levels 2 - 5)

Total number of patients per level ATC code	***PER***	***PHDC***	***Cohort***	***Master List***
A02	0	0	4	4
A02AA04	0	0	36	36
A02AA05	0	37	3	40
A02AB01	0	3	10	13
A02AD01	0	0	40	40
A02AH	0	0	41	41
A02B	0	0	1	1
A02BA01	0	0	1	1
A02BA02	0	1	0	1
A02BB01	0	7	2	9
A02BC01	0	3	0	3
A02BC03	0	6	1	7
A02BX05	0	0	1	1
A02BX13	0	0	69	69
A03BA01	0	1	0	1
A03BB01	0	2	1	3
A03FA01	0	0	3	3
A06	0	0	4	4
A06AA02	0	0	2	2
A06AB02	0	1	9	10
A06AB05	0	0	1	1
A06AB06	0	13	3	15
A06AD04	13	0	7	20
A06AD11	0	5	3	8
A06AD65	0	0	4	4

A06AG01	0	1	0	1
A06AG04	0	2	0	2
A06AG11	0	6	0	6
A07AA02	0	0	1	1
A07DA03	3	8	11	17
A10AB01	0	8	2	8
A10AC01	0	0	3	3
A10BA02	1	13	5	14
A10BB12	1	5	4	6
A10BD02	0	0	6	6
A11AA03	0	0	17	17
A11DA01	0	1	0	1
A11DB	0	0	10	10
A11EA	0	0	74	74
A11GA01	0	9	29	36
A11GB01	0	0	1	1
A11HA02	2	162	5	163
A11JA	0	0	3	3
A11JB	0	0	1	1
A12	0	0	1	1
A12AA03	0	0	2	2
A12AA04	2	0	8	10
A12BA02	0	0	4	4
A12BA51	0	0	1	1
A12CA01	0	2	1	3
A12CB01	0	2	1	3
A12CC02	0	0	1	1
A12CE01	0	2	1	3
A12CX	0	0	1	1
B01AA03	1	0	0	1
B01AB05	0	1	0	1
B03AA07	809	160	742	936
B03AD	0	0	4	4
B03AD02	7	0	43	49

B03BA01	0	1	0	1
B03BB01	805	161	748	936
B05AA05	0	2	0	2
B05CB04	7	0	6	13
B05XA01	0	1	0	1
C01BB01	0	2	0	2
C02	1	0	0	1
C02AB01	0	19	5	19
C03AA03	7	12	23	28
C03CA01	0	1	0	1
C05AX02	0	0	12	12
C07AB03	0	1	0	1
C08CA01	0	0	3	3
C08CA05	5	1	0	6
C09AA02	3	6	6	8
C10AA01	1	2	3	4
C10AA05	0	1	0	1
D01AC01	4	44	41	79
D01AE12	0	0	1	1
D01AE13	0	0	1	1
D01AE17	0	0	1	1
D02	0	1	9	10
D02AB	0	0	1	1
D02AC	3	37	32	64
D02B	0	0	2	2
D04	0	7	1	8
D04AB06	0	1	1	2
D04AX	0	0	4	4
D06AX09	0	0	2	2
D07	0	0	4	4
D07AA02	0	0	2	2
D07AB09	0	0	4	4
D07AC01	0	4	3	7
D07AC04	0	0	1	1

D07AC15	0	0	1	1
D07AD01	0	1	0	1
D07CC02	0	4	0	4
D08A	0	0	1	1
D08AC02	0	0	1	1
D08AE05	0	0	1	1
D08AG02	0	4	0	4
D08AK04	0	0	1	1
G01	0	0	1	1
G01AF	0	0	11	11
G01AF02	3	0	2	5
G03AA07	0	4	0	4
G03AA09	0	0	1	1
G03AB03	0	0	4	4
G03AC01	0	0	34	34
G03AC06	0	0	78	78
G03AC08	0	0	24	24
G03DA04	0	0	1	1
G03XB01	0	3	0	3
G04B	0	0	51	51
G04BC	0	0	23	23
H01	0	0	3	3
H02AB07	1	5	2	7
H03	0	0	1	1
H03AA01	0	1	0	1
H03BB01	0	1	0	1
J01AA02	0	0	5	5
J01CA	0	0	12	12
J01CA04	12	59	34	99
J01CE01	12	0	31	43
J01CF05	0	19	1	19
J01CR02	3	38	7	44
J01DB04	0	1	0	1
J01DC02	0	7	0	7

J01DD04	33	0	5	36
J01DH03	0	1	0	1
J01EC01	0	0	3	3
J01EE01	0	32	4	36
J01FA10	35	46	11	84
J01MA02	0	9	4	12
J01XA01	0	1	0	1
J01XD01	33	68	90	164
J01XE01	0	3	0	3
J04AB	0	0	36	36
J04AC01	3	156	7	157
J04AM	0	0	8	8
J05AB01	0	0	1	1
J05AE03	0	2	0	2
J05AE08	0	1	0	1
J05AE10	0	1	0	1
J05AF01	8	2	0	10
J05AF04	0	1	0	1
J05AF05	9	15	0	23
J05AF06	1	5	0	5
J05AF07	149	37	1	174
J05AF09	148	357	0	374
J05AG01	5	13	0	14
J05AG03	146	41	0	173
J05AG04	1	1	0	2
J05AH02	0	3	0	3
J05AJ03	0	1	0	1
J05AM02	0	3	0	3
J05AR	2	20	78	95
J05AR01	3	21	0	24
J05AR02	0	5	2	7
J05AR03	0	19	0	19
J05AR06	21	0	385	390
J05AR10	8	26	9	30

J05AR11	0	0	2	2
J07	0	0	17	17
J07BB01	226	0	3	227
M01AB01	0	0	1	1
M01AB05	1	1	4	6
M01AC01	0	0	1	1
M01AE01	0	38	45	80
M01AE51	0	0	2	2
M02AC	0	9	5	14
N02	0	0	12	12
N02AJ01	0	0	14	14
N02AJ06	0	0	1	1
N02AJ08	0	0	1	1
N02AJ15	0	0	1	1
N02AX02	0	22	18	35
N02BA01	1	15	252	260
N02BE01	19	169	415	499
N02BE51	0	0	3	3
N03AB02	1	1	2	2
N03AE01	0	0	1	1
N03AG01	0	0	1	1
N05AA01	0	0	1	1
N05AD01	0	1	0	1
N05AN01	0	0	1	1
N05AX08	0	3	2	3
N06AA09	1	9	2	11
N06AB03	1	2	1	4
N06AB04	0	0	1	1
N06AX03	0	1	0	1
N06BC01	0	0	2	2
N07BC02	0	0	1	1
P02BA01	0	1	0	1
P02CA01	0	2	0	2
P03AA04	0	0	2	2

P03AX01	2	12	4	17
R01.	0	0	21	21
R01AA04	0	0	1	1
R01AA05	0	0	5	5
R01AA07	0	3	6	9
R01AD08	0	2	3	4
R01BA01	0	0	2	2
R01BA02	0	0	30	30
R01BA03	0	0	8	8
R01BA52	0	0	1	1
R03AC02	6	15	12	21
R03AK06	1	0	0	1
R03AK12	0	0	4	4
R03BA02	4	9	2	10
R03CC02	0	0	1	1
R03D	0	0	1	1
R03DA04	0	0	71	71
R05.	0	0	66	66
R05CA03	0	0	38	38
R05DA04	0	0	4	4
R05DA09	0	0	9	9
R06AA02	0	0	56	56
R06AA09	0	0	5	5
R06AB04	3	46	57	99
R06AC01	0	0	1	1
R06AD	0	0	1	1
R06AD02	0	3	1	3
R06AE03	0	1	2	3
R06AE07	0	3	2	5
R06AX02	0	0	4	4
S01	0	0	1	1
S01AA01	0	2	0	2
S01CB03	2	17	8	24
S01EC01	1	0	0	1

S01KA02	0	1	0	1
S02AA10	0	1	0	1
S02DC	0	1	0	1
V	0	2	0	2
V03AF03	0	0	1	1
V03AN01	0	0	1	1
V04	0	4	1	5
Traditional Medicine	0	0	146	146
Herbal and complementary Remedies	0	0	124	124
Home Remedies	0	0	100	100
None	131	195	20	2

Supplementary Table 2: Total amount of times a medication exposure were reported (ATC code level 2 – 5)

Total reported medication per ATC code	***PER***	***PHDC***	***Cohort***	***Master List***
A02	0	0	7	7
A02AA04	0	0	72	72
A02AA05	0	53	3	56
A02AB01	0	3	11	14
A02AD01	0	0	80	80
A02AH	0	0	62	62
A02B	0	0	1	1
A02BA01	0	0	4	4
A02BA02	0	1	0	1
A02BB01	0	8	2	10
A02BC01	0	4	0	4
A02BC03	0	12	1	13
A02BX05	0	0	3	3
A02BX13	0	0	240	240
A03BA01	0	3	0	3
A03BB01	0	2	2	4
A03FA01	0	0	3	3
A06	0	0	7	7
A06AA02	0	0	3	3
A06AB02	0	2	20	22
A06AB05	0	0	1	1
A06AB06	0	14	5	19
A06AD04	13	0	13	26
A06AD11	0	5	4	9
A06AD65	0	0	7	7
A06AG01	0	1	0	1
A06AG04	0	4	0	4
A06AG11	0	6	0	6
A07AA02	0	0	1	1

A07DA03	3	8	18	29
A10AB01	0	82	4	86
A10AC01	0	0	3	3
A10BA02	1	69	5	75
A10BB12	1	18	8	27
A10BD02	0	0	11	11
A11AA03	0	0	24	24
A11DA01	0	6	0	6
A11DB	0	0	10	10
A11EA	0	0	104	104
A11GA01	0	12	32	44
A11GB01	0	0	1	1
A11HA02	3	426	5	434
A11JA	0	0	4	4
A11JB	0	0	1	1
A12	0	0	1	1
A12AA03	0	0	2	2
A12AA04	3	0	12	15
A12BA02	0	0	8	8
A12BA51	0	0	1	1
A12CA01	0	2	1	3
A12CB01	0	2	1	3
A12CC02	0	0	1	1
A12CE01	0	2	1	3
A12CX	0	0	1	1
B01AA03	1	0	0	1
B01AB05	0	1	0	1
B03AA07	1233	292	1365	2890
B03AD	0	0	6	6
B03AD02	7	0	47	54
B03BA01	0	1	0	1
B03BB01	1228	307	1382	2917
B05AA05	0	4	0	4
B05CB04	7	0	6	13

B05XA01	0	2	0	2
C01BB01	0	2	0	2
C02	1	0	0	1
C02AB01	0	51	7	58
C03AA03	8	57	40	105
C03CA01	0	2	0	2
C05AX02	0	0	27	27
C07AB03	0	1	0	1
C08CA01	0	0	3	3
C08CA05	5	1	0	6
C09AA02	3	29	10	42
C10AA01	1	3	7	11
C10AA05	0	5	0	5
D01AC01	4	56	107	167
D01AE12	0	0	1	1
D01AE13	0	0	1	1
D01AE17	0	0	2	2
D02	0	4	14	18
D02AB	0	0	2	2
D02AC	3	58	59	120
D02B	0	0	2	2
D04	0	9	1	10
D04AB06	0	1	1	2
D04AX	0	0	6	6
D06AX09	0	0	5	5
D07	0	0	4	4
D07AA02	0	0	3	3
D07AB09	0	0	4	4
D07AC01	0	5	4	9
D07AC04	0	0	1	1
D07AC15	0	0	1	1
D07AD01	0	1	0	1
D07CC02	0	4	0	4
D08A	0	0	1	1

D08AC02	0	0	1	1
D08AE05	0	0	1	1
D08AG02	0	4	0	4
D08AK04	0	0	1	1
G01	0	0	2	2
G01AF	0	0	21	21
G01AF02	3	0	3	6
G03AA07	0	4	0	4
G03AA09	0	0	1	1
G03AB03	0	0	5	5
G03AC01	0	0	34	34
G03AC06	0	0	78	78
G03AC08	0	0	25	25
G03DA04	0	0	1	1
G03XB01	0	4	0	4
G04B	0	0	87	87
G04BC	0	0	29	29
H01	0	0	3	3
H02AB07	1	5	2	8
H03	0	0	1	1
H03AA01	0	6	0	6
H03BB01	0	4	0	4
J01AA02	0	0	9	9
J01CA	0	0	17	17
J01CA04	12	71	69	152
J01CE01	22	0	64	86
J01CF05	0	20	2	22
J01CR02	3	43	10	56
J01DB04	0	1	0	1
J01DC02	0	9	0	9
J01DD04	34	0	16	50
J01DH03	0	2	0	2
J01EC01	0	0	3	3
J01EE01	0	74	6	80

J01FA10	36	53	30	119
J01MA02	0	10	9	19
J01XA01	0	3	0	3
J01XD01	36	80	267	383
J01XE01	0	3	0	3
J04AB	0	0	70	70
J04AC01	3	414	7	424
J04AM	0	0	9	9
J05AB01	0	0	1	1
J05AE03	0	14	0	14
J05AE08	0	8	0	8
J05AE10	0	6	0	6
J05AF01	8	5	0	13
J05AF04	0	2	0	2
J05AF05	10	47	0	57
J05AF06	1	11	0	12
J05AF07	154	84	1	239
J05AF09	153	1681	0	1834
J05AG01	5	48	0	53
J05AG03	151	99	0	250
J05AG04	1	6	0	7
J05AH02	0	3	0	3
J05AJ03	0	7	0	7
J05AM02	0	9	0	9
J05AR	2	51	143	196
J05AR01	3	74	0	77
J05AR02	0	12	3	15
J05AR03	0	79	0	79
J05AR06	21	0	820	841
J05AR10	9	87	10	106
J05AR11	0	0	2	2
J07	0	0	27	27
J07BB01	227	0	5	232
M01AB01	0	0	2	2

M01AB05	1	1	9	11
M01AC01	0	0	1	1
M01AE01	0	45	85	130
M01AE51	0	0	6	6
M02AC	0	11	6	17
N02	0	0	17	17
N02AJ01	0	0	15	15
N02AJ06	0	0	1	1
N02AJ08	0	0	1	1
N02AJ15	0	0	1	1
N02AX02	0	42	36	78
N02BA01	1	51	935	987
N02BE01	20	274	1527	1821
N02BE51	0	0	3	3
N03AB02	1	4	4	9
N03AE01	0	0	3	3
N03AG01	0	0	3	3
N05AA01	0	0	1	1
N05AD01	0	11	0	11
N05AN01	0	0	1	1
N05AX08	0	20	4	24
N06AA09	1	41	4	46
N06AB03	1	9	1	11
N06AB04	0	0	2	2
N06AX03	0	2	0	2
N06BC01	0	0	2	2
N07BC02	0	0	1	1
P02BA01	0	1	0	1
P02CA01	0	2	0	2
P03AA04	0	0	3	3
P03AX01	2	15	8	25
R01.	0	0	44	44
R01AA04	0	0	1	1
R01AA05	0	0	9	9

R01AA07	0	3	11	14
R01AD08	0	7	6	13
R01BA01	0	0	3	3
R01BA02	0	0	83	83
R01BA03	0	0	9	9
R01BA52	0	0	1	1
R03AC02	10	39	28	77
R03AK06	1	0	0	1
R03AK12	0	0	8	8
R03BA02	4	24	2	30
R03CC02	0	0	1	1
R03D	0	0	2	2
R03DA04	0	0	126	126
R05.	0	0	88	88
R05CA03	0	0	65	65
R05DA04	0	0	4	4
R05DA09	0	0	9	9
R06AA02	0	0	108	108
R06AA09	0	0	8	8
R06AB04	3	67	140	210
R06AC01	0	0	1	1
R06AD	0	0	1	1
R06AD02	0	3	1	4
R06AE03	0	2	4	6
R06AE07	0	3	5	8
R06AX02	0	0	7	7
S01	0	0	1	1
S01AA01	0	2	0	2
S01CB03	2	20	14	36
S01EC01	1	0	0	1
S01KA02	0	3	0	3
S02AA10	0	1	0	1
S02DC	0	1	0	1
V	0	2	0	2

V03AF03	0	0	1	1
V03AN01	0	0	2	2
V04	0	13	1	14
Traditional Medicine	0	0	227	227
Herbal and complementary Remedies	0	0	236	236
Home Remedies	0	0	155	155
None	131	195	20	2

Supplementary Table 3: Proportion of women who filled one or more prescriptions during pregnancy per dataset (ATC level 1)

Distinguishable medication reported at least once as per 1st ATC level							*Total N:*	*967*
1st level ATC classification	PER		PHDC		Self-Report		Master list	
	N	%	N	%	N	%	N	%
A: Alimentary tract and metabolism	22	2%	233	24%	281	29%	446	46%
B: Blood and blood forming organs	817	84%	168	17%	753	78%	939	97%
C: Cardiovascular system	13	1%	31	3%	38	4%	57	6%
D: Dermatologicals	7	1%	82	8%	102	11%	162	17%
G: Genito urinary system and sex hormones	3	0%	7	1%	196	20%	205	21%
H: Systemic hormonal preparations, excluding sex hormones and insulins	1	0%	7	1%	6	1%	13	1%
J: Anti-infectives for systemic use	395	41%	455	47%	535	55%	704	73%
M: Musculo-skeletal system	1	0%	43	4%	56	6%	94	10%
N: Nervous system	23	2%	181	19%	555	57%	624	65%
P: Antiparasitic products, insecticides and repellents	2	0%	15	2%	6	1%	22	2%
R: Respiratory system	10	1%	63	7%	233	24%	269	28%
S: Sensory organs	3	0%	22	2%	9	1%	31	3%
V: Various	0	0%	6	1%	3	0%	9	1%
Traditional Medicine	0	0%	0	0%	146	15%	146	15%
Herbal and complementary Remedies	0	0%	0	0%	124	13%	124	13%
Home Remedies	0	0%	0	0%	100	10%	100	10%
None	131	14%	195	20%	20	2%	2	0%

Supplementary Table 4. Total number of times a medication exposure were reported (ATC code level 1)

Total Reported at 1st level

1st level ATC classification	PER (N)	PHDC (N)	Self-Report (N)	Master list (N)
A: Alimentary tract and metabolism	24	745	811	1580
B: Blood and blood forming organs	2476	607	2806	5889
C: Cardiovascular system	18	151	94	263
D: Dermatologicals	7	142	222	371
G: Genito urinary system and sex hormones	3	8	286	297
H: Systemic hormonal preparations, excluding sex hormones and insulins	1	15	6	22
J: Anti-infective for systemic use	891	3116	1600	5607
M: Musculo-skeletal system	1	57	109	167
N: Nervous system	24	454	2562	3040
P: Antiparasitic products, insecticides and repellents	2	18	11	31
R: Respiratory system	18	148	775	941
S: Sensory organs	3	27	15	45
V: Various	0	15	4	19
Traditional Medicine	0	0	227	237
Herbal and complementary Remedies	0	0	236	236
Home Remedies	0	0	155	155
None	131	195	20	2
Total	3599	5698	9939	18892

Supplementary Table 5. Total number of times a medication exposure were reported per therapeutic class (i.e. number of prescriptions)

ATC CODE		***PER***	***PHDC***	***Cohort***	***Master List***
A	**ALIMENTARY TRACT AND METABOLISM**	22	300	440	737
A01	Stomatological preparations	0	0	0	0
A02	Drugs for acid-related disorders	0	57	209	266
A02A	Antacids	0	40	130	170
A02B	Medications for peptic ulcer and gastro-oesophageal reflux	0	17	75	92
A03	Drugs for functional and motility gastrointestinal disorders	0	3	4	7
A04	Antiemetics and antinauseants	0	0	0	0
A05	Bile and Liver therapy	0	0	0	0
A06	Laxatives	13	28	33	73
A07	Anti-diarrhoeals	3	8	12	18
A09	Digestives, including enzymes	0	0	0	0
A10	Drugs used in diabetes	2	26	20	37
A10A	Insulin	0	8	5	11
A10B	Blood glucose lowering drugs, excluding insulins	2	18	15	26
A11	Vitamins	2	172	140	306
A12	Mineral supplements	2	6	21	29
B	**BLOOD AND BLOOD-FORMING ORGANS**	1629	326	1543	1944
B01	Antithrombotic agents	1	1	0	2
B01AB	Heparins	0	1	0	1
B01AC	Platelet aggregation inhibitors	0	0	0	0
B02	Anti-haemorrhagics	0	0	0	0
B03	Anti-anaemic preparations	1621	322	1537	1926
B03A	Iron	816	160	789	989
B03B	Folic acid	805	162	748	937
B05	Plasma expanders, osmotic diuretics, and parenteral nutrition solutions	7	3	6	16
C	**CARDIOVASCULAR SYSTEM**	17	45	52	86
C01	Cardiac therapy	0	2	0	2
C02	Antihypertensives	1	19	5	20
C02AB01	Methyldopa	0	19	5	19
C03	Diuretics	7	13	23	29
C07	Beta-blocking agents	0	1	0	1
C08	Calcium-channel blockers	5	1	3	9
C09	Agents acting on the renin-angiotensin system	3	6	6	8
C09A	Ace inhibitors	3	6	6	8
C10	Serum lipid-modifying agents	1	3	3	5
D	**DERMATOLOGICALS**	7	103	115	207
D01	Antifungals for dermatological use	4	44	44	82
D02	Emollients and protectants	3	38	44	77
D03	Preparations for the treatment of wounds	0	0	0	0
D04	Anti-pruritics	0	8	6	14

D05	Anti-psoriatics	0	0	0	0
D06	Antibiotics and chemotherapeutics for dermatological use	0	0	2	2
D07	Corticosteroids, dermatological preperations	0	9	15	24
D08	Antiseptics and disinfectants	0	4	4	8
D10	Anti-acne preperations	0	0	0	0
D11	Other dermatologicals	0	0	0	0
G	**GENITOURINARY SYSTEM AND SEX HORMONES**	3	7	230	240
G01	Gynaecological anti-infectives and antiseptics	3	0	14	17
G02	Other gynaecologicals	0	0	0	0
G02CA	Sympathomimetics, labour repressants	0	0	0	0
G02CB	Prolactin inhibitors	0	0	0	0
G03	Sex hormones, modulators of the genital system and contraception	0	7	142	149
G03A	Hormonal contraceptives	0	4	141	145
G03C	Estrogens	0	0	0	0
G03D	Progestogens	0	0	1	1
G03G	Gonadotrophins	0	0	0	0
G04	Urologicals	0	0	74	74
H	**SYSTEMIC HORMONAL PREPERATIONS, EXCLUDING SEX HORMONES AND INSULINS**	1	7	230	237
H01	Pituitary and hypothalamic hormones and analogues	0	0	3	3
H02	Corticosteroids for systemic use	1	5	2	7
H03	Thyroid therapy	0	2	1	3
H03A	Thyroid hormones	0	1	0	1
H03B	Antithyroid preperations	0	1	0	1
H04	Pancreatic hormones	0	0	0	0
H05	Hypercalcaemia and metabolic bone disease	0	0	0	0
J	**GENERAL ANTI-INFECTIVES FOR SYSTEMIC USE**	858	1014	756	2370
J01	Anti-bacterials for systemic use	128	284	207	570
J02	Anti-mycotics for systemic use	0	0	0	0
J04	Anti-mycobacterials	3	156	51	201
J05	Antivirals for systemic use	501	574	478	1355
J05AF	Nucleoside and nucleotide reverse transcriptase inhibitors	315	417	1	587
J05AG	Non-nucleoside and nucleotide reverse transcriptase inhibitors	152	55	0	189
J05AR	ARV combinations	34	91	476	567
J05AE	Protease inhibitors	0	4	0	4
J05AX	Other ARV's	0	0	0	0
J06	Immunoglobulins	0	0	0	0
J07	Vaccines	226	0	20	244
M	**MUSCULOSKELETAL SYSTEM**	1	48	58	104
M01	Anti-inflammatory and antirheumatic products	1	39	53	90
M02	Topical products for joint and muscular pain	0	9	5	14
M03	Muscle relaxants	0	0	0	0
M04	Antigout preperations	0	0	0	0
N	**CENTRAL NERVOUS SYSTEM**	154	418	752	858
N01	Anaesthetics	0	0	0	0
N02	Analgesics	20	206	717	826
N02BE	Non-opioid analgesics	19	169	418	502

N02CC	Selective serotonin agonists	0	0	0	0
N03	Antiepileptics	1	1	4	4
N04	Antiparkinsonian agents	0	0	0	0
N05	Psycholeptics	0	4	4	6
N06	Psychoanaleptics	2	12	6	19
N06A	Antidepressants	2	12	4	17
N07B	Methadone	0	0	1	1
N07	Other nervous system drugs	0	0	1	1
P	**ANTIPARASITIC PRODUCTS**	2	15	6	22
P01	Anti-protozoals	0	0	0	0
P02	Anti-helmintics	0	3	0	3
P03	Ectoparasiticides, including scabicides	2	12	6	19
R	**RESPIRATORY SYSTEM**	14	82	414	484
R01.	Nasal decongestants	0	0	21	21
R03.	Drugs for obstructive airway disease	0	0	0	0
R03A	Adrenergic inhalants	7	15	16	26
R03B	Other inhalants	4	9	2	10
R05.	Cough and cold preparations	0	0	66	66
R06.	Antihistamines for systemic use	0	0	0	0
S	**SENSORY ORGANS**	3	22	9	31
S01	Opthalmologicals	3	20	9	29
S02	Otologicals	0	2	0	2
V	**VARIOUS**	0	6	3	9
V03	Other therapeutic products	0	0	2	2
V08	Contrast media	0	0	0	0