The use of unlicensed and off label drugs in Tygerberg - Hospital neonatal intensive care unit -

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April 2014

A Dissertation Submitted to the

Faculty of Medicine and Health Sciences

In part fulfilment of the Requirements

For the Degree of -
M MED PAED -

Department of Pediatrics and Child Health -

Stellenbosch University -

2013 -

Signature Page

The use of unlicensed and off label drugs in Tygerberg Hospital neonatal intensive care unit

A Dissertation Presented -

By -

Dr Angeline Thomas -

As the Supervisor and Principal Investigator, I hereby certify that I have read this dissertation prepared under my direction and recommend that it be accepted as fulfilling the dissertation requirement.

Signed: _____ Date: 2014

Professor M. Kruger

DECLARATION

I, the undersigned, hereby declare that the work contained in this assignment is my original work and that I have not previously submitted it, in its entirety or in part, at any university for a degree.

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ACKNOWLEDGEMENTS

I would like to thank my supervisor Professor M. Kruger for her wisdom, guidance and support. Her enthusiasm and passion for the topic was a great inspiration and a push forward for me in the right direction. I would also like to thank Mrs Anita Fourie for all her help and organization skills. I appreciate the teamwork and motivation from my research colleagues. I acknowledge my dear friend and colleague Dr Deepthi Abraham for her inspiration and support. My family, have been my pillar of strength and I dedicate this to them, especially to my husband Jim Koshy. Above all, I praise and thank God for guiding me through and making all things possible.

ABSTRACT

OBJECTIVE

The aim of this study is to establish the frequency of unlicensed and off label drug use in infants admitted to the neonatal intensive care unit (NICU) in Tygerberg Hospital.

METHOD

This was a prospective descriptive survey conducted over 3 consecutive months (September 2011-November 2011) of all medicine charts of neonates admitted during this time period to the NICU. Data collected included demography, diagnoses, medicines prescribed according to dose, frequency, route of administration and indication. Medicine use was defined as unlicensed, licensed or off label use according to the latest South African Medicines Formulary (2012) and the manufacturer's package insert. Unlicensed drug use is per definition a drug not registered with South African Medicine Control Council (SA MCC) for children and off label drug use is where the use is outside of its authorized license with SA MCC.

RESULTS

There were 112 neonates enrolled in the study, of whom 51% were preterm and 49% term infants. The most common diagnoses on admission for the preterm babies were hyaline membrane disease (33%) and sepsis (21%), while it was hypoxic ischemic encephalopathy (42%) and post-operative care (22%) for term infants. There were 759 drug events of which 37% were licensed and followed all the licensing terms, 51% were prescribed in an off label manner and the remaining 12% were of unlicensed drugs. The most common reasons off label drug use were for weight (74%), followed by age (44%), frequency (44%), indication (21%), or a route not described in the licensing terms (13%). There was a lack of pediatric data for 9% of the drugs prescribed. In 203 drug events (27%) a drug was used in an off label manner for more than one reason. Sixty one percent of the drugs used had no information on the use of the drug in neonates.

CONCLUSION

This is the first study conducted in an African NICU, according to our knowledge and the results are similar to studies conducted in Europe and America. Neonates are exposed to a

significant proportion of unlicensed and off label drugs. Neonatal clinical trials should be conducted to address the need for proven safe and efficacious treatment for neonates.

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DEFINITIONS

Neonate:

This is the term for a new-born up to chronological age of 28 days after birth.

Gestational age:

This refers to the time period between conception and birth.

Premature:

This is the term used for a baby born at less than 37 weeks gestational age.

Term:

This refers to a baby born between 38 and 42 weeks gestational age.

Chronological age:

This refers to the time period after birth.

HIV exposed:

Babies who were born to Human Immunodeficiency Virus infected women.

Pharmacokinetics:

This is the study of the mechanism by which a drug is absorbed, distributed, metabolized and eliminated in the body.

Pharmacodynamics:

This is the study of the effects of a drug on the body.

Off label:

Refers to a drug that is used differently to the instructions given in the package insert or the way the drug is registered to be used. This can be in terms of weight, age, indication, lack of pediatric data, route of administration and frequency.

Unlicensed drug:

This is a drug that is used before it is registered with the licensing authority of a country. If a registered drug is reformulated, it is then also considered as an unlicensed drug.

Extemporaneous compounding:

This refers to a drug that is converted from one form to another in order for easier administration to the patient, and thus changing some of its properties. For example, a tablet form of a drug is crushed and mixed with a liquid medium so children can easily swallow it.

Special formulations:

These are drugs, already licensed in one form, but specially reformulated under a special license and changed to another form.

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1. Introduction

1.1. Literature Review

There is a high incidence of the use of off label and unlicensed drugs in children, as documented in North America and Europe, but little has been documented from Africa.[1] The neonate population receives the majority of unlicensed drugs and off label drugs and is often excluded from clinical drug trials due to the vulnerability of this group.[2] The majority of the drugs are essential for the treatment of the neonates and there is no alternative medication available. [3]

Drug licensing was first introduced in the United States of America (USA) after the tragedies that took place in the 1960's. [4] Pregnant women were given thalidomide for morning sickness during their pregnancy and this resulted in their children being born with phocomelia. New-born babies, who received intravenous chloramphenicol, developed "grey baby" syndrome because they did not have the necessary enzymes to metabolize the drug. [5] Subsequently the USA established a statutory body to regulate medicines control and for registration of medicines after they had been proven to be safe for use. In the USA it is the Food and Drug Administration (FDA), in Europe the European Medicines Agency (EMEA) and in South Africa the Medicines Control Council (MCC) that has the authority of licensing a drug .[6-8]

There is a general lack of neonatal clinical drug trials mainly due to the vulnerability of neonates and small incentives for pharmaceutical companies to change a product licence of a drug that is already in use. [9] Many practitioners are forced to use off label drugs because there are no alternative drugs for children and the practice is acceptable provided the practitioner can prove that it was based on expert medical judgment in the best interests of the patient. [10, 11]

A study done in France showed that there is an increased risk of adverse drug reactions with the use of off label drugs in a pediatric setting.[12] Most of these drugs have only been tested in adults and are now being given to children. The pharmacokinetics and pharmacodynamics of drugs in children differ from that of adults.[13] This means that the absorption, metabolism and clearance of a drug are different in neonates compared to that in adults. Reasons for this include an immature gut, liver and kidneys in neonates, which

results in slower absorption, metabolism and excretion. Compared to adults, newborns have delayed gastric emptying and decreased gastric acid secretion. Drugs that are acid labile (example: penicillin) will therefore have an increased bioavailability than drugs that are weakly acidic (example: phenobarbitone). Neonates also have lower albumin levels and lower protein binding capacity, which influences drug availability. The rate of blood flow to the kidneys is approximately 10 times lower at birth compared to an adult. This will delay renal excretion of some drugs such as theophylline and increase their half-life. The percentage of body water content also causes differences in the volume of distribution of drugs like aminoglycosides. The water content is the highest in preterm neonates (80%) compared to term (70%) and even less in adults (60%). In a similar way, the pharmacodynamics and pharmacokinetics differs between preterm neonates, term neonates and infants, and gestational age must be taken into consideration when prescribing drugs. [13]

In the case of unlicensed drugs that are extemporaneously compounded, there is an increased risk of having errors in calculation, incorrect quantities mixed and inappropriate medium used, especially if not done by a qualified experienced pharmacist. This could result in an unstable product that could have fatal consequences and a short shelf life .[14, 15] It is essential to prove that potentially efficacious drugs are safe in children and there should be guidelines on how they should be administered. This can be done in two ways: The manufacturers can be encouraged to do clinical trials to determine the safety and efficacy of drugs in children, which can be motivated by establishing a national pediatric pharmacology research unit where the trials can be conducted. [9] Alternatively the safe use of off- label drugs can be promoted via case presentations, medical literature, conferences and expert advice from colleagues. [7] The first option is the ideal solution, but it is considered to be time consuming and expensive. Legislation is one option to ensure that the necessary drug studies are conducted in vulnerable populations to ensure that they also benefit from better medicines.[16] The USA took the lead in 1997 when the FDA provided a 6 month extension of patent protection of medicines and later in 1999 established the ‘Pediatric rule’ which made it a requirement that all the new drugs to be released into the market, had to be first tested in children. It was the “Best pharmaceuticals for children’s Act” in 2002 that made the provision for the study of neonatal medicine. Europe followed in the same year by releasing a document entitled “Better medicines for children” which later became legislation, demonstrating the European

Union's commitment to the issue.[16] Similar steps are yet to be taken by the rest of the world.

It is very important that parents are educated about off label and unlicensed use of drugs as most parents are not even aware of this practice. [17] It has been suggested by an article by Lenk, et al. that the best way to encourage our parent population to enrol their children into clinical trials will be by educating the parents about how common the use of off label drugs is and of how much value there is in the clinical trials.[17] It is also important to educate the medical practitioners of the experiences of their peers with the use of off label and unlicensed drugs so that a standard accepted form of treatment takes place. This can be done in a medical newsletter designed for this sole purpose, making it easier for practitioners to stay updated. [17]

In South Africa the Medicines and Related Substances Act 101 of 1965 and Regulation 45 do not allow pharmaceutical companies to disperse any information (written or oral) regarding off label use of a medicine to the public or other medical practitioners. [7] This would mean that South African doctors have limited resources for information on off label and unlicensed use of drugs in pediatrics. In countries like India, it is even illegal to prescribe off label and unlicensed drugs. [16] Despite this, the practice of off label drug use continues and most physicians are not even aware that they are doing so. The only way that a physician can ensure that he is not faced with litigation because of adverse effects from a drug used in an off label manner is to ensure that these drugs are safe through clinical trials.[18] The first step is to create awareness of this practice and its extent. There is currently only limited data from Africa and this study was done to show that this is not just a problem in Europe and United States of America, but that Africa is just as equally affected and therefore also needs to be part of a solution.

2. Aims

The aim of this study is to determine the use of unlicensed and off label drugs to neonates in the neonatal intensive care unit (NICU) setting in an academic hospital in South Africa, and to identify the drugs commonly used in this manner.

2.1. Primary Objectives

- To determine the use of unlicensed and off label drugs in NICU over 3 months, with regards to weight, age, indication, lack of pediatric data, route of administration and frequency.

2.2. Secondary Objectives

- To create a greater awareness of this practice of off label and unlicensed drug use in neonates.
- To promote the ruling that all new drugs should undergo drug trials in neonates before acquiring licensing.

3. Methodology

This was a prospective descriptive survey. The study population included all the neonates admitted to NICU at Tygerberg Hospital, an academic tertiary hospital in Cape Town, South Africa. This study was conducted over three consecutive months, September 2011 to November 2011, and data was updated daily during this period. The Tygerberg Hospital NICU is able to accommodate 12 babies at the same time, with 8 beds dedicated for the critically ill and 4 beds dedicated for those patients that need only high care.

A waiver of consent was obtained from the ethics committee as the data from each patient's file was linked to a unique study number, and no identifiable data was collected. Demographic data was collected for each patient that comprised of the age, weight, sex, and diagnosis. Details of their prescription were obtained from the prescription charts and included the dose, frequency, indication, and route of all medicines prescribed per patient and categorized as licensed, unlicensed or off label for age, weight, frequency, indication and route of administration. Two patients were readmitted during the period of study and therefore sampled twice.

The unlicensed drugs fell into 3 categories. The first category included the drugs that were already licensed in one form and then specially reformulated under a special licence and changed to another form, while the second category included licensed drugs that were extemporaneously compounded (tablet form crushed and mixed with water to form a suspension) and the third category was for imported drugs licensed for use in another country, but not South Africa.

The Health Research Ethics Committee of Stellenbosch University approved the protocol (ethics reference no: n11/07/214).

3.1. Inclusion criteria

A neonate that was admitted to Tygerberg Hospital NICU during the period of data collection (September 2011 to November 2011), and had received some form of medication during the stay, was included in the study.

3.2. Exclusion criteria

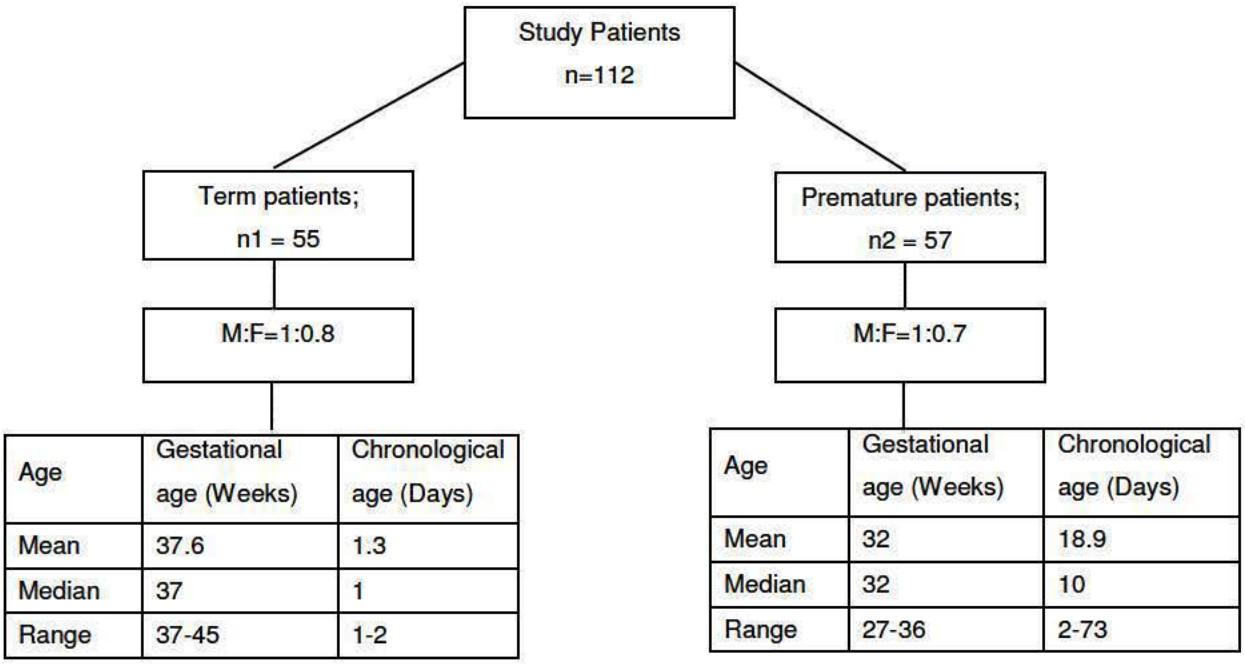
Babies who were older than 28 days or whose corrected gestational age was greater than 1 month, were not included in the study, as well as neonates not receiving any medication.

4. Results

4.1. Demographics

During the 3-month study period, 117 patients were admitted to NICU. Of these, 112 were enrolled in the study. Five patients were excluded, because they did not fit the inclusion criteria: namely 2 babies were dead on arrival in the NICU, 2 were only admitted for blood exchange transfusion and 1 baby with Trisomy 13 died soon after admission who had not received any medication from NICU. More than half (51%) of the neonates were premature (figure 1). The preterm babies had a mean gestational age of 32 weeks (median age of 32 weeks; range 27 to 36 weeks). The mean age was 18.9 days (median age 10 day, range: 2 to 73 days). The male to female ratio was 1:0.7.

Figure 1: Demographics of the neonates admitted to NICU at Tygerberg Hospital



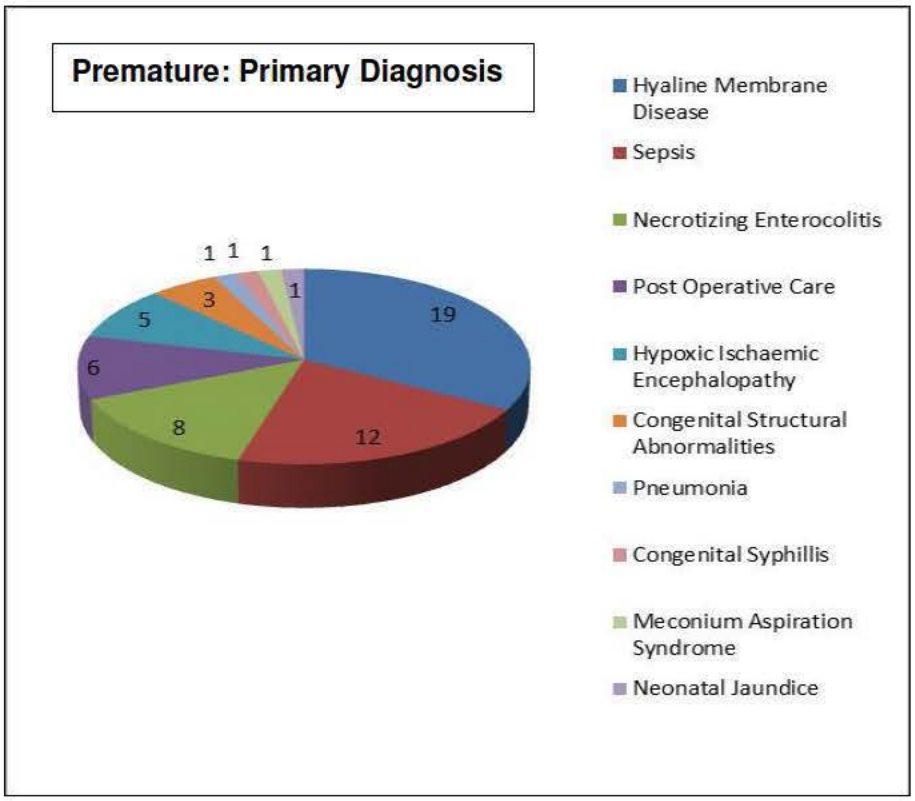
Age	Gestational age (Weeks)	Chronological age (Days)
Mean	37.6	1.3
Median	37	1
Range	37-45	1-2

Age	Gestational age (Weeks)	Chronological age (Days)
Mean	32	18.9
Median	32	10
Range	27-36	2-73

4.2. Diagnoses:

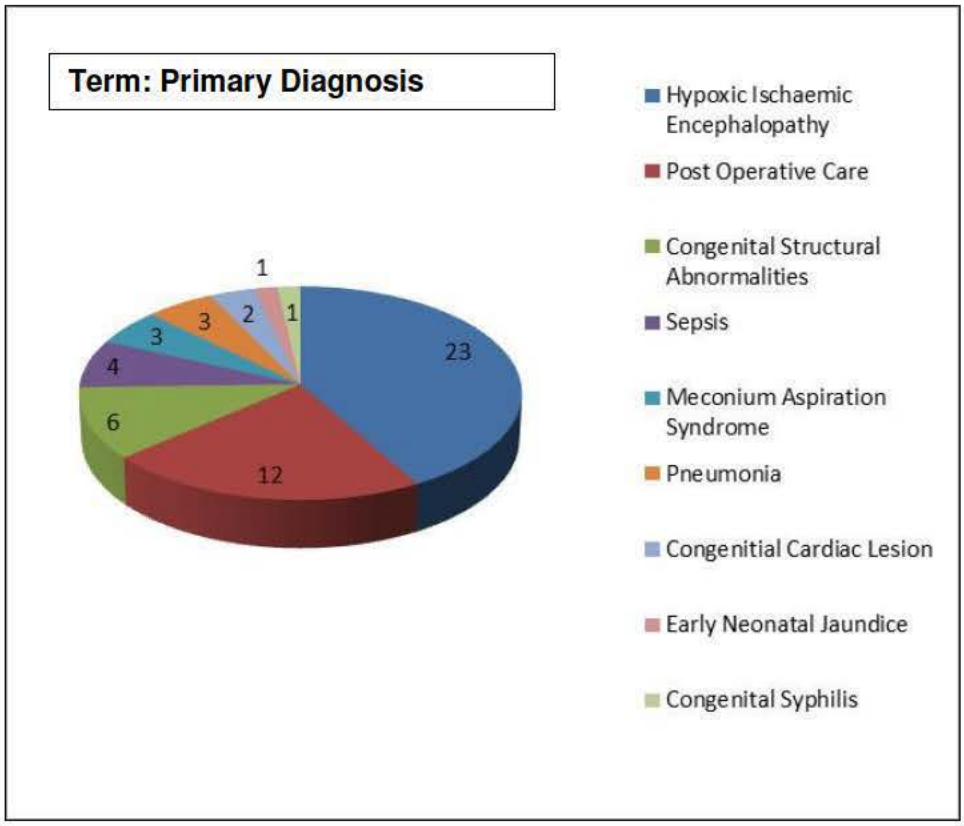
The primary diagnoses of the premature babies were hyaline membrane disease (33%), sepsis (21%), necrotizing enterocolitis (14%), post-operative care (10%), hypoxic ischemic encephalopathy (9%), congenital structural abnormality (5%), pneumonia (2%), meconium aspiration syndrome (2%), early neonatal jaundice (2%) and congenital syphilis (2%) in descending order (figure 2).

Figure 2: The most common diagnoses of the premature babies



For the term babies, the mean gestational age was 37. 6 weeks (median age of 37 weeks, range 37 to 45 weeks). The chronological mean age was 1.3 days (median age of 1 day, range 1 to 2 days). The male to female ratio was 1:0.8. Hypoxic ischemic encephalopathy was the most common diagnosis in term neonates (42%), followed by post-operative care (22%), congenital structural abnormality (11%), sepsis (7%), meconium aspiration syndrome (5%), pneumonia (5%), congenital cardiac lesion (4%), early neonatal jaundice (2%) and congenital syphilis (2%). (Figure 3) Twenty-seven babies of the 112 were diagnosed as HIV exposed and the majority of these exposed infants were term babies (63 %) and the rest (37%) were preterm.

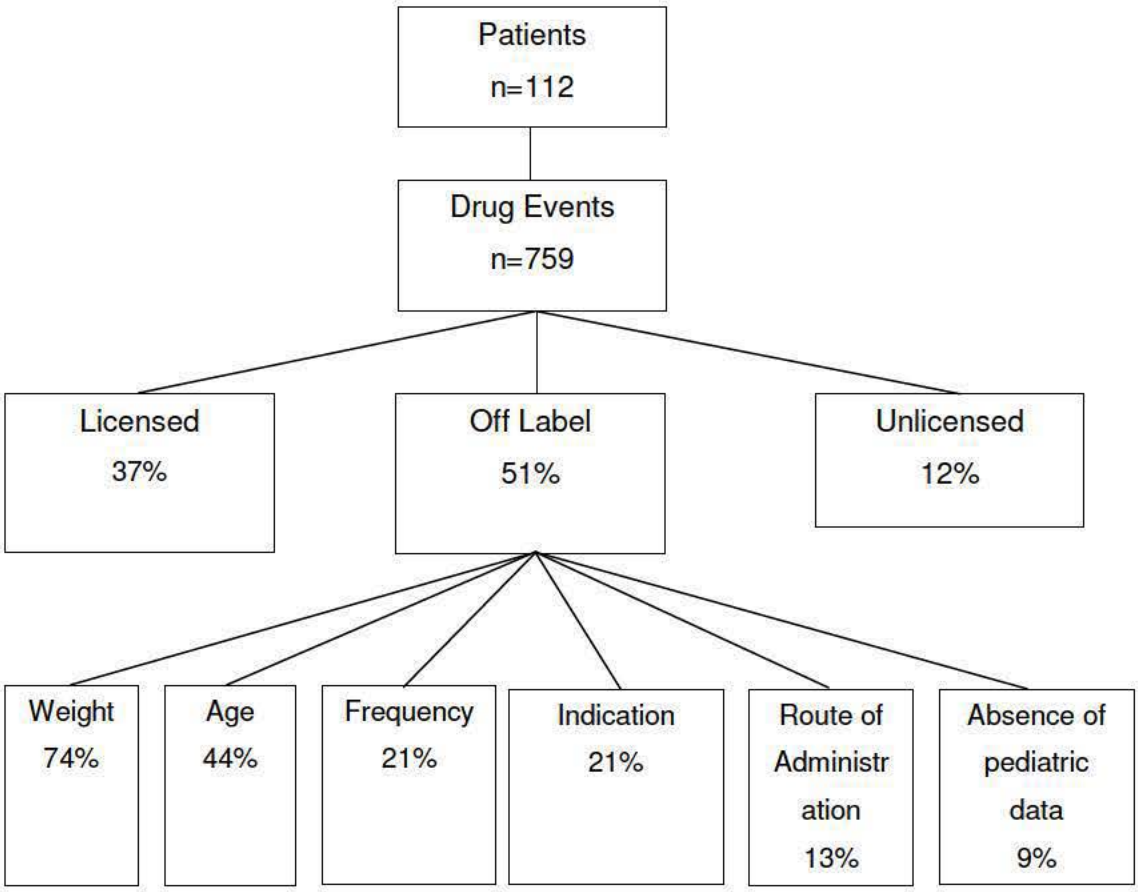
Figure 3: The most common diagnoses of the term babies



4.3. Drugs:

There were 759 drug events in the study population with 74 different drugs prescribed during the data collection period, excluding fluids, blood products and mineral supplements. Each patient received between 1 to 26 different drugs per admission. The majority (88%) of the prescriptions were licensed drugs, of which 51% were used off label and 12% were unlicensed. (Figure 4)

Figure 4: Drug events defined as licensed or unlicensed, including off label drug use



The most common reason for off label use per drug events was due to a different dose prescribed for the recommended weight (74%), followed by drugs inappropriately prescribed for age (44%), frequency (21%), indication (21%), for a route not described in the licensing terms (13%) or absence of pediatric data (9%).

For the 203 drug events, a drug was used in an off label manner for two or more reasons in 27% drug events. One hundred and two patients (91%) received at least one unlicensed or off label drug during their admission to the NICU.

The 10 most commonly prescribed drugs were penicillin (9%), gentamycin (7.6%) aminophylline (7.2%), meropenem (7.1%), vancomycin (6.7%), phenobarbitone (4%), paracetamol (3.8%), tilidine (3.6%), vitamin K (3.3%) and glycerine suppositories (3%). (Table 1).

Table 1: The 10 most commonly prescribed drugs

Drug	No of prescription episode	Percentage
Penicillin	70	9
Gentamycin	58	7,6
Aminophylline	55	7,2
Meropenem	54	7,1
Vancomycin	51	6,7
Phenobarbitone	30	4
Paracetamol	29	3,8
Tilidine	27	3,6
Vitamin K	25	3,3
Glycerine suppository	23	3

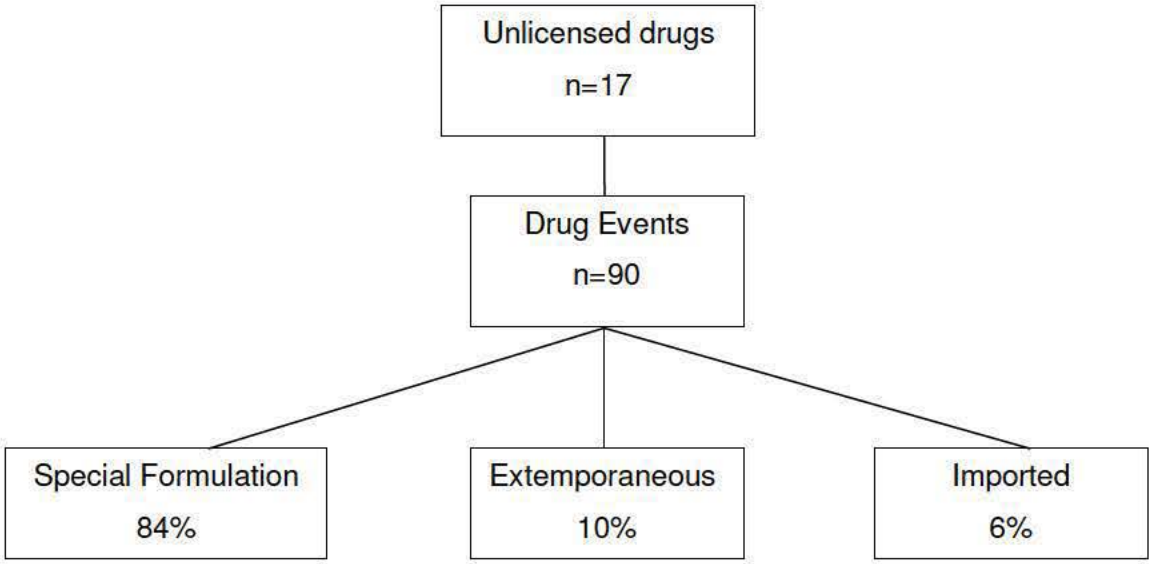
The five drugs, that were most frequently prescribed in an off label or unlicensed manner, were aminophylline, meropenem, vancomycin, intravenous paracetamol (Perfalgan®) and tilidine (Valoron®) in descending order (Table 2). Only two anti-retroviral drugs were prescribed to the neonates (nevirapine and zidovudine) and they formed 3.5% of the total prescriptions. Both were given in an off label manner. The anti-tuberculosis drugs formed a very small proportion (0.5%) of the total number of prescription and were only prescribed to two patients. The three anti-tuberculosis drugs prescribed were Rifampicin, Isoniazid and Pyrazinamide. Rifampicin was given in an off label manner while Isoniazid and Pyrazinamide were part of the "special formulation" made by the pharmacy and therefore unlicensed.

Table 2: The most commonly prescribed drugs in an off label or unlicensed manner

Drug	No. of Prescriptions	Status
Aminophylline	55 (7%)	Off- label for age
Meropenem	54 (7%)	Off- label for age
Vancomycin	50 (7%)	Off- label for dose
Tilidine	27 (4%)	Off- label for age
Paracetamol (ivi)	25 (3%)	Off- label for age

The unlicensed drugs fell into 3 categories with the majority of the drugs under the "special formulations" (84%) category, followed by extemporaneously compounded drugs (10%) and imported drugs (6%). (Figure 5)

Figure 5: Reasons for unlicensed drug use in 90 drug events



The drugs were also classified into drug groups according to the latest Anatomical Therapeutic Chemical (ATC) classification, suggested by the World Health Organization. The most prescribed drugs were anti-infectives for systemic use (41.4%), followed by drugs for the nervous system (20%), alimentary tract and metabolism (9.6%), respiratory tract (9.3%), cardiovascular system (8.3%), blood and blood forming organs (3.3%), musculoskeletal (3.3%), systemic hormonal preparations (2.5%), genito-urinary system and sex hormones (0.9%), anti-parasitic products (0.8%), sensory organs (0.4%) and a few other drugs (0.1%). (Table 3)

Table 3: Drug categories according to ATC Classification

Therapeutic class	WHO ATC	Active substance	Number of drug events	Number of off label drug events	Criterion of off label use
A Alimentary tract and metabolism					
A02 drugs for acid related disorders					
Proton pump inhibitors	A02BC	Omeprazole	4	4	Dose
H2-receptor antagonists	A02BA	Cimetidine	15	11	Frequency, Dose
A06 drugs for constipation					
Enema	A06AG	Glycerine suppository	23	23	Dose
A07 antidiarrheal, intestinal anti-inflammatory/anti-infective agents					
Antibiotics	A07AA	Nystatin	1	1	Absence of Pediatric information
A10 drugs used in diabetes					
Insulins and analogues for injection, fast-acting	A10AB	Insulin short acting	3	0	
A11 vitamins					
Vitamin D and analogues	A11CC	Vitamin D	9	0	
A16 other alimentary tract and metabolism products					
Amino acids and derivatives	A16AA	L-carnitine	1	0	Unlicensed
B Blood and blood forming organs					
B02 antihemorrhagics					
Vitamin K	B02BA	Vitamin K	25	11	Dose, frequency
C cardiovascular system					
C01 cardiac therapy					
Adrenergic and dopaminergic agents	C01CA	Dopamine	20	0	
		Dobutamine	12	12	Dose
		Adrenaline	8	1	Dose
Antiarrhythmics, class III	C01BD	Amiodarone	1	1	Absence of Pediatric information
Other cardiac preparations	C01EB	Adenosine	1	1	Dose
C03 diuretics					

Aldosterone antagonists	C03DA	Spironolactone	2	1	Dose
Thiazides, plain	C03AA	Hydrochlorothiazide	1	1	Dose
Sulfonamides, plain	C03CA	Furosemide	17	10	Indication, frequency, dose
C09 agents acting on the renin-angiotensin system					
ACE inhibitors, plain	C09AA	Enalapril	1	1	Absence of Pediatric information
G Genito urinary system and sex hormones					
G02 other gynecologicals					
Prostaglandins	G02AD	Prostin E2	3	3	Absence of Pediatric information, Indication, dose
G04 urologicals					
Drugs used in erectile dysfunction	G04BE	Sildenafil	4	4	Absence of Pediatric information, frequency, dose
H Systemic hormonal preparations, excl. sex hormones and insulins					
H02 corticosteroids for systemic use					
Mineralocorticoids	H02AA	Fludrocortisone	1	1	Absence of Pediatric information
Glucocorticoids	H02AB	Prednisone	1	1	Route
		Dexamethasone	6	6	Indication, frequency, dose
		Hydrocortisone	11	11	Route, Indication, frequency, dose
J.Anti-infective for systemic use					
J01 Antibacterials for systemic use					
Carbapenems	J01DH	Meropenem	54	54	Age, frequency, dose
Glycopeptideantibacterials	J01XA	Vancomycin	51	50	Frequency, dose
Combinations of sulfonamides and trimethoprim, incl. derivatives	J01EE	Cotrimoxazole	1	1	Frequency, dose

Third-generation cephalosporins	J01DD	Ceftazidime	1	0	
		Cefotaxime	5	3	Frequency, dose
Second-generation cephalosporins	J01DC	Cefuroxime	1	0	
Beta-lactamase resistant penicillins	J01CF	Cloxacillin	2	2	Dose
Combinations of penicillins, incl. beta-lactamase inhibitors	J01CR	Augmentin	1	1	Frequency, dose
Beta-lactamase sensitive penicillins	J01CE	Benzylpenicillin	70	14	Frequency, dose
Penicillins with extended spectrum	J01CA	Ampicillin	3	2	Frequency
Other aminoglycosides	J01GB	Gentamycin	54	0	
		Amikacin	3	0	
Polymyxins	J01XB	Colistin	3	0	unlicensed
Other antibacterials	J01XX	Linezolid	1	1	Frequency
Fluoroquinolones	J01MA	Ciprofloxacin	3	2	Indication, dose
Macrolides	J01FA	Erythromycin	4	2	Frequency, dose
JO4 Antimycobacterial					
Drugs for treatment of tuberculosis: Antibiotics	J04AB	Pyrazinamide	1	0	
		Rifampicin	2	2	Route
		INH	1	1	Dose
J05 Antivirals					
Nucleosides and nucleotides excl. reverse transcriptase inhibitors	J05AB	Acyclovir	4	0	
		Gancyclovir	1	1	Age
Nucleoside and nucleotide reverse transcriptase inhibitors	J05AF	Zidovudine (AZT)	7	7	Frequency, dose
Non-nucleoside reverse transcriptase inhibitors	J05AG	Nevirapine	20	12	Dose, route
J02 antimycotics for systemic use					
Triazole derivatives	J02AC	Fluconazole	16	10	Frequency, dose
J06 immune sera and immunoglobulins					
Specific immunoglobulins	J06BB	Palivizumab	1	0	

M Musculo-skeletal system					
M03 muscle relaxants					
Other quaternary ammonium compounds	M03AC	Pancuronium	2	2	Dose
Choline derivatives	M03AB	Suxamethonium	15	0	
Propionic acid derivatives	M01AE	Ibuprofen	8	8	Route, frequency
N Nervous system					
N05 psycholeptics					
Hypnotics and sedatives: Benzodiazepine derivatives	N05CD	Lorazepam	2	0	
		Midazolam	10	10	Route, indication
N01 anaesthetics					
Amides	N01BB	Bupivacaine	2	2	Dose
		Lignocaine	1	1	Indication
Opioid anesthetics	N01AH	Fentanyl	20	20	Absence of Pediatric information
Other general anesthetics	N01AX	Ketamine	18	0	
N06 psychoanaleptics					
Xanthine derivatives	N06BC	Caffeine	9	0	Unlicensed
N02 analgesics					
Other opioids	N02AX	Tilidine (valoron)	27	27	Age, dose
Anilides	N02BE	Paracetamol	29	28	Age, dose, frequency
Other antimigraine preparations	N02CX	Clonidine	1	1	Age, indication
Natural opium alkaloids	N02AA	Morphine	1	1	Dose
N03 antiepileptics					
Hydantoin derivatives	N03AB	Phenytoin	2	1	Dose
Barbiturates and derivatives	N03AA	Phenobarbitone	30	3	Dose
P Antiparasitic products, insecticides and repellents					
P01 antiprotozoals					
Nitroimidazole derivatives	P01AB	Metronidazole	6	6	Age, frequency, dose
R Respiratory system					

R01 nasal preparations					
Other nasal preparations	R01AX	Bactroban	2	2	Absence of Pediatric information, frequency
R03 drugs for obstructive airway diseases					
Xanthines	R03DA	Aminophylline	55	55	Age, indication, frequency
R07 other respiratory system products					
Respiratory stimulants	R07AB	Doxapram	2	2	Absence of Pediatric information, frequency, age, dose indication,
Lung surfactants	R07AA	Poractant alfa	10	3	Dose, Indication
		Beractant	2	2	Dose
S Sensory organs					
S01 ophthalmologicals					
Antibiotics	S01AA	Chloramphenicol	1	1	Absence of Pediatric information
Anticholinergics	S01FA	Cyclomydril	2	0	
V Various					
V03 all other therapeutic products					
Drugs for treatment of hypoglycemia	V03AH	Diazoxide	1	0	Unlicensed

5. Discussion

The use of drugs in children, based on drug trials conducted in adults and extrapolated to children, shows ignorance of the important differences that exist in the pharmacokinetics and pharmacodynamics of drugs between adults and children. [19] The extent of unlicensed and off label drug use in pediatrics has been well highlighted since the 1960's in the US and Europe. This has subsequently resulted in changes made by the respective authorities in facilitating drug trials in children to improve the access to safe and efficacious medicines for children. Studies in Australia, as well as the United Kingdom have shown a higher incidence of unlicensed and off label drug use in NICUs compared to drug use among pediatric patients in general medical and surgical wards.[9]

This study is the only one reported from a NICU in Africa and our results regarding the proportion of unlicensed and off label drugs (12% and 51% respectively) are similar to that reported by Dell'Aera et al. (12.0% and 50.5%) in 2004 in an Italian NICU, [5] O'Donnell et al. (11% and 47%) in 2002 in Australia [19] and Conroy et al. (9.9% and 54.7%) in 1999 in United Kingdom. [16] In this study 91% of neonates, admitted over the 3 month period, received at least one off label or unlicensed drug, which was similar to the results in the review by Cuzzolin et al, where more than 80% of neonates are exposed to at least one off label or unlicensed drug. [16,20] The main reason for off label drug use was inappropriate dosing for the recommended weight; this is similar to the findings in the study by Conroy, et al, but different from the findings by O'Donnell, et al in Australia where the most common reason for off label drug use was for indication. [19,20]

Aminophylline was the most commonly prescribed drug in an off label or unlicensed manner. Aminophylline, theophylline and caffeine belong to the group of drugs known as methylxanthines and have been used to reduce apnoea and stimulate breathing. Aminophylline is registered for use in pediatrics, but only for children older than 6 months

of age. [21]Recurrent apnoea is a common problem among the preterm babies and a Cochrane review in 2010 by Hendersen-Smart, et al, demonstrated that methylxanthine was effective in reducing apnoea in premature infants. [22] Caffeine is unlicensed in South Africa, as well as in Europe, and yet it is considered the safest of the methylxanthines for the treatment of apnoea of prematurity. [23] Another drug that was used in our setting for the treatment of apnoea of prematurity is doxapram, a stimulant of the respiratory centre in the brain. This drug is contraindicated in neonates in Japan because of its side effects, yet its use continues in many parts of the world, with only a few studies done to investigate its use in neonates. [24] Hendersen-Smart, et al. only found 1 randomized control trial (RCT) in a Cochrane review from 1966 to April 2009, which indicates that doxapram may reduce apnoea in the first 48 hours of treatment, but it was a small study with a wide confidence interval and long-term outcomes were not measured. Therefore the conclusion was that more studies are needed to confirm the role of doxapram for the treatment of apnoea in preterm infants. [25]

The antibiotic, most frequently used in an off label manner in our study was the intravenous form of meropenem. This carbapenem has been used in neonates to treat severe infections due to gram-negative or gram-positive organisms, including nosocomial infections, although safety and efficacy in children less than 3 months of age has not yet been established. [26]

Meconium retention in low birth weight infants causes bowel dysfunction. [27] Significant delays to pass meconium have been observed in preterm babies compared to term babies. A glycerine suppository, which was among the 10 most commonly prescribed drugs in our study, is used to stimulate passage of meconium and reduce feeding intolerance. According to a review done by Shah et al in 2007, the evidence was inconclusive regarding the effectiveness of glycerine suppositories for improving feeding intolerance in preterm babies. [28] This review was done based on two studies, including a randomized control study, which showed no benefit and an observational cohort study,

which showed benefit in terms of achieving full feeds earlier with reduced sepsis due to deep lines for enteral feeds. [28] This is a clear indication that more studies are needed to make a proper decision.

Although the anti-tuberculosis drugs only formed a small proportion (0.5%) of our total prescriptions, it was given in off label or unlicensed manner. The highest rate of this global pandemic of tuberculosis (TB) occurs in sub-Saharan African countries and goes hand in hand with the HIV epidemic. [29] As the trend goes, children were left out of the initial series of clinical trials for TB treatment and have been receiving drug doses extrapolated from adult doses. It only became evident in 2007 that the children were under dosed and that drugs like isoniazid had to be doubled in dose when given to children to achieve the same isoniazid concentration in adults. [30] Children however are still not receiving the right doses because the formulations of anti-TB drugs are not pediatric friendly. The anti-TB drugs used in this study and the available formulations at Tygerberg Hospital include the fixed drug combination tablets, single drug tablets, and capsules. Although a syrup formulation is more suitable for pediatrics, it is not commercially available. The Tygerberg pharmacy makes its own syrup for drugs like isoniazid, using a complex recipe. This formulation is only stable for a limited period and is not available to surrounding clinics including the TB hospital in the region.

In this study only two antiretroviral drugs (ARV) to prevent mother to child transmission of HIV were used and they made up 3.5 % of the total prescriptions. Both are available in solution form and therefore easier to administer to the neonates. They were both used in an off- label manner because of dose and frequency different to the recommendations in the SAMF and the ARV dosing chart for children and adolescents by the South African HIV Clinicians Society. It is important to note that there were variations between the two references regarding the recommendations in children <3kg.[31] There has been a renewed interest in anti-tuberculosis drugs and ARVs in the last couple of years which has resulted in a deliberate effort by pharmaceutical companies to produce these drugs in a more

tolerable form that would be easier to administer. There are concerns raised about whether clinical trials are ethical in neonates considering the informed consent, assent and risks involved versus potential benefit. [9] What is certain is that it is more unethical to give drugs that have not been proven to be safe and efficacious to neonates.[19]

6. Limitations:

It was difficult to compare studies done in similar settings because the definitions of unlicensed and off label drugs differed between the authors. The number of prescriptions for drugs like fentanyl, dopamine and dobutamine may have been more than what was recorded in the study, as some of these prescriptions may erroneously been written on the fluid chart instead of the drug chart. The results in this study were similar to that published from Europe and the United States of America since Tygerberg Hospital NICU offers top services for neonatal care in South Africa and may therefore differ to other neonatal services provided by the different levels of health care in other countries in Africa. The period of 3 months for this study might not have been sufficient to represent the generalized population. Prescription errors may have affected the off label results, for example prednisone was wrongly prescribed to be given intravenously but it was given per os.

7. Conclusion

Children should be afforded the same importance and chance as adults when it comes to receiving safe and efficacious drugs. It is the role of regulatory authorities to pressurize pharmaceutical companies to perform clinical trials in children. The USA and Europe have taken the first steps already, an example that should be followed by the rest of the world.[32] Practical, legislative and ethical difficulties do exist with pediatric clinical trials, but the improvement in health and safety of all children should be our responsibility and is it therefore important to conduct clinical trials in neonatology for drugs seen as essential to improve their health.

8. Bibliography

1. Pandolfini C, Bonati M. A literature review on off label drug use in children. Eur J Pediatr 2005; 164: 552-558.
2. Joseph R, Tobin, MD. Use of pharmaceuticals 'Off Label' in the neonate. Best Practice & Research Clinical Anesthesiology 2010; 24: 451-460.
3. Kairuz TE, Gargiulo D, Bunt C, Garg S. Quality, Safety and Efficacy in the 'Off Label' Use of Medicines.Curr Drug Saf. 2007; 2: 89–95.
4. Jain SS, Bavdekar SB, Gogtay NJ, Sadawarte PA. Off label drug use in children. Indian Jr Pediatr 2008; Sep 22: 75: 1133-1136.
5. Dell'Aera M, Gasbarro A.R, Padovano M, Laforgia N, Capodiferro D, Solarino B, Quaranta R and Dell'Erba A.S. Unlicensed and off label use of medicines at a neonatology clinic in Italy, Pharm World Sci 29(4)(2007); Epub 2007 Mar 10: 361–367.
6. Committee on Drugs, American Academy of Pediatrics. Uses of drugs not described in the package insert (off label uses). Pediatrics 2002; 110: 181-183.
7. Jansen R.M. The off label use of medication in South Africa, what about some information for medical practitioners? SAMJ. June 2009; Vol. 99: No. 6.
8. Hsien L, Breddemann A, Frobel AK, Heusch A, Schmidt KG, Laer S. off Label drug use among hospitalised children: identifying areas with the highest need for research. Pharm World Sci. 2008; 30(5): 497-502.
9. Turner S, Longworth A, Nunn AJ, Choonara I. Unlicensed and off label drug use in pediatric wards: prospective study. BMJ 1998; 316: 343–345.
10. Khamar B, MS (Ophthalmology). Off label use of medicines: Medical research and medical practice. Indian J Ophthalmol. 2007 Nov–Dec; 55(6): 411–412.
11. Jansen R-M, Gouws C. Clinical, legal and ethical implications of the intraocular (off-label) use of bevacizumab (Avastin) – a South African perspective. S Afr Med J 2009; 99: 446-449.
12. Horen B, Montastruc JL, Lapeyre-Mestre M: Adverse drug reactions and off label drug use in pediatric outpatients. Br J ClinPharmacol 2002; 54: 665-70.
13. Schellack N, Schellack G. Drug therapy in the neonate, Department of Pharmacy, Faculty of Health Sciences, University of Limpopo. Professional Nursing Today 2010; 14(6): 5-17.
14. Kairuz TE, Gargiulo D, Bunt C, Garg S. Quality, Safety and Efficacy in the 'Off Label' Use of Medicines.Curr Drug Saf. 2007; 2: 89–95.
15. Bavdekar SB, Gogtay NJ. Unlicensed and off label drug use in children. J Postgrad Med 2005; 51: 249-52.

16. Conroy S, McIntyre J. The use of unlicensed and off label medicines in the neonate. Seminars in Fetal & Neonatal Medicine 2005; 10: 115-122.
17. Lenk C, Koch Ph, Zappel H, Wiesemann C. Off label, Off-limits? Parental Awareness and Attitudes towards off label Use in Pediatrics'. European Journal of Pediatrics (2009); 168: 1473–1478.
18. Hill P, off license and off label prescribing in children: litigation fears for physicians. Arch Dis Child. 2005 February; 90(Suppl 1): i17–i18.
19. O'Donnell CP, Stone RJ, Morley CJ. Unlicensed and off label drug use in an Australian neonatal intensive care unit. Pediatrics. 2002; 110: e52.
20. Conroy S, McIntyre J, Choonara I, Unlicensed and off label drug use in neonates. Arch Dis Child Fetal Neonatal Ed. 1999 March; 80(2): F142–F145.
21. Cuzzolin L, Atzei A, Fanos V, off label and unlicensed prescribing for newborns and children in different settings: a review of the literature and a consideration about drug safety. Exp Opin Drug Saf.2006; 5: 703-18.
22. Division of Clinical Pharmacology, Faculty of Health Sciences, University of Cape Town. South African Medicines Formulary – Tenth Edition. Cape Town: Health and Medical Publishing Group, 2012.
23. Henderson-Smart DJ, De Paoli AG. Methylxanthine treatment for apnoea in preterm infants. Cochrane Database System Rev 2010; 12: CD000432.
24. Anthony R. Jenny T. James R. Rebecca G., Marianna DK, Jenna P, Hannelie S, Guidelines for the safe use of procedural sedation and analgesia for diagnostic and therapeutic procedures in children: 2010. S Afr J Anaesthesiol Analg 2010; 16(5)(Supplement 1): S1-S37.
25. Henderson-Smart DJ, Steer PA. Doxapram treatment for apnea in preterm infants. Cochrane Database System Rev 2009; 4: CD000074.
26. De Cunto, A., M. Tana, V. Vendettuoli, C. Tirone, S. Boccacci, G. Vento, and C. Romagnoli. 2007. Use of Meropenem in preterm newborns. Survey of the literature and case series. Minerva Pediatric 59: 755-60.
27. Rojhan A, Lingren CG. Enteral feeding in infants <1250 g starting within 24 h post-partum. Eur J Pediatr 2001; 160: 629-32.
28. Vibhuti Shah, MD, 1,2NevartChirinian, NP, 3 Shoo Lee, MD, 4, 5, 6 and EPIQ Evidence Review Group. Does the use of glycerin laxatives decrease feeding intolerance in preterm infants? Paediatr Child Health. 2011 November; 16(9): e68–e70.
29. Zar HJ. Global pediatric pulmonology: out of Africa. Pediatr Respir Rev.2006; 1: S226-8.
30. McIlleron H, Willemse M, Werely C.J, Hussey G.D, Schaaf H.S, Smith P.J and Donald P.R. Isoniazid Plasma Concentrations in a Cohort of South African Children with Tuberculosis:

Implications for International Pediatric Dosing Guidelines Clinical Infectious Diseases 2009; 48: 1547–53.

31. Department of Health, Antiretroviral Drug Dosing Chart for Children 2012. http://www.sahivsoc.org/upload/documents/2012%20ARV%20Dosing%20Chart%20for%20Children%20and%20Adolescents.pdf. (Accessed November 2013).
32. Kling S. Off label drug use in childhood asthma. Current Allergy & Clinical Immunology, March 2011 Vol 24; No. 1: 38-41.